

References

- Amin, P.B., Diebel, L.N. and Liberati, D.M. (2008) The synergistic effect of ethanol and shock insults on Caco-2 cytokine production and apoptosis. *Shock* 29, 631–635.
- Arbabi, S., García, I., Bauer, G.J. and Maier, R.V. (1999) Alcohol (ethanol) inhibits IL-8 and TNF: role of the p38 pathway. *Journal of Immunology* 162, 7441–7445.
- Bird, M.D., Choudhry, M.A., Molina, P.E. and Kovacs, E.J. (2009) Alcohol and trauma: a summary of the Satellite Symposium at the 30th Annual Meeting of the Shock Society. *Alcohol* 43, 247–252.
- Bird, M.D., Morgan, M.O., Ramirez, L., Yong, S. and Kovacs, E.J. (2010a) Decreased pulmonary inflammation after ethanol exposure and burn injury in intercellular adhesion molecule-1 knockout mice. *Journal of Burn Care Research* 31, 652–660.
- Bird, M.D., Zahs, A., Deburghgraeve, C., Ramirez, L., Choudhry, M.A., et al. (2010b) Decreased pulmonary inflammation following ethanol and burn injury in mice deficient in TLR4 but not TLR2 signaling. *Alcoholism: Clinical and Experimental Research* 34, 1733–1741.
- Boe, D.M., Nelson, S., Zhang, P., Quinton, L. and Bagby, G.J. (2003) Alcohol-induced suppression of lung chemokine production and the host defense response to *Streptococcus pneumoniae*. *Alcoholism: Clinical and Experimental Research* 27, 1838–1845.
- Boe, D.M., Vandivier, R.W., Burnham, E.L. and Moss, M. (2009) Alcohol abuse and pulmonary disease. *Journal of Leukocyte Biology* 86, 1097–1104.
- Bone, R.C. (1996) Sir Isaac Newton, sepsis, SIRS, and CARS. *Critical Care Medicine* 24, 1125–1128.
- Callaci, J.J., Juknalis, D., Patwardhan, A., Sartori, M., Frost, N., et al. (2004) The effects of binge alcohol exposure on bone resorption and biomechanical and structural properties are offset by concurrent bisphosphonate treatment. *Alcoholism: Clinical and Experimental Research* 28, 182–191.
- Cao, Q., Mak, K.M. and Lieber, C.S. (2002) Dilinoleoylphosphatidylcholine decreases LPS-induced TNF α generation in Kupffer cells of ethanol-fed rats: respective roles of MAPKs and NF- κ B. *Biochemical and Biophysical Research Communications* 294, 849–853.
- Centers for Disease Control (2011) Alcohol and Public Health [Online]. Available at: <http://www.cdc.gov/alcohol/> (accessed 1 April 2011).
- Choudhry, M.A., Fazal, N., Goto, M., Gamelli, R.L. and Sayeed, M.M. (2002) Gut-associated lymphoid T cell suppression enhances bacterial translocation in alcohol and burn injury. *American Journal of Physiology—Gastrointestinal and Liver Physiology* 282, G937–G947.
- Cook, R.T., Schlueter, A.J., Coleman, R.A., Tygrett, L., Ballas, Z.K., et al. (2007) Thymocytes, pre-B cells, and organ changes in a mouse model of chronic ethanol ingestion—absence of subset-specific glucocorticoid-induced immune cell loss. *Alcoholism: Clinical and Experimental Research* 31, 1746–1758.
- D'souza El-Guindy, N.B., Kovacs, E.J., De Witte, P., Spies, C., Littleton, J.M., et al. (2010) Laboratory models available to study alcohol-induced organ damage and immune variations: choosing the appropriate model. *Alcoholism: Clinical and Experimental Research* 34, 1489–1511.
- Dai, Q. and Pruett, S.B. (2006) Ethanol suppresses LPS-induced Toll-like receptor 4 clustering, reorganization of the actin cytoskeleton, and associated TNF-alpha production. *Alcoholism: Clinical and Experimental Research* 30, 1436–1444.
- Dai, Q., Zhang, J. and Pruett, S.B. (2005) Ethanol alters cellular activation and CD14 partitioning in lipid rafts. *Biochemical and Biophysical Research Communications* 332, 37–42.
- Diebel, L.N., Liberati, D.M., Dulchavsky, S.A., Diglio, C.A. and Brown, W.J. (2002) Ethanol impairs intestinal barrier defense by modulation of immunoglobulin A transport. *Surgery* 132, 573–581; discussion 581.
- Dolganiciuc, A., Kodys, K., Kopasz, A., Marshall, C., Mandrekar, P., et al. (2003) Additive inhibition of dendritic cell allostimulatory capacity by alcohol and hepatitis C is not restored by DC maturation and involves abnormal IL-10 and IL-2 induction. *Alcoholism: Clinical and Experimental Research* 27, 1023–1031.
- Dolganiciuc, A., Bakis, G., Kodys, K., Mandrekar, P. and Szabo, G. (2006) Acute ethanol treatment modulates Toll-like receptor-4 association with lipid rafts. *Alcoholism: Clinical and Experimental Research* 30, 76–85.
- Driscoll, T.R., Harrison, J.A. and Steenkamp, M. (2004) Review of the role of alcohol in drowning associated with recreational aquatic activity. *Injury Prevention* 10, 107–113.
- Esper, A., Burnham, E.L. and Moss, M. (2006) The effect of alcohol abuse on ARDS and multiple organ dysfunction. *Minerva Anestesiologica* 72, 375–381.
- Fitzgerald, K.A., Rowe, D.C. and Golenbock, D.T. (2004) Endotoxin recognition and signal transduction by the TLR4/MD2-complex. *Microbes and Infection* 6, 1361–1367.
- Fukui, H., Brauner, B., Bode, J.C. and Bode, C. (1991) Plasma endotoxin concentrations in patients with alcoholic and

- non-alcoholic liver disease: reevaluation with an improved chromogenic assay. *Journal of Hepatology* 12, 162–169.
- Goral, J. and Kovacs, E.J. (2005) In vivo ethanol exposure down-regulates TLR2-, TLR4-, and TLR9- mediated macrophage inflammatory response by limiting p38 and ERK1/2 activation. *Journal of Immunology* 174, 456–463.
- Goral, J., Choudhry, M.A. and Kovacs, E.J. (2004) Acute ethanol exposure inhibits macrophage IL-6 production: role of p38 and ERK1/2 MAPK. *Journal of Leukocyte Biology* 75, 553–559.
- Goral, J., Karavitis, J. and Kovacs, E.J. (2008) Exposure-dependent effects of ethanol on the innate immune system. *Alcohol* 42, 237–247.
- Greiffenstein, P., Mathis, K.W., Stouwe, C.V. and Molina, P.E. (2007) Alcohol binge before trauma/hemorrhage impairs integrity of host defense mechanisms during recovery. *Alcoholism: Clinical and Experimental Research* 31, 704–715.
- Hancock, J.F. (2006) Lipid rafts: contentious only from simplistic standpoints. *Nature Reviews Molecular Cell Biology*, 7, 456–462.
- Hanna, E.Z., Chou, S.P. and Grant, B.F. (1997) The relationship between drinking and heart disease morbidity in the United States: results from the National Health Interview Survey. *Alcoholism: Clinical and Experimental Research*, 21, 111–118.
- He, H.T., Lellouch, A. and Marguet, D. (2005) Lipid rafts and the initiation of T cell receptor signaling. *Seminars in Immunology* 17, 23–33.
- Hines, I.N. and Wheeler, M.D. (2004) Recent advances in alcoholic liver disease III. Role of the innate immune response in alcoholic hepatitis. *American Journal of Physiology – Gastrointestinal and Liver Physiology* 287, G310–G314.
- Hingson, R. (2004) Advances in measurement and intervention for excessive drinking. *American Journal of Preventive Medicine* 27, 261–263.
- Hritz, I., Mandrekar, P., Velayudham, A., Catalano, D., Dolganiuc, A., et al. (2008) The critical role of tolllike receptor (TLR) 4 in alcoholic liver disease is independent of the common TLR adapter MyD88. *Hepatology* 48, 1224–1231.
- Janeway, C.A., Jr and Medzhitov, R. (2002) Innate immune recognition. *Annual Reviews of Immunology* 20, 197–216.
- Jerrells, T.R. (2002) Association of alcohol consumption and exaggerated immunopathologic effects in the liver induced by infectious organism. *Frontiers in Bioscience* 7, d1487.
- Kawai, T. and Akira, S. (2006) TLR signaling. *Cell Death and Differentiation* 13, 816–825.
- Khoruts, A., Stohnke, L., McClain, C.J., Logan, G. and Allen, J.I. (1991) Circulating tumor necrosis factor, interleukin-1 and interleukin-6 concentrations in chronic alcoholic patients. *Hepatology* 13, 267–276.
- Kishore, R., McMullen, M.R. and Nagy, L.E. (2001) Stabilization of tumor necrosis factor alpha mRNA by chronic ethanol: role of A + U-rich elements and p38 mitogen-activated protein kinase signaling pathway. *Journal of Biological Chemistry* 276, 41930–41937.
- Kishore, R., Hill, J.R., McMullen, M.R., Frenkel, J. and Nagy, L.E. (2002) ERK1/2 and Egr-1 contribute to increased TNF-alpha production in rat Kupffer cells after chronic ethanol feeding. *American Journal of Physiology– Gastrointestinal and Liver Physiology* 282, G6–G15.
- Kishore, R., McMullen, M.R., Cocuzzi, E. and Nagy, L.E. (2004) Lipopolysaccharide-mediated signal transduction: Stabilization of TNF-alpha mRNA contributes to increased lipopolysaccharide-stimulated TNF-alpha production by Kupffer cells after chronic ethanol feeding. *Comparative Hepatology* 3 Suppl 1, S31.
- Kolls, J.K., Xie, J., Lei, D., Greenberg, S., Summer, W.R., et al. (1995) Differential effects of in vivo ethanol on LPS-induced TNF and nitric oxide production in the lung. *American Journal of Physiology* 268, L991–L998.
- Lieber, C.S. and Decarli, L.M. (1976) Animal models of ethanol dependence and liver injury in rats and baboons. *Federation Proceedings* 35, 1232–1236.
- Machida, K., Tsukamoto, H., Mkrtchyan, H., Duñan, L., Dynnyk, A., et al. (2009) Toll-like receptor 4 mediates synergism between alcohol and HCV in hepatic oncogenesis involving stem cell marker Nanog. *Proceedings of the National Academy of Sciences of the United States of America* 106, 1548–1553.
- Magnotti, L.J. and Deitch, E.A. (2005) Burns, bacterial translocation, gut barrier function, and failure. *Journal of Burn Care and Rehabilitation* 26, 383–391.
- Mandal, P., Pritchard, M.T. and Nagy, L.E. (2010) Anti-inflammatory pathways and alcoholic liver disease: role of an adiponectin/interleukin-10/heme oxygenase-1 pathway. *World Journal of Gastroenterology* 16, 1330–1336.
- Mandrekar, P. and Szabo, G. (2009) Signalling pathways in alcohol-induced liver inflammation. *Journal of Hepatology* 50, 1258–1266.
- Mandrekar, P., Catalano, D. and Szabo, G. (1999) Inhibition of lipopolysaccharide-mediated NFκB activation by ethanol in human monocytes. *International Immunology*, 11, 1781–1790.
- Mandrekar, P., Catalano, D., Dolganiuc, A., Kodys, K. and Szabo, G. (2004) Inhibition of myeloid dendritic cell accessory cell function and induction of T cell anergy by alcohol correlates with decreased IL-12 production. *Journal of Immunology* 173, 3398–3407.
- Mandrekar, P., Jeliazkova, V., Catalano, D. and Szabo, G. (2007) Acute alcohol exposure exerts anti-inflammatory ef-

