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Abstract: Ageing is characterized by immunosenescence and the progressive decline in immunity in association with an increased frequency of infections and chronic disease. This complex process affects both the innate and adaptive immune systems with a progressive decline in most immune cell populations and defects in activation resulting in loss of function. Although host genetics and environmental factors, such as stress, exercise and diet can impact on the onset or course of immunosenescence, the mechanisms involved are largely unknown. This review focusses on identifying the most significant aspects of immunosenescence and on the evidence that nutritional intervention might delay this process, and consequently improve the quality of life of the elderly.

December 5th 2013

Editors,
Mechanisms of Ageing and Development

Dear Sir/Madam,

On behalf of all of the authors I pleased to submit a revised version of the manuscript entitled “Nutrition, diet and immunosenescence” for consideration for inclusion in the NU_AGE issue of *Mechanisms of Ageing and Development*.

The manuscript has been revised according to comments received from the reviewers.

Sincerely,

Simon R. Carding
On behalf of all authors

***Detailed Response to Reviewers**

December 5th, 2013

Dear Editor,

We would like to thank the reviewers for their careful review of our manuscript, which has been revised accordingly. Below, we have provided a point-by-point reply to the issues raised:

5. Regarding the inflammaging concept, please also cite the following papers:

a. Franceschi et al., 2000 Inflamm-aging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci. 908:244-54
b. Cevenini et al., 2013. Inflamm-aging -Curr Opin Clin Nutr Metab Care

These papers have been added in the corresponding part of the paper.

6. As partner of the NU-AGE project, please add the Acknowledgements to the project.

Done.

Yours sincerely,

Simon R. Carding, PhD

On behalf of all authors

Highlights

- We reviewed the effect of ageing on both innate and adaptive immune system
- We examined the ability of dietary components to influence immunity in ageing
- Dietary components have the potential to improve immunity in ageing
- Mechanism underlying effects of diet on immunity remain to be largely determined
- Pathways of chronic inflammation are a potential target for dietary intervention

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Review:

Nutrition, diet and immunosenescence

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Abstract

Ageing is characterized by immunosenescence and the progressive decline in immunity in association with an increased frequency of infections and chronic disease. This complex process affects both the innate and adaptive immune systems with a progressive decline in most immune cell populations and defects in activation resulting in loss of function. Although host genetics and environmental factors, such as stress, exercise and diet can impact on the onset or course of immunosenescence, the mechanisms involved are largely unknown. This review focusses on identifying the most significant aspects of immunosenescence and on the evidence that nutritional intervention might delay this process, and consequently improve the quality of life of the elderly.

Keywords: Immunosenescence, ageing, nutrition

1. Introduction

Ageing is an irreversible process although improvements in public health, vaccination and healthier diets have contributed to an increase in average lifespans of the majority of citizens of developed countries. Ageing is associated with the functional decline of the immune system and ability to defend against infection by environmental pathogens, vaccine failure, and an increased incidence of autoimmunity and cancer (Castle, 2000; Dewan et al., 2012).

Immunosenescence affects both innate and adaptive immunity (DelaRosa et al., 2006; Gomez et al., 2008; Pawelec, 2006; Shaw et al., 2010; Solana et al., 2006), with alterations in constituent cells of both (Figure 1), linked to the onset of chronic disease. The design of interventional strategies to delay or possibly reverse immunosenescence requires a detailed understanding of how different immune cells become senescent.

Although there is considerable heterogeneity among individuals owing largely to variations in genetics and polymorphisms of immune response genes such as MHC which cannot be altered, some factors such as lifestyle choices and nutrition (Pae et al, 2012) are amenable to modification and impacting the progression of immunosenescence. Of particular interest is the use of diet and

nutritional supplementation to improve immune function in the elderly. This is rationalised on geographically distinct patterns of ageing and the decreased incidence of cardiovascular and other chronic diseases and increased longevity in populations such as those in regions of the Mediterranean that consume a diet rich in fruit, vegetables, legumes, unrefined cereals and olive oil, with low intake of meat and dairy products and moderate alcohol consumption, (Trichopoulou et al., 2003; Vasto et al., 2012).

The design of studies to evaluate the effects of nutrient supplementation is important and critical for determining efficacy and impact (Chandra, 2004). Different protocols exist for selecting participants for these studies. In 1984 the first specific criterion for participants in studies of immune ageing was described by the EU Concerted Action Programme on Ageing (EURAGE). Subsequently, the SENIEUR protocol was defined to better characterize "healthiness" (Ligthart et al., 1984) and excludes subjects who have chronic diseases, take medications or are in residential care. In recognising that undernutrition is common in elderly populations a nutritional criterion to measures the protein status of the subjects was added in 1988. Finally, as micronutrient deficiencies may influence the immune response of elderly subjects, new criteria relating to micronutrient levels have been added (Lesourd and Mazari, 1999) and currently, elderly subjects who fulfil the SENIEUR criteria should have a serum albumin level of ≥ 39 g/l and no deficit in Zn, Se, Folic acid and vitamins C, E, B6 and B12.

In this review we will summarise the impact ageing has on immune cells of both the innate (neutrophils, macrophages, NK cells) and adaptive (mainly T and B populations) immune system and the cells that bridge the two (DC) in addition to the effect that nutritional (micronutrients, macronutrients, functional foods, and whole diets) interventions have on these cells.

2. Immunosenescence and inflammaging

Advancing age is associated with an increased susceptibility of developing infections, frailty, cardiovascular disease, autoimmune disease (e.g. rheumatoid arthritis), metabolic syndrome, type II diabetes and cancer (Mitchell et al., 2010). This results in increases in healthcare costs, the need for residential care and a reduced quality of life. Immunosenescence describes age-related alterations in immune function, chronic inflammation and their link to increased risk of infection and age-associated disease (Mitchell et al., 2010). Age-related changes to the immune system include dysfunctional B cells, T cells, monocytes, natural killer (NK) cells and neutrophils, thymic involution and a decline in T cell production, alterations in T-helper 1/ T-helper 2 (Th1/ Th2) profiles and the occurrence of an immune risk profile (IRP) characterized by an inverted CD4/CD8 ratio associated with persistent cytomegalovirus infection and an increases in the number of $CD3^{+}CD8^{+}CD28^{-}$ cells (Wikby et al., 2008). Increased susceptibility to infection is associated with decreased levels of interferon (IFN)-γ and increased levels of interleukin (IL)-4 and IL-10 (Rink et al., 1998). The reduction in IFN-γ is linked to decreased numbers of effector memory T cells and $CD8^{+}$ cytotoxic T cells (Rink et al., 1998), which has been linked to lack of expression of the cell surface receptor CD28 and is a contributing factor to poor vaccine responses (Goronzy et al., 2001a; McElhaney et al., 2012). However, levels of other pro-inflammatory cytokines such tumor necrosis factor (TNF)-α and IL-6 may be higher in healthy elderly subjects compared to young adults (Goronzy et al., 2012; Wordsworth and Dunn-Walters, 2011), contributing to inflammaging and recurrent and persistent infections in the elderly (Larbi et al., 2008a; McElhaney et al., 2012). The immune response in the

frail elderly however, differs to that of the healthy elderly (Jing et al., 2009). Of note, the proportion of elderly within the general population who fulfil strict inclusion criteria of the SENIEUR protocol is low; only 10-15% (Uyemura et al., 2002) meaning that the results from studies using the SENIEUR protocol for subject recruitment may not be representative of the majority of elderly people within the general population.

