Paradox of Immunodeficiency and Inflammation and Autoimmunity in Aged Humans: Role of Dendritic Cells

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Abstract—Aging represents a paradoxical state of immunodeficiency, inflammation and autoimmunity. The progressive impairment in immune functions include progressive T cell deficiency, and B cell dysfunctions as revealed by impaired specific antibody response to vaccines, autoimmunity, and hyperimmunoglobulinemia, and inflammation as evident by increased inflammatory cytokines and diseases of aging associated with inflammation.

Keywords — Enter 3 to 7 keywords, separated by commas.

I. IMMUNOSENESCENCE

PROGRESSIVE T cell immunodeficiency is the hallmark of aging. For a long time, thymic involution was considered as a major mechanism of T cell immunosenescence [1-12]. However, it appears that increased apoptosis of subsets of CD4+ and CD8+ T cells, an accumulation of oligoclonal CD8+ T cells with limited repertoire, and impaired priming of T cells by dendritic cells also appear to contribute significantly to progressive T cell immunosenescence. Furthermore, there is growing evidence that the aging of hematopoietic stem cells (HSCs) directly contributes to immunosenescence [13].

Thymus and Immunesenescence

Thymus involution is considered central to immunosenescence. This results in decreased production of naïve cells. In mice, the evidence points towards problems in the epithelial component of the thymus and the production of IL-7 (interleukin 7). The transcription factor FOXN1 is critical throughout thymic epithelial cell (TEC) differentiation in the fetal and postnatal thymus [14], is downregulated with age in thymic stroma. Bredenkemp et al [15] have shown that forced TEC-specific upregulation of FOXN1 in the fully invovled thymus in mice results in full regeneration of thymus characterized by increased thymopoiesis and increased output of naïve T cells. Therefore, FOXN1 is considered as primary target in age-related thymus involution.

Qi and colleague [16] have recently reported that highly diverse repertoire is maintained despite thymic involution; however, in the repertoire of aged T cells they observed large naïve T-cell clones that are distinct from memory clones, suggesting uneven homeostatic proliferation without development of a memory cell phenotype

Apoptosis and Immunosenescence

We proposed that increased apoptosis of T cells may also contribute to immunosenescence. We, and others have reported that aged human T cells display increased sensitivity to activation-induced, Fas (CD95)- induced, and TNF-induced apoptosis, which is associated increased activation of caspase 3 and caspase 9 [17-25]. We have also reported decreased naïve (TN) and central memory (TCM) CD4+ and CD8+ T cells in human aging [25]. Furthermore, TN and TCM T cells subsets of both CD4+ and CD8+ T cells in aged humans display increased sensitivity to CD95 and TNF-induced apoptosis [25-27]. Increased TNF-induced apoptosis is associated with decreased expression of adapter molecules involved in survival signals, TRAF-2 and RIP. Furthermore, phosphorylation of JNK, IKKα/β, and 1xBα and decreased NF-xB activation was observed in both TN and TCM CD8+ cells from aged subjects as compared to young controls. Finally, expressions of anti-apoptotic targets of NF-xB including Bcl-xL, cIAP1, A20, and FLIP-L and FLIP-S in TN and TCM CD8+ cells from aged were decreased (unpublished data). These data suggest that increased apoptosis of TN and TCM CD4+ and CD8+ cells from aged is due to an impaired expression/function of molecules that confer survival signals and may contribute to immunosenescence.

Dendritic cells and Immunosenescence

DCs are unique antigen-presenting cells because of their capacity to prime naïve T cells and to set a stage for the development of effector functions [28]. The aged DCs appear to have impaired capacity to prime naïve T cells, therefore, may contribute to immunosenescence [29-31]. We have observed that influenza-activated DCs from aged display a deficiency in priming both CD4 and CD8 T cells [30].

II. INFLAMM-AGING

An increase levels of circulating IL-6, CRP, and TNF-α and higher basal levels of IFN-γ, IL-12p70, CXCL-10 and CXCL9
have been reported in aged humans [2, 5, 31]. Several of these proinflammatory cytokines correlate with pathological inflammation associated with aging and diseases of aging. For example, elevated levels of IL-6 in aging is a strong predictor for thrombomembolic and cardiovascular disease, whereas TNF-α concentrations correlate with frailty, increased risk of malignancy, neurodegeneration and depression [32, 33]. Overall, elevated pro-inflammatory cytokine levels in aged individuals predict more than 3-fold higher risk of mortality, independently of other health measures of health status. T and macrophages from aged humans are impaired in their capacity to secrete proinflammatory cytokines. Majority of proinflammatory cytokines in aging are contributed by B cells [5] and dendritic cells.