- fects by inhibiting IkappaB kinase activity and p65 phosphorylation in human monocytes. *Journal of Immunology*, 178, 7686–7693.
- McClain, C., Hill, D., Schmidt, J. and Diehl, A.M. (1993) Cytokines and alcoholic liver disease. *Seminars in Liver Disease* 13, 170–182.
- McClain, C.J., Barve, S., Deaciuc, I., Kugelmas, M. and Hill, D. (1999) Cytokines in alcoholic liver disease. *Seminars in Liver Disease* 19, 205–219.
- McDonald, A.J., 3rd, Wang, N. and Camargo, C.A., Jr (2004) US emergency department visits for alcoholrelated diseases and injuries between 1992 and 2000. *Archives of Internal Medicine* 164, 531–537.
- Mokdad, A.H., Marks, J.S., Stroup, D.F. and Gerberding, J.L. (2004) Actual causes of death in the United States, 2000. *Journal of the American Medical Association* 291, 1238–1245.
- Molina, P.E., Zambell, K.L., Norenberg, K., Eason, J., Phelan, H., et al. (2004) Consequences of alcoholinduced early dysregulation of responses to trauma/hemorrhage. *Alcohol* 33, 217–227.
- Moss, M., Steinberg, K.P., Guidot, D.M., Duhon, G.F., Treece, P., et al. (1999) The effect of chronic alcohol abuse on the incidence of ARDS and the severity of the multiple organ dysfunction syndrome in adults with septic shock: an interim and multivariate analysis. *Chest* 116, 97S–98S.
- Moss, M., Guidot, D.M., Wong-Lambertina, M., Ten Hoor, T., Perez, R.L., et al. (2000) The effects of chronic alcohol abuse on pulmonary glutathione homeostasis. *American Journal of Respiratory and Critical Care Medicine*, 161, 414–419.
- Murphy, T.J., Paterson, H.M., Mannick, J.A. and Lederer, J.A. (2004) Injury, sepsis, and the regulation of Toll-like receptor responses. *Journal of Leukocyte Biology* 75, 400–407.
- Nagy, L.E. (2003) Recent insights into the role of the innate immune system in the development of alcoholic liver disease. *Experimental Biology and Medicine (Maywood)* 228, 882–890. Nagy, L.E. (ed) (2008) *Alcohol: Methods and Protocols*. Humana Press, New Jersey.
- Nelson, S. and Kolls, J.K. (2002) Alcohol, host defence and society. *Nature Reviews in Immunology* 2, 205–209.
- Nelson, S., Bagby, G.J., Bainton, B.G. and Summer, W.R. (1989) The effects of acute and chronic alcoholism on tumor necrosis factor and the inflammatory response. *Journal of Infectious Disease* 160, 422–429.
- Oak, S., Mandrekar, P., Catalano, D., Kodys, K. and Szabo, G. (2006) TLR2- and TLR4-mediated signals determine attenuation or augmentation of inflammation by acute alcohol in monocytes. *Journal of Immunology* 176, 7628–7635.
- Omidvari, K., Casey, R., Nelson, S., Olariu, R. and Shellito, J.E. (1998) Alveolar macrophage release of tumor necrosis factor-alpha in chronic alcoholics without liver disease. *Alcoholism: Clinical and Experimental Research* 22, 567–572.
- Osborne, D.L., Aw, T.Y., Cepinskas, G. and Kvietys, P.R. (1994) Development of ischemia/reperfusion tolerance in the rat small intestine. An epithelium-independent event. *Journal of Clinical Investigation* 94, 1910–1918.
- Peters, T.J. and Preedy, V.R. (1998) Metabolic consequences of alcohol ingestion. *Novartis Foundation Symposium* 216, 19–24; discussion 24–34.
- Phelan, H., Stahls, P., Hunt, J., Bagby, G.J. and Molina, P.E. (2002) Impact of alcohol intoxication on hemodynamic, metabolic, and cytokine responses to hemorrhagic shock. *Journal of Trauma* 52, 675–682.
- Pike, L.J. (2003) Lipid rafts: bringing order to chaos. *Journal of Lipid Research* 44, 655–67.
- Plackett, T.P. and Kovacs, E.J. (2008) Acute models of ethanol exposure to mice. *Methods in Molecular Biology* 447, 3–9.
- Pruett, S.B., Zheng, Q., Fan, R., Matthews, K. and Schwab, C. (2004) Acute exposure to ethanol affects Toll-like receptor signaling and subsequent responses: an overview of recent studies. *Alcohol* 33, 235–239.
- Pruett, S.B., Fan, R., Zheng, Q. and Schwab, C. (2005) Differences in IL-10 and IL-12 production patterns and differences in the effects of acute ethanol treatment on macrophages *in vivo* and *in vitro*. *Alcohol* 37, 1–8.
- Qin, L., He, J., Hanes, R.N., Pluzarev, O., Hong, J.S. and Crews, F.T. (2008) Increased systemic and brain cytokine production and neuroinflammation by endotoxin following ethanol treatment. *Journal of Neuroinflammation* 5, 10.
- Rao, R.K., Seth, A. and Sheth, P. (2004) Recent advances in alcoholic liver disease I. Role of intestinal permeability and endotoxemia in alcoholic liver disease. *American Journal of Physiology–Gastrointestinal and Liver Physiology* 286, G881–G884.
- Regev, A. and Jeffers, L.J. (1999) Hepatitis C and alcohol. *Alcoholism: Clinical and Experimental Research* 23, 1543–1551.
- Rehm, J., Gmel, G., Sempos, C.T. and Trevisan, M. (2003) Alcohol-related morbidity and mortality. *Alcohol Research and Health* 27, 39–51.
- Saeed, R.W., Varma, S., Peng, T., Tracey, K.J., Sherry, B., et al. (2004) Ethanol blocks leukocyte recruitment and endothelial cell activation *in vivo* and *in vitro*. *Journal of Immunology* 173, 6376–6383.
- Schermer, C.R. (2006) Alcohol and injury prevention. *Journal of Trauma* 60, 447–451.
- Standiford, T.J. and Danforth, J.M. (1997) Ethanol feeding inhibits proinflammatory cytokine expression from murine alveolar macrophages *ex vivo*. *Alcoholism: Clinical and Experimental Research* 21, 1212–1217.
- Szabo, G. and Mandrekar, P. (2009) A recent perspective on alcohol, immunity, and host defense. *Alcoholism: Clinical and Experimental Research* 33, 220–232.

- Szabo, G., Mandrekar, P., Dolganic, A., Catalano, D. and Kodys, K. (2001) Reduced alloreactive T-cell activation after alcohol intake is due to impaired monocyte accessory cell function and correlates with elevated IL-10, IL-13, and decreased IFN γ levels. *Alcoholism: Clinical and Experimental Research* 25, 1766–1772.
- Szabo, G., Dolganic, A., Dai, Q. and Pruitt, S.B. (2007) TLR4, ethanol, and lipid rafts: a new mechanism of ethanol action with implications for other receptor-mediated effects. *Journal of Immunology* 178, 1243–1249.
- Szabo, G., Mandrekar, P., Petrasek, J. and Catalano, D. (2011) The unfolding web of innate immune dysregulation in alcoholic liver injury. *Alcoholism: Clinical and Experimental Research* 35, 782–786.
- Takeda, K., Kaisho, T. and Akira, S. (2003) Toll-like receptors. *Annual Reviews of Immunology* 21, 335–376.
- Thakur, V., Pritchard, M.T., McMullen, M.R., Wang, Q. and Nagy, L.E. (2006) Chronic ethanol feeding increases activation of NADPH oxidase by lipopolysaccharide in rat Kupffer cells: role of increased reactive oxygen in LPS-stimulated ERK1/2 activation and TNF- α production. *Journal of Leukocyte Biology* 79, 1348–1356.
- Thurman, R.G., Bradford, B.U., Iimuro, Y., Knecht, K.T., Arteel, G.E., et al. (1998) The role of gut-derived bacterial toxins and free radicals in alcohol-induced liver injury. *Journal of Gastroenterology and Hepatology* 13 Suppl, S39–S50.
- US Department of Health and Human Services and US Department of Agriculture (2010) Dietary Guidelines for Americans, 7th edn. Government Printing Office, Washington, DC.
- Uesugi, T., Froh, M., Arteel, G.E., Bradford, B.U. and Thurman, R.G. (2001) Toll-like receptor 4 is involved in the mechanism of early alcohol-induced liver injury in mice. *Hepatology* 34, 101–108.
- Wang, H.J., Zakhari, S. and Jung, M.K. (2010) Alcohol, inflammation, and gut-liver-brain interactions in tissue damage and disease development. *World Journal of Gastroenterology* 16, 1304–1313.
- World Health Organization (2010) Global Strategy to Reduce the Harmful Use of Alcohol. WHO Press, Geneva, Switzerland.
- Wu, D. and Cederbaum, A.I. (2009) Oxidative stress and alcoholic liver disease. *Seminars in Liver Disease* 29, 141–154.
- Yin, M., Bradford, B.U., Wheeler, M.D., Uesugi, T., Froh, M., et al. (2001) Reduced early alcohol-induced liver injury in CD14-deficient mice. *Journal of Immunology* 166, 4737–4742.
- Zambell, K.L., Phelan, H., Vande Stouwe, C., Zhang, P., Shellito, J.E., et al. (2004) Acute alcohol intoxication during hemorrhagic shock: impact on host defense from infection. *Alcoholism: Clinical and Experimental Research* 28, 635–642.
- Zhong, P., Nelson, S., Summer, W.R. and Spitzer, J.A. (1997) Acute ethanol intoxication suppresses the pulmonary inflammatory response in rats challenged with intrapulmonary endotoxin. *Alcoholism: Clinical and Experimental Research* 21, 773–778.
- Abe, E., Miyaura, C., Sakagami, H., Takeda, M., Konno, K., et al. (1981) Differentiation of mouse myeloid leukemia cells induced by 1 α ,25-dihydroxyvitamin D3. *Proceedings of the National Academy of Sciences of the United States of America* 78, 4990–4994.
- Abe, E., Miyaura, C., Tanaka, H., Shiina, Y., Kuribayashi, T., et al. (1983) 1 α ,25-dihydroxyvitamin D3 promotes fusion of mouse alveolar macrophages both by a direct mechanism and by a spleen cell-mediated indirect mechanism. *Proceedings of the National Academy of Sciences of the United States of America* 80, 5583–5587.
- Adams, J.S. and Gacad, M.A. (1985) Characterization of 1 α -hydroxylation of vitamin D3 sterols by cultured alveolar macrophages from patients with sarcoidosis. *The Journal of Experimental Medicine* 161, 755–765.
- Adams, J.S., Sharma, O.P., Gacad, M.A. and Singer, F.R. (1983) Metabolism of 25-hydroxyvitamin D3 by cultured pulmonary alveolar macrophages in sarcoidosis. *The Journal of Clinical Investigation* 72, 1856–1860.
- Adams, J.S., Singer, F.R., Gacad, M.A., Sharma, O.P., Hayes, M.J., et al. (1985) Isolation and structural identification of 1,25-dihydroxyvitamin D3 produced by cultured alveolar macrophages in sarcoidosis. *Journal of Clinical Endocrinology and Metabolism* 60, 960–966.
- Almerighi, C., Sinistro, A., Cavazza, A., Ciaprini, C., Rocchi, G., et al. (2009) 1Alpha,25-dihydroxyvitamin D3 inhibits CD40L-induced pro-inflammatory and immunomodulatory activity in human monocytes. *Cytokine* 45, 190–197.
- Alroy, I., Towers, T.L. and Freedman, L.P. (1995) Transcriptional repression of the interleukin-2 gene by vitamin D3: direct inhibition of NFATp/AP-1 complex formation by a nuclear hormone receptor. *Molecular and Cellular Biochemistry* 15, 5789–5799.
- Baeke, F., Korf, H., Overbergh, L., van, E.E., Verstuyf, A., et al. (2010) Human T lymphocytes are direct targets of 1,25-dihydroxyvitamin D3 in the immune system. *Journal of Steroid Biochemistry and Molecular Biology* 121, 221–227.
- Baeke, F., Korf, H., Overbergh, L., Verstuyf, A., Thorrez, L., et al. (2011) The vitamin D analog, TX527, promotes a human CD4+CD25highCD127low regulatory T cell profile and induces a migratory signature specific for homing to sites of inflammation. *The Journal of Immunology* 186, 132–142.
- Baird, G.L., Coburn, J.W., Slatopolsky, E., Norman, A.W. and Horst, R.L. (1981) Hypercalcemia in an anephric patient with sarcoidosis: evidence for extrarenal generation of 1,25-dihydroxyvitamin D. *New England Journal of Medicine* 305, 440–443.
- Burger-Lux, M.J., Heaney, R.P., Dowell, S., Chen, T.C. and Holick, M.F. (1998) Vitamin D and its major metabolites: serum levels after graded oral dosing in healthy men. *Osteoporosis International* 8, 222–230.
- Barnes, M.S., Horigan, G., Cashman, K.D., Hill, T.R., Forsythe, L.K., et al. (2011) Maintenance of wintertime vitamin

