

Reference

Chapter 11

1. Meyer GA, Lieber RL. Elucidation of extracellular matrix mechanics from muscle fibers and fiber bundles. *J Biomech.* 2011;44(4):771–773.
2. Magnusson SP, Narici MV, Maganaris CN, Kjaer M. Human tendon behaviour and adaptation, *in vivo*. *J Physiol.* 2008;586(1):71–81.
3. Heinemeier KM, Olesen JL, Haddad F, et al. Expression of collagen and related growth factors in rat tendon and skeletal muscle in response to specific contraction types. *J Physiol.* 2007;582(pt 3):1303–1316.
4. Kjaer M. Role of extracellular matrix in adaptation of tendon and skeletal muscle to mechanical loading. *Physiol Rev.* 2004;84(2):649–698.
5. Lieber RL, Ward SR. Cellular mechanisms of tissue fibrosis. 4. Structural and functional consequences of skeletal muscle fibrosis. *Am J Physiol Cell Physiol.* 2013;305: C241–C252.
6. Trotter JA, Purslow PP. Functional morphology of the endomysium in series fibered muscles. *J Morphol.* 1992;212(2):109–122.
7. Patel TJ, Lieber RL. Force transmission in skeletal muscle: from actomyosin to external tendons. *Exerc Sport Sci Rev.* 1997;25:321–363.
8. Huijing PA. Muscle as a collagen fiber reinforced composite: a review of force transmission in muscle and whole limb. *J Biomech.* 1999;32(4):329–345.
9. Street SF. Lateral transmission of tension in frog myofibers: a myofibrillar network and transverse cytoskeletal connections are possible transmitters. *J Cell Physiol.* 1983;114(3):346–364.
10. Passerieux E, Rossignol R, Letellier T, Delage JP. Physical continuity of the perimysium from myofibers to tendons: involvement in lateral force transmission in skeletal muscle. *J Struct Biol.* 2007;159(1):19–28.
11. Zhang C, Gao Y. Effects of aging on the lateral transmission of force in rat skeletal muscle. *J Biomech.* 2014;47(5):944–948.
12. Smith LR, Lee KS, Ward SR, Chambers HG, Lieber RL. Hamstring contractures in children with spastic cerebral palsy result from a stiffer extracellular matrix and increased *in vivo* sarcomere length. *J Physiol.* 2011;589(pt 10):2625–2639.
13. Borg TK, Caulfield JB. Morphology of connective tissue in skeletal muscle. *Tissue Cell.* 1980;12(1):197–207.
14. Purslow PP. The structure and functional significance of variations in the connective tissue within muscle. *Comp Biochem Physiol A Mol Integr Physiol.* 2002;133(4):947–966.
15. Miller BF, Olesen JL, Hansen M, et al. Coordinated collagen and muscle protein synthesis in human patella tendon and quadriceps muscle after exercise. *J Physiol.* 2005;567(pt 3):1021–1033.
16. Holm L, van Hall G, Rose AJ, et al. Contraction intensity and feeding affect collagen and myofibrillar protein synthesis rates differently in human skeletal muscle. *Am J Physiol Endocrinol Metab.* 2010;298(2):E257–E269.
17. Doessing S, Heinemeier KM, Holm L, et al. Growth hormone stimulates the collagen synthesis in human tendon and skeletal muscle without affecting myofibrillar protein synthesis. *J Physiol.* 2010;588(pt 2):341–351.
18. Nielsen RH, Clausen NM, Schjerling P, et al. Chronic alterations in growth hormone/ insulin-like growth factor-I signaling lead to changes in mouse tendon structure. *Matrix Biol.* 2014;34:96–104.
19. Hansen M, Skovgaard D, Reitelseder S, Holm L, Langberg H, Kjaer M. Effects of estrogen replacement and lower androgen status on skeletal muscle collagen and myofibrillar protein synthesis in postmenopausal women. *J Gerontol A Biol Sci Med Sci.* 2012;67(10):1005–1013.
20. Cramer RM, Langberg H, Teisner B, et al. Enhanced procollagen processing in skeletal muscle after a single bout of eccentric loading in humans. *Matrix Biol.* 2004;23(4):259–264.
21. Cramer RM, Aagaard P, Qvortrup K, Langberg H, Olesen J, Kjaer M. Myofibre damage in human skeletal muscle: effects of electrical stimulation versus voluntary contraction. *J Physiol.* 2007;583(pt 1):365–380.
22. Mackey AL, Brandstetter S, Schjerling P, et al. Sequenced response of extracellular matrix deadhesion and fibrotic regulators after muscle damage is involved in protection against future injury in human skeletal muscle. *FASEB J.* 2011;25(6):1943–1959.
23. Saclier M, Yacoub-Youssef H, Mackey AL, et al. Differentially activated macrophages orchestrate myogenic precursor cell fate during human skeletal muscle regeneration. *Stem Cells.* 2013;31(2):384–396.
- 23a. Murphy MM, Lawson JA, Mathew SJ, Hutcheson DA, Kardon G. Satellite cells, connective tissue fibroblasts and their interactions are crucial for muscle regeneration. *Development.* 2011;138:3625–3637.
24. Urciuolo A, Quarta M, Morbidoni V, et al. Collagen VI regulates satellite cell self-renewal and muscle regeneration. *Nat Commun.* 2013;4:1964.
25. Tidball JG, Salem G, Zernicke R. Site and mechanical conditions for failure of skeletal muscle in experimental strain injuries. *J Appl Physiol.* 1993;74(3):1280–1286.
26. Roffino S, Carnino A, Chopard A, Mutin M, Marini JF. Structural remodeling of unweighted soleus myotendinous junction in monkey. *CR Biol.* 2006;329(3):172–179.
27. Cien AP, Luques IU, Dias FJ, Yokomizo de Almeida SR, Iyomasa MM, Watanabe IS. Ultrastructure of the myotendinous junction of the medial pterygoid muscle of adult and aged Wistar rats. *Micron.* 2010;41(8):1011–1014.
28. Knudsen AB, Larsen M, Mackey AL, et al. The human myotendinous junction: an ultrastructural and 3D analysis study. *Scand J Med Sci Sports.* 2015;25:e116–e123.
29. Trotter JA. Structure-function considerations of muscle-tendon junctions. *Comp Biochem Physiol A Mol Integr Physiol.* 2002;133(4):1127–1133.

30. Kojima H, Sakuma E, Mabuchi Y, et al. Ultrastructural changes at the myotendinous junction induced by exercise. *J Orthop Sci.* 2008;13(3):233–239.
31. Finni T, Komi PV, Lepola V. In vivo human triceps surae and quadriceps femoris muscle function in a squat jump and counter movement jump. *Eur J Appl Physiol.* 2000;83(4–5):416–426.
32. Magnusson SP, Aagaard P, Dyhre-Poulsen P, Kjaer M. Load-displacement properties of the human triceps surae aponeurosis in vivo. *J Physiol.* 2001;531(pt 1):277–288.
33. Kastelic J, Galeski A, Baer E. The multicomposite structure of tendon. *Connect Tissue Res.* 1978;6(1):11–23.
34. Kadler KE, Holmes DF, Trotter JA, Chapman JA. Collagen fibril formation. *Biochem J.* 1996;316(pt 1):1–11.
35. Bailey AJ. Molecular mechanisms of ageing in connective tissues. *Mech Ageing Dev.* 2001;122(7):735–755.
36. Riley GP. Gene expression and matrix turnover in overused and damaged tendons. *Scand J Med Sci Sports.* 2005;15(4):241–251.
37. Haraldsson BT, Aagaard P, Krosgaard M, Alkjaer T, Kjaer M, Magnusson SP. Region-specific mechanical properties of the human patella tendon. *J Appl Physiol.* 2005;98(3):1006–1012.
38. Haraldsson BT, Aagaard P, Qvortrup K, et al. Lateral force transmission between human tendon fascicles. *Matrix Biol.* 2008;27(2):86–95.
39. Parry DA, Barnes GR, Craig AS. A comparison of the size distribution of collagen fibrils in connective tissues as a function of age and a possible relation between fibril size distribution and mechanical properties. *Proc R Soc Lond B Biol Sci.* 1978;203(1152):305–321.
40. Provenzano PP, Vanderby Jr R. Collagen fibril morphology and organization: implications for force transmission in ligament and tendon. *Matrix Biol.* 2006;25(2):71–84.
41. Svensson RB, Hassenkam T, Hansen P, Kjaer M, Magnusson SP. Tensile force transmission in human patellar tendon fascicles is not mediated by glycosaminoglycans. *Connect Tissue Res.* 2011;52:415–421.
42. Hansen P, Haraldsson BT, Aagaard P, et al. Lower strength of the human posterior patellar tendon seems unrelated to mature collagen cross-linking and fibril morphology. *J Appl Physiol.* 2010;108(1):47–52.
43. Buehler MJ. Nanomechanics of collagen fibrils under varying cross-link densities: atomistic and continuum studies. *J Mech Behav Biomed Mater.* 2008;1(1):59–67.
44. Fratzl P, Misof K, Zizak I, Rapp G, Amenitsch H, Bernstorff S. Fibrillar structure and mechanical properties of collagen. *J Struct Biol.* 1998;122(1–2):119–122.
45. Mosler E, Folkhard W, Knorzer E, Nemetschek-Gansler H, Nemetschek T, Koch MH. Stress-induced molecular rearrangement in tendon collagen. *J Mol Biol.* 1985;182(4):589–596.
46. Sasaki N, Odajima S. Elongation mechanism of collagen fibrils and force-strain relations of tendon at each level of structural hierarchy. *J Biomech.* 1996;29(9):1131–1136.
47. Svensson RB, Mulder H, Kovanen V, Magnusson SP. Fracture mechanics of collagen fibrils: influence of natural cross-links. *Biophys J.* 2013;104(11):2476–2484.
48. Rumian AP, Wallace AL, Birch HL. Tendons and ligaments are anatomically distinct but overlap in molecular and morphological features—a comparative study in an ovine model. *J Orthop Res.* 2007;25(4):458–464.
49. Suzuki D, Takahashi M, Abe M, Nagano A. Biochemical study of collagen and its crosslinks in the anterior cruciate ligament and the tissues used as a graft for reconstruction of the anterior cruciate ligament. *Connect Tissue Res.* 2008;49(1):42–47.
50. Ker RF, Alexander RM, Bennett MB. Why are mammalian tendons so thick? *J Zoo Lond.* 1988;216:309–324.
51. Rosager S, Aagaard P, Dyhre-Poulsen P, Neergaard K, Kjaer M, Magnusson SP. Loaddisplacement properties of the human triceps surae aponeurosis and tendon in runners and non-runners. *Scand J Med Sci Sports.* 2002;12(2):90–98.
52. Hansen P, Aagaard P, Kjaer M, Larsson B, Magnusson SP. Effect of habitual running on human Achilles tendon load deformation properties and cross-sectional area. *J Appl Physiol.* 2003;95(6):2375–2380.
53. Couppe C, Svensson RB, Grosset JF, et al. Life-long endurance running is associated with reduced glycation and mechanical stress in connective tissue. *Age (Dordr).* 2014;36(4):9665.
54. Couppe C, Kongsgaard M, Aagaard P, et al. Habitual loading results in tendon hypertrophy and increased stiffness of the human patellar tendon. *J Appl Physiol.* 2008;105(3):805–810.
55. Kongsgaard M, Reitelseder S, Pedersen TG, et al. Region specific patellar tendon hypertrophy in humans following resistance training. *Acta Physiol (Oxf).* 2007;191(2):111–121.
56. Michna H. Morphometric analysis of loading-induced changes in collagen-fibril populations in young tendons. *Cell Tissue Res.* 1984;236(2):465–470.
57. Patterson-Kane JC, Parry DA, Birch HL, Goodship AE, Firth EC. An age-related study of morphology and cross-link composition of collagen fibrils in the digital flexor tendons of young thoroughbred horses. *Connect Tissue Res.* 1997;36(3):253–260.
58. Patterson-Kane JC, Firth EC, Parry DA, Wilson AM, Goodship AE. Effects of training on collagen fibril populations in the suspensory ligament and deep digital flexor tendon of young thoroughbreds. *Am J Vet Res.* 1998;59(1):64–68.
59. Kongsgaard M, Qvortrup K, Larsen J, et al. Fibril morphology and tendon mechanical properties in patellar tendinopathy: effects of heavy slow resistance training. *Am J Sports Med.* 2010;38(4):749–756.
60. Bailey AJ, Paul RG, Knott L. Mechanisms of maturation and ageing of collagen. *Mech Ageing Dev.* 1998;106(1–2):1–56.
61. Kongsgaard M, Kovanen V, Aagaard P, et al. Corticosteroid injections, eccentric decline squat training and heavy slow resistance training in patellar tendinopathy. *Scand J Med Sci Sports.* 2009;19(6):790–802.
62. Verzijl N, DeGroot J, Oldehinkel E, et al. Age-related accumulation of Maillard reaction products in human articular cartilage collagen. *Biochem J.* 2000;350(pt 2):381–387.

63. Narici MV, Maganaris CN. Plasticity of the muscle-tendon complex with disuse and aging. *Exerc Sport Sci Rev.* 2007;35(3):126–134.
64. Suetta C, Hvid LG, Justesen L, et al. Effects of ageing on human skeletal muscle after immobilisation and re-training. *J Appl Physiol.* 2009;107:1172–1180.
65. de Boer MD, Maganaris CN, Seynnes OR, Rennie MJ, Narici MV. Time course of muscular, neural and tendinous adaptations to 23 day unilateral lower-limb suspension in young men. *J Physiol (Lond).* 2007;583(pt 3):1079–1091.
66. Matsumoto F, Trudel G, Uhthoff HK, Backman DS. Mechanical effects of immobilization on the Achilles' tendon. *Arch Phys Med Rehabil.* 2003;84(5):662–667.
67. Rumian AP, Draper ER, Wallace AL, Goodship AE. The influence of the mechanical environment on remodelling of the patellar tendon. *J Bone Joint Surg Br.* 2009;91(4):557–564.
68. Eliasson P, Fahlgren A, Pašternak B, Aspenberg P. Unloaded rat Achilles tendons continue to grow, but lose viscoelasticity. *J Appl Physiol.* 2007;103(2):459–463.
69. Kinugasa R, Hodgson JA, Edgerton VR, Shin DD, Sinha S. Reduction in tendon elasticity from unloading is unrelated to its hypertrophy. *J Appl Physiol.* 2010;109(3):870–877.
70. Shin D, Finni T, Ahn S, et al. Effect of chronic unloading and rehabilitation on human Achilles tendon properties: a velocity-encoded phase-contrast MRI study. *J Appl Physiol.* 2008;105(4):1179–1186.
71. Reeves ND, Maganaris CN, Ferretti G, Narici MV. Influence of 90-day simulated microgravity on human tendon mechanical properties and the effect of resistive countermeasures. *J Appl Physiol.* 2005;98(6):2278–2286.
72. Majima T, Yasuda K, Tsuchida T, et al. Stress shielding of patellar tendon: effect on small-diameter collagen fibrils in a rabbit model. *J Orthop Sci.* 2003;8(6):836–841.
73. Nakagawa Y, Hayashi K, Yamamoto N, Nagashima K. Age-related changes in biomechanical properties of the Achilles tendon in rabbits. *Eur J Appl Physiol Occup Physiol.* 1996;73(1–2):7–10.
74. Nakagawa Y, Totsuka M, Sato T, Fukuda Y, Hirota K. Effect of disuse on the ultrastructure of the achilles tendon in rats. *Eur J Appl Physiol Occup Physiol.* 1989;59(3):239–242.
75. Tsuchida T, Yasuda K, Kaneda K, et al. Effects of in situ freezing and stress-shielding on the ultrastructure of rabbit patellar tendons. *J Orthop Res.* 1997;15(6):904–910.
76. Boesen AP, Dideriksen K, Couppe C, et al. Tendon and skeletal muscle matrix gene expression and functional responses to immobilisation and rehabilitation in young males: effect of growth hormone administration. *J Physiol.* 2013;591(pt 23):6039–6052.
77. Majima T, Yasuda K, Fujii T, Yamamoto N, Hayashi K, Kaneda K. Biomechanical effects of stress shielding of the rabbit patellar tendon depend on the degree of stress reduction. *J Orthop Res.* 1996;14(3):377–383.
78. Chiquet M, Gelman L, Lutz R, Maier S. From mechanotransduction to extracellular matrix gene expression in fibroblasts. *Biochim Biophys Acta.* 2009;1793(5):911–920.
79. Yang G, Crawford RC, Wang JH. Proliferation and collagen production of human patellar tendon fibroblasts in response to cyclic uniaxial stretching in serum-free conditions. *J Biomech.* 2004;37(10):1543–1550.
80. Schild C, Trueb B. Mechanical stress is required for high-level expression of connective tissue growth factor. *Exp Cell Res.* 2002;274(1):83–91.
81. Abrahamsson SO, Lohmander S. Differential effects of insulin-like growth factor-I on matrix and DNA synthesis in various regions and types of rabbit tendons. *J Orthop Res.* 1996;14(3):370–376.
82. Hansson HA, Engström AM, Holm S, Rosenqvist AL. Somatomedin C immunoreactivity in the Achilles tendon varies in a dynamic manner with the mechanical load. *Acta Physiol Scand.* 1988;134(2):199–208.
83. Heinemeier KM, Olesen JL, Schjerling P, et al. Short-term strength training and the expression of myostatin and IGF-I isoforms in rat muscle and tendon: differential effects of specific contraction types. *J Appl Physiol.* 2007;102(2):573–581.
84. Olesen JL, Heinemeier KM, Haddad F, et al. Expression of insulin-like growth factor I, insulin-like growth factor binding proteins, and collagen mRNA in mechanically loaded plantaris tendon. *J Appl Physiol.* 2006;101(1):183–188.
85. Gumucio JP, Sugg KB, Mendias CL. TGF-beta superfamily signaling in muscle and tendon adaptation to resistance exercise. *Exerc Sport Sci Rev.* 2015;43:93–99.
86. Langberg H, Skovgaard D, Petersen LJ, Bulow J, Kjaer M. Type I collagen synthesis and degradation in peritendinous tissue after exercise determined by microdialysis in humans. *J Physiol.* 1999;521(pt 1):299–306.
87. Langberg H, Rosendal L, Kjaer M. Training-induced changes in peritendinous type I collagen turnover determined by microdialysis in humans. *J Physiol.* 2001;534(pt 1):297–302.
88. Dideriksen K, Sindby AK, Krogsbaard M, Schjerling P, Holm L, Langberg H. Effect of acute exercise on patella tendon protein synthesis and gene expression. *SpringerPlus.* 2013;2(1):109.
89. Hansen M, Kongsgaard M, Holm L, et al. Effect of estrogen on tendon collagen synthesis, tendon structural characteristics, and biomechanical properties in postmenopausal women. *J Appl Physiol.* 2009;106(4):1385–1393.
90. Hansen M, Miller BF, Holm L, et al. Effect of administration of oral contraceptives in vivo on collagen synthesis in tendon and muscle connective tissue in young women. *J Appl Physiol.* 2009;106(4):1435–1443.
91. Petersen SG, Miller BF, Hansen M, Trappe TA, Kjaer M, Holm L. Exercise and NSAID: effect on muscle protein synthesis in knee osteoarthritis patients? *Med Sci Sports Exerc.* 2010;43:425–431.
92. Heinemeier KM, Bjerrum SS, Schjerling P, Kjaer M. Expression of extracellular matrix components and related growth factors in human tendon and muscle after acute exercise. *Scand J Med Sci Sports.* 2013;23(3):e150–e161.

93. Sullivan BE, Carroll CC, Jemiolo B, et al. Effect of acute resistance exercise and sex on human patellar tendon structural and regulatory mRNA expression. *J Appl Physiol*. 2009;106(2):468–475.
94. Heinemeier KM, Schjerling P, Heinemeier J, Magnusson SP, Kjaer M. Lack of tissue renewal in human adult Achilles tendon is revealed by nuclear bomb (14)C. *FASEB J*. 2013;27(5):2074–2079.
95. Bank RA, TeKoppele JM, Oostingh G, Hazleman BL, Riley GP. Lysylhydroxylation and non-reducible crosslinking of human supraspinatus tendon collagen: changes with age and in chronic rotator cuff tendinitis. *Ann Rheum Dis*. 1999;58(1):35–41.
96. Thorpe CT, Streeter I, Pinchbeck GL, Goodship AE, Clegg PD, Birch HL. Aspartic acid racemization and collagen degradation markers reveal an accumulation of damage in tendon collagen that is enhanced with aging. *J Biol Chem*. 2010;285(21):15674–15681.
97. McAnulty RJ, Laurent GJ. Collagen synthesis and degradation in vivo. Evidence for rapid rates of collagen turnover with extensive degradation of newly synthesized collagen in tissues of the adult rat. *Coll Relat Res*. 1987;7(2):93–104.
98. Gumucio JP, Phan AC, Ruehlmann DG, Noah AC, Mendias CL. Synergist ablation induces rapid tendon growth through the synthesis of a neotendon matrix. *J Appl Physiol*. 2014;117:1287–1291. *jap* 00720 02014.
99. Tan Q, Lui PP, Lee YW. In vivo identity of tendon stem cells and the roles of stem cells in tendon healing. *Stem Cells Dev*. 2013;22(23):3128–3140.
100. Mendias CL, Gumucio JP, Bakurin KI, Lynch EB, Brooks SV. Physiological loading of tendons induces scleraxis expression in epitendon fibroblasts. *J Orthop Res*. 2012;30(4):606–612.
101. Heinegard D. Proteoglycans and more—from molecules to biology. *Int J Exp Pathol*. 2009;90(6):575–586.
102. Vincent TL, McLean CJ, Full LE, Peston D, Saklatvala J. FGF-2 is bound to perlecan in the pericellular matrix of articular cartilage, where it acts as a chondrocyte mechanotransducer. *Osteoarthritis Cartilage*. 2007;15(7):752–763.
103. Helmark IC, Mikkelsen UR, Borglum J, et al. Exercise increases interleukin-10 levels both intraarticularly and peri-synovially in patients with knee osteoarthritis: a randomized controlled trial. *Arthritis Res Ther*. 2010;12(4):R126.
104. Saadat E, Lan H, Majumdar S, Rempel DM, King KB. Long-term cyclical in vivo loading increases cartilage proteoglycan content in a spatially specific manner: an infrared microspectroscopic imaging and polarized light microscopy study. *Arthritis Res Ther*. 2006;8(5):R147.
105. Arokoski JP, Jurvelin JS, Vaatainen U, Helminen HJ. Normal and pathological adaptations of articular cartilage to joint loading. *Scand J Med Sci Sports*. 2000;10(4):186–198.
106. Eckstein F, Hudelmaier M, Putz R. The effects of exercise on human articular cartilage. *J Anat*. 2006;208(4):491–512.
107. Eckstein F, Lemberger B, Gratzke C, et al. In vivo cartilage deformation after different types of activity and its dependence on physical training status. *Ann Rheum Dis*. 2005;64(2):291–295.
108. Rosen CJ. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. New York: Wiley Blackwell; 2013.
109. Frost HM. Bone's mechanostat: a 2003 update. *Anat Rec A Discov Mol Cell Evol Biol*. 2003;275(2):1081–1101.
110. Price JS, Sugiyama T, Galea GL, Meakin LB, Sunters A, Lanyon LE. Role of endocrine and paracrine factors in the adaptation of bone to mechanical loading. *Curr Osteoporos Rep*. 2011;9(2):76–82.
111. Rubin CT, Lanyon LE. Dynamic strain similarity in vertebrates; an alternative to allometric limb bone scaling. *J Theor Biol*. 1984;107(2):321–327.
112. Pollack SR, Salzstein R, Pienkowski D. The electric double layer in bone and its influence on stress-generated potentials. *Calcif Tissue Int*. 1984;36(suppl 1):S77–S81.
113. Katsumi A, Orr AW, Tzima E, Schwartz MA. Integrins in mechanotransduction. *J Biol Chem*. 2004;279(13):12001–12004.
114. Duncan RL, Hruska KA, Misler S. Parathyroid hormone activation of stretch-activated cation channels in osteosarcoma cells (UMR-106.01). *FEBS Lett*. 1992;307(2):219–223.
115. Coughlin TR, Voisin M, Schaffler MB, Niebur GL, McNamara LM. Primary cilia exist in a small fraction of cells in trabecular bone and marrow. *Calcif Tissue Int*. 2015;96(1):65–72.
116. David V, Martin A, Lafage-Proust MH, et al. Mechanical loading down-regulates peroxisome proliferator-activated receptor gamma in bone marrow stromal cells and favors osteoblastogenesis at the expense of adipogenesis. *Endocrinology*. 2007;148(5):2553–2562.
117. Zayzafoon M, Gathings WE, McDonald JM. Modeled microgravity inhibits osteogenic differentiation of human mesenchymal stem cells and increases adipogenesis. *Endocrinology*. 2004;145(5):2421–2432.
118. Xiong J, Onal M, Jilka RL, Weinstein RS, Manolagas SC, O'Brien CA. Matrixembedded cells control osteoclast formation. *Nat Med*. 2011;17(10):1235–1241.
119. Qin YX, Hu M. Mechanotransduction in musculoskeletal tissue regeneration: effects of fluid flow, loading, and cellular-molecular pathways. *Biomed Res Int*. 2014;2014:863421.
120. Jorgensen NR, Henriksen Z, Brot C, et al. Human osteoblastic cells propagate intercellular calcium signals by two different mechanisms. *J Bone Miner Res*. 2000;15(6):1024–1032.
121. Jorgensen NR, Henriksen Z, Sorensen OH, Eriksen EF, Civitelli R, Steinberg TH. Intercellular calcium signaling occurs between human osteoblasts and osteoclasts and requires activation of osteoclast P2X7 receptors. *J Biol Chem*. 2002;277(9):7574–7580.
122. Wiltink A, Nijweide PJ, Scheenen WJ, Ypey DL, Van Duijn B. Cell membrane stretch in osteoclasts triggers a self-reinforcing Ca²⁺ entry pathway. *Pflugers Arch*. 1995;429(5):663–671.
123. Maycas M, Ardura JA, de Castro LF, Bravo B, Gortazar AR, Esbrit P. Role of the parathyroid hormone type 1 receptor (PTH1R) as a mechanosensor in osteocyte survival. *J Bone Miner Res*. 2014;30:1231–1244.
124. Lian JB, Stein GS, van Wijnen AJ, et al. MicroRNA control of bone formation and homeostasis. *Nat Rev Endocrinol*. 2012;8(4):212–227.

125. Luzi E, Marini F, Sala SC, Tognarini I, Galli G, Brandi ML. Osteogenic differentiation of human adipose tissue-derived stem cells is modulated by the miR-26a targeting of the SMAD1 transcription factor. *J Bone Miner Res.* 2008;23(2):287–295.
126. Kapinas K, Kessler CB, Delany AM. miR-29 suppression of osteonectin in osteoblasts: regulation during differentiation and by canonical Wnt signaling. *J Cell Biochem.* 2009;108(1):216–224.
127. Lambers FM, Schulte FA, Kuhn G, Webster DJ, Muller R. Mouse tail vertebrae adapt to cyclic mechanical loading by increasing bone formation rate and decreasing bone resorption rate as shown by time-lapsed *in vivo* imaging of dynamic bone morphometry. *Bone.* 2011;49(6):1340–1350.
128. Burr DB, Robling AG, Turner CH. Effects of biomechanical stress on bones in animals. *Bone.* 2002;30(5):781–786.
129. Rubin CT, Lanyon LE. Regulation of bone mass by mechanical strain magnitude. *Calcif Tissue Int.* 1985;37(4):411–417.
130. Rubin CT, Lanyon LE. Regulation of bone formation by applied dynamic loads. *J Bone Joint Surg Am.* 1984;66(3):397–402.
131. Srinivasan S, Weimer DA, Agans SC, Bain SD, Gross TS. Low-magnitude mechanical loading becomes osteogenic when rest is inserted between each load cycle. *J Bone Miner Res.* 2002;17(9):1613–1620.
132. Kennedy OD, Laudier DM, Majeska RJ, Sun HB, Schaffler MB. Osteocyte apoptosis is required for production of osteoclastogenic signals following bone fatigue *in vivo*. *Bone.* 2014;64:132–137.
133. Robling AG, Burr DB, Turner CH. Partitioning a daily mechanical stimulus into discrete loading bouts improves the osteogenic response to loading. *J Bone Miner Res.* 2000;15(8):1596–1602.
134. Howe TE, Shea B, Dawson LJ, et al. Exercise for preventing and treating osteoporosis in postmenopausal women. *Cochrane Database Syst Rev.* 2011;7:CD000333.
135. Gusi N, Raimundo A, Leal A. Low-frequency vibratory exercise reduces the risk of bone fracture more than walking: a randomized controlled trial. *BMC Musculoskelet Disord.* 2006;7:92.
136. von Stengel S, Kemmler W, Engelke K, Kalender WA. Effects of whole body vibration on bone mineral density and falls: results of the randomized controlled ELVIS study with postmenopausal women. *Osteoporos Int.* 2011;22(1):317–325.
137. Nikander R, Sievanen H, Heinonen A, Daly RM, Uusi-Rasi K, Kannus P. Targeted exercise against osteoporosis: a systematic review and meta-analysis for optimising bone strength throughout life. *BMC Med.* 2010;8:47.
138. Maddalozzo GF, Snow CM. High intensity resistance training: effects on bone in older men and women. *Calcif Tissue Int.* 2000;66(6):399–404.
139. Basso N, Heersche JN. Effects of hind limb unloading and reloading on nitric oxide synthase expression and apoptosis of osteocytes and chondrocytes. *Bone.* 2006;39(4):807–814.
140. Dalsky GP. The role of exercise in the prevention of osteoporosis. *Compr Ther.* 1989;15(9):30–37.
141. Edwards WB, Schnitzer TJ, Troy KL. The mechanical consequence of actual bone loss and simulated bone recovery in acute spinal cord injury. *Bone.* 2014;60:141–147.
142. Lee TQ, Shapiro TA, Bell DM. Biomechanical properties of human tibias in long-term spinal cord injury. *J Rehabil Res Dev.* 1997;34(3):295–302.
143. Frey-Rindova P, de Bruin ED, Stussi E, Dambacher MA, Dietz V. Bone mineral density in upper and lower extremities during 12 months after spinal cord injury measured by peripheral quantitative computed tomography. *Spinal Cord.* 2000;38(1):26–32.
144. Lang T, LeBlanc A, Evans H, Lu Y, Genant H, Yu A. Cortical and trabecular bone mineral loss from the spine and hip in long-duration spaceflight. *J Bone Miner Res.* 2004;19(6):1006–1012.

Chapter 12

1. Bunt JC. Hormonal alterations due to exercise. *Sports Med.* 1986;3(33):1–345.
2. Hackney AC. Exercise as a stressor to the neuroendocrine system. *Medicina.* 2006;42(10):788–797.
3. Galbo H. The hormonal response to exercise. *Diabetes Metab Rev.* 1986;1(4):385–408.
4. Urhausen A, Gabriel H, Kindermann W. Blood hormones as markers of training stress and overtraining. *Sports Med.* 1995;20:251–276.
5. Garber CE, Blissmer B, Deschenes MR, et al. American College of Sports Medicine (ACSM) position stand: quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc.* 2011;43(7):334–359.
6. Joyner MJ. Physiologic limiting factors and distance running: influence of gender and age on record performances. *Exerc Sport Sci Rev.* 1993;21:103–133.
7. Joyner MJ, Coyle EF. Endurance exercise performance: the physiology of champions. *J Physiol.* 2008;586(1):35–44.
8. Rowell LB. Cardiovascular adjustments to thermal stress. In: Lindsey M, Hester R, eds. *Handbook of Physiology, The Cardiovascular System, Peripheral Circulation and Organ Blood Flow (Supplement 8)*. New York, NY: Wiley-Blackwell; 1983:967–1023.
9. Saltin B, Astrand PO. Maximal oxygen uptake in athletes. *J Appl Physiol.* 1967;23:353–358.
10. Kraemer W, Fleck S. *Optimizing Strength Training: Designing Nonlinear Periodization Workouts*. Champaign, IL: Human Kinetics Publishing; 2007.
11. Galbo H. *Hormonal and Metabolic Adaptation to Exercise*. Stuttgart, Germany: Thieme Verlag; 1983.
12. Hackney AC. Stress and the neuroendocrine system: the role of exercise as a stressor and modifier of stress. *Expert Rev Endocrinol Metab.* 2006;1(6):783–792.
13. Viru A, Viru M. *Biochemical Monitoring of Sport Training*. Champaign, IL: Human Kinetics; 2001.

14. Viru A. Hormonal Ensemble in Exercise—Hormones in Muscular Activity, vol. 1. Boca Raton, FL: CRC Press; 1985.
15. Christensen NJ, Galbo H. Sympathetic nervous activity during exercise. *Annu Rev Plant Physiol Plant Mol Biol*. 1983;45:139–145.
16. Kjaer M, Secher NH, Galbo H. Physical stress and catecholamine release. *Baillieres Clin Endocrinol Metab*. 1987;1(2):279–298.
17. Viru A. Plasma hormones and physical exercise. *Int J Sports Med*. 1992;13(3):201–209.
18. Davies CT, Few JD. Effects of exercise on adrenocortical function. *J Appl Physiol*. 1973;35(6):887–891.
19. Steenberg A, Fischer CP, Keller C, Møller K, Pedersen BK. IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans. *Am J Physiol Endocrinol Metab*. 2003;285(2): E433–E437.
20. Radomski MW, Cross M, Buguet A. Exercise-induced hyperthermia and hormonal responses to exercise. *Can J Physiol Pharmacol*. 1998;76:547–552.
21. Hackney AC, Viru A. Research methodology: issues with endocrinological measurements in exercise science and sport medicine. *J Athl Train*. 2008;43(6):631–639.
22. Goodman HM. Endocrinology concepts for medical students. *Adv Physiol Educ*. 2001;25:213–224.
23. Widmaier EP. Metabolic feedback in mammalian endocrine systems. *Horm Metab Res*. 1992;24:147–153.
24. Brooks G, Fahey TD, White TP, Booth F. Exercise Physiology: Human Bioenergetics and Its Application. 4th ed. New York, NY: McGraw Hill Company; 2005.
25. Meeusen R, Duclos M, Gleeson M, Rietjens G, Steinacker J, Urhausen A. Prevention, diagnosis and treatment of the Overtraining Syndrome: ECSS position statement ‘Task Force’. *Eur J Sport Sci*. 2006;6:1–14.
26. Lehmann M, Foster C, Keul J. Overtraining in endurance athletes: a brief review. *Med Sci Sports Exerc*. 1993;25:854–862.
27. Lehmann M, Knizia K, Gastmann U, et al. Influence of 6-week, 6 days per week training on pituitary function in recreational athletes. *Br J Sports Med*. 1993;27:186–192.
28. Lehmann M, Lormes W, Opitz-Gress A, et al. Training and overtraining: an overview and experimental results in endurance sports. *J Sports Med Phys Fitness*. 1997;37:7–17.
29. Budgett R. Fatigue and underperformance in athletes: the overtraining syndrome. *Br J Sports Med*. 1998;32:107–110.
30. Robson-Ansley PJ, Blannin A, Gleeson M. Elevated plasma interleukin-6 levels in trained male triathletes following an acute period of intensive interval training. *Eur J Appl Physiol*. 2007;99:353–360.
31. Robson-Ansley JP, Lakier-Smith L. Causes of extreme fatigue in underperforming athletes—a synthesis of recent hypotheses and reviews. *S Afr J Sports Med*. 2006;18:108–114.
32. Smith LL. Tissue trauma: the underlying cause of the overtraining syndrome? *J Strength Cond Res*. 2004;18:185–193.
33. Raglin J, Barzdukas A. Overtraining in athletes: the challenge of prevention—a consensus statement. *Health Fit J*. 1999;3:27–31.
34. Viru A. The mechanism of training effects: a hypothesis. *Int J Sports Med*. 1985;5(5):219–227.
35. Fry AC, Steinacker JM, Meeusen R. Endocrinology of overtraining. In: Kraemer WJ, Rogol AD, eds. The Endocrine System in Sports and Exercise. Oxford, UK: Blackwell Publishing; 2005:584–593.
36. Hackney AC. Hormonal changes at rest in overtrained endurance athletes. *Biol Sport*. 1991;8:49–56.
37. Barron JL, Noakes TD, Levy W, Smith C, Millar RP. Hypothalamic dysfunction in overtrained athletes. *J Clin Endocrinol Metab*. 1985;60:803–806.
38. Hackney AC. Effects of endurance exercise on the reproductive system of men: the “exercise-hypogonadal male condition” *J Endocrinol Invest*. 2008;31:932–938.
39. Selye H. A syndrome produced by diverse noxious agents. *Nature*. 1936;138:32–33.
40. Robson PJ. Elucidating the ‘unexplained underperformance syndrome’ in endurance athletes. *Sports Med*. 2003;33:771–781.
41. Hackney AC, Battaglini C. The overtraining syndrome: neuroendocrine imbalances in athletes. *Braz J Biomotricity*. 2007;1(2):34–44.
42. Kreider R, Fry AC, O’Toole M. Overtraining in sport: terms, definitions, and prevalence. In: Kreider R, Fry AC, O’Toole M, eds. Over-training in Sport. Champaign, IL: Human Kinetics; 1998.
43. Hackney AC, Koltun KJ. The immune system and overtraining in athletes: clinical implications. *Acta Clin Croat*. 2012;51(4):633–641.
44. Evans RM. The steroid and thyroid hormone receptor super-family. *Science*. 1988;240:889–895.
45. Maggiolini M, Picard D. The unfolding stories of GPR30, a new membrane-bound estrogen receptor. *J Endocrinol*. 2010;204(2):105–114.
46. Novac N, Heinzel T. Nuclear receptors: overview and classification. *Curr Drug Targets Inflamm Allergy*. 2004;3:335–346.
47. Pearson RK, Anderson B, Dixon JE. Molecular biology of the peptide hormone families. *Endocrinol Metab Clin North Am*. 1993;22:753–774.
48. Jansen RP. Endocrine response in the fallopian tube. *Endocr Rev*. 1984;5:525–551.
49. Barre’s R, Yan J, Egan B, et al. Acute exercise remodels promoter methylation in human skeletal muscle. *Cell Metab*. 2012;15(3):405–411.
50. Eccleston A, Dewitt N, Gunter C, Marte B, Nath D. Introduction epigenetics. *Nature*. 2007;447:396–400.
51. Ntanasis-Stathopoulos J, Tzanninis JG, Philippou A, Koutsilieris M. Epigenetic regulation on gene expression induced by physical exercise. *J Musculoskelet Neuronal Interact*. 2013;13(2):133–146.
52. Hiroi H, Christenson LK, Strauss JF. III Regulation of transcription of the steroidogenic acute regulatory protein (StAR) gene: temporal and spatial changes in transcription factor binding and histone modification. *Mol Cell Endocrinol*. 2004;215:119–126.
53. Zang X, Ho SM. Epigenetics meets endocrinology. *J Mol Endocrinol*. 2011;46(1): R11–R32.
54. Fowden AL, Forhead AJ. Hormones as epigenetic signals in developmental programming. *Exp Physiol*. 2009;94(6):607–625.
55. West DW, Phillips SM. Anabolic processes in human skeletal muscle: restoring the identities of growth hormone and testosterone. *Phys Sportsmed*. 2010;38(3):97–104.

56. Vingren JL, Kraemer WJ, Ratamess NA, Anderson JM, Volek JS, Maresh CM. Testosterone physiology in resistance exercise and training: the up-stream regulatory elements. *Sports Med.* 2010;40(12):1037–1053.
57. Fry AC, Kraemer WJ. Resistance exercise overtraining and overreaching: neuroendocrine responses. *Sports Med.* 1997;23(2):106–129.
58. Phillips BE, Williams JP, Gustafsson T, et al. Molecular networks of human muscle adaptation to exercise and age. *PLoS Genet.* 2013;9(3):1–15 [e1003389].

Chapter 13

1. Eckardt K, Gorgens SW, Raschke S, Eckel J. Myokines in insulin resistance and type 2 diabetes. *Diabetologia.* 2014;57:1087–1099.
2. Pedersen BK, Febbraio MA. Muscles, exercise and obesity: skeletal muscle as a secretory organ. *Nat Rev Endocrinol.* 2012;8:457–465.
3. Raschke S, Eckardt K, Bjorklund HK, Jensen J, Eckel J. Identification and validation of novel contraction-regulated myokines released from primary human skeletal muscle cells. *PLoS One.* 2013;8:e62008.
4. Raschke S, Eckel J. Adipo-myokines: two sides of the same coin—mediators of inflammation and mediators of exercise. *Mediators Inflamm.* 2013;2013:320724.
5. Lee S, Kuk JL, Davidson LE, et al. Exercise without weight loss is an effective strategy for obesity reduction in obese individuals with and without type 2 diabetes. *J Appl Physiol (1985).* 2005;99:1220–1225.
6. Pedersen BK. Muscle as a secretory organ. *Compr Physiol.* 2013;3:1337–1362.
7. Serrano AL, Baeza-Raja B, Perdigero E, Jardi M, Munoz-Canoves P. Interleukin-6 is an essential regulator of satellite cell-mediated skeletal muscle hypertrophy. *Cell Metab.* 2008;7:33–44.
8. Fischer CP. Interleukin-6 in acute exercise and training: what is the biological relevance? *Exerc Immunol Rev.* 2006;12:6–33.
9. Willoughby DS, McFarlin B, Bois C. Interleukin-6 expression after repeated bouts of eccentric exercise. *Int J Sports Med.* 2003;24:15–21.
10. Keller C, Steensberg A, Pilegaard H, et al. Transcriptional activation of the IL-6 gene in human contracting skeletal muscle: influence of muscle glycogen content. *FASEB J.* 2001;15:2748–2750.
11. Steensberg A, Febbraio MA, Osada T, et al. Interleukin-6 production in contracting human skeletal muscle is influenced by pre-exercise muscle glycogen content. *J Physiol.* 2001;537:633–639.
12. Kohut ML, McCann DA, Russell DW, et al. Aerobic exercise, but not flexibility/ resistance exercise, reduces serum IL-18, CRP, and IL-6 independent of beta-blockers, BMI, and psychosocial factors in older adults. *Brain Behav Immun.* 2006;20:201–209.
13. Bruun JM, Helge JW, Richelsen B, Stallknecht B. Diet and exercise reduce low-grade inflammation and macrophage infiltration in adipose tissue but not in skeletal muscle in severely obese subjects. *Am J Physiol Endocrinol Metab.* 2006;290:E961–E967.
14. Rokling-Andersen MH, Reseland JE, Veierod MB, et al. Effects of long-term exercise and diet intervention on plasma adipokine concentrations. *Am J Clin Nutr.* 2007;86:1293–1301.
15. Bruunsgaard H, Bjerregaard E, Schroll M, Pedersen BK. Muscle strength after resistance training is inversely correlated with baseline levels of soluble tumor necrosis factor receptors in the oldest old. *J Am Geriatr Soc.* 2004;52:237–241.
16. Broholm C, Laye MJ, Brandt C, et al. LIF is a contraction-induced myokine stimulating human myocyte proliferation. *J Appl Physiol (1985).* 2011;111:251–259.
17. Broholm C, Mortensen OH, Nielsen S, et al. Exercise induces expression of leukaemia inhibitory factor in human skeletal muscle. *J Physiol.* 2008;586:2195–2201.
18. Haugen F, Norheim F, Lian H, et al. IL-7 is expressed and secreted by human skeletal muscle cells. *Am J Physiol Cell Physiol.* 2010;298:C807–C816.
19. Andersson H, Bohn SK, Raastad T, Paulsen G, Blomhoff R, Kadi F. Differences in the inflammatory plasma cytokine response following two elite female soccer games separated by a 72-h recovery. *Scand J Med Sci Sports.* 2010;20:740–747.
20. Kraemer WJ, Hatfield DL, Comstock BA, et al. Influence of HMB supplementation and resistance training on cytokine responses to resistance exercise. *J Am Coll Nutr.* 2014;33:247–255.
21. Nieman DC, Davis JM, Henson DA, et al. Carbohydrate ingestion influences skeletal muscle cytokine mRNA and plasma cytokine levels after a 3-h run. *J Appl Physiol (1985).* 2003;94:1917–1925.
22. Rinnov A, Yfanti C, Nielsen S, et al. Endurance training enhances skeletal muscle interleukin-15 in human male subjects. *Endocrine.* 2014;45:271–278.
23. Tamura Y, Watanabe K, Kantani T, Hayashi J, Ishida N, Kaneki M. Upregulation of circulating IL-15 by treadmill running in healthy individuals: is IL-15 an endocrine mediator of the beneficial effects of endurance exercise? *Endocr J.* 2011;58:211–215.
24. Riechman SE, Balasekaran G, Roth SM, Ferrell RE. Association of interleukin-15 protein and interleukin-15 receptor genetic variation with resistance exercise training responses. *J Appl Physiol (1985).* 2004;97:2214–2219.
25. Nielsen AR, Mounier R, Plomgaard P, et al. Expression of interleukin-15 in human skeletal muscle effect of exercise and muscle fibre type composition. *J Physiol.* 2007;584:305–312.
26. McPherron AC, Lawler AM, Lee SJ. Regulation of skeletal muscle mass in mice by a new TGF-beta superfamily member. *Nature.* 1997;387:83–90.
27. Hittel DS, Axelson M, Sarna N, Shearer J, Huffman KM, Kraus WE. Myostatin decreases with aerobic exercise and associates with insulin resistance. *Med Sci Sports Exerc.* 2010;42:2023–2029.
28. Harber MP, Crane JD, Dickinson JM, et al. Protein synthesis and the expression of growth-related genes are altered by running in human vastus lateralis and soleus muscles. *Am J Physiol Regul Integr Comp Physiol.* 2009;296:R708–R714.

29. Kim JS, Cross JM, Bamman MM. Impact of resistance loading on myostatin expression and cell cycle regulation in young and older men and women. *Am J Physiol Endocrinol Metab.* 2005;288:E1110–E1119.
30. Dieli-Conwright CM, Spektor TM, Rice JC, Sattler FR, Schroeder ET. Hormone therapy and maximal eccentric exercise alters myostatin-related gene expression in postmenopausal women. *J Strength Cond Res.* 2012;26:1374–1382.
31. Dalbo VJ, Roberts MD, Sunderland KL, et al. Acute loading and aging effects on myostatin pathway biomarkers in human skeletal muscle after three sequential bouts of resistance exercise. *J Gerontol A Biol Sci Med Sci.* 2011;66:855–865.
32. Amthor H, Nicholas G, McKinnell I, et al. Follistatin complexes myostatin and antagonises myostatin-mediated inhibition of myogenesis. *Dev Biol.* 2004;270:19–30.
33. Miura T, Kishioka Y, Wakamatsu J, et al. Decorin binds myostatin and modulates its activity to muscle cells. *Biochem Biophys Res Commun.* 2006;340:675–680.
34. Kanzleiter T, Rath M, Gorgens SW, et al. The myokine decorin is regulated by contraction and involved in muscle hypertrophy. *Biochem Biophys Res Commun.* 2014;450:1089–1094.
35. Heinemeier KM, Bjerrum SS, Schjerling P, Kjaer M. Expression of extracellular matrix components and related growth factors in human tendon and muscle after acute exercise. *Scand J Med Sci Sports.* 2013;23:e150–e161.
36. Shi Y, Massague J. Mechanisms of TGF-beta signaling from cell membrane to the nucleus. *Cell.* 2003;113:685–700.
37. Ouchi N, Oshima Y, Ohashi K, et al. Follistatin-like 1, a secreted muscle protein, promotes endothelial cell function and revascularization in ischemic tissue through a nitric oxide synthase-dependent mechanism. *J Biol Chem.* 2008;283:32802–32811.
38. Ogura Y, Ouchi N, Ohashi K, et al. Therapeutic impact of follistatin-like 1 on myocardial ischemic injury in preclinical models. *Circulation.* 2012;126:1728–1738.
39. Gorgens SW, Raschke S, Holven KB, Jensen J, Eckardt K, Eckel J. Regulation of follistatin-like protein 1 expression and secretion in primary human skeletal muscle cells. *Arch Physiol Biochem.* 2013;119:75–80.
40. Norheim F, Raastad T, Thiede B, Ruštan AC, Drevon CA, Haugen F. Proteomic identification of secreted proteins from human skeletal muscle cells and expression in response to strength training. *Am J Physiol Endocrinol Metab.* 2011;301:E1013–E1021.
41. Matthews VB, Astrom MB, Chan MH, et al. Brain-derived neurotrophic factor is produced by skeletal muscle cells in response to contraction and enhances fat oxidation via activation of AMP-activated protein kinase. *Diabetologia.* 2009;52:1409–1418.
42. Huang EJ, Reichardt LF. Neurotrophins: roles in neuronal development and function. *Annu Rev Neurosci.* 2001;24:677–736.
43. Ferris LT, Williams JS, Shen CL. The effect of acute exercise on serum brain-derived neurotrophic factor levels and cognitive function. *Med Sci Sports Exerc.* 2007;39:728–734.
44. Gold SM, Schulz KH, Hartmann S, et al. Basal serum levels and reactivity of nerve growth factor and brain-derived neurotrophic factor to standardized acute exercise in multiple sclerosis and controls. *J Neuroimmunol.* 2003;138:99–105.
45. Schmidt-Kassow M, Schadle S, Otterbein S, et al. Kinetics of serum brain-derived neurotrophic factor following low-intensity versus high-intensity exercise in men and women. *Neuroreport.* 2012;23:889–893.
46. Griffin EW, Mullally S, Foley C, Warmington SA, O’Mara SM, Kelly AM. Aerobic exercise improves hippocampal function and increases BDNF in the serum of young adult males. *Physiol Behav.* 2011;104:934–941.
47. Goekint M, De Pauw K, Roelands B, et al. Strength training does not influence serum brain-derived neurotrophic factor. *Eur J Appl Physiol.* 2010;110:285–293.
48. Rasmussen P, Brassard P, Adser H, et al. Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. *Exp Physiol.* 2009;94:1062–1069.
49. Mattson MP. Energy intake and exercise as determinants of brain health and vulnerability to injury and disease. *Cell Metab.* 2012;16:706–722.
50. Kersten S, Lichtenstein L, Steenbergen E, et al. Caloric restriction and exercise increase plasma ANGPTL4 levels in humans via elevated free fatty acids. *Arterioscler Thromb Vasc Biol.* 2009;29:969–974.
51. Catoire M, Alex S, Paraskevopoulos N, et al. Fatty acid-inducible ANGPTL4 governs lipid metabolic response to exercise. *Proc Natl Acad Sci USA.* 2014;111:E1043–E1052.
52. Norheim F, Hjorth M, Langleite TM, et al. Regulation of angiopoietin-like protein 4 production during and after exercise. *Physiol Rep.* 2014;2:e12109.
53. Qin S, LaRosa G, Campbell JJ, et al. Expression of monocyte chemoattractant protein-1 and interleukin-8 receptors on subsets of T cells: correlation with transendothelial chemotactic potential. *Eur J Immunol.* 1996;26:640–647.
54. Vella L, Caldow MK, Larsen AE, et al. Resistance exercise increases NF-kappaB activity in human skeletal muscle. *Am J Physiol Regul Integr Comp Physiol.* 2012;302: R667–R673.
55. Della Gatta PA, Garnham AP, Peake JM, Cameron-Smith D. Effect of exercise training on skeletal muscle cytokine expression in the elderly. *Brain Behav Immun.* 2014;39:80–86.
56. Tantiwong P, Shanmugasundaram K, Monroy A, et al. NF-kappaB activity in muscle from obese and type 2 diabetic subjects under basal and exercise-stimulated conditions. *Am J Physiol Endocrinol Metab.* 2010;299:E794–E801.
57. Peake JM, Suzuki K, Hordern M, Wilson G, Nosaka K, Coombes JS. Plasma cytokine changes in relation to exercise intensity and muscle damage. *Eur J Appl Physiol.* 2005;95:514–521.
58. Ogawa K, Sanada K, Machida S, Okutsu M, Suzuki K. Resistance exercise training-induced muscle hypertrophy was associated with reduction of inflammatory markers in elderly women. *Mediators Inflamm.* 2010;2010:171023.
59. Glintborg D, Christensen LL, Kvorning T, et al. Strength training and testosterone treatment have opposing effects on migration inhibitor

