specific adaptation (134) and the contributions of synthesis and degradation to changes in the abundance of individual proteins (135) in exercised skeletal muscle.

THE FUTURE – INTEGRATIVE OMIC INVESTIGATION

Overall, in the future, more extensive integrative 'OMIC' investigations using current epigenomic, transcriptomic (discussed above), proteomic analysis at the tissue and single cell levels, in combination with genetic profiling using the latest technological sequencing advancements, are required in exercising knock-out, overexpression and compensatory hypertrophy rodent models, and importantly in human exercise intervention studies. This will enable the field to delve into the deepest regulatory networks and take molecular exercise physiology into the next generation of research to uncover the mechanistic underpinnings of exercise adaptation.

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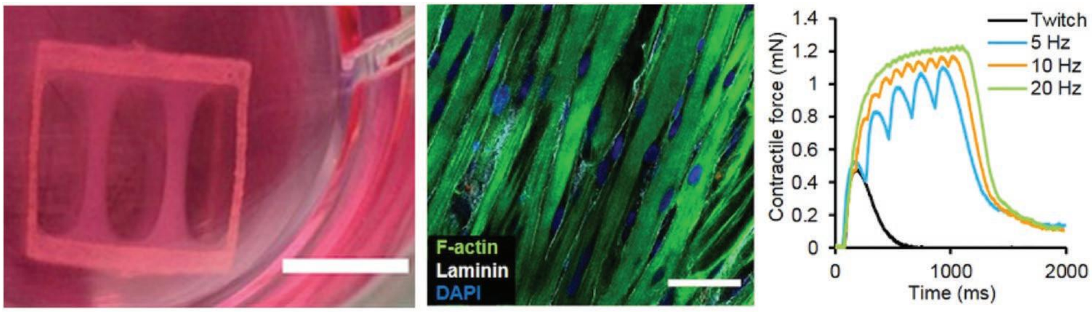

Figure 2.15 **Left** – 3D fibrin matrix hydrogel system with human derived skeletal muscle cells; **middle** – immuno-cytology image of the mature myotubes in the 3D muscle construct demonstrating aligned myotubes with actin filaments, surrounding a laminin ECM and myonuclei (DAPI stained); **right** – contractile force produced after various electrical stimulation twitches of varying frequencies. All images are taken from Madden L, et al. 2021 (102) as an open access (Attribution 4.0 International -CC BY 4.0 https://creativecommons.org/licenses/by/4.0/) article in *Elife* where permissions are not required provided the work is properly cited.

subject to electrical stimulation and demonstrated relevant twitch and tetanic contractions (**Figure 2.15**), as well as functional and mature acetylcholine receptors and even hypertrophy following administration of anabolic agents.

In summary, cells can be isolated from biopsies and used in culture systems to mimic exercise stimuli. These can serve as useful tools to investigate mechanisms of skeletal muscle adaptation in highly controlled laboratory conditions. The research question, the type of *in-vitro* model and whether the results are relevant to human exercise *in-vivo* should be considered when using these types of cell models in exercise studies. *In-vitro* systems that can simultaneously electrically stimulate and mechanically load to represent both the stimuli of muscle contraction and lengthening's are likely to continue in their development in the near future (13).

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However, there are reasons to be optimistic. Advances in the human genome sequence (www.ncbi.nlm.nih.gov/Genbank or www.ebi.ac.uk.embl), DNA sequence variability (www.1000.genomes.org), the structure and functions of noncoding DNA (ENCODE) (www.encodeproject.org), the role of genotype on tissue specific gene expression (GTEx) (https://commonfund.nih.gov/gtex), high-throughput technologies, GWASs with large panels of SNPs, gene expression profiling, DNA methylation and histone profiling, and screening of the proteome and metabolome are giving more fire power to the efforts aimed at understanding the connection between genotype and phenotype. Moreover, computational biology and bioinformatics combined with the availability of online genomic resources provided by non-profit scientifically driven organizations are improving the odds of success to a considerable extent. The task is gigantic, which we did not realize in the beginning, but there are reasons to believe that progress is possible.

Review questions

- Explain why is it useful to study the heritability of exercise-related traits?
- Describe the central dogma of molecular biology and its relevance in the response to acute exercise and when adapting to the demands of exercise training.
- Describe what types of DNA sequence variants can potentially influence exercise capacity?
- Discuss the limitations of using genetic testing for talent identification and sports performance.