- D status with cholecalciferol supplementation is not associated with alterations in serum cytokine concentrations among apparently healthy younger or older adults. *The Journal of Nutrition* 141, 476–481.
- Barrat, F.J., Cua, D.J., Boonstra, A., Richards, D.F., Crain, C., et al. (2002) In vitro generation of interleukin 10-producing regulatory CD4(+) T cells is induced by immunosuppressive drugs and inhibited by T helper type 1 (Th1)- and Th2-inducing cytokines. *The Journal of Experimental Medicine* 195, 603–616.
- Bartels, L.E., Jorgensen, S.P., Agnholt, J., Kelsen, J., Hvas, C.L., et al. (2007) 1,25-dihydroxyvitamin D3 and dexamethasone increase interleukin-10 production in CD4+ T cells from patients with Crohn's disease. *International Immunopharmacology* 7, 1755–1764.
- Bell, N.H., Stern, P.H., Pantzer, E., Sinha, T.K. and DeLuca, H.F. (1979) Evidence that increased circulating 1 alpha, 25-dihydroxyvitamin D is the probable cause for abnormal calcium metabolism in sarcoidosis. *The Journal of Clinical Investigation* 64, 218–225.
- Bellia, A., Garcovich, C., D'Adamo, M., Lombardo, M., Tesuero, M., et al. (2011) Serum 25-hydroxyvitamin D levels are inversely associated with systemic inflammation in severe obese subjects. *Internal and Emergency Medicine* DOI: 10.1007/s11739-011-0559-x.
- Berg, A.H. and Scherer, P.E. (2005) Adipose tissue, inflammation, and cardiovascular disease. *Circulation Research* 96, 939–949.
- Bhalla, A.K., Amento, E.P., Clemens, T.L., Holick, M.F. and Krane, S.M. (1983) Specific high-affinity receptors for 1,25-dihydroxyvitamin D3 in human peripheral blood mononuclear cells: presence in monocytes and induction in T lymphocytes following activation. *Journal of Clinical Endocrinology and Metabolism* 57, 1308–1310.
- Bhalla, A.K., Amento, E.P., Serog, B. and Glimcher, L.H. (1984) 1,25-Dihydroxyvitamin D3 inhibits antigeninduced T cell activation. *The Journal of Immunology* 133, 1748–1754.
- Bhalla, A.K., Amento, E.P. and Krane, S.M. (1986) Differential effects of 1,25-dihydroxyvitamin D3 on human lymphocytes and monocyte/macrophages: inhibition of interleukin-2 and augmentation of interleukin-1 production. *Cellular Immunology* 98, 311–322.
- Boonstra, A., Barrat, F.J., Crain, C., Heath, V.L., Savelkoul, H.F., et al. (2001) 1alpha,25-Dihydroxyvitamin d3 has a direct effect on naive CD4(+) T cells to enhance the development of Th2 cells. *The Journal of Immunology* 167, 4974–4980.
- Chen, S., Sims, G.P., Chen, X.X., Gu, Y.Y., Chen, S., et al. (2007) Modulatory effects of 1,25-dihydroxyvitamin D3 on human B cell differentiation. *The Journal of Immunology* 179, 1634–1647.
- Cippitelli, M. and Santoni, A. (1998) Vitamin D3: a transcriptional modulator of the interferon-gamma gene. *European Journal of Immunology* 28, 3017–3030.
- Colin, E.M., Asmawidjaja, P.S., van Hamburg, J.P., Mus, A.M., van, D.M., et al. (2010) 1,25-dihydroxyvitamin D3 modulates Th17 polarization and interleukin-22 expression by memory T cells from patients with early rheumatoid arthritis. *Arthritis and Rheumatism* 62, 132–142.
- Colston, K., Colston, M.J. and Feldman, D. (1981) 1,25-dihydroxyvitamin D3 and malignant melanoma: the presence of receptors and inhibition of cell growth in culture. *Endocrinology* 108, 1083–1086.
- Correale, J., Ysrraelit, M.C. and Gaitan, M.I. (2009) Immunomodulatory effects of Vitamin D in multiple sclerosis. *Brain* 132, 1146–1160.
- D'Ambrosio, D., Cippitelli, M., Coccio, M.G., Mazzeo, D., Di Lucia, P., et al. (1998) Inhibition of IL-12 production by 1,25-dihydroxyvitamin D3. Involvement of NF-kappaB downregulation in transcriptional repression of the p40 gene. *The Journal of Clinical Investigation* 101, 252–262.
- Dong, X., Craig, T., Xing, N., Bachman, L.A., Paya, C.V., et al. (2003) Direct transcriptional regulation of RelB by 1alpha,25-dihydroxyvitamin D3 and its analogs: physiologic and therapeutic implications for dendritic cell function. *Journal of Biological Chemistry* 278, 49378–49385.
- Dusso, A.S., Brown, A.J. and Slatopolsky, E. (2005) Vitamin D. *American Journal of Physiology, Renal Physiology* 289, F8–F28.
- Edfeldt, K., Liu, P.T., Chun, R., Fabri, M., Schenk, M., et al. (2010) T-cell cytokines differentially control human monocyte antimicrobial responses by regulating vitamin D metabolism. *Proceedings of the National Academy of Sciences of the United States of America* 107, 22593–22598.
- Eisman, J.A., Martin, T.J., MacIntyre, I. and Moseley, J.M. (1979) 1,25-dihydroxyvitamin-D-receptor in breast cancer cells. *Lancet* 2, 1335–1336.
- Farmer, P.K., He, X., Schmitz, M.L., Rubin, J. and Nanes, M.S. (2000) Inhibitory effect of NF-kappaB on 1,25-dihydroxyvitamin D(3) and retinoid X receptor function. *American Journal of Physiology, Endocrinology and Metabolism* 279, E213–E220.
- Fritzsche, J., Mondal, K., Ehrnsperger, A., Andreesen, R. and Kreutz, M. (2003) Regulation of 25-hydroxyvitamin D3-1 alpha-hydroxylase and production of 1 alpha,25-dihydroxyvitamin D3 by human dendritic cells. *Blood* 102, 3314–3316.
- Froicu, M., Weaver, V., Wynn, T.A., McDowell, M.A., Welsh, J.E., et al. (2003) A crucial role for the vitamin D receptor in experimental inflammatory bowel diseases. *Molecular Endocrinology* 17, 2386–2392.

