Published in final edited form as:
Expert Rev Clin Immunol. 2012 January ; 8(1): 73–80. doi:10.1586/eci.11.77.

Dendritic cells and aging: consequences for autoimmunity

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Abstract

The immune system has evolved to mount immune responses against foreign pathogens and to remain silent against self-antigens. A balance between immunity and tolerance is required as any disturbance may result in chronic inflammation or autoimmunity. Dendritic cells (DCs) actively participate in maintaining this balance. Under steady-state conditions, DCs remain in an immature state and do not mount an immune response against circulating self-antigens in the periphery, which maintains a state of tolerance. By contrast, foreign antigens result in DC maturation and DC-induced T-cell activation. Inappropriate maturation of DCs due to infections or tissue injury may cause alterations in the balance between the tolerogenic and immunogenic functions of DCs and instigate the development of autoimmune diseases. This article provides an overview of the effects of advancing age on DC functions and their implications in autoimmunity.

Keywords

aging; autoimmunity; dendritic cells; self-tolerance

The immune system undergoes continuous morphological and functional changes throughout an individuals lifetime and gradually declines with age [1–4]. Paradoxically, this decline in protective immune responses to exogenous and infectious agents is accompanied by an increased reactivity towards self or endogenous antigens [5,6]. There is an increase in autoantibody production and a propensity towards developing autoimmune diseases, such as Hashimoto's thyroiditis and Sjögren's disease with age. This suggests that a loss of self-tolerance is associated with immunosenescence. Although alterations in T and B lymphocytes are considered to be the primary culprits, there is a scarcity of information regarding the contribution of innate immune system cells, such as dendritic cells (DCs).

DCs are the most potent APCs and have a pivotal role in the onset and regulation of adaptive immune response. They control Th1/Th2 and Th17/Treg polarization, and the state of tolerance to self-antigens [7–9]. Immature DCs induce Treg cells, thus promoting tolerance, whereas mature DCs stimulate effector T cells, supporting immunity [7–10]. DCs also have the ability to regulate inflammatory responses through secretion of cytokines and chemokines [8,9].

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Financial & competing interests disclosure
This study is supported in part by grant AG027512 from the NIH and partly by a new scholar grant from the Ellison Medical Foundation. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.
No writing assistance was utilized in the production of this manuscript.

DCs are critical mediators of both tolerance and immunity [10]. Uptake and ingestion of apoptotic cells by DCs is considered to be one of the major mechanisms in inducing peripheral self-tolerance [11,12]. Under steady-state conditions, immature DCs continuously sample the self-antigens from apoptotic cells in the periphery, eventually leading to the induction of T-cell tolerance mechanisms [11,12]. Impaired clearance of apoptotic cells has been implicated in the pathology of various autoimmune disorders, including lupus and rheumatoid arthritis (RA) [13,14]. Numerous studies have shown a strong correlation between apoptosis and aging [15–17]. Apoptosis of T lymphocytes, particularly $CD8^+$ T cells, has been reported to increase in association with aging [17,18]. In addition, aging is often associated with increased oxidative stress, which leads to accumulation of damaged proteins and nuclear antigens such nucleic acids. These can be expressed on cell membranes during programmed cell death and may induce auto-reactivity [19,20]. The present article focuses on the role of DCs in age-associated autoimmunity.

