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Current Opinion in Immunology

Plasmacytoid dendritic cells in autoimmunity

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Plasmacytoid dendritic cells (pDC) is a unique cell population that produces large amounts of type I interferon upon recognition of nucleic acids placing them at the crossroad of both innate and adaptive immunity. Their ability to produce interferon makes them central to anti-viral responses. They are also responsive to circulating autoantibodies bound to nuclear antigens and in that scenario the release of interferons initiate self-directed immune responses. There are now a growing number of autoimmune disorders where unabated activation of pDC is suspected to be pathogenic. Here, we discuss the different mechanisms responsible for breaking tolerance to self-nucleic acids by pDC, including the novel role of IgE autoantibodies in systemic lupus erythematosus. We also summarized the recent progress on therapies undergoing clinical testing that target either pDC or type I interferons.

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Current Opinion in Immunology 2017, **44**:20–25

This review comes from a themed issue on **Innate immunity**

Edited by **Marco Colonna**

For a complete overview see the Issue and the Editorial

Available online 14th November 2016

http://dx.doi.org/10.1016/j.coi.2016.10.006

Introduction

Plasmacytoid dendritic cells (pDC) correspond to a subset of dendritic cells that originate at the bone marrow and exhibit plasma cell morphology. Currently, there are three cell surface markers that are unique to human pDC, the blood-derived dendritic cell antigen-2 (BDCA-2), BDCA-4 and immunoglobulin-like transcript 7 (ILT7) [1,2]. They also express HLA-DR, CD4 and CD123 but not CD11c, a common dendritic cell marker. Through their production of type I interferons (IFNs) and other pro-inflammatory cytokines, pDC initiate an immune response that involves the activation of other myeloid cells, as well as B cells, T cells and natural killer (NK) cells. Viral nucleic acids are sensed in the endosome by Toll-like receptor (TLR)7 and TLR9. Activation of these receptors leads to pDC maturation and the initiation of an inflammatory response that is characterized by the secretion of large quantities of IFN-α [3] which ultimately results in the upregulation of IFN-induced genes [4], the activation of B cells and generation of antibody secreting plasma cells [5]. Along with the generation of a robust interferon response, mature human pDC secrete the proinflammatory cytokines TNF and IL-6, chemokines, and express costimulatory molecules at the cell surface that allows them to present antigens to T cells. Altogether, activation of TLR7 and TLR9 result in the initiation of a complex anti-viral program that places pDC at the center of both innate and adaptive immune responses [6].

Increased expression of genes regulated by type I IFNs, termed the interferon gene signature has been found in the blood and/or involved tissues of patients with autoimmune disorders [7,8]. Interferons are key drivers of autoimmunity, as they support the functions of monocytes and T cells, the activation and proliferation of B cells, and the differentiation of plasma cells into autoantibody-producing cells [9]. Administration of interferons result in lupus-like syndrome [10] and their pathogenic role in autoimmunity has now been clinically validated in two phase 2 clinical trials [11••,12••]. The secretion of type I IFN can be induced by autoantibodies that bind to nucleic acids or proteins that in turn bind to nucleic acids like nucleosomes. Upon binding to self-antigens released by dead cells, these autoantibodies form immune complexes (ICs) that activate pDC and initiate interferon responses. Most studies have focused on describing the pathogenic role of autoantibodies of the IgG subclass. Recent studies have now also associated autoantibodies of the IgE subclass to systemic lupus erythomatosus (SLE) pathogenesis. IgE facilitates degranulation of mast cells and basophils and promote Th2 immunity, mechanisms that are central to allergies. Recently, others and we have shown that IgE autoantibodies that bind to nucleic acids are present in SLE and induce robust type I IFN responses by pDC. Here, we will review the latest understanding of the links between pDC and autoimmunity, including their recently described ability to respond to IgE autoantibodies. We will also summarize the latest clinical trials focusing on targeting pDC or type I IFN in autoimmunity.

PDC in infection

The importance of pDC on anti-viral response has been recently demonstrated in mice models. Depletion of pDC in adult animals reduced early type I interferon production and resulted in increased viral burden in early stage of both MCMV and VSV infection [13]. Conditional targeting of pDC-specific transcription factor Tcf4 severely reduce interferon response in pDC and its migration to peripheral lymphoid organs and tissues [14]. Constitutive loss of pDC in this model produced a impaired response to chronic LCMV infection characterized by reduced

number and function of CD4 and CD8 T cells [14]. Type I IFNs released by pDC are central to controlling viral infections [15•]. IFNs restrict viral infections by inhibiting viral replication and inducing apoptosis of the infected cells [16,17]. Type I IFN induces cross priming of CD8 T cells, enhances the clonal expansion of antigen specific CD8 T cells [18], and also acts synergistically with IL-27 to differentiate naïve T cells into Th1 cells during viral infections [19]. While the potent antiviral role of type I IFNs is clear, their role in host defense against bacterial infections is enigmatic and may exert opposite functions depending on the bacterium, and the stage of infection. Low levels of type I IFNs may be required at an early stage of infection to initiate cell-mediated immune responses. High concentrations however may be detrimental to control bacterial infection due to reduced Th17 responses [20] and macrophage activation [15•].