- Gønnægå-Yared, M.H., Azoury, M., Mansour, I., Bøddoura, R., Hølaby, G., et al. (2003) Effects of a shortterm calcium and vitamin D treatment on serum cytokines, bone markers, insulin and lipid concentrations in healthy post-menopausal women. *Journal of Endocrinological Investigations* 26, 748–753.
- Geldmeyer-Hilt, K., Heine, G., Hartmann, B., Baumgrass, R., Radbruch, A., et al. (2011) 1,25-dihydroxyvitamin D(3) impairs NF- κ B activation in human naïve B cells. *Biochemical and Biophysical Research Communications* 407, 699–702.
- Gottfried, E., Rehli, M., Hahn, J., Holler, E., Andreesen, R., et al. (2006) Monocyte-derived cells express CYP27A1 and convert vitamin D3 into its active metabolite. *Biochemical and Biophysical Research Communications* 349, 209–213.
- Gynther, P., Toropainen, S., Matilainen, J.M., Seuter, S., Carlberg, C., et al. (2011) Mechanism of 1 α ,25-dihydroxyvitamin D(3)-dependent repression of interleukin-12B. *Biochimica et Biophysica Acta* 1813, 810–818.
- Hansdottir, S., Monick, M.M., Lovan, N., Powers, L., Gerke, A., et al. (2010) Vitamin D decreases respiratory syncytial virus induction of NF- κ B-linked chemokines and cytokines in airway epithelium while maintaining the anti-viral state. *The Journal of Immunology* 184, 965–974.
- Heine, G., Niesner, U., Chang, H.D., Steinmeyer, A., Zugel, U., et al. (2008) 1,25-dihydroxyvitamin D(3) promotes IL-10 production in human B cells. *European Journal of Immunology* 38, 2210–2218.
- Hewison, M., Freeman, L., Hughes, S.V., Evans, K.N., Bland, R., et al. (2003) Differential regulation of vitamin D receptor and its ligand in human monocyte-derived dendritic cells. *The Journal of Immunology* 170, 5382–5390.
- Holick, M.F. (2007) Vitamin D deficiency. *New England Journal of Medicine* 357, 266–281.
- Iho, S., Kura, F., Sugiyama, H., Takahashi, T. and Hoshino, T. (1985) The role of monocytes in the suppression of PHA-induced proliferation and IL 2 production of human mononuclear cells by 1,25-dihydroxyvitamin D3. *Immunology Letters* 11, 331–336.
- Inanir, A., Ozoran, K., Tutkak, H. and Mermerci, B. (2004) The effects of calcitriol therapy on serum interleukin-1, interleukin-6 and tumour necrosis factor-alpha concentrations in post-menopausal patients with osteoporosis. *The Journal of International Medical Research* 32, 570–582.
- Jeffery, L.E., Burke, F., Mura, M., Zheng, Y., Qureshi, O.S., et al. (2009) 1,25-Dihydroxyvitamin D3 and IL-2 Combine to Inhibit T Cell Production of Inflammatory Cytokines and Promote Development of Regulatory T Cells Expressing CTLA-4 and FoxP3. *The Journal of Immunology* 183, 5458–5467.
- Jiang, Z., Yin, X. and Jiang, Q. (2011) Natural forms of vitamin E and 13-carboxychromanol, a long-chain vitamin E metabolite, inhibit leukotriene generation from stimulated neutrophils by blocking calcium influx and suppressing 5-lipoxygenase activity, respectively. *The Journal of Immunology* 186, 1173–1179.
- Khoo, A.L., Choi, L.Y., Koenen, H.J., Kullberg, B.J., Joosten, I., et al. (2011a) 1,25-dihydroxyvitamin D3 modulates cytokine production induced by *Candida albicans*: impact of seasonal variation of immune responses. *The Journal of Infectious Diseases* 203, 122–130.
- Khoo, A.L., Choi, L.Y., Koenen, H.J., Sweep, F.C., Joosten, I., et al. (2011b) Regulation of cytokine responses by seasonality of vitamin D status in healthy individuals. *Clinical and Experimental Immunology* 164, 72–79.
- Koeffler, H.P., Reichel, H., Bishop, J.E. and Norman, A.W. (1985) gamma-Interferon stimulates production of 1,25-dihydroxyvitamin D3 by normal human macrophages. *Biochemical and Biophysical Research Communications* 127, 596–603.
- Lappe, J.M. (2011) The role of vitamin D in human Health: a paradigm shift. *Journal of Evidence-Based Complementary and Alternative Medicine* 16, 58–72.
- Lemire, J.M., Adams, J.S., Kermani-Arab, V., Bakke, A.C., Sakai, R., et al. (1985) 1,25-Dihydroxyvitamin D3 suppresses human T helper/inducer lymphocyte activity in vitro. *The Journal of Immunology* 134, 3032–3035.
- Lysandropoulos, A.P., Jaquiere, E., Jilek, S., Pantaleo, G., Schluep, M., et al. (2011) Vitamin D has a direct immunomodulatory effect on CD8+ T cells of patients with early multiple sclerosis and healthy control subjects. *Journal of Neuroimmunology* 233, 240–244.
- Mahon, B.D., Gordon, S.A., Cruz, J., Cosman, F. and Cantorna, M.T. (2003a) Cytokine profile in patients with multiple sclerosis following vitamin D supplementation. *Journal of Neuroimmunology* 134, 128–132.
- Mahon, B.D., Wittke, A., Weaver, V. and Cantorna, M.T. (2003b) The targets of vitamin D depend on the differentiation and activation status of CD4 positive T cells. *Journal of Cellular Biochemistry* 89, 922–932.
- Manolagas, S.C., Haussler, M.R. and Deftos, L.J. (1980) 1,25-dihydroxyvitamin D3 receptors in cancer. *Lancet* 1, 828.
- Martineau, A.R., Wilkinson, K.A., Newton, S.M., Floto, R.A., Norman, A.W., et al. (2007) IFN-gamma and TNF-independent vitamin D-inducible human suppression of mycobacteria: the role of cathelicidin LL-37. *The Journal of Immunology* 178, 7190–7198.
- Matilainen, J.M., Husso, T., Toropainen, S., Seuter, S., Turunen, M.P., et al. (2010a) Primary effect of 1 α ,25(OH)D on IL-10 expression in monocytes is short-term down-regulation. *Biochimica et Biophysica Acta* 1803, 1276–1286.
- Matilainen, J.M., Rasanen, A., Gynther, P. and Vaisanen, S. (2010b) The genes encoding cytokines IL-2, IL-10 and IL-12B are primary 1 α ,25(OH)2D3 target genes. *Journal of Steroid Biochemistry and Molecular Biology* 121, 142–145.
- McCollum, E.V., Simmonds, N. and Becker, J.E. (1922) Studies on experimental rickets. XXI. An experimental demonstration of the existence of a vitamin which promotes calcium deposition. *Journal of Biological Chemistry* 53, 293–312.

- Muller, K., Diamant, M. and Bendtzen, K. (1991) Inhibition of production and function of interleukin-6 by 1,25-dihydroxyvitamin D3. *Immunology Letters* 28, 115–120.
- Muller, K., Haaahr, P.M., Diamant, M., Rieneck, K., Kharazmi, A. et al. (1992) 1,25-Dihydroxyvitamin D3 inhibits cytokine production by human blood monocytes at the post-transcriptional level. *Cytokine* 4, 506–512.
- Nemere, I., Wilson, C., Jensen, W., Steinbeck, M., Rohe, B., et al. (2006) Mechanism of 24,25-dihydroxyvitamin D3-mediated inhibition of rapid, 1,25-dihydroxyvitamin D3-induced responses: role of reactive oxygen species. *Journal of Cellular Biochemistry* 99, 1572–1581.
- Nonn, L., Peng, L., Feldman, D. and Peehl, D.M. (2006) Inhibition of p38 by vitamin D reduces interleukin-6 production in normal prostate cells via mitogen-activated protein kinase phosphatase 5: implications for prostate cancer prevention by vitamin D. *Cancer Research* 66, 4516–4524.
- Papapoulos, S.E., Clemens, T.L., Fraher, L.J., Lewin, I.G., Sandler, L.M., et al. (1979) 1, 25-dihydroxycholecalciferol in the pathogenesis of the hypercalcaemia of sarcoidosis. *Lancet* 1, 627–630.
- Peelen, E., Knippenberg, S., Muris, A.H., Thewissen, M., Smolders, J., et al. (2011) Effects of vitamin D on the peripheral adaptive immune system: A review. *Autoimmunity Reviews* 10, 733–743.
- Penna, G. and Adorini, L. (2000) 1 Alpha,25-dihydroxyvitamin D3 inhibits differentiation, maturation, activation, and survival of dendritic cells leading to impaired alloreactive T cell activation. *Journal of Immunology* 164, 2405–2411.
- Penna, G., Armuchastequi, S., Giarratana, N., Daniel, K.C., Vulcano, M., et al. (2007) 1 Alpha,25- dihydroxyvitamin D3 selectively modulates tolerogenic properties in myeloid but not plasmacytoid dendritic cells. *The Journal of Immunology* 178, 145–153.
- Prabhu, A.S., Selvaraj, P. and Narayanan, P.R. (2009) Effect of 1,25 dihydroxyvitamin D3 on intracellular IFN-gamma and TNF-alpha positive T cell subsets in pulmonary tuberculosis. *Cytokine* 45, 105–110.
- Provvedini, D.M. and Manolagas, S.C. (1989) 1 Alpha,25-dihydroxyvitamin D3 receptor distribution and effects in subpopulations of normal human T lymphocytes. *Journal of Clinical Endocrinology and Metabolism* 68, 774–779.
- Provvedini, D.M., Tsoukas, C.D., Deftoes, L.J. and Manolagas, S.C. (1983) 1,25-dihydroxyvitamin D3 receptors in human leukocytes. *Science* 221, 1181–1183.
- Reichel, H., Koeffler, H.P., Barbers, R. and Norman, A.W. (1987a) Regulation of 1,25-dihydroxyvitamin D3 production by cultured alveolar macrophages from normal human donors and from patients with pulmonary sarcoidosis. *Journal of Clinical Endocrinology and Metabolism* 65, 1201–1209.
- Reichel, H., Koeffler, H.P., Tobler, A. and Norman, A.W. (1987b) 1 alpha,25-Dihydroxyvitamin D3 inhibits gamma-interferon synthesis by normal human peripheral blood lymphocytes. *Proceedings of the National Academy of Sciences of the United States of America* 84, 3385–3389.
- Rigby, W.F. and Waugh, M.G. (1992) Decreased accessory cell function and costimulatory activity by 1,25-dihydroxyvitamin D3-treated monocytes. *Arthritis and Rheumatism* 35, 110–119.
- Rigby, W.F., Stacy, T. and Fanger, M.W. (1984) Inhibition of T lymphocyte mitogenesis by 1,25-dihydroxyvitamin D3 (calcitriol). *The Journal of Clinical Investigation* 74, 1451–1455.
- Rigby, W.F., Denome, S. and Fanger, M.W. (1987) Regulation of lymphokine production and human T lymphocyte activation by 1,25-dihydroxyvitamin D3. Specific inhibition at the level of messenger RNA. *The Journal of Clinical Investigation* 79, 1659–1664.
- Sadeghi, K., Wessner, B., Laggner, U., Ploder, M., Tamandl, D., et al. (2006) Vitamin D3 down-regulates monocyte TLR expression and triggers hyporesponsiveness to pathogen-associated molecular patterns. *European Journal of Immunology* 36, 361–370.
- Schleithoff, S.S., Zittermann, A., Tenderich, G., Berthold, H.K., Stehle, P., et al. (2006) Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized placebo-controlled trial. *American Journal of Clinical Nutrition* 83, 754–759.
- Sigmundsdottir, H., Pan, J., Debes, G.F., It, C., Habtezion, A., et al. (2007) DCs metabolize sunlightinduced vitamin D3 to ‘program’ T cell attraction to the epidermal chemokine CCL27. *Nature Immunology* 8, 285–293.
- Smolders, J., Peelen, E., Thewissen, M., Cohen Tervaert, J.W., Menheere, P., et al. (2010) Safety and T cell modulating effects of high dose vitamin D3 supplementation in multiple sclerosis. *PLoS One*. 5, e15235.
- Staeva-Vieira, T.P. and Freedman, L.P. (2002) 1,25-dihydroxyvitamin D3 inhibits IFN-gamma and IL-4 levels during in vitro polarization of primary murine CD4+ T cells. *The Journal of Immunology* 168, 1181–1189.
- Stoffels, K., Overbergh, L., Giulietti, A., Verlinden, L., Bouillon, R., et al. (2006) Immune regulation of 25-hydroxyvitamin-D3-1alpha-hydroxylase in human monocytes. *Journal of Bone and Mineral Research* 21, 37–47.
- Stoffels, K., Overbergh, L., Bouillon, R. and Mathieu, C. (2007) Immune regulation of 1alpha-hydroxylase in murine peritoneal macrophages: unravelling the IFNgamma pathway. *Journal of Steroid Biochemistry and Molecular Biology* 103, 567–571.
- Stubbs, J.R., Idiculla, A., Slusser, J., Menard, R. and Quarles, L.D. (2010) Cholecalciferol supplementation alters calcitriol-responsive monocyte proteins and decreases inflammatory cytokines in ESRD. *Journal of the American Society of Nephrology* 21, 353–361.

