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Miscellaneous

Plasmacytoid dendritic cells: Key players in viral infections and autoimmune diseases

Karina Santana-de Anda, MD[a], Diana Gómez-Martín, MD, PhD[a], Rodrigo Soto-Solís, MD[b], Jorge Alcocer-Varela, MD, PhD[a,*]

[a] Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Tlalpan, Mexico City, Mexico
[b] Department of Gastroenterology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Tlalpan, Mexico City, Mexico

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ABSTRACT

Objective: Describe the main activation and inhibitory pathways and receptors by which pDC regulate type I interferon secretion, as well as its association with autoimmune pathology.
Methods: A PubMed search for articles was conducted using the following key words: plasmacytoid dendritic cells, autoimmune diseases, viral infections and type I interferon. The search was limited to publications in English and from 1957 to 2012. Sixty-five of these articles are included in this review. The most relevant primary research articles identified were critically evaluated and compiled together. Particularly, areas of consensus and controversy were identified and analyzed.
Results: Plasmacytoid dendritic cells have been closely related to viral infections and autoimmune disease, mainly because of these immune cells are able to secrete large amounts of type I interferon. This function is linked with their expression of Toll-like receptors, specially TLR7 and TLR9, which are designed to sense nucleic acids in the early endosomes. Activated pDC can promote immunity and autoimmunity, however, the exact mechanisms by which pDC promote one vs. the other are not well understood.
Conclusions: Plasmacytoid dendritic cells play a key role in both, immunity and autoimmunity. Current evidence suggests that the sustained overproduction of type-I interferon drives aberrant immune responses and the development of autoimmune pathology.

Introduction

Plasmacytoid dendritic cells (pDC) are professional antigen presenting cells derived from the bone marrow and are specialized in type I IFN secretion mainly in response to virus or immune complexes after Toll-like receptor (TLR) engagement and activation. pDC have constitutive expression of interferon regulatory factor 7 (IRF7), which is a transcription factor devoted to induce rapid interferon responses, implicated in both, protective immunity and tolerance induction [1,2]. pDC constitute 0.2–0.8% of the peripheral blood cells in humans [3].

Many systemic autoimmune diseases show persistent and elevated production of type-I interferon and display increased expression of type-I interferon related genes; this molecular signature has been related to pDC activation by immune complexes via the toll-like receptors, mainly TLR-7 and TLR-9 [4]. In contrast to myeloid dendritic cells, pDC only express TLR-7 and TLR-9 (intracellular receptors that recognize viral or microbial nucleic acids within early endosomal compartments) [5]. These TLR, in humans, are only expressed in pDC, macrophages and B cells [6]. The aim of this revision is to analyze the current findings that link pDC function, type I interferon production and autoimmune disease pathogenesis.

Methods

A PubMed search for articles was conducted using the following key words: plasmacytoid dendritic cells, autoimmune diseases, viral infections and type I interferon. The search was limited to publications in English language from 1957 to 2012. Searches of PubMed yielded 426 articles; 186 articles were screened based on the relevance of titles and abstracts. Sixty-five of these articles are included in this review. The most relevant primary research articles identified were critically assessed. The findings in those reports were compiled together, with emphasis towards identification and analysis of areas of consensus and controversy. Articles were excluded for the following reasons: duplicate or nonrelevance.

pDC: History, development and phenotype

Plasmacytoid dendritic cells were identified for the first time by pathologists in the 1950s, they were designated as T cells or

* Corresponding author.
E-mail address: jorgealcocer2@gmail.com (J. Alcocer-Varela).

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plasmacytoid monocytes because of their plasma cell morphology, as reviewed previously [7]. By the 1980s these were described as natural type-I-interferon producing cells by virologists and immunologists, owing to its capacity to produce important amounts of type I interferons when co-cultured with viruses [8]. In 1997 Grouard et al. isolated different dendritic cells subsets from tonsils and found that the subset classified as the CD4+CD123+lineageneg was the same as the plasmacytoid monocytes and finally were defined as plasmacytoid dendritic cells [9]. In 1999 Siegal et al. found that pDC in contact with viruses secrete 100–1000-fold higher levels of interferon than other blood cells [10]. pDC have recombination activating gene products and also show D-J rearrangements of the immunoglobulin heavy chains, which distinguish them from the classic dendritic cells [11]. These findings supported the idea that pDC were derived from lymphoid progenitors, however, Chicha et al. found that pDC can arise not only from lymphoid, but also from myeloid progenitors. In this study, the authors used human lymphoid and myeloid committed progenitor cells and evaluated their developmental potential simultaneously promoting interferon producing cells (IPC) and CD11c+ dendritic cells mainly by ILT3/ILT3L stimulation. Lymphoid and myeloid-derived CD11c+ cells became functional DCs after overnight LPS maturation, as determined by surface marker expression and capacity to stimulate allogenic T cells [12]. Moreover, pDC lineage is controlled by expression of the transcription factor E2-2, a member of the E protein family [13]. E2-2 controls the expression of many proteins produced by pDC, like IRF-7 and IRF-8 [13,14], hence the transcription factor E2-2 regulates pDC development by promoting the expression of genes related to increased type-I interferon production. Phenotypic characterization of pDC is not as clearly defined as for other DC subsets. Recently, a number of different pDC markers have been identified. Among these, blood DC antigen 2 (BDCA-2) has been described as a member of the C-type lectin family of transmembrane glycoproteins, which is specific for pDC [15]. Other specific pDC receptors include the immunoglobulin like transcript 7 (ILT-7) and BDCA-4/neuropilin-1 a, which are members of the semaphorin family [16,17]. The signaling pathway via ILT7 is not well established; Cao et al. hypothesized that ILT7 could pair with an adapter molecule via charged interaction within the plasma membrane via the arginine 449 residue located to the transmembrane domain. Although pDC lack the expression of ITAM components, they express FcεRIγ and DAP12 (ITAM-bearing adapters). Moreover, ILT7 associates FcεRIγ to form a stable receptor complex with signaling potential and consequent activation of NFAT [18]. However, the precise ITAM-mediated signaling pathway for pDC remains elusive (Table 1).

Interestingly, the physiologic ligand of ILT7 is BST2, which is expressed on the surface of cells in an inflammatory scenario. BST2 is a 180-aa glycoprotein identified as an ILT7 specific ligand which is able to regulate TLR responses in pDC [19]. Also, BST2 negatively regulates the secretion of IFN-α and TNF-α when activated by TLR agonists, without altering the expression of co-stimulatory molecules, which suggests that BST2-ILT7 interaction modulates pDC IFN responses mainly via TLR. This interaction might play as an important negative feedback mechanism for preventing prolonged IFN production, and it may be considered a defense mechanism towards the development of autoimmune pathology.

Table 1
Main pDC activating sensors and their physiologic ligands.

Receptor	Physiologic ligand
RLR (RIG-1, MDA5, LGP2)	Viral nucleic acids
??	NETs
DAI	Cytosolic DNA
TLR-7	ssRNA, synthetic oligoribonucleotