Published in final edited form as:

Curr Opin Immunol. 2013 August ; 25(4): 535–541. doi:10.1016/j.coi.2013.05.016.

Impact of Aging on Antigen Presentation Cell Function of Dendritic Cells

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Abstract

Older people exhibit increased mortality to infections and cancer as compared to younger people, indicating that aging impairs immunity. Dendritic cells (DCs) are key for bridging the innate and adaptive arms of the immune system by priming antigen specific T cells. Discerning how aging impacts DC function to initiate adaptive immune responses is of great biomedical importance as this could lead to the development of novel therapeutics to enhance immunity with aging. This review details reports indicating that aging impairs the antigen presenting function of DCs but highlights other studies indicating preserved DC function with aging. How aging impacts antigen presentation by DCs is complex and without a clear unifying biological underpinning.

Introduction

Initiation and activation of cells of the adaptive immune system, in particular CD4⁺ T cells, is critical for protection from pathogens or tumors. Antigen presenting cells (APCs) are critical in the uptake of foreign antigens and presenting these antigens to naïve T cells so that an effective immune response is generated. To enhance communication with T cells, APCs upregulate lymphoid-homing chemokines, (e.g. CCR7), costimulatory molecules (e.g., CD40 and CD86), and produce proinflammatory cytokines (e.g., IL-12 or IL-23). Therefore, APCs are key orchestrators of an immune response.

Aging has a diverse impact on the immune system. Most studies have examined aspects of the adaptive immune system and have investigated how aging alters the function of T cell or B cells [1–3]. Generally, aging induces a decline in function of both these cells. Although aging likely impairs the intrinsic function of these cells, the emerging appreciation of how the innate immune system initiates adaptive immunity suggests that alterations within the innate immune system with aging could impact subsequent adaptive immunity. The innate immune system acts as the “first line of defense” to noxious stimuli, including infections, tumors and sterile inflammation [4]. APCs are cellular components of the innate system that communicate with the adaptive arm, predominantly through activating T cells [5]. Determining how aging impacts the function of APCs is important as APC function relates to effective immunity to pathogens, tumors, auto and alloimmunity.

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Several immune cells possess APC functions including dendritic cells (DCs), macrophages and B cells. This review will summarize recent findings of how aging impacts the function of the most potent APCs, DCs.

Dendritic cells and aging

DCs play a pivotal role in priming T cells upon immune challenge [5]. DCs can be classified into two subsets: myeloid DCs, also known as conventional DCs (cDCs); and plasmacytoid DCs (pDCs) that are of a lymphoid lineage. Both cDCs and pDCs arise from a common DC precursor that originates from hematopoietic stem cells in the bone marrow [6]. cDCs are the most common form of DCs and can be subdivided into resident and migratory DCs [7]. Based on the expression of surface markers, resident cDCs in the lymphoid tissue can be further classified into CD4⁺, CD8⁺, and CD4[−]CD8[−] (double negative) DCs, while the two distinct migratory DCs subsets are recognized by the expression of CD103 and CD11b (i.e., CD103⁺CD11b[−] and CD103[−]CD11b⁺) [7]. pDCs are CD123⁺BDCA2⁺BDCA4⁺ and are best known for their ability to produce large amounts of type 1 interferons (IFN) in response to viral infection [8].

Impact of aging on DC distribution and turnover

One potential mechanism by which aging impacts the overall function of DCs is by alterations in number or distribution of these cells. This has been investigated in mice, non-human primates and humans.

In a recent study, mice aged up to 18 months on the C57BL/6 background, exhibited a two fold increased in the total number of cDCs in the lungs in comparison to young mice. However, this was not apparent in aged BALB/c mice [9]. In both strains of mice, there were similar numbers and proportions of cDCs within the spleen and peripheral lymph nodes. Furthermore, the engraftment and turnover of cDCs was not altered, as aged bone marrow cells exhibited a similar ability to reconstitute lethally irradiated young hosts as compared to young bone marrow cells [9].