- Szeles, L., Keresztes, G., Torocsik, D., Balajthy, Z., Krenacs, L., et al. (2009) 1,25-dihydroxyvitamin D₃ is an autonomous regulator of the transcriptional changes leading to a tolerogenic dendritic cell phenotype. *The Journal of Immunology* 182, 2074–2083.
- Takeuchi, A., Reddy, G.S., Kobayashi, T., Okano, T., Park, J., et al. (1998) Nuclear factor of activated T cells (NFAT) as a molecular target for 1 α ,25-dihydroxyvitamin D₃-mediated effects. *The Journal of Immunology* 160, 209–218.
- Tangpricha, V., Pearce, E.N., Chen, T.C. and Holick, M.F. (2002) Vitamin D insufficiency among free-living healthy young adults. *The American Journal of Medicine* 112, 659–662.
- Thien, R., Baier, K., Pietschmann, P., Peterlik, M. and Willheim, M. (2005) Interactions of 1 α ,25-dihydroxyvitamin D₃ with IL-12 and IL-4 on cytokine expression of human T lymphocytes. *The Journal of Allergy and Clinical Immunology* 116, 683–689.
- Tsoukas, C.D., Wotry, D., Escobar, S.S., Provvedini, D.M., Dinarello, C.A., et al. (1989) Inhibition of interleukin-1 production by 1,25-dihydroxyvitamin D₃. *Journal of Clinical Endocrinology and Metabolism* 69, Urry, Z., Xystrakis, E., Richards, D.F., McDonald, J., Sattar, Z., et al. (2009) Ligation of TLR9 induced on human IL-10-secreting Tregs by 1 α ,25-dihydroxyvitamin D₃ abrogates regulatory function. *The Journal of Clinical Investigation* 119, 387–398.
- Veldman, C.M., Cantorna, M.T. and DeLuca, H.F. (2000) Expression of 1,25-dihydroxyvitamin D(3) receptor in the immune system. *Archives of Biochemistry and Biophysics* 374, 334–338.
- Wagner, D., Hanwell, H.E., Schnabl, K., Yazdanpanah, M., Kimball, S., et al. (2011) The ratio of serum 24,25-dihydroxyvitamin D(3) to 25-hydroxyvitamin D(3) is predictive of 25-hydroxyvitamin D(3) response to vitamin D(3) supplementation. *Journal of Steroid Biochemistry and Molecular Biology* 126, 72–77.
- Willheim, M., Thien, R., Schrattbauer, K., Bajna, E., Holub, M., et al. (1999) Regulatory effects of 1 α ,25-dihydroxyvitamin D₃ on the cytokine production of human peripheral blood lymphocytes. *Journal of Clinical Endocrinology and Metabolism* 84, 3739–3744.
- Wortsman, J., Matsuoka, L.Y., Chen, T.C., Lu, Z. and Holick, M.F. (2000) Decreased bioavailability of vitamin D in obesity. *American Journal of Clinical Nutrition* 72, 690–693.
- Yu, X.P., Bellido, T. and Manolagas, S.C. (1995) Down-regulation of NF- κ B protein levels in activated human lymphocytes by 1,25-dihydroxyvitamin D₃. *Proceedings of the National Academy of Sciences of the United States of America* 92, 10990–10994.
- Yusupov, E., Li-Ng, M., Pollack, S., Yeh, J.K., Mikhail, M., et al. (2010) Vitamin D and serum cytokines in a randomized Clinical trial. *International Journal of Endocrinology* 2010.
- Zhang, Y., Leung, D.Y.M., Richers, B.N., Liu, Y., Remigio, L.K., et al. (2012) Vitamin D inhibits monocyte/macrophage proinflammatory cytokine production by targeting MAPK phosphatase-1. *The Journal of Immunology* 188, 2127–2135.
- Zittermann, A., Dembinski, J. and Stehle, P. (2004) Low vitamin D status is associated with low cord blood levels of the immunosuppressive cytokine interleukin-10. *Pediatric Allergy and Immunology* 15, 242–246.
- Zittermann, A., Frisch, S., Berthold, H.K., Gotting, C., Kuhn, J., et al. (2009) Vitamin D supplementation enhances the beneficial effects of weight loss on cardiovascular disease risk markers. *American Journal of Clinical Nutrition* 89, 1321–1327.
- Barker, T. and Traber, M.G. (2011) Does vitamin E and C supplementation improve the recovery from anterior cruciate ligament surgery. *Journal of Evidence-Based Complementary and Alternative Medicine* 16, 114–128.
- Barker, T., Leonard, S.W., Hansen, J., Trawick, R.H., Ingram, R., et al. (2009a) Vitamin E and C supplementation does not ameliorate muscle dysfunction following anterior cruciate ligament surgery. *Free Radical Biology and Medicine* 47, 1611–1618.
- Barker, T., Leonard, S.W., Trawick, R.H., Martins, T.B., Kjeldsberg, C.R., et al. (2009b) Modulation of inflammation by vitamin E and C supplementation prior to anterior cruciate ligament surgery. *Free Radical Biology and Medicine* 46, 599–606.
- Barker, T., Martins, T.B., Hill, H.R., Kjeldsberg, C.R., Trawick, R.H., et al. (2011) Vitamins E and C modulate the association between reciprocally regulated cytokines after an anterior cruciate ligament injury and surgery. *American Journal of Physical Medicine and Rehabilitation* 90, 638–647.
- Beharka, A.A., Wu, D., Han, S.N. and Meydani, S.N. (1997) Macrophage prostaglandin production contributes to the age-associated decrease in T cell function which is reversed by the dietary antioxidant vitamin E. *Mechanisms of Ageing and Development* 93, 59–77.
- Belisle, S.E., Leka, L.S., Delgado-Lista, J., Jacques, P.F., Ordovas, J.M., et al. (2009) Polymorphisms at cytokine genes may determine the effect of vitamin E on cytokine production in the elderly. *The Journal of Nutrition* 139, 1855–1860.
- Belisle, S.E., Hamer, D.H., Leka, L.S., Dallal, G.E., Delgado-Lista, J., et al. (2010) IL-2 and IL-10 gene polymorphisms are associated with respiratory tract infection and may modulate the effect of vitamin E on lower respiratory tract infections in elderly nursing home residents. *American Journal of Clinical Nutrition* 92, 106–114.
- Boscoboinik, D., Szewczyk, A., Hensey, C. and Azzi, A. (1991) Inhibition of cell proliferation by alpha-tocopherol. Role of protein kinase C. *Journal of Biological Chemistry* 266, 6188–6194.
- Bruno, R.S., Leonard, S.W., Atkinson, J., Montine, T.J., Ramakrishnan, R., et al. (2006) Faster plasma vitamin E disap-

- pearance in smokers is normalized by vitamin C supplementation. *Free Radical Biology and Medicine* 40, 689–697.
- Cachia, O., Benza, J.E., Pedruzzi, E., Descomps, B., Gougerot-Pocidalo, M.A., et al. (1998) α -tocopherol inhibits the respiratory burst in human monocytes. Attenuation of p47(phox) membrane translocation and phosphorylation. *Journal of Biological Chemistry* 273, 32801–32805.
- Cannon, J.G., Meydani, S.N., Fielding, R.A., Fiatarone, M.A., Meydani, M., et al. (1991). Acute phase response in exercise. II. Associations between vitamin E, cytokines, and muscle proteolysis. *American Journal of Physiology* 260, R1235–R1240.
- Christen, S., Woodall, A.A., Shigenaga, M.K., Southwell-Keely, P.T., Duncan, M.W., et al. (1997) γ -tocopherol traps mutagenic electrophiles such as NO(X) and complements α -tocopherol: physiological implications. *Proceedings of the National Academy of Sciences of the United States of America* 94, 3217–3222.
- Dendorfer, U., Oettgen, P. and Libermann, T.A. (1994) Multiple regulatory elements in the interleukin-6 gene mediate induction by prostaglandins, cyclic AMP, and lipopolysaccharide. *Molecular and Cellular Biology* 14, 4443–4454.
- Devaraj, S. and Jialal, I. (1999) α -tocopherol decreases interleukin-1 β release from activated human monocytes by inhibition of 5-lipoxygenase. *Arteriosclerosis, Thrombosis, and Vascular Biology* 19, 1125–1133.
- Devaraj, S. and Jialal, I. (2000a) α tocopherol supplementation decreases serum C-reactive protein and monocyte interleukin-6 levels in normal volunteers and type 2 diabetic patients. *Free Radical Biology and Medicine* 29, 790–792.
- Devaraj, S. and Jialal, I. (2000b) Low-density lipoprotein postsecretory modification, monocyte function, and circulating adhesion molecules in type 2 diabetic patients with and without macrovascular complications: the effect of $\{\alpha\}$ -tocopherol supplementation. *Circulation* 102, 191–196.
- Devaraj, S. and Jialal, I. (2005) α -tocopherol decreases tumor necrosis factor- α mRNA and protein from activated human monocytes by inhibition of 5-lipoxygenase. *Free Radical Biology and Medicine* 38, 1212–1220.
- Devaraj, S., Li, D. and Jialal, I. (1996) The effects of α tocopherol supplementation on monocyte function. Decreased lipid oxidation, interleukin 1 β secretion, and monocyte adhesion to endothelium. *The Journal of Clinical Investigation* 98, 756–763.
- Devaraj, S., Venugopal, S.K., Singh, U. and Jialal, I. (2005) Hyperglycemia induces monocytic release of interleukin-6 via induction of protein kinase c- $\{\alpha\}$ and - $\{\beta\}$. *Diabetes* 54, 85–91.
- Devaraj, S., Tang, R., Adams-Huet, B., Harris, A., Seenivasan, T., et al. (2007) Effect of high-dose α -tocopherol supplementation on biomarkers of oxidative stress and inflammation and carotid atherosclerosis in patients with coronary artery disease. *American Journal of Clinical Nutrition* 86, 1392–1398.
- Devaraj, S., Leonard, S., Traber, M.G. and Jialal, I. (2008) Gamma-tocopherol supplementation alone and in combination with α -tocopherol alters biomarkers of oxidative stress and inflammation in subjects with metabolic syndrome. *Free Radical Biology and Medicine* 44, 1203–1208.
- Egger, T., Schuligoj, R., Wintersperger, A., Amann, R., Malle, E., et al. (2003) Vitamin E (α -tocopherol) attenuates cyclooxygenase 2 transcription and synthesis in immortalized murine BV-2 microglia. *Biochemical Journal* 370, 459–467.
- Evans, H.M. and Bishop, K.S. (1922) On the existence of a hitherto unrecognized dietary factor essential for reproduction. *Science* 56, 650–651.
- Fischer, C.P., Hiscock, N.J., Penkowa, M., Basu, S., Vessby, B., et al. (2004) Supplementation with vitamins C and E inhibits the release of interleukin-6 from contracting human skeletal muscle. *The Journal of Physiology (London)* 558, 633–645.
- Fox, E.S., Brower, J.S., Bellezze, J.M. and Leingang, K.A. (1997) N-acetylcysteine and α -tocopherol reverse the inflammatory response in activated rat Kupffer cells. *The Journal of Immunology* 158, 5418–5423.
- Fujimoto, Y., Uno, E. and Sakuma, S. (2004) Effects of reactive oxygen and nitrogen species on cyclooxygenase- 1 and -2 activities. *Prostaglandins, Leukotrienes, and Essential Fatty Acids* 71, 335–340.
- Grisanti, L.A., Woster, A.P., Dahlman, J., Sauter, E.R., Combs, C.K., et al. (2011) $\{\alpha\}$ 1-Adrenergic receptors positively regulate Toll-like receptor cytokine production from human monocytes and macrophages. *The Journal of Pharmacology and Experimental Therapeutics* 338, 648–657.
- Halpern, A.D., Handelman, G.J., Harris, J.M., Belmont, C.A. and Blumberg, J.B. (1998) Protection of vitamin C of loss of vitamin E in cultured rat hepatocytes. *Archives of Biochemistry and Biophysics* 359, 305–309.
- Handelman, G.J., Machlin, L.J., Fitch, K., Weiter, J.J. and Dratz, E.A. (1985) Oral α -tocopherol supplements decrease plasma gamma-tocopherol levels in humans. *The Journal of Nutrition* 115, 807–813.
- Hayek, M.G., Mura, C., Wu, D., Beharka, A.A., Han, S.N., et al. (1997) Enhanced expression of inducible cyclooxygenase with age in murine macrophages. *The Journal of Immunology* 159, 2445–2451.
- Hemler, M.E. and Lands, W.E. (1980) Evidence for a peroxide-initiated free radical mechanism of prostaglandin biosynthesis. *Journal of Biological Chemistry* 255, 6253–6261.
- Himmelfarb, J., Kane, J., McMonagle, E., Zaltas, E., Bobzin, S., et al. (2003) Alpha and gamma tocopherol metabolism in healthy subjects and patients with end-stage renal disease. *Kidney International* 64, 978–991.
- Jeschke, M.G., Barrow, R.E., Suzuki, F., Rai, J., Benjamin, D., et al. (2002) IGF-I/IGFBP-3 equilibrates ratios of