The ageing organism is also characterized by a low grade chronic inflammation that results from alterations in the balance of production of pro-inflammatory versus anti-inflammatory mediators and cytokines and is termed 'inflammaging' (Wordsworth and Dunn-Walters, 2011). It would appear that inflammaging is under genetic control and is detrimental for longevity (Chung et al., 2002; Franceschi et al., 2000; Zanni et al., 2003). This age-related chronic inflammatory activity, leading to long term tissue damage, is related to increased mortality risk from all causes in old persons. Inflammaging is believed to be a consequence of a cumulative lifetime exposure to antigenic load caused by both clinical and subclinical infections as well as exposure to noninfective antigens (De Martinis et al., 2005). If true this would mean that, immunosenescence and probably morbidity and mortality will be accelerated in those subjects who are exposed to the highest burden of antigenic load. More recently, however it has been suggested that events taking place in the gastrointestinal tract may play an important role in triggering and/or nurturing the inflammaging process (Cevenini et al., 2013; Guigoz et al., 2008). Regardless of its origin, the consequent inflammatory response, tissue damage and production of reactive oxygen species that cause oxidative damage elicits the release of additional, amplifying cytokines, principally from cells of the innate immune system (Cannizzo et al., 2011). This results in a vicious cycle that, drives immune system remodelling and favour a chronic proinflammatory state where pathophysiological changes, tissue injury and healing proceed simultaneously. Irreversible cellular and molecular damage that is not clinically evident accumulates over decades.

3. Ageing of the innate immune system

3.1. Neutrophils in ageing

Neutrophil numbers remain unchanged in the elderly (Chatta et al., 1993)) although their functionality is decreased (Gomez et al., 2008). Chemotaxis (Fortin et al., 2006; Fulop et al., 2004) and phagocytosis (Butcher et al., 2001; Wenisch et al., 2000) is decreased in healthy aged individuals and in advanced age there is delayed cellular apoptosis during inflammatory responses (Fortin et al., 2007; Fulop et al., 1997; Tortorella et al., 2001; Tortorella et al., 2006). Studies of ROS production by neutrophils in the elderly have produced conflicting findings with some showing an increased production (De la Fuente, 2008; Ogawa et al., 2008) whereas others have reported decreased production of superoxide and hydrogen peroxide (Di Lorenzo et al., 1999; Fulop et al., 1985; Nagel et al., 1982). The use of different stimuli and bacterial strains in the different studies may explain these conflicting results. Age-related changes in intracellular signalling pathways have also been described including reduced phosphorylation of extracellular receptor-activated kinase (ERK) and mitogen-activated protein (MAP) (Fulop et al., 2004; Larbi et al., 2005), signal tyrosine phosphatase-1 (SHT-1), and suppressor of cytokine signalling (SOCS) (Tortorella et al., 2006).

3.2. Monocytes and macrophages in ageing

Monocyte/macrophage function changes with age although there are species differences (Gomez et al., 2008). While some studies in aged humans and mice have shown decreased macrophage chemotaxis and phagocytosis (De La Fuente, 1985; Fietta et al., 1993), similar studies in aged rats have reported opposite results (Corsini et al., 2005; Hilmer et al., 2007). In humans, although the total number of monocytes in the elderly are similar compared to that in younger individuals, there is a decrease in macrophage precursors in the bone marrow of the elderly (Ogawa et al., 2000). Antigen presentation is also decreased, probably due to reduced expression of MHC class II molecules (Herrero et al., 2002; Plowden et al., 2004; Zissel et al., 1999). Production of superoxide anion (Plackett et al., 2004), and phagocytic ability is reduced as are the levels of macrophage inhibitory protein (MIP)-1α, MIP-1β, MIP-2 and eotaxin production (Swift et al., 2001). Expression and function of certain Toll-like receptors (TLRs) and other pattern recognition receptors are also affected in monocytes (Alvarez-Rodriguez et al., 2012) as is the ability to express CD80/CD86 co-stimulatory receptors after stimulation via TLRs (van Duin et al., 2007).

3.3. NK cells in ageing

The effect of ageing on the main DC56^{bright} and CD56^{dim} NK cell subsets and the expression and function of activating and inhibitory receptors has been extensively studied (Camous et al., 2012; Gayoso et al., 2011; Gomez et al., 2008). An increase in the absolute number of NK cells in the elderly (Borrego et al., 1999; Chidrawar et al., 2006; Le Garff-Tavernier et al., 2010), is associated with a decline in CD56^{bright} NK cells and an increase in the CD56^{dim} subset (Borrego et al., 1999; Chidrawar et al., 2006). Cytotoxicity, cytokine and chemokine production, proliferation and receptor expression are also adversely affected with age (Camous et al., 2012). CD56^{bright} NK cells in the aged produce less chemokines in response to the activating cytokines IL-2 and IL-12 (Mariani et al., 2002a; Mariani et al., 2002b). In contrast, CD16 the low-affinity IgG receptor (FcγRIII-A) involved in antibody dependent cell cytotoxicity is not affected by ageing, although interestingly cord blood and infant NK cells display very low CD16-dependent cytotoxicity compared with healthy adults (Le Garff-Tavernier et al., 2010; Solana et al., 1999; Solana and Mariani, 2000).

Few studies of NKT cells in the elderly have been carried out and their numbers may increase during ageing (Dubey et al., 2000; Faunce et al., 2005; Ishimoto et al., 2004). This may be attributed to a longer life span (Berzins et al., 2006) rather than an increased proliferative capacity (DelaRosa et al., 2002; Peralbo et al., 2007; Peralbo et al., 2006).

4. Antigen Presenting Cells (APCs)

Antigen presentation is a critical event in the regulation of antigen-specific immune response. APCs including macrophages, B cells and dendritic cells (DCs) (Uyemura et al., 2002) acquire, process and present pathogen-associated antigens to T cells resulting in antigen-specific immune responses and long lived immunity (Wordsworth and Dunn-Walters, 2011). This review focuses primarily on DCs.

