

The Role of Food in Maintaining Immune Health in Ageing

Fiona McEvoy Ph.D. & Christine Loscher Ph.D.

Part 1: Introduction to the Ageing Immune System



Healthy Ageing - an Increasing Global Dilemma

The global population is currently undergoing unprecedented demographic changes. The number of older persons (aged 60 years or over) is expected to more than double, from 841 million people in 2013 to more than 2 billion in 2050¹. This demographic shift is, in part, due to an increase in life span. In 150 years, the average global life span has increased from 40 years to approximately 80 years². Although the news that we are living longer is positive, this situation presents new challenges to individuals and to society as a whole. Ageing is often associated with chronic disease and an increased susceptibility to infection that can negatively impact an individual's quality of life. In addition to this, there are rising healthcare costs and economic consequences associated with this demographic shift. For this reason, interventions that can either slow or reverse the negative effects of ageing, thereby increasing health span would have major benefits for individuals and society.

During the process of ageing, the human body accumulates damage at the molecular, cellular and organ levels, which results in diminished or dysregulated function and increased risk of disease and death. Advancing age is associated with an increased susceptibility of developing infections, frailty cardiovascular disease, autoimmune diseases, metabolic syndrome, type 2 diabetes and cancer ³. These age-related changes are well exemplified in the immune system.

The Ageing Immune System

Ageing leads to marked changes in the composition, function and competence of both the innate and adaptive immune systems. Ageing is associated with increased risk of infection, however the severity and morbidity associated with these infections also increases with age. This is evidenced by the fact that over 90% of deaths associated with influenza occur in individuals aged over 65 years ⁸. This problem is exacerbated by the fact that there is an age-related decline in response to vaccinations ⁹. The overall change to the immune system with age is termed immunosenescence and has a multifactorial aetiology, a consequence of the complexity of the immune system as well as multiple genetic and environmental influences. In addition to increased risk of infection, immunosenescence may also have a role in cancer risk (more than 60% of new cancers and more than 70% of cancer deaths occur in elderly subjects >65 years)¹⁰ and autoimmunity ¹¹.

Inflammation is beneficial as an acute, transient immune response to harmful conditions such as traumatic tissue injury or an invading pathogen. This response also facilitates the repair, turnover, and adaptation of many tissues. However, acute inflammatory responses to pathogens become impaired during ageing, leading to increased susceptibility to infection. Chronic inflammation has many features of acute inflammation but is usually persistent and of low grade, resulting in responses that lead to tissue degeneration. Increased circulating levels of inflammatory biomarkers such as C-reactive protein, TNF- α and IL-6 are commonly found in older individuals ¹². This chronic, low grade inflammation is referred to as 'Inflamm-ageing' and has been hypothesised to contribute to the pathogenesis of most age-associated diseases including sarcopenia, inflammatory bowel disease (IBD), cardiovascular disease and Alzheimer's disease ¹³.

Fiona McEvoy, Ph.D. is a postdoctoral researcher at Dublin City University. Her studies primarily focus on identifying novel compounds that can modulate the immune system to provide therapeutic benefits using in vitro and in vivo models.

Christine Loscher, Ph.D. is an Associate Professor of Immunology at Dublin City University. She is also the Lead Investigator of the Immunomodulation Research Group and has developed significant expertise in commercial research and industry engagement. She has secured over €4.5M in external funding (€400K directly from industry) for her research.

References:

- United Nations, Department of Economic and Social Affairs, P. D. (2015). World Population Ageing 2015. World Popul. Ageing 2015 (ST/ESA/SER.A/390).
- Aw, D., Silva, A. B. & Palmer, D. B. Immunosenescence: Emerging challenges for an ageing population. Immunology 120, 435-446 (2007).
- 3. Maijo, M., Clements, S. J., Ivory, K., Nicoletti, C. & Carding, S. R. Nutrition, diet and immunosenescence. *Mech. Ageing Dev.* **136-137**, 116-128 (2014).
- 4. Medzhitov, R. Recognition of microorganisms and activation of the immune response. *Nature* 449, 819–26 (2007).
- 5. Kumar, H., Kawai, T. & Akira, S. Toll-like receptors and innate immunity. *Biochem. Biophys. Res. Commun.* 388, 621–625 (2009).
- 6. Mosmann, T. R. & Sad, S. The expanding universe of T-cell subsets: Th1, Th2 and more. *Immunol. Today* **17**, 138–146 (1996).
- 7. Zhu, J., Yamane, H. & Paul, W. Differentiation of effector CD4 T cell populations. Annu Rev Immunol. 28, 445-489 (2010).
- 8. Katz, J. M., Renshaw-hoelscher, M. & Tumpey, T. M. Immunity to Influenza. Immunol. Res. 29, 113–124 (2004).
- 9. Weinberger, B., Herndler-Brandstetter, D., Schwanninger, A., Weiskopf, D. & Grubeck-Loebenstein, B. Biology of immune responses to vaccines in elderly persons. *Clin Infect Dis* **46**, 1078–1084 (2008).
- 10. Fulop, T. et al. Potential role of immunosenescence in cancer development. Ann. N. Y. Acad. Sci. 1197, 158-165 (2010).
- 11. Prelog, M. Aging of the immune system: A risk factor for autoimmunity? *Autoimmun. Rev.* **5**, 136–139 (2006).
- 12. Krabbe, K. S., Pedersen, M. & Bruunsgaard, H. Inflammatory mediators in the elderly. Exp. Gerontol. 39, 687-699 (2004).
- 13. Michaud, M. et al. Proinflammatory cytokines, aging and age-related diseases. J. Am. Med. Disord. Assoc. 14, 877-882 (2013).
- 14. Shaw, A. C., Joshi, S., Greenwood, H., Panda, A. & Lord, J. M. Aging of the innate immune system. *Curr. Opin. Immunol.* **22**, 507-13 (2010).
- 15. Fortin, C. F., Larbi, A., Lesur, O., Douziech, N. & Fulop Jr., T. Impairment of SHP-1 down-regulation in the lipid rafts of human neutrophils under GM-CSF stimulation contributes to their age-related, altered functions. *J. Leukoc. Biol.* **79**, 1061–1072 (2006).
- Wenisch, C., Patruta, S., Daxböck, F., Krause, R. & Hörl, W. Effect of age on human neutrophil function. J. Leukoc. Biol. 67, 40-45 (2000).