- pro- to anti-inflammatory cytokines, which are predictors for organ function in severely burned pediatric patients. *Molecular Medicine* 8, 238–246.
- Jiang, Q. and Ames, B.N. (2003) Gamma-tocopherol, but not alpha-tocopherol, decreases proinflammatory eicosanoids and inflammation damage in rats. *The Journal of the Federation of American Societies for Experimental Biology* 17, 816–822.
- Jiang, Q., Elson-Schwab, I., Courtemanche, C. and Ames, B.N. (2000) gamma-tocopherol and its major metabolite, in contrast to alpha-tocopherol, inhibit cyclooxygenase activity in macrophages and epithelial cells. *Proceedings of the National Academy of Sciences of the United States of America* 97, 11494–11499.
- Jiang, Q., Christen, S., Shigenaga, M.K. and Ames, B.N. (2001) gamma-tocopherol, the major form of vitamin E in the US diet, deserves more attention. *American Journal of Clinical Nutrition* 74, 714–722.
- Jiang, Q., Lykkesfeldt, J., Shigenaga, M.K., Shigenaga, E.T., Christen, S., et al. (2002) Gamma-tocopherol supplementation inhibits protein nitration and ascorbate oxidation in rats with inflammation. *Free Radical Biology and Medicine* 33, 1534–1542.
- Jiang, Z., Yin, X. and Jiang, Q. (2011) Natural forms of vitamin E and 13'-carboxychromanol, a long-chain vitamin E metabolite, inhibit leukotriene generation from stimulated neutrophils by blocking calcium influx and suppressing 5-lipoxygenase activity, respectively. *The Journal of Immunology* 186, 1173–1179.
- Kempna, P., Reiter, E., Arock, M., Azzi, A. and Zingg, J.M. (2004) Inhibition of HMC-1 mast cell proliferation by vitamin E: involvement of the protein kinase B pathway. *Journal of Biological Chemistry* 279, 50700–50709.
- Lehmann, J., Martin, H.L., Lashley, E.L., Marshall, M.W. and Judd, J.T. (1986) Vitamin E in foods from high and low linoleic acid diets. *Journal of the American Dietetic Association* 86, 1208–1216.
- Leonard, S.W., Peterson, E., Atkinson, J.K., Ramakrishnan, R., Cross, C.E., et al. (2005) Studies in humans using deuterium-labeled alpha- and gamma-tocopherols demonstrate faster plasma gamma-tocopherol disappearance and greater gamma-metabolite production. *Free Radical Biology and Medicine* 38, 857–866.
- Malmberg, K.J., Lenkei, R., Petersson, M., Ohlum, T., Ichihara, F., et al. (2002) A short-term dietary supplementation of high doses of vitamin E increases T helper 1 cytokine production in patients with advanced colorectal cancer. *Clinical Cancer Research* 8, 1772–1778.
- Mastaloudis, A., Morrow, J.D., Hopkins, D.W., Devaraj, S. and Traber, M.G. (2004) Antioxidant supplementation prevents exercise-induced lipid peroxidation, but not inflammation, in ultramarathon runners. *Free Radical Biology and Medicine* 36, 1329–1341.
- McLaughlin, P.J. and Wehrach, J.L. (1979) Vitamin E content of foods. *Journal of the American Dietetic Association* 75, 647–665.
- Meydani, S.N., Bärlund, M.P., Liu, S., Meydani, M., Miller, R.A., et al. (1990) Vitamin E supplementation enhances cell-mediated immunity in healthy elderly subjects. *American Journal of Clinical Nutrition* 52, 557–563.
- Mol, M.J., de Rijke, Y.B., Demacker, P.N. and Stalenhoef, A.F. (1997) Plasma levels of lipid and cholesterol oxidation products and cytokines in diabetes mellitus and cigarette smoking: effects of vitamin E treatment. *Atherosclerosis* 129, 169–176.
- Nagel, J.E., Chopra, R.K., Chrest, F.J., McCoy, M.T., Schneider, E.L., et al. (1988) Decreased proliferation, interleukin 2 synthesis, and interleukin 2 receptor expression are accompanied by decreased mRNA expression in phytohemagglutinin-stimulated cells from elderly donors. *The Journal of Clinical Investigation* 81, 1096–1102.
- Nakarai, T., Robertson, M.J., Streuli, M., Wu, Z., Ciardelli, T.L., et al. (1994) Interleukin 2 receptor gamma chain expression on resting and activated lymphoid cells. *The Journal of Experimental Medicine* 180, 241–251.
- Pallast, E.G., Schouten, E.G., de Waart, F.G., Fonk, H.C., Doeke, G., et al. (1999) Effect of 50- and 100-mg vitamin E supplements on cellular immune function in noninstitutionalized elderly persons. *American Journal of Clinical Nutrition* 69, 1273–1281.
- Pedersen, B.K., Åkerstrom, T.C., Nielsen, A.R. and Fischer, C.P. (2007) Role of myokines in exercise and metabolism. *Journal of Applied Physiology* 103, 1093–1098.
- Petersen, E.W., Ostrowski, K., Ibafet, T., Richelle, M., Offord, E., Halkjær-Kristensen, J. and Pedersen, B.K. (2001) Effect of vitamin supplementation on cytokine response and on muscle damage after strenuous exercise. *American Journal of Physiology. Cell Physiology* 280, C1570–C1575.
- Reiter, E., Jiang, Q. and Christen, S. (2007) Anti-inflammatory properties of alpha- and gamma-tocopherol. *Molecular Aspects Medicine* 28, 668–691.
- Ricciarelli, R., Tasinato, A., Clement, S., Ozer, N.K., Boscoboinik, D., et al. (1998) alpha-Tocopherol specifically inactivates cellular protein kinase C alpha by changing its phosphorylation state. *Biochemical Journal* 334, 243–249.
- Rink, L., Çakman, I. and Kirchner, H. (1998) Altered cytokine production in the elderly. *Mechanisms of Ageing and Development* 102, 199–209.
- Suldean, T., Li, D. and Mehta, J.L. (1999) Differential effects of alpha- and gamma-tocopherol on low-density lipoprotein oxidation, superoxide activity, platelet aggregation and arterial thrombogenesis. *Journal of American College of Cardiology* 34, 1208–1215.

- Smith, K.S., Lee, C.L., Ridlington, J.W., Leonard, S.W., Devaraj, S., et al. (2003) Vitamin E supplementation increases circulating vitamin E metabolites tenfold in end-stage renal disease patients. *Lipids* 38, 813–819.
- Sanceau, J., Kaisho, T., Hirano, T. and Wietzerbin, J. (1995) Triggering of the human interleukin-6 gene by interferon-gamma and tumor necrosis factor-alpha in monocytic cells involves cooperation between interferon regulatory factor-1, NF kappa B, and Sp1 transcription factors. *Journal of Biological Chemistry* 270, 27920–27931.
- Suzuki, Y.J. and Packer, L. (1993a) Inhibition of NF-kappa B activation by vitamin E derivatives. *Biochemical and Biophysical Research Communications* 193, 277–283.
- Suzuki, Y.J. and Packer, L. (1993b) Inhibition of NF-kappa B DNA binding activity by alpha-tocopheryl succinate. *Biochemistry and Molecular Biology International* 31, 693–700.
- Tasinato, A., Boscoboinik, D., Bartoli, G.M., Maroni, P. and Azzi, A. (1995) d-alpha-Tocopherol inhibition of vascular smooth muscle cell proliferation occurs at physiological concentrations, correlates with protein kinase C inhibition, and is independent of its antioxidant properties. *Proceedings of the National Academy of Sciences of the United States of America* 92, 12190–12194.
- Traber, M.G. (2007) Vitamin E regulatory mechanisms. *Annual Review of Nutrition* 27, 347–362.
- Traber, M.G. and Atkinson, J. (2007) Vitamin E, antioxidant and nothing more. *Free Radical Biology and Medicine* 43, 4–15.
- Traber, M.G. and Kayden, H.J. (1989) Preferential incorporation of alpha-tocopherol vs gamma-tocopherol in human lipoproteins. *American Journal of Clinical Nutrition* 49, 517–526.
- Traber, M.G., Rudel, L.L., Burton, G.W., Hughes, L., Ingold, K.U., et al. (1990a) Nascent VLDL from liver perfusions of cynomolgus monkeys are preferentially enriched in RRR- compared with SRR-alpha-tocopherol: studies using deuterated tocopherols. *Journal of Lipid Research* 31, 687–694.
- Traber, M.G., Sokol, R.J., Burton, G.W., Ingold, K.U., Papas, A.M., et al. (1990b) Impaired ability of patients with familial isolated vitamin E deficiency to incorporate alpha-tocopherol into lipoproteins secreted by the liver. *The Journal of Clinical Investigation* 85, 397–407.
- Traber, M.G., Burton, G.W., Hughes, L., Ingold, K.U., Hidaka, H., et al. (1992) Discrimination between forms of vitamin E by humans with and without genetic abnormalities of lipoprotein metabolism. *Journal of Lipid Research* 33, 1171–1182.
- Van Damme, J., Opdenakker, G., Simpson, R.J., Rubira, M.R., Cayphas, S., et al. (1987) Identification of the human 26-kD protein, interferon beta 2 (IFN-beta 2), as a B cell hybridoma/plasmacytoma growth factor induced by interleukin 1 and tumor necrosis factor. *The Journal of Experimental Medicine* 165, 914–919.
- van Tits, L.J., Demacker, P.N., de Graaf, J., Hak-Lemmers, H.L. and Stalenhoef, A.F. (2000) a-Tocopherol supplementation decreases production of superoxide and cytokines by leukocytes ex vivo in both normolipidemic and hypertriglyceridemic individuals. *American Journal of Clinical Nutrition* 71, 458–464.
- Vassilakopoulos, T., Katsaounou, P., Karatza, M.H., Kollintza, A., Zakythinos, S., et al. (2002) Strenuous Resistive Breathing Induces Plasma Cytokines: Role of Antioxidants and Monocytes. *American Journal of Respiratory and Critical Care Medicine* 166, 1572–1578.
- Vassilakopoulos, T., Karatza, M.H., Katsaounou, P., Kollintza, A., Zakythinos, S., et al. (2003) Antioxidants attenuate the plasma cytokine response to exercise in humans. *Journal of Applied Physiology* 94, 1025–1032.
- Venugopal, S.K., Devaraj, S., Yang, T. and Jialal, I. (2002) Alpha-tocopherol decreases superoxide anion release in human monocytes under hyperglycemic conditions via inhibition of protein kinase C-alpha. *Diabetes* 51, 3049–3054.
- Wagner, J.G., Jiang, Q., Harkema, J.R., Illek, B., Patel, D.D., et al. (2007) Ozone enhancement of lower airway allergic inflammation is prevented by gamma-tocopherol. *Free Radical Biology and Medicine* 43, 1176–1188.
- Waldmann, T.A. (1989) The multi-subunit interleukin-2 receptor. *Annual Review of Biochemistry* 58, 875–911.
- Walker, C., Kristensen, F., Bettens, F. and deWeck, A.L. (1983) Lymphokine regulation of activated (G1) lymphocytes. I. Prostaglandin E2-induced inhibition of interleukin 2 production. *The Journal of Immunology* 130, 1770–1773.
- Williams, J.A. and Shacter, E. (1997) Regulation of macrophage cytokine production by prostaglandin E2. Distinct roles of cyclooxygenase-1 and -2. *Journal of Biological Chemistry* 272, 25693–25699.
- Wiser, J., Alexis, N.E., Jiang, Q., Wu, W., Robinette, C., et al. (2008) In vivo gamma-tocopherol supplementation decreases systemic oxidative stress and cytokine responses of human monocytes in normal and asthmatic subjects. *Free Radical Biology and Medicine* 45, 40–49.
- Wu, D., Mura, C., Beharka, A.A., Han, S.N., Paulson, K.E., et al. (1998) Age-associated increase in PGE2 synthesis and COX activity in murine macrophages is reversed by vitamin E. *American Journal of Physiology. Cell Physiology* 275, C661–C668.
- Wu, J.H., Ward, N.C., Indrawan, A.P., Almeida, C.A., Hodgson, J.M., et al. (2007) Effects of alpha-tocopherol and mixed tocopherol supplementation on markers of oxidative stress and inflammation in type 2 diabetes. *Clinical Chemistry* 53, 511–519.
- Yoshikawa, S., Morinobu, T., Hamamura, K., Hirahara, F., Iwamoto, T., et al. (2005) The effect of gamma-tocopherol administration on alpha-tocopherol levels and metabolism in humans. *European Journal of Clinical Nutrition* 59, 900–905.
- Aasheim, E.T., Hofso, D., Hjelmesæth, J., Birkeland, K.I. and Bohmer, T. (2008) Vitamin status in morbidly obese patients: a cross-sectional study. *The American Journal of Clinical Nutrition* 87, 362–369.
- Aguirre, R. and Moy, J.M. (2008) Inflammation in the vascular bed: importance of vitamin C. *Pharmacology and*