4.1. APC in ageing: macrophages and B cells

Activated macrophages from aged mice have been shown to display reduced expression of MHC class II molecules (Herrero et al., 2001; Plowden et al., 2004; Varas et al., 2003) and were found to have a reduced antigen presenting ability compared to cells from younger animals (Vetvicka et al.,

1985). A similar age-related distinction in APC activity was reported among alveolar macrophages (Zissel et al., 1999) which was associated with an increased risk of pulmonary infections in older animals. Monocyte-macrophage derived APCs in old mice were of a similar phenotype to that of cells from younger animals although they displayed a reduction in cytotoxicity and greater migratory capacity compared to young mice (Donnini et al., 2002).

A study investigating the antigen presenting ability of B cells and monocytes in a small number of aged and young subjects found that in some of the older individuals appeared to have reduced APC capability in the B cells. This was not however, related to changes in the ability of B cells or monocytes to process or present antigens so there was no significant difference in the antigen presentation capability of these cells among young and old subjects which were comparable in the two age groups (Clark et al., 2012), this means that an internal process could be the cause of the poor antigen presentation in some of the subjects.

4.2. APC in aging: DCs

DCs are capable of activating naïve T cells (Uyemura et al., 2002). They capture antigens via various mechanisms including micropinocytosis, phagocytosis of pathogenic material, internalisation of heat shock proteins via receptors and by receptor-mediated endocytosis using the pattern recognition receptors (PRRs) C-type lectins and Fcγ receptors (Agrawal et al., 2007b). DCs act as the main interface between the innate and adaptive immune systems. Understanding how ageing impacts on their behaviour and function is therefore of central importance to understanding mechanisms of immunosenescence.

4.2.1. Numbers of DC subsets with age

The numbers of DC as a whole and of various DC subsets has been extensively investigated in studies making comparisons between young and aged subjects. Significant decreases in plasmacytoid DCS (pDCs) and $CD11c^{+}CD8^{+}$ DCs along with a significant increase in $CD11c^{+}CD8^{-}$ myeloid DCs (mDCs) are observed in aged mice (Wong et al., 2010). Similarly, significant decreases in pDCs were observed in elderly human subjects (Canaday et al., 2010; Jing et al., 2009; Pérez-Cabezas et al., 2007; Shodell and Siegal, 2002) although the oldest sub-group of subjects tested were 50-65 years of age, which is considered middle-aged by others (Mysliwska, 1999; Shodell and Siegal, 2002). Significantly lower numbers of mDCs and pDCs have been observed in the frail elderly when compared to both healthy young and healthy elderly subjects (Jing et al., 2009). Others however have found no significant differences between peripheral mDCs and pDCs between young and elderly subjects (Agrawal et al., 2007a) and one study observed a reduction in mDCs with age (Della Bella et al., 2007). Some of this conflicting data may be attributed to using the SENIEUR protocol for recruitment of subjects. Investigations of monocyte derived DCs (MODCs) have found that DCs subsets are similar in aged and young subjects (Lung et al., 2000; Steger et al., 1996). This variation in opinion regarding changes in numbers of DC subsets with age may reflect differences in experimental protocols and the number of subjects recruited in the different studies (Jing et al., 2009). DCs are a minority cell population of blood and there is considerable individual variation in numbers of pDCs and mDCs with circulating blood DCs estimated to constitute between 0.1 and 1.0% of the leucocyte population (Fearnley et al., 1999).

4.2.2. Phenotypic alterations/maturation of DCs during ageing

With increasing age expression of CD25 and ICAM-1 are significantly reduced in mature MODCs (Ciaramella et al., 2011), though in this study comparisons were made between only 10 subjects in each age group. Also, in mature MODCs a significant negative correlation was found between age and anti-inflammatory IL-10 production along with a significant positive correlation between inflammatory IL-18 and IL-6 production with age. No differences were found in expression of the surface markers CD40, DC80, CD86 and MHC II (Wong et al., 2010) and CD86, CD80, CD54 and HLA-DR (Agrawal et al., 2007a; Lung et al., 2000) on mDCs and pDCs, which are indicative of maturation, or in the response to bacterial lipopolysaccharide (LPS) between young and old subjects. These findings have led to the suggestion that DC functionality is unimpaired in the elderly and that DCs may not play a part in declining T cell function with ageing.

4.2.3. Cytokine expression by DCs during ageing

The production of key inflammatory immune defence cytokines such as IFN-γ is driven by DC-derived IL-12, which is inhibited by the anti-inflammatory cytokine IL-10. Age-associated alterations in cytokine secretion by DCs can therefore impact on the nature and potency of T cell responses (Agrawal et al., 2007b). A reduction in IFN-α production by pDCs has been observed in mice (Stout-Delgado et al., 2008) and in geriatric individuals when compared to young controls, which could not be explained by changes in apoptosis (Canaday et al., 2010; Sridharan et al., 2011). These findings indicate that reduced responses of the immune system in the elderly to influenza and other viruses may be due to the age-associated decreases in pDCs (Jing et al., 2009; Pérez-Cabezas et al., 2007; Shodell and Siegal, 2002). Impaired IFN-I and -III production by pDCs may be linked to an alteration in IRF-7 phosphorylation, which is impaired in DCs of aged subjects but increased in young subjects (Sridharan et al., 2011). Recent findings reveal that the age-associated reduction in the ability of monocyte derived DCs to produce IFN-I and III in response to influenza virus is linked to alterations in chromatin structure (Prakash et al., 2012). Surface expression of CD54 and MHC II that improve contact between APCs and T cells is comparable between young and elderly subjects with increases observed upon exposure to influenza vaccine and in the production of IL-12 and TNF-α (Saurwein-Teissl et al., 1998). This indicates that there is no defect in DC function with age, with the reduction in their number perhaps contributing to the age-associated reductions in response to vaccines and susceptibility to infection.

5. Ageing of the acquired immune system

Ageing affects both the humoral and cellular arms of the acquired immune system.

5.1 Naïve and memory T cells in aging

During normal ageing the number of naïve T cells decreases while the number of memory T cells increases (Saule et al., 2006). There is an accompanying loss of functional capacity, cellular integrity, and diversity of both $CD4^+$ and $CD8^+$ T cell repertoires (Dewan et al., 2012; Haynes and Maue, 2009; Larbi et al., 2008; Weiskopf et al., 2009). T cells develop in the thymus, which atrophies with age (Flores et al., 1999; Ginaldi et al., 2001), changing the proportions of naïve and memory T cells in the periphery. Although memory $CD4^+$ and $CD8^+$ T cells are increased with ageing they are functionally compromised exhibiting reductions in proliferation, cytokine production, and reduced cognate helper function, compared with young naïve cells. Significant increases in effector/cytotoxic T cells ($CD28^-CD95^+$) and decreased numbers of naïve T cells ($CD28^+CD95^-$) have also been described (Zanni

et al., 2003). These findings are consistent with age-associated thymic involution resulting in reduced numbers of "virgin" naive T cells produced (Figure 2). Overall, changes in T cell effector function and repertoire are contributing factors in the age-associated decline of immunity to pathogen challenge and vaccination and increased predisposition to cancer (Hakim and Gress, 2007).