Aging & autoimmunity

Advancing age is characterized by an erosion of tolerance, resulting in increased reactivity to self-antigens [21,22]. Therefore, age is recognized as an important factor in the appearance of autoimmune disease. Autoimmune diseases are prominent in younger patients and are certainly not limited to the elderly; nevertheless, the frequency of autoantibodies increases substantially with advancing age [23]. For instance, postmenopausal women have the highest incidence of RA [24]. Furthermore, epidemiological studies have shown that the majority older of patients diagnosed with RA have an increased prevalence of rheumatoid factor when compared with younger counterparts [25]. Similarly, antinuclear antibodies found in 11–14% of elderly individuals, have been shown to target chromatin elements of DNA [26]. Furthermore, although the appearance of lupus is associated with women of child-bearing age, a study showed that the incidence of lupus peaks in women 50–55 years of age and men 70–72 years of age [27]. These findings are consistent with observations in lupus-prone mice [28]. Many studies have shown that senescence-prone (SAM-P/1) mice develop autoantibodies and immune complex deposition over time [29]. A recent study demonstrated an age-dependent increase in serum antimurine hemoglobin autoantibodies in mice prone to systemic autoimmunity [30]. Elevated levels of plasma anti-Apo AI autoantibodies in old mice have also been observed, indicating the involvement in functional alteration and clearance of high-density lipoprotein immune complexes in aging mice [31]. Additionally, another study has shown that healthy centenarians had very low levels of autoantibodies to their thyroid, adrenal, pituitary and hypothalamus [32] compared with controls 60–70 years of age. Similar findings have been reported in aged mice [33]. A group has recently demonstrated a correlation between the reduction of apoptotic debris in aged mice and an increase in signs of autoimmunity, such as presence of antinuclear antibodies and kidney pathologies [34]. These studies again reinforce both the detrimental effects and the increased expression of autoantibodies with age.

Autoantibody production in the elderly has been attributed to altered T- and B-cell function [1]. Although B-cell antibody secretion is not affected with age, a decrease in antibody affinity maturation has been reported [35]. Decline in B-cell lymphopoiesis is accompanied by an increase in the memory B-cell population and autoreactive $CD5^+$ B1 and marginal zone B cells [36]. Long-lived plasma cells also accumulate and may be responsible for autoantibody production [37]. Age-associated defects in B-cell receptor signaling or threshold of activation have also been proposed as mechanisms that may contribute to age-associated autoimmunity [38].

Aging affects T cells in a myriad of ways. The age-associated involution of the thymus, often deemed the ‘immunologic clock’, has been sugested to explain decreased immune

surveillance and increased autoimmunity [2]. This loss in thymic function results in a decreased naive T-lymphocyte population, thereby decreasing self-tolerance and cell-mediated responses to foreign antigens. Reduced thymic output has also been linked with compensatory mechanisms, such as increased autoproliferation of T cells that may lead to premature T-cell maturation and decreased tolerance to self-antigens [39]. Simultaneously, studies have shown an accumulation of memory T cells in the periphery with a $CD28^-$ phenotype [38,40,41]. CD28, a major costimulatory molecule, plays a crucial role in antigen-mediated T-cell activation, proliferation and survival. In the aged population, approximately 15% of $CD4^+$ and 60% of $CD8^+$ T cells have lost the expression of CD28 [42].

$CD4^+CD28^+$ T cells also accumulate in several autoimmune diseases, such as multiple sclerosis (MS), RA, Wegener's granulomatosis and diabetes mellitus, and in inflammatory vascular complications, including stroke, acute coronary syndrome and plaque rupture [43]. The lack of CD28 expression has been shown to render $CD4^+$ T cells resistant to apoptosis, which could explain the accumulation of these effectors T cells, and the production of inflammatory cytokine that further perpetuate chronic inflammation and autoimmunity [44,45]. However, at the same time, $CD8^+CD28^-$ T cells have been shown to display enhanced cytotoxicity and suppressive functions. Interestingly, the accumulation of $CD8^+$ T cells has been observed to correlate with reduced antibody responses to vaccination, validating the suppressive function of CD8 $CD28^-$ cells [45]. Thus, these T cells appear to contribute to immune defects in the elderly.

