Jos A. Bosch · Anna C. Phillips
Janet M. Lord *Editors*

Immunosenescence

Psychosocial and Behavioral Determinants

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Foreword by Keith W. Kelley, Ph.D.

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Foreword

The post-World War II generation of babies born in the USA between 1946 and 1964 began to reach their 65th birthday earlier this year. This explosion in births, amounting to 76 million American children, temporarily stemmed the tide in the USA's declining birth rate. Similarly, most western European countries experienced an increase in births immediately following the end of World War II. As these baby boomers join organizations like the American Association of Retired Persons (AARP), they want clearer answers and more effective treatments for their medical ailments. This book, *Immunosenescence: Psychosocial and behavioural determinants*, specifically addresses those needs.

Arguably, baby boomer kids across the United States and Western Europe grew up to become the largest, wealthiest, most rebellious, optimistic and free-thinking generation that the modern world has ever known. Baby boomers redefined traditional values of the Western world. In 1946, the year following the end of World War II, Winston Churchill described an "Iron Curtain" that had fallen over the European continent. The baby boomer generation grew up under this dark shadow and the constant threat of a nuclear Armageddon, only to witness dismantling of the infamous Berlin Wall in 1989 and an end to the Cold War in 1992. During this time, major events occurred. Baby boomers throughout the world remember names and movements like Fidel Castro, the Suez Canal crisis, Charles de Gaulle, Neil Armstrong, John F. Kennedy, Martin Luther King, freedom riders of the civil rights movement, the Chicago Seven, Elvis Presley, anti-Vietnam protests that pervaded Europe and the USA, Kent State killings, Watergate scandal, Beatles, hippies, free love, Woodstock, Three Mile Island and Chernobyl**,** just to name a few. These names stir the collective memory of baby boomers because this was their generation.

The post-World War II era witnessed incredible discoveries in medicine. The medical community saw birth of the first test tube baby, hip transplants, the birth control pill, heart-lung transplants, polio vaccine, genetic engineering, pacemakers, lasers, MRI scanners, stem cells, Prozac and the discovery of and treatment for human immunodeficiency virus. These advances encouraged development of specialists, such as surgeons who were experts in orthopedic, vascular, neurological, maxillofacial, cardiovascular, colon/rectal, hand, thoracic and plastic surgery. Other medical

specialties developed, such as interventional cardiologists, nuclear medicine specialists, addiction psychiatrists, sleep disorders specialists, sports medicine specialists, reproductive endocrinologists, preventative medicine specialists, pain management specialists, medical geneticists, hyperbaric physicians and nuclear medicine specialists. These kinds of doctors remind of the Pete Seeger song of the early '60s, "Where have all the flowers gone?" Baby boomers did not grow up with these kinds of physicians. Today, as they begin to turn 65 years of age, they are asking, "Where have all the doctors gone?"

Baby boomers were born into a world that considered doctors to be what is now known as "infectious disease specialists." But, perhaps because of the logarithmic explosion in medical specialists during the past 30 years, a new "specialist" has appeared on the scene. Just two years ago, it became possible for M.D.s to be certified and boarded as Diplomates of the American Board of Hospital Medicine (ABHM; http://abpsus.org/hospital-medicine). Hospitalists are interdisciplinary since they care for all cases of acutely ill patients in hospitals and serve to coordinate and manage medical care between patients and medical specialists. It could be that despite all the wonderful advances that have been made in medicine since the birth of the first baby boomer, medical "providers" are finally being asked to consider patients as more than simply a human body with some sort of dysfunction. This reminds of the oft-repeated phrase, "The whole is greater than the sum of its parts."

It is the baby boomer recognition of the need for interdisciplinary and integrative medicine that created a niche for this book, *Immunosenescence: Psychosocial and behavioural determinants*. It is ironic that this idea in nothing more than a return to their roots. When boomers were babies, most physicians were well-trained in all aspects of physiology. This integrative science is derived from the Greek prefix "*physis*" which means "nature or origin" and the suffix "*logia*," or "the study of." For me, systemic physiology means the study of function, and it focuses on how the major organs of the body, such as the heart, lungs, kidneys and brain, not only function independently but also communicate with each other. Lungs depend on the heart to pump blood through oxygen-rich alveoli, and the heart depends on kidneys to regulate plasma volume. The study of regulatory physiology conveys a sound understanding of the numerous routes of communication among different organ systems. One strength of this book is that it reminds us of the important theme of immunophysiology because it emphasizes the concept that the immune system is just another organ system, like the heart, lungs and kidneys. It is a diffuse system that wanders throughout the entire body searching for foreigners. Once a stranger is recognized by cells of the immune system, it sends an alert message to the brain and other organs. The five classical sensory systems of touch, sight, smell, taste and sound did not evolve to recognize a foreign substance that invades the body. But the innate immune system can detect these foreigners. Indeed, cells of the immune system are now known to send both neuronal and humoral signals to inform the brain that an infection has occurred in the periphery. As Ed Blalock correctly hypothesized in his seminal paper published in the *Journal of Immunology* in 1984 (132:1067), the innate immune system is our "sixth sense."