5.1.1. Age-associated changes in $CD4^+$ and $CD8^+$ T cells effector functions

Age-associated functional declines in $CD4^+$ and $CD8^+$ T cells impact on TCR signalling, cognate B cell helper function, vaccine responses, cell proliferation and cytokine production.

$CD8^+$ T cell cytotoxicity and proliferation decline during ageing (Haynes and Maue, 2009) whereas memory and cytotoxic $CD8^+$ T cells show significantly increased expression of IFN-γ and TNF-α compared to those from younger individuals (Zanni et al., 2003). Thus, virus-specific memory $CD8^+$ T cells have impaired proliferation and IL-2 production (Effros and Walford, 1983). Whit these changes in $CD8^+$ T cell functionality, aged people are more vulnerable to viral infections (Webster, 2000). Non-regulatory $CD8^+CD45RO^+CD25^+$ T cells that share phenotypic and functional characteristics of naïve $CD8^+$ T cells are present in ~30% of the healthy elderly and can still generate protective humoral immune response to vaccines (Herndler-Brandstetter et al., 2005; Schwaiger et al., 2003; Weiskopf et al., 2009). Oligoclonal populations of $CD8^+$ T cells appear in aged humans (Hong et al., 2004). There is an association between the increase in the prevalence of $CD8^+$ T cell oligoclonal expansion and cytomegalovirus infectious status, which establishes life-long latent infection (Akbar and Fletcher, 2005; Almanzar et al., 2005; Khan et al., 2002). These observations suggest a potential role for chronic antigenic stimulations such as cytomegalovirus infection in expanding memory $CD8^+$ T cells, with aging (Clambey et al., 2007; Vasto et al., 2007).

Naïve $CD4^+$ T cell function in the aged decreases due to the accumulation of intrinsic and extrinsic defects, effectively limiting effective antibody responses (Pfister et al., 2006). The TCR signalling cascade shows age-related modifications as in the case of JAK/STAT pathway (Fulop et al., 2006) and the lipid raft polarization that affects IL-2 and IL-6 receptor signalling in T cells. Lipid rafts are dynamic structures that control T-cell activation and immune responses by the time-dependent recruitment or exclusion of signalling proteins (Alonso and Millan, 2001).

Also, $CD4^+$ T helper cells show different regulatory properties in old age (Haynes et al., 2005). Animals studies have shown a reduced ability of naïve T cells from aged animals to expand, produce cytokines, or differentiate, leading to the generation of poorly polarized T helper (Th) subsets (both Th1 and Th2) (Haynes et al., 1999; Haynes and Maue, 2009). Th1 and Th2 effector subsets however retain the ability to generate functional Th17 effector cells (Haynes and Maue, 2009). As a result aged Th17 effectors still produce high levels of IL-17-related cytokines (IL-17, IL-21, IL-22) and can promote antigen specific B-cell expansion and germinal centre formation (Maue et al., 2009). And, while naive $CD4^+$ T cells from ageing individuals retain the ability to respond well to IL-1, IL-6, TGF-β, and IL-23 to generate TH17 effectors, the IL-12 (for Th1) and IL-4 (for Th2) response is declined (Haynes and Maue, 2009). This is an important point for further studies to know how to focus the vaccine therapy.

Mechanistically the ability to produce high levels of IL-17 by aged T cells can be explained by the observation that $CD4^+$T cells from elderly individuals show increased expression of the IL-1β receptor, required for the generation of IL-17-producing $CD4^+$ T cells (Lee et al., 2010).

5.1.2. Age-associated changes in B cells

Compared to T cells the influence of age on B cells, is less understood although age-associated effects on T cells have been linked to potential alterations in the APC they interact with, including B cells (Magrone et al., 2008). Moderate decreases have been described in the number of naïve B cells, IgM memory B cell ($IgG^-IgA^-CD27^+$) and switch memory B cell (IgG^+IgA^+), and in the proportion of IgM memory B cells and switch memory B cells (Blomberg and Frasca, 2011). Other studies however have reported an increase in memory B cells (Gibson et al., 2009). Alterations in humoral immune responses have a direct impact on the ability of the elderly to respond to infection (Frasca et al., 2011). This was particularly evident in early work on a mouse model of infection with *S. pneumoniae.* These studies showed that anti-pneumococci antibody from young and aged mice differed in structure and protective activity against pneumococci infection (Nicoletti et al., 1991; Nicoletti et al., 1993). It has been suggested that ageing does not result in a reduction in the function of B cells but a decrease in B cell responses to new antigens (Weksler, 2000). This infers alterations in the B cell repertoire, particularly in the heavy chain of the B cell receptor (BCR) (Buffa et al., 2011).

The number of naïve B cells (IgD^+CD27^-) may also be reduced in the elderly along with increases in the numbers of IgD^-CD27^- B cells which behave like $CD27^+$ memory B cells and may have a role in immunosenescence and reduced vaccine responses (Colonna-Romano et al., 2009). This may impact on the availability of naïve B cells required for responses to new antigens (Buffa et al., 2011). Further investigations have shown that the proportion of $IgM^+IgD^-CD27^-$ memory B cells in the elderly is significantly decreased and that they produce high levels of IL-10 and TNF-α (Buffa et al., 2011). Analysis of the CDR3 region of the Ig heavy chain from elderly and young subjects revealed a decreased diversity of antibody diversity in elderly subjects, which may be a biomarker of frailty. Evidence of clonality between CDR3 regions from selected samples was also observed indicating the B cell repertoire consisted of a greater proportion of antigen experienced B cells (Gibson et al., 2009).

Although the elderly consistently demonstrate immune responses after immunisation, this response decreases in successive years (Goronzy et al., 2001b; Murasko et al., 2002). Similarly, pneumonia vaccination in the elderly yields a similar concentration of antibodies to that of younger subjects but they are less effective and opsonise bacteria less efficiently (Schenkein et al., 2008). Elderly subjects demonstrate significant reductions in $CD27^+$ switch memory B cells in response to influenza vaccination although naïve and memory IgM B cells are comparable to those seen in young subjects (Frasca et al., 2010).

6. Dietary influence on the aged immune response (improvement/restoration)

Most of the parameters affected by immunosenescence appear to be under control genetic (Franceschi et al., 1999). Lifestyle factors such as diet and nutritional status, physical activity and stress can influence the ability to mount effective immune responses to infectious challenge (Lesourd, 2006). In particular, immunocompetence is directly affected by nutrition as deficiencies in

several vitamins and minerals, protein-energy malnutrition and excessive intakes of saturated fatty acids can impair immune responses (Enos et al., 2013; Lesourd, 2006; Pae et al., 2012).

Many studies have investigated the influence of nutritional factors on the immune response in healthy or apparently-healthy elderly subjects, although the majority did not use the first SENIEUR criteria that includes some health and nutritional factors (Lesourd and Mazari, 1999). In this section we will summarise the most relevant nutritional studies.