**Dendritic cells and Inflamm-aging**

DCs are the major antigen-presenting cells that bridge the innate and adaptive immune responses. DCs sense and respond to pathogens via the pathogen recognition receptors (PRRs) such as Toll like receptors (TLRs). Activation of DCs results in the secretion of pro-inflammatory cytokines, which play an important role in host-defense and are critical in directing the T cell proliferation and polarization [28]. DC function becomes dysregulated with age and may contribute to age-associated inflammation [34]. Our studies demonstrate that DCs from aged subjects display an enhanced basal level of inflammation which alters their response to both foreign and self-antigens [29, 35]. We have reported that DCs from aged individuals display an inflammatory phenotype as evidenced by increased basal level activation of NF-κB [35]. Since NF-κB is a major signaling pathway in DCs for the induction of inflammatory cytokines, its activation also leads to spontaneous secretion of pro-inflammatory mediators, TNF-α, CXCL-10, IL-6 and ADAM metalloproteinases by aged DCs in the absence of any stimulation [36]. Panda et al [37] have also observed an increase in the basal level of TNF-α secretion by DCs from aged individuals. Furthermore, we have observed that proinflammatory cytokines, TNF-α and IL-6 secretion in response to TLR4 ligand, Lipopolysaccharide (LPS) as well to pathogens such as *Chlamydia pneumonia* is significantly increased in the DCs from aged subjects compared to their young counterparts [29, 38]. This low level basal activation and chronic inflammatory secretion by aged DCs indicates a deficiency in the regulatory mechanisms involved in controlling inflammation.

**Dendritic cells and regulation of Inflammation**

Excessive inflammatory cytokine production results in tissue damage and toxicity that is harmful to the host. Therefore, strong inducers of inflammatory cytokines also activate homeostatic mechanisms that serve to limit cell activation, cytokine production, and tissue damage. One key homeostatic mechanism is the induction of IL-10, a potent anti-inflammatory cytokine that mediates a feedback inhibition loop that limits the production of pro-inflammatory cytokines [39, 40]. IL-10 also inhibits multiple macrophages and DC effector functions and plays a critical role in limiting tissue injury during infections and in preventing autoimmunity by limiting the duration and intensity of immune and inflammatory reactions [40]. Evidence suggests that production of IL-10 becomes dysregulated with age [30, 38]. This is particularly apparent in DCs. Though we observe an increased propensity of DCs from aged subjects to secrete inflammatory cytokines after stimulation with LPS [29]; there is no concomitant up-regulation in the production of IL-10 from aged DCs to prevent inflammation. We also find that the pro-inflammatory cytokine production by aged DCs extends to other stimuli besides LPS. For example, aged DCs stimulated with *Chlamydia pneumoniae* also secreted significantly higher levels of TNF-α, IL-6 and CXCL-10 while IL-10 production was significantly decreased [38]. Similar impairment in IL-10 induction was also observed upon stimulation of aged DCs with the TLR1/2 ligand Pam3Csk4 [38]. Altogether, these results suggest that DCs from aged individuals display an intrinsic defect in the production of IL-10 and are more prone to secrete inflammatory cytokines. This would affect their capacity to maintain tolerance and lead to inflamm-aging.

**AUTOIMMUNITY IN AGING**

In contrast to immunosenescence, there is an increased reactivity to self and endogenous antigens as evidenced by the presence and increased titers of a variety of autoantibodies [6, 8, 10, 11], which suggest a loss of peripheral tolerance in aging. DCs can prime or tolerate T cells. Under physiological conditions, DCs play a role in unresponsiveness to self-antigens. DCs are essential for both central and peripheral tolerance. Apoptosis plays an important role in immune homeostasis. One of the critical steps is a rapid uptake of apoptotic cells and apoptotic bodies by neighboring phagocytes (e.g. DCs, macrophages), resulting in intracellular degradation of self-antigens, and induction of anti-inflammatory response and generation of Treg. We have shown that aged DCs are impaired in their capacity to uptake apoptotic cells [31]. As a consequence apoptotic cells would undergo secondary necrosis with additional proteolytic degradation of specific autoantigens, which may release endogenous danger signals like nuclear antigens clustered in apoptotic blebs and bodies, resulting in maturation of DCs, and T cell immunity to self-antigens, and production of autoantibodies. Impaired clearance of apoptotic cells has been implicated in autoimmune diseases like lupus [41]. We have demonstrated that DNA-primed monocyte-derived DCs (mDCs) from aged subjects, upregulated co-stimulatory molecules, and secreted increase levels of IL-6 and IFN-α as compared to young mDCs [35]. 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. We also observed an increased activation of interferon-responsive factor-3 (IRF-3) in mDCs from aged in response to Intracellular self-DNA.

Human DNA is generally inert and does not stimulate DCs. We show 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 [42]. We 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.

In summary, increased apoptosis, impaired clearance of apoptotic cells, increased reactivity to self-antigens (e.g., DNA), and epigenetic changes of hypomethylation of aged DNA appear to contribute to autoimmunity and inflammation in aged humans, and DCs appear to play a major role. Furthermore, impaired capacity of aged DCs to prime naïve T cells to exogenous (foreign) antigen and increased apoptosis of naïve and central memory T cell subsets may contribute to immunosenescence.

References