- factor levels in ageing men. *Mediators Inflamm.* 2013;2013:539156.
60. Hojbjerre L, Rosenzweig M, Dela F, Bruun JM, Stallknecht B. Acute exercise increases adipose tissue interstitial adiponectin concentration in healthy overweight and lean subjects. *Eur J Endocrinol.* 2007;157:613–623.
61. Plomgaard P, Nielsen AR, Fischer CP, et al. Associations between insulin resistance and TNF-alpha in plasma, skeletal muscle and adipose tissue in humans with and without type 2 diabetes. *Diabetologia.* 2007;50:2562–2571.
62. Greiwe JS, Cheng B, Rubin DC, Yarasheski KE, Semenkovich CF. Resistance exercise decreases skeletal muscle tumor necrosis factor alpha in frail elderly humans. *FASEB J.* 2001;15:475–482.
63. Febbraio MA, Steensberg A, Starkie RL, McConell GK, Kingwell BA. Skeletal muscle interleukin-6 and tumor necrosis factor-alpha release in healthy subjects and patients with type 2 diabetes at rest and during exercise. *Metabolism.* 2003;52:939–944.
64. Gielen S, Adams V, Mobius-Winkler S, et al. Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure. *J Am Coll Cardiol.* 2003;42:861–868.
65. Golbidi S, Laher I. Exercise induced adipokine changes and the metabolic syndrome. *J Diabetes Res.* 2014;2014:726861.
66. Pedersen BK, Akerstrom TC, Nielsen AR, Fischer CP. Role of myokines in exercise and metabolism. *J Appl Physiol.* 2007;103:1093–1098.
67. Paulsen G, Mikkelsen UR, Raastad T, Peake JM. Leucocytes, cytokines and satellite cells: what role do they play in muscle damage and regeneration following eccentric exercise? *Exerc Immunol Rev.* 2012;18:42–97.
68. Revollo JR, Korneff A, Mills KF, et al. Nampt/PBEF/Visfatin regulates insulin secretion in beta cells as a systemic NAD biosynthetic enzyme. *Cell Metab.* 2007;6:363–375.
69. Costford SR, Bajpeyi S, Pasarica M, et al. Skeletal muscle NAMPT is induced by exercise in humans. *Am J Physiol Endocrinol Metab.* 2010;298:E117–E126.
70. Brandauer J, Vienberg SG, Andersen MA, et al. AMP-activated protein kinase regulates nicotinamide phosphoribosyl transferase expression in skeletal muscle. *J Physiol.* 2013;591:5207–5220.
71. Frydelund-Larsen L, Akerstrom T, Nielsen S, Keller P, Keller C, Pedersen BK. Visfatin mRNA expression in human subcutaneous adipose tissue is regulated by exercise. *Am J Physiol Endocrinol Metab.* 2007;292:E24–E31.
72. Ghanbari-Niaki A, Saghebjoo M, Soltani R, Kirwan JP. Plasma visfatin is increased after high-intensity exercise. *Ann Nutr Metab.* 2010;57:3–8.
73. Choi KM, Kim JH, Cho GJ, Baik SH, Park HS, Kim SM. Effect of exercise training on plasma visfatin and eotaxin levels. *Eur J Endocrinol.* 2007;157:437–442.
74. Haus JM, Solomon TP, Marchetti CM, et al. Decreased visfatin after exercise training correlates with improved glucose tolerance. *Med Sci Sports Exerc.* 2009;41:1255–1260.
75. Lee KJ, Shin YA, Lee KY, Jun TW, Song W. Aerobic exercise training-induced decrease in plasma visfatin and insulin resistance in obese female adolescents. *Int J Sport Nutr Exerc Metab.* 2010;20:275–281.
76. Delaigle AM, Jonas JC, Bauche IB, Cornu O, Brichard SM. Induction of adiponectin in skeletal muscle by inflammatory cytokines: in vivo and in vitro studies. *Endocrinology.* 2004;145:5589–5597.
77. Van Berendoncks AM, Garnier A, Beckers P, et al. Functional adiponectin resistance at the level of the skeletal muscle in mild to moderate chronic heart failure. *Circ Heart Fail.* 2010;3:185–194.
78. Bluher M, Bullen Jr JW, Lee JH, et al. Circulating adiponectin and expression of adiponectin receptors in human skeletal muscle: associations with metabolic parameters and insulin resistance and regulation by physical training. *J Clin Endocrinol Metab.* 2006;91:2310–2316.
79. Van Berendoncks AM, Garnier A, Beckers P, et al. Exercise training reverses adiponectin resistance in skeletal muscle of patients with chronic heart failure. *Heart.* 2011;97:1403–1409.
80. Wang J, Liu R, Hawkins M, Barzilai N, Rossetti L. A nutrient-sensing pathway regulates leptin gene expression in muscle and fat. *Nature.* 1998;393:684–688.
81. Wolsk E, Mygind H, Grondahl TS, Pedersen BK, van Hall G. Human skeletal muscle releases leptin in vivo. *Cytokine.* 2012;60:667–673.
82. Lappas M, Yee K, Permezel M, Rice GE. Release and regulation of leptin, resistin and adiponectin from human placenta, fetal membranes, and maternal adipose tissue and skeletal muscle from normal and gestational diabetes mellitus-complicated pregnancies. *J Endocrinol.* 2005;186:457–465.
83. Kolset SO, Pejler G. Serglycin: a structural and functional chameleon with wide impact on immune cells. *J Immunol.* 2011;187:4927–4933.
84. Yamauchi T, Iwabu M, Okada-Iwabu M, Kadokawa T. Adiponectin receptors: a review of their structure, function and how they work. *Best Pract Res Clin Endocrinol Metab.* 2014;28:15–23.
85. Moschen AR, Wieser V, Tilg H. Adiponectin: key player in the adipose tissue-liver crosstalk. *Curr Med Chem.* 2012;19:5467–5473.
86. Han SH, Quon MJ, Kim JA, Koh KK. Adiponectin and cardiovascular disease: response to therapeutic interventions. *J Am Coll Cardiol.* 2007;49:531–538.
87. Christiansen T, Bruun JM, Paulsen SK, et al. Acute exercise increases circulating inflammatory markers in overweight and obese compared with lean subjects. *Eur J Appl Physiol.* 2013;113(6):1635–1642.
88. Bobbert T, Wegewitz U, Brechtel L, et al. Adiponectin oligomers in human serum during acute and chronic exercise: relation to lipid metabolism and insulin sensitivity. *Int J Sports Med.* 2007;28:1–8.
89. Ferguson MA, White LJ, McCoy S, Kim HW, Petty T, Wilsey J. Plasma adiponectin response to acute exercise in healthy subjects. *Eur J Appl Physiol.* 2004;91:324–329.
90. Jamurtas AZ, Theocharis V, Koukoulis G, et al. The effects of acute exercise on serum adiponectin and resistin levels and their relation to insulin sensitivity in overweight males. *Eur J Appl Physiol.* 2006;97:122–126.

91. Bouassida A, Lakhdar N, Benissa N, et al. Adiponectin responses to acute moderate and heavy exercises in overweight middle aged subjects. *J Sports Med Phys Fitness*. 2010;50:330–335.
92. Numao S, Katayama Y, Hayashi Y, Matsuo T, Tanaka K. Influence of acute aerobic exercise on adiponectin oligomer concentrations in middle-aged abdominally obese men. *Metabolism*. 2011;60:186–194.
93. Saunders TJ, Palombella A, McGuire KA, Janiszewski PM, Despres JP, Ross R. Acute exercise increases adiponectin levels in abdominally obese men. *J Nutr Metab*. 2012;2012:148729.
94. Christiansen T, Paulsen SK, Bruun JM, Pedersen SB, Richelsen B. Exercise training versus diet-induced weight-loss on metabolic risk factors and inflammatory markers in obese subjects: a 12-week randomized intervention study. *Am J Physiol Endocrinol Metab*. 2010;298:E824–E831.
95. Hulver MW, Zheng D, Tanner CJ, et al. Adiponectin is not altered with exercise training despite enhanced insulin action. *Am J Physiol Endocrinol Metab*. 2002;283: E861–E865.
96. Moghadasi M, Mohebbi H, Rahmani-Nia F, Hassan-Nia S, Noroozi H. Effects of short-term lifestyle activity modification on adiponectin mRNA expression and plasma concentrations. *Eur J Sport Sci*. 2013;13:378–385.
97. Polak J, Klimcakova E, Moro C, et al. Effect of aerobic training on plasma levels and subcutaneous abdominal adipose tissue gene expression of adiponectin, leptin, interleukin 6, and tumor necrosis factor alpha in obese women. *Metabolism*. 2006;55:1375–1381.
98. Kondo T, Kobayashi I, Murakami M. Effect of exercise on circulating adipokine levels in obese young women. *Endocr J*. 2006;53:189–195.
99. Klimcakova E, Polak J, Moro C, et al. Dynamic strength training improves insulin sensitivity without altering plasma levels and gene expression of adipokines in subcutaneous adipose tissue in obese men. *J Clin Endocrinol Metab*. 2006;91:5107–5112.
100. Phillips MD, Patrizi RM, Cheek DJ, Wooten JS, Barbee JJ, Mitchell JB. Resistance training reduces subclinical inflammation in obese, postmenopausal women. *Med Sci Sports Exerc*. 2012;44:2099–2110.
101. Fatouros IG, Tournis S, Leontsini D, et al. Leptin and adiponectin responses in overweight inactive elderly following resistance training and detraining are intensity related. *J Clin Endocrinol Metab*. 2005;90:5970–5977.
102. Fatouros IG, Chatzinikolaou A, Tournis S, et al. Intensity of resistance exercise determines adipokine and resting energy expenditure responses in overweight elderly individuals. *Diabetes Care*. 2009;32:2161–2167.
103. Munzberg H, Morrison CD. Structure, production and signaling of leptin. *Metabolism*. 2014;64(1):13–23.
104. Keller P, Keller C, Steensberg A, Robinson LE, Pedersen BK. Leptin gene expression and systemic levels in healthy men: effect of exercise, carbohydrate, interleukin-6, and epinephrine. *J Appl Physiol (1985)*. 2005;98:1805–1812.
105. Perusse L, Collier G, Gagnon J, et al. Acute and chronic effects of exercise on leptin levels in humans. *J Appl Physiol (1985)*. 1997;83:5–10.
106. Varady KA, Bhutani S, Church EC, Phillips SA. Adipokine responses to acute resistance exercise in trained and untrained men. *Med Sci Sports Exerc*. 2010;42:456–462.
107. Essig DA, Alderson NL, Ferguson MA, Bartoli WP, Durstine JL. Delayed effects of exercise on the plasma leptin concentration. *Metabolism*. 2000;49:395–399.
108. Olive JL, Miller GD. Differential effects of maximal- and moderate-intensity runs on plasma leptin in healthy trained subjects. *Nutrition*. 2001;17:365–369.
109. Yang CB, Chuang CC, Kuo CS, Hsu CH, Tsao TH. Effects of an acute bout of exercise on serum soluble leptin receptor (sOB-R) levels. *J Sports Sci*. 2014;32:446–451.
110. O’Leary VB, Marchetti CM, Krishnan RK, Stetzer BP, Gonzalez F, Kirwan JP. Exercise-induced reversal of insulin resistance in obese elderly is associated with reduced visceral fat. *J Appl Physiol (1985)*. 2006;100:1584–1589.
111. Harris RA, Padilla J, Hanlon KP, Rink LD, Wallace JP. The flow-mediated dilation response to acute exercise in overweight active and inactive men. *Obesity (Silver Spring)*. 2008;16:578–584.
112. Baturcam E, Abubaker J, Tiss A, et al. Physical exercise reduces the expression of RANTES and its CCR5 receptor in the adipose tissue of obese humans. *Mediators Inflamm*. 2014;2014:627150.
113. Abubaker J, Tiss A, Abu-Farha M, et al. DNAJB3/HSP-40 cochaperone is downregulated in obese humans and is restored by physical exercise. *PLoS One*. 2013;8: e69217.
114. Nicklas BJ, Ambrosius W, Messier SP, et al. Diet-induced weight loss, exercise, and chronic inflammation in older, obese adults: a randomized controlled clinical trial. *Am J Clin Nutr*. 2004;79:544–551.
115. Dandona P, Aljada A, Bandyopadhyay A. Inflammation: the link between insulin resistance, obesity and diabetes. *Trends Immunol*. 2004;25:4–7.
116. Duncan BB, Schmidt MI, Pankow JS, et al. Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study. *Diabetes*. 2003;52:1799–1805.
117. Kern PA, Ranganathan S, Li C, Wood L, Ranganathan G. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. *Am J Physiol Endocrinol Metab*. 2001;280:E745–E751.
118. Codoner-Franch P, Alonso-Iglesias E. Resistin: insulin resistance to malignancy. *Clin Chim Acta*. 2014;438C:46–54.
119. de Luis DA, Aller R, Izaola O, Sagrado MG, Conde R. Influence of ALA54THR polymorphism of fatty acid binding protein 2 on lifestyle modification response in obese subjects. *Ann Nutr Metab*. 2006;50:354–360.
120. Berndt J, Klöting N, Kralisch S, et al. Plasma visfatin concentrations and fat depot-specific mRNA expression in humans. *Diabetes*. 2005;54:2911–2916.
121. Cullberg KB, Christiansen T, Paulsen SK, Bruun JM, Pedersen SB, Richelsen B. Effect of weight loss and exercise on angiogenic factors in the circulation and in adipose tissue in obese subjects. *Obesity (Silver Spring)*. 2013;21:454–460.

Chapter 14

- Medzhitov R. Inflammation 2010: new adventures of an old flame. *Cell.* 2010;140:771–776.
- Tauber AI. Metchnikoff and the phagocytosis theory. *Nat Rev Mol Cell Biol.* 2003;4:897–901.
- Handschin C, Spiegelman BM. The role of exercise and PGC1alpha in inflammation and chronic disease. *Nature.* 2008;454:463–469.
- Lemanne D, Cassileth B, Gubili J. The role of physical activity in cancer prevention, treatment, recovery, and survivorship. *Oncology.* 2013;27:580–585.
- Beavers KM, Brinkley TE, Nicklas BJ. Effect of exercise training on chronic inflammation. *Clin Chim Acta.* 2010;411:785–793.
- Walsh NP, Gleeson M, Shephard RJ, et al. Position statement. Part one: immune function and exercise. *Exerc Immunol Rev.* 2011;17:6–63.
- Nieman DC, Henson DA. Role of endurance exercise in immune senescence. *Med Sci Sports Exerc.* 1994;26:172–181.
- Niess AM, Simon P. Response and adaptation of skeletal muscle to exercise—the role of reactive oxygen species. *Front Biosci.* 2007;12:4826–4838.
- Hollander J, Fiebig R, Gore M, Ookawara T, Ohno H, Ji LL. Superoxide dismutase gene expression is activated by a single bout of exercise in rat skeletal muscle. *Pflugers Arch—Eur J Physiol.* 2001;442:426–434.
- Gomez-Cabrera MC, Borras C, Pallardo FV, Sastre J, Ji LL, Vina J. Decreasing xanthine oxidase-mediated oxidative stress prevents useful cellular adaptations to exercise in rats. *J Physiol.* 2005;567:113–120.
- Kramer HF, Goodyear LJ. Exercise, MAPK, and NF-kappaB signaling in skeletal muscle. *J Appl Physiol.* 2007;103:388–395.
- Kim JS, Saengsirisuwan V, Sloniger JA, Teachey MK, Henriksen EJ. Oxidant stress and skeletal muscle glucose transport: roles of insulin signaling and p38 MAPK. *Free Radic Biol Med.* 2006;41:818–824.
- Widegren U, Wretman C, Lionikas A, Hedin G, Henriksson J. Influence of exercise intensity on ERK/MAP kinase signalling in human skeletal muscle. *Pflugers Arch—Eur J Physiol.* 2000;441:317–322.
- Wretman C, Lionikas A, Widegren U, Lannergren J, Westerblad H, Henriksson J. Effects of concentric and eccentric contractions on phosphorylation of MAPK(erk1/2) and MAPK(p38) in isolated rat skeletal muscle. *J Physiol.* 2001;535:155–164.
- Kharraz Y, Guerra J, Mann CJ, Serrano AL, Munoz-Canoves P. Macrophage plasticity and the role of inflammation in skeletal muscle repair. *Mediat Inflamm.* 2013;2013:491497.
- Proske U, Morgan DL. Muscle damage from eccentric exercise: mechanism, mechanical signs, adaptation and clinical applications. *J Physiol.* 2001;537:333–345.
- Proske U, Allen TJ. Damage to skeletal muscle from eccentric exercise. *Exerc Sport Sci Rev.* 2005;33:98–104.
- Smith LL, Anwar A, Fragen M, Rananto C, Johnson R, Holbert D. Cytokines and cell adhesion molecules associated with high-intensity eccentric exercise. *Eur J Appl Physiol.* 2000;82:61–67.
- Peake J, Nosaka K, Suzuki K. Characterization of inflammatory responses to eccentric exercise in humans. *Exerc Immunol Rev.* 2005;11:64–85.
- Rigamonti E, Zordan P, Sciorati C, Rovere-Querini P, Brunelli S. Macrophage plasticity in skeletal muscle repair. *Biomed Res Int.* 2014;2014:560629.
- Sen CK. Glutathione homeostasis in response to exercise training and nutritional supplements. *Mol Cell Biochem.* 1999;196:31–42.
- Sen CK, Khanna S, Reznick AZ, Roy S, Packer L. Glutathione regulation of tumor necrosis factor-alpha-induced NF-kappa B activation in skeletal muscle-derived L6 cells. *Biochem Biophys Res Commun.* 1997;237:645–649.
- Markworth JF, Vella LD, Figueiredo VC, Cameron-Smith D. Ibuprofen treatment blunts early translational signaling responses in human skeletal muscle following resistance exercise. *J Appl Physiol.* 2014;117:20–28.
- Markworth JF, Vella L, Lingard BS, et al. Human inflammatory and resolving lipid mediator responses to resistance exercise and ibuprofen treatment. *Am J Physiol Regul Integr Comp Physiol.* 2013;305:R1281–R1296.
- Minari AL, Oyama LM, Dos Santos RV. Downhill exercise-induced changes in gene expression related with macrophage polarization and myogenic cells in the triceps long head of rats. *Inflammation.* 2014;38:209–217.
- Perdigero E, Kharraz Y, Serrano AL, Munoz-Canoves P. MKP-1 coordinates ordered macrophage-phenotype transitions essential for stem cell-dependent tissue repair. *Cell Cycle.* 2012;11:877–886.
- Ruffell D, Mourkoti F, Gambardella A, et al. A CREB-C/EBPbeta cascade induces M2 macrophage-specific gene expression and promotes muscle injury repair. *Proc Natl Acad Sci USA.* 2009;106:17475–17480.
- Burzyn D, Kuswanto W, Kolodin D, et al. A special population of regulatory T cells potentiates muscle repair. *Cell.* 2013;155:1282–1295.
- Ostrowski K, Rohde T, Zacho M, Asp S, Pedersen BK. Evidence that interleukin-6 is produced in human skeletal muscle during prolonged running. *J Physiol.* 1998;508(pt 3):949–953.
- Pal M, Febbraio MA, Whitham M. From cytokine to myokine: the emerging role of interleukin-6 in metabolic regulation. *Immunol Cell Biol.* 2014;92:331–339.
- Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. *J Appl Physiol.* 2005;98(4):1154–1162.
- Petersen AM, Pedersen BK. The role of IL-6 in mediating the anti-inflammatory effects of exercise. *J Physiol Pharmacol.* 2006;57(suppl 10):43–51.
- Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The antiinflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nat Rev Immunol.* 2011;11(9):607–615.
- Maynard CL, Weaver CT. Diversity in the contribution of interleukin-10 to T-cellmediated immune regulation. *Immunol Rev.* 2008;226:219–233.
- Steensberg A, Fischer CP, Keller C, Moller K, Pedersen BK. IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans. *Am J Physiol Endocrinol Metabol.* 2002;263:E101–E106.

- crinol Metab. 2003;285: E433–E437.
- Suzuki K, Yamada M, Kurakake S, et al. Circulating cytokines and hormones with immunosuppressive but neutrophil-priming potentials rise after endurance exercise in humans. *Eur J Appl Physiol*. 2000;81:281–287.
- Sugama K, Suzuki K, Yoshitani K, Shiraishi K, Kometani T. IL-17, neutrophil activation and muscle damage following endurance exercise. *Exerc Immunol Rev*. 2012;18:116–127.
- Korn T, Bettelli E, Oukka M, Kuchroo VK. IL-17 and Th17 cells. *Annu Rev Immunol*. 2009;27:485–517.
- Bosenberg AT, Brock-Utne JG, Gaffin SL, Wells MT, Blake GT. Strenuous exercise causes systemic endotoxemia. *J Appl Physiol*. 1988;65:106–108.
- Brock-Utne JG, Gaffin SL, Wells MT, et al. Endotoxaemia in exhausted runners after a long-distance race. *S Afr Med J*. 1988;73:533–536.
- Jalal I, Rajamani U. Endotoxemia of metabolic syndrome: a pivotal mediator of metainflammation. *Metab Syndr Relat Disord*. 2014;12:454–456.
- Van Wijck K, Lenaerts K, Grootjans J, et al. Physiology and pathophysiology of splanchnic hypoperfusion and intestinal injury during exercise: strategies for evaluation and prevention. *Am J Physiol Gastrointest Liver Physiol*. 2012;303:G155–G168.
- Thuijls G, Derikx JP, de Haan JJ, et al. Urine-based detection of intestinal tight junction loss. *J Clin Gastroenterol*. 2010;44:e14–e19.
- Thuijls G, de Haan JJ, Derikx JP, et al. Intestinal cytoskeleton degradation precedes tight junction loss following hemorrhagic shock. *Shock*. 2009;31:164–169.
- Uchida M, Oyanagi E, Kawanishi N, et al. Exhaustive exercise increases the TNF-alpha production in response to flagellin via the upregulation of toll-like receptor 5 in the large intestine in mice. *Immunol Lett*. 2014;158:151–158.
- Starkie R, Ostrowski SR, Jauffred S, Febraio M, Pedersen BK. Exercise and IL-6 infusion inhibit endotoxin-induced TNF-alpha production in humans. *FASEB J*. 2003;17:884–886.
- Lancaster GI, Khan Q, Drysdale P, et al. The physiological regulation of toll-like receptor expression and function in humans. *J Physiol*. 2005;563:945–955.
- Oliveira M, Gleeson M. The influence of prolonged cycling on monocyte toll-like receptor 2 and 4 expression in healthy men. *Eur J Appl Physiol*. 2010;109:251–257.
- Simpson RJ, McFarlin BK, McSporran C, Spielmann G, o Hartaigh B, Guy K. Toll-like receptor expression on classic and pro-inflammatory blood monocytes after acute exercise in humans. *Brain Behav Immun*. 2009;23:232–239.
- Gleeson M, McFarlin B, Flynn M. Exercise and toll-like receptors. *Exerc Immunol Rev*. 2006;12:34–3.
- Prigent H, Maxime V, Annane D. Science review: mechanisms of impaired adrenal function in sepsis and molecular actions of glucocorticoids. *Crit Care*. 2004;8:243–252.
- Cupps TR, Fauci AS. Corticosteroid-mediated immunoregulation in man. *Immunol Rev*. 1982;65:133–155.
- Kitamura H, Shiva D, Woods JA, Yano H. Beta-adrenergic receptor blockade attenuates the exercise-induced suppression of TNF-alpha in response to lipopolysaccharide in rats. *Neuroimmunomodulation*. 2007;14:91–96.
- Pepys MB. C-reactive protein fifty years on. *Lancet*. 1981;1:653–657.
- Koenig W. High-sensitivity C-reactive protein and atherosclerotic disease: from improved risk prediction to risk-guided therapy. *Int J Cardiol*. 2013;168(6):5126–5134.
- Lai HY, Chang HT, Lee YL, Hwang SJ. Association between inflammatory markers and frailty in institutionalized older men. *Maturitas*. 2014;79(3):329–333.
- Zhang W, He J, Zhang F, et al. Prognostic role of C-reactive protein and interleukin-6 in dialysis patients: a systematic review and meta-analysis. *J Nephrol*. 2013;26(2):243–253.
- Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med*. 1997;336:973–979.
- Ridker PM, Rifai N, Pfeffer MA, et al. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events (CARE) Investigators. *Circulation*. 1998;98:839–844.
- Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA*. 2001;286:327–334.
- Cesari M, Penninx BW, Newman AB, et al. Inflammatory markers and onset of cardiovascular events: results from the Health ABC study. *Circulation*. 2003;108:2317–2322.
- Penninx BW, Kritchevsky SB, Newman AB, et al. Inflammatory markers and incident mobility limitation in the elderly. *J Am Geriatr Soc*. 2004;52:1105–1113.
- Nicklas BJ, You T, Pahor M. Behavioural treatments for chronic systemic inflammation: effects of dietary weight loss and exercise training. *CMAJ*. 2005;172:1199–1209.
- Lavie CJ, Church TS, Milani RV, Earnest CP. Impact of physical activity, cardiorespiratory fitness, and exercise training on markers of inflammation. *J Cardiopulm Rehabil Prev*. 2011;31:137–145.
- Nicklas BJ, Hsu FC, Brinkley TJ, et al. Exercise training and plasma C-reactive protein and interleukin-6 in elderly people. *J Am Geriatr Soc*. 2008;56(11):2045–2052.
- Park YM, Myers M, Vieira-Potter VJ. Adipose tissue inflammation and metabolic dysfunction: role of exercise. *Mo Med*. 2014;111(1):65–72.
- Lancaster GI, Febbraio MA. The immunomodulating role of exercise in metabolic disease. *Trends Immunol*. 2014;35(6):262–269.
- Neefkes-Zonneveld CR, Bakkum AJ, Bishop NC, van Tulder MW, Janssen TW. The effect of long-term physical activity and acute exercise on markers of systemic inflammation in persons with spinal cord injury: a systematic review. *Arch Phys Med Rehabil*. 2015;96(1):30–42.