6.1. Micronutrients

Below, we discuss the effects of different micronutrients including vitamin A, B6 and E, beta-carotene and zinc all of which have been intensively studied (Belisle et al., 2008; Bogden et al., 1990; Corridan et al., 2001; De la Fuente et al., 2008; Duchateau et al., 1981; Fortes et al., 1998; Hodkinson et al., 2007).

6.1.1. Vitamin E

Vitamin E is a lipid-soluble antioxidant that enhances immune function (Gebremichael et al., 1984; Kowdley et al., 1992) and is present in the membrane of all nucleated cells and is particularly abundant in the membrane of immune cells. Vitamin E includes tocopherols and tocotrienols that exhibit the biological activity of α-tocopherol with both synthetic and natural forms of tocopherols being used experimentally. Results from animal studies have established that vitamin E can enhance T cell functions by directly influencing membrane integrity and signal transduction or, indirectly by reducing production of suppressive factors such as PGE_2 by macrophages (Meydani et al., 2005; Wu and Meydani, 2008). Many studies have reported beneficial effects of vitamin E supplementation in healthy elderly people (Belisle et al., 2008; De la Fuente et al., 2008; Meydani et al., 1990; Meydani et al., 1997; Pallast et al., 1999) with the majority finding improvements in immune function. However, responses to vitamin E supplementation are influenced by individual factors such as genetic background and previous immune status (Pae et al., 2012). One study examining the interaction between vitamin E treatment and cytokine production (IFN-γ, TNF-α, IL-1β, and IL-6) found that only subjects with prior high basal levels of cytokine production responded to 200 IU/d of dl-α-tocopherol and multivitamin and mineral supplements for 1 year with increased cytokine production (Belisle et al., 2008). However, other factors such as single cytokine (TNF-α) gene polymorphisms may influence how an individual responds to vitamin E (Belisle et al., 2009).

6.1.2. Zinc

Zinc is an essential mineral with its deficiency leading to reduced immune cell proliferation, cytokine production, and specific reductions in NK cell activity and neutrophil function (Prasad, 2008a; Prasad, 2008b). Several studies have shown beneficial effects of zinc supplementation on cell-mediated immunity and humoral responses in elderly people. Early studies showed that zinc supplementation improved DTH (delayed type hypersensitivity) responses (Cossack, 1989; Prasad, 2003) and that consumption of 45 mg of zinc/day (as gluconate) for 6 months increased expression of IL-2 and IL-2 receptor (IL-2R) α mRNAs in PBMC (Prasad et al., 2006). The effects of Zn on lymphocyte populations are more varied. One study reported that institutionalized healthy elderly (≥65y) subjects had increased numbers of activated ($HLA\text{-}DR^+$) $CD4^+$ and cytotoxic lymphocytes after 3 months of zinc supplementation (25mg/d as zinc sulphate) (Fortes et al., 1998), while other studies

reported a reduction in activated ($CD25^+$) $CD4^+$ T cells with no difference in Th2/Th1 ($CCR4^+/CCR5^+$) profiles (Kahmann et al., 2006). Zinc supplementation has also been tested for its potential enhancement of vaccination efficacy in the elderly although the results are inconclusive (Pae et al., 2012).

6.1.3. Carotenoids

Carotenoids such as beta-carotene are stored in tissues and accumulate in the plasma and can be converted to vitamin A (Watson et al., 1991). They are linked to enhanced immune function as demonstrated by a reduction in $CD45RO^+$ cells after supplementation and increases in sIL-2R production after depletion of β-carotene, lycopene and lutein. Bactericidal activity is also increased in supplemented individuals, while depleted subjects display elevated levels of ROS, indicative of the protective properties of carotenoids against oxidative stress (Farges et al., 2012). Elderly subjects given carotenoid supplements (30 mg β-carotene, 15 mg lycopene and 9mg lutein) had higher serum IgA levels, a reduction in B lymphocyte numbers, a shift to T cells expressing a mature phenotype and an increase in NK cells (Farges et al., 2012). While supplementation with low doses of lycopene (13.3 mg) or β-carotene (8.2 mg) resulted in numbers of lymphocyte subsets comparable to non-supplemented individuals, no differences were seen in expression of adhesion molecules or MHC class II molecules, lymphocyte proliferation or cytokine production (Corridan et al., 2001). This lack of a functional response with a low dose of carotenoids may be due to the subjects having a "near-optimal" immune status with diets already sufficient in carotenoids (Corridan et al., 2001). Investigations of higher doses (30-60 mg/ day) have shown improvements in immune function including increases in NK cell numbers and T-helper cell function (Watson et al., 1991) suggesting that low doses are insufficient to affect immune responses, although these higher doses may not be achievable in the diets of the majority of the general public.

Fruit and vegetables containing carotenoids, flavonoids and vitamin C, with increased fruit and vegetable consumption from ≤2 portions per day to ≥5 portions per day have been shown to significantly improve the responses of 65-85 year old subjects to Pneumovax II vaccination. This finding was however restricted to subjects with no history of previous exposure to this vaccine (Gibson et al., 2012) suggesting that the influence of increasing fruit and vegetable intake may target naïve B cells rather than antigen experienced memory B cells. This finding may be related to the observation that serum levels of IgG2 increase with age, and that IgG2 is produced against polysaccharide antigens required for defence against bacteria such as pneumococci (Paganelli et al., 1992).

6.2. Probiotics

Probiotics are live microorganisms that may confer a health benefit to the host (consumer). The most characterized probiotic microorganisms are members of the genera *Lactobacillus*, *Bifidobacterium* and *Streptococcus*. Probiotics can modulate 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. Populations of these beneficial microbes can be reduced in resident populations of GI-tract bacteria in elderly people in association with decreased intestinal antigen-specific secretory IgA responses that protect against bacteria, viruses and fungi (Nova et al., 2007). It is presumed therefore that elderly people would benefit from consumption of probiotics.