Another study documented an increase in CD8[−] cDC population in the spleens of 26 month old C57BL/6 mice as compared to young (i.e. 2 months of age) counterparts, but found reductions in both splenic pDCs and CD8⁺cDC [10]. One report found that 18 month old C57BL/6 mice exhibited reductions in total CD11c⁺ cells in the spleen in addition to a reduction in cDCs, but no significant reductions in splenic pDCs [11]. In rhesus macaques aging leads to an increase in the proportion of cDCs but similar proportion of pDCs in the circulation in young (i.e., <4 years of age) as compared to aged (i.e., > 19 years of age) primates [12]. Healthy older people (aged range 64–92 year of age) exhibit similar proportions of cDCs and pDCs in the blood as compared to young people, although these proportions decrease in frail elderly people (aged 61–95 years of age, with frailty defined as the presence of at least one disabling disease such as Alzheimer's or the presence of 2 chronic diseases such as arthritis or cognitive impairment) [13]. Overall, these studies give a mixed picture as to how aging impacts the distribution and maintenance of DCs and mechanisms for any age-associated alteration are not clear. Possibilities include alterations in cell proliferation or apoptosis or differential homing patterns. Differences between studies may reflect the health status of subjects or animals, strain backgrounds or ages employed.

Impact of aging on DC inflammatory responses

DCs respond to innate immune activation by upregulating costimulatory molecules, lymphoid homing chemokines and producing proinflammatory cytokines. As these parameters influence subsequent T cell priming, they have been examined in the context of aging in rodents, non-human primates and humans.

In mice, one study found that the upregulation of costimulatory molecules (e.g., CD40 and CD86), chemokines (e.g., CCR7) and the production of proinflammatory cytokines (e.g., IL-6, IL-12p40 and TNF- α) in response to different doses of Toll like receptor (TLR) activators (e.g., LPS [TLR4 activator], flagellin [TLR5 activator], CpG [TLR9 activator]) was preserved in cDCs (splenic and bone marrow derived) obtained from mice aged (22–26 months of age) on either the C57BL/6 or CBA strain background [14]. This study also examined the effects of TLR activation both *in vitro* and *in vivo*. Similar *in vitro* findings were noted in a later study [15]. Another study found that bone marrow derived cDCs obtained from C57BL/6 mice aged between 20–24 months of age exhibit a reduction in IL-6 and TNF- α but an enhanced IL-10 response to a single dose of LPS *in vitro* [16]. This study also found that non-activated cDCs display a reduced expression of DC-SIGN, a c-type lectin with aging [16]. One report found similar impairments in cytokine responses to a dose range of LPS in aged splenic cDCs although IL-10 was reduced in aged as compared to young cDCs *in vitro* (3). Significant reductions in IFN- γ , IL-6 and TNF- α , but not IL-12p70 or IL-10, in addition to impaired CD40 upregulation with aging were noted in another report in aged murine splenic cDCs as compared to young cDCs that were stimulated a single dose of LPS *in vitro* [11]. However, another study failed to show reductions in TNF- α by cDCs in response to LPS but did show an impaired upregulation in CD86 [17]. The differences noted between some of these reports may be due to different doses of LPS employed or use of different types of TLR activators, or subtle differences in the health status of mice.

To evaluate the *in vivo* immune response to a pathogen, a recent study examined the accumulation of CD8⁺ cDCs and upregulation of costimulatory molecules on these cells after systemic infection with an intracellular bacterium, *Listeria monocytogenes*. The study found that after infection, splenic CD8⁺ cDCs from aged mice (18–22 months of age) exhibit a reduced upregulation of CD40 and CD86 as compared to young CD8⁺ cDCs [18]. Using a microspirodial pathogen, *E. cuniculi*, one study reported that pDCs from aged mice (12 months of age) exhibit an enhanced upregulation of the negative costimulatory molecule, PD-L1, compared to young DCs [19]. Interestingly, pDCs from older mice impaired *in vitro* inflammatory responses of cDCs obtained from young mice via a PD-L1-dependent mechanism [19]. pDCs express TLRs 7 and 9 within their endosomes and activation of these receptors leads to the production of type I IFN that are critical for certain viral infections. One report found that C57BL/6 mice aged to 18–20 months exhibit reduced type I IFN in response to systemic herpes viral infections (herpes simplex or cytomegalovirus), which are known to activate TLR9, as compared to young mice [20]. This defect in type I IFN impaired viral clearance and is due in part to defective upregulation of IRF-7, a critical signal transducer downstream of TLR9 [20]. Increased reactive oxidative stress with aging contributes to this phenotype [20]. Furthermore, the defective viral clearance synergizes with enhanced inflammatory responses to induce lethal liver inflammation with aging [21].