- Austin MW, Ploughman M, Glynn L, Corbett D. Aerobic exercise effects on neuroprotection and brain repair following stroke: a systematic review and perspective. *Neurosci Res.* 2014;87C:8–15.
- Vieira VJ, Hu L, Valentine RJ, et al. Reduction in trunk fat predicts cardiovascular exercise training-related reductions in C-reactive protein. *Brain Behav Immun.* 2009;23(4):485–491.
- Nimmo MA, Leggate M, Viana JL, King JA. The effect of physical activity on mediators of inflammation. *Diabetes Obes Metab.* 2013;15(suppl 3):S1–S60.
- Pai JK, Pisched T, Ma J, et al. Inflammatory markers and the risk of coronary heart disease in men and women. *N Engl J Med.* 2004;351:2599–2610.
- Blankenberg S, Luc G, Ducimetiere P, et al. Interleukin-18 and the risk of coronary heart disease in European men: the Prospective Epidemiological Study of Myocardial Infarction (PRIME). *Circulation.* 2003;108:2453–2459.
- Gray SR, Baker G, Wright A, Fitzsimons CF, Mutrie N, Nimmo MA. The effect of a 12 week walking intervention on markers of insulin resistance and systemic inflammation. *Prev Med.* 2009;48:39–44.
- Church TS, Earnest CP, Thompson AM, et al. Exercise without weight loss does not reduce CRP: the INFLAME study. *Med Sci Sports Exerc.* 2010;42(4):708–716.
- Trayhum P. Hypoxia and adipose tissue function and dysfunction in obesity. *Physiol Rev.* 2013;93(1):1–21.
- Vieira VJ, Valentine RJ, Wilund KR, Antao N, Baynard T, Woods JA. Effects of exercise and low-fat diet on adipose tissue inflammation and metabolic complications in obese mice. *Am J Physiol Endocrinol Metab.* 2009;296(5):E1164–E1171.
- Smith JK, Dykes R, Douglas JE, Krishnaswamy G, Berk S. Long-term exercise and atherogenic activity of blood mononuclear cells in persons at risk of developing ischemic heart disease. *JAMA.* 1999;281:1722–1727.
- Mifsud EJ, Tan AC, Jackson DC. TLR agonists as modulators of the innate immune response and their potential as agents against infectious disease. *Front Immunol.* 2014;5:79.
- Martin SA, Pence BD, Greene RM, et al. Effects of voluntary wheel running on LPS-induced sickness behavior in aged mice. *Brain Behav Immun.* 2013;29:113–123.
- Scheele C, Nielsen S, Pedersen BK. ROS and myokines promote muscle adaptation to exercise. *Trends Endocrinol Metab.* 2009;20:95–99.
- Gielen S, Adams V, Mobius-Winkler S, et al. Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure. *J Am Coll Cardiol.* 2003;42:861–868.

Chapter 15

1. Nieman DC, Johanssen LM, Lee JW. Infectious episodes in runners before and after a roadrace. *J Sports Med Phys Fitness.* 1989;29(3):289–296.
2. Nieman DC, Henson DA, Gusewitch G, et al. Physical activity and immune function in elderly women. *Med Sci Sports Exerc.* 1993;25(7):823–831.
3. Walsh NP, Gleeson M, Shephard RJ, et al. Position statement. Part one: immune function and exercise. *Exerc Immunol Rev.* 2011;17:6–63.
4. Simpson RJ. The effects of exercise on blood leukocyte numbers. In: Gleeson M, Bishop NC, Walsh NP, eds. *Exercise Immunology.* Oxford, UK, New York, USA: Routledge; 2013:64–105.
5. Anane LH, Edwards KM, Burns VE, et al. Mobilization of gammadelta T lymphocytes in response to psychological stress, exercise, and beta-agonist infusion. *Brain Behav Immun.* 2009;23(6):823–829.
6. Steppich B, Dayyani F, Gruber R, Lorenz R, Mack M, Ziegler-Heitbrock HW. Selective mobilization of CD14(+)CD16(+) monocytes by exercise. *Am J Physiol Cell Physiol.* 2000;279(3):C578–C586.
7. Peake J, Wilson G, Hordern M, et al. Changes in neutrophil surface receptor expression, degranulation, and respiratory burst activity after moderate- and high-intensity exercise. *J Appl Physiol.* 2004;97(2):612–618.
8. Campbell JP, Riddell NE, Burns VE, et al. Acute exercise mobilises CD8+ T lymphocytes exhibiting an effector-memory phenotype. *Brain Behav Immun.* 2009;23(6):767–775.
9. Simpson RJ, Cosgrove C, Chee MM, et al. Senescent phenotypes and telomere lengths of peripheral blood T-cells mobilized by acute exercise in humans. *Exerc Immunol Rev.* 2010;16:36–51.
10. Simpson RJ, Florida-James GD, Cosgrove C, et al. High-intensity exercise elicits the mobilization of senescent T lymphocytes into the peripheral blood compartment in human subjects. *J Appl Physiol.* 2007;103(1):396–401.
11. Simpson RJ, Florida-James GD, Whyte GP, Guy K. The effects of intensive, moderate and downhill treadmill running on human blood lymphocytes expressing the adhesion/ activation molecules CD54 (ICAM-1), CD18 (beta2 integrin) and CD53. *Eur J Appl Physiol.* 2006;97(1):109–121.
12. Bosch JA, Berntson GG, Cacioppo JT, Dhabhar FS, Marucha PT. Acute stress evokes selective mobilization of T cells that differ in chemokine receptor expression: a potential pathway linking immunologic reactivity to cardiovascular disease. *Brain Behav Immun.* 2003;17(4):251–259.
13. Schedlowski M, Hosch W, Oberbeck R, et al. Catecholamines modulate human NK cell circulation and function via spleen-independent beta 2-adrenergic mechanisms. *J Immunol.* 1996;156(1):93–99.
14. Dimitrov S, Lange T, Born J. Selective mobilization of cytotoxic leukocytes by epinephrine. *J Immunol.* 2010;184(1):503–511.
15. Okutsu M, Suzuki K, Ishijima T, Peake J, Higuchi M. The effects of acute exercise-induced cortisol on CCR2 expression on human monocytes. *Brain Behav Immun.* 2008;22(7):1066–1071.

16. Berkow RL, Dodson RW. Functional analysis of the marginating pool of human polymorphonuclear leukocytes. *Am J Hematol*. 1987;24(1):47–54.
17. Okutsu M, Ishii K, Niu KJ, Nagatomi R. Cortisol-induced CXCR4 augmentation mobilizes T lymphocytes after acute physical stress. *Am J Physiol Regul Integr Comp Physiol*. 2005;288(3):R591–R599.
18. Ortega E, Collazos ME, Maynar M, Barriga C, De la Fuente M. Stimulation of the phagocytic function of neutrophils in sedentary men after acute moderate exercise. *Eur J Appl Physiol Occup Physiol*. 1993;66(1):60–64.
19. Nieman DC, Nehls-Cannarella SL, Fagoaga OR, et al. Effects of mode and carbohydrate on the granulocyte and monocyte response to intensive, prolonged exercise. *J Appl Physiol*. 1998;84(4):1252–1259.
20. Ortega E. Neuroendocrine mediators in the modulation of phagocytosis by exercise: physiological implications. *Exerc Immunol Rev*. 2003;9:70–93.
21. Bishop NC, Gleeson M, Nicholas CW, Ali A. Influence of carbohydrate supplementation on plasma cytokine and neutrophil degranulation responses to high intensity intermittent exercise. *Int J Sport Nutr Exerc Metab*. 2002;12(2):145–156.
22. Dziedziak W. The effect of incremental cycling on physiological functions of peripheral blood granulocytes. *Biol Sport*. 1990;7:239–247.
23. Pyne DB. Regulation of neutrophil function during exercise. *Sports Med*. 1994;17(4): 245–258.
24. Suzuki K, Nakaji S, Yamada M, et al. Impact of a competitive marathon race on systemic cytokine and neutrophil responses. *Med Sci Sports Exerc*. 2003;35(2):348–355.
25. Nieman DC, Miller AR, Henson DA, et al. Effects of high- vs moderate-intensity exercise on natural killer cell activity. *Med Sci Sports Exerc*. 1993;25(10):1126–1134.
26. Bigley AB, Rezvani K, Chew C, et al. Acute exercise preferentially redeploys NK-cells with a highly-differentiated phenotype and augments cytotoxicity against lymphoma and multiple myeloma target cells. *Brain Behav Immun*. 2014;39:160–171.
27. Bishop NC, Walker GJ, Gleeson M, Wallace FA, Hewitt CR. Human T lymphocyte migration towards the supernatants of human rhinovirus infected airway epithelial cells: influence of exercise and carbohydrate intake. *Exerc Immunol Rev*. 2009;15:127–144.
28. Simpson RJ, Spielmann G, Hanley PJ, Bolland CM. A single bout of exercise augments the expansion of multi-virus specific T-cells in healthy humans. In: Psychoneuroimmunology Research Society (PNIRS) 21st Annual Scientific Meeting; Philadelphia, PA, USA; 2014.
29. Nieman DC, Miller AR, Henson DA, et al. Effect of high- versus moderate-intensity exercise on lymphocyte subpopulations and proliferative response. *Int J Sports Med*. 1994;15(4):199–206.
30. Bishop NC, Walker GJ, Bowley LA, et al. Lymphocyte responses to influenza and tetanus toxoid in vitro following intensive exercise and carbohydrate ingestion on consecutive days. *J Appl Physiol*. 2005;99(4):1327–1335.
31. Green KJ, Rowbottom DG, Mackinnon LT. Exercise and T-lymphocyte function: a comparison of proliferation in PBMC and NK cell-depleted PBMC culture. *J Appl Physiol*. 2002;92(6):2390–2395.
32. Bruunsgaard H, Hartkopp A, Mohr T, et al. In vivo cell-mediated immunity and vaccination response following prolonged, intense exercise. *Med Sci Sports Exerc*. 1997;29(9):1176–1181.
33. Harper Smith AD, Coakley SL, Ward MD, Macfarlane AW, Friedmann PS, Walsh NP. Exercise-induced stress inhibits both the induction and elicitation phases of in vivo T-cell-mediated immune responses in humans. *Brain Behav Immun*. 2011;25(6):1136–1142.
34. Pascoe AR, Fatarone Singh MA, Edwards KM. The effects of exercise on vaccination responses: a review of chronic and acute exercise interventions in humans. *Brain Behav Immun*. 2014;39:33–41.
35. Bishop NC, Gleeson M. Acute and chronic effects of exercise on markers of mucosal immunity. *Front Biosci*. 2009;14:4444–4456.
36. Gleeson M, Bishop NC, Walsh NP. *Exercise Immunology*. Oxford, UK, New York, USA: Routledge; 2013.
37. Simpson RJ, Florida-James GD, Whyte GP, Black JR, Ross JA, Guy K. Apoptosis does not contribute to the blood lymphocytopenia observed after intensive and downhill treadmill running in humans. *Res Sports Med*. 2007;15(3):157–174.
38. Gannon GA, Rhind SG, Suzui M, et al. Beta-endorphin and natural killer cell cytolytic activity during prolonged exercise. Is there a connection? *Am J Physiol*. 1998;275(6 pt 2): R1725–R1734.
39. Diment BC, Fortes MB, Edwards JP, et al. Exercise intensity and duration effects on in vivo immunity. *Med Sci Sports Exerc*. 2014;47:1390–1398.
40. Kunz H, Bishop NC, Spielmann G, et al. Fitness level impacts salivary antimicrobial protein responses to a single bout of cycling exercise. *Eur J Appl Physiol*. 2015;115: 1015–1027.
41. Simpson RJ, Lowder TW, Spielmann G, Bigley AB, Lavoy EC, Kunz H. Exercise and the aging immune system. *Ageing Res Rev*. 2012;11:404–420.
42. Simpson RJ, Cosgrove C, Ingram LA, et al. Senescent T-lymphocytes are mobilised into the peripheral blood compartment in young and older humans after exhaustive exercise. *Brain Behav Immun*. 2008;22(4):544–551.
43. Ceddia MA, Price EA, Kohlmeier CK, et al. Differential leukocytosis and lymphocyte mitogenic response to acute maximal exercise in the young and old. *Med Sci Sports Exerc*. 1999;31(6):829–836.
44. Spielmann G, Bolland CM, Bigley AB, et al. The effects of age and latent cytomegalovirus infection on the redeployment of CD8+ T cell subsets in response to acute exercise in humans. *Brain Behav Immun*. 2014;39:142–151.
45. Feldman RD, Limbird LE, Nadeau J, Robertson D, Wood AJ. Alterations in leukocyte beta-receptor affinity with aging. A potential explanation for altered beta-adrenergic sensitivity in the elderly. *N Engl J Med*. 1984;310(13):815–819.
46. Davison G, Simpson RJ. Immunity. In: Lanham-New SA, Stear SJ, Shirreffs SM, Collins AL, eds. *Sport and Exercise Nutrition*. Oxford, UK: Wiley-Blackwell; 2011:281–303.
47. Walsh NP, Gleeson M, Pyne DB, et al. Position statement. Part two: maintaining immune health. *Exerc Immunol Rev*. 2011;17:64–103.

48. Pistillo M, Bigley AB, Spielmann G, et al. The effects of age and viral serology on gammadelta T-cell numbers and exercise responsiveness in humans. *Cell Immunol.* 2013;284(1–2):91–97.
49. Turner JE, Aldred S, Witard OC, Drayson MT, Moss PM, Bosch JA. Latent cytomegalovirus infection amplifies CD8 T-lymphocyte mobilisation and egress in response to exercise. *Brain Behav Immun.* 2010;24(8):1362–1370.
50. Bigley AB, Lowder TW, Spielmann G, et al. NK-cells have an impaired response to acute exercise and a lower expression of the inhibitory receptors KLRG1 and CD158a in humans with latent cytomegalovirus infection. *Brain Behav Immun.* 2012;26(1):177–186.
51. Bigley AB, Rezvani K, Pistillo M, et al. Acute exercise preferentially redeploys NK-cells with a highly-differentiated phenotype and augments cytotoxicity against lymphoma and multiple myeloma target cells. Part II: impact of latent cytomegalovirus infection and catecholamine sensitivity. *Brain Behav Immun.* 2015. [epub ahead of print].
52. LaVoy EC, Nieman DC, Henson DA, et al. Latent cytomegalovirus infection and innate immune function following a 75 km cycling time trial. *Eur J Appl Physiol.* 2013;113(10):2629–2635.
53. Lavoy EC, Bigley AB, Spielmann G, et al. CMV amplifies T-cell redeployment to acute exercise independently of HSV-1 serostatus. *Med Sci Sports Exerc.* 2014;46:257–267.
54. Pedersen BK, Ullum H. NK cell response to physical activity: possible mechanisms of action. *Med Sci Sports Exerc.* 1994;26(2):140–146.
55. Spence L, Brown WJ, Pyne DB, et al. Incidence, etiology, and symptomatology of upper respiratory illness in elite athletes. *Med Sci Sports Exerc.* 2007;39(4):577–586.
56. Gleeson M. Immune responses to intensified periods of training. In: Gleeson M, Bishop NC, Walsh NP, eds. *Exercise Immunology*. Oxford, UK, New York, USA: Routledge; 2013:186–206.
57. Horn PL, Pyne DB, Hopkins WG, Barnes CJ. Lower white blood cell counts in elite athletes training for highly aerobic sports. *Eur J Appl Physiol.* 2010;110(5):925–932.
58. Baj Z, Kantorski J, Majewska E, et al. Immunological status of competitive cyclists before and after the training season. *Int J Sports Med.* 1994;15(6):319–324.
59. Gleeson M, McDonald WA, Pyne DB, et al. Immune status and respiratory illness for elite swimmers during a 12-week training cycle. *Int J Sports Med.* 2000;21(4):302–307.
60. Suzui M, Kawai T, Kimura H, et al. Natural killer cell lytic activity and CD56(dim) and CD56(bright) cell distributions during and after intensive training. *J Appl Physiol.* 2004;96(6):2167–2173.
61. Lancaster GI, Halson SL, Khan Q, et al. Effects of acute exhaustive exercise and chronic exercise training on type 1 and type 2T lymphocytes. *Exerc Immunol Rev.* 2004;10: 91–106.
62. Verde TJ, Thomas SG, Moore RW, Shek P, Shephard RJ. Immune responses and increased training of the elite athlete. *J Appl Physiol.* 1992;73(4):1494–1499.
63. Prieto-Hinojosa A, Knight A, Compton C, Gleeson M, Travers PJ. Reduced thymic output in elite athletes. *Brain Behav Immun.* 2014;39:75–79.
64. Gleeson M, Pyne DB, Austin JP, et al. Epstein-Barr virus reactivation and upperrespiratory illness in elite swimmers. *Med Sci Sports Exerc.* 2002;34(3):411–417.
65. He CS, Handzlik M, Muhamad A, Gleeson M. Influence of CMV/EBV serostatus on respiratory infection incidence during 4 months of winter training in a student cohort of endurance athletes. *Eur J Appl Physiol.* 2013;113(10):2613–2619.
66. Mehta SK, Crucian BE, Stowe RP, et al. Reactivation of latent viruses is associated with increased plasma cytokines in astronauts. *Cytokine.* 2013;61(1):205–209.
67. Glaser R, Friedman SB, Smyth J, et al. The differential impact of training stress and final examination stress on herpesvirus latency at the United States Military Academy at West Point. *Brain Behav Immun.* 1999;13(3):240–251.
68. Sarid O, Anson O, Yaari A, Margalith M. Human cytomegalovirus salivary antibodies as related to stress. *Clin Lab.* 2002;48(5–6):297–305.
69. Gleeson M, McDonald WA, Pyne DB, et al. Salivary IgA levels and infection risk in elite swimmers. *Med Sci Sports Exerc.* 1999;31(1):67–73.
70. Neville V, Gleeson M, Folland JP. Salivary IgA as a risk factor for upper respiratory infections in elite professional athletes. *Med Sci Sports Exerc.* 2008;40(7):1228–1236.
71. Kohut ML, Arntson BA, Lee W, et al. Moderate exercise improves antibody response to influenza immunization in older adults. *Vaccine.* 2004;22(17–18):2298–2306.
72. Woods JA, Keylock KT, Lowder T, et al. Cardiovascular exercise training extends influenza vaccine seroprotection in sedentary older adults: the immune function intervention trial. *J Am Geriatr Soc.* 2009;57(12):2183–2191.
73. Spielmann G, McFarlin BK, O'Connor DP, Smith PJ, Pircher H, Simpson RJ. Aerobic fitness is associated with lower proportions of senescent blood T-cells in man. *Brain Behav Immun.* 2011;25(8):1521–1529.
74. Shinkai S, Kohno H, Kimura K, et al. Physical activity and immune senescence in men. *Med Sci Sports Exerc.* 1995;27(11):1516–1526.
75. Pedersen BK, Bruunsgaard H. Possible beneficial role of exercise in modulating lowgrade inflammation in the elderly. *Scand J Med Sci Sports.* 2003;13(1):56–62.
76. Yan H, Kuroiwa A, Tanaka H, Shindo M, Kiyonaga A, Nagayama A. Effect of moderate exercise on immune senescence in men. *Eur J Appl Physiol.* 2001;86(2):105–111.
77. Phillips MD, Flynn MG, McFarlin BK, Stewart LK, Timmerman KL. Resistance training at eight-repetition maximum reduces the inflammatory milieu in elderly women. *Med Sci Sports Exerc.* 2010;42(2):314–325.
78. Woods JA, Ceddia MA, Wolters BW, Evans JK, Lu Q, McAuley E. Effects of 6 months of moderate aerobic exercise training on immune

- function in the elderly. *Mech Ageing Dev.* 1999;109(1):1–19.
79. Drela N, Kozdron E, Szczypiorski P. Moderate exercise may attenuate some aspects of immunosenescence. *BMC Geriatr.* 2004;4:8.
 80. Simpson RJ, Bosch JA. Special issue on exercise immunology: current perspectives on aging, health and extreme performance. *Brain Behav Immun.* 2014;39:1–7.
 81. Lowder T, Padgett DA, Woods JA. Moderate exercise protects mice from death due to influenza virus. *Brain Behav Immun.* 2005;19(5):377–380.
 82. Hojman P, Dethlefsen C, Brandt C, Hansen J, Pedersen L, Pedersen BK. Exercise-induced muscle-derived cytokines inhibit mammary cancer cell growth. *Am J Physiol Endocrinol Metab.* 2011;301(3):E504–E510.
 83. Simpson RJ. Aging, persistent viral infections, and immunosenescence: can exercise “make space”? *Exerc Sport Sci Rev.* 2011;39(1):23–33.
 84. ElKassar N, Gress RE. An overview of IL-7 biology and its use in immunotherapy. *J Immunotoxicol.* 2010;7(1):1–7.
 85. Andersson A, Yang SC, Huang M, et al. IL-7 promotes CXCR3 ligand-dependent T cell antitumor reactivity in lung cancer. *J Immunol.* 2009;182(11):6951–6958.
 86. Haugen F, Norheim F, Lian H, et al. IL-7 is expressed and secreted by human skeletal muscle cells. *Am J Physiol Cell Physiol.* 2010;298(4):C807–C816.
 87. Fairey AS, Courneya KS, Field CJ, Bell GJ, Jones LW, Mackey JR. Randomized controlled trial of exercise and blood immune function in postmenopausal breast cancer survivors. *J Appl Physiol.* 2005;98(4):1534–1540.
 88. Nieman DC, Nehls-Cannarella SL, Markoff PA, et al. The effects of moderate exercise training on natural killer cells and acute upper respiratory tract infections. *Int J Sports Med.* 1990;11(6):467–473.
 89. Perna FM, LaPerriere A, Klimas N, et al. Cardiopulmonary and CD4 cell changes in response to exercise training in early symptomatic HIV infection. *Med Sci Sports Exerc.* 1999;31(7):973–979.
 90. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Maestana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nat Rev Immunol.* 2011;11(9):607–615.
 91. Steensberg A, Fischer CP, Keller C, Moller K, Pedersen BK. IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans. *Am J Physiol Endocrinol Metab.* 2003;285(2): E433–E437.
 92. Cupps TR, Fauci AS. Corticosteroid-mediated immunoregulation in man. *Immunol Rev.* 1982;65:133–155.
 93. Bergmann M, Gornikiewicz A, Sautner T, et al. Attenuation of catecholamine-induced immunosuppression in whole blood from patients with sepsis. *Shock.* 1999;12(6):421–427.
 94. McFarlin BK, Flynn MG, Phillips MD, Stewart LK, Timmerman KL. Chronic resistance exercise training improves natural killer cell activity in older women. *J Gerontol A Biol Sci Med Sci.* 2005;60(10):1315–1318.
 95. Kawanishi N, Yano H, Yokogawa Y, Suzuki K. Exercise training inhibits inflammation in adipose tissue via both suppression of macrophage infiltration and acceleration of phenotypic switching from M1 to M2 macrophages in high-fat-diet-induced obese mice. *Exerc Immunol Rev.* 2010;16:105–118.
 96. Shaikh SR, Edidin M. Polyunsaturated fatty acids, membrane organization, T cells, and antigen presentation. *Am J Clin Nutr.* 2006;84(6):1277–1289.
 97. Bosch JA, Fischer JE, Fischer JC. Psychologically adverse work conditions are associated with CD8+ T cell differentiation indicative of immunosenescence. *Brain Behav Immun.* 2009;23(4):527–534.
 98. Sachdev S, Davies KJ. Production, detection, and adaptive responses to free radicals in exercise. *Free Radic Biol Med.* 2008;44(2):215–223.
 99. Mobius-Winkler S, Hilberg T, Menzel K, et al. Time-dependent mobilization of circulating progenitor cells during strenuous exercise in healthy individuals. *J Appl Physiol.* 2009;107(6):1943–1950.

