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Role of Dendritic Cells in Autoimmunity in Aged Humans

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Abstract

Immunological tolerance to self-antigen is mediated by deletion of self-reactive lymphocytes by apoptosis, unresponsiveness to self-antigens (anergy), regulation by T cells (Treg), and efficient removal of apoptotic bodies by phagocytic cells. Dendritic cells (DCs) play an important role in both tolerance (predominantly via induction of Treg) and inthe induction of immune response to non-self antigens. Therefore, an impairment of DCs functions may result in the loss of tolerance and induction of immune response to self-antigens, resulting in autoimmunity. Aging represents a paradox of impaired response to non-self antigens, and an increased response to self-antigens, resulting in an increased susceptibility to infections, and development of autoimmunity in aged humans. I have reviewed the role of DCs and mechanisms involved in autoimmunity, including epigenetic changes in aged DNA, and histone modifications in chromatin in human aging.

Keywords: Epigenetic changes; IFN-I; IFN-III; mDC; pDC; Chromatin modification; Cytokines; Treg

Introduction

Aging represents a unique paradox of autoimmunity and impaired response to exogenous antigens resulting in an increased susceptibility to infections. This is of particular significance since patients with autoimmune diseases are not at risk for increased susceptibility to infections, unless on immunosuppressive/biological therapy. Aged humans develop a variety of autoantibodies, and display poor response to vaccines and increased susceptibility to both viral and bacterial infections. The progressive impairment in immune functions include progressive T cell deficiency, which is contributed by thymic involution [1], increased apoptosis of T cells and T cell subsets [2-4], and impaired priming of T cells by DCs [5-7]; B cell dysfunctions are revealed by impaired specific antibody response to vaccines, and development of autoimmunity [8-12].

Dendritic cells are a heterogeneous population of hematopoietic antigen-presenting cells. They play a major role in initiating and shaping both innate and adaptive immune responses, and in the maintenance of immunological tolerance [13-20]. Recent studies in humans and experimental models suggest that DCs are involved in the pathogenesis of autoimmune diseases. There are two major subpopulations of DCs, namely "conventional" (cDCs), which are also known as myeloid DCs, and plasmacytoid DCs (pDCs). The cDCs are known to differentiate from the common myeloid hematopoietic precursors. It appears there is a significant plasticity in the DC lineage. pDCs could be derived from either myeloid or lymphoid precursors [21]. Furthermore, pDCs and cDCs maintain plasticity even after their differentiation [22]. Therefore, a numbers of functions are shared between two subtypes of DCs; for example, production of IFN-I and IFN-III, albeit their relative concentrations may be different among two DC subtypes, and priming of naïve T cells. The cDCs exist in peripheral tissues, secondary lymphoid organs, and in the circulating blood. pDCs circulate in the blood and enter lymphoid organs through high endothelial venules. Compare to cDCs, pDCs express different sets of Toll like receptors (TLRs) [23]. pDCs express TLR7 and TLR9 and upon stimulation secrete large amounts of IFN-α [24]. In response to microbial infection, monocytes migrate into inflammatory sites and differentiate into DCs [24]. In humans, *in vitro* activation of monocytes with GM-CSF and IL-4 induces differentiation of monocytes into monocyte-derived DCs, which serves as a model for cDCs. In this review I will refer them as mDCs.

The Role of DCs in Immune Tolerance and Autoimmunity

Knight and colleague [25] provided initial evidence for the role of DCs in autoimmunity. They demonstrated that DCs from animals with EAE could transfer the disease in naïve recipients.

DCs play a role in both central and peripheral tolerance. In the central tolerance, thymic DCs have shown to cross present self-antigens, which have been acquired from medullary thymic epithelial cells (mTECs) [26,27]. In addition, thymic DCs may also facilitate generation of natural Treg (nTreg) [28]. There is also an evidence that peripheral DCs might migrate into the thymus, and present peripheral self-antigens to induce clonal deletion or to generate Treg [29,30]. In general, DCs appear to play only a minor role in central tolerance; mTECs appear to play the major role in inducing central tolerance.

