Kerry Health and Nutrition Institute.

The Role of Food in Maintaining Immune Health in Ageing

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

Part 3: Can Food Impact Immune Health in Ageing?

Immunosenescence (decreasing strength of the immune system with age) is a complex process that affects the immune system on the whole and compromises the ability to adequately respond to invading pathogens. It seems there is no single impairment to be blamed; rather it is a multi-faceted dysfunction that affects individuals to different extents. As a result of this, elderly individuals are predisposed to increased susceptibility to infections, decreased responses to vaccinations and poorer responses to known and new antigens. In addition to this, the elderly population tend to present a chronic low-grade inflammatory state (inflamm-ageing) that has been linked to the development of many age-related diseases (atherosclerosis, Alzheimer's disease and diabetes) [46]. The reduced responsiveness of the elderly immune system to pathogens, prolonging infection duration and severity may contribute to this inflammatory state. In order to increase immune health in the ageing population we need to look to therapies that will, on one hand increase the ability of our immune cells in combating new and recurrent infections, but at the same time not exacerbate one's inflammatory status.

Like the age-related changes that occur in other systems of the body, immunosenescence is universal in who it affects, but the degree to which it can affect us can differ depending largely on the interaction of genetics, environment, lifestyle and nutrition. Nutrition as a modifiable factor in impacting immune health has been studied for a few decades, and this research has developed into a field known as nutritional immunology. The impact of nutrition on immune health is often studied by comparing patterns of ageing, disease, and longevity across populations from geographically distinct areas. For example, people in regions of the Mediterranean that consume a diet rich in fruit, vegetables, legumes, unrefined cereals and olive oil often show decreased incidence of heart disease [47]. Nutritional interventions are an effective, logistically feasible and cost-effective approach to tackle immunosenescence and its associated complications.

Vitamin E

Vitamin E is a lipid soluble antioxidant present in the membrane of all cells and is particularly abundant in immune cells. Naturally occurring sources of vitamin E include almonds and raw seeds such as sunflower, pumpkin and sesame seeds, plant oils and leafy greens.

Vitamin E is considered one of the most effective nutrients at enhancing immune function. A number of both animal and human studies have indicated that vitamin E deficiency impairs immune functions [48]. Vitamin E supplementation, particularly in the elderly, has been shown to enhance immune response and cell mediated immunity. Healthy elderly people (>60 y) who received vitamin E supplementation (800mg/d) for one month displayed a significant improvement in Delayed Type Hypersensitivity (DTH) response, *ex vivo* T cell proliferation, IL-2 production and a significant decrease in plasma lipid peroxidation - all measures of an enhanced immune response [49]. In a study of independently living elderly, who received 60, 200 or 800 mg/d of vitamin E for 4.5 months, the subjects receiving 200mg/d showed significant increases in antibody response following hepatitis B and tetanus vaccinations [50]. Following on from this, a more recent study has shown that elderly subjects receiving 200mg/d of vitamin E displayed higher levels of lymphocyte proliferative response to phytohemagglutinin (an inducer of T cell activation) and neutrophil chemotaxis and phagocytosis [51]. Results from animal studies have helped determine the mechanism by which vitamin E has an immune enhancing effect in the aged. In general, vitamin E can enhance age-associated deficits in T cell mediated function by directly influencing membrane integrity and signal transduction in T cells, or indirectly by reducing the production of suppressive factors such as prostaglandin E2 by macrophages [52].

Immunosenescence is associated with both increased incidence of infections and prolonged infection times. **Thus, it is anticipated that providing the elderly with vitamin E supplementation would prove a useful strategy to enhance their resistance to infection by improving immune function**. To date a number of both animal and human studies have reported a protective effect of vitamin E against infection. Vitamin E supplementation has been shown to reduce influenza viral titres in old mice more significantly than young mice [53,54]. Fewer investigators have directly examined the effect of vitamin E supplementation in humans; however, a retrospective study in healthy elderly showed that plasma vitamin E levels were negatively related to the number of past infections [55]. Another study that determined the effects of one year's vitamin E supplementation on objectively recorded respiratory infection in elderly nursing home residents showed significantly fewer participants contracting one or more infection and a lower incidence of common colds in the vitamin E group [56].

Vitamin D

Vitamin D may be derived from three sources: nutritional sources, UVB-dependent endogenous production (i.e. created in our skin from sunlight) and supplements. In humans, vitamin D is mainly synthesised in the skin after exposure to UVB, whereas only a minor part is derived from dietary sources. Few natural, non-fortified products such as fatty fish (salmon, mackerel, sardines, cod liver oil) or some types of mushrooms (Shiitake), contain relevant amounts of one of the two major forms cholecalciferol (vitamin D3) or ergocalciferol (vitamin D2). The classical, hormonal actions of vitamin D are related to mineral metabolism and skeletal health. Over the last decade however, the perspective on how vitamin D influences human health has changed dramatically based on the finding that the vitamin D receptor (VDR) and the vitamin D activating enzyme 1-α-hydroxylase (CYP27B1) are expressed in many cell types which are not involved in bone and mineral metabolism, such as the intestine, pancreas, prostate and cells of the immune system [57].

Vitamin D levels decline with age [25] and vitamin D deficiency is very common in elderly populations worldwide [59]. The role that vitamin D plays in the immune system has been well documented [60]. The vitamin D receptor is found in many cells related to inflammation and immunity, including macrophages that also have the capacity of converting 25-OH-D into its active metabolite by expressing 1α-hydroxylase. Vitamin D may play a role in silencing the immune response, which helps turn off the inflammation signal when it is no longer needed. The activation of the VDR in macrophages up-regulates the inhibition of NF-κB, resulting in decreased production of TNF-α and induced hyporesponsiveness to antigenic stimulation [61]. Vitamin D also reduces proinflammatory cytokine secretion from lymphocytes and adipocytes, favouring immunomodulation and resolution of chronic inflammation [62].

These findings support the theory that vitamin D deficiency in the elderly could be linked with inflamm-ageing. However, there have been conflicting reports to date regarding the association between vitamin D deficiency in the elderly and altered immune responses. Some groups have reported an association between vitamin D deficiency and anaemia of inflammation [63], whereas others have reported associations between vitamin D deficiency and higher circulating levels of IL-6 and CRP [64]. Besides its potential immune benefits, evidence supports the use of vitamin D in combination with calcium supplementation to help prevent osteoporosis in people aged 50 years or older [65].

Probiotics

Our gastrointestinal tract (GI tract) must be able to distinguish between positive (e.g. nutrients from food) and negative components (e.g. harmful bacteria in food) in everything we consume, meaning a strong immune response in the GI tract is essential. Probiotics are defined as live microorganisms that reach the intestinal tract in sufficient numbers and exert health benefits on the person consuming them [66]. The most characterised probiotic microorganisms are members of the genera *Lactobacillus, Bifidobacterium and Streptococcus*. Probiotics can alter immune function in the gastrointestinal (GI) tract and more distant tissues via their impact on the mucosal immune system and circulating immune cells that traffic to and from mucosal sites. Ageing is associated with a reduction in the numbers of beneficial microbes in the GI tract [67]. Ageing also results in reduced antigen-specific IgA response, which is a response that helps protect the host by preventing harmful bacteria, viruses and fungi from entering our bodies [68]. There is also decline in the number of lymphocytes and a decreased ability of T cells to proliferate and respond to invaders [69].

There is now an increasing body of evidence to support a beneficial role for probiotics in both the mucosal (GI tract) and systemic (whole body) immune systems [70]. Since both mucosal and systemic immune functions are known to decline with ageing, it is expected that the aged would benefit from consumption of probiotics. In a study of healthy elderly people, administration of the probiotic *Bacillus lactis* for six weeks resulted in a significant improvement in the immune response following ingestion of a harmful pathogen. Specifically, the study found improvements in neutrophil phagocytic and bactericidal activity and enhanced secretion of interferon-alpha from peripheral blood mononuclear cells following *Staphylococcus aureus* (a harmful pathogen) challenge [71]. It has also been reported that healthy elderly people residing in nursing homes displayed improved antibody responses to influenza vaccination after 13 weeks of daily consumption of a product containing probiotics *L. casei, S. thermophilus and L. bulgaricus* [72]. Healthy, independently living elderly people supplemented with a fermented dairy drink (Actimel®), containing the same probiotics reported a shorter cumulative duration and average duration per episode for all common infectious diseases [73]. **On average, probiotic supplementation reduced the duration of all common infectious diseases by 1-1.5 days**. A similar study reported that elderly supplemented with yoghurt fermented with *L. bulgaricus and S. thermophilus* for 12 weeks had a significant reduction in occurrence of the common cold or influenza virus infection compared to the control group [74].