Age-associated alterations in the T-cell cytokine profile have also been theorized to contribute to the increased occurrence of autoimmune diseases with age. Studies have shown that the predominant cytokine pathways change from Th1 to Th2 during antigen responses with increasing age, with increased production of Th2 cytokines, such as IL-4 and IL-6 [35,40]. IL-6, which is a potent therapeutic target in RA, has been shown to have a potent effect on the development of disability in elderly individuals [46,47]. The increase in Th2 inflammatory cytokines, which favor B-cell antibody production, could explain the increased level of auto-antibodies in the elderly [35]. Recent reports indicate that aging leads to an imbalance of Th17/Treg cells [48,49]. Most of the studies reported comparable number/frequency of $CD4^+CD25^+FOX3P^+$ Treg cells in the young and elderly subjects [50]. Of interest, four studies showed up to a 2.4-fold increase in Tregs in the aged population compared with young counterparts [51–53]. Although the link between aging and the number of Treg cells is controversial, a recent study suggested that aging could affect the capacity of $CD4^+$ Treg cells to produce the anti-inflammatory cytokine IL-10 [50]. Defects in Treg function have been used to explain several human autoimmune diseases, including MS, RA, autoimmune polyglandular syndrome Type 2, autoimmune myasthenia gravis, Kawasaki disease, insulin-dependent diabetes mellitus and systemic lupus erythematosus (SLE) [54]. Interestingly, in most of the aforementioned autoimmune disorders, the total number of $CD4^+CD25^+$ Tregs was comparable between autoimmune patients and healthy controls [54,55]. However, the Tregs derived from auto-immune patients displayed a reduced capacity to inhibit the proliferation of naive T cells [54,55]. Besides Tregs, an increase in the number of IL-17-secreting T helper cells has also been observed in the elderly [49]. Th17 cells have been implicated in the development of numerous autoimmune diseases, such as MS and RA [56].

Aging is also characterized by an increased secretion of pro-inflammatory cytokines that contribute to autoimmunity and often establish the profile for the disease [2,5]. Potent inflammatory cytokines such as TNF-α, C-reactive protein and chemokines such as IL-8, MCP-1 and RANTES have an increased level of circulation in elderly individuals and can sometimes be indicative of an underlying disease state [57,58]. In particular, patients with

RA have been shown to have increased levels of IL-6, TNF-α and IL-1β, among others [47,59]. The synergistic effect of these inflammatory cytokines recruits inflammatory cells and contributes to autoimmunity, which ultimately results in joint damage [59]. Chronic systemic inflammation is related to several autoimmune disorders, such as SLE, Sjögren's syndrome and fibromyalgia. Chronic inflammation is also believed to be the underlying cause of various neurodegenerative diseases, such as Alzheimer's and Parkinson's disease.

According to the UN population division, by 2035 one in five people are expected to be 65 years of age or older. The improved life-spans of elderly individuals necessitates the exploration of possible explanations for the increased prevalence of autoimmune diseases with increasing age. Furthermore, there is a scarcity of information regarding the effect of age on the severity of auto-immune diseases, which would have a major impact on the quality of life in the elderly compared with young individuals.

DCs & autoimmunity

DCs are crucial for induction of immunity and tolerance [60,61]. DCs constitute a complex system of cells that line portals of pathogen entry, such as the airways and skin. Capture of antigen by DCs induces maturation of DCs into professional APCs via upregulation of the expression of MHC and costimulatory molecules [62]. Mature DCs can effectively prime T-cell responses and generate immunity [10,62]. In contrast to mobilization of the immune response, induction of tolerance is a function of immature DCs [10,12]. Under steady-state condition, tissue-resident DCs take up peripheral tissue antigens and apoptotic cells and transport them to lymph nodes [63]. During migration, DCs undergo phenotypic changes, such as downregulation of adhesion molecules and the upregulation of antigen processing and presentation on MHC class II or cross-presentation on MHC class I molecules. These DCs express high levels of MHC and costimulatory molecules but lack the production of cytokines IL-1β, IL-6, TNF-α and IL-12 and consequently will establish IL-10-producing $CD4^+$ Treg cells. These mechanisms of antigen-specific tolerance induction are critical for the prevention of autoimmunity and maintenance of immune homeostasis. Therefore, alterations in DC functions compromise the efficiency of the immune response.