DCs appear to play a role in peripheral tolerance by supporting the homeostasis of peripheral Treg cells. DCs can polarize naïve CD4+ T cells to Treg cells (iTreg) in the presence of TGF-β [31,32]. Recently it has been suggested that migratory cDCs and not the resident DCs in the lymph nodes induce the development of Treg specific to a particular self-antigen [33]. It appears that DCs facilitate the induction and/or maintenance of Treg cells; however; they are not indispensible for both the induction and maintenance of Treg. This is further supported by lack of significant autoimmunity in patients with primary immunodeficiency of DCs [34]. In peripheral tolerance, nTreg generated in the thymus by mTECs may more important than iTreg generated by DCs in the periphery. In general, DCs may induce tolerance by inducing Treg and induction of energy.

A role of DCs have been demonstrated in a number of autoimmune

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diseases and animal models of autoimmune diseases, including systemic lupus erythematosus (SLE), multiple sclerosis (MS), experimental autoimmune encephalitis (EAE), and autoimmune myocarditis [35].

Role of Apoptosis in Tolerance and Autoimmunity

Apoptosis (programmed cell death) also plays an important role in maintaining tolerance and immune homeostasis [2]. Almost every cell is programmed and equipped to die only to be replaced by new cell to main homeostasis. These apoptotic cells contains a number of self-antigens, and therefore, must be removed by neighboring phagocytic cells and self-antigens degraded to avoid their uptake by DCs and presentation to self-reactive lymphocytes. Apoptosis is induced by death receptor pathway, mitochondrial pathway, and endoplasmic reticulum stress pathway [2,36-38]. Apoptotic cells express a number of surface antigens to provide a 'eat me' signals, which are recognized by receptors on phagocytic cells. Apoptosis also provide a major mechanism for deletion of self-reactive T cells (central tolerance). Therefore, disorders of apoptosis are associated with autoimmunity and autoimmune diseases [39]. An impaired apoptosis, resulting in failure to remove self-reactive lymphocytes, and increased apoptosis with excessive load for the phagocytic cells, and defects in uptake of phagocytic cells may lead to late necrosis of apoptotic blebs resulting in increased release and therefore, exposure of self-antigens to DCs resulting in autoimmunity and autoimmune diseases.

Role of Interferons in Autoimmunity

Secretion of interferons (IFNs) from virus-infected cells is a hallmark of host antiviral immunity. In addition, interferons modulate both innate and adaptive immune responses. DCs are major producers of both IFN-I (IFN-α, IFN-β, IFN-κ, IFN-ω) and IFN-III [IFN-λ1 (IL-29), λ2 (IL-28a), λ3 (IL-28b)]. mDCs produce greater amount of IFN-III, whereas pDCs are major source of IFN-I [13,14,17,40,41].

IFN-I promote the differentiation of naïve CD4+ T cells to TH1 cells, and survival of activated T cells, and enhance the cytotoxicity of CD8+ T cells and NK Cells [42-44]. In addition, IFN-I enhance antibody production, and induces isotype class switch in B cells [45-47]. Furthermore, IFN-I enhances antigen cross presentation and maturation by DCs by up-regulating co-stimulatory molecules and TLRs, and inducing secretion of pro-inflammatory cytokines [48,49]. IFN-I and IFN-I regulated genes are increased in systemic [50,51], and organ-specific autoimmune diseases [52], suggesting its role in autoimmunity. Autoantigens from apoptotic cells stimulate pDCs to prduce large amounts of IFN-I, which induces B cell differentiation and Ig class switch, including autoreactive B cells resulting in autoantibody production.

IFN-III (IFN-λs) is family of interferons encoded by 3 different genes that were discovered in 2003 [53,54]. They play a major role in viral defense; however, provides much better protection at mucosal surfaces than IFN-I [40,55].

Though IFN-I and IFN-III signal through different receptors, they share a common downstream signaling pathway, a common set of interferon-stimulated genes (ISGs), and share many biological properties, including anti-viral and anti-proliferative activities [55,56].

Since a role of IFN-I in autoimmunity and autoimmune diseases has been demonstrated [50-52], it is expected that IFN-III may also play a role in autoimmunity and autoimmune diseases. Increased serum IFN-λ1 levels have been observed in patients with rheumatoid arthritis as compared to healthy controls and patients with osteoarthritis [57]. Lin et al. [58] reported dysregulated expression of IL-28α (IFN-λA) in patients with SLE.

Mannechet et al. [59] have shown that *in vitro*, IFN-λ-treated DCs induce proliferation of FoxP3-expressing regulatory T cells. More recently, Rynda et al. [60] have demonstrated that endogenous IFN-III (IL-28) protects against EAE in the absence of Treg cells, and treatment of animals with neutralizing antibodies against IL-28 render mice susceptible to EAE, suggesting a role of IFN-III in tolerance.

Autoimmunity in Aging

Role of apoptosis in autoimmunity in aging

In contrast to progressive decline in immune functions with advancing age, there is an increased reactivity to self and endogenous antigens as evidenced by the presence and increased titers of a variety of autoantibodies [8-12], which suggest a loss of peripheral tolerance in aging. The information regarding mechanisms of impaired tolerance in human aging is limited. Apoptosis plays an important role in the effector functions and immune homeostasis. One of the critical steps in apoptosis is a rapid uptake of apoptotic cells and apoptotic bodies by neighboring phagocytic cells, resulting in intracellular degradation of self-antigens, and induction of anti-inflammatory response and generation of Treg. We have shown that in aging, apoptosis of T cells and T cell subsets is increased [2-4,61,62], whereas DCs are impaired in their capacity to uptake apoptotic cells [63]. As a consequence apoptotic cells would undergo secondary necrosis with additional proteolytic degradation of specific autoantigens, leading to the release endogenous danger signals like nuclear antigens clustered in apoptotic blebs and bodies (e.g. chromatic, DNA, RNA, histones etc), resulting in maturation of DCs, presentation of self-antigens to lymphocytes and induction of T cell immunity to self antigens, and stimulation of autoreactive B cells and production of autoantibodies.

Role of DCs in Autoimmunity in Aging

Increased reactivity of aged DCs to self-DNA

DCs are unique antigen-presenting cells because of their capacity to prime naïve T cells [14,16-18]. DCs therefore function as initiators of T cell immunity. DCs can prime or tolarize T cells. Under physiological conditions, DCs play a role in unresponsiveness to self-antigens. DCs are essential for both central and peripheral tolerance. Impaired clearance of apoptotic cells has been implicated in autoimmune diseases like lupus [64,65]. Therefore, we examined the priming capacity of young and aged DCs to self-DNA. DNA was purified from young humans and delivered intracellularly to mDCs from young and aged subjects and examined for the activation and cytokine production by mDCs and their capacity to induce T cell proliferation [66]. DNA-primed mDCs from aged subjects upregulated co-stimulatory molecules, and secreted increase levels of IL-6 and IFN-α as compared to young mDCs. Similar increased in cytokine secretion was observed by aged mDCs in response to late apoptotic cells. Furthermore, young DNA-primed aged mDCs induced autologous T cell proliferation, whereas young DNA-primed young mDCs did not induce T cell proliferation, suggesting a role of DCs in increased reactivity to self-DNA and a loss of tolerance in aged humans. This increased reactivity to DNA is independent of TLR-9. Furthermore, expression of the cytosolic DNA sensor DAM1 was comparable between young and aged, suggesting steps downstream of cytosolic sensor may be involved in self-reactivity to DNA by aged DCs. Since there are several DNA censors, a possibility of involvement of one of the other DNA sensors cannot be excluded. One of the steps

downstream of DNA censors is the interferon-responsive factor-3 (IRF-3). We observed an increased activation of IRF-3 transcription factor in mDCs from aged in response to Intracellular self-DNA [61]. Furthermore, mDCs from aged display higher basal levels of NF-kB activation, suggesting that DCs from aged are in an activated state. Panda et al. [67] also observed increased basal levels of cytokines in aged DCs.

Role of Epigenetic modifications in aging DNA in autoimmunity

Epigenetic regulation of gene expression occurs via chemical modification such as histone acetylation and methylation, without alteration in the nucleotide sequence in the genome [68]. Human DNA undergoes age-associated genetic and epigenetic changes [69,70]. During aging, cells and tissues become hypomethylated while selected genes become progressively hypermethylated [71]. There is a relationship between genomic instability, DNA damage, and DNA repair mechanisms, which are in aging resulting in DNA lesions with single and double-stranded breaks [72]. Furthermore, oxidative damage to DNA has been implicated in aging and age-related degenerative disorders [73].