Studies in non-human primates and humans have generally found impairments in inflammatory responses of DCs, principally to TLR activation. In rhesus macaques, cDCs from aged donors (> 19 years of age) produce less IL-6 and TNF- α in response to TLR2/6, TLR4 or TLR9 activation as compared to young primates [12]. In this study, pDCs from aged primates exhibit a small reduction in type I IFN in response to CpG, which activates TLR9. A human study found that pDCs from older people exhibit reduced type I IFN responses to influenza virus *in vitro*, a virus that activates TLR7 [13,22]. Another study also reported reductions in type I and type III IFN in pDCs from older humans (aged 65–90 years of age) as compared to younger donors (20–35 years of age) to *in vitro* stimulation with influenza virus [23], a pathogen which induces higher mortality in older people [24]. Furthermore, this study also found defects in IRF-7 phosphorylation in the aged pDCs as compared to young pDCs but did not find alterations in the expression of TLR7 or TLR9

with aging [23]. Another study found that pDCs and cDCs from older humans (age range 58–86 years of age) also exhibit reduced type I IFN production in response to West Nile viral infection, a single stranded RNA virus, as compared to pDCs from young donors (21–33 years of age) [25]. This represents an important finding as older people exhibit more severe infections to this pathogen than younger people [26]. Compatible with the other human study [23] and the murine study above [20], this report found that DCs from older donors exhibit a defective expression of IRF-7 (and STAT-1) as compared to young DCs during viral infection [25].

One study derived cDCs from peripheral blood monocytes from older or young people after *in vitro* culture with GM-CSF [27]. cDCs were then stimulated with a single dose of LPS or single stranded RNA (which stimulates TLR7 [22]) and proinflammatory cytokines were measured. The study found that there is a general increase in the production of cytokines by aged cDCs, specifically the production of IL-6, IL-12p40/70, TNF- α and IL-10, as compared to young cDCs [27]. However, the study found that aged cDCs exhibit reduced phagocytosis, and migration of cDCs towards chemokine gradients *in vitro*, which was correlated with reduced PI3 kinase signaling [27]. A follow up study noted that cDCs from older people exhibit increased proinflammatory cytokine production and upregulation of costimulatory molecules in response to human DNA [28]. The authors postulated that human DNA acts as a self-antigen, and the elevated inflammatory responses noted in the study may explain the phenomenon of increased circulating cytokine levels that occur in older people [29,30]. These studies [27,28] contrast with a later one in which a general reduction in the production of IL-6 and TNF- α in cDCs was noted in aged as compared to young humans in response to a broad range of TLR activators [31]. A possible explanation for the discrepancy between the studies may be related to the preparation of cells: whereas the earlier studies propagated cDCs after culture with GM-CSF to increase cellular yield [27,28], the later study employed multi-parameter flow cytometry to measure cytokine production by cDCs within peripheral blood cells [31].

Impact of aging on priming function of DCs

25 years ago, a study examined the ability aged splenic DCs, which were not activated with any stimulants, to prime T cells [32]. This study obtained DCs from mice aged 2 months, 10 months and 23 months of age, and found that the ability of DCs to prime allogeneic and syngeneic T cells *in vitro* was preserved with aging [32]. This study agrees with a more recent one in which the ability of cDCs, at base line or after TLR activation, to prime antigen specific T cells, either viral reactive CD8⁺ T cells or alloreactive CD4⁺ T cells, is preserved with aging [14]. Furthermore, another study demonstrated that either aged bone marrow derived cDCs or splenic cDCs, which were not activated with TLRs, exhibit similar priming of allogeneic T cells as compared to young cDCs both *in vitro* and *in vivo* [33]. This agrees with another report that found that aged splenic cDCs prime T cell receptor (TCR) transgenic CD4⁺ T cells *in vitro* to a similar degree than young cDCs [34]. Finally, a human study found that aged cDCs that were exposed to human DNA display an enhanced ability as compared to young cDCs to prime polyclonal T cells [28].

There are several reports indicating that aging impairs the priming of T cells by DCs. Specifically, one report indicates that mucosal (CD11c⁺) DCs are less able to prime T cells after *E. cuniculi* oral infection as compared to young DCs [35]. Interestingly, decreased IL-15 expression within aged cDCs appears to be responsible for the defective priming response [35]. Another report found that the aged host environment does not support the priming of young TCR transgenic CD8⁺ T cells to respond to a pathogen (*L. monocytogenes*) that was engineered to express the cognate antigen that the transgenic T cells respond to (ovalbumin [OVA]) as compared to the young host environment [18]. This correlates with a reduced accumulation of CD8⁺ cDCs in the spleens of aged mice [18].