The mechanisms underlying the initiation of autoimmune responses that lead to the activation and/or induction of auto-reactive lymphocytes and to the breakdown of immunological self-tolerance are not yet fully understood. Emerging clues suggest that DC dysregulation might be involved in the development of various autoimmune disorders [64–66]. It has been well established that, in the absence of an inflammatory or pathogenic response, there is a continual flow of steady-state DCs – subsets that carry self-antigens from the periphery to the lymph nodes that induce unresponsiveness in both $CD4^+$ and $CD8^+$ T lymphocytes [65,66]. DCs in mice have been shown to transport melanin granules from the epidermis to draining lymphoid organs without causing an autoimmune response against the self tissue [67,68]. This flow of steady-state DCs carrying self-antigens has been shown to tolerize self-reactive T cells through a variety of mechanisms. Direct methods of DC-induced tolerance include clonal anergy [69] and apoptotic elimination of self-specific T cells [70,71]. DCs can also induce Treg cells, which maintain peripheral tolerance by suppressing the autoreactive T cells through a variety of mechanisms [72,73]. Studies have also shown that the ability of the DC to induce tolerance is highly dependent on the stage of DC maturation and the T effector cell it acts on. For example, immature DCs have been shown to tolerize $CD8^+$ T lymphocytes through inhibitory signal molecules PD-1 and CTLA-4 [74]. It has also been observed that mice lacking one of the above signals develop autoimmune diseases, such as lethal dilated cardiomyophathy [74]. Others have speculated that the type of DC determines whether it is involved in an immune response or in inducing

tolerance. While resident lymphoid DCs may induce self-tolerance, migratory DCs, such as myeloid DCs may be involved only in the immune response [75,76].

Hyperactivation and chronic maturation of DCs within native tissues has also been shown to increase the immunogenicity of the DCs, thereby culminating in exacerbated immune responses and autoimmunity [77]. The increased maturation of DCs within tissues may be a consequence of tissue necrosis during trauma or injury. Many cellular contents, including heat shock proteins, released during necrosis may activate DCs by signaling through cell-surface receptors including Toll-like receptors, CD40, CD91, CCR5 and scavenger receptors, such as LOX-1 and SREC-1 [78,79]. Increased stimulation of DCs is observed in numerous autoimmune diseases, such as insulin-dependent diabetes mellitus, SLE and RA. Further evidence for DC involvement in autoimmune disease comes from the fact that transfer of DCs from autoimmune mice to naive mice induces autoimmunity in the recipient [75].

Autoimmunity may also be induced by the release of type I interferons (IFN-I) by plasmacytoid DCs (pDCs), a type of DC characterized by their plasma cell-like morphology and copious production of IFN-I [80]. Robust production of IFN-I (particularly IFN-α) in response to viral and other infections is considered a key event in establishing a multifaceted antimicrobial response [81]. The secretion of IFN-α helps mobilize the adaptive immune response through downstream signaling pathways that influence the activation and proliferation of T and B cells [82]. Increased levels of IFN-α have also been found in the serum of patients diagnosed with MS and SLE [83]. It has been speculated that the anti-self-DNA complexes in the serum of SLE patients activate pDCs that secrete high levels of IFN-α, which then mobilizes self-reactive T lymphocytes [83]. Additionally, pDCs secreting high levels of IFN-α have been found in the skin of patients with cutaneous forms of SLE [84]. This increased IFN-α may contribute to the activation of self-reactive T cells that have escaped both thymic and peripheral tolerance, although the precise mechanisms of this contribution remain unclear.

In addition to IFN-α secretion, pDCs activated with self-antigens can themselves shape the nature of the adaptive immune response through mechanisms often characteristic of myeloid DCs. Upon maturation, pDCs lose their ability to produce IFN-I and develop into APCs with increased expression of MHC class I and class II molecules, and other costimulatory molecules [82]. Upregulation of these molecules on the pDC membrane initiates adaptive immune responses leading to $CD4^+$ and $CD8^+$ T-cell activation [81]. Therefore, pDCs stimulated with local self-antigens can have a dual role in the induction of autoimmune diseases through the production of IFN-Is and direct stimulation of autoreactive T lymphocytes.

Although the failure of central and peripheral tolerance mechanisms contributes to the survival of self-reactive T cells, studies have shown that nontolerant T lymphocytes are only reactive against self-antigens following sustained stimulation by DCs [85]. Additionally, high levels of circulating DCs and DC-associated proinflammatory cytokines have been found in the serum of patients diagnosed with MS, RA and juvenile chronic arthritis [86,87]. Immature DCs are attracted to the tissue by the inflammatory DC-mediated secretion of TNF-α, IL-23, IL-12p70 and prostaglandins [60]. Subsequently, the newly recruited immature DCs also mature into inflammatory DCs, and migrate to the lymph nodes to mediate the activation and proliferation of potentially autoreactive T lymphocytes through nonspecific bystander activation. These DC-secreted cytokines coupled with chemokines (IL-8, CCL17, CCL18 and CCL22) are also involved in Th1, Th2 and Th17 immune responses, which are seen in many autoimmune diseases [88].