- 17. Fortin, C. F., Larbi, A., Dupuis, G., Lesur, O. & Fülöp, T. GM-CSF activates the Jak/STAT pathway to rescue polymorphonuclear neutrophils from spontaneous apoptosis in young but not elderly individuals. *Biogerontology* **8**, 173-187 (2007).
- 18. Geissman, F. et al. Development of monocytes, macrophages, and dendritic cells. J. Microbiol. Immunol. Infect. 656-662 (2010).
- 19. Gordon, S. & Taylor, P. R. Monocyte and macrophage heterogeneity. Nat. Rev. Immunol. 5, 953-64 (2005).
- 20. Linehan, E. & Fitzgerald, D. C. Ageing and the immune system: focus on macrophages. *Eur. J. Microbiol. Immunol. (Bp).* **5**, 14-24 (2015).
- 21. Boehmer, E. D., Goral, J., Faunce, D. E. & Kovacs, E. J. Age-dependent decrease in Toll-like receptor 4-mediated proinflammatory cytokine production and mitogen- activated protein kinase expression. *J. Leukoc. Biol.* **75**, 342–349 (2004).
- 22. Chelvarajan, R. L., Collins, S. M., Van Willigen, J. M. & Bondada, S. The unresponsiveness of aged mice to polysaccharide antigens is a result of a defect in macrophage function. *J. Leukoc. Biol.* **77**, 503–12 (2005).
- 23. Renshaw, M. et al. Cutting edge: impaired Toll-like receptor expression and function in aging. *J. Immunol.* **169**, 4697-701 (2002).
- 24. Van Duin, H. et al. Function Age-Associated Defect in Human TLR-1/2 Age-Associated Defect in Human TLR-1/2 Function. J Immunol Ref. **178**, 970–975 (2007).
- 25. Maggio, D. et al. 25(OH)D Serum levels decline with age earlier in women than in men and less efficiently prevent compensatory hyperparathyroidism in older adults. *J. Gerontol. A. Biol. Sci. Med. Sci.* **60**, 1414–1419 (2005).
- 26. Guermonprez, P., Valladeau, J., Zitvogel, L., Théry, C. & Amigorena, S. ANTIGEN PRESENTATION AND T CELL STIMULATION BY DENDRITIC CELLS. *Annu. Rev. Immunol* **20**, 621-67 (2002).
- 27. Jing, Y. et al. Aging is associated with a numerical and functional decline in plasmacytoid dendritic cells, whereas myeloid dendritic cells are relatively unaltered in human peripheral blood. *Hum. Immunol.* **70**, 777–784 (2009).
- Agrawal, A. et al. Altered Innate Immune Functioning of Dendritic Cells in Elderly Humans: A Role of Phosphoinositide 3-Kinase-Signaling Pathway. J. Immunol. 178, 6912-6922 (2007).