The 13 chapters in this timely book highlight the multiple physiological systems that are impacted by the immune system during aging. As the immune system grows older, its dialogue with the brain changes. These changes affect how the aging baby boomer population responds to stress, how well they sleep, how they adjust to loss of independence that often accompanies aging, the rate at which they will heal after surgery and how they will deal with losing a spouse or living alone. The authors are internationally-respected scholars in the interdisciplinary field of brain, behavior and immunity. They have all published cutting edge, peer-reviewed papers in leading journals on the multitude of issues that confront gerontologists on topics that range from health psychology to host resistance to infections.

Immunosenescence: Psychosocial and behavioural determinants helps to push back the frontiers of immunophysiology. It espouses the philosophy that a better understanding of the aging immune system will be achieved only if we learn how its afferent and efferent communication signals affect other organs, particularly the brain. As a child who was born at the beginning of the baby boom, I applaud the direction and learning trajectory that this book is taking us.

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Introduction to Ageing of the Innate Immune System

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1.1 Introduction

Over the past century, human life expectancy has doubled in developed countries and is continuing to increase at a rate of 2 years per decade. However, although life expectancy has increased, advanced age is accompanied by an increase in susceptibility towards infection and development of chronic illnesses that have a negative impact on an individual's quality of life. Even adults considered to have undergone healthy ageing show a significant decline in immune competence, termed immunosenescence, which is responsible for the increased rate of infections with advancing age (DiCarlo et al. 2009). Recent studies have also reported a reduced ability to mount a robust immune response to vaccination, combat new pathogens or maintain immunity to persistent infections such as *Herpes zoster* in older adults (Gavazzi and Krause 2002b; Trzonkowski et al. 2009; Weinberger et al. 2008). Delaying or reversing the effects of ageing on the immune system may therefore be extremely beneficial to the health and quality of life of the elderly population (Dorshkind et al. 2009).

1.2 Inflammaging

A universal feature of physiological ageing is a higher basal production of pro-inflammatory cytokines (IL-1β, IL-6, IL8, TNFα and IL-15), accompanied by a reduced production of anti-inflammatory cytokines (IL-10) known as 'Inflammaging' (Franceschi et al. 2007). Importantly, inflammaging is a predictor of frailty and mortality in aged humans. Studies in centenarians (Di Bona et al. 2009) and extremely long-lived mice (Arranz et al. 2010) show that long-lived individuals maintain the cytokine profile of younger adults. In addition to increased cytokines, other inflammatory markers including C-reactive protein (CRP) and clotting factors (fibrinogen)

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are also increased with age. The underlying mechanisms driving inflammaging are thought to be varied (Krabbe et al. 2004) and include: the increase in adipose tissue which is a significant source of inflammatory cytokines and pro-inflammatory hormones termed adipokines (Fantuzzi 2005); decreased production of sex steroids many of which are anti-inflammatory (Nilsson 2007); sub-clinical infections (Effros 2001); a sedentary lifestyle (Lavoie et al. 2010) and constitutive low-level production of cytokines by monocytes (discussed below).

The rest of this chapter will focus upon the age-related changes to the functioning of the cells of the innate immune system as it is these changes that dramatically affect the ability to combat bacterial and viral infections in old age.

1.3 Age-Related Changes to Innate Immune Cell Production

The innate immune system acts as the first barrier encountered by pathogens and is responsible for immediate and robust responses to micro-organisms. In aged subjects, a breakdown in the integrity of innate physical barriers such as the skin, gastrointestinal tract and lung occurs, resulting in increased susceptibility to invasion by pathogens and an increased burden on the cells of the innate immune system.