DCs & age-associated autoimmunity

Aging is associated with multiple changes in the cytokine micro-environment that could affect the activation and/or maturation of DCs [2,89]. The increased levels of TNF-α and prostaglandins would result in premature DC activation, altering their antigen uptake capacity [90].

Although aging is associated with multiple changes in the micro-environment that could affect the maturation of DCs, there is a scarcity of information regarding the tolerance inducing function of DCs. DC maturation acts as the checkpoint between tolerance and immunity and increased age-associated circulation of proinflammatory mediators can trigger the activation and maturation of DCs [63]. These activated DCs can subsequently become reactive to circulating self-antigens from apoptotic cells or injured tissue. Indeed, we [21,91] and others [92] have reported that DCs from aged subjects display a higher basal level of activation compared with their young counterparts. Panda *et al.* reported an increased secretion of proinflammatory cytokines, such as TNF-α and IL-6, from circulating in DC of aged subjects [92]. Studies from our laboratory have reported similar findings. We observed that DCs from aged individuals displayed a higher basal level of NF-κB activation, which is indicative of an activated state [21]. Interestingly, in both studies, there was no upregulation of costimulatory activation markers, such as CD86 and CD80, which suggests that the aged DCs are only partially activated. When we determined whether these partially activated DCs from aged subjects were more reactive to self-antigens, we observed that these DCs displayed increased IFN-α and IL-6 secretion in response to self DNA (self-antigen released by apoptotic cells) [21]. As mentioned, increased levels of IFN-α have been implicated in numerous autoimmune pathologies. T-cell priming capacity of these DCs was also significantly enhanced, demonstrating that aged DCs were impaired in their capacity to induce tolerance to self-antigens. Such a scenario will also lead to an accumulation of chronic inflammatory DCs since the activation of DCs results in a decrease in their phagocytic capacity that would result in impaired clearance of apoptotic cells and an increase in circulating self-antigens.

Our observations demonstrate that aged DCs are indeed defective in their capacity to phagocytose antigens and apoptotic cells [91]. Defective clearance of apoptotic cells has been implicated in a number of autoimmune diseases, such as SLE [13,14,19,20]. Recent studies have revealed that defective clearance of apoptotic cells causes self-antigen accumulation, which could trigger the activation of autoreactive lymphocytes in lupus [19,93–96]. For example, mice injected with irradiated apoptotic cells displayed auto-antibodies to nuclear components and cardiolipin [97,98]. These data indicate that an overload of apoptotic cells beyond the phagocytic capacity of the reticuloendothelial system can also induce an autoantibody response. Recent evidence also suggests that DC uptake of apoptotic or necrotic neutrophils alone does not shift the immune response from tolerance to autoimmunity in systemic vasculitis. However, cytokines found at sites of inflammation in vasculitis patients may act as maturation factors for DCs and may lead to an autoimmune phenotype in combination with apoptotic neutrophils [99]. Such a scenario can readily be envisaged during aging, where there is an increase in the levels of proinflammatory cytokines. The mechanisms underlying the increased activation of aged DCs are not clear. Age-associated increases in circulating levels of proinflammatory mediators may be one of the contributing factors. Another possibility is that age-associated modifications in existing self-antigens may enhance their immunogenic potential. This is supported by our observations in which we reported that DNA from aged individuals becomes hypomethylated and hypomethylation of DNA increases its immunogenicity [22]. The uptake of hypomethylated or aged DNA by DCs resulted in enhanced activation and IFN-I

secretion by DCs. Thus, changes in self-antigens coupled with changes in the activation state of DCs can together result in increased autoreactivity in aged subjects.

