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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.

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 (Fig. 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 $\geq$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.

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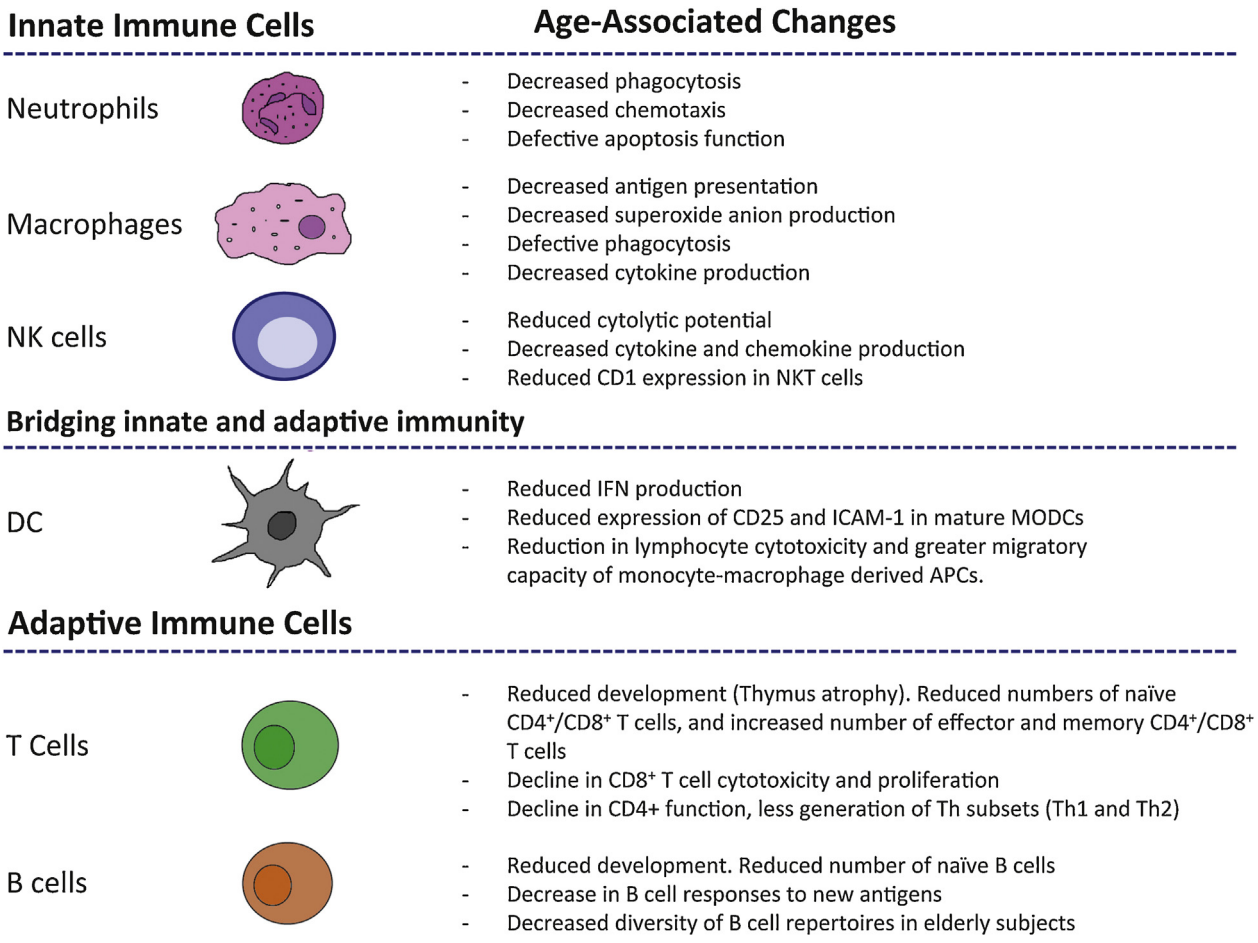

Fig. 1. Age-associated changes observed in innate and adaptive immune cell populations. Decreased cellular function in old age has been documented in neutrophils, macrophages, NK cells, monocyte-derived (MO) and dendritic cells (DCs). And a reduced development of T and B cells as well an impaired functionality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

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., 2001; 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., 2008; 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

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