Chapter 16

- 1.Bramble DM, Lieberman DE. Endurance running and the evolution of Homo. *Nature.* 2004;432:345–352.
- 2.Marino FE. The evolutionary basis of thermoregulation and exercise performance. *Med Sport Sci.* 2008;53:1–13.
- 3.Mattson MP. Evolutionary aspects of human exercise—born to run purposefully. *Ageing Res Rev.* 2012;11:347–352.
- 4.Spirduso WW, Clifford P. Replication of age and physical activity effects on reaction and movement time. *J Gerontol.* 1978;33:26–30.
- 5.Voss MW, Vivar C, Kramer AF, van Praag H. Bridging animal and human models of exercise-induced brain plasticity. *Trends Cogn Sci.* 2013;17:525–544.
- 6.Erickson KI, Kramer AF. Aerobic exercise effects on cognitive and neural plasticity in older adults. *Br J Sports Med.* 2009;43:22–24.
- 7.Erickson KI, Miller DL, Roecklein KA. The aging hippocampus: interactions between exercise, depression, and BDNF. *Neuroscientist.* 2012;18:82–97.
- 8.Maass A, Duzel S, Goerke M, et al. Vascular hippocampal plasticity after aerobic exercise in older adults. *Mol Psychiatry.* 2015;20:585–593.
- 9.Vogiatzis I, Louvaris Z, Habazettl H, et al. Frontal cerebral cortex blood flow, oxygen delivery and oxygenation during normoxic and hypoxic exercise in athletes. *J Physiol.* 2011;589:4027–4039.
- 10.Ten Brinke LF, Bolandzadeh N, Nagamatsu LS, et al. Aerobic exercise increases hippocampal volume in older women with probable mild cognitive impairment: a 6-month randomised controlled trial. *Br J Sports Med.* 2015;49(4):248–254.
- 11.Gothe NP, Kramer AF, McAuley E. The effects of an 8-week Hatha yoga intervention on executive function in older adults. *J Gerontol A Biol Sci Med Sci.* 2014;69:1109–1116.

- 12.Skriver K, Roig M, Lundbye-Jensen J, et al. Acute exercise improves motor memory: exploring potential biomarkers. *Neurobiol Learn Mem.* 2014;116:46–58.
- 13.Rovio S, Kareholt I, Helkala EL, et al. Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. *Lancet Neurol.* 2005;4:705–711.
- 14.Arcoverde C, Deslandes A, Moraes H, et al. Treadmill training as an augmentation treatment for Alzheimer's disease: a pilot randomized controlled study. *Arq Neuropsiquiatr.* 2014;72:190–196.
- 15.Clark PJ, Kohman RA, Miller DS, et al. Genetic influences on exercise-induced adult hippocampal neurogenesis across 12 divergent mouse strains. *Genes Brain Behav.* 2011;10:345–353.
- 16.Clark PJ, Brzezinska WJ, Thomas MW, et al. Intact neurogenesis is required for benefits of exercise on spatial memory but not motor performance or contextual fear conditioning in C57BL/6J mice. *Neuroscience.* 2008;155:1048–1058.
- 17.Yuede CM, Zimmerman SD, Dong H, et al. Effects of voluntary and forced exercise on plaque deposition, hippocampal volume, and behavior in the Tg2576 mouse model of Alzheimer's disease. *Neurobiol Dis.* 2009;35:426–432.
- 18.Uysal N, Kiray M, Sisman A, et al. Effects of voluntary and involuntary exercise on cognitive functions, and VEGF and BDNF levels in adolescent rats. *Biotech Histochem.* 2015;90:55–68.
- 19.Ang ET, Dawe GS, Wong PT, Moochhala S, Ng YK. Alterations in spatial learning and memory after forced exercise. *Brain Res.* 2006;1113:186–193.
- 20.Mokhtari-Zaer A, Ghodrati-Jaldbakhan S, Vafaei AA, et al. Effects of voluntary and treadmill exercise on spontaneous withdrawal signs, cognitive deficits and alterations in apoptosis-associated proteins in morphine-dependent rats. *Behav Brain Res.* 2014;271:160–170.
- 21.Arida RM, Scorza CA, da Silva AV, Scorza FA, Cavalheiro EA. Differential effects of spontaneous versus forced exercise in rats on the staining of parvalbumin-positive neurons in the hippocampal formation. *Neurosci Lett.* 2004;364:135–138.
- 22.Niemann C, Godde B, Voelcker-Rehage C. Not only cardiovascular, but also coordinative exercise increases hippocampal volume in older adults. *Front Aging Neurosci.* 2014;6:170.
- 23.van de Rest O, van der Zwaluw NL, Tieland M, et al. Effect of resistance-type exercise training with or without protein supplementation on cognitive functioning in frail and pre-frail elderly: secondary analysis of a randomized, double-blind, placebo-controlled trial. *Mech Ageing Dev.* 2014;136–137:85–93.
- 24.Alves CR, Merege Filho CA, Benatti FB, et al. Creatine supplementation associated or not with strength training upon emotional and cognitive measures in older women: a randomized double-blind study. *PLoS One.* 2013;8:e76301.
- 25.Chang YK, Ku PW, Tomporowski PD, Chen FT, Huang CC. Effects of acute resistance exercise on late-middle-age adults' goal planning. *Med Sci Sports Exerc.* 2012;44:1773–1779.
- 26.Tamaki T, Uchiyama S, Nakano S. A weight-lifting exercise model for inducing hypertrophy in the hindlimb muscles of rats. *Med Sci Sports Exerc.* 1992;24:881–886.
- 27.Aparicio VA, Nebot E, Porres JM, et al. Effects of high-whey-protein intake and resistance training on renal, bone and metabolic parameters in rats. *Br J Nutr.* 2011;105:836–845.
- 28.Cassilhas RC, Reis IT, Venancio D, et al. Animal model for progressive resistance exercise: a detailed description of model and its implications for basic research in exercise. *Motriz-Revista De Educacao Fisica.* 2013;19:178–184.
- 29.Cassilhas RC, Lee KS, Fernandes J, et al. Spatial memory is improved by aerobic and resistance exercise through divergent molecular mechanisms. *Neuroscience.* 2012;202:309–317.
- 30.Cassilhas RC, Lee KS, Venancio DP, et al. Resistance exercise improves hippocampus-dependent memory. *Braz J Med Biol Res.* 2012;45:1215–1220.
- 31.Seo DY, Lee SR, Kim N, et al. Humanized animal exercise model for clinical application. *Pflugers Arch.* 2014;466:1673–1687.
- 32.Tine M. Acute aerobic exercise: an intervention for the selective visual attention and reading comprehension of low-income adolescents. *Front Psychol.* 2014;5:575.
- 33.Etnier J, Labban JD, Piepmeier A, Davis ME, Henning DA. Effects of an acute bout of exercise on memory in 6th grade children. *Pediatr Exerc Sci.* 2014;26:250–258.
- 34.Siette J, Reichelt AC, Westbrook RF. A bout of voluntary running enhances context conditioned fear, its extinction, and its reconsolidation. *Learn Mem.* 2014;21:73–81.
- 35.Erickson KI, Voss MW, Prakash RS, et al. Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci USA.* 2011;108:3017–3022.
- 36.Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol Sci.* 2003;14:125–130.
- 37.van Praag H, Christie BR, Sejnowski TJ, Gage FH. Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proc Natl Acad Sci USA.* 1999;96:13427–13431.
- 38.van Praag H, Kempermann G, Gage FH. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat Neurosci.* 1999;2:266–270.
- 39.Meeusen R, De Meirlier K. Exercise and brain neurotransmission. *Sports Med.* 1995;20:160–188.
- 40.Giannaki CD, Sakkas GK, Karatzafiri C, et al. Effect of exercise training and dopamine agonists in patients with uremic restless legs syndrome: a six-month randomized, partially double-blind, placebo-controlled comparative study. *BMC Nephrol.* 2013;14:194.
- 41.Melancon MO, Lorrain D, Dionne IJ. Changes in markers of brain serotonin activity in response to chronic exercise in senior men. *Appl Physiol Nutr Metab.* 2014;39:1–7.

- 42.Mabandla MV, Kellaway LA, Daniels WM, Russell VA. Effect of exercise on dopamine neuron survival in prenatally stressed rats. *Metab Brain Dis.* 2009;24:525–539.
- 43.Kim H, Heo HI, Kim DH, et al. Treadmill exercise and methylphenidate ameliorate symptoms of attention deficit/hyperactivity disorder through enhancing dopamine synthesis and brain-derived neurotrophic factor expression in spontaneous hypertensive rats. *Neurosci Lett.* 2011;504:35–39.
- 44.Renoir T, Chevarin C, Lanfumey L, Hannan AJ. Effect of enhanced voluntary physical exercise on brain levels of monoamines in Huntington disease mice. *PLoS Curr.* 2011;3:RRN1281. <http://dx.doi.org/10.1371/currents.RRN1281>.
- 45.Jasienska G, Ziolkiewicz A, Thune I, Lipson SF, Ellison PT. Habitual physical activity and estradiol levels in women of reproductive age. *Eur J Cancer Prev.* 2006;15:439–445.
- 46.Erickson KI, Colcombe SJ, Elavsky S, et al. Interactive effects of fitness and hormone treatment on brain health in postmenopausal women. *Neurobiol Aging.* 2007;28:179–185.
- 47.Garcia-Mesa Y, Pareja-Galeano H, Bonet-Costa V, et al. Physical exercise neuroprotects ovariectomized 3 Tg-AD mice through BDNF mechanisms. *Psychoneuroendocrinology.* 2014;45:154–166.
- 48.Gomez-Pinilla F, Dao L, So V. Physical exercise induces FGF-2 and its mRNA in the hippocampus. *Brain Res.* 1997;764:1–8.
- 49.Ding Q, Vaynman S, Akhavan M, Ying Z, Gomez-Pinilla F. Insulin-like growth factor I interfaces with brain-derived neurotrophic factor-mediated synaptic plasticity to modulate aspects of exercise-induced cognitive function. *Neuroscience.* 2006;140:823–833.
- 50.Neeper SA, Gomez-Pinilla F, Choi J, Cotman CW. Physical activity increases mRNA for brain-derived neurotrophic factor and nerve growth factor in rat brain. *Brain Res.* 1996;726:49–56.
- 51.Vaynman S, Gomez-Pinilla F. License to run: exercise impacts functional plasticity in the intact and injured central nervous system by using neurotrophins. *Neurorehabil Neural Repair.* 2005;19:283–295.
- 52.Cotman CW, Berchtold NC. Exercise: a behavioral intervention to enhance brain health and plasticity. *Trends Neurosci.* 2002;25:295–301.
- 53.de Lange FP, Koers A, Kalkman JS, et al. Increase in prefrontal cortical volume following cognitive behavioural therapy in patients with chronic fatigue syndrome. *Brain.* 2008;131:2172–2180.
- 54.Rasmussen P, Brassard P, Adser H, et al. Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. *Exp Physiol.* 2009;94:1062–1069.
- 55.Ding Q, Ying Z, Gomez-Pinilla F. Exercise influences hippocampal plasticity by modulating brain-derived neurotrophic factor processing. *Neuroscience.* 2011;192:773–780.
- 56.Griffin EW, Mullally S, Foley C, et al. Aerobic exercise improves hippocampal function and increases BDNF in the serum of young adult males. *Physiol Behav.* 2011;104:934–941.
- 57.Novaes Gomes FG, Fernandes J, Vannucci Campos D, et al. The beneficial effects of strength exercise on hippocampal cell proliferation and apoptotic signaling is impaired by anabolic androgenic steroids. *Psychoneuroendocrinology.* 2014;50:106–117.
- 58.Sato K, Ogoh S, Hirasawa A, Oue A, Sadamoto T. The distribution of blood flow in the carotid and vertebral arteries during dynamic exercise in humans. *J Physiol.* 2011;589:2847–2856.
- 59.Berggren KL, Kay JJ, Swain RA. Examining cerebral angiogenesis in response to physical exercise. *Methods Mol Biol.* 2014;1135:139–154.
- 60.Rhyu IJ, Bytheway JA, Kohler SJ, et al. Effects of aerobic exercise training on cognitive function and cortical vascularity in monkeys. *Neuroscience.* 2010;167: 1239–1248.
- 61.Van der Borght K, Kobor-Nyakas DE, Klauke K, et al. Physical exercise leads to rapid adaptations in hippocampal vasculature: temporal dynamics and relationship to cell proliferation and neurogenesis. *Hippocampus.* 2009;19:928–936.
- 62.Liu JK, Yeo HC, Overvick-Douki E, et al. Chronically and acutely exercised rats: biomarkers of oxidative stress and endogenous antioxidants. *J Appl Physiol.* 2000;89:21–28.
- 63.Radak Z, Toldy A, Szabo Z, et al. The effects of training and detraining on memory, neurotrophins and oxidative stress markers in rat brain. *Neurochem Int.* 2006;49:387–392.
- 64.Ogonovszky H, Berkes I, Kumagai S, et al. The effects of moderate-, strenuous- and over-training on oxidative stress markers, DNA repair, and memory, in rat brain. *Neurochem Int.* 2005;46:635–640.
- 65.Marosi K, Bori Z, Hart N, et al. Long-term exercise treatment reduces oxidative stress in the hippocampus of aging rats. *Neuroscience.* 2012;226:21–28.
- 66.Navarro A, Gomez C, Lopez-Cepero JM, Boveris A. Beneficial effects of moderate exercise on mice aging: survival, behavior, oxidative stress, and mitochondrial electron transfer. *Am J Physiol Regul Integr Comp Physiol.* 2004;286:R505–R511.
- 67.Kerr AL, Swain RA. Rapid cellular genesis and apoptosis: effects of exercise in the adult rat. *Behav Neurosci.* 2011;125:1–9.
- 68.Hamilton GF, Boschen KE, Goodlett CR, Greenough WT, Klintsova AY. Housing in environmental complexity following wheel running augments survival of newly generated hippocampal neurons in a rat model of binge alcohol exposure during the third trimester equivalent. *Alcohol Clin Exp Res.* 2012;36:1196–1204.
- 69.Uysal N, Tugyan K, Kayatekin BM, et al. The effects of regular aerobic exercise in adolescent period on hippocampal neuron density, apoptosis and spatial memory. *Neurosci Lett.* 2005;383:241–245.
- 70.Kim DH, Ko IG, Kim BK, et al. Treadmill exercise inhibits traumatic brain injury-induced hippocampal apoptosis. *Physiol Behav.* 2010;101:660–665.
- 71.Abel JL, Rissman EF. Running-induced epigenetic and gene expression changes in the adolescent brain. *Int J Dev Neurosci.* 2013;31:382–

- 390.
- 72.Gomez-Pinilla F, Zhuang Y, Feng J, Ying Z, Fan G. Exercise impacts brain-derivedneurotrophic factor plasticity by engaging mechanisms of epigenetic regulation. *Eur J Neurosci*. 2011;33:383–390.
- 73.Bayod S, Menella I, Sanchez-Roige S, et al. Wnt pathway regulation by long-termmoderate exercise in rat hippocampus. *Brain Res*. 2014;1543:38–48.
- 74.Augustinack JC, van der Kouwe AJ, Salat DH, et al. H.M.’s contributions to neuro- science: a review and autopsy studies. *Hippocampus*. 2014;24:1267–1286.
- 75.Altman J. Are new neurons formed in the brains of adult mammals? *Science*. 1962;135:1127–1128.
- 76.Eadie BD, Redila VA, Christie BR. Voluntary exercise alters the cytoarchitecture of the adult dentate gyrus by increasing cellular proliferation, dendritic complexity, and spine density. *J Comp Neurol*. 2005;486:39–47.
- 77.Freund J, Brandmaier AM, Lewejohann L, et al. Emergence of individuality in genet- ically identical mice. *Science*. 2013;340:756–759.
- 78.Marlatt MW, Potter MC, Lucassen PJ, van Praag H. Running throughoutmiddle-age improves memory function, hippocampal neurogenesis, and BDNF levels in female C57BL/6J mice. *Dev Neurobiol*. 2012;72:943–952.
- 79.Creer DJ, Romberg C, Saksida LM, van Praag H, Bussey TJ. Running enhances spatial pattern separation in mice. *Proc Natl Acad Sci USA*. 2010;107:2367–2372.
- 80.Groves JO, Leslie I, Huang GJ, et al. Ablating adult neurogenesis in the rat has no effect on spatial processing: evidence from a novel pharmacogenetic model. *PLoS Genet*. 2013;9:e1003718.
- 81.Christie BR, Swann SE, Fox CJ, et al. Voluntary exercise rescues deficits in spatial memory and long-term potentiation in prenatal ethanol-exposed male rats. *Eur J Neurosci*. 2005;21:1719–1726.
- 82.Helfer JL, Goodlett CR, Greenough WT, Klintsova AY. The effects of exercise on adolescent hippocampal neurogenesis in a rat model of binge alcohol exposure during the brain growth spurt. *Brain Res*. 2009;1294:1–11.
- 83.Thomas JD, Sather TM, Whinery LA. Voluntary exercise influences behavioral devel- opment in rats exposed to alcohol during the neonatal brain growth spurt. *Behav Neu- rosci*. 2008;122:1264–1273.
- 84.Radak Z, Hart N, Sarga L, et al. Exercise plays a preventive role against Alzheimer’s disease. *J Alzheimers Dis*. 2010;20:777–783.
- 85.Liu HL, Zhao G, Zhang H, Shi LD. Long-term treadmill exercise inhibits the progres- sion of Alzheimer’s disease-like neuropathology in the hippocampus of APP/PS1 transgenic mice. *Behav Brain Res*. 2013;256:261–272.
- 86.Walker JM, Klakotskaia D, Ajit D, et al. Beneficial effects of dietary EGCG and voluntary exercise on behavior in an Alzheimer’s disease mouse model. *J Alzheimers Dis*. 2015;44:561–572.
- 87.May PA, Baete A, Russo J, et al. Prevalence and characteristics of fetal alcohol spectrum disorders. *Pediatrics*. 2014;134:855–866.
- 88.Lupton C, Burd L, Harwood R. Cost of fetal alcohol spectrum disorders. *Am J Med Genet C Semin Med Genet*. 2004;127C:42–50.
- 89.Klintsova AY, Goodlett CR, Greenough WT. Therapeutic motor training ameliorates cerebellar effects of postnatal binge alcohol. *Neuro- toxicol Teratol*. 2000;22: 125–132.
- 90.Brocado PS, Boehme F, Patten A, et al. Anxiety- and depression-like behaviors are accompanied by an increase in oxidative stress in a rat model of fetal alcohol spectrum disorders: protective effects of voluntary physical exercise. *Neuropharmacology*. 2012;62:1607–1618.
- 91.Sim YJ, Kim H, Shin MS, et al. Effect of postnatal treadmill exercise on c-Fosexpres- sion in the hippocampus of rat pups born from the al- cohol-intoxicatedmothers. *BrainDev*. 2008;30:118–125.
- 92.Redila VA, Christie BR. Exercise-induced changes in dendritic structure and com- plexity in the adult hippocampal dentate gyrus. *Neuro- science*. 2006;137:1299–1307.
- 93.Boehme F, Gil-Mohapel J, Cox A, et al. Voluntary exercise induces adult hippocampal neurogenesis and BDNF expression in a rodent model of fetal alcohol spectrum disor- ders. *Eur J Neurosci*. 2011;33:1799–1811.
- 94.Alzheimer’s Association. 2014 Alzheimer’s disease facts and figures. *Alzheimers Dement*. 2014;10:e47–e92.
- 95.Um HS, Kang EB, Koo JH, et al. Treadmill exercise represses neuronal cell death in an aged transgenic mouse model of Alzheimer’s dis- ease. *Neurosci Res*. 2011;69: 161–173.
- 96.Churchill JD, Galvez R, Colcombe S, et al. Exercise, experience and the aging brain. *Neurobiol Aging*. 2002;23:941–955.
- 97.Floel A, Ruscheweyh R, Kruger K, et al. Physical activity and memory functions: are neurotrophins and cerebral gray matter volume the missing link? *Neuroimage*. 2010;49:2756–2763.
- 98.Nagamatsu LS, Chan A, Davis JC, et al. Physical activity improves verbal and spatial memory in older adults with probable mild cognitive impairment: a 6-monthrandom- ized controlled trial. *J Aging Res*. 2013;2013:861893.
- 99.Rand D, Eng JJ, Liu-Ambrose T, Tawashy AE. Feasibility of a 6-month exercise and recreation program to improve executive functioning and memory in individuals with chronic stroke. *Neurorehabil Neural Repair*. 2010;24:722–729.
- 100.Luo CX, Jiang J, Zhou QG, et al. Voluntary exercise-induced neurogenesis in the post- ischemic dentate gyrus is associated with spatial memory recovery from stroke. *J Neurosci Res*. 2007;85:1637–1646.
- 101.Cechetti F, Worm PV, Elsner VR, et al. Forced treadmill exercise prevents oxidative stress and memory deficits following chronic cerebral hypoperfusion in the rat. *Neuro- biol Learn Mem*. 2012;97:90–96.
- 102.Shih PC, Yang YR, Wang RY. Effects of exercise intensity on spatial memory perfor- mance and hippocampal synaptic plasticity in tran- sient brain ischemic rats. *PLoS One*. 2013;8:e78163.
- 103.Chang HC, Yang YR, Wang SG, Wang RY. Effects of treadmill training on motor performance and extracellular glutamate level in striatum in rats with or without tran- sient middle cerebral artery occlusion. *Behav Brain Res*. 2009;205:450–455.
- 104.Mang CS, Campbell KL, Ross CJ, Boyd LA. Promoting neuroplasticity for motor rehabilitation after stroke: considering the effects of

- aerobic exercise and genetic variation on brain-derived neurotrophic factor. *Phys Ther.* 2013;93:1707–1716.
105. Ploughman M, Windle V, MacLellan CL, et al. Brain-derived neurotrophic factor contributes to recovery of skilled reaching after focal ischemia in rats. *Stroke.* 2009;40:1490–1495.
106. Wojtowicz JM, Askew ML, Winocur G. The effects of running and inhibiting adult neurogenesis on learning and memory in rats. *Eur J Neurosci.* 2008;27:1494–1502.

Chapter 17

1. Krammer PH, Arnold R, Lavrik IN. Life and death in peripheral T cells. *Nat Rev Immunol.* 2007;7(7):532–542.
2. Korsmeyer SJ. Programmed cell death and the regulation of homeostasis. *Harvey Lect.* 1999–2000;95:21–41.
3. Curtin JF, Cotter TG. Live and let die: regulatory mechanisms in Fas-mediated apoptosis. *Cell Signal.* 2003;15(11):983–992.
4. Kerr JF, Wyllie AH, Currie AR. Apoptosis: a basic biological phenomenon with wideranging implications in tissue kinetics. *Br J Cancer.* 1972;26:239–257.
5. Blander JM. A long-awaited merger of the pathways mediating host defence and programmed cell death. *Nat Rev Immunol.* 2014;14(9):601–618.
6. Ishizaki Y, Cheng L, Mudge AW, Raff MC. Programmed cell death by default in embryonic cells, fibroblasts, and cancer cells. *Mol Biol Cell.* 1995;6(11):1443–1458.
7. Wajant H. Principles and mechanisms of CD95 activation. *Biol Chem.* 2014;395(12):1401–1416.
8. Cory S, Adams JM. The Bcl2 family: regulators of the cellular life-or-death switch. *Nat Rev Cancer.* 2002;2:647–656.
9. Kru̇ger K, Mooren FC. Exercise-induced leukocyte apoptosis. *Exerc Immunol Rev.* 2014;20:117–134.
10. Vorobjeva NV, Pinegin BV. Neutrophil extracellular traps: mechanisms of formation and role in health and disease. *Biochemistry (Mosc).* 2014;79(12):1286–1296.
11. Atamaniuk J, Stuhlmeier KM, Vidotto C, Tschan H, Dossenbach-Glaninger A, Mueller M. Effects of ultra-marathon on circulating DNA and mRNA expression of pro- and anti-apoptotic genes in mononuclear cells. *Eur J Appl Physiol.* 2008;104(4):711–717.
12. Mooren FC, Lechtermann A, Völker K. Exercise-induced apoptosis of lymphocytes depends on training status. *Med Sci Sports Exerc.* 2004;36(9):1476–1483.
13. Mooren FC, Bloming D, Lechtermann A, Lerch MM, Volker K. Lymphocyte apoptosis after exhaustive and moderate exercise. *J Appl Physiol.* 2002;93(1):147–153.
14. Levada-Pires AC, Cury-Boaventura MF, Gorjão R, et al. Induction of lymphocyte death by short- and long-duration triathlon competitions. *Med Sci Sports Exerc.* 2009;41(10):1896–1901.
15. Navalta JW, Sedlock DA, Park KS. Effect of exercise intensity on exercise induced lymphocyte apoptosis. *Int J Sports Med.* 2007;28(6):539–542.
16. Kru̇ger K, Agnischock S, Lechtermann A, et al. Intensive resistance exercise induces lymphocyte apoptosis via cortisol and glucocorticoid receptor-dependent pathways. *J Appl Physiol.* 2011;110(5):1226–1232.
17. Kru̇ger K, Frost S, Most E, Völker K, Pallauf J, Mooren FC. Exercise affects tissue lymphocyte apoptosis via redox-sensitive and Fas-dependent signaling pathways. *Am J Physiol Regul Integr Comp Physiol.* 2009;296(5):R1518–R1527.
18. Quadrilatero J, Hoffman-Goetz L. N-Acetyl-L-cysteine prevents exercise-induced intestinal lymphocyte apoptosis by maintaining intracellular glutathione levels and reducing mitochondrial membrane depolarization. *Biochem Biophys Res Commun.* 2004;319(3):894–901.
19. Syu GD, Chen HI, Jen CJ. Severe exercise and exercise training exert opposite effects on human neutrophil apoptosis via altering the redox status. *PLoS One.* 2011;6(9): e24385.
20. Mooren FC, Völker K, Klocke R, Nikol S, Waltenberger J, Kru̇ger K. Exercise delays neutrophil apoptosis by a G-CSF-dependent mechanism. *J Appl Physiol.* 2012;113(7):1082–1090.
21. Beiter T, Fragasso A, Hartl D, Nieß AM. Neutrophil extracellular traps: a walk on the wild side of exercise immunology. *Sports Med.* 2015;45(5):625–640.
22. Tower J. Programmed cell death in aging. *Ageing Res Rev.* 2015;23(pt A):90–100.
23. Brooks NE, Myburgh KH. Skeletal muscle wasting with disuse atrophy is multidimensional: the response and interaction of myonuclei, satellite cells and signaling pathways. *Front Physiol.* 2014;5:99.
24. Paulsen G, Mikkelsen UR, Raastad T, Peake JM. Leucocytes, cytokines and satellite cells: what role do they play in muscle damage and regeneration following eccentric exercise? *Exerc Immunol Rev.* 2012;18:42–97.
25. Marzetti E, Privitera G, Simili V, et al. Multiple pathways to the same end: mechanisms of myonuclear apoptosis in sarcopenia of aging. *Sci World J.* 2010;10:340–349.
26. Marzetti E, Calvani R, Bernabei R, Leeuwenburgh C. Apoptosis in skeletal myocytes: a potential target for interventions against sarcopenia and physical frailty—a mini-review. *Gerontology.* 2012;58(2):99–106.
27. Song W, Kwak HB, Lawler JM. Exercise training attenuates age-induced changes in apoptotic signaling in rat skeletal muscle. *Antioxid Redox Signal.* 2006;8(3–4): 517–528.
28. Nieman DC. Exercise, infection, and immunity. *Int J Sports Med.* 1994;15(suppl 3): S131–S141.
29. Simpson RJ. Aging, persistent viral infections, and immunosenescence: can exercise “make space”? *Exerc Sport Sci Rev.* 2011;39(1):23–33.
30. Mooren FC, Kru̇ger K. Apoptotic lymphocytes induce progenitor cell mobilization after exercise. *J Appl Physiol (1985).* 2015;119(2):135–139. <http://dx.doi.org/10.1152/japplphysiol.00287.2015>.