Fatty Acids

Dietary fatty acids are not only fundamental energy-providing nutrients, but also greatly impact specific cell functions. Different classifications of dietary fatty acids (FA) have differing impacts on the immune system [75]. There are different classifications for FAs including essential (omega-3 and omega-6), saturated, monounsaturated and polyunsaturated fatty acids (PUFA). The most studied FAs are the omega-3 (n-3) and omega-6 (n-6) PUFA families. n-6 PUFAs are derived from plants and land animals. n-3 PUFAs are found mainly in fish and fish products and in some plants (flax seeds). Marine animal-derived n-3 PUFAs (mainly eicosapentaenoic acid or EPA, and docosahexaenoic acid or DHA) have the most significant effect on immune cell functions compared to other FAs. Consumption of long chain n-3 PUFA or fish

oil has been shown to have beneficial effects on several prevalent, age-related diseases such as cardiovascular disease, degenerative neurological diseases, inflammatory and autoimmune diseases, and age-related macular degeneration [76].
In general, n-3 PUFAs are anti-inflammatory, having been shown repeatedly to inhibit production of inflammatory mediators including proinflammatory cytokines (IL-1β, TNF-α, IL-6), chemokines (IL-8, MCP-1), adhesion molecules (ICAM-1, VCAM-1, selectins), platelet activating factor, and reactive oxygen and nitrogen species [77]. They also suppress both innate (mainly inflammation) and adaptive (T cell-mediated) immune responses, which can impair immunity to infectious and neoplastic disease [78]. Fish oils have been shown to inhibit pro-inflammatory cytokine production by lymphocytes, macrophages and dendritic cells [78-80]. **Thus, while n-3 PUFA may be helpful in fighting inflamm-ageing, it is also important to consider the drawbacks of n-3 PUFA supplementation in individuals that have impaired immune responses, such as the elderly**.

There have been a few studies focusing particularly on the effect of n-3 PUFA supplementation on immune responses in the elderly. Reduction in cytokine production and an inhibition in mitogen-induced PBMC proliferation were observed in older people given low levels of n-3 PUFA (1.68 g EPA and 0.72 g DHA/d) for three months [81]. Another study in older people (70–83 years of age) consuming habitual amounts of low doses of PUFA (30 mg EPA and 150 mg DHA/d) for six weeks showed a decrease in lymphocyte proliferation in response to different T cell stimuli [82]. Providing EPA to older and younger males for 12 weeks led to dose-dependent decreases in neutrophil respiratory bursts, especially in the older male group [78]. Healthy elderly people supplemented with high doses of EPA (1.8 g) and DHA (1.8 g) equivalent to ten portions of oily fish per week for 26 weeks displayed decreased levels of free fatty acids and triglycerides and a reduction in pro-inflammatory genes including NF-κB target genes and pro-inflammatory cytokines [83]. Since n-3 PUFA can attenuate inflammatory and T cell-mediated immune responses, which are key components in the body's defence against microbial infection, it is important to know if increased intake of n-3 PUFA can actually compromise the host's defence against infection. Prospective investigation into the effect of n-3 PUFAs on infection suggests that with increased intake of palmitic acid and EPA the risk of infection increases [84]. While this observation was made in women, a similar study in men found an inverse association between n-3 and n-6 and pneumonia risk [85], which could be due to gender differences or to interactions of n-3 and n-6 PUFAs. In general, findings from animal studies suggest that n-3 PUFA supresses the immune response resulting in lower resistance to infection [77]. **The data to date suggests that n-3 PUFAs do not improve immunosenescence. However, the advantages of taking n-3 PUFA may outweigh the potential adverse effects under certain circumstances**. For example, increasing n-3 PUFA intake might be beneficial to treat inflammatory and autoimmune diseases such as rheumatoid arthritis and inflammatory bowel disease or diseases in which inflammation is an underlying factor of pathogenesis such as type 2 diabetes, cardiovascular disease and Alzheimer's disease.