Several studies have examined the effects of a probiotic supplementation in healthy elderly people (Arunachalam et al., 2000; Gill et al., 2001b; Ouwehand et al., 2008; Schiffrin et al., 2009) although they are all relatively short-term interventions of less than 6 weeks. Certain strains of probiotics improve innate immune responses such as phagocytosis and cytotoxicity in ageing people (Arunachalam et al., 2000; Gill et al., 2001a; Gill et al., 2001b). Arunachalam et al (2000) showed a significant increase in PMN cell phagocytic and bactericidal activity to *Staphylococcus aureus* challenge after the administration of *B. lactis* ($3x10^{11}$ CFUs/d) to healthy elderly subjects for 6 weeks. Gill et al. (2001a) supplemented the diet of elderly subjects with *L. rhamnosus* HN001 ($5x10^{10}$ CFUs/d) or *B. lactis* NH019 ($5x10^{9}$ CFUs/d) for 3 weeks and showed increases in both peripheral blood NK cells and their tumoricidal activity. Subsequent studies using two different doses of HN019 (low dose $5x10^{9}$ CFUs/d or typical dose $5x10^{10}$ CFUs/d) for 3 weeks revealed increases in the phagocytic activity of PBNC and PMN cells as well as NK cell activity for both doses (Gill et al., 2001b). More recently, consumption of the probiotic *L. casei* Shirota ($1.3x10^{10}$ CFU/ day) for 4 weeks has shown significant increases in NK cell activity and significant decreases in expression of CD25 by resting T lymphocytes, along with a trend for an increase in the ratio IL-10 to IL-12 in older subjects (Dong et al., 2013). However, this increase in NK cell activity was greater in women, but as men had higher levels at baseline this could indicate that NK cell activity is modulated back to normal levels but is not further enhanced. Overall, the number of studies focussing on the impact of probiotics on immune responses in the elderly has grown in recent years. Improvements in age-related defects in the immune system have been demonstrated, indicating that probiotics may reduce the incidence and severity of infectious diseases in the elderly. Further studies are required to confirm these effects since the research to date has only trialled short intervention periods, and as there are numerous different probiotics the observed effects may be strain specific.

6.3. Prebiotics

Prebiotics comprise substrates for "beneficial" gut bacteria aimed at increasing their growth. A novel galactooligosaccharide (B-GOS) is able to significantly increase NK cell activity after 5 weeks administration, reducing production of TNF-α, IL-1β and IL-6, and increasing IL-10 production by PBMCs, as well as increasing phagocytic activity of neutrophils and monocytes (Vulevic et al., 2008). These findings parallel increases in beneficial bacteria such as bifidobacteria, with the immune enhancing effects thought to be due to prebiotics binding to specific receptors of immune cells. Fructooligosaccharides (FOS) have also been shown to enhance immune function in the frail elderly with reductions in IL-6 and TNF-α mRNA after 12 weeks of FOS ingestion (Guigoz et al., 2002) while phagocytic activity was decreased after FOS ingestion for 3 weeks in older subjects (Schiffrin et al., 2007). While, 6g/ day of a mixture of the prebiotics raftilose (70%) and raftiline (30%) did not change any immunological parameters tested after influenza or pneumococcal vaccination compared to the placebo, maltodextrin, in healthy elderly subjects (Bunout et al., 2002), which is suggested to be due to a potential maximum effect being achieved such that the immunological function is maintained as the subjects were healthy and had good nutritional status. A limited number of studies have investigated the impact of prebiotic intervention specifically on immune parameters in the elderly, with the results to date indicating potential beneficial effects.

The use of probiotics and prebiotics together, synbiotics, has demonstrated improvements in gut microbiota profiles and constipation in adults (Fateh et al., 2011; Nova et al., 2011; Waitzberg et al., 2013) though investigations in the elderly to date are limited, particularly regarding their effect on

immune parameters. One study found that faecal levels of PGE_2 were significantly increased in elderly subjects (≥ 65 years) after 2 weeks consumption of lactitol and *L. acidophilus* NCFM, as well as increases in bifidobacteria numbers (Ouwehand et al., 2009). This indicates an improvement in mucosal function and possibly the mucosal immune system which can impact on circulatory immune cells. Similarly, alterations in the gut microbiota impact on immune function such that the gut is considered an important target for improving immune health (Hamilton-Miller, 2004)

6.4. Polyphenols

Polyphenols are compounds found within many foods and beverages including red wine, fruit juices, fruit, vegetables, tea, coffee, cocoa and cereals (Bravo, 1998; Magrone et al., 2008). Polyphenolic compounds mostly consist of flavonoids, which can be further split into flavonols, flavones, isoflavones and flavanols (Magrone et al., 2008). *In vitro* investigations using MNCs from healthy young subjects exposed to purified polyphenols from red wine found that a dose equivalent to one glass of wine per day influenced the production of key cytokines including IL-12, IL-10 and IL-1β . The authors also showed that these polyphenols also influence B cell function and increase production of protective IgA and IgG. Based on the notion that polyphenols can partially restore the function of aged macrophages (Tasat et al., 2003) the authors speculated that moderate intake of red wine may be beneficial in ageing. Animal models of ageing have shown positive results with resveratrol, a polyphenol found in grape skins and berries, significantly increasing T helper cells in aged rats (Yuan et al., 2012) and that the phytochemical, *Echinacea purpurea*, can increase NK cell numbers in aged mice to levels observed in young adult mice, as well as significantly increasing NK cell cytolytic activity (Currier and Miller, 2000). Limited investigations in elderly subjects have been carried out to date, with consumption of 40g/day cocoa (rich in flavonoids) by elderly subjects at high risk of cardiovascular disease (CVD) showing significantly lower expression of the cell adhesion molecules VLA-4, CD40 and CD36 on monocytes and lower circulating levels of the inflammatory markers P-selectin and ICAM-1 (Monagas et al., 2009).

6.5. Macronutrients: Fatty acids

Cellular fatty acids have various roles including energy provision, providing structures to cell membranes and effecting gene expression via signalling molecules with some polyunsaturated fatty acids (PUFAs) acting as precursors for the synthesis of prostaglandins, leukotrienes, lipoxins and resolvins (Yaqoob and Calder, 2007). Different classifications of dietary fatty acids have differing impacts on the immune system (Yaqoob, 2004). The most studied fatty acids are the n-3 PUFA and n-6 PUFA families, also called essentials FAs. Whereas saturated fatty acids and n-6 PUFAs have minimal effect on lymphocyte proliferation, cytokine production or natural killer cell activity, oleic acid and n-3 PUFA can inhibit lymphocyte and NK cell activity (Yaqoob, 2004). N-6 PUFAs are the most polyunsaturated FAs and are derived from plants and land animals. N-3 PUFAs are found mainly in fish and fish products and in some plants (flax seeds) with marine n-3 PUFAs, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), having the most significant immune cell impact of all the n-3 PUFAs (Pae et al., 2012). Consumption of long chain n-3 PUFA products can improve cardiovascular disease, degenerative neurological disease, inflammatory and autoimmune diseases, and age-related macular degeneration (Pae et al., 2012). N-3 PUFA have anti-inflammatory properties inhibiting formation of eicosanoids (thromboxane A2) required for platelet aggregation and clot formation and proinflammatory cytokines (IL-1β, TNF-α, IL-6), chemokines (IL-8, MCP-1),

adhesion molecules (ICAM-1, VCAM-1, selectins), and reactive oxygen and nitrogen species (Calder, 2010; Galli and Calder, 2009). They also suppress both innate (mainly inflammation) and adaptive (T cell mediated) immune responses, which can impair immunity to infectious and neoplastic disease. Fish oils have been shown to inhibit pro-inflammatory cytokine production by lymphocytes and macrophages in mice (Wallace et al., 2001). In considering the use of these PUFAs in the elderly it is important to consider the possible drawbacks of n-3 PUFA supplementation in individuals that have impaired immune responses, and that high doses of n-3 PUFAs can increase lipid peroxidation (Bechoua et al., 2003) and suppress IL-2 production and lymphocyte proliferation in older women (Meydani et al., 1991).