All immune cells are formed from differentiation of the multipotent haematopoietic stem cell (HSC) which is responsible for continuously replenishing the immune system. HSCs differentiate into multipotent progenitor cells, which can produce cells of either myeloid (neutrophils, monocytes, macrophages, dendritic cells, eosinophils and megakaryocytes/platelets) or lymphoid (T cells, B cells and NK cells) lineage. HSCs from older donors have a reduced ability for self-renewal and a myeloid skewing of their differential potential; suggesting profound changes in multiple levels of HSC differentiation during ageing (Chambers et al. 2007; Dykstra and de Haan 2008). Molecular factors contributing to HSC ageing include accumulation of DNA damage, altered gene expression patterns and epigenetic deregulation (Warren and Rossi 2009). Skewing of the HSCs with age is thought to be responsible for declining immuno-competence, increased autoimmunity, anemia, diminished stress response and increased predisposition to a spectrum of diseases including myeloid leukemia (Warren and Rossi 2009).

1.4 Neutrophils

Neutrophils are the most abundant leukocyte and a key element of the innate immune system and are one of the first cells to migrate into the site of infection. They are responsible for recognising, ingesting and destroying pathogens, most importantly rapidly dividing bacteria, yeast and fungi. The increased incidence of bacterial infections in older adults suggests (Bonomo 2002; Gavazzi and Krause 2002a) that neutrophil numbers and/or function are reduced with age.

Neutrophils have a very short life span (5.4 days) in peripheral blood and are lost due to spontaneous apoptosis, and as a consequence they are produced in large numbers ($1–2 \times 10^{11}$ per day) (Wessels et al. 2010). The bone-marrow content of precursors for the neutrophil lineage as well as their number in blood remains unchanged in the healthy elderly (Chatta et al. 1993; Gomez et al. 2008). During an infection, a large increase in neutrophil production is observed (neutrophilia) in order to combat infection. Studies have shown that older adults are able to mount a normal neutrophilia in response to an infection (Lord et al. 2001). Neutrophil's life span is controlled by growth factors (IL-3), chemokines and lineage specific cytokines, specifically granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) (Chatta et al. 1993). Even though neutrophils from older donors have a diminished ability to respond to anti-apoptotic mediators such as G-CSF, their responses to GM-CSF and IL-3 are unaltered with age; resulting in an ability to maintain neutrophil numbers with age (Fulop et al. 2002).

During an infection, neutrophils leave the circulation (extravasation), roll along and then adhere to vascular endothelial cells, followed by migration to the site of infection along a gradient of chemotactic factors. Once the neutrophils have reached the site of infection via chemotaxis, they engulf the invading microbes by phagocytosis. Pathogen phagocytosis by neutrophils is followed by microbial killing by several mechanisms, including generation of reactive oxygen and nitrogen species, release of proteolytic enzymes from intracellular granules and the extrusion of DNA coated with antimicrobial compounds, termed neutrophil extracellular traps (NETs).

Adherence of neutrophils to endothelium, which is essential for neutrophil extravasation, is slightly increased or unaltered with age. The expression of markers CD11a and CD11b, necessary for neutrophil extravasation, remains unaltered with age. However, an increase in the expression of CD15, responsible for binding of E-selectin on endothelium, has been reported in older adults (Butcher et al. 2001; Esparza et al. 1996), suggesting that reduced extravasation of neutrophils is not responsible for the increase rate of bacterial infections in older adults.

Chemotactic molecules (IL-8, fMLP, complement C5a) are responsible for attracting neutrophils to the site of infection. There is a significant degree of discordance in the literature regarding chemotaxis of neutrophils from the elderly; some studies have reported that it remains unchanged with age (MacGregor and Shalit 1990), whilst others have reported reduced chemotaxis (directional movement) of neutrophils in response to fMLP and GM-CSF in the elderly, whilst chemokinesis (non-directional movement) remains unaltered (Antonaci et al. 1984; Niwa et al. 1989; Wenisch et al. 2000). The decrease in chemotaxis may be particularly important, as it would compromise efficiency of recruitment of neutrophils to the infection focus. Even though neutrophils are capable of migrating towards the infection site, the data suggest that they have reduced directional control and will take a longer route to the infection site. This will result in an increased exposure of tissue to proteases that neutrophils release during the migratory process, consequently damaging healthy tissue. Further research is required to determine the mechanisms underlying reduced directional migration in neutrophils from older donors.