Human DNA is generally inert and does not stimulate DCs. We demonstrated that DNA from aged mononuclear cells when introduced into young mDCs resulted in upregulation of co-stimulatory molecules CD80 and CD86, and increased secretion of IFN-α, as compared to young DNA, suggesting an increased immunogenicity of aged DNA [74]. We also showed that DNA from aged subjects is hypomethylated, and when aged DNA was hypermethylated comparable to methylation of young DNA, aged DCs could no longer induced increased secretion of IFN-α, demonstrating that immunogenicity of mammalian DNA correlates inversely with DNA methylation. Finally, we observed that intracellular delivery of oxidative-damaged DNA did not result in the activation of mDCs, which suggest that DNA damage per se does not increase immunogenicity of aged DNA, and hypomethylation of DNA is responsible for its increased immunogenicity in aging. It remains to be determined which site-specific hypomethylation confer increased immunogenicity to self-DNA.

Interferons in aging

The role of interfrons in defense against viruses is well established. IFN-I are known to have anti-proliferative and antitumor activities [44,49,56]. IFN-III also display anti-viral activity; however, predominantly at mucosal surfaces because of more restricted expression of IFN-III receptors as compared to IFN-I receptors, which are more widely expressed [75,76]. IFN-II has predominantly immunoregulatory role. A role of IFN-Iα in autoimmunity and autoimmunity is well documented. IFN-Iα expression is increased in autoimmune diseases [40,50-52] and IFN-Iα treatment has been associated with exacerbation or development of certain autoimmune diseases [77-79]. This is in contrast to use of IFN-β in the treatment of multiple sclerosis, an autoimmune disease. A role of IFN-III in immune regulation and autoimmunity has not yet established; however, abnormal and dysregulated expression of IFN-III and IFN-III receptors in certain autoimmune diseases, including rheumatoid arthritis and systemic lupus erythematosus has been reported [57,58].

Because of increased susceptibility of aged humans to viral infection, especially respiratory tract infections, and development of autoimmunity, others and we have investigated the production of IFN-I and IFN-III by DCs from healthy young and aged subjects. pDC from aged are impaired in secreting both IFN-I and IFN-III in response to Influenza virus (TLR signal) and CpG (TLR9 signaling) [7,67,80-83]. However, the expression of TLR7 and TLR9 on aged pDCs is comparable to young [7]. Furthermore, we demonstrated that the protein expression of downstream signaling molecules IRAK-1, Myd88, and IRF-7 in aging pDCs is comparable to young; however, CpG and influenza virus-induced IRF-7 phosphorylation in aged pDCs is impaired [7]. pDCs from aged are also impaired in priming CD8+ T cells as determined by proliferation, perforin and granzyme production, and IFN-γ secretion [7]. pDCs are also impaired in priming of CD4+ T cells as determined by CD4+ T cell proliferation.

We also examined a role of mDCs in responses to influenza virus. The phenotype of aged and young mDcs was comparable following activation with heat-inactivated influenza virus. However, mDCs from aged were impaired in their ability to produce Influenza virus-induced both IFN-I and IFN-III. Panda et al. [67] also demonstrated decreased IFN-I production in aged mDCs. We examine whether histone modification (epigenetic changes) play a role in impaired interferon secretion by mDCs in aged humans [84]. Association of IFN-A2 and IFN-l1 (IL-29) promoter to H3K4me3 and H3K9me3 is altered in aged DCs. This impaired association was specific to IFN-A2 and IFN-l1 since no such impairment of association was observed between histones and TNF-α promoter, and no association of IFN-2A, and IL-29 (IFN-λ) non-promoter to H3K4me3 and H3K9me3 was observed. Additionally association of IFN-A2, IFN-l, TNF-a promoter to H3K4me and HeK9me in aged mDCs is unstable. Both IFN-α and IFN-β have shown to mediate their effects though a common IFNAR1 and IFNAR2 [85,86]. However, recently it has been reported that IFN-β may not use IFNR2 and uses a different partner with IFNAR1 [85]. The expression of IFNAR1/2 and response to IFN-β remains to be studied.

Since functions of mDCs and pDCs and production of both IFN-I and IFN-III are impaired, it is unlikely that altered IFN production in aging plays an significant role in autoimmunity in aging; perhaps impaired uptake of apoptotic bodies, and increased reactivity to self-antigen and production of pro-inflammatory cytokines by aged DCs may predominantly contribute to autoimmunity associated with aging. An impaired interferon production may be responsible for increased susceptibility to viral infections in aged humans.

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