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Dendritic Cells in Immunosenescence

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Abstract

Nascimento MPP, Lara VS. Dendritic Cells in Immunosenescence, Mini Review. ARBS Annu Rev Biomed Sci 2011;13:9-16. The term immunosenescence usually refers to the aging of the immune system. Aging is associated with the progressive decline in immune function, resulting in an increasing susceptibility of the body to infection, taking into account the specific changes in T- cells, macrophages, neutrophils and dendritic cells. Dendritic cells (DCs) are play a key role in the induction of both innate and adaptive immunity. There are immature and mature forms located in the non-lymphatic organs and lymph nodes, respectively. DCs initiate and regulate the highly pathogen-specific adaptive immune responses, and are central to the development of immunologic memory and tolerance. In this text, we will briefly review DCs and changes associated with human aging, such as cytokine secretion, antigen capture, migration and priming of T cells. This functional decline would lead to major morbidity associated with infections such as influenza and pneumonia, which affect mucosal surfaces; in addition the increased incidence of cancer in the elderly is associated with the potential role of DCs.
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Table of Contents

1. Introduction

According to the 2007 World Economic and Social Survey, in 2050, almost 2 billion people will be aged 60 years or over, reducing the total number of children and young people, and simultaneously increasing the number of elderly. However, these older persons should receive adequate support during old

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age, access to decent employment in order to remain economically active (Department of Economic and Social Affairs, 2007).

The increasing of life expectancy in the world population has enabled observation of the phenomenon of immunosenescence, alteration in the immune system of the elderly, characterized by decreasing efficiency in combating infections (Pawelec, 2006). With population ageing, this phenomenon will become increasingly common among older people. This will make it necessary to conduct studies about these changes, with the aim of acquiring better understanding of the mechanisms of immunosenescence, thereby contributing to ensuring better health status of the elderly, increase in life expectancy and improved quality of life.

2. Background History

2.1. Immunosenescence

The term immunosenescence refers to the ageing of the immune system. However, this ageing is not necessarily associated with disease, but with a series of functional and morphological changes in the cells that are part of the immune system. This term was first introduced by Dr. Roy Walford in 1969, according to whom, it refers to decreasing immune function due to ageing, with an important decline in response to infection, either by the innate and/or the adaptive immune systems, leading to serious damage to health in the elderly.

The immunosenescence is secondary to a number of factors such as hormonal decline, especially stress and thymic involution. Increase in autoantibody production is indicative of the presence of inflammatory processes associated with autoimmune diseases in the elderly. Decrease in naive T cell frequency, commonly observed in the ageing, leads to a reduced immune effector cell response against infectious microorganisms. The specific functions of T and B cells also decline with age, and is characterized by T cells that might evoke a detrimental immune response to specific antigens, changing cytokine secretion patterns, changes in naive T cells and memory, decreased cytotoxic T cell response, inability to produce antibodies with high affinity and to generate long-term memory, and defects in signal transduction (Gupta, 1989, McElhaney *et al.* 1992; Song *et al.* 1993; Pawelec *et al.*, 2002). Paradoxically, ageing is associated with low-grade chronic inflammation and high levels of circulating proinflammatory mediators, including IL-6, TNF-a, IL-1 b and prostaglandin E2 (Ershler, 1993; Fagiolo *et al.* 1993; Brunnsgaard *et al.*, 2003, Trzonkowski *et al.*, 2004). Many studies have focused on the quantification of IL-6, which has been called the cytokine of gerontologists (Wei *et al.* 1992; Ershler, 1993). Some studies have reported increased levels of cytokines in serum or plasma as the aging process advances (Hager *et al.* 1994; Brunnsgaard *et al.*, 1999), while others have reported that no differences were observed in comparison with the young population (Peterson *et al.* 1994; Beharka *et al.*, 2001). Similarly, some studies in older populations have found the plasma levels of TNF-a increased (Paolisso *et al.* 1998) and positively correlated with the concentration of plasma IL-6 (Brunnsgaard *et al.*, 1999), while others found no differences between older or young populations (Fagiolo *et al.*, 1993, Peterson *et al.*, 1994). The reported discrepancies are probably due to variation in sensitivity of the study method, such as ELISA, standardization of the health status of all elderly participants, and age differences (Krabbe *et al.*, 2004).