31. Vainshtein A, Grumati P, Sandri M, Bonaldo P. Skeletal muscle, autophagy, and physical activity: the me' nage à trois of metabolic regulation in health and disease. *J Mol Med (Berl)*. 2014;92(2):127–137.
32. Lim J, Lachenmayer ML, WuS, et al. Proteotoxic stress induces phosphorylation of p62/ SQSTM1 by ULK1 to regulate selective autophagic clearance of protein aggregates. *PLoS Genet*. 2015;11(2):e1004987.
33. Masiero E, Agatea L, Mammucari C, et al. Autophagy is required to maintain muscle mass. *Cell Metab*. 2009;10(6):507–515.
34. Sandri M. Autophagy in skeletal muscle. *FEBS Lett*. 2010;584(7):1411–1416.
35. Zhang J, Kim J, Alexander A, et al. A tuberous sclerosis complex signalling node at the peroxisome regulates mTORC1 and autophagy in response to ROS. *Nat Cell Biol*. 2013;15(10):1186–1196.
36. Rubinsztein DC, Shpilka T, Elazar Z. Mechanisms of autophagosome biogenesis. *Curr Biol*. 2012;22(1):R29–R34.
37. Zhang J. Teaching the basics of autophagy and mitophagy to redox biologists— mechanisms and experimental approaches. *Redox Biol*. 2015;4:242–259.
38. Dunlop EA, Tee AR. mTOR and autophagy: a dynamic relationship governed by nutrients and energy. *Semin Cell Dev Biol*. 2014;36:121–129.
39. Russell RC, Tian Y, Yuan H, et al. ULK1 induces autophagy by phosphorylating Beclin-1 and activating VPS34 lipid kinase. *Nat Cell Biol*. 2013;15(7):741–750.
40. Johansen T, Lamark T. Selective autophagy mediated by autophagic adapter proteins. *Autophagy*. 2011;7(3):279–296.
41. Mostowy S, Sancho-Shimizu V, Hamon MA, et al. p62 and NDP52 proteins target intracytosolic Shigella and Listeria to different autophagy pathways. *J Biol Chem*. 2011;286(30):26987–26995.
42. Kim J, Kim YC, Fang C, et al. Differential regulation of distinct Vps34 complexes by AMPK in nutrient stress and autophagy. *Cell*. 2013;152(1–2):290–303.
43. Mammucari C, Milan G, Romanello V, et al. FoxO3 controls autophagy in skeletal muscle in vivo. *Cell Metab*. 2007;6(6):458–471.
44. Grumati P, Coletto L, Schiavonato A, et al. Physical exercise stimulates autophagy in normal skeletal muscles but is detrimental for collagen VI-deficient muscles. *Autophagy*. 2011;7(12):1415–1423.
45. Jamart C, Francaux M, Millet GY, Deldicque L, Fre're D, Fe'asson L. Modulation of autophagy and ubiquitin-proteasome pathways during ultra-endurance running. *J Appl Physiol (1985)*. 2012;112(9):1529–1537.
46. Jamart C, Benoit N, Raymackers JM, Kim HJ, Kim CK, Francaux M. Autophagy-related and autophagy-regulatory genes are induced in human muscle after ultraendurance exercise. *Eur J Appl Physiol*. 2012;112(8):3173–3177.
47. He C, Bassik MC, Moresi V, et al. Exercise-induced BCL2-regulated autophagy is required for muscle glucose homeostasis. *Nature*. 2012;481(7382):511–515.
48. Kim YA, Kim YS, Song W. Autophagic response to a single bout of moderate exercise in murine skeletal muscle. *J Physiol Biochem*. 2012;68(2):229–235.
49. Schwalm C, Jamart C, Benoit N, et al. Activation of autophagy in human skeletal muscle is dependent on exercise intensity and AMPK activation. *FASEB J*. 2015;29(8):3515–3526.
50. Fry CS, Drummond MJ, Glynn EL, et al. Skeletal muscle autophagy and protein breakdown following resistance exercise are similar in younger and older adults. *J Gerontol A Biol Sci Med Sci*. 2013;68(5):599–607.
51. Smuder AJ, Kavazis AN, Min K, Powers SK. Exercise protects against doxorubicin-induced markers of autophagy signaling in skeletal muscle. *J Appl Physiol (1985)*. 2011;111(4):1190–1198.
52. Feng Z, Bai L, Yan J, et al. Mitochondrial dynamic remodeling in strenuous exercise-induced muscle and mitochondrial dysfunction: regulatory effects of hydroxytyrosol. *Free Radic Biol Med*. 2011;50(10):1437–1446.
53. Lira VA, Okutsu M, Zhang M, et al. Autophagy is required for exercise training-induced skeletal muscle adaptation and improvement of physical performance. *FASEB J*. 2013;27(10):4184–4193.
54. Luo L, Lu AM, Wang Y, et al. Chronic resistance training activates autophagy and reduces apoptosis of muscle cells by modulating IGF-1 and its receptors, Akt/mTOR and Akt/FOXO3a signaling in aged rats. *Exp Gerontol*. 2013;48(4):427–436.
55. Lindqvist LM, Heinlein M, Huang DC, Vaux DL. Prosurvival Bcl-2 family members affect autophagy only indirectly, by inhibiting Bax and Bak. *Proc Natl Acad Sci USA*. 2014;111(23):8512–8517.
56. Rubinstein AD, Eisenstein M, Ber Y, Bialik S, Kimchi A. The autophagy protein Atg12 associates with antiapoptotic Bcl-2 family members to promote mitochondrial apoptosis. *Mol Cell*. 2011;44(5):698–709.

Chapter 18

1. O'Connor TP, Crystal RG. Genetic medicines: treatment strategies for hereditary disorders. *Nat Rev Genet*. 2006;7:261–276.
2. Ratajczak MZ. A novel view of the adult bone marrow stem cell hierarchy and stem cell trafficking. *Leukemia*. 2015;29:776–782.
3. Hass R, Kasper C, Bohm S, Jacobs R. Different populations and sources of human mesenchymal stem cells (MSC): a comparison of adult and neonatal tissue-derived MSC. *Cell Commun Signal*. 2011;9:12.
4. Timmermans F, Plum J, Yoder MC, Ingram DA, Vandekerckhove B, Case J. Endothelial progenitor cells: identity defined? *J Cell Mol Med*. 2009;13:87–102.
5. Charge SB, Rudnicki MA. Cellular and molecular regulation of muscle regeneration. *Physiol Rev*. 2004;84:209–238.
6. Bentzinger CF, Wang YX, von Maltzahn J, Rudnicki MA. The emerging biology of muscle stem cells: implications for cell-based therapies. *Bioessays*. 2012;35:231–241.
7. Li L, Clevers H. Coexistence of quiescent and active adult stem cells in mammals. *Science*. 2010;327:542–545.

8. Seib DR, Martin-Villalba A. Neurogenesis in the normal ageing hippocampus: a minireview. *Gerontology*. 2015;61:327–335.
9. Barker N, van Es JH, Kuipers J, et al. Identification of stem cells in small intestine and colon by marker gene Lgr5. *Science*. 2007;449:1003–1007.
10. Kretzschmar K, Watt FM. Markers of epidermal stem cell subpopulations in adult mammalian skin. *Cold Spring Harb Perspect Med*. 2014;4:10.
11. Shin S, Kaestner KH. The origin, biology, and therapeutic potential of facultative adult hepatic progenitor cells. *Curr Top Dev Biol*. 2014;107:269–292.
12. Leri A, Rota M, Hosoda T, Goichberg P, Anversa P. Cardiac stem cell niches. *Stem Cell Res*. 2014;13:631–646.
13. Wansleeben C, Barkauskas CE, Rock JR, Hogan BL. Stem cells of the adult lung: their development and role in homeostasis, regeneration, and disease. *Wiley Interdiscip Rev Dev Biol*. 2013;2:131–148.
14. Till JE, McCulloch EA. A direct measurement of the radiation sensitivity of normal mouse bone marrow cells. *Radiat Res*. 1961;14:213–222.
15. Bhatia M, Wang JC, Kapp U, Bonnet D, Dick JE. Purification of primitive human hematopoietic cells capable of repopulating immune-deficient mice. *Proc Natl Acad Sci USA*. 1997;94:5320–5325.
16. McGovern Jr JJ, Russell PS, Atkins L, Webster EW. Treatment of terminal leukemic relapse by total-body irradiation and intravenous infusion of stored autologous bone marrow obtained during remission. *N Engl J Med*. 1959;260:675–683.
17. Thomas ED, Lochte Jr HL, Cannon JH, Sahler OD, Ferrebee JW. Supralethal whole body irradiation and isologous marrow transplantation in man. *J Clin Invest*. 1959;38:1709–1716.
18. Purton LE, Scadden DT. Limiting factors in murine hematopoietic stem cell assays. *Cell Stem Cell*. 2007;1:263–270.
19. Dick JE, Bhatia M, Gan O, Kapp U, Wang JC. Assay of human stem cells by repopulation of NOD/SCID mice. *Stem Cells*. 1997;15(Suppl 1):199–203. Discussion 204–7.
20. Ema H, Morita Y, Yamazaki S, et al. Adult mouse hematopoietic stem cells: purification and single-cell assays. *Nat Protoc*. 2007;1:2979–2987.
21. Kiel MJ, Yilmaz OH, Iwashita T, et al. SLAM family receptors distinguish hematopoietic stem and progenitor cells and reveal endothelial niches for stem cells. *Cell*. 2005;121:1109–1121.
22. Oguro H, Ding L, Morrison SJ. SLAM family markers resolve functionally distinct subpopulations of hematopoietic stem cells and multipotent progenitors. *Cell Stem Cell*. 2013;13:102–116.
23. Sutherland DR, Anderson L, Keeney M, Nayar R, Chin-Yee I. The ISHAGE guidelines for CD34+ cell determination by flow cytometry. International Society of Hematotherapy and Graft Engineering. *J Hematother*. 1996;5:213–226.
24. Challen GA, Boles N, Lin K-YK, Goodell MA. Mouse hematopoietic stem cell identification and analysis. *Cytometry A*. 2009;75A:14–24.
25. Wardyn GG, Rennard SI, Brusnahan SK, et al. Effects of exercise on hematological parameters, circulating side population cells, and cytokines. *Exp Hematol*. 2008;36:216–223.
26. De Lisio M, Parise G. Exercise and hematopoietic stem and progenitor cells: protection, quantity, and function. *Exerc Sport Sci Rev*. 2013;1(2):116–122.
27. Barrett AJ, Longhurst P, Sneath P, Watson JG. Mobilization of CFU-C by exercise and ACTH induced stress in man. *Exp Hematol*. 1978;6:590–594.
28. Heal JM, Brightman A. Exercise and circulating hematopoietic progenitor cells (CFU-GM) in humans. *Transfusion (Paris)*. 1987;27:155–158.
29. Jootar S, Chaisiripoomkere W, Thaikla O, Kaewborworn M. Effect of running exercise on hematological changes, hematopoietic progenitor cells (CFU-GM) and fibrinolytic system in humans. *J Med Assoc Thai*. 1992;75:94–98.
30. Morici G, Zangla D, Santoro A, et al. Supramaximal exercise mobilizes hematopoietic progenitors and reticulocytes in athletes. *Am J Physiol Regul Integr Comp Physiol*. 2005;289:R1496–R1503.
31. Sandri M, Adams V, Gielen S, et al. Effects of exercise and ischemia on mobilization and functional activation of blood-derived progenitor cells in patients with ischemic syndromes: results of 3 randomized studies. *Circulation*. 2005;111:3391–3399.
32. Bonsignore MR, Morici G, Riccioni R, et al. Hemopoietic and angiogenetic progenitors in healthy athletes: different responses to endurance and maximal exercise. *J Appl Physiol*. 2010;109:60–67.
33. Kroepfl JM, Pekovits K, Stelzer I, et al. Exercise increases the frequency of circulating hematopoietic progenitor cells, but reduces hematopoietic colony-forming capacity. *Stem Cells Dev*. 2012;21:2915–2925.
34. Thijssen DHJ, Vos JB, Verseyden C, et al. Haematopoietic stem cells and endothelial progenitor cells in healthy men: effect of aging and training. *Aging Cell*. 2006;5:495–503.
35. Zaldivar F, Eliakim A, Radom-Aizik S, Leu S-Y, Cooper DM. The effect of brief exercise on circulating CD34+ stem cells in early and late pubertal boys. *Pediatr Res*. 2007;61:491–495.
36. Bonsignore MR, Morici G, Santoro A, et al. Circulating hematopoietic progenitor cells in runners. *J Appl Physiol*. 2002;93:1691–1697.
37. M€obius-Winkler S, Hilberg T, Menzel K, et al. Time-dependent mobilization of circulating progenitor cells during strenuous exercise in healthy individuals. *J Appl Physiol*. 2009;107:1943–1950.
38. Adams V, Linke A, Breuckmann F, et al. Circulating progenitor cells decrease immediately after marathon race in advanced-age marathon runners. *Eur J Cardiovasc Prev Rehabil*. 2008;15:602–607.
39. Stelzer I, Fuchs R, Schraml E, et al. Decline of bone marrow-derived hematopoietic progenitor cell quality during aging in the rat. *Exp Aging Res*. 2010;36:359–370.

40. Baker JM, De Lisio M, Parise G. Endurance exercise training promotes medullary hematopoiesis. *FASEB J.* 2011;25:4348–4357.
41. De Lisio M, Parise G. Characterization of the effects of exercise training on hematopoietic stem cell quantity and function. *J Appl Physiol.* 2012;113(10):1576–1584.
42. D’Ascenzi F, Zacà V, Maiorca S, et al. A quantitative assessment of circulating progenitor cells in competitive athletes and in sedentary subjects. *J Sports Med Phys Fitness.* 2015;55:241–248.
43. Witkowski S, Lockard MM, Jenkins NT, et al. Relationship between circulating progenitor cells, vascular function and oxidative stress with long-term training and shortterm detraining in older men. *Clin Sci (Lond).* 2010;118:303–311.
44. Nu’n~ez-Espinosa C, Ferreira I, Ríos-Kristjánsson JG, et al. Effects of intermittent hypoxia and light aerobic exercise on circulating stem cells and side population, after strenuous eccentric exercise in trained rats. *Curr Stem Cell Res Ther.* 2015;10:132–139.
45. Park J-H, Miyashita M, Kwon Y-C, et al. A 12-week after-school physical activity programme improves endothelial cell function in overweight and obese children: a randomised controlled study. *BMC Pediatr.* 2012;12:111.
46. Walther C, Gaede L, Adams V, et al. Effect of increased exercise in school children on physical fitness and endothelial progenitor cells: a prospective randomized trial. *Circulation.* 2009;120:2251–2259.
47. Wang J-S, Lee M-Y, Lien H-Y, Weng T-P. Hypoxic exercise training improves cardiac/muscular hemodynamics and is associated with modulated circulating progenitor cells in sedentary men. *Int J Cardiol.* 2014;170:315–323.
48. Asahara T, Murohara T, Sullivan A, et al. Isolation of putative progenitor endothelial cells for angiogenesis. *Science.* 1997;275(5302):964–967.
49. Basile DP, Yoder MC. Circulating and tissue resident endothelial progenitor cells. *J Cell Physiol.* 2014;229:10–16.
50. Goligorsky MS, Salven P. Concise review: endothelial stem and progenitor cells and their habitats. *Stem Cells Transl Med.* 2013;2(7):499–504.
51. Yoder MC. Is endothelium the origin of endothelial progenitor cells? *Arterioscler Thromb Vasc Biol.* 2010;30(6):1094–1103.
52. Yoder MC. Defining human endothelial progenitor cells. *J Thromb Haemost.* 2009;7:49–52.
53. Peichev M, Naiyer AJ, Pereira D, et al. Expression of VEGFR-2 and AC133 by circulating human CD34(+) cells identifies a population of functional endothelial precursors. *Blood.* 2000;95(3):952–958.
54. Timmermans F, Van Hauwermeiren F, De Smedt M, et al. Endothelial outgrowth cells are not derived from CD133+ cells or CD45+ hematopoietic precursors. *Arterioscler Thromb Vasc Biol.* 2007;27(7):1572–1579.
55. Case J, Mead LE, Bessler WK, et al. Human CD34+AC133+VEGFR-2+ cells are not endothelial progenitor cells but distinct, primitive hematopoietic progenitors. *Exp Hematol.* 2007;35(7):1109–1118.
56. Medina R, O’Neill C, Sweeney M, et al. Molecular analysis of endothelial progenitor cell (EPC) subtypes reveals two distinct cell populations with different identities. *BMC Med Genomics.* 2010;3(1):18.
57. Hill JM, Zalos G, Halcox JP, et al. Circulating endothelial progenitor cells, vascular function, and cardiovascular risk. *N Engl J Med.* 2003;348(7):593–600.
58. Rohde E, Bartmann C, Schallmoser K, et al. Immune cells mimic the morphology of endothelial progenitor colonies in vitro. *Stem Cells.* 2007;25(7):1746–1752.
59. Rohde E, Malischnik C, Thaler D, et al. Blood monocytes mimic endothelial progenitor cells. *Stem Cells.* 2006;24(2):357–367.
60. Richardson MR, Yoder MC. Endothelial progenitor cells: quo vadis? *J Mol Cell Cardiol.* 2011;50(2):266–272.
61. Hur J, Yang H-M, Yoon C-H, et al. Identification of a novel role of T cells in postnatal vasculogenesis: characterization of endothelial progenitor cell colonies. *Circulation.* 2007;116(15):1671–1682.
62. Yoder MC. Endothelial progenitor cell: a blood cell by many other names may serve similar functions. *J Mol Med (Berl).* 2013;91(3):285–295.
63. Asahara T, Kawamoto A, Masuda H. Concise review: circulating endothelial progenitor cells for vascular medicine. *Stem Cells.* 2011;29(11):1650–1655.
64. Schmidt-Lucke C, Rossig L, Fichtlscherer S, et al. Reduced number of circulating endothelial progenitor cells predicts future cardiovascular events: proof of concept for the clinical importance of endogenous vascular repair. *Circulation.* 2005;111(22):2981–2987.
65. Werner N, Kosiol S, Schiegl T, et al. Circulating endothelial progenitor cells and cardiovascular outcomes. *N Engl J Med.* 2005;353(10):999–1007.
66. Fadini GP, Coracina A, Baesso I, et al. Peripheral blood CD34+KDR+ endothelial progenitor cells are determinants of subclinical atherosclerosis in a middle-aged general population. *Stroke.* 2006;37(9):2277–2282.
67. Fadini GP, de Kreutzenberg S, Agostini C, et al. Low CD34+ cell count and metabolic syndrome synergistically increase the risk of adverse outcomes. *Atherosclerosis.* 2009;207(1):213–219.
68. Fadini GP, de Kreutzenberg SV, Coracina A, et al. Circulating CD34+ cells, metabolic syndrome, and cardiovascular risk. *Eur Heart J.* 2006;27(18):2247–2255.
69. Fadini GP, Maruyama S, Ozaki T, et al. Circulating progenitor cell count for cardiovascular risk stratification: a pooled analysis. *PLoS One.* 2010;5(7):e11488.
70. Fadini GP, Miorin M, Facco M, et al. Circulating endothelial progenitor cells are reduced in peripheral vascular complications of type 2 diabetes mellitus. *J Am Coll Cardiol.* 2005;45(9):1449–1457.
71. Fadini GP, Schiavon M, Cantini M, Avogaro A, Agostini C. Circulating CD34+ cells, pulmonary hypertension, and myelofibrosis. *Blood.* 2006;108(5):1776–1777.
72. Mora S, Cook N, Buring JE, Ridker PM, Lee I-M. Physical activity and reduced risk of cardiovascular events: potential mediating mech-

- anisms. *Circulation*. 2007;116(19):2110–2118.
73. Witkowski S, Jenkins NT, Hagberg JM. Enhancing treatment for cardiovascular disease: exercise and circulating angiogenic cells. *Exerc Sport Sci Rev*. 2011;39(2):93–101.
74. De Biase C, De Rosa R, Luciano R, et al. Effects of physical activity on endothelial progenitor cells (EPCs). *Front Physiol*. 2013;4:414.
75. Ribeiro F, Ribeiro IP, Alves AJ, et al. Effects of exercise training on endothelial progenitor cells in cardiovascular disease: a systematic review. *Am J Phys Med Rehabil*. 2013;92(11):1020–1030.
76. Rehman J, Li J, Parvathaneni L, et al. Exercise acutely increases circulating endothelial progenitor cells and monocyte-/macrophage-derived angiogenic cells. *J Am Coll Cardiol*. 2004;43(12):2314–2318.
77. Adams V, Lenk K, Linke A, et al. Increase of circulating endothelial progenitor cells in patients with coronary artery disease after exercise-induced ischemia. *Arterioscler Thromb Vasc Biol*. 2004;24(4):684–690.
78. Sandri M, Bernhard Beck E, Adams V, et al. Maximal exercise, limb ischemia, and endothelial progenitor cells. *Eur J Cardiovasc Prev Rehabil*. 2011;18(1):55–64.
79. Van Craenenbroeck EM, Bruyndonckx L, Van Berckelaer C, Hoymans VY, Vrints CJ, Conraads VM. The effect of acute exercise on endothelial progenitor cells is attenuated in chronic heart failure. *Eur J Appl Physiol*. 2011;111(9):2375–2379.
80. Van Craenenbroeck EM, Beckers PJ, Possemiers NM, et al. Exercise acutely reverses dysfunction of circulating angiogenic cells in chronic heart failure. *Eur Heart J*. 2010;31(15):1924–1934.
81. Jenkins NT, Witkowski S, Spangenburg EE, Hagberg JM. Effects of acute and chronic endurance exercise on intracellular nitric oxide in putative endothelial progenitor cells: role of NADPH oxidase. *Am J Physiol Heart Circ Physiol*. 2009;297(5):H1798–H1805.
82. Sarto P, Balducci E, Balconi G, et al. Effects of exercise training on endothelial progenitor cells in patients with chronic heart failure. *J Card Fail*. 2007;13(9):701–708.
83. Laufs U, Werner N, Link A, et al. Physical training increases endothelial progenitor cells, inhibits neointima formation, and enhances angiogenesis. *Circulation*. 2004;109(2):220–226.
84. Van Craenenbroeck EM, Hoymans VY, Beckers PJ, et al. Exercise training improves function of circulating angiogenic cells in patients with chronic heart failure. *Basic Res Cardiol*. 2010;105(5):665–676.
85. Kruger K, Pilat C, Schild M, et al. Progenitor cell mobilization after exercise is related to systemic levels of G-CSF and muscle damage. *Scand J Med Sci Sports*. 2015;25: e283–e291.
86. Goto C, Nishioka K, Umemura T, et al. Acute moderate-intensity exercise induces vasodilation through an increase in nitric oxide bioavailability in humans. *Am J Hypertens*. 2007;20(8):825–830.
87. Aicher A, Heeschen C, Mildner-Rihm C, et al. Essential role of endothelial nitric oxide synthase for mobilization of stem and progenitor cells. *Nat Med*. 2003;9(11):1370–1376.
88. Cubbon RM, Murgatroyd SR, Ferguson C, et al. Human exercise-induced circulating progenitor cell mobilization is nitric oxide-dependent and is blunted in South Asian men. *Arterioscler Thromb Vasc Biol*. 2010;30(4):878–884.
89. Fleissner F, Thum T. Critical role of the nitric oxide/reactive oxygen species balance in endothelial progenitor dysfunction. *Antioxid Redox Signal*. 2011;15(4):933–948.
90. Guhanarayanan G, Jablonski J, Witkowski S. Circulating angiogenic cell population responses to 10 days of reduced physical activity. *J Appl Physiol*. 2014;117:500–506.
91. Steiner S, Niessner A, Ziegler S, et al. Endurance training increases the number of endothelial progenitor cells in patients with cardiovascular risk and coronary artery disease. *Atherosclerosis*. 2005;181(2):305–310.
92. Cheng XW, Kuzuya M, Kim W, et al. Exercise training stimulates ischemia-induced neovascularization via phosphatidylinositol 3-kinase/Akt-dependent hypoxia-induced factor-1 α reactivation in mice of advanced age. *Circulation*. 2010;122:707–716.
93. Pula G, Mayr U, Evans C, et al. Proteomics identifies thymidine phosphorylase as a key regulator of the angiogenic potential of colony-forming units and endothelial progenitor cell cultures. *Circ Res*. 2009;104(1):32–40.
94. Urbich C, Aicher A, Heeschen C, et al. Soluble factors released by endothelial progenitor cells promote migration of endothelial cells and cardiac resident progenitor cells. *J Mol Cell Cardiol*. 2005;39(5):733–742.
95. Yang Z, von Ballmoos MW, Faessler D, et al. Paracrine factors secreted by endothelial progenitor cells prevent oxidative stress-induced apoptosis of mature endothelial cells. *Atherosclerosis*. 2010;211(1):103–109.
96. Friedenstein AJ, Petrakova KV, Kurolesova AI, Frolova GP. Heterotopic of bone marrow. Analysis of precursor cells for osteogenic and hematopoietic tissues. *Transplantation*. 1968;6:230–247.
97. Owen M, Friedenstein AJ. Stromal stem cells: marrow-derived osteogenic precursors. *Ciba Found Symp*. 1988;136:42–60.
98. Dominici M, Le Blanc K, Mueller I, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy*. 2006;8:315–317.
99. Bianco P, Robey PG, Simmons PJ. Mesenchymal stem cells: revisiting history, concepts, and assays. *Cell Stem Cell*. 2008;2:313–319.
100. Bianco P, Cao X, Frenette PS, et al. The meaning, the sense and the significance: translating the science of mesenchymal stem cells into medicine. *Nat Med*. 2013;19:35–42.
101. Phinney DG, Galipeau J, Krampera M, Martin I, Shi Y, Sensebe L. MSCs: science and trials. *Nat Med*. 2013;19:812.
102. Kittler EL, McGrath H, Temeles D, Crittenden RB, Kister VK, Quesenberry PJ. Biologic significance of constitutive and subliminal growth factor production by bone marrow stroma. *Blood*. 1992;79:3168–3178.
103. Pittenger MF, Mackay AM, Veck SC, et al. Multilineage potential of adult human mesenchymal stem cells. *Science*. 1999;284:143–147.
104. Ocarino NM, Boeloni JN, Goes AM, Silva JF, Marubayashi U, Serakides R. Osteogenic differentiation of mesenchymal stem cells from