Importantly, treatment of aged hosts during bacterial infection with FLT3 ligand increases the number CD8⁺ cDCs and improves priming of TCR transgenic T cells [18]. Another study also employed TCR transgenic CD4⁺ T cells and found that the aged host environment is inferior to the young environment for T cell expansion after immunization with cognate antigen, in a non-infectious murine model [11]. This result correlates with CD11c⁺ DCs from the lymph nodes of aged mice being less able to uptake antigen than DCs from young mice [11]. Hence, these studies provide evidence of reduced priming of T cells by populations of DCs with aging, although these findings need to be examined in other infectious models (e.g., virus) or disease models (e.g., tumor models.)

Regarding tumor immunity, one study provided evidence that bone marrow derived CD11c⁺CD4⁻, CD8⁻ cDCs from aged murine donors that are pulsed with OVA are less able, after adoptive transfer to young hosts, to induce regression of an OVA expressing tumor than young OVA pulsed cDCs [16]. A follow up study demonstrated that murine cDCs that are pulsed with OVA are less able than young cDCs to induce proliferation of OVA responding TCR transgenic T cells *in vitro*. This correlates with a reduced ability of aged cDCs to uptake antigen as compared to young cDCs [36]. Additionally, in young mice, which bear OVA expressing tumors, aged cDCs pulsed with OVA are less able to induce tumor shrinkage and enhance antigen specific CD8⁺ T cell responses including cytokine secretion and proliferation as compared to young cDCs [36].

In humans, inflammatory responses (e.g., IL-12-40 and TNF-) of cDCs and pDCs are positively correlated with antibody seroconversion after influenza virus vaccination [31]. As it is established that influenza vaccination is less efficacious with aging [37], this study provides circumstantial evidence that the impaired TLR activation of cDCs and pDCs noted with aging, may be related to reduced humoral responses to vaccination with aging [31]. However, specific tests to assess priming of T cells by cDCs or pDCs were not evaluated in this study.

In sum, the effects of aging on the inflammatory responses and subsequent priming of T cells by different DC subsets are complex with most studies showing impaired responses, some showing preserved responses and a few enhanced responses (see Table 1 and Figure 1). Experimental studies that have *in vivo* correlations are likely to be more significant than those based on purely *in vitro* approaches (see Table 1). There is some consensus for reduced inflammatory responses by cDCs with aging. T cell priming by DCs with aging may depend on the context: reduced during systemic bacterial infection [18] and respiratory viral lung infection [39] and tumor models [16] but preserved in response to systemic viral infections [14]. There is a broad consensus across studies that aging impairs the function of pDCs to produce type I IFN to viral infection and that defective IRF-7 nuclear translocation, due to increased oxidative stress, is a probable underlying mechanism.

Aged environment and priming of a T cell response

The aged environment extrinsic to the DC may influence the priming of T cells by DCs. One study demonstrated that young viral reactive, TCR transgenic CD8⁺ T cells adoptively transferred into either aged or young mice, exhibit similar activation, cytokine production and proliferation in either young or aged mice during lymphocytic choriomeningitis viral infection [14]. Another study revealed that aged mice were less able to support the proliferation of adoptively transferred young CD8⁺ TCR transgenic T cells within the spleen after *i.v.* infection of influenza virus as compared to young mice, although the alteration within aged mice that was responsible for this phenotype was not determined [38]. A recent study demonstrated that during respiratory viral infections, aged mice exhibit increased PGD2 levels within the lung [39]. The increased in PGD2 impaired the migration of DCs into the lungs to reduce T cell priming and increase mortality during several viral pathogens

(e.g., influenza virus and respiratory syncytial virus) [39]. Although the source responsible for increased PGD2 levels with aging has not yet been identified. If translated to humans, this study suggests that elevated PGD2 levels with aging may be targeted to improve outcomes after respiratory infections in older people.