The reduced immune response observed during the ageing process is closely related to changes that occur in the thymus during senescence (Aspinall *et al.*, 2007). During the ageing process, decreases in the proportion of naive T cells when compared with memory T cells and mature and immature T cells, partly associated with thymic involution, are considered by Malaguarnera et al (2001) the main anatomical and histological changes observed in the elderly. These decreases contribute to damage to the cells involved in the phenomenon of eliminating an invading pathogen, as well as to low immune response to antigens, vaccine and the reduced generation of immunological memory, which consequently lead to reduced levels of vaccine protection observed in the elderly.

Some researchers have proposed a different view on immunosenescence, suggesting that the ageing process of the immune system would result from the remodeling of immune functions, in which some functions are reduced while others are increased through compensatory mechanisms, or remain unchanged, considering immunosenescence to be a highly dynamic process and not only a unidirectional decline in all functions of the immune system (Globerson and Effros, 2000).

2.2. Dendritic Cell

Dendritic cells (DCs) were first described by Steinman and Cohn in 1973. They are powerful antigen presenting cells, extremely efficient in the activation of CD4 + and CD8+ (Steinman *et al.*, 2003). They are considered specialized cells, known as professional antigen presenting cells, due to their ability to induce strong immune response by T cells, despite the low number of these cells in the body (Castle, 2000). Considering that the innate immune response is critical in the development of subsequent adaptive immune responses, the DCs appear as a typical example of this connection between the two forms of immunity (Kapsenberg, 2003; Hackstein and Thomson, 2004; Rossi and Young, 2005; Dubsky *et al.* 2005; Schuurhuis *et al.*, 2006, Hugues *et al.* 2006; Reis e Souza, 2006).

Their main role is to capture and transport protein antigens to the draining lymph nodes. During this process, the interaction between chemokine receptor CCR7 and its connector (MIP3-b) is essential for normal migration of mature DCs from the periphery to lymph nodes (Agrawal *et al.*, 2007). Here the DCs complete their maturation, to become extremely efficient antigen presenting cells required for the stimulation of the T naive lymphocytes. The maturation occurs in response to microbial products or to the signals sent by the activated T cells or macrophages (Agrawal *et al.*, 2007). The mature or activated DCs reside in the T cell areas of lymph nodes, and in this location they present antigens to T cells. The properties of DCs for induction and regulation of the immune responses has aroused interest in the use of these cells (Elkord *et al.*, 2005), mainly for production of vaccines against infectious diseases and cancer. These cells have also shown to be promising for gene therapy in the treatment of tumors or immune diseases, in addition to their role in inducing tolerance to T cells (Banchereau *et al.*, 1998, Steinman *et al.*, 2003). In a recent study, it was reported that DCs can prevent, inhibit or modulate T cell mediated responses through a variety of mechanisms, ranging from the production of pleiotropic anti-inflammatory factors that exert broadly attenuating effects to the induction of antigen-specific T cell responses, resulting in anergy, suppression or instruction of the regulatory T cells (Tregs) (Maldonado and Andrian, 2010). The Treg cells have been shown to play a crucial role in controlling autoimmunity and chronic inflammation and the failure in their function has been implicated in the development of many autoimmune processes.

The DCs capture antigens by several mechanisms including micropinocytosis or Fcy receptors that belong to the immunoglobulin superfamily of receptors Fc and are the most important receptors for inducing phagocytosis of opsonized microbes (Fridman W, 1991), apoptotic and necrotic cells, viruses and bacteria, including mycobacteria. Internalization of heat shock proteins, hsp 70 or complex peptide gp-96, through multiple receptors including Toll-like receptors (TLR2/TLR4) also are considered mechanisms of antigen capture (Dubsky *et al.*, 2005). The TLR are pattern-recognition receptors (PRRs) involved in recognizing the pathogen-associated molecular patterns (PAMPs) (Janeway and Medzhitov, 2002). These receptors are located in a large number of mammalian cells in the body, but mainly in the cells of the innate immune system, such as macrophages and dendritic cells (Hallman *et al.*, 2001). The activation of these receptors by PAMPs induces both phagocytosis and release of cytokines and chemical mediators that act on the immune system (Barton and Medzhitov, 2002). The PRPs expressed by the DCs include C-type lectins and DC1a, which also recognize molecular characteristics expressed in pathogens (van Kooyk and Geijtenbeek, 2003; Colonna, 2006). Therefore, an efficient catchment of antigens is essential for the generation of a specific immune response (Agrawal *et al.*, 2007).