Proteins

Proteins are essential nutrients for the human body. Proteins are polymer chains made of amino acids linked together by peptide bonds. Sources of protein include grains, legumes and nuts, as well as animal sources such as meats, dairy products, fish and eggs. They make up part of the building blocks of body tissue, and can also serve as a fuel source. In elderly subjects, an optimal dietary intake of proteins is of paramount importance for the maintenance of muscle and for prevention of sarcopenia (age-related decline in muscle mass) [86]. Despite this fact, elderly people tend to consume less than the recommended dietary allowance of protein, which may be due to reduced appetite seen with age and an inability to tolerate certain foods. This can result in accelerated body protein loss and impaired physiological functions [87]. Undernutrition is defined as "a state of energy, protein or other specific nutrient deficiency, which produces a measurable change in body function and is associated with worse outcome from illness as well as being specifically reversed by nutritional support" [88]. In the elderly, protein undernutrition impacts both physiological and biochemical systems and has been associated strongly with impaired immune response, impaired muscle and respiratory function, delayed wound healing, overall increased complications, longer rehabilitation, greater length of hospital stay and increased mortality [89]. For these reasons it is thought that protein supplementation in the elderly would contribute to healthy ageing. Research in this area has focused on identifying proteins with added functional value to provide older adults with protein at the same time as impacting positively on one or more body systems that are known to decline with age. Certain proteins from bovine milk have thus far been identified as having immune-modulating properties that could prove helpful as a supplement in the context of both protein malnutrition and immunosenescence.

Whey proteins account for about 20% of the total protein content of bovine milk and represent, together with casein, the high-quality fraction of milk proteins. They can be extracted from the liquid by-product from cheese manufacturing processes [90]. Their high digestibility, quick absorption and elevated content in essential amino acids make whey the ideal nutritional supplement for the ageing individual. The putative beneficial effects of whey proteins are due to their favourable composition that allows a quick digestion and absorption, and thus higher concentrations of amino acids in blood immediately after a meal [86]. Whey is made up a number of protein fractions such as beta-lactoglobulin (55-65%), alpha-lactalbumin (15-25%), glycomacropeptide and lactoferrin. Some of these peptides are capable of affecting biological functions and boosting the immune system. These effects can be antimicrobial and probiotic, i.e. prevent the growth and proliferation of undesirable and pathogenic organisms, or they may promote the growth of desirable bacteria in the digestive tract of humans and animals [91]. Protein peptides have also been shown to influence the immune system directly by modulating the cells involved in the immune response [92]. These biological effects may play an important role in the development of functional foods that treat or mitigate the effects of ageing on the immune system.

In vitro studies conducted on human neutrophils have shown that whey protein extracts can stimulate NF-κB and MAPK signalling, both of which play a crucial role in immune responses [93]. This was also associated with a significant and dose-dependent increase of their chemotaxis, superoxide production, phagocytosis and degranulation in response to stimulation [94]. The data from *in vivo* studies is still limited. Studies have shown that supplementation of elderly women with whey proteins results in increased circulating insulin-like growth factor 1 (IGF-1) levels, a negative modulator of the inflammatory response [95]. Several studies have assessed the effect of whey supplementation on inflammatory markers in adult subjects. The majority these studies concluded that whey supplementation is not associated with a decrease in serum CRP levels in various settings, including individuals with obesity [96], hypertension [97] and metabolic syndrome [98]. Only a small number of studies conducted in healthy subjects or in patients undergoing surgery were consistent with the hypothesised beneficial effects of whey supplementation on circulating CRP levels [99,100].

The results of these studies were recently combined into a meta-analysis by Zhou et al., who summarised that the current state of evidence does not support the role of whey supplements in actively improving immune health in adult subjects[101]. Although the benefit of protein may not be in supporting the immune system in ageing populations, the fact that optimal dietary intake of proteins is of paramount importance for the maintenance of muscle and for prevention of sarcopenia in the elderly suggests that whey supplementation would still benefit elderly individuals.

The Future

It is clear that there is substantial evidence to support the use of food to modulate immune health. However, in the context of ageing, the use of immune-supporting nutrients alongside protein may have significant advantages over some of the other foods outlined in this paper such as fats and vitamins alone. Protein with added functional value could enable us to provide older adults with much-needed protein at the same time as impacting positively on their immune system. If we work to create novel nutrient combinations, which can positively impact the immune system, we may be able to create new ingredients which can be advantageous for muscle health, immune health and overall wellness in older adults - a worthy target.

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.

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