Recent evaluation of other APCs with aging

Other immune cells such as B cells possess antigen presenting cell function. A recent study evaluated the ability of B cells obtained from older people (age range between 62–92 years of age) or younger healthy donors to prime a T cell hybridoma [40]. All subjects recruited expressed the same MHC class II so that MHC expression was not a confounder for analysis [40]. The investigators noted that the older people recruited were predominantly pre-frail or frail [40]. The investigators found that B cells that were enriched from the peripheral blood via density centrifugation exhibit similar activation of T cell hybridoma with aging [40]. Similar results were noted with monocytes [40].

Conclusions and future investigation

Overall, the study of DC function and aging is complex. A unifying underlying biological mechanism as to how aging impacts DC antigen presenting capabilities has not been identified. This may reflect that most studies have emphasized functional cellular consequences rather than cell biological or molecular signatures with aging. Furthermore, the heterogeneity of DC subpopulations further complicate analysis. In the future it will be interesting to examine different subpopulations of DCs, and other APCs, via non-biased approaches to discern the pathways that are altered by aging. Importantly, future investigations should examine how aging impacts molecular function of DCs. This could include how aging alters autophagy, cell metabolism and the production of reactive oxygen species. This may yield clues as to how aging impacts the function of DCs and how this relates to altered immunity with aging. Furthermore, it may allow novel therapeutics to be discovered to improve immune function with aging.

Acknowledgments

DRG is supported by National Institutes of Health grants: AG028082, AG033049 and an Established Investigator Award (0940006N) from The American Heart Association.

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Highlights

1. How aging impacts the immune priming capabilities of dendritic cells is complex.
2. Some studies show reduced function, while others show preserved DC priming function with aging.
3. Lack of consensus may reflect subtle differences in the health status of mice and methods employed.

Figure 1. Functional changes with age in different dendritic cell subsets

Downregulation of co-stimulatory molecules and MHC class II are observed in cDCs, CD8⁺ cDCs and pDCs with aging. Aging decreases the capability of CD8⁺ cDCs to uptake bacterial components. With aging, pDCs exhibit a defect in IRF7 and PI3K upregulation but increased PD-L1 expression, which can inhibit priming of cDC to activate CD8⁺ T cells. IFN- production by pDCs following viral infection is reduced in old mice and humans. The investigation of cDCs with aging has yielded mixed results with either decreased or preserved production of proinflammatory cytokines and upregulation of costimulatory molecules noted.

Table 1

Key Studies on DCs and Aging

Type of study	DC subset	Mode of activation	Measured response	Changes with aging	Reference
Experimental-mouse *	cDC	TLR both <i>in vivo</i> + <i>in vitro</i>	Cytokines, costim expression, <i>in vitro</i> priming	-	<i>In vivo</i> and <i>in vitro</i> [14] <i>in vitro</i> findings [15]
Experimental – mouse *	pDC	TLR <i>in vitro</i> , virus <i>in vivo</i>	Cytokines, transcription factors, viral clearance		[20]
Experimental-mouse	cDC	TLR <i>in vitro</i>	Cytokines, surface receptors, adoptive transfer tumor model		[16]
Experimental-mouse	cDC	TLR <i>in vitro</i>	Cytokines, <i>in vitro</i> priming	Cytokines <i>in vitro</i> priming assays -	[34]
Experimental-mouse	cDC	TLR <i>in vitro</i> Immunization to model antigen <i>in vivo</i>	Cytokines, uptake of peptide		[11]
Experimental-mouse *	CD8 ⁺ cDC	Systemic bacterial infection <i>in vivo</i>	Accumulation of DCs in spleen, costim expression		[18]
Experimental-mouse *	Migratory cDC	<i>In vivo</i> models of viral lung infection	PGD2, Mortality	PGD2 Mortality	[39]
Experimental-mouse *	pDC	<i>In vivo</i> model of oral <i>E. cuniculi</i> infection	costim expression	PDL1 priming of cDCs	[19]
Experimental-non-human primate *	cDCs + pDCs	TLR <i>in vitro</i>	Cytokines		[12]
Human	cDCs cultured ex vivo with GM-CSF	<i>In vitro</i> infection with West Nile Virus	Cytokine expression, transcription factors		[25]
Human	cDCs cultured ex vivo with GM-CSF	TLR activators or human DNA	Cytokines		[27,28]
Human *	pDCs	<i>In vitro</i> influenza viral infection	Cytokines, transcription factors		[23]
Human *	cDCs	TLR <i>in vitro</i>	Cytokines		[31]

* denotes study in mice with *in vivo* correlation or human study of special significance.