PDC in autoimmunity

Evidence linking pDC to autoimmunity

Infiltration of pDC into involved tissues and evidence of interferon responses have been found in a number of autoimmune disorders including SLE, Sjogren's syndrome, systemic sclerosis, psoriasis, and alopecia areata [3,7,8,21,22]. The expression of type I IFN genes in blood correlates with disease activity and plasma levels of antinuclear autoantibodies in SLE [23–25]. pDC are the main source of IFN-α and once activated by nucleic acid-containing ICs they migrate from the blood into inflamed tissues including the skin [26] and kidney [27]. The central role of pDC in autoimmunity has been demonstrated in lupus prone mouse models. Mono allelic loss of the transcription factor Tcf4 causes specific impairment of pDC functions (such as ability to produce IFN-α in response to TLR9 agonist). In a murine SLE-prone background, the genetic impairment of pDC function induced by Tcf4 haplodeficiency nearly abolished key disease manifestations such as anti-DNA antibody production and glomerulonephritis [28••]. In a different model, transient ablation of pDC reduced splenomegaly and lymphadenopathy, impaired expansion and activation of T and B cells, reduced antibodies against nuclear autoantigens (ANA) and improved kidney pathology. Amelioration of pathology coincided with decreased transcription of interferon-regulated genes in tissues [29••]. The role of pDC in lupus seems to be largely driven by type I IFNs as lupus prone animals lacking the ability to sense nucleic acid containing autoantibodies due to defective endosomal TLR signaling showed an absence of autoantibody formation, reduced lymphadenopathy and splenomegaly, and extended survival [30].

Mechanism of self-nucleic acid recognition in pDC

Sensing nucleic acids through endosomal TLRs is probably the most important mechanism by which pDC recognize and respond to ongoing viral infections. These ligands however, are a feature shared by both host and pathogens. It is then paramount to have safeguards in place that avoid undesirable recognition of self-nucleic acids. Compartmentalization of TLR7 and TLR9 inside the cells is one of those measures. Endolysosomal location drastically limits their ability to respond to host extracellular nucleic acids that are shed by dead cells. The importance of concealing these receptors intracellularly is highlighted by the lethal autoinflammatory disease caused by the expression of a modified version of TLR9 at the cell surface in hematopoietic stem cells in mouse [31]. There is now ample evidence showing that autoantibodies that bind directly or indirectly to host nucleic acids form ICs that bypass those safeguards and cause autoimmunity. Nucleic acid containing ICs initiate phagocytosis by binding to FcγRIIa (CD32A) at the plasma membrane of pDC (Figure 1) [32,33]. The engulfed nucleic acids are then delivered into a phagosomal compartment where TLR7 and TLR9 sense them. Activation of either of these intracellular TLRs triggers the recruitment of the adaptor protein Myd88 and the subsequent activation of the transcription factor NF-κB, which results in the production of pro-inflammatory cytokines (such as TNF and IL-6) and chemokines (such as CXCL8, or CXCL10) [6]. As the phagosome matures into an acidic compartment the transcription factor interferon regulatory factor 7 (IRF7) is then activated and initiates the secretion of large amounts of type I IFNs. Activation of IRF7 is dependent on the recruitment of the autophagy protein microtubule-associated protein 1A/1B-light chain 3 (LC3) to the phagosome, a process that is known as LC3-associated phagocytosis (LAP) to distinguish it from canonical autophagy [34]. While LAP mediates IFN responses from large compartments such as phagosomes containing pathogenic ICs, adaptor protein 3 (AP3) is responsible for initiating responses from smaller endosomal compartments [35]. Genome-wide association studies have identified polymorphisms in the autophagy gene Atg5 as a marker of predisposition for SLE [36,37], suggesting an important role for autophagy proteins and potentially LAP in SLE. Nonetheless, autophagy functions are not likely to be restricted to pDC and the IFN pathway. As shown by recent studies autophagy in B cells and macrophage may be also important for autoimmunity. In a Tlr7 transgenic mouse model, ablation of autophagy in B cells largely reduced inflammatory markers in the serum (such as type I IFNs, type III IFNs, IL-12 and IL-6), and the formation of ANA. As a result, glomerulonephritis was ameliorated and survival extended [38]. Specific ablation of LAP components in macrophages however resulted in an inflammatory lupus-like response. This was largely due to a defect in phagosomal maturation and defective clearance of dead cells [39•], the latest being a recognized driver of SLE pathology [40]. As new data and models arise focusing on investigating the role of autophagy in autoimmunity, it is becoming evident that those roles are bound to be context and cell dependent.