There are few studies focussing on the use of n-3 PUFA in healthy aged people. 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 3 months (Meydani et al., 1991). Another study in very old people (70-83 years of age) consuming habitual amounts of low doses of PUFA (30 mg EPA and 150 mg DHA/d) for 6 weeks showed a decrease in lymphocyte proliferation in response to different stimuli (Bechoua et al., 2003). The effects of consuming different doses of EPA in young and older males has shown lower neutrophil respiratory burst in older males with higher doses of EPA after 12 weeks (Rees et al., 2006). Supplementation 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 was found to decrease levels of free fatty acids and triglycerides in association with more than 900 unique changes in PBMC gene expression and a reduction in pro-inflammatory genes including NF-κB target genes, pro-inflammatory cytokines and genes involved in eicosanoid synthesis (Bouwens et al., 2009). Lower levels of responses were seen with low doses of EPA (0.4 g) and DHA (0.4 g) equivalent to more realistic portions of oily fish (2 per week). Also, doses as low as 600 mg marine oil, consisting of 150 mg DHA and 30 mg EPA (with adequate amounts of vitamin E) given to healthy elderly people revealed a significant reduction in lymphocyte proliferation to mitogens and a significant decrease in glutathione peroxidase activity (Bechoua et al., 2003). These findings suggest that a lower dose of n-3 PUFAs can be beneficial and may be more suitable and achievable for older people, which would represent an increase in current consumption by UK elderly population who consume on average 85 g per week which is much less than the recommended one portion per week (140 g) (Bates et al., 2012).

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 (Alperovich et al., 2007). 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 (Merchant et al., 2005), which could be due to gender differences or to interactions of n-3 and n-6 PUFAs.

Overall it appears that elderly individuals are more sensitive to the immunologic effects of n-3 PUFA, which is advantageous for the beneficial effects observed but some disadvantages such as increased lipid peroxidation or reductions in anti-inflammatory cytokines have also been observed with higher doses. As the doses used and the study designs differ between studies, more research is required to confirm the effects of n-3 PUFA in this age group, as well as the need to clarify the molecular pathways affected.

6.6. Whole diet approaches

Variations in dietary intake depend, partly, on geography as each country has its customs and culinary habits, which in turn influence habitual diets. Most studies investigating diet and immunosenescence have incorporated aspects of the Mediterranean diet (MD) with increasing evidence suggesting that it has a beneficial influence on several age-related diseases and improves immune responses (Hadziabdic et al., 2012; Martinez-Gonzalez et al., 2009; Sofi et al., 2010; Sofi et al., 2008). The MD refers to dietary patterns found in olive-growing regions of the Mediterranean characterized by a high consumption of olive oil, vegetables, fruit, nuts, cereals, and diverse antioxidants combined with a moderate intake of fish, poultry, and unsaturated fatty acids, a low intake of dairy products, red meat, processed meats, and sweets with moderate intake of alcoholic beverages, mostly wine, consumed with meals (Willett et al., 1995). The MD is associated with a significant and substantial reduction in overall mortality (Lasheras et al., 2000; Osler and Schroll, 1997; Trichopoulou et al., 2003).

The MD has been shown to influence cellular and circulating levels of inflammatory biomarkers related to atherogenesis in subjects at high risk of CVD (Estruch et al., 2013; Psaltopoulou et al., 2004; Salas-Salvado et al., 2008). Additional experimental and clinical studies have shown that olive oil consumption is associated with changes in endothelia VCAM-1, ICAM-1 and E-selectin expression (Dell'Agli et al., 2006) and decreased plasma concentrations of sICAM-1, sVCAM-1, SE-selectin, IL-6, and CRP in high-risk patients (Carluccio et al., 2003; Cortes et al., 2006). Dementia, an important disease affecting the elderly, has been the focus of several studies. Valls-Pedret et al. (2012) have described improved cognitive performance in an elderly cohort at high cardiovascular risk (Valls-Pedret et al., 2012), re-enforcing previous studies showing a slower cognitive decline (Tangney et al., 2011), a reduction in the incidence of mild cognitive impairment (Scarmeas et al., 2009), neurodegenerative disorders like Parkinson (Gao et al., 2007) and Alzheimer's diseases in individuals adhering to the MD (Feart et al., 2009; Scarmeas et al., 2006). Although the MD has beneficial effects on the health of elderly people, few studies have focused on if, or how, it affects the immune system. The MD has been associated with the down-regulation of CD49d and CD40 expression among circulating monocytes and the inflammatory biomarkers sICAM-1, vCAM-1, CRP, and IL-6 were also decreased. In other studies high levels of anti-inflammatory cytokines (IL-10) and a lower production of pro-inflammatory cytokines such as TNF-α and IL-12 were observed after adherence to the MD (Azzini et al., 2011).

The role of the diet in age-related disease needs to be investigated further. The NU-AGE project aims to address this need by including studies to investigate whether nutrition can act as a modulator of inflammaging and other age-related outcomes. This aspect of the NU-AGE project includes 1250 older (65-79y) individuals from France, Italy, Poland, the Netherlands and the United Kingdom. The participants are randomised to consume the MD or remain on their normal diet. Within the UK a cohort of 125 elderly subjects has been recruited at The University of East Anglia (UEA) to assess at baseline and after 1 year of dietary intervention changes in inflammatory and immunological status, function and regulation. This will include expression and responsiveness of pattern recognition receptors, inflammatory and regulatory cytokines, expression of co-stimulatory molecules, DC population dynamics and innate and adaptive immune cell functionality. The aim of this work is to determine whether elderly subjects having conformed to the MD for one year show improvements in immune function.

7. Conclusion

Globally, life expectancy is increasing, which means that each year the number of people over the age of 60 years increases. It is important therefore that older people extend their years of good health. Changes in nutrition and lifestyle can be effective at preventing or at least ameliorating age-related illnesses and possibly immunosenesence. As we have summarized here, changes in the immune system of elderly people are well documented, indicating that most aspects of the innate and acquired immune systems are affected by immunosenescence. A major challenge now is to understand which molecular pathways of chronic inflammation (inflammaging) can be effectively targeted by dietary approaches. Nutritional interventions have shown some promising results in targeting some of the impairments of the immune system observed with ageing. Combining the interventions trialled thus far into a whole diet approach, such as the MD, is a realistic approach to take in the future. This approach is particularly suited to providing specific dietary guidelines, tailored to different stages of ageing.

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Figure legends:

Figure 1. Age-associated changes observed in innate and adaptive immune cell populations. Decreased cellular function in old age has been documented in neutrophils, macrophages, NK cells, monocyte-derived (MO) and dendritic cells (DCs). And a reduced development of T and B cells as well an impaired functionality of theses populations in elderly people.