An age-related decline has also been reported in the percentage of phagocytosing neutrophils and the ability of neutrophils to ingest opsonised bacteria and yeast (Butcher et al. 2001; Wenisch et al. 2000). However, neutrophil ability to phagocytose unopsonised bacteria remains unaltered with age (Emanuelli et al. 1986), suggesting that it is the response via opsonin receptors (Fcγ and C3b complement receptors) that is affected by ageing. A number of intracellular defects that contribute to reduced phagocytic ability with age may include: impaired calcium mobilisation, reduced hexose transport (phagocytosis is an energy-dependent process), reduced CD16 expression, impaired downstream signalling events (PI-3 kinase, MAP kinase activation) and reduced ligand-induced actin polymerisation (Butcher et al. 2001; Rao 1986; Wessels et al. 2010). In addition to these intrinsic factors, extrinsic factors such as altered circulating cytokine levels also contribute towards reduced neutrophil functioning efficiency with age.

Ingested microbes are destroyed by two different microbicidal mechanisms; production of reactive oxygen species and degranulation, both of which lead to the release of cytotoxic proteases. Regarding the first mechanism, studies of neutrophil respiratory burst have reported unaltered superoxide production in response to phorbol myristate acetate (PMA) (Braga et al. 1998; Butcher et al. 2000; Esparza et al. 1996). Antibody Fc-receptor-mediated neutrophil superoxide generation in response to gram-positive bacteria such as *Staphylococcus aureus* has been shown to be reduced (Wenisch et al. 2000), whereas superoxide generation in response to *Escherichia coli* is unaltered with age (Panda et al. 2009; Wessels et al. 2010) or reduced (Tortorella et al. 2000). Studies have also reported a decline in degranulation in response to microbial products (Fulop et al. 1986).

In addition to phagocytosing pathogens and destroying them by generation of ROS, neutrophils are also capable of engulfing and destroying pathogens via extrusion of NETs (Brinkmann et al. 2004). So far, no studies have examined the effect of age on NET generation.

Impaired neutrophil functioning detected in older adults can be a result of modifications in signalling pathways and receptor distribution with age. Alterations in physiochemical properties of neutrophil membranes such as reduced membrane fluidity due to altered cholesterol/phospholipid content and changes in actin cytoskeleton have been reported with age in rodents (Alvarez et al. 2001). Altered membrane fluidity results in impaired neutrophil signal transduction as the functioning of lipid rafts is affected and this could explain, to a large extent, the reduced signalling through PI-3 kinase, MAP kinase, protein kinase B, Jak-STAT and SHP-1 signalling seen in neutrophils with increasing age (Shaw et al. 2010). Ca^{2+} ion mobilisation plays a central role in intracellular signal transduction resulting in activation of cytosolic proteins. Resting neutrophils of older adults have an increased level of Ca^{2+} (Wenisch et al. 2000). As a result, older adults are unable to mount a proper Ca^{2+} mobilisation response (Fulop et al. 1989). TREM-1 is a recently identified receptor, responsible for initiating neutrophil inflammatory responses including phagocytosis, superoxide production and degranulation. TREM-1 engagement is impaired in the neutrophils of aged donors resulting in altered neutrophil early activation events; potentially due to alterations in lipid raft engagement of TREM-1 with age (Fortin et al. 2007).

1.5 Macrophages/Monocytes

Macrophages are widely distributed innate immune cells that act as 'pathogen sensors' and are essential for the initiation of immunological responses (against bacteria, viruses, parasites and tumour cells) as well as regulation of adaptive immune responses. Monocytes leave the bone marrow and enter the bloodstream to migrate into body tissues including skin, liver, lungs, spleen, where they differentiate into macrophages. Numerous studies have reported alterations in macrophage functioning with age; altered gene expression, accumulation of DNA mutations and impaired DNA repair appear to be the basis of this impairment in functioning (Lloberas and Celada 2002). Although the absolute number of blood monocytes remains unaltered with age (Gomez et al. 2008; Takahashi et al. 1985), the bone marrow of the elderly has lower numbers of $CD68^{+}$ macrophage precursors (Lloberas and Celada 2002; Ogawa et al. 2000). A decline in haematopoietic cell proliferation due to replicative senescence and increased apoptosis could explain the reduction in macrophage precursors. However, the number, size, DNA content and cell-surface markers expressed during macrophage maturation (e.g., Mac 1) are similar in macrophages from aged to young mice (Sebastian et al. 2005).