The mechanisms by which the DCs perform their activities are varied and still remain misunderstood (Maldonado and Andrian, 2010). Immature DCs are not yet fully functional antigen-presenting cells (Agrawal and Gupta, 2011); they are typically tolerogenic (Steinman et al, 2003) until they mature, which means that the lack of maturity provides a clue to their tolerogenic capacity. However, immature DCs are composed of several different subgroups that have distinct abilities to present antigens, secrete cytokines, in addition to inducing tolerance (Ueno *et al.*, 2007). Upon stimulation DCs start to mature and migrate to draining lymph nodes, where they become fully functional antigen-presenting cells (APC) capable of priming naive T cells (Agrawal and Gupta, 2011).

When DCs are stimulated to maturation or activation, they increase their expression of major histocompatibility complex class II (MHC-II) and several co-stimulatory molecules, resulting in the loss of ability to capture and process antigens, but they increase their antigen-presenting function. This activation is associated with several events, including loss of endocytic/phagocytic receptor, increase in the regulation of MHC and co-stimulatory molecules (e.g. DC40, DC58, DC80, DC40L, DC70, 4-IBB-l), changes in adhesion molecules and secretion of a wide spectrum of cytokines and other inflammatory mediators, which allow them to communicate with each other and other immune cells (Shuurhuis *et al.*, 2006). Consequently, DCs can modulate the adaptive immune response in two ways: 1) by modulating the

expression of co-stimulatory/inhibitory molecules of DCs, which regulate the priming of T and B cells; and 2) by producing cytokines in response to the pathogens that are largely responsible for determining the type of response, whether it will be T helper (Th) 1, Th2 or Th3 (Kapsenberg, 2003).

DCs differ from other antigen-presenting cells because they are the only cells that can cross-present antigens (Burgdorf *et al.*, 2008; Amigorena and Savina, 2010) in the immune response, whereas the other APCs (B cells and macrophages) are involved in the amplification of immune responses. The DCs plays an important role in adaptive immunity, induction of tolerance and immunity (Kapsenberg, 2003; Schuurhuis *et al.*, 2006, Hugues *et al.* 2006; Reis e Sousa, 2006). Immature DCs induce tolerance by activation/ induction of regulatory T cells and deletion of auto-reactive clones by apoptosis, while mature DCs induce immune responses by T and B cells, which are the key mediators of immune activity (Banchereau and Steinman, 2001).

These cells also act as potent immunostimulatory cells leading the clonal expansion of T cells and the immunomodulatory cytokines such as interleukin (IL)-10 and IL-12, promoting the development of Th1 or Th2 cells (Steinman *et al.* 1991; Elkord *et al.*, 2005).

In the past few years, the tolerogenic potential of DCs has been experimentally explored for the expansion of regulatory T cells that express FOXP3 (important transcription factor in the suppressive activity) and suppression of inflammation, either in autoimmune diseases, such as response in allogeneic transplantation. Many believe that the expansion of regulatory T cells in the presence of DCs is an important strategy to induce immune regulation in the clinic (Coelho *et al.*, 2007).

Peripheral blood monocytes (PBMCs) are the precursor cells of the dendritic cells and they can be differentiated by exposure to some pathogens or inflammatory factors (Zhou and Tedder, 1996; Geissmann *et al.*, 2010). Blood is the most accessible tissue for the study of dendritic cells in humans (Freudenthal and Steinman, 1990). Therefore, reports of TANG and co-workers (2005) have demonstrated the development of a new and simple method of DC generation, using recombinant human granulocyte-macrophage-colony-stimulating factor (rhGM-CSF) and recombinant human interleukin-4 (rhIL-4) for the differentiation of monocytes. The DCs produced by this method acquired morphologic and antigenic characteristics of DCs. These authors have also used TFN-a to induce DCs maturation, and the presence of TNF-a or LPS during the differentiation of the DCs significantly stimulated the proliferation of T cells (Tang *et al.*, 2005). In this experiment, the authors reported that DC1a is the major molecular marker of DCs derived from monocytes, and is related to the process of antigen presentation by these cells. Furthermore, the authors described that DC83 is a specific marker of activated DCs; DC14 is a specific marker of monocytes, which gradually decreases its expression during differentiation of monocytes into DCs, and that DC80 and DC86 are important co-stimulatory factors in the proliferation of T lymphocytes by the DCs, in agreement with other researchers (Bender *et al.* 1996; Labeur et al, 1999; Duperrier *et al.* 2000; Ebner *et al.*, 2001).