- Therapeutics 119, 96–103.
- Antoniades, C., Antonopoulos, A.S., Tousoulis, D., Marinou, K. and Stefanidis, C. (2009) Homocysteine and coronary atherosclerosis: from folate fortification to the recent Clinical trials. European Heart Journal, 30 6–15.
- Block, G., Jensen, C., Dietrich, M., Norkus, E.P., Hudes, M., et al. (2004) Plasma C-reactive protein concentrations in active and passive smokers: influence of antioxidant supplementation. Journal of the American College of Nutrition, 23, 141–147.
- Block, G., Jensen, C.D., Dälvi, T.B., Norkus, E.P., Hudes, M., et al. (2009) Vitamin C treatment reduces elevated C-reactive protein. Free Radical Biology and Medicine 46, 70–77.
- Bo, S., Ciccone, G., Durazzo, M., Gambino, R., Massarenti, P., et al. (2007) Efficacy of antioxidant treatment in reducing resistin serum levels: a randomized study. PLoS Clinical trials 2, e17.
- Bowie, A.G. and O'Neill, L.A. (2000) Vitamin C inhibits NF- κ B activation by TNF via the activation of p38 mitogen-activated protein kinase. Journal of Immunology 165, 7180–7188.
- Brightenti, F., Valtuena, S., Pellegrini, N., Ardigo, D., Del Rio, D., et al. (2005) Total antioxidant capacity of the diet is inversely and independently related to plasma concentration of high-sensitivity C-reactive protein in adult Italian subjects. The British Journal of Nutrition 93, 619–625.
- Bruunsgaard, H., Poulsen, H.E., Pedersen, B.K., Nyssonnen, K., Käikonen, J., et al. (2003) Long-term combined supplementations with α -tocopherol and vitamin C have no detectable anti-inflammatory effects in healthy men. The Journal of Nutrition 133, 1170–1173.
- Campbell, J.D., Cole, M., Bunditrutavorn, B. and Vella, A.T. (1999) Ascorbic acid is a potent inhibitor of various forms of T cell apoptosis. Cellular Immunology 194, 1–5.
- Carcamo, J.M., Borquez-Ojeda, O. and Golde, D.W. (2002a) Vitamin C inhibits granulocyte macrophage colony-stimulating factor-induced signaling pathways. Blood 99, 3205–3212.
- Carcamo, J.M., Pedraza, A., Borquez-Ojeda, O. and Golde, D.W. (2002b) Vitamin C suppresses TNF α -induced NF κ B activation by inhibiting I κ B α phosphorylation. Biochemistry 41, 12995–13002.
- Chambers, J.C., Ueland, P.M., Obeid, O.A., Wrigley, J., Refsum, H., et al. (2000) Improved vascular endothelial function after oral B vitamins: An effect mediated through reduced concentrations of free plasma homocysteine. Circulation 102, 2479–2483.
- Chiang, E.P., Bagley, P.J., Selhub, J., Nadeau, M. and Roubenoff, R. (2003) Abnormal vitamin B(6) status is associated with severity of symptoms in patients with rheumatoid arthritis. The American Journal of Medicine 114, 283–287.
- Choi, J.S., Choi, Y.J., Park, S.H., Kang, J.S. and Kang, Y.H. (2004) Flavones mitigate tumor necrosis factor- α -induced adhesion molecule upregulation in cultured human endothelial cells: role of nuclear factor- κ B. The Journal of Nutrition 134, 1013–1019.
- Clarke, R. and Armitage, J. (2000) Vitamin supplements and cardiovascular risk: review of the randomized trials of homocysteine-lowering vitamin supplements. Seminars in Thrombosis and Hemostasis 26, 341–348.
- Das, U.N. (2003) Folic acid says NO to vascular diseases. Nutrition 19, 686–692. Devaraj, S., Singh, U. and Jialal, I. (2009) The evolving role of C-reactive protein in atherothrombosis. Clinical Chemistry 55, 229–238.
- Durga, J., Van Tits, L.J., Schouten, E.G., Kok, F.J. and Verhoef, P. (2005) Effect of lowering of homocysteine levels on inflammatory markers: a randomized controlled trial. Archives of Internal Medicine 165, 1388–1394.
- Dusitanond, P., Eikelboom, J.W., Hankey, G.J., Thom, J., Gilmore, G., et al. (2005) Homocysteine-lowering treatment with folic acid, cobalamin, and pyridoxine does not reduce blood markers of inflammation, endothelial dysfunction, or hypercoagulability in patients with previous transient ischemic attack or stroke: a randomized substudy of the VITATOPS trial. Stroke; a Journal of Cerebral Circulation 36, 144–146.
- Esmailzadeh, A., Kimiaoglu, M., Mehrabi, Y., Azodbakht, L., Hu, F.B., et al. (2006) Fruit and vegetable intakes, C-reactive protein, and the metabolic syndrome. The American Journal of Clinical Nutrition 84, 1489–1497.
- Esposito, K. and Giugliano, D. (2004) The metabolic syndrome and inflammation: association or causation? Nutrition, Metabolism, and Cardiovascular Diseases 14, 228–232.
- Folsom, A.R., Desvarieux, M., Nieto, F.J., Boland, L.L., Ballantyne, C.M., et al. (2003) B vitamin status and inflammatory markers. Atherosclerosis 169, 169–174.
- Ford, E.S., Liu, S., Mannino, D.M., Giles, W.H. and Smith, S.J. (2003) C-reactive protein concentration and concentrations of blood vitamins, carotenoids, and selenium among United States adults. European Journal of Clinical Nutrition 57, 1157–1163.
- Freese, R., Vaarala, O., Turpeinen, A.M. and Mutanen, M. (2004) No difference in platelet activation or inflammation markers after diets rich or poor in vegetables, berries and apple in healthy subjects. European Journal of Nutrition 43, 175–182.
- Friso, S., Jacques, P.F., Wilson, P.W., Rosenberg, I.H. and Selhub, J. (2001) Low circulating vitamin B(6) is associated with elevation of the inflammation marker C-reactive protein independently of plasma homocysteine levels. Circulation 103, 2788–2791.
- Friso, S., Girelli, D., Martinelli, N., Olivieri, O., Lotto, V., et al. (2004) Low plasma vitamin B-6 concentrations and modulation of coronary artery disease risk. The American Journal of Clinical Nutrition 79, 992–998.
- Gao, X., Bermudez, O.I. and Tucker, K.L. (2004) Plasma C-reactive protein and homocysteine concentrations are