Interestingly, monocytes share some functions with neutrophils they can directly resolve infection by migrating towards invading pathogens followed by phagocytosis and killing. A decline in the ability of macrophages to migrate towards the site of infection has been reported with age. Impaired chemotactic responses of macrophages in older adults towards complement factors may contribute towards delayed pathogen clearance (Fietta et al. 1993). However, the data examining the effect of ageing on macrophage phagocytic ability are contradictory. Studies of murine and human cells have reported a decline in macrophage phagocytic ability with age (Fietta et al. 1994; Khare et al. 1996; Plowden et al. 2004; Swift et al. 2001). In contrast, studies in rats have reported an increase in the phagocytic ability of specialised liver macrophages (kuppfer cells) and alveolar macrophages with age (Hilmer et al. 2007; Mancuso et al. 2001). The impact of ageing on phagocytosis-promoting receptors (CD14, CD36, mannose receptor, scavenger receptor, MARCO and MER) and signal transduction pathways still remain unreported. Further research in this direction might be helpful in developing a better understanding of the effect of ageing on macrophage phagocytosis.

Macrophages from old donors also demonstrate impaired intracellular killing of pathogens due to lower production of reactive oxygen intermediates in response to IFNγ, PMA or opsonised zymogen stimulation with age (Davila et al. 1990; Ding et al. 1994). Studies examining an alternative macrophage anti-microbial mechanism, reactive nitrogen intermediate production, have reported conflicting results. Reduced levels of inducible nitric oxide synthase (iNOS) mRNA have been shown in response to lipopolysaccharide (LPS), resulting in decreased production of reactive nitrogen intermediates (Kissin et al. 1997). Conversely, an increase in iNOS levels and NO_{2^-} and other intermediates in response to LPS stimulation has also been reported (Chen et al. 1996). Macrophages display different production of reactive nitrogen intermediates in response to different stimuli (LPS, IFNγ), and the

different experimental protocols and conditions used during these studies might be responsible for the conflicting data.

Importantly, macrophages activate other inflammatory cells via secretion of a range of cytokines (TNFα, IL-6), chemokines (IL-8), growth factors (GM-CSF, M-CSF), coagulation factors and prostaglandin E2. As stated above, ageing is associated with an increase in constitutive levels of serum pro-inflammatory cytokines. In contrast, macrophage production of pro-inflammatory cytokines (IL-6, TNFα, IL12, IL-1β) upon LPS stimulation is less in aged mice and humans in comparison with the young (Boehmer et al. 2004; Chelvarajan et al. 2005; Delpedro et al. 1998; Renshaw et al. 2002), which may contribute to reduced immune responses. Reduced expression of several genes including MHC class II, TLR1 and TLR4 in aged macrophages, due to epigenetic modifications and reduced levels of transcription factors with age, contribute to the observed reduction in cytokine production upon stimulation (Chelvarajan et al. 2005; Gomez et al. 2005; Renshaw et al. 2002; van Duin and Shaw 2007). Studies have also reported impairments in TLR-mediated signalling pathways including lower expression of MAP kinases p38 and Jun Kinases in macrophages with age resulting in lowered activation upon LPS stimulation, which will also contribute to the decline in macrophage pro-inflammatory cytokine production (Boehmer et al. 2004; Chelvarajan et al. 2005). In addition to impaired TLR expression on monocytes with age, a decline in their ability to upregulate co-stimulatory molecules such as CD80 upon TLR engagement has been reported with age (van Duin and Shaw 2007).

Interestingly, an up-regulation of the production of the anti-inflammatory cytokine (IL-10) has been observed in macrophages by some groups (Chelvarajan et al. 2005; Kelly et al. 2007), which may also contribute to poor macrophage-based immunity. Activated macrophages produce higher levels of prostaglandin E2 with age, which is responsible for increased IL-10 production and decreased expression of class II major histocompatibility (MHC) on macrophages resulting in lower antigen presentation and poorer $CD4^+$ T-cell responses (Herrero et al. 2001; Solana et al. 2006).

Macrophages also play an essential role during wound repair by keeping the site free from infection and secreting growth factors to promote angiogenesis (VEGF) and infiltration of fibroblasts (Barbul and Regan 1995). Studies in human and rodent models have reported a significant decline in wound healing with age (Gosain and DiPietro 2004). A delay in macrophage infiltration in the wound site due to lower expression of adhesion molecules (VCAM-1, ICAM-1), occurs with age (Ashcroft et al. 1998), and a 37 % decline in VEGF production has been reported in macrophages from aged mice resulting in diminished angiogenesis, delayed wound closure and a higher risk of developing an infection at site of injury (Swift et al. 1999; Thomas 2001).