2.3. Immunosenescence and Dendritics Cells Tissues and cells

DC function is usually quite limited in the elderly (AGRAWAL *et al.*, 2007), in addition to the quantity of these cells and their precursors being reduced with the ageing process (Della-Bella *et al.*, 2007). The role of the DC in the immune phenomena of the elderly is still poorly understood (Agrawal *et al.*, 2007). In elderly individuals, Pietschmann and co-workers (2000) observed a reduced capacity of DCs to cross the transendothelial barrier, an important activity in the identification of several pathogens in different tissues.

The changes in the role of DCs in immunosenescence can be attributed to changes in the balance of these cells under conditions of chronic inflammation, as reported by Kim *et al.* (2007) and observed in the chemotaxis and phagocytosis in neutrophils (Agrawal *et al.* 2007; Gasparotto *et al.*, 2009). Moreover, DCs from aged humans show increased reactivity to autoantigens released during apoptosis, and similar increases in cytokines have been observed in aged DCs in response to late apoptotic cells (Agrawal and Gupta, 2011). In the elderly, DCs can stimulate CD8 T cells, but seem to fail in the proper stimulation of CD4 T cells (Agrawal *et al.*, 2007), resulting in an emerging paradigm of the behavior of both CD4 and CD8 T cells, which can be observed in states of infections (Appay *et al.*, 2007), autoimmunity (Goronzy *et al.*, 2006, Witkowski *et al.*, 2007) or cancer (Pawelec *et al.*, 2006). It is possible that changes in the signal transduction mechanisms may be responsible for some of these aspects of immunosenescence, but detailed mechanisms are still not well understood (Agrawal *et al.*, 2007).

The differentiation and proliferation of the DCs after the interaction with the T cells may also be involved in ageing or chronic diseases, due to decreased production of GM-CSF, an important growth

factor for DCs (Pawelec and Wagner, 1999, Plackett *et al.*, 2004).

In recent times, some relevant clinical studies on elderly people have revealed new approaches to the involvement of Toll-like receptor, which may lead to the decreased immune response after influenza vaccination (van Duin *et al.*, 2007).

The activation of the DCs via Toll-like receptor 2 or 4, results in the secretion of anti-inflammatory cytokine (IL-10) and proinflammatory (TNF-a, IL-6, IL-12p70, IL-23). The secretion of IL-12 by DCs leads to production of IFN-g (Th1), while anti-inflammatory cytokine IL-10 inhibits the secretion of IL-12 by DCs, leading to Th2 responses (Agrawal *et al.*, 2007). Recent studies have shown that activation of DCs through a combination of receptor TLR-2 and C-lectin results in the secretion of IL-10, which leads to the Th3 response (regulatory). Therefore, any change in the pattern of cytokine secretion by DCs in the ageing process may influence the nature of the immune response by T cells. However, there are no detailed reports describing the expression and work of Toll-like receptors in DCs in elderly mice and humans (Agrawal *et al.*, 2007).

According to Simioni *et al.* (2010) there are reports indicating that DCs derived from peripheral blood of humans do not exhibit significant phenotypic or functional changes in the ageing process. On the other hand, DCs differentiated in vitro from precursors obtained from bone marrow of elderly mice, have increased secretion of IL-10 and a reduced secretion of tumor necrosis factor alpha (TNF-α) and IL-6 after stimulation with lipopolysaccharide, when compared with DCs obtained from young mice (Grolleau-Julius *et al.*, 2006). Furthermore the ageing process and genetic heritage may also influence susceptibility to the induction or maintenance of oral tolerance (Moreau *et al.* 1996; de Faria *et al.* 1998; Lahmann *et al.*, 1992).

