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Plasmacytoid Dendritic Cells: The Potential of Synergistic Crosstalk between Innate and Adaptive Immunity

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Mini Review

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Abstract

In rodents, a combination of innate and adaptive immune responses is critical in controlling infection. The adaptive immune components, comprising B cells, CD4 T cells, CD8 T cells, pathogen specific secretory antibodies, and Treg cells have been exhibited to play an indispensable role in comprising and eliminating various infections. Also, there are several innate immune components that help to control infections, such as soluble mediators, lymphotoxin (LT) signaling in innate epithelial cells, TLRs, signaling adaptor MyD88, inflammasomes, CXCL9, P-selectin glycoprotein ligand-1 (PSGL-1). Little is known about the molecules that mediate the crosstalk between innate and adaptive immune response during infection. The work presented here has unravelled the potential of plasmacytoid dendritic cells (pDC) in the immune system in providing the first line of defense during natural infection as well as subsequent adaptive host defense against pathogens. In this work the potential that pDC might have in infection has been investigated in order to understand the basis of the development of protective and pathological responses during infection. These findings would help set up future avenues of research to elucidate a key mechanism of action of these cells and provide new therapeutic insights.

Keywords: Type I IFN-producing Cells, CD4 T Cells, CD8 T Cell, Treg Cell, Th17 Response, NK Cell, Soluble Mediators, Secretory Antibodies

Abbreviations: LT: Lymphotoxin; PSGL-1: P-Selectin Glycoprotein Ligand-1; pDC: plasmacytoid Dendritic Cells; HIV: Human Immunodeficiency Virus; HSV: Herpes Simplex Virus; MCMV: Murine Cytomegalo Virus; LCMV: Lymphocytic Choriomeningitis Virus.

Introduction

pDC are a unique population of bone marrow derived leukocytes that are developmentally and functionally distinct from conventional DCs [1,2]. In the steady state, pDC reside primarily in the lymphoid organs and are recruited by infection and inflammatory mediators [2-4]. For instance, accumulations of pDC are prevalent in the skin in psoriasis [5] and SLE [6], in the mucosal tissues in allergic rhinitis [7], in the lungs in pneumonia [8] and respiratory syncytial virus [9], in the mucosal space in colon and mesenteric LN in IBDs [10], in vagina in genital HSV-2 infection [11]. pDC can differentiate into antigen-presenting dendritic cells as a result of their link to several cellular receptors that promptly detect nucleic acids in pathogens [2,12]. These powerful networks of molecular and cellular events permit pDC to bridge the innate and adaptive immune systems resulting in a concerted pathogen response.

pDC during Infection

As the major type I IFN-producing cells in the innate immune system, pDC respond to a wide range of viruses, including human immunodeficiency virus type I (HIV-1), influenza virus, sendai virus, herpes simplex virus (HSV), murine cytomegalovirus (MCMV) and lymphocytic choriomeningitis virus (LCMV) etc [13]. However, their role in non-viral diseases was not much appreciated until recently a handful of studies have begun to explore the contribution of pDC to bacterial immune responses and autoimmunity. For instance, pDC produce IFN-I upon recognition of bacterial RNA [14,15] and when exposed to Borrelia burgdorferi in vitro [16], they can activate CD4 T cells via antigen presentation and IL12 secretion in response to toxoplasma infection [17]. Also, pDC can suppress induction of CD4 T cells and initiate CD8 T cell responses [18]. pDC can infiltrate the mesenteric LN and spleen of Listeria-infected mice [19], although they are not responsible for the elevated systemic IFN-I levels [20] that interfere with the clearance of Listeria [21]. pDC have also been shown to drive Th17 responses in patients with GVHD [22] and pDC produce LN homing of NK cells [23]. The potential of pDC to induce Treg has been illustrated in numerous disease models [24-27]. Depletion of pDC results in an upregulation of T cell immune responses, increased production of thymic regulatory T (Treg) cells, fewer Treg cells in the gut, decreased generation of induced Treg cells and an increased frequency Th17 cells [28]. Recently, pDC have been found to be associated with the development of central tolerance in the thymus [29]. This work supports earlier studies that suggest a tolerogenic role for pDC in some circumstances.

pDC a Specialized Type I Interferon Secreting Cells

pDC, a distinctive subset of DCs is able to secrete type I IFNs more quickly than other cell types to a large array of viral and non-viral molecules [30-32]. Though comprising only 0.2–0.8% of human blood cells, pDC are able to produce more than 95% of type I IFNs by peripheral blood mononuclear cells following viral insult [33,34]. pDC are proficient in secreting up to 10 pg/cell of type I IFN, producing them 10–100-fold more than other cell types including moDC [35]. Within 6 h of activation, human pDC contribute 60% of their transcriptional activity to secrete type I IFNs, comprising entire transcripts of nineteen diverse subclasses of type I IFN [36]. pDC express a wide range of ifna genes compared to other professional antigen-presenting cells (APCs). Human pDC express the entire subtypes of type I IFNs including IFN-α, IFN-β, IFN-γ, IFN-ω, and IFN-τ [1]. Ablation of pDC in vivo abolished the IFN-α secretion in response to cytomegalovirus infection in mice [37,38].