- 29. Della Bella, S. et al. Peripheral blood dendritic cells and monocytes are differently regulated in the elderly. *Clin. Immunol.* **122**, 220-228 (2007).
- 30. Prakash, S., Agrawal, S., Cao, J., Gupta, S. & Agrawal, A. Impaired secretion of interferons by dendritic cells from aged subjects to influenza : role of histone modifications. *Age (Dordr)*. **35**, 1785-97 (2013).
- Qian, F. et al. Impaired interferon signaling in dendritic cells from older donors infected in vitro with West Nile virus.
 J. Infect. Dis. 203, 1415-24 (2011).
- 32. Colpitts, T. M., Conway, M. J., Montgomery, R. R. & Fikrig, E. West Nile Virus: biology, transmission, and human infection. *Clin. Microbiol. Rev.* **25**, 635-48 (2012).
- 33. Hardy, R. R. & Hayakawa, K. B Cell development PAthways. Annu. Rev. Immunol. 19, 595-621 (2001).
- Ademokun, A., Wu, Y. C. & Dunn-Walters, D. The ageing B cell population: Composition and function. Biogerontology 11, 125-137 (2010).
- 35. Gibson, K. L. et al. B-cell diversity decreases in old age and is correlated with poor health status. Aging Cell 8, 18-25 (2009).
- Chong, Y. et al. CD27+ (memory) B cell decrease and apoptosis-resistant CD27- (naive) B cell increase in aged humans: Implications for age-related peripheral B cell developmental disturbances. *Int. Immunol.* 17, 383–390 (2005).
- 37. Sasaki, S. et al. Limited efficacy of inactivated influenza vaccine in elderly individuals is associated with decreased production of vaccine-specific antibodies. *J. Clin. Invest.* **121**, 3109–3119 (2011).
- 38. Roukens, A. H. et al. Elderly subjects have a delayed antibody response and prolonged viraemia following yellow fever vaccination: A prospective controlled cohort study. *PLoS One* **6**, 1–6 (2011).
- Tscharke, D. C., Croft, N. P., Doherty, P. C. & La Gruta, N. L. Sizing up the key determinants of the CD8+ T cell response. Nat. Rev. Immunol. 15, 705-716 (2015).
- 40. Aspinall, R. & Andrew, D. Thymic involution in aging. J. Clin. Immunol. 20, 250–256 (2000).
- 41. Ferrando-Mart??nez, S. et al. Age-related deregulation of naive T cell homeostasis in elderly humans. *Age (Omaha).* **33**, 197-207 (2011).
- 42. Colonna-Romano, G. et al. Impact of CMV and EBV seropositivity on CD8 T lymphocytes in an old population from West-Sicily. *Exp. Gerontol.* **42**, 995–1002 (2007).
- Akbar, A. N. & Fletcher, J. M. Memory T cell homeostasis and senescence during aging. *Curr. Opin. Immunol.* 17, 480-485 (2005).
- 44. Mempel, T. R., Henrickson, S. E. & von Andrian, U. H. T-cell priming by dendriticcells in lymph nodes occurs in three distinct phases. *Nature* **427**, 154–159 (2004).
- 45. Weng, N., Akbar, A. N. & Goronzy, J. CD28– T cells: their role in the age-associated decline of immune function. *Trends Immunol.* **30**, 306–312 (2009).
- 46. Franceschi, C. & Campisi, J. Chronic inflammation (Inflammaging) and its potential contribution to age-associated diseases. Journals Gerontol. - Ser. *A Biol. Sci. Med. Sci.* 69, S4–S9 (2014).
- 47. Trichopoulou, A. Traditional Mediterranean diet and longevity in the elderly: a review. *Public Health Nutr.* 7, 943–947 (2004).
- 48. Brambilla, D. et al. The role of antioxidant supplement in immune system, neoplastic, and neurodegenerative disorders: a point of view for an assessment of the risk/benefit profile. *Nutr. J.* **7**, 29 (2008).
- 49. Meydani, S. N. et al. Vitamin E supplementation enhances cell-mediated immunity in healthy elderly subjects. *Am. J. Clin. Nutr.* **52**, 557-563 (1990).
- 50. Meydani, S. N. et al. Vitamin E supplementation and in vivo immune response in healthy elderly subjects. A randomized controlled trial. *JAMA* **277**, 1380-6 (1997).
- 51. De la Fuente, M., Hernanz, A., Guayerbas, N., Victor, V. M. & Arnalich, F. Vitamin E ingestion improves several immune functions in elderly men and women. *Free Radic. Res.* **42**, 272-80 (2008).
- 52. Wu, D. & Meydani, S. N. Age-associated changes in immune and inflammatory responses: impact of vitamin E intervention. *J. Leukoc. Biol.* **84**, 900–14 (2008).
- Hayek, M. G. et al. Vitamin E supplementation decreases lung virus titers in mice infected with influenza.
 J. Infect. Dis. 176, 273-6 (1997).

- 54. Han, S. N. et al. Vitamin E supplementation increases T helper 1 cytokine production in old mice infected with influenza virus. *Immunology* **100**, 487–493 (2000).
- 55. Chavance, M., Herbeth, B., Fournier, C., Janot, C. & Vernhes, G. Vitamin status, immunity and infections in an elderly population. *Eur. J. Clin. Nutr.* **43**, 827-35 (1989).
- 56. Meydani, S. N., Han, S. N. & Wu, D. Vitamin E and immune response in the aged: Molecular mechanisms and clinical implications. *Immunol. Rev.* **205**, 269–284 (2005).
- 57. Battault, S. et al. Vitamin D metabolism, functions and needs: From science to health claims. *Eur. J. Nutr.* **52**, 429-441 (2013).
- 58. Borel, P., Caillaud, D. & Cano, N. J. Vitamin D bioavailability: state of the art. Crit. Rev. Food Sci. Nutr. 55, 1193–205 (2015).
- 59. Hilger, J. et al. A systematic review of vitamin D status in populations worldwide. *Br. J. Nutr.* **111**, 23-45 (2014).
- 60. Prietl, B., Treiber, G., Pieber, T. R. & Amrein, K. Vitamin D and immune function. *Nutrients* 5, 2502–2521 (2013).
- 61. Sadeghi, K. et al. Vitamin D3 down-regulates monocyte TLR expression and triggers hyporesponsiveness to pathogen-associated molecular patterns. *Eur. J. Immunol.* **36**, 361–370 (2006).
- 62. Calton, E. K., Keane, K. N., Newsholme, P. & Soares, M. J. The impact of Vitamin D levels on inflammatory status: A systematic review of immune cell studies. *PLoS One* **10**, 1-12 (2015).
- 63. Perlstein, T. S., Pande, R., Berliner, N. & Vanasse, G. J. Prevalence of 25-hydroxyvitamin D deficiency in subgroups of elderly persons with anemia: Association with anemia of inflammation. *Blood* **117**, 2800-2806 (2011).
- Laird, E. et al. Vitamin D deficiency is associated with inflammation in older irish adults.
 J. Clin. Endocrinol. Metab. 99, 1807–1815 (2014).
- 65. Tang, B. M., Eslick, G. D., Nowson, C., Smith, C. & Bensoussan, A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. *Lancet* **370**, 657-666 (2007).
- Schrezenmeir, J. & de Vrese, M. Probiotics, prebiotics, and synbiotics--approaching a definition.
 Am. J. Clin. Nutr. 73, 361S-364S (2001).
- 67. Biagi, E., Candela, M., Fairweather-Tait, S., Franceschi, C. & Brigidi, P. Aging of the human metaorganism: the microbial counterpart. *Age (Dordr)*. **34**, 247-67 (2012).
- 68. Man, A. L., Gicheva, N. & Nicoletti, C. The impact of ageing on the intestinal epithelial barrier and immune system. *Cell. Immunol.* **289**, 112-118 (2014).
- Fujihashi, K. & Kiyono, H. Mucosal immunosenescence: new developments and vaccines to control infectious diseases. Trends Immunol. 30, 334-343 (2009).
- 70. Yan, F. & Polk, D. B. Probiotics and immune health. *Curr. Opin. Gastroenterol.* 27, 496–501 (2011).
- 71. Maneerat, S. et al. Consumption of Bifidobacterium lactis Bi-07 by healthy elderly adults enhances phagocytic activity of monocytes and granulocytes. *J. Nutr. Sci.* **2**, (2013).
- 72. Boge, T. et al. A probiotic fermented dairy drink improves antibody response to influenza vaccination in the elderly in two randomised controlled trials. *Vaccine* **27**, 5677–5684 (2009).
- 73. Guillemard, E., Tondu, F., Lacoin, F. & Schrezenmeir, J. Consumption of a fermented dairy product containing the probiotic Lactobacillus casei DN-114 001 reduces the duration of respiratory infections in the elderly in a randomised controlled trial. *Br. J. Nutr.* **103**, 58 (2010).
- 74. Makino, S. et al. Reducing the risk of infection in the elderly by dietary intake of yoghurt fermented with Lactobacillus delbrueckii ssp. bulgaricus OLL1073R-1. *Br. J. Nutr.* **104**, 998–1006 (2010).
- 75. Fritsche, K. Fatty acids as modulators of the immune response. Annu. Rev. Nutr. 26, 45-73 (2006).
- 76. Calder, P. C. The 2008 ESPEN Sir David Cuthbertson lecture: Fatty acids and inflammation From the membrane to the nucleus and from the laboratory bench to the clinic. *Clin. Nutr.* **29**, 5–12 (2010).
- 77. Pae, M., Meydani, S. N. & Wu, D. The role of nutrition in enhancing immunity in aging. Aging Dis. 3, 91-129 (2012).
- 78. Rees, D. et al. Dose-related effects of eicosapentaenoic acid on innate immune function in healthy humans: a comparison of young and older men. *Am. J. Clin. Nutr.* **83**, 331–342 (2006).
- 79. Draper, E. et al. Omega-3 fatty acids attenuate dendritic cell function via NF-κB independent of PPARγ.
 J. Nutr. Biochem. 22, 784-790 (2011).

- Weldon, S. M., Mullen, A. C., Loscher, C. E., Hurley, L. A. & Roche, H. M. Docosahexaenoic acid induces an anti-inflammatory profile in lipopolysaccharide-stimulated human THP-1 macrophages more effectively than eicosapentaenoic acid. *J. Nutr. Biochem.* 18, 250–258 (2007).
- 81. Meydani, S. N. et al. Oral (n-3) fatty acid supplementation suppresses cytokine production and lymphocyte proliferation: comparison between young and older women. *J. Nutr.* **121**, 547–55 (1991).
- 82. Bechoua, S. et al. Influence of very low dietary intake of marine oil on some functional aspects of immune cells in healthy elderly people. *Br. J. Nutr.* **89**, 523–31 (2003).
- 83. Bouwens, M. et al. Fish-oil supplementation induces antiinflammatory gene expression profiles in human blood mononuclear cells. *Am J Clin Nutr* **90**, 415-424 (2009).
- 84. Alperovich, M., Neuman, M. I., Willett, W. C. & Curhan, G. C. Fatty acid intake and the risk of community-acquired pneumonia in U.S. women. *Nutrition* **23**, 196–202 (2007).
- 85. Merchant, A. T., Curhan, G. C., Rimm, E. B., Willett, W. C. & Fawzi, W. W. Intake of n6 and n3 fatty acids and fish and risk of community- acquired pneumonia in US men 1 3. *Am. J. Clin. Nutr.* **82**, 668–674 (2005).
- Boirie, Y., Morio, B., Caumon, E. & Cano, N. J. Nutrition and protein energy homeostasis in elderly. Mech. Ageing Dev. 136-137, 76-84 (2014).
- 87. Gryson, C. et al. 'Fast proteins' with a unique essential amino acid content as an optimal nutrition in the elderly: Growing evidence. *Clin. Nutr.* **33**, 642–648 (2014).
- 88. Allison, S. P. Malnutrition, disease, and outcome. *Nutrition* 16, 590-593 (2000).
- 89. Milne, a. C., Potter, J., Vivanti, a & Avenell, a. Protein and energy supplementation in older people at risk from malnutrition (2009). *Australas. J. Ageing* **29**, 144 (2010).
- 90. Marshall, K. Therapeutic applications of whey protein. *Altern. Med. Rev.* 9, 136–156 (2004).
- 91. Brandenburg, K., Heinbockel, L., Correa, W. & Lohner, K. Peptides with dual mode of action: Killing bacteria and preventing endotoxin-induced sepsis. *Biochim. Biophys. Acta Biomembr.* **1858**, 971–979 (2016).
- 92. Chatterton, D. E. W., Nguyen, D. N., Bering, S. B. & Sangild, P. T. Anti-inflammatory mechanisms of bioactive milk proteins in the intestine of newborns. *Int. J. Biochem. Cell Biol.* **45**, 1730-1747 (2013).
- 93. Rusu, D., Drouin, R., Pouliot, Y., Gauthier, S. & Poubelle, P. E. A bovine whey protein extract can enhance innate immunity by priming normal human blood neutrophils. *J. Nutr.* **139**, 386–393 (2009).
- 94. Rusu, D., Drouin, R., Pouliot, Y., Gauthier, S. & Poubelle, P. E. A bovine whey protein extract stimulates human neutrophils to generate bioactive IL-1Ra through a NF-kappaB- and MAPK-dependent mechanism. *J. Nutr.* **140**, 382-91 (2010).
- 95. Chevalley, T., Hoffmeyer, P., Bonjour, J. P. & Rizzoli, R. Early serum IGF-I response to oral protein supplements in elderly women with a recent hip fracture. *Clin. Nutr.* **29**, 78–83 (2010).
- 96. Pal, S. & Ellis, V. The chronic effects of whey proteins on blood pressure, vascular function, and inflammatory markers in overweight individuals. *Obesity (Silver Spring).* **18**, 1354–1359 (2010).
- 97. Lee, Y. M., Skurk, T., Hennig, M. & Hauner, H. Effect of a milk drink supplemented with whey peptides on blood pressure in patients with mild hypertension. *Eur. J. Nutr.* **46**, 21–27 (2007).
- 98. Gouni-Berthold, I. et al. The whey fermentation product malleable protein matrix decreases TAG concentrations in patients with the metabolic syndrome: a randomised placebo-controlled trial. *Br. J. Nutr.* **107**, 1694–706 (2012).
- 99. Petyaev, I. M., Dovgalevsky, P. Y., Klochkov, V. A., Chalyk, N. E. & Kyle, N. Whey protein lycosome formulation improves vascular functions and plasma lipids with reduction of markers of inflammation and oxidative stress in prehypertension. *ScientificWorldJournal.* **2012**, 269476 (2012).
- 100. Bharadwaj, S., Naidu, T. A. G., Betageri, G. V., Prasadarao, N. V. & Naidu, A. S. Inflammatory responses improve with milk ribonuclease-enriched lactoferrin supplementation in postmenopausal women. *Inflamm. Res.* **59**, 971–978 (2010).
- 101. Zhou, L. M. et al. Effect of whey supplementation on circulating C-reactive protein: A meta-analysis of randomized controlled trials. *Nutrients* **7**, 1131–1143 (2015).