T cell mediated immune response to tumors and bacterial or viral infections is mainly based on their cognition of antigenic peptides processed and presented to the T cells by DCs (Timmerman and Levy, 1999; Turley *et al.*, 2000, Steinman and Nussenzweig, 2002). It has been shown that when compared with young mice, aged mice were ten times more susceptible to the challenge with tumor cells (Shi *et al.*, 2005) suggesting that the aged microenvironment affects the antitumor response by DCs. (Sharma *et al.*, 2006) and that there are also intrinsic defects in aged DCs. (Grolleau-Julius *et al.*,2006). However, DCs are an important target in the study and development of potential anticancer treatments and vaccines, mainly involving the elderly population, since it is preferentially affected by diseases with potential for treatment with immunotherapy based on DCs (Shurin *et al.*, 2007).

3. Concluding Remarks

It has been hypothesized that normal aging alters the coordinated interactions between the immune system and the other systems of the body. Impaired immunoregulation may predispose older individuals to an increased frequency of peripheral infections. The senescent cells accumulated in vivo, are presumed to contribute to the pathogenesis of age-related diseases. Therefore, studies in immunosenescence, as well as its causes and factors responsible for its development, are still contradictory, considering the variety of divergent results in the literature. As the data related to the ageing process and DCs are relatively scarce and sometimes conflicting, it is of crucial importance to conduct further studies in this area, because the effects of ageing on these powerful antigen-presenting cells are not well known. Understanding how immunity is affected by age is important, because DCs play an integral role in propagating inflammatory signals that are initiated in the periphery. The majority of studies have used an allostimulatory model to study DC-induced T cell proliferation. Additional studies on the numerical and functional alterations of these cells in the aging process may contribute to the achievement of preventive and therapeutic strategies, particularly with regard to infectious diseases, such as influenza, pneumonia and cancer, in order to seek a better quality of life for the growing elderly population.

4. References

Agrawal A, Agrawal S, Gupta S. Dendritic cells in human aging. Exp Gerontol 2007; 42:421-6.

Amigorena, S., Savina, A. Intracellular mechanisms of antigen cross presentation in dendritic cells. Curr Opin Immunol 2010; 109–17.

Anshu Agrawal, Sudhir Gupta. Impact of aging on dendritic cell functions in humans. Ageing Res Rev 2011; 336–45.

Appay V, Bosio A, Lokan S, Wiencek Y, Biervert C, Küsters D, Devevre E, Speiser D, Romero P, Rufer N, Leyvraz S. Sensitive gene expression profiling of human T cell subsets reveals parallel post-thymic differentiation for CD4+ and CD8+ lineages. J Immunol 2007;179(11):7406-14.

Aspinal R, Pido-Lopez J, Imami N, Henson SM, Ngom PT, Morre M, Niphuis H, Remarque E, Rosenwirth B, Heeney JL. Old rhesus macaques treated with interleukin-7 show increased TREC levels and respond well to influenza vaccination. Rejuvenation Res 2007;10-5-17.

Banchereau J, Steinman RM. Dendritic cells and the control of immunity. Nature 1998;392:245-52.

Barton GM, Medzhitov R. Control of adaptive immune responses by Toll-like receptors. Curr Opin Immunol 2002;14(3):380-3.

Bender A, Sapp M, Schuler G, Steinman RM, Bhardwaj N. Improved methods for the generation of dendritic cells from nonproliferating progenitors in human blood. J Immunol Methods 1996;196(2):121-35.

Beharka AA, Meydani M, Wu D, Leka LS, Meydani A, Meydani SN. Interleukin-6 production does not increase with age. J Gerontol A Biol Sci Med Sci 2001;56:B81-8.

Bruunsgaard H, Andersen-Ranberg K, Jeune B, Pedersen NA, Skinhoj P, Pedersen BK. A high plasma concentration of TNF-alpha is associated with dementia in centenarians. J Gerontol A Biol Sci Med Sci 1999;54:M357-64.

Bruunsgaard H, Andersen-Ranberg K, Hjelmborg JB,, Pedersen BK, Jeune B.Elevated levels of tumor necrosis factor alpha and mortality in centenarians. Am J Med 2003;115:278-283.