1.6 Dendritic Cells

Dendritic cells (DC) represent a rare population of circulating cells that form about 1 % of total peripheral blood cells and play a key role in bridging the adaptive and innate immune systems (Schuurhuis et al. 2006). They are major antigen-presenting

cells interacting with T and B cells and modulating the composition of cytokines produced by T cells (Th1, Th2, Th17), which in turn influences the nature of the immune response. DCs in humans have been divided into two categories—those that are present in peripheral blood (myeloid and plasmacytoid DC) and those that are present in tissues such as mucosa, skin and internal organs. Developmental and functional alterations in DCs with age are additional factors contributing towards immune malfunctioning.

Using multiple cell-surface marker analysis to define DC's one study reported no significant differences in numbers of circulating myeloid DCs and plasmacytoid DCs between aged and young humans (Agrawal et al. 2007). Also, a decreased frequency of tissue DCs has been reported in Peyer's patches with age, which might contribute towards age-associated mucosal dysregulation (Fujihashi and McGhee 2004). However, there have been contradictory reports that have failed to find alterations in numbers of DCs with age (Grolleau-Julius et al. 2006). Furthermore, another study reported that a dense network of DCs pervaded brain areas in aged mice (Stichel and Luebbert 2007). In addition to alterations in DC numbers, their phenotype appears to alter with age, with a decline in expression of MHC class II, CD86, CD40 and CD54 expression reported in DCs from older individuals (Varas et al. 2003).

Immature DCs are remarkably efficient in capturing antigens, which is essential for generating specific immune responses. DCs capture antigens by several mechanisms including: macropinocytosis (non-selective endocytosis), receptor-mediated endocytosis and phagocytosis (Agrawal et al. 2007). DCs are capable of recognising pathogens through the presence of pathogen recognition receptors (PRRs) such as TLRs, NODs and C-type lectin receptors. According to a recent study, normal TLR function and expression has been reported in circulating mDCs and bone marrow derived DCs from aged mice (Tesar et al. 2006). Even though expression of PRRs is unaltered in DCs with age, a decline in DC's ability to uptake antigens has been reported (Tesar et al. 2006), which may have an effect on antigen presentation by MHC class II molecules to T cell resulting in decreased T-cell priming and reduced vaccination responses.

DCs are also responsible for phagocytosing self-antigens such as apoptotic cells and for maintaining peripheral tolerance to the body's own tissues. With age, inefficient removal of apoptotic cells by DCs has been reported, which may be responsible for higher risk of autoimmunity and reduced capacity to clear infections associated with ageing (Agrawal et al. 2007, 2008). In addition to antigen presentation, DCs are also capable of secreting cytokines that stimulate T-cell proliferation. LPS activated DCs in the elderly produce increased levels of IL6 and TNF-α but IL-10 levels remain unaltered (Agrawal et al. 2008). Increased secretion of pro-inflammatory cytokines by DCs might be one of the factors responsible for chronic inflammation (inflammaging) in the elderly.

Phosphatidylinositol 3 Kinase (PI3 K) acts as a negative feedback regulator of inflammation (Guha and Mackman 2002). PI3 K is responsible for blocking p38 MAPK activation in DCs, whilst AKT acts as a negative regulator of MAPK activation. A decline in AKT activation has been reported in DCs from older adults, which can be associated with upregulation of p38MAPK activity in DCs (Fukao et al. 2002).

PI3 K-AKT pathway positively regulates DC migration and phagocytosis, lowered PI3 K activation results in impaired phagocytic ability and migration of DCs with age (Agrawal et al. 2007).