- osteopenic rats subjected to physical activity with and without nitric oxide synthase inhibition. *Nitric Oxide*. 2008;19:320–325.
105. Hell RC, Ocarino NM, Boeloni JN, et al. Physical activity improves age-related decline in the osteogenic potential of rats' bone marrow-derived mesenchymal stem cells. *Acta Physiol (Oxf)*. 2012;205:292–301.
106. David V, Martin A, Lafage-Proust MH, et al. Mechanical loading down-regulates peroxisome proliferator-activated receptor gamma in bone marrow stromal cells and favors osteoblastogenesis at the expense of adipogenesis. *Endocrinology*. 2007;148:2553–2562.
107. Mauro A. Satellite cell of skeletal muscle fibers. *J Biophys Biochem Cytol*. 1961;9:493–495.
108. Sacco A, Doyonnas R, Kraft P, Vitorovic S, Blau HM. Self-renewal and expansion of single transplanted muscle stem cells. *Nature*. 2008;456:502–506.
109. Sambasivan R, Yao R, Kissenpfennig A, et al. Pax7-expressing satellite cells are indispensable for adult skeletal muscle regeneration. *Development*. 2011;138:3647–3656.
110. McCarthy JJ, Mula J, Miyazaki M, et al. Effective fiber hypertrophy in satellite cell-depleted skeletal muscle. *Development*. 2011;138:3657–3666.
111. Starkey JD, Yamamoto M, Yamamoto S, Goldhamer DJ. Skeletal muscle cells are committed to myogenesis and do not spontaneously adopt nonmyogenic fates. *J Histochem Cytochem*. 2011;59:33–46.
112. Cermak NM, Snijders T, McKay BR, et al. Eccentric exercise increases satellite cell content in type II muscle fibers. *Med Sci Sports Exerc*. 2013;45:230–237.
113. Bellamy LM, Joannis S, Grubb A, et al. The acute satellite cell response and skeletal muscle hypertrophy following resistance training. *PLoS One*. 2014;9:e109739.
114. Farup J, Rahbek SK, Knudsen IS, de Paoli F, Mackey AL, Vissing K. Whey protein supplementation accelerates satellite cell proliferation during recovery from eccentric exercise. *Amino Acids*. 2014;46:2503–2516.
115. Snijders T, Verdijk LB, Smeets JS, et al. The skeletal muscle satellite cell response to a single bout of resistance-type exercise is delayed with aging in men. *Age*. 2014;36:9699.
116. Roth SM, Martel GF, Ivey FM, et al. Skeletal muscle satellite cell characteristics in young and older men and women after heavy resistance strength training. *J Gerontol A Biol Sci Med Sci*. 2001;56:B240–B247.
117. Crameri RM, Langberg H, Magnusson P, et al. Changes in satellite cells in human skeletal muscle after a single bout of high intensity exercise. *J Physiol*. 2004;558:333–340.
118. Mackey AL, Esmarck B, Kadi F, et al. Enhanced satellite cell proliferation with resistance training in elderly men and women. *Scand J Med Sci Sports*. 2007;17:34–42.
119. Petrella JK, Kim JS, Mayhew DL, Cross JM, Bamman MM. Potent myofiber hypertrophy during resistance training in humans is associated with satellite cell-mediated myonuclear addition. *J Appl Physiol*. 2008;104:1736–1742.
120. Verdijk LB, Gleeson BG, Jonkers RA, et al. Skeletal muscle hypertrophy following resistance training is accompanied by a fiber type-specific increase in satellite cell content in elderly men. *J Gerontol A Biol Sci Med Sci*. 2009;64:332–339.
121. Verdijk LB, Snijders T, Drost M, Delhaas T, Kadi F, van Loon LJ. Satellite cells in human skeletal muscle; from birth to old age. *Age*. 2014;36:545–547.
122. Charifi N, Kadi F, Feasson L, Denis C. Effects of endurance training on satellite cell frequency in skeletal muscle of old men. *Muscle Nerve*. 2003;28:87–92.
123. Kadi F, Schjerling P, Andersen LL, et al. The effects of heavy resistance training and detraining on satellite cells in human skeletal muscles. *J Physiol*. 2004;558: 1005–1012.
124. Umnova MM, Seene TP. The effect of increased functional load on the activation of satellite cells in the skeletal muscle of adult rats. *Int J Sports Med*. 1991;12:501–504.
125. Mounier R, Chretien F, Chazaud B. Blood vessels and the satellite cell niche. *Curr Top Dev Biol*. 2011;96:121–138.
126. Fry CS, Lee JD, Jackson JR, et al. Regulation of the muscle fiber microenvironment by activated satellite cells during hypertrophy. *FASEB J*. 2014;28:1654–1665.
127. Malm C, Sjodin TL, Sjoberg B, et al. Leukocytes, cytokines, growth factors and hormones in human skeletal muscle and blood after uphill or downhill running. *J Physiol*. 2004;556:983–1000.
128. Mikkelsen UR, Langberg H, Helmark IC, et al. Local NSAID infusion inhibits satellite cell proliferation in human skeletal muscle after eccentric exercise. *J Appl Physiol*. 2009;107:1600–1611.
129. Shefer G, Rauner G, Stuelsatz P, Benayahu D, Yablonka-Reuveni Z. Moderate-intensity treadmill running promotes expansion of the satellite cell pool in young and old mice. *FEBS J*. 2013;280:4063–4073.
130. Hawke TJ, Garry DJ. Myogenic satellite cells: physiology to molecular biology. *J Appl Physiol*. 2001;91:534–551.
131. Macaluso F, Myburgh KH. Current evidence that exercise can increase the number of adult stem cells. *J Muscle Res Cell Motil*. 2012;33:187–198.
132. McKay BR, O'Reilly CE, Phillips SM, Tarnopolsky MA, Parise G. Co-expression of IGF-1 family members with myogenic regulatory factors following acute damaging muscle-lengthening contractions in humans. *J Physiol*. 2008;586:5549–5560.
133. Toth KG, McKay BR, De Lisio M, Little JP, Tarnopolsky MA, Parise G. IL-6 induced STAT3 signaling is associated with the proliferation of human muscle satellite cells following acute muscle damage. *PLoS One*. 2011;6:e17392.
134. Guerci A, Lahoute C, Hebrard S, et al. *Cell Metab*. 2012;15:25–37.
135. Qu-Petersen Z, Deasy B, Jankowski R, et al. Identification of a novel population of muscle stem cells in mice: potential for muscle regeneration. *J Cell Biol*. 2002;157:851–864.

136. Motohashi N, Uezumi A, Yada E, et al. Muscle CD31(+)CD45(+) side population cells promote muscle regeneration by stimulating proliferation and migration of myoblasts. *Am J Pathol.* 2008;173:781–791.
137. Joe AW, Yi L, Natarajan A, et al. Muscle injury activates resident fibro/adipogenic progenitors that facilitate myogenesis. *Nat Cell Biol.* 2010;12:153–163.
138. Mitchell KJ, Pannerec A, Cadot B, et al. Identification and characterization of a nonsatellite cell muscle resident progenitor during postnatal development. *Nat Cell Biol.* 2010;12:257–266.
139. Uezumi A, Fukada S, Yamamoto N, Takeda S, Tsukuda K. Mesenchymal progenitors distinct from satellite cells contribute to ectopic fat cell formation in skeletal muscle. *Nat Cell Biol.* 2010;12:143–152.
140. Doyle MJ, Zhou S, Tanaka KK, et al. Abcg2 labels multiple cell types in skeletal muscle and participates in muscle regeneration. *J Cell Biol.* 2011;195:147–163.
141. Valero MC, Huntsman HD, Liu J, Zou K, Boppart MD. Eccentric exercise facilitates mesenchymal stem cell appearance in skeletal muscle. *PLoS One.* 2012;7:e29760.
142. Boppart MD, De Lisio M, Zou K, Huntsman HD. Defining a role for non-satellite stem cells in the regulation of muscle repair following exercise. *Front Physiol.* 2013;4:310.
143. Gussoni E, Soneoka Y, Strickland CD, et al. Dystrophin expression in the mdx mouse restored by stem cell transplantation. *Nature.* 1999;401:390–394.
144. Asakura A, Seale P, Grgis-Gabardo A, Rudnicki MA. Myogenic specification of side population cells in skeletal muscle. *J Cell Biol.* 2002;159:123–134.
145. Pannerec A, Formicola L, Besson V, Marazzi G, Sasoon DA. Defining skeletal muscle resident progenitors and their cell fate potentials. *Development.* 2013;140:2879–2891.
146. Birbrair A, Zhang T, Wang ZM, et al. Role of pericytes in skeletal muscle regeneration and fat accumulation. *Stem Cells Dev.* 2013;22:2298–2314.
147. Zou K, Huntsman HD, Valero MC, et al. Mesenchymal stem cells augment the adaptive response to eccentric exercise. *Med Sci Sports Exerc.* 2015;47:315–325.
148. Huntsman HD, Zachwieja N, Zou K, et al. Mesenchymal stem cells contribute to vascular growth in skeletal muscle in response to eccentric exercise. *Am J Physiol Heart Circ Physiol.* 2013;304:H72–H81.
149. De Lisio MD, Jensen T, Sukienik RA, Huntsman HD, Boppart MD. Substrate and strain alter the muscle-derived mesenchymal stem cell secretome to promote myogenesis. *Stem Cell Res Ther.* 2014;5:74.
150. Hyldahl RD, O’Fallon KS, Schwartz LM, Clarkson PM. Activation of nuclear factorkB following muscle eccentric contractions in humans is localized primarily to skeletal muscle-residing pericytes. *FASEB J.* 2011;25:2956–2966.

Chapter 19

- Hawley JA, Hargreaves M, Joyner MJ, Zierath JR. Integrative biology of exercise. *Cell.* 2014;159:738–749.
- Heinonen I, Kalliokoski KK, Hannukainen JC, Duncker DJ, Nuutila P, Knuuti J. Organ-specific physiological responses to acute physical exercise and long-term training in humans. *Physiology.* 2014;29:421–436.
- Bassel-Duby R, Olson EN. Signaling pathways in skeletal muscle remodeling. *Annu Rev Biochem.* 2006;75:19–37.
- Egan B, Zierath JR. Exercise metabolism and the molecular regulation of skeletal muscle adaptation. *Cell Metab.* 2013;17:162–184.
- Perry CGR, Lally J, Holloway GP, Heigenhauser GJF, Bonen A, Spratt LL. Repeated transient mRNA bursts precede increases in transcriptional and mitochondrial proteins during training in human skeletal muscle. *J Physiol.* 2010;588:4795–4810.
- Egan B, O’Connor PL, Zierath JR, O’Gorman DJ. Time course analysis reveals gene-specific transcript and protein kinetics of adaptation to short-term aerobic exercise training in human skeletal muscle. *PLoS One.* 2013;8:e74098.
- Kraniou GN, Cameron-Smith D, Hargreaves M. Effect of short-term training on GLUT4 mRNA and protein expression in human skeletal muscle. *Exp Physiol.* 2004;89:559–563.
- McCoy M, Proietto J, Hargreaves M. Effect of detraining on GLUT4 protein in human skeletal muscle. *J Appl Physiol.* 1994;77:1532–1536.
- Holloszy JO, Coyle EF. Adaptations of skeletal muscle to endurance exercise and their metabolic consequences. *J Appl Physiol.* 1984;56:831–838.
- Williams RS, Salmons S, Newsholme EA, Kaufman RE, Mellor J. Regulation of nuclear and mitochondrial gene expression by contractile activity in skeletal muscle. *J Biol Chem.* 1986;261:376–380.
- Neufer PD, Dohm GL. Exercise induces a transient increase in transcription of the GLUT4 gene in skeletal muscle. *Am J Physiol.* 1993;265:C1597–C1603.
- Kraniou Y, Cameron-Smith D, Misso M, Collier G, Hargreaves M. Effects of exercise on GLUT4 and glycogenin gene expression in human skeletal muscle. *J Appl Physiol.* 2000;88:794–796.
- Koval JA, DeFronzo RA, O’Doherty RM, et al. Regulation of hexokinase II activity and expression in human skeletal muscle by moderate exercise. *Am J Physiol.* 1998;274:E304–E308.
- Seip RL, Mair K, Cole TG, Semenkovich CF. Induction of human skeletal muscle lipoprotein lipase gene expression by short-term exercise is transient. *Am J Physiol.* 1997;272:E255–E261.
- Pilegaard H, Ordway GA, Saltin B, Neufer PD. Transcriptional regulation of gene expression in human skeletal muscle during recovery from exercise. *Am J Physiol.* 2000;279:E806–E814.
- Keller C, Steensberg A, Pilegaard H, et al. Transcriptional activation of the IL-6 gene in human contracting skeletal muscle: influence of

- muscle glycogen content. *FASEB J.* 2001;15:2748–2750.
17. Pilegaard H, Saltin B, Neufer PD. Exercise induces transient transcriptional activation of the PGC-1 α gene in human skeletal muscle. *J Physiol.* 2003;546:851–858.
18. Russell AP, Hesselink MK, Lo SK, Schrauwen P. Regulation of metabolic transcriptional co-activators and transcription factors with acute exercise. *FASEB J.* 2005;19:986–988.
19. Yang Y, Creer A, Jemiolo B, Trappe S. Time course of myogenic and metabolic gene expression in response to acute exercise in human skeletal muscle. *J Appl Physiol.* 2005;98:1745–1752.
20. Gibala MJ, McGee SL, Garnham AP, Howlett KF, Snow RJ, Hargreaves M. Brief intense interval exercise activates AMPK and p38 MAPK signaling and increases the expression of PGC-1 α in human skeletal muscle. *J Appl Physiol.* 2009;106:929–934.
21. Coffey VG, Shield A, Canny BJ, Carey KA, Cameron-Smith D, Hawley JA. Interaction of contractile activity and training history on mRNA abundance in skeletal muscle from trained athletes. *Am J Physiol.* 2006;290:E849–E855.
22. Arkinstall MJ, Tunstall RJ, Cameron-Smith D, Hawley JA. Regulation of metabolic genes in human skeletal muscle by short-term exercise and diet manipulation. *Am J Physiol.* 2004;287:E25–E31.
23. Pilegaard H, Keller C, Steensberg A, et al. Influence of pre-exercise muscle glycogen content on exercise-induced transcriptional regulation of metabolic genes. *J Physiol.* 2002;541:261–271.
24. Civitarese AE, Hesselink MKC, Russell AP, Ravussin E, Schrauwen P. Glucose ingestion blunts exercise-induced gene expression of skeletal muscle fat oxidative genes. *Am J Physiol.* 2005;289:E1023–E1029.
25. Cluberton LJ, McGee SL, Murphy RM, Hargreaves M. Effect of carbohydrate ingestion on exercise-induced alterations in metabolic gene expression. *J Appl Physiol.* 2005;99: 1359–1363.
26. Hulmi JJ, Kovanen V, Sela-nne H, Kraemer WK, Haikkinen K, Mero AA. Acute and long-term effects of resistance exercise with or without protein ingestion on muscle hypertrophy and gene expression. *Amino Acids.* 2009;37:297–308.
27. Mahoney DJ, Parise G, Melov S, Safdar A, Tarnopolsky MA. Analysis of global mRNA expression in human skeletal muscle during recovery from endurance exercise. *FASEB J.* 2005;19:1498–1500.
28. Catoire M, Mensink M, Boekschooten MV, et al. Pronounced effects of acute endurance exercise on gene expression in resting and exercising human skeletal muscle. *PLoS One.* 2012;7:e51066.
29. Stepto NK, Coffey VG, Carey AL, et al. Global gene expression in skeletal muscle from well-trained strength and endurance athletes. *Med Sci Sports Exerc.* 2009;41:546–565.
30. KraniouGN, Cameron-Smith D, HargreavesM. Acute exercise and GLUT4 expression in human skeletal muscle: influence of exercise intensity. *J Appl Physiol.* 2006;101:934–937.
31. Leick L, Plomgaard P, Gronlokke L, Al-Abajji F, Wojtaszewski JF, Pilegaard H. Endurance exercise induces mRNA expression of oxidative enzymes in human skeletal muscle late in recovery. *Scand J Med Sci Sports.* 2010;20:593–599.
32. Steensberg A, van Hall G, Keller C, et al. Muscle glycogen content and glucose uptake during exercise in humans: influence of prior exercise and dietary manipulation. *J Physiol.* 2002;541:273–281.
33. Richter EA, Hargreaves M. Exercise, GLUT4 and skeletal muscle glucose uptake. *Physiol Rev.* 2013;93:993–1017.
34. Knight JB, Eyster CA, Griesel BA, Olson AL. Regulation of the GLUT4 gene promoter: interaction between a transcriptional activator and myocyte enhancer factor 2A. *Proc Natl Acad Sci USA.* 2003;100:14725–14730.
35. McGee SL, van Denderen BJ, Howlett KF, et al. AMP-activated kinase regulates GLUT4 transcription by phosphorylating histone deacetylase 5. *Diabetes.* 2008;57:860–867.
36. Smith JAH, Kohn TA, Chetty AK, Ojuka EO. CaMK activation during exercise is required for histone hyperacetylation and MEF2A binding at the MEF2 site on the Glut4 gene. *Am J Physiol.* 2008;295:E698–E704.
37. MacLean PS, Zhang D, Jones JP, Olson AL, Dohm GL. Exercise-induced transcription of the muscle glucose transporter (GLUT4) gene. *Biochem Biophys Res Commun.* 2002;292:409–414.
38. McGee SL, Fairlie E, Garnham AP, Hargreaves M. Exercise-induced histone modifications in human skeletal muscle. *J Physiol.* 2009;587:5951–5958.
39. McGee SL, Hargreaves M. Exercise and myocyte enhancer factor 2 regulation in human skeletal muscle. *Diabetes.* 2004;53:1208–1214.
40. McGee SL, Howlett KF, Starkie RL, Cameron-Smith D, Kemp BE, Hargreaves M. Exercise increases nuclear AMPK alpha2 in human skeletal muscle. *Diabetes.* 2003;52:926–928.
41. McGee SL, Sparling D, Olson AL, Hargreaves M. Exercise increases MEF2 and GEF DNA binding activity in human skeletal muscle. *FASEB J.* 2006;20:348–349.
42. Murgia M, Elbenhardt JT, Cusinato M, Garcia M, Richter EA, Schiaffino S. Multiple signaling pathways redundantly control GLUT4 gene transcription in skeletal muscle. *J Physiol.* 2009;587:4319–4327.
43. Holmes BF, Lang DB, Birnbaum MJ, Mu J, Dohm GL. AMP kinase is not required for the GLUT4 response to exercise and denervation in skeletal muscle. *Am J Physiol.* 2004;287:E739–E743.
44. Garcia-Roves PM, Jones TE, Otani K, Han DH, Holloszy JO. Calcineurin does not mediate exercise-induced increase in muscle GLUT4. *Diabetes.* 2005;54:624–628.
45. McGee SL, Swinton C, Morrison S, et al. Compensatory regulation of HDAC5 in muscle maintains metabolic adaptive responses and metabolism in response to energetic stress. *FASEB J.* 2014;28:3384–3395.
46. Yan Z, Okutsu M, Akhtar YN, Lira VA. Regulation of exercise-induced fiber type transformation, mitochondrial biogenesis, and angiogenesis in skeletal muscle. *J Appl Physiol.* 2011;110:264–274.

47. Baar K, Wende AR, Jones TE, et al. Adaptations of skeletal muscle to exercise: rapid increase in the transcriptional coactivator PGC-1. *FASEB J.* 2002;16:1879–1886.
48. Wright DC, Han DH, Garcia-Roves PM, Geiger PC, Jones TE, Holloszy JO. Exercise-induced mitochondrial biogenesis begins before the increase in muscle PGC-1 α expression. *J Biol Chem.* 2007;282:194–199.
49. Little JP, Safdar A, Cermak N, Tarnopolsky MA, Gibala MJ. Acute endurance exercise increases the nuclear abundance of PGC-1 α in trained human skeletal muscle. *Am J Physiol.* 2010;298:R912–R917.
50. Little JP, Safdar A, Bishop D, Tarnopolsky MA, Gibala MJ. An acute bout of highintensity interval training increases the nuclear abundance of PGC-1 α and activates mitochondrial biogenesis in human skeletal muscle. *Am J Physiol.* 2011;300: R1303–R1310.
51. Safdar A, Little JP, Stokl AJ, Hettinga BP, Akhtar M, Tarnopolsky MA. Exercise increases mitochondrial PGC-1 α content and promotes nuclear-mitochondrial crosstalk to coordinate mitochondrial biogenesis. *J Biol Chem.* 2011;286:10605–10617.
52. Smith BK, Mukai K, Lally JS, et al. AMP-activated protein kinase is required for exercise-induced peroxisome proliferator-activated receptor γ co-activator 1 α translocation to subsarcolemmal mitochondria in skeletal muscle. *J Physiol.* 2013;591:1551–1561.
53. Bird A. Perceptions of epigenetics. *Nature.* 2007;447:396–398.
54. Everitt AG, Zee BM, Garcia BA. Modern approaches for investigating epigenetic signaling pathways. *J Appl Physiol.* 2010;109:927–933.
55. Yan ST, Li CL, Tian H, et al. MiR-199a is overexpressed in plasma of type 2 diabetes patients which contributes to type 2 diabetes by targeting GLUT4. *Mol Cell Biochem.* 2014;397:45–51.
56. Barres R, Yan J, Egan B, et al. Acute exercise remodels promoter methylation in human skeletal muscle. *Cell Metab.* 2012;15:405–411.
57. Nitert MK, Dayeh T, Volkov P, et al. Impact of an exercise intervention on DNA methylation in skeletal muscle from first-degree relatives of patients with type 2 diabetes. *Diabetes.* 2012;61:3322–3332.
58. Alibegovic AL, Sonne MP, Højberre L, et al. Insulin resistance induced by physical inactivity is associated with multiple transcriptional changes in skeletal muscle in young men. *Am J Physiol.* 2010;299:E752–E763.
59. Terruzzi I, Senesi P, Montesano A, et al. Genetic polymorphisms of the enzymes involved in DNA methylation and synthesis in elite athletes. *Physiol Genomics.* 2011;43:965–973.
60. Laker RC, Lillard TS, Okutsu M, et al. Exercise prevents maternal high-fat diet-induced hypermethylation of the Pgc-1 α gene and age-dependent metabolic dysfunction in the offspring. *Diabetes.* 2014;63:1605–1611.
61. Lu C, Thompson CB. Metabolic regulation of epigenetics. *Cell Metab.* 2012;16:9–17.
62. Yu M, Stepto NK, Chibalin AV, et al. Metabolic and mitogenic signal transduction in human skeletal muscle after intense cycling exercise. *J Physiol.* 2003;546:327–335.
63. Potthoff MJ, Wu H, Arnold MA, et al. Histone deacetylase degradation and MEF2 activation promote the formation of slow-twitch myofibers. *J Clin Invest.* 2007;117:2459–2467.
64. Timmons JA, Knudsen S, Rankinen T, et al. Using molecular classification to predict gains in maximal aerobic capacity following endurance exercise training in humans. *J Appl Physiol.* 2010;108:1487–1496.
65. Bouchard C, Sarzynski MA, Rice TK, et al. Genomic predictors of the maximal O₂ uptake response to standardized exercise training programs. *J Appl Physiol.* 2011;110: 1160–1170.
66. Keller P, Vollaard NB, Gustafsson T, et al. A transcriptional map of the impact of endurance exercise training on skeletal muscle phenotype. *J Appl Physiol.* 2011;110:46–59.
67. Phillips BE, Atherton JP, Gustafsson T, et al. Molecular networks of human muscle adaptation to exercise and age. *PLoS Genet.* 2013;9:e1003389.
68. Ghosh S, Vivar JC, Sarzynski MA, et al. Integrative pathway analysis of a genome-wide association study of VO₂ max response to exercise training. *J Appl Physiol.* 2013;115:1343–1359.
69. Rowlands DS, Page RA, Sukala WR, et al. Multi-omic integrated networks connect DNA methylation and miRNA with skeletal muscle plasticity to chronic exercise in type 2 diabetic obesity. *Physiol Genomics.* 2014;46:747–765.
70. Philp A, Rowland T, Perez-Schindler J, Schenk S. Understanding the acetylome: translating target proteomics into meaningful physiology. *Am J Physiol.* 2014;307: C763–C773.
71. Thalacker-Mercer A, Stec M, Cui X, Cross J, Windham S, Bamman M. Cluster analysis reveals differential transcript profiles associated with resistance training-induced human skeletal muscle hypertrophy. *Physiol Genomics.* 2013;45:499–507.
72. Rowlands DS, Thomson JS, Timmons BW, et al. Transcriptome and translational signaling following endurance exercise in trained skeletal muscle: impact of dietary protein. *Physiol Genomics.* 2011;43:1004–1020.
73. Greenhaff PL, Hargreaves M. ‘Systems biology’ in human exercise physiology: is it something different from integrative physiology? *J Physiol.* 2011;589:1031–1036.