Burgdorf, S., Schölz, C., Kautz, A., Tampé, R., Kurts, C. Spatial and mechanistic separation of cross-presentation and endogenous antigen presentation. Nat Immunol 2008; 9, 558–566.

Castle SC. Clinical relevance of age-related immune disfunction. Clin Infect Dis 2000;31:578-85.

Coelho V, Caldas Ramos C, Kalil Filho JE. Imunobiologia do Alotransplante –Temas de Reumatologia Clínica - Vol. 8 - Nº 2, 2007.

Colonna M. Toll-like receptors and IFN-alpha: partners in autoimmunity. J Clin Invest 2006;116(9):2319-22.

Della Bella S, Bierti L, Presicce P, Arienti R, Valenti M, Saresella M, Vergani C, Villa ML. Peripheral blood dendritic cells and monocytes are differently regulated in the elderly. Clin Immunol 2007;122:220-8.

Department of Economic and Social Affairs. World Economic and Social Survey 2007.

Development in an Ageing World. United Nations New York, 2007. Disponível em: www.un.org/en/development/desa/policy/wess/wess.../2007wess.pdf. Acesso em: 23 setembro 2011.

Dubsky P, Ueno H, Piqueras B, Connoly H, Bachereau J, Palucka AK. Human dendritic cell subsets for vaccination. J Clin Immunol 2005;25:551-72.

Duperrier K, Eljaafari A, Dezutter-Dambuyant C, Bardin C, Jacquet C, Yoneda K, Schmitt D, Gebuhrer L, Rigal D. Distinct subsets of dendritic cells resembling dermal DCs can be generated in vitro from monocytes, in the presence of different serum supplements. J Immunol Methods 2000;238:119-31.

Ebner S, Neyer S, Hofer S, Nussbaumer W, Romani N, Heufler C. Generation of large numbers of human dendritic cells from whole blood passaged through leukocyte removal filters: an alternative to standard buffy coats. J Immunol Methods 2001;252:93-104.

Elkord E, Williams PE, Kynaston H, Rowbottom AW. Human monocyte isolation methods influence cytokine production from in vitro generated dendritic cells. Immunology 2005;114:204-12.

Ershler WB. Interleukin-6: a cytokine for gerontologists. J Am Geriatr Soc 1993;41:176-181.

Fagiolo U, Cossarizza A, Scala E, Fanales-Belasio,E, Ortolani C, Cozzi E, Monti D, Franceschi C, Paganelli E. Increased cytokine production in mononuclear cells of healthy elderly people. Eur J Immunol 1993;23:2375-78.

de Faria AM, Ficker SM, Speziali E, Menezes JS, Stransky B, Silva Rodrigues V, Vaz NM. Aging affects oral tolerance induction but not its maintenance in mice. Mech Ageing Dev 1998 May 1;102(1):67-80.

Freudenthal PS, Steinman RM. The distinct surface of human blood dendritic cells, as observed after an improved isolation method. Proc Natl Acad Sci USA 1990;87(19):7698-702.

Fridman W. Fc receptors and immunoglobulin binding factors. FASEB J 1991;12:2684–90.

Gasparoto TH, Vieira NA, Porto VC, Campanelli AP, Lara VS. Ageing exacerbates damage of systemic and salivary neutrophils from patients presenting Candida-related denture stomatitis. Immun Ageing 2009;6:1-12.

Geissmann F, Manz MG, Jung S, Sieweke MH, Merad M, Ley K. Development of monocytes, macrophages, and dendritic cells. Science 2010;327(5966):656-61.

Globerson A, Effros RB.. Ageing of lymphocytes and lymphocytes in the aged. Immunol Today 2000:515-21.

Goronzy JJ, Fujii H, Weyand CM. Telomeres, immune aging and autoimmunity. Exp Gerontol 2006;41:246-51.

Grolleau-Julius A, Garg MR, Mo R, Stoolman LL, Yung RL. Effect of aging on bone marrow-derived murine CD11c+CD4-CD8alpha- dendritic cell function. J Gerontol A Biol Sci Med Sci 2006;1039-47.