DCs regulate T and B cells via co-stimulatory and inhibitory molecules expressed on their surface. With age, no significant alteration in the expression of co-stimulatory molecules has been observed. While the effect of ageing on expression of inhibitory molecules has not been examined (Agrawal et al. 2007). DCs are capable of driving T-cell polarisation via cytokine production, secretion of pro-inflammatory cytokines (IL-12) drives TH1 responses while IL-10 drives Th2 responses. A decline in TNFα and IL-6 output and increased IL-10 secretion upon LPS stimulation has been observed in DCs of aged subjects (Agrawal et al. 2009). The stimulatory capacity of DCs to induce proliferation of T cells is preserved with age (Steger et al. 1997). With respect to B-cell stimulation, aged DCs have lower cell surface expression of complement receptors (CD21) and lower antigen: antibody complexes, resulting in lower B-cell stimulation (Plackett et al. 2004). Follicular DC of aged mice often remain trapped within the sub-capsular sinus of lymph nodes and are unable to reach B-cell follicles resulting in decreased germinal centre formation (Kapsenberg 2003).

1.7 NK/NKT Cells

1.7.1 NK Cells

Natural killer (NK) cells are non-T-lymphocyte cytotoxic cells capable of recognising and killing cells infected with intracellular pathogens (predominantly viruses) and tumour cells. NK cells account for about 10–20 % of peripheral blood lymphocytes and have been divided into two separate subsets on the basis of relative expression of the adhesion molecule CD56 and the Fcγ receptor CD16, namely CD16+, $CD56^{dim}$ and the CD16+, $CD56^{bright}$ (Cooper et al. 2001). Approximately 90 % of NK cells are $CD56^{dim}$; these cells have high cytotoxicity towards virus-infected cells and tumour cells. Even though only 10 % of NK cells in the blood are $CD56^{bright}$; these cells make up to 90 % of NK cells in lymph nodes. $CD56^{bright}$ cells have immunomodulatory properties and are capable of initiating adaptive immune responses, activation of DCs and production of immunoregulatory cytokines (IL-10, IL-13, TNFα, IFNγ; Cooper et al. 2001; Vitale et al. 2004).

NK cell functioning and dynamics are affected by ageing. There is a 40–60 % decline in NK-cell proliferation with age in response to IL-2 due to lower Ca^{2+} mobilisation (Borrego et al. 1999), but this is balanced by an increased number of circulating NK cells (Almeida-Oliveira et al. 2011; Franceschi et al. 1995; Sansoni et al. 1993) possibly due to a higher proportion of long-lived NK cells in aged donors. The increase in the number of NK cells results from an expansion of the $CD56^{dim}$ subset but there is also a decline in the number of $CD56^{bright}$ NK cells (Chidrawar et al. 2006; Vitale et al. 1992) suggesting a phenotypic and functional shift in NK cells with age.

A decline in NK cell cytotoxicity on a per cell basis has been consistently reported with age (Di Lorenzo et al. 1999; Mariani et al. 1998), though the mechanisms are only partially understood. NK cells' ability to recognise and bind to target cells and perforin (a key component of cytotoxic granules) expression in NK cells is preserved with age (Mariani et al. 1992; Vitale et al. 1992), but defective transmembrane signalling; especially involving protein kinase C (PKC)-dependent pathways has been reported. Antibody-dependant cellular cytotoxicity (ADCC) in NK cells is mediated via signalling molecule CD16, and CD16 expression on NK cells is unaltered with age resulting in unaltered ADCC in NK cells with age (Mariani et al. 1998; Sansoni et al. 1993).

In addition to cytotoxic functions during early responses against infection, NK cells are also responsible for promoting adaptive responses against infections via secretion of immunoregulatory cytokines. Cytokine (IFNγ, IFNα) and chemokine (MIP-1α, Rantes, IL-8) production by NK cells in response to IL-2 is lower in elderly subjects compared with the young (Mariani et al. 2002). However, an increase in IL-4 and IL-10 production by NK cells and unaltered TNFα production has been reported with age (Solana et al. 1999). NK cells in the elderly show lower proliferation responses to IL-2 and a parallel impaired expression of CD69 activation antigen (Solana et al. 1999). The decreased proliferation response has been ascribed to reduced Ca^{2+} mobilisation with age (Borrego et al. 1999).

Natural cytotoxicity receptors (NCRs) such as NKp46 play an important role in NK cell cytotoxicity and cytokine production. NKp30 plays a central role in the crosstalk between NK cells and DCs. Recently, a study has reported a decline in NKp46 and NKp30 receptor expression with age (Almeida-Oliveira et al. 2011). CD94/NKG2 and KIR receptors have been known to regulate NK cell activation. An increase in KIR expression and decreased CD94/NKG2 A expression has been reported with age (Lutz et al. 2005). Altered NK cell receptor expression pattern with age may have an influence on susceptibility to infections and inflammatory diseases.