Further reading

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such as the myostatin IVS1+5 G→A allele. It is currently unclear how much of the muscle mass and strength variation in human populations is due to common polymorphisms and rare DNA sequence variants. Transgenic mouse models and inbred mouse strains show that the variation of muscle mass and strength depends on DNA sequence variants that affect the number of muscle fibres within a given muscle and on the size of muscle fibres. Also, mouse studies demonstrate that a combination of gain- or loss-of-function mutations can increase muscle mass at least 4-fold compared to wildtype mice. Key candidate genes are found within the PKB/Akt-mTOR and myostatin-Smad signal transduction pathways which have also been implicated in the adaptation to resistance exercise, covered in Chapter **8**. GWAS and NGS studies are now beginning to be performed for muscle phenotypes that will further advance our understanding in the coming years.

REVIEW QUESTIONS

- Draw a diagram to illustrate what factors limit muscle mass and strength. Ensure to include common and rare DNA sequence variations as one of the causative factors.
- Discuss what is known about the heritability of human muscle size and strength?
- Describe the discovery of the *ACTN3* R577X polymorphism. Can an *ACTN3* R577X genetic test alone be used to identify, with good likelihood, someone who has the potential to become a world class sprinter?
- Describe the experimental strategy that researchers have used to identify a mutation in the myostatin gene as a rare DNA sequence variation responsible for doubling muscle mass in a toddler.
- Explain and compare two transgenic mouse models where a transgene in either the PKB/Akt-mTOR or myostatin-Smad pathway has increased muscle size. What is the maximal muscle size increase that has been achieved in a transgenic mouse model when compared to the wildtype (controls)?
- How do GWASs and NGS studies improve our ability to identify DNA sequence variants related to muscle mass and strength?

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divergent exercise types.

- Critically appraise the exercise mimetic concept as it pertains to molecular exercise physiology and likelihood of delivering meaningful health impacts to patients with lifestyle-related chronic disease.

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increases myofibrillar protein synthesis and breakdown. Myofibrillar protein balance will only become positive when sufficient essential amino acids are ingested. Resistance exercise and leucine-rich amino acids lead to the activation of the mTORC1 pathway, which then increases the translational activity of the cell by targeting proteins that increase the rate of initiation and elongation. The translational capacity is also increased by prolonged activation of mTORC1 through the production of new ribosomes. The mTORC1 pathway integrates the input of several positive signals, including hormones, such as IGF-I and insulin, resistance exercise and essential amino acids. Additionally, mTORC1 can be inhibited by catabolic pathways, including AMPK, which is activated by acute endurance exercise, a caloric deficit and low glycogen. Myostatin inhibits muscle growth by decreasing myofibrillar protein synthesis and increasing degradation. Both of these effects could be mediated through the Smad2/3-dependent inhibition of PIP3/Akt signalling. A decrease in Akt signalling would decrease hormonal activation of mTORC1 and increase the activity of FoxO resulting in a decrease in protein synthesis and an increase in degradation, respectively. Following resistance exercise, myostatin-Smad2/3 activity is decreased in the exercised muscle because of the cleavage and activation of notch, a transmembrane protein that can block Smad2/3 activity. Satellite cells are the resident stem cells of skeletal muscle. They express Pax7 and are normally quiescent in uninjured skeletal muscle. With a growth- or injury-stimulus, satellite cells become activated, express MyoD, proliferate until sufficient cell mass is created, and then either turn on myogenin and differentiate or turn off MyoD and return to quiescence, a process called self-renewal. Satellite cells are not essential for hypertrophy of small muscle fibres (like those found in rodents) but are perhaps more important in the hypertrophy of larger fibres (like those found in humans), and for regenerating a skeletal muscle after injury. The force produced by the extra motor proteins added during muscle hypertrophy needs to be transferred to the bone through matrix proteins such as collagen and these proteins are required for the increase in strength with resistance exercise.

REVIEW QUESTIONS

- What is known about the effects of resistance exercise on myofibrillar protein synthesis?
- Discuss the evidence for the hypothesis that mTORC1 is a key mediator of the protein synthesis response to resistance exercise and other forms of skeletal muscle overload.
- Explain how mTORC1 regulates protein synthesis.
- Discuss the evidence that myostatin is a key regulator of the muscle growth adaptation to resistance exercise.
- Describe how myostatin-Smad2/3 activity is inhibited in muscles following resistance exercise.
- Explain what satellite cells are.
- Compare and contrast the function of Pax7 and MyoD in relation to satellite cells.
- Describe the ‘myonuclear domain hypothesis’ and discuss whether it has been experimentally confirmed.
- Discuss whether satellite cells are required for skeletal muscle hypertrophy and regeneration after muscle injury.

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the mitochondria and therefore the replication of mitochondrial DNA. PGC-1α, together with ERRα, drives the expression of VEGF, which results in the formation of new capillaries after exercise.