Figure 1. Effects of age on the production and distribution of lymphocytes. Modified from (Dorshkind et al., 2009) and (Nikolich-Zugich, 2008). Young and adult individuals present a normal T and B cell production. In contrast, elderly people have a decreased production of naïve T and B cells and an increase in the memory T cell poll. These changes result from decreased T‑cell production from involuted thymus and an increase in the homeostatic cycling that drives proliferating naïve T cells into memory cells, and from a decline in the bone marrow function producing fewer B cell precursors (Dunn-Walters and Ademokun, 2010).

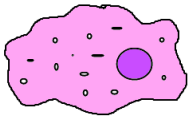
Figure 1

Innate Immune Cells

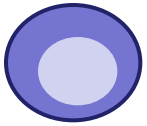
Age-Associated Changes

Neutrophils 

- Decreased phagocytosis
- Decreased chemotaxis
- Defective apoptosis function

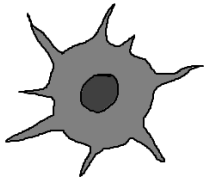
Macrophages 

- Decreased antigen presentation
- Decreased superoxide anion production
- Defective phagocytosis
- Decreased cytokine production

NK cells 

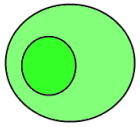
- Reduced cytolytic potential
- Decreased cytokine and chemokine production
- Reduced CD1 expression in NKT cells

Bridging innate and adaptive immunity

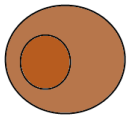
DC 

- Reduced IFN production
- Reduced expression of CD25 and ICAM-1 in mature MODCs
- Reduction in lymphocyte cytotoxicity and greater migratory capacity of monocyte-macrophage derived APCs.

Adaptive Immune Cells

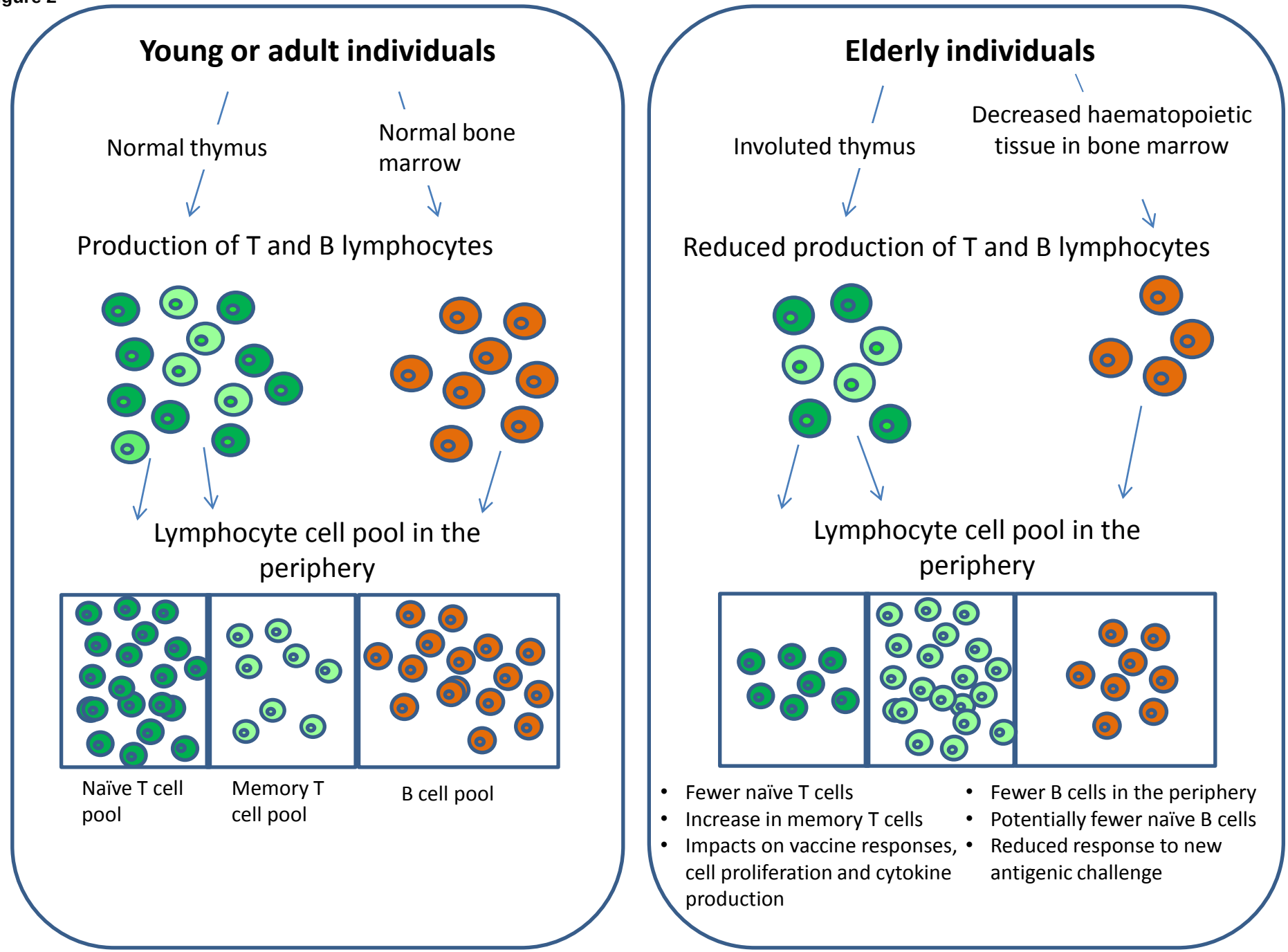
T Cells 

- Reduced development (Thymus atrophy). Reduced numbers of naïve $CD4^+/CD8^+$ T cells, and increased number of effector and memory $CD4^+/CD8^+$ T cells
- Decline in $CD8^+$ T cell cytotoxicity and proliferation
- Decline in CD4+ function, less generation of Th subsets (Th1 and Th2)

B cells 

- Reduced development. Reduced number of naïve B cells
- Decrease in B cell responses to new antigens
- Decreased diversity of B cell repertoires in elderly subjects

Figure 2


Young or adult individuals
Normal thymus
Normal bone marrow
Production of T and B lymphocytes
Lymphocyte cell pool in the periphery
Naïve T cell pool
Memory T cell pool
B cell pool
Elderly individuals
Involuted thymus
Decreased haematopoietic tissue in bone marrow
Reduced production of T and B lymphocytes
Lymphocyte cell pool in the periphery
• Fewer naïve T cells
• Increase in memory T cells
• Impacts on vaccine responses, cell proliferation and cytokine production
• Fewer B cells in the periphery
• Potentially fewer naïve B cells
• Reduced response to new antigenic challenge