1.7.2 NKT Cells

NKT cells are "innate immune lymphocytes" that in addition to NK cell markers express T-cell receptor (TCR). The origin and function of NKT cells is poorly understood, although they have been suggested to play an important role in immune regulation via cytokine production. In addition to immune regulation, NKT cells have cytotoxic potential and are directly capable of killing target cells. Studies done in rodents have reported an increase in the number of NKT cells with age (Dubey et al. 2000; Faunce et al. 2005), and a decline in NKT cell cytotoxicity and impaired IFNγ production has been reported in aged mice and humans (Mocchegiani and Malavolta 2004). Thus, the limited data available suggests that the age-related changes in NKT cells are similar to those of NK cells.

Table 1.1 Significant changes in innate immune cells with advancing age

Cell population	Changes with age	Direction of change
Neutrophils	Numbers at site of infection	↔
	Chemotaxis	↓
	Phagocytic ability	↓
	Superoxide production	↓
	Ability to be rescued from apoptosis	↓
Monocytes	Absolute numbers	↔
	Migratory ability	↓
	Phagocytic ability	↓
	Intracellular killing of pathogens	↓
	Production of pro-inflammatory cytokines upon activation	↓
	Wound-healing function	↓
Dendritic cells	Number of circulating DCs	↓
	Migratory ability	↓
	Phagocytic ability	↓
	Ability to induce T-cell proliferation	↔
	Production of pro-inflammatory cytokines	↑
NK cells	NK cell numbers in circulation	↑
	NK cell cytotoxicity	↓
	Cytokine and chemokine production	↓
NKT cells	Absolute numbers	↑
	NKT cell cytotoxicity	↓
	Cytokine production (IFNγ)	↓

1.8 Concluding Remarks

Over the past decades, extensive evidence concerning a decline in immune system functioning has increased in parallel with other biological systems with age. Age-related alterations in several immunological parameters in both adaptive and innate immune systems have been reported. Given this decline in immune functioning in the aged, their ability to mount an adequate immune response to infection is questionable, resulting in increased susceptibility towards infections. Defects have been reported in functioning of all cells of the innate immune system as a result of intrinsic defects and altered extrinsic environment, summarised in Table 1.1. Impaired immune responses in the elderly thus appear to be a major factor responsible for the increased risk of bacterial and viral infection in the aged, resulting in increased morbidity and mortality. Although the past decade has seen a rapid explosion in research in the field of immunosenescence, the effect of ageing on innate immune responses is still incompletely understood, notably our understanding of the underlying molecular causes is incomplete. Moreover, our understanding of how the changes in the immune system with age are influenced by psychosocial factors mediated via neuroendocrine-immune interactions is a field that is still in its relative infancy. A detailed understanding of the impact of ageing on the innate immune system and

its interaction with endocrine factors will enable us to develop therapeutic strategies; both lifestyle and pharmaceutical, to provide protection against infections and develop better strategies to control diseases in older adults.

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Chapter 2
Introduction to Ageing of the Adaptive Immune System

Ludmila Müller and Graham Pawelec

2.1 Introduction

Like other somatic tissues and organs, the vertebrate immune system manifests age-associated alterations to its components and their functions. Unlike in invertebrates, in addition to the innate arm, vertebrates also possess adaptive immunity mediated by both cellular and humoral components. This chapter reviews data on age-associated alterations to adaptive immunity specifically in humans, mostly originating from cross-sectional studies (i.e., comparing young with old people). We summarise what is known about the effects of age on the different components of the adaptive immune system, particularly T cells, which appear most obviously different in the elderly. We consider the serious limitations inherent in cross-sectional studies, and discuss the crucial requirement to perform longitudinal studies (i.e., following the same individuals over time). Despite the logistical and financial constraints, longitudinal follow-up has provided the most biologically meaningful information about which of the many biomarkers apparently changing with age are actually relevant to medical parameters and for late-life health and longevity, and which, in contrast, may change with age but without clinical relevance. Given the lack of consistent data currently available, as a result of performing studies on heterogeneous populations using different analytical techniques, we emphasize the necessity for more numerous, more extensive and more detailed studies including assessments of the impact of psychosocial, nutritional and other thus-far rarely considered parameters on immunological and other biomarkers in longitudinal studies. We consider the mechanisms responsible for the disparate age-associated changes observed, beginning at the level of hematopoiesis, where alterations in the stem cell niches and the stem cells themselves contribute to

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