REVIEW QUESTIONS

- Describe and explain the strategy you would recommend for the prescription of an endurance training programme which takes the variation in trainability into account.
- Give an example for and explain a signal transduction pathway that regulates physiological (athlete's heart) and pathological cardiac hypertrophy (hypertrophic cardiomyopathy).
- Compare and contrast type I, IIa, IIx and IIb muscle fibres. What is special about IIb fibres? What is the effect of endurance exercise on fibre-type percentages?
- Describe the arguments for and against the hypothesis that the calcineurin pathway is a major regulator of fibre type.
- Explain and discuss mechanisms that may contribute to the on/off regulation of myosin heavy chain isoforms in skeletal muscle.
- Discuss how endurance exercise stimulates mitochondrial biogenesis.
- Explain how an increased energy turnover, changed oxygen levels and increased blood flow may stimulate capillary growth in response to endurance exercise.

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3. Explain the molecular processes regulating mTORC1 activity in response to amino acid ingestion.
4. Critically evaluate the role of macronutrient availability (with specific emphasis on CHO and fat) in regulating training-induced oxidative adaptations in skeletal muscle.

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5. How might altitude affect the circadian clock?

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circulating nutrients and amino acids, resulting in energy and amino acid deficits for other tissues such as the skeletal muscle mass (117). Mathematical modelling of tumour energy costs in metastatic settings suggests that the high glucose turnover resulting from anaerobic metabolism can result in cachexia. Second, tumour cells secrete numerous catabolic factors. These may lower muscle protein synthesis and activate proteolysis in skeletal muscle, both through the ubiquitin-proteasome system and through autophagy (118). Different cytokines and pro-inflammatory molecules, generated through tumour-immune system interactions, leads to an increase in circulating stress hormones (e.g. adrenalin, cortisol and glucagon), which results in increased resistance towards insulin and other growth factors in muscle and therefore impaired anabolism (119, 120). Furthermore, transcription of autophagy- and ubiquitin-proteasome system related genes are directly activated by several pro-inflammatory factors originating from the tumour, immune cells or both (118). Also, the low circulating levels of amino acids, as a result of the high tumour uptake, may further activate muscle protein breakdown (121, 122). In summary, immune cell-tumour cell interactions leads to lowered muscle protein synthesis and increased muscle protein breakdown (**see Chapters 7 and 8**), resulting in body weight loss specifically caused by loss of skeletal muscle mass.

From a clinical perspective, it is still unknown whether exercise may counteract or prevent cancer cachexia in patients. A 2021 Cochrane review by Grande and co-workers only identified four clinical trials evaluating the effect of exercise in cachexic settings (123). The authors conclude that together these four studies offer minimal information on the effectiveness, acceptability and safety of exercise in these settings and that the body of evidence is shallow with a high risk of bias. There are, however, studies underway at the moment that may help shed more light on this area in the future.

SUMMARY

Cancer is one of the leading causes of death in the Western world. Due to improvements in early detection and treatment, relapse-free survival is improving for several cancer forms. Nevertheless, cancer treatment is still associated with troublesome side-effects and late effects (i.e. "side-effects" occurring or persisting beyond a year after completing treatment).

Exercise may reduce the risk of developing several cancers. Emerging evidence from preclinical studies have improved our understanding of the potential role of exercise in risk of cancer incidence. These mechanisms include improved genomic control and increased cancer cell apoptosis, improved tumour vascularisation and reduced tumour hypoxia, altered cancer cell metabolism, and improved immune detection. Exercise may also improve the circulatory environment, in terms of lower levels of stimulating hormones and growth factors. Furthermore, exercise is a valuable strategy during cancer treatment, as it may help relieve the symptom burden (i.e. less cancer-related fatigue and improved QoL) and help patients maintain their physical function. In addition, exercise prior to cancer treatment (i.e. prehabilitation) may help prepare patients for major cancer surgery. Thus, exercise plays an important role in all phases of the cancer continuum.

REVIEW QUESTIONS

1. What is cancer, and how does it occur?
2. What are the most common ways of treating cancer?
3. In which way may exercise reduce the risk of developing cancer?
4. In which way may exercise improve the effects of intravenously administrated anti-cancer therapies?
5. How can exercise help cancer patients going through treatment?
6. What is the potential effect of exercise in cancer cachexia, and what do we know from clinical research in this area?

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REVIEW QUESTIONS

- Describe what satellite cells are and explain their function during muscle adaptation.
- Describe the molecular regulation of myogenesis.
- Explain and discuss how satellite cells respond both acutely and chronically to resistance and endurance exercise.
- Discuss the important (or not important) role of satellite cells in muscle hypertrophy.
- Describe and discuss the differences in satellite cell function as a result of ageing and exercise.

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