Chapter 20

- Russell AP, Hesselink MK, Lo SK, Schrauwen P. Regulation of metabolic transcriptional co-activators and transcription factors with acute exercise. *FASEB J.* 2005;19:986–988.
- Short KR, Vittone JL, Bigelow ML, et al. Impact of aerobic exercise training on age-related changes in insulin sensitivity and muscle oxidative capacity. *Diabetes.* 2003;52:1888–1896.
- Keller C, Steensberg A, Pilegaard H, et al. Transcriptional activation of the IL-6 gene in human contracting skeletal muscle: influence of muscle glycogen content. *FASEB J.* 2001;15:2748–2750.
- McGee SL, Sparling D, Olson AL, Hargreaves M. Exercise increases MEF2- and GEF DNA-binding activity in human skeletal muscle.

- FASEB J. 2006;20:348–349.
5. McGee SL, Fairlie E, Garnham AP, Hargreaves M. Exercise-induced histone modifications in human skeletal muscle. *J Physiol*. 2009;587:5951–5958.
 6. Barres R, Yan J, Egan B, et al. Acute exercise remodels promoter methylation in human skeletal muscle. *Cell Metab*. 2012;15:405–411.
 7. Nakajima K, Takeoka M, Mori M, et al. Exercise effects on methylation of ASC gene. *Int J Sports Med*. 2010;31:671–675.
 8. Lee RC, Feinbaum RL, Ambros V. The *C. elegans* heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. *Cell*. 1993;75:843–854.
 9. Reinhart BJ, Slack FJ, Basson M, et al. The 21-nucleotide let-7 RNA regulates developmental timing in *Caenorhabditis elegans*. *Nature*. 2000;403:901–906.
 10. Brennecke J, Stark A, Russell RB, Cohen SM. Principles of microRNA–target recognition. *PLoS Biol*. 2005;3:e85.
 11. Hu Z, Bruno AE. The influence of 30UTRs on microRNA function inferred from human SNP data. *Comp Funct Genomics*. 2011;2011:1–9.
 12. Huili G, Ingolia NT, Weissman JS, Bartel DP. Mammalian microRNAs predominantly act to decrease target mRNA levels. *Nature*. 2010;466:835–840.
 13. Pillai RS, Bhattacharyya SN, Artus CG, et al. Inhibition of translational initiation by Let-7 microRNA in human cells. *Science*. 2005;309:1573–1576.
 14. Vasudevan S, Tong Y, Steitz JA. Switching from repression to activation: microRNAs can up-regulate translation. *Science*. 2007;318:1931–1934.
 15. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell*. 2004;116:281–297.
 16. Sood P, Krek A, Zavolan M, Macino G, Rajewsky N. Cell-type-specific signatures of microRNAs on target mRNA expression. *Proc Natl Acad Sci USA*. 2006;103:2746–2751.
 17. Callis TE, Deng Z, Chen J-F, Wang D-Z. Muscling through the microRNA world. *Exp Biol Med*. 2008;233:131–138.
 18. McCarthy JJ, Esser KA. MicroRNA-1 and microRNA-133a expression are decreased during skeletal muscle hypertrophy. *J Appl Physiol*. 2007;102:306–313.
 19. Guller I, Russell AP. MicroRNAs in skeletal muscle: their role and regulation in development, disease and function. *J Physiol*. 2010;588:4075–4087.
 20. Rao PK, Kumar RM, Farkhondeh M, Baskerville S, Lodish HF. Myogenic factors that regulate expression of muscle-specific microRNAs. *Proc Natl Acad Sci USA*. 2006;103:8721–8726.
 21. Rosenberg MI, Georges SA, Asawachaicharn A, Analau E, Tapscott SJ. MyoD inhibits Fstl1 and Utrn expression by inducing transcription of miR-206. *J Cell Biol*. 2006;175:77–85.
 22. van Rooij E, Quiat D, Johnson BA, et al. A family of microRNAs encoded by myosin genes governs myosin expression and muscle performance. *Dev Cell*. 2009;17:662–673.
 23. Rivas DA, Lessard SJ, Rice NP, et al. Diminished skeletal muscle microRNA expression with aging is associated with attenuated muscle plasticity and inhibition of IGF-1 signaling. *FASEB J*. 2014;28:4133–4147.
 24. Zacharewicz E, Della Gatta PA, Reynolds J, et al. Identification of microRNAs linked to regulators of muscle protein synthesis and regeneration in young and old skeletal muscle. *PLoS One*. 2014;9:e114009.
 25. Nakasa T, Ishikawa M, Shi M, et al. Acceleration of muscle regeneration by local injection of muscle-specific microRNAs in rat skeletal muscle injury model. *J Cell Mol Med*. 2010;14:2495–2505.
 26. Lee Y, Ahn C, Han J, et al. The nuclear RNase III Drosha initiates microRNA processing. *Nature*. 2003;425:415–419.
 27. Lund E, Gu “ttinger S, Calado A, Dahlberg JE, Kutay U. Nuclear export of microRNA precursors. *Science*. 2004;303:95–98.
 28. Lee I, Ajay SS, Yook JI, et al. New class of microRNA targets containing simultaneous 50-UTR and 30-UTR interaction sites. *Genome Res*. 2009;19:1175–1183.
 29. Russell AP, Lamon S, Boon H, et al. Regulation of miRNAs in human skeletal muscle following acute endurance exercise and short-term endurance training. *J Physiol*. 2013;591:4637–4653.
 30. Drummond MJ, McCarthy JJ, Fry CS, Esser KA, Rasmussen BB. Aging differentially affects human skeletal muscle microRNA expression at rest and after an anabolic stimulus of resistance exercise and essential amino acids. *Am J Physiol Endocrinol Metab*. 2008;58: E1333–E1340.
 31. Lund E, Guttinger S, Calado A, Dahlberg JE, Kutay U. Nuclear export of microRNA precursors. *Science*. 2004;303:95–98.
 32. Fry AC. The role of resistance exercise intensity on muscle fibre adaptations. *Sports Med*. 2004;34:663–679.
 33. Koopman R, Gleeson B, Gijsen AP, et al. Post-exercise protein synthesis rates are only marginally higher in type I compared with type II muscle fibres following resistance-type exercise. *Eur J Appl Physiol*. 2011;111:1871–1878.
 34. Kumar V, Selby A, Rankin D, et al. Age-related differences in the dose–response relationship of muscle protein synthesis to resistance exercise in young and old men. *J Physiol*. 2009;587:211–217.
 35. Le ’ger B, Cartoni R, Praz M, et al. Akt signalling through GSK-3beta, mTOR and OXO1 is involved in human skeletal muscle hypertrophy and atrophy. *J Physiol*. 2006;576:923–933.
 36. Phillips SM. Physiologic and molecular bases of muscle hypertrophy and atrophy: impact of resistance exercise on human skeletal muscle (protein and exercise dose effects). *Appl Physiol Nutr Metab*. 2009;34:403–410.
 37. Elia L, Contu R, Quintavalle M, et al. Reciprocal regulation of microRNA-1 and insulin-like growth factor-1 signal transduction cascade in cardiac and skeletal muscle in physiological and pathological conditions. *Circulation*. 2009;120:2377–2385.
 38. Doghman M, El Wakil A, Cardinaud B, et al. Regulation of insulin-like growth factor/mammalian target of rapamycin signaling by microRNA in childhood adrenocortical tumors. *Cancer Res*. 2010;70:4666–4675.

39. Fornari F, Milazzo M, Chieco P, et al. miR-199a-3p regulates mTOR and c-Met to influence the doxorubicin sensitivity of human hepatocarcinoma cells. *Cancer Res.* 2010;70:5184–5193.
40. Hou T, Ou J, Zhao X, et al. MicroRNA-196a promotes cervical cancer proliferation through the regulation of FOXO1 and p27. *Br J Cancer.* 2014;110:1260–1268.
41. Jin Y, Tymen SD, Chen D, et al. MicroRNA-99 family targets AKT/mTOR signaling pathway in dermal wound healing. *PLoS One.* 2013;8:e64434.
42. Lerman G, Avivi C, Mardoukh C, et al. miRNA expression in psoriatic skin: reciprocal regulation of hsa-miR-99a and IGF-1R. *PLoS One.* 2011;6:e20916.
43. Lin RJ, Lin YC, Yu AL. miR-149* induces apoptosis by inhibiting Akt1 and E2F1 in human cancer cells. *Mol Carcinog.* 2010;49:719–727.
44. Wei F, Liu Y, Guo Y, et al. miR-99b-targeted mTOR induction contributes to irradiation resistance in pancreatic cancer. *Mol Cancer.* 2013;12:81.
45. Davidsen PK, Gallagher IJ, Hartman JW, et al. High responders to resistance exercise training demonstrate differential regulation of skeletal muscle microRNA expression. *J Appl Physiol.* 2011;110:309–317.
46. Nielsen S, Scheele C, Yfanti C, et al. Muscle specific microRNAs are regulated by endurance exercise in human skeletal muscle. *J Physiol.* 2010;588:4029–4037.
47. Keller P, Vollaard NB, Gustafsson T, et al. A transcriptional map of the impact of endurance exercise training on skeletal muscle phenotype. *J Appl Physiol.* 2011;110:46–59.
48. Rommel C, Bodine SC, Clarke BA, et al. Mediation of IGF-1-induced skeletal myotube hypertrophy by PI(3)K/Akt/mTOR and PI(3)K/Akt/GSK3 pathways. *Nat Cell Biol.* 2001;3:1009–1013.
49. Durieux AC, Desplanches D, Freyssenet D, Fluck M. Mechanotransduction in striated muscle via focal adhesion kinase. *Biochem Soc Trans.* 2007;35:1312–1313.
50. Russell AP, Wada S, Vergani L, et al. Disruption of skeletal muscle mitochondrial network genes and miRNAs in amyotrophic lateral sclerosis. *Neurobiol Dis.* 2013;49: 107–117.
51. Russell AP, Feilchenfeldt J, Schreiber S, et al. Endurance training in humans leads to fiber type-specific increases in levels of peroxisome proliferator-activated receptor-gamma coactivator-1 and peroxisome proliferator-activated receptor-alpha in skeletal muscle. *Diabetes.* 2003;52:2874–2881.
52. Ikeda S, Kawamoto H, Kasaoka K, et al. Muscle type-specific response of PGC-1 alpha and oxidative enzymes during voluntary wheel running in mouse skeletal muscle. *Acta Physiol (Oxf).* 2006;188:217–223.
53. Safdar A, Abadi A, Akhtar M, Hettinga BP, Tarnopolsky MA. miRNA in the regulation of skeletal muscle adaptation to acute endurance exercise in C57Bl/6J male mice. *PLoS One.* 2009;4:e5610.
54. Wada S, Kato Y, Sawada S, et al. MicroRNA-23a has minimal effect on endurance exercise-induced adaptation of mouse skeletal muscle. *Pflugers Arch.* 2015;467:389–398 [Epub ahead of print].
55. Chen X, Ba Y, Ma L, et al. Characterization of microRNAs in serum: a novel class of biomarkers for diagnosis of cancer and other diseases. *Cell Res.* 2008;18:997–1006.
56. Gilad S, Meiri E, Yoge Y, et al. Serum microRNAs are promising novel biomarkers. *PLoS One.* 2008;3:e3148.
57. Valadi H, Ekstrom K, Bossios A, et al. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. *Nat Cell Biol.* 2007;9:654–659.
58. Vickers KC, Palmisano BT, Shoucri BM, Shamburek RD, Remaley AT. MicroRNAs are transported in plasma and delivered to recipient cells by high-density lipoproteins. *Nat Cell Biol.* 2011;13:423–433.
59. Kosaka N, Iguchi H, Yoshioka Y, et al. Secretory mechanisms and intercellular transfer of microRNAs in living cells. *J Biol Chem.* 2010;285:17442–17452.
60. Pritchard CC, Kroh E, Wood B, et al. Blood cell origin of circulating microRNAs: a cautionary note for cancer biomarker studies. *Cancer Prev Res.* 2012;5:492–497.
61. Wang K, Zhang S, Weber J, Baxter D, Galas DJ. Export of microRNAs and microRNA-protective protein by mammalian cells. *Nucleic Acids Res.* 2010;38:7248–7259.
62. Pegtel DM, Cosmopoulos K, Thorley-Lawson DA, et al. Functional delivery of viral miRNAs via exosomes. *Proc Natl Acad Sci USA.* 2010;107:6328–6333.
63. D’Alessandra Y, Devanna P, Limana F, et al. Circulating microRNAs are new and sensitive biomarkers of myocardial infarction. *Eur Heart J.* 2010;31:2765–2773.
64. Freedman J, Ercan B, Morin K, et al. The distribution of circulating microRNA and their relation to coronary disease. *F1000Research.* 2012;1:1–12.
65. Mitchell PS, Parkin RK, Kroh EM, et al. Circulating microRNAs as stable blood-based markers for cancer detection. *Proc Natl Acad Sci USA.* 2008;105:10513–10518.
66. Mouillet JF, Chu T, Hubel CA, et al. The levels of hypoxia-regulated microRNAs in plasma of pregnant women with fetal growth restriction. *Placenta.* 2010;31:781–784.
67. Ho AS, Huang X, Cao H, et al. Circulating miR-210 as a novel hypoxia marker in pancreatic cancer. *Transl Oncol.* 2010;3:109–113.
68. Baggish AL, Hale A, Weiner RB, et al. Dynamic regulation of circulating microRNA during acute exhaustive exercise and sustained aerobic exercise training. *J Physiol.* 2011;589:3983–3994.
69. Nielsen S, Akerstrom T, Rinnov A, et al. The miRNA plasma signature in response to acute aerobic exercise and endurance training. *PLoS*

- One. 2014;9:e87308.
70. Baggish AL, Park J, Min PK, et al. Rapid upregulation and clearance of distinct circulating microRNAs after prolonged aerobic exercise. *J Appl Physiol*. 2014;116: 522–531.
71. Uhlemann M, Mobius-Winkler S, Fikenzer S, et al. Circulating microRNA-126 increases after different forms of endurance exercise in healthy adults. *Eur J Prev Cardiol*. 2012;21:484–491.
72. Mooren FC, Viereck J, Kruger K, Thum T. Circulating microRNAs as potential biomarkers of aerobic exercise capacity. *Am J Physiol Heart Circ Physiol*. 2014;306: H557–H563.
73. Sawada S, Kon M, Wada S, et al. Profiling of circulating microRNAs after a bout of acute resistance exercise in humans. *PLoS One*. 2013;8:e70823.
74. Aoi W, Ichikawa H, Mune K, et al. Muscle-enriched microRNA miR-486 decreases in circulation in response to exercise in young men. *Front Physiol*. 2013;4:80.
75. Banzet S, Chennaoui M, Girard O, et al. Changes in circulating microRNAs levels with exercise modality. *J Appl Physiol*. 2013;115:1237–1244.
76. Kuehbacher A, Urbich C, Zeiher AM, Dimmeler S. Role of Dicer and Drosha for endothelial microRNA expression and angiogenesis. *Circ Res*. 2007;101:59–68.
77. Poliseno L, Tuccoli A, Mariani L, et al. MicroRNAs modulate the angiogenic properties of HUVECs. *Blood*. 2006;108:3068–3071.
78. Chan SY, Zhang YY, Hemann C, et al. MicroRNA-210 controls mitochondrial metabolism during hypoxia by repressing the iron-sulfur cluster assembly proteins ISCU1/2. *Cell Metab*. 2009;10:273–284.
79. Krichevsky AM, Gabriely G. miR-21: a small multi-faceted RNA. *J Cell Mol Med*. 2009;13:39–53.
80. Chen J-F, Mandel EM, Thomson JM, et al. The role of microRNA-1 and microRNA-133 in skeletal muscle proliferation and differentiation. *Nat Genet*. 2006;38:228–233.
81. Aoi W, Naito Y, Mizushima K, et al. The microRNA miR-696 regulates PGC-1 α in mouse skeletal muscle in response to physical activity. *Am J Physiol Endocrinol Metab*. 2010;298:E799–E806.
82. Russell AP, Lamon S, Boon H, et al. Regulation of miRNAs in human skeletal muscle following acute endurance exercise and short term endurance training. *J Physiol*. 2013;591:4637–4653.
83. van Solingen C, Seghers L, Bijkerk R, et al. Antagomir-mediated silencing of endothelial cell specific microRNA-126 impairs ischemia-induced angiogenesis. *J Cell Mol Med*. 2009;13:1577–1585.
84. Wang S, Aurora AB, Johnson BA, et al. The endothelial-specific microRNA miR-126 governs vascular integrity and angiogenesis. *Dev Cell*. 2008;15:261–271.
85. Hitachi K, Nakatani M, Tsuchida K. Myostatin signaling regulates Akt activity via the regulation of miR-486 expression. *Int J Biochem Cell Biol*. 2014;47:93–103.
86. Dews M, Homayouni A, Yu D, et al. Augmentation of tumor angiogenesis by a Mycactivated microRNA cluster. *Nat Genet*. 2006;38:1060–1065.
87. McAlexander MA, Phillips MJ, Witwer KW. Comparison of methods for miRNA extraction from plasma and quantitative recovery of RNA from plasma and cerebrospinal fluid. *Front Genet*. 2013;4:83.
88. Connes P, Simmonds MJ, Brun J-F, Baskurt OK. Exercise hemorheology: classical data, recent findings and unresolved issues. *Clin Hemorheol Microcirc*. 2013;53:187–199.
89. Tanimura Y, Kon M, Shimizu K, et al. Effect of 6-day intense Kendo training on lymphocyte counts and its expression of CD95. *Eur J Appl Physiol*. 2009;107:227–233.
90. Tonevitsky A, Maltseva D, Abbasi A, et al. Dynamically regulated miRNA-mRNA networks revealed by exercise. *BMC Physiol*. 2013;13:9.
91. Devlin C, Greco S, Martelli F, Ivan M. miR-210: more than a silent player in hypoxia. *IUBMB Life*. 2011;63:94–100.
92. Chan SY, Loscalzo J. MicroRNA-210: a unique and pleiotropic hypoxamir. *Cell Cycle*. 2010;9:1072–1083.
93. Bye A, Røsjø H, Aspenes ST, et al. Circulating microRNAs and aerobic fitness—the HUNT Study. *PLoS One*. 2013;8:e57496.
94. Leuenberger N, Robinson N, Saugy M. Circulating miRNAs: a new generation of antidoping biomarkers. *Anal Bioanal Chem*. 2013;405:9617–9623.
95. Radom-Aizik S, Zaldivar F, Haddad F, Cooper DM. Impact of brief exercise on peripheral blood NK cell gene and microRNA expression in young adults. *J Appl Physiol*. 2013;114:628–636.
96. Radom-Aizik S, Zaldivar Jr F, Leu SY, et al. Effects of exercise on microRNA expression in young males peripheral blood mononuclear cells. *Clin Transl Sci*. 2012;5:32–38.
97. Radom-Aizik S, Zaldivar Jr F, Oliver S, Galassetti P, Cooper DM. Evidence for micro RNA involvement in exercise-associated neutrophil gene expression changes. *J Appl Physiol*. 2010;109:252–261.
98. Chilton WL, Marques FZ, West J, et al. Acute exercise leads to regulation of telomere associated genes and microRNA expression in immune cells. *PLoS One*. 2014;9:e92088.
99. van Rooij E, Sutherland LB, Qi X, et al. Control of stress-dependent cardiac growth and gene expression by a microRNA. *Science*. 2007;316:575–579.

Chapter 21

1. WHO. Noncommunicable Diseases Country Profiles 2014. Switzerland: World Health Organization; 2014.
2. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and Inter-national Association for the Study of Obesity. *Circulation*. 2009;120(16):1640–1645.
3. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet*. 2005;365(9468):1415–1428.
4. Pedersen BK, Saltin B. Evidence for prescribing exercise as therapy in chronic disease. *Scand J Med Sci Sports*. 2006;16(suppl 1):3–63.
5. Eckel RH. Lipoprotein lipase. A multifunctional enzyme relevant to common metabolic diseases. *N Engl J Med*. 1989;320(16):1060–1068.
6. Jensen MD, Caruso M, Heiling V, Miles JM. Insulin regulation of lipolysis in nondiabetic and IDDM subjects. *Diabetes*. 1989;38(12):1595–1601.
7. Zambon A, Hokanson JE, Brown BG, Brunzell JD. Evidence for a new pathophysiological mechanism for coronary artery disease regression: hepatic lipase-mediated changes in LDL density. *Circulation*. 1999;99(15):1959–1964.
8. WorldHealthOrganization.Aboutdiabetes;2014.http://www.who.int/diabetes/action_online/basics/en/. Accessed 16.10.14.
9. Yki-Jarvinen H. Toxicity of hyperglycaemia in type 2 diabetes. *Diabetes Metab Rev*. 1998;14(suppl 1):S45–S50.
10. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. *JAMA*. 1979;241(19):2035–2038.
11. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360(9349):1903–1913.
12. Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. *Compr Physiol*. 2012;2(2):1143–1211.
13. McGinnis JM, Foege WH. Actual causes of death in the United States. *JAMA*. 1993;270(18):2207–2212.
14. Kushi LH, Doyle C, McCullough M, et al. American Cancer Society Guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. *CA Cancer J Clin*. 2012;62(1):30–67.
15. Arias E, Anderson RN, Kung HC, Murphy SL, Kochanek KD. Deaths: final data for 2001. *Natl Vital Stat Rep*. 2003;52(3):1–115.
16. AmericanCancerSociety.CancerFactsandFigures.Washington,DC:AmericanCancer Society; 2004.
17. Querfurth HW, LaFerla FM. Alzheimer’s disease. *N Engl J Med*. 2010;362(4):329–344.
18. American Diabetes Association. The cost of diabetes website; 2014. <http://www.diabetes.org/advocate/resources/cost-of-diabetes.html>. Accessed September 15.
19. Finkelstein EA, Trodron JG, Cohen JW, Dietz W. Annual medical spending attributable to obesity: payer- and service-specific estimates. *Health Aff (Millwood)*. 2009;28(5): w822–w831.
20. AmericanHeartAssociation.HeartDiseaseandStrokeStatistics—2014Update.AHASta-tistical Update Web site; <http://circ.ahajournals.org/content/early/2013/12/18/01.cir.0000441139.02102.80.full.pdf>; 2014 Accessed September 17.
21. NationalCancerInstitute.Cancerprevalenceandcostofcareprojectionswebsite;2014.<http://costprojections.cancer.gov>. Accessed September 15.
22. Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States, 2000. *JAMA*. 2004;291(10):1238–1245.
23. Centers for Disease Control and Prevention. Exercise or physical activity. NCHS FastStats Web site; 2014. <http://www.cdc.gov/nchs/faststats/exercise.htm>. Accessed September 18.
24. Matthews CE, Chen KY, Freedson PS, et al. Amount of time spent in sedentary behaviors in the United States, 2003–2004. *Am J Epidemiol*. 2008;167(7):875–881.
25. King AC, Blair SN, Bild DE, et al. Determinants of physical activity and interventions in adults. *Med Sci Sports Exerc*. 1992;24(6 suppl):S221–S236.
26. American College of Sports Medicine Position Stand. The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults. *Med Sci Sports Exerc*. 1998;30(6):975–991.
27. Hallal PC, Andersen LB, Bull FC, Guthold R, Haskell W, Ekelund U. Global physical activity levels: surveillance progress, pitfalls, and prospects. *Lancet*. 2012;380(9838): 247–257.
28. Booth FW, Laye MJ. Lack of adequate appreciation of physical exercise’s complexities can pre-empt appropriate design and interpretation in scientific discovery. *J Physiol*. 2009;587(pt 23):5527–5539.
29. Paffenbarger Jr RS, Hyde RT, Wing AL, Hsieh CC. Physical activity, all-cause mortality, and longevity of college alumni. *N Engl J Med*. 1986;314(10):605–613.
30. Schoenborn CA, Stommel M. Adherence to the 2008 adult physical activity guidelines and mortality risk. *Am J Prev Med*. 2011;40(5):514–521.
31. Arrieta A, Russell LB. Effects of leisure and non-leisure physical activity on mortality in U.S. adults over two decades. *Ann Epidemiol*. 2008;18(12):889–895.
32. Garatachea N, Santos-Lozano A, Sanchis-Gomar F, et al. Elite athletes live longer than the general population: a meta-analysis. *Mayo Clin Proc*. 2014;89(9):1195–1200.
33. Naci H, Ioannidis JP. Comparative effectiveness of exercise and drug interventions on mortality outcomes: metaepidemiological study. *BMJ*. 2013;347:f5577.
34. Fiuzza-Luces C, Garatachea N, Berger NA, Lucia A. Exercise is the real polypill. *Physiology (Bethesda)*. 2013;28(5):330–358.
35. Umpierre D, Ribeiro PA, Kramer CK, et al. Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2011;305(17):1790–1799.