Another interesting and relatively unexplored possibility is the epigenetic changes in the DC DNA that can affect DC functions. Recently, there has been a growing appreciation of the role of chromatin structure in gene regulation [100,101]. Methylation of histone at specific lysine sites can regulate the activity of the promoters [100–102]. For example, methylation of lysine residues at positions 9 (H3K9) and 27 (H3K27) of histone 3 are associated with transcriptional repression, while methylation of lysine 4 of the same histone (H3K4) is considered to induce activation of transcription [102–105]. The association of NF-κB with H3K4 or H3K9 may be altered with age. This is an important area of future investigation.

Expert commentary

It is clear that advancing age is associated with loss of tolerance and increased reactivity to self. Chronic inflammation and impaired adaptive immune functions have long been considered to be the main culprits for these alterations. However, there is growing evidence showing that innate immune cells, such as DCs, are key players in the induction and maintenance of tolerance. DCs do not react to self-antigens by remaining in an inactivated state. The priming of T cells in the absence of costimulation by inactivated DCs results in the generation of a T-regulatory or -inhibitory response. During autoimmunity, DCs become activated either due to inflammatory mediators present in the tissues and/or circulation or due to intrinsic changes in the DCs themselves. These activated DCs induce autoimmunity by mounting an immune response against self-antigens. DCs from aged subjects also display increased basal levels of activation compared with young subjects, which increases their reactivity to self-antigens (such as DNA) and results in loss of self-tolerance and chronic inflammation. In addition to age-associated changes in DCs, aging also leads to modifications in self-antigens, making them more visible to the immune system. For example, age-associated hypomethylation of DNA makes it more immunogenic. The majority of studies on DCs in aging focus on responses to foreign antigens and there is a scarcity of information on their role in inducing tolerance. Delineating the mechanisms by which aged DCs become impaired in maintaining self-tolerance may provide novel therapeutic targets aimed at improving the outcome of age-associated chronic diseases. It may also enhance responses of DCs from aged subjects towards foreign antigens.

Five-year view

The study of DCs in aging is still in its infancy owing to numerous reasons, including the lack of a suitable animal model. Since rodents are inbred and maintained in pathogen-free environments, they may not display the age-associated changes observed in humans. Lack of tissue samples from aged subjects poses another major hindrance that has forced most human studies to focus on DCs in circulation, which are limited in number. With the development of new technologies for purification of DCs from blood and other techniques, such as multiplexing of cytokines, that allow simultaneous detection of multiple mediators in a small volume, it is becoming possible to gain more insight into DC functions in aged subjects. Such technologies allow the use of very small number of cells, and are desirable for the study of aged subjects.

Most studies so far have focused on activating DCs with either Toll-like receptor agonists or whole viruses, such as influenza. There is a scarcity of information regarding the behavior of aged DCs after activation with other pattern recognition receptors (PRRs), such as C-type lectin receptors, which are particularly important in the generation of Treg cells. Other PRRs such as NOD-like receptors that activate the inflammasome may also be more important

from the perspective of ageing because of their involvement in auto-immunity and age-associated chronic diseases. In addition to cytokine secretion by aged DCs in response to these PRRs, important information may be obtained regarding the T-cell priming and polarizing capacity of these DCs in aged subjects.

Refinements in genetic and epigenetic techniques can facilitate studies that focus on delineating the mechanistic changes in aged DCs that may be responsible for loss of self-tolerance. This is a rapidly growing field and age-associated chromatin and histone modifications may provide novel insights into regulation of DC functions.

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Key issues

- Advancing age is associated with loss of tolerance and increased reactivity to self.
- There is an increase in autoantibodies, such as rheumatoid factor and anti-DNA antibodies, with age.
- Dendritic cells (DCs) are critical in the maintenance of self-tolerance and altered functions of DCs have been implicated in the pathogenesis of a number of autoimmune diseases, such as rheumatoid arthritis and lupus.
- DCs from aged subjects display an increased basal level of activation even without stimulation. They secrete increased basal levels of proinflammatory cytokines that is accompanied by increased NF-κB activation.
- The enhanced activated state of DCs from aged subjects results in the generation of immune responses to self-antigens, such as DNA and loss of tolerance.
- An age-associated modification in self-antigens, such as decreased methylation of the DNA, allows aged DCs to view them as novel antigens and mount immune responses against them.