Gupta S. Mechanisms of transmembrane signalling in human T cell activation. Mol Cell Biochem 1989;91:45-50.
Hackstein H, Thomson AW. Dendritic cells: emerging pharmacological targets of immunosuppressive drugs. Nat Rev Immunol 2004; 4:24-34.
Hager K, Machein U, Krieger S, Platt D, Seefried G, Bauer J. Interleukin-6 and selected plasma proteins in healthy persons of different ages. Neurobiol Aging 1994;15:771-2.
Hallman M, Rämet M, Ezekowitz RA.Toll-like receptors as sensors of pathogens. Pediatr Res 2001;50:315-21.
Hugues S, Boissonnas A, Amigorena S, Fetler L. The dynamics of dendritic cell-T interactions in priming and tolerance.Curr Op Immunol 2006;18:491-195.
Janeway CA Jr, Medzhitov R. Innate immune recognition. Annu Rev Immunol 2002;20:197-216.
Kapsenberg ML. Dendritic cell control of pathogen-driven T cell polarization. Nat Rev Immunol 2003;3:984-93.
Kim HJ, Barajas B, Chan RC, Nel AE. Glutathione depletion inhibits dendritic cell maturation and delayed-type hypersensitivity: implications for systemic disease and immunosenescence . J Allergy Clin Immunol. 2007;119:1225-33.
Krabbe KS, Pedersen M, Bruunsgaard H. Inflammatory mediators in the elderly. Exp Gerontol 2004;39:687-99.
Labeur MS, Roters B, Pers B, Mehling A, Luger TA, Schwarz T, Grabbe S. Generation of tumor immunity by bone marrow-derived dendritic cells correlates with dendritic cell maturation stage. J Immunol 1999;162:168-75.
Lahmann WM, Menezes JS, Verdolin BA, Vaz NM. Influence of age on the induction of oral tolerance in mice and its adoptive transfer by spleen cells. Braz J Med Biol Res 1992;25:813-21.
Malaguarnera L, Ferlito L, Imbesi RM, Gulizia GS, Di Mauro S, Maugeri D, *et al.* Immunosenescence:a review. Arch Gerontol Geriatr 2001;32:1-14.
Maldonado RA, von Andrian UH. How tolerogenic dendritic cells induce regulatory T cells. Adv Immunol 2010;108:111-65.
McElhaney JE, Meneilly GS, Beattie BL, Helgason CD, Lee SF, Devine RD, Bleackley RC. The effect of influenza vaccination on IL2 production in healthy elderly: implications for current vaccination practices. J Gerontol 1992;47:M3-8.
Moreau MC, Gaboriau-Routhiau V. Res Immunol.The absence of gut flora, the doses of antigen ingested and aging affect the long-term peripheral tolerance induced by ovalbumin feeding in mice. Res Immunol 1996;147:49-59.
Paolisso G, Rizzo MR, Mazziotti G, Tagliamonte MR, Gambardella A, Rotondi M, Carella C, Giugliano D, Varricchio M, DOnofrio F. Advancing age and insulin resistance:role of plasma tumor necrosis factor-alpha. Am J Physiol 1998;38:E294-9.
Pawelec G, Wagner W, Adibzadeh M, Engel A. T cell immunosenescence in vitro and in vivo. Exp Gerontol 1999;34:419-29.
Pawelec G , *et al.* T cells and aging. Front Biosci 2002;7:d1056-183.
Pawelec G. Immunity and ageing in man. Exp Gerontol 2006;41:1239-42.
Peterson PK, Chao CC, Carson P, Hu S, Nichol K, Janoof EN. Levels of tumor necrosis factor alpha, interleukin 6, interleukin 10, and transforming growth factor beta are normal in the serum of the healthy elderly. Clin Infect Dis1994; 19:1158-9.
Plackett TP, Boehmer ED, Faunce DE, Kovacs EJ. Aging and innate immune cells. J Leukoc Biol 2004; 76:291-9.
Pietschmann P, Hahn P, Kudlacek S, Thomas R, Peterlik M. Surface markers and transendothelial migration of dendritic cells from elderly subjects. Exp Gerontol 2000;35:213-24.
Reis e Sousa C. Dentric cells in a mature age. Nat Rev Immunol 2006;6:476-83.
Rossi M, Young JW. Human dendritic cells: potent antigen-presenting cells at the crossroads of innate and adaptive immunity. J Immunol 2005;175:1373-81.
Roy L Walford. The immunologic theory of aging. Scandinavian university books Munksgaard p. 205-241,1969.
Schuurhuis DH, Fu N, Ossendorp F, Melief CJM. Ins and outs of dendritic cell. Int Arch Allergy Immunol 2006;140:53-72a.
Sharma S, Dominguez AL, Lustgarten J. Aging affect the anti-tumor potential of dendritic cell vaccination, but it can be overcome by co-stimulation with anti-OX40 or anti-4-1BB.Exp Gerontol 2006;41:78-84.
Shi M, Su L, Hao S, Guo X, Xiang J. Fusion hybrid of dendritic cells and engineered tumor cells expressing interleukin-12 induces type 1 immune responses against tumor.Tumori 2005;91:531-8.

Shurin MR, Shurin GV, Chatta GS. Aging and the dendritic cell system: implications for cancer. Crit Rev Oncol Hematol 2007;64:90-105.Review.

Simioni PU, Fernandes LG, Gabriel DL, Tamashiro WM. Effect of aging and oral tolerance on dendritic cell function. Braz J Med Biol Res 2010 Jan;43:68-76.

Song L, Kim YH, Chopra RK, Proust JJ, Nagel JE, Nordin AA, Adler WH. Age-related effects in T cell activation and proliferation. Exp Gerontol 1993;28:313-21.

Steinman RM, Cohn ZA. Identification of a novel cell type in peripheral lymphoid organs of mice. I. Morphology, quantitation, tissue distribution. J Exp Med 1973;137:1142-62.

Steinman RM. The dendritic cell system and its role in immunogenicity. Annu Rev Immunol 1991; 9:271-96.

Steinman RM, Nussenzweig MC. Avoiding horror autotoxicus: the importance of dendritic cells in peripheral T cell tolerance. Proc Natl Acad Sci USA 2002;99:351-8.

Steinman RM, Hawigeer D, Nussenzwig MC. Tolerogenic dendritic cells. Annu Rev Immunol 2003;21:685-711.

Tang LL, Zhang Z. Zheng J, Sheng J, Liu K. Phenotypic and functional characterisitics of dendritic cells derived from human peripheral blood monocytes. J Zhejiang Univ Sci B 2005: 6:1176-81.

Timmerman JM, Levy R. Dendritic cell vaccines for cancer immunotherapy. Annu Rev Med 1999;50:507-29.

Trzonkowski P, Myśliwska J, Godlewska B, Szmit E, Łukaszuk K, Wieckiewicz J, Brydak L, Machała M, Landowski J, Myśliwski A. Immune consequences of the spontaneous pro-inflammatory status in depressed elderly patients. Brain Behav Immun 2004;18:135-48.

Turley SJ, Inaba K, Garrett WS, Ebersold M, Unternaehrer J, Steinman RM, Mellman I. Transport of peptide-MHC class II complexes in developing dendritic cells. Science 2000; 288(5465):522-7.

Ueno H, Klechevsky E, Morita R, Aspord C, Cao T, Matsui T, Di Pucchio T, Connolly J, Fay JW, Pascual V, Palucka AK, Banchereau J. Dendritic cell subsets in health and disease. Immunol Rev 2007;219:118-42.

van Duin D, Allore HG, Mohanty S, Ginter S, Newman FK, Belshe RB, Medzhitov R, Shaw AC. Prevaccine determination of the expression of costimulatory B7 molecules in activated monocytes predicts influenza vaccine responses in young and older adults. J Infect Dis 2007;195:1590-7.

van Kooyk Y, Geijtenbeek TB. DC-SIGN: escape mechanism for pathogens. Nat Rev Immunol 2003;3:697-709.

Wei J, Xu H, Davies Jl, Hemmings GP. Increase of plasma IL-6 concentration with age in healthy subjects. Life Sci1992;51:1953-6.

Witkowski Jm, Soroczynska-Cybula M, Bryl E, Smolenska Z, Jozwik A. Klotho- a common link in physiological and rheumatoid arthritis-related aging of human CD4+ lymphocytes. J Immunol 2007;178:771-7.

Zhou LJ, Tedder TF. CD14+ blood monocytes can differentiate into functionally mature CD83+ dendritic cells. Proc Natl acad Sci USA 1996;93:2588-92.