- related to frequent fruit and vegetable intake in Hispanic and non-Hispanic white elders. *The Journal of Nutrition* 134, 913–918.
- Giugliano, D., Ceriello, A. and Esposito, K. (2006) The effects of diet on inflammation: emphasis on the metabolic syndrome. *Journal of the American College of Cardiology* 48, 677–685.
- Hansson, G.K., Robertson, A.K. and Soderberg-Naucler, C. (2006) Inflammation and atherosclerosis. *Annual Review of Pathology* 1, 297–329.
- Härtel, C., Strunk, T., Bucsky, P. and Schultz, C. (2004) Effects of vitamin C on intracytoplasmic cytokine production in human whole blood monocytes and lymphocytes. *Cytokine* 27, 101–106.
- Haynes, W.G. (2002) Hyperhomocysteinemia, vascular function and atherosclerosis: effects of vitamins. *Cardiovascular Drugs and Therapy* 16, 391–399.
- Hu, F.B. (2002) Dietary pattern analysis: a new direction in nutritional epidemiology. *Current Opinion in Lipidology* 13, 3–9.
- Hu, F.B. and Willett, W.C. (2002) Optimal diets for prevention of coronary heart disease. *JAMA : the Journal of the American Medical Association* 288, 2569–2578.
- Humphrey, L.L., Fu, R., Rogers, K., Freeman, M. and Helfand, M. (2008) Homocysteine level and coronary heart disease incidence: a systematic review and meta-analysis. *Mayo Clinic Proceedings*. Mayo Clinic 83, 1203–1212.
- Jacques, P.F., Selhub, J., Bostom, A.G., Wilson, P.W. and Rosenberg, I.H. (1999) The effect of folic acid fortification on plasma folate and total homocysteine concentrations. *The New England Journal of Medicine* 340, 1449–1454.
- Jessup, W., Krisharides, L. and Stocker, R. (2004) Lipid oxidation in atherogenesis: an overview. *Biochemical Society Transactions* 32, 134–138.
- Kaptoge, S., Di Angelantonio, E., Lowe, G., Pepys, M.B., Thompson, S.G., et al. (2010) C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet* 375, 132–140.
- Kelley, D.S. and Bendich, A. (1996) Essential nutrients and immunologic functions. *The American Journal of Clinical Nutrition* 63, 994S–996S.
- Kelley, D.S., Rasooly, R., Jacob, R.A., Kader, A.A. and Mackey, B.E. (2006) Consumption of Bing sweet cherries lowers circulating concentrations of inflammation markers in healthy men and women. *The Journal of Nutrition* 136, 981–986.
- Klerk, M., Durga, J., Schouten, E.G., Kluft, C., Kok, F.J., et al. (2005) No effect of folic acid supplementation in the course of 1 year on haemostasis markers and C-reactive protein in older adults. *Thrombosis and Haemostasis* 94, 96–100.
- Libby, P., Ridker, P.M. and Maseri, A. (2002) Inflammation and atherosclerosis. *Circulation* 105, 1135–1143.
- Mangoni, A.A. (2006) Folic acid, inflammation, and atherosclerosis: false hopes or the need for better trials? *Clinica Chimica Acta; International Journal of Clinical Chemistry* 367, 11–19.
- Mangoni, A.A., Arya, R., Ford, E., Asonganyi, B., Sherwood, R.A., et al. (2003) Effects of folic acid supplementation on inflammatory and thrombogenic markers in chronic smokers. A randomised controlled trial. *Thrombosis Research* 110, 13–17.
- Mangoni, A.A., Sherwood, R.A., Asonganyi, B., Swift, C.G., Thomas, S., et al. (2005) Short-term oral folic acid supplementation enhances endothelial function in patients with type 2 diabetes. *American Journal of Hypertension* 18, 220–226.
- Maron, D.J. (2004) Flavonoids for reduction of atherosclerotic risk. *Current Atherosclerosis Reports* 6, 73–78.
- McCully, K.S. (1969) Vascular pathology of homocysteinemia: implications for the pathogenesis of arteriosclerosis. *The American Journal of Pathology* 56, 111–128.
- Meydani, S.N., Ribaya-Mercado, J.D., Russell, R.M., Sahyoun, N, Morrow, F.D., et al. (1991) Vitamin B-6 deficiency impairs interleukin 2 production and lymphocyte proliferation in elderly adults. *The American Journal of Clinical Nutrition* 53, 1275–1280.
- Nakou, E.S., Liberopoulos, E.N., Milionis, H.J. and Elisaf, M.S. (2008) The role of C-reactive protein in atherosclerotic cardiovascular disease: an overview. *Current Vascular Pharmacology* 6, 258–270.
- Nelson, M. (1991) The validation of dietary assessments. In: Margetts, M.B. and Nelson, M. (eds) *Design Concepts in Nutritional Epidemiology*. Oxford Medical Publication, New York, pp. 241–272.
- Ntaios, G., Savopoulos, C., Grekas, D. and Hatzitolios, A. (2009) The controversial role of B-vitamins in cardiovascular risk: An update. *Archives of Cardiovascular Diseases* 102, 847–854.
- Ntaios, G.C., Savopoulos, C.G., Chatzinikolaou, A.C., Kaita, G.D. and Hatzitolios, A. (2008) Vitamins and stroke: the homocysteine hypothesis still in doubt. *The Neurologist* 14, 2–4.
- Oliveira, A., Rodriguez-Artalejo, F. and Lopes, C. (2009) The association of fruits, vegetables, antioxidant vitamins and fibre intake with high-sensitivity C-reactive protein: sex and body mass index interactions. *European Journal of Clinical Nutrition* 63, 1345–1352.
- Parikh, P., McDaniel, M.C., Ashen, M.D., Miller, J.I., Sorrentino, M., et al. (2005) Diets and cardiovascular disease: an evidence-based assessment. *Journal of the American College of Cardiology* 45, 1379–1387.
- Pearson, T.A., Mensah, G.A., Alexander, R.W., Anderson, J.L., Cannon, R.O., 3rd, et al. (2003) Markers of inflammation and cardiovascular disease: application to Clinical and public Health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 107, 499–511.
- Perez-Cruz, I., Cárceles, J.M. and Golde, D.W. (2003) Vitamin C inhibits FAS-induced apoptosis in monocytes and U937 cells. *Blood* 102, 336–343.
- Rall, L.C. and Meydani, S.N. (1993) Vitamin B6 and immune competence. *Nutrition Reviews* 51, 217–225.
- Reilly, M.P., Lehrke, M., Wolfe, M.L., Rohatgi, A., Lazar, M.A., et al. (2005) Resistin is an inflammatory marker of atherosclerosis in humans. *Circulation* 111, 932–939.

- Ridker, P.M. (2007) Inflammatory biomarkers and risks of myocardial infarction, stroke, diabetes, and total mortality: implications for longevity. *Nutrition Reviews* 65, S253–S259.
- Riso, P., Visioli, F., Grande, S., Guarneri, S., Gardana, C., et al. (2006) Effect of a tomato-based drink on markers of inflammation, immunomodulation, and oxidative stress. *Journal of Agricultural and Food Chemistry* 54, 2563–2566.
- Rizzo, M.R., Abbatecola, A.M., Barbieri, M., Vietri, M.T., Cioffi, M., et al. (2008) Evidence for anti-inflammatory effects of combined administration of vitamin E and C in older persons with impaired fasting glucose: impact on insulin action. *Journal of the American College of Nutrition* 27, 505–511.
- Robinson, K., Arheart, K., Refsum, H., Brattstrom, L., Boers, G., et al. (1998) Low circulating folate and vitamin B6 concentrations: risk factors for stroke, peripheral vascular disease, and coronary artery disease. *European COMAC Group. Circulation* 97, 437–443.
- Ross, R. (1999) Atherosclerosis—an inflammatory disease. *The New England Journal of Medicine* 340, 115–126.
- Roubenoff, R., Roubenoff, R.A., Selhub, J., Nadeau, M.R., Cannon, J.G., et al. (1995) Abnormal vitamin B6 status in rheumatoid cachexia. Association with spontaneous tumor necrosis factor alpha production and markers of inflammation. *Arthritis and Rheumatism* 38, 105–109.
- Saiben, S., Cattaneo, M., Vecchi, M., Zighetti, M.L., Lecchi, A., et al. (2003) Low vitamin B(6) plasma levels, a risk factor for thrombosis, in inflammatory bowel disease: role of inflammation and correlation with acute phase reactants. *The American Journal of Gastroenterology* 98, 112–117.
- Sánchez-Moreno, C., Cano, M.P., De Ancos, B., Plaza, L., Olmedilla, B., et al. (2003) High-pressureized orange juice consumption affects plasma vitamin C, antioxidative status and inflammatory markers in healthy humans. *The Journal of Nutrition* 133, 2204–2209.
- Sánchez-Moreno, C., Cano, M.P., De Ancos, B., Plaza, L., Olmedilla, B., et al. (2004) Consumption of highpressureized vegetable soup increases plasma vitamin C and decreases oxidative stress and inflammatory biomarkers in healthy humans. *The Journal of Nutrition* 134, 3021–3025.
- Schulze, M.B. and Hoffmann, K. (2006) Methodological approaches to study dietary patterns in relation to risk of coronary heart disease and stroke. *The British Journal of Nutrition* 95, 860–869.
- Shen, J., Lai, C.Q., Mattei, J., Ordovas, J.M. and Tucker, K.L. (2010) Association of vitamin B-6 status with inflammation, oxidative stress, and chronic inflammatory conditions: the Boston Puerto Rican Health Study. *The American Journal of Clinical Nutrition* 91, 337–342.
- Silswal, N., Singh, A.K., Aruna, B., Mukhopadhyay, S., Ghosh, S., et al. (2005) Human resistin stimulates the pro-inflammatory cytokines TNF-alpha and IL-12 in macrophages by NF-kappaB-dependent pathway. *Biochemical and Biophysical Research Communications* 334, 1092–1101.
- Sitzer, M., Markus, H.S., Mendall, M.A., Liehr, R., Knorr, U., et al. (2002) C-reactive protein and carotid intimal medial thickness in a community population. *Journal of Cardiovascular Risk* 9, 97–103.
- Talaulikar, V.S. and Manyonda, I.T. (2011) Vitamin C as an antioxidant supplement in women's Health: a myth in need of urgent burial. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, 157, 10–13.
- Tice, J.A., Ross, E., Coxson, P.G., Rosenberg, I., Weinstein, M.C., et al. (2001) Cost-effectiveness of vitamin therapy to lower plasma homocysteine levels for the prevention of coronary heart disease: effect of grain fortification and beyond. *JAMA : the Journal of the American Medical Association* 286, 936–943.
- Ullegaddi, R., Powers, H.J. and Gariballa, S.E. (2004) B-group vitamin supplementation mitigates oxidative damage after acute ischaemic stroke. *Clinical science (London)* 107, 477–484.
- Valtuena, S., Pellegrini, N., Fronzini, L., Bianchi, M.A., Ardigo, D., et al. (2008) Food selection based on total antioxidant capacity can modify antioxidant intake, systemic inflammation, and liver function without altering markers of oxidative stress. *The American Journal of Clinical Nutrition* 87, 1290–1297.
- Van Herpen-Broekmans, W.M., Klopping-Ketelaars, I.A., Bots, M.L., Kluft, C., Princen, H., et al. (2004) Serum carotenoids and vitamins in relation to markers of endothelial function and inflammation. *European Journal of Epidemiology* 19, 915–921.
- Vermeulen, E.G., Rauwerda, J.A., Van Den Berg, M., De Jong, S.C., Schalkwijk, C., et al. (2003) Homocysteine-lowering treatment with folic acid plus vitamin B6 lowers urinary albumin excretion but not plasma markers of endothelial function or C-reactive protein: further analysis of secondary endpoints of a randomized Clinical trial. *European Journal of Clinical Investigation* 33, 209–215.
- Wald, D.S., Law, M. and Morris, J.K. (2002) Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. *Bristish Medical Journal* 325, 1202.
- Wannamethee, S.G., Lowe, G.D., Rumley, A., Bruckdorfer, K.R. and Whincup, P.H. (2006) Associations of vitamin C status, fruit and vegetable intakes, and markers of inflammation and hemostasis. *The American Journal of Clinical Nutrition* 83, 567–574.
- Watzl, B., Kulling, S.E., Moseneder, J., Barth, S.W. and Bub, A. (2005) A 4-wk intervention with high intake of carotenoid-rich vegetables and fruit reduces plasma C-reactive protein in healthy, nonsmoking men. *The American Journal of Clinical Nutrition* 82, 1052–1058.
- Willett, W.C. (1998) Nutritional Epidemiology. Oxford University Press, New York. Williams, K.J. and Tabas, I. (1998) The response-to-retention hypothesis of atherosclerosis reinforced. *Current Opinion in Lipidology* 9, 471–474.