Role of pDC as a Linker of Innate and Adaptive Immunity

Type I IFNs produced by pDC induce a cellular antiviral response and recruits a network of molecular and cellular events and thus linking the innate with adaptive immunity [39] (Figure 1). Type I IFNs activate NK cell cytolytic activity, however, protect uninfected cells from NK cell–mediated lysis [40,41]. pDC induce production of IFNγin NK cells via IL-12 secretion [42]. Type I interferons released by pDC cause T cells to produce IL-10, IFNγ and also induce a Th1 polarization and thus promote clearance of intracellular pathogens [43,44]. Type I interferons can upregulate early activation markers CD69 on T cells [45,46] and generation of long-term antitumor immune response [47]. Through the production of both type I interferons and IL-6, pDC promote human B cells to differentiate into antibody secreting plasma cells facilitating the production of anti-viral antibodies [48,49]. Plasma cells induced by pDC predominantly secrete IgG rather than IgM, suggesting that pDC may trigger memory B cells [50,51]. Type I IFNs can increase cross-presentation during viral infection, and induce antigen-specific CD8+ T cells, and the differentiation of naive T cells into Th1 cells using the STAT1, STAT3 activation and T-bet expression [52-54]. Type I IFNs trigger immature cDCs to produce IL-12, IL-15, IL-18, and IL-23, cytokines that are not secreted by human pDC [55,56]. pDC are likewise competent producers of chemokines, mostly CCL3, which can aid

them to trigger additional leukocytes to inflamed tissues [57,58].

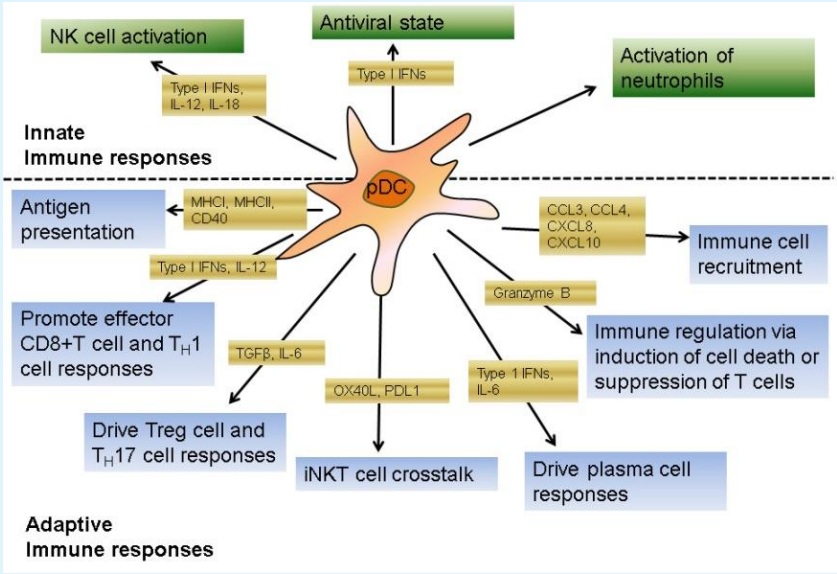

Figure 1: Diverse mechanisms of pDC.

pDC are important drivers for both innate and adaptive immune responses. pDC production of MHC class I, Class II and costimulatory molecule CD40 enable pDCs to present antigen to CD4 cells. pDC production of type I IFNs and IL-12 enable pDCs to promote effector CD8 T cells as well as polarization of CD4 cells to Th1 responses.pDC production of TGFβ and IL-6 drive either Treg or Th17 cell responses. The crosstalk between pDCs and NKT cells occur via OX40L and PDL1 ligand. pDC production of type 1 IFNs and IL-6 drive plasma cell responses. Granzyme B enablepDCs to induce apoptosis or cell death as well as suppression of T cells. pDCs induce chemokines including CCL3, CCL4, CCL8 and CXCL10 which can attract other immune cells to the site of infection.pDC can activate neutrophils. pDC production of type 1 IFNs can produce an antiviral adaptive immune responses.pDC production of type 1 IFNs, IL-12 and IL-18 can activate NK cells.

Concluding Remarks

The role of pDC has been exhibited in two distinct immune systems, one of which gives rise to the other. pDC, which are typically believed to be as antiviral, enact a central role in host control of bacterial infections. The findings in this study can be extended to other undiagnosed bacterial and parasite infections. Also, additional studies are required on pDC in different type of infections to hypothesize extended knowledge on the vivid character of these cells and mechanisms contributing to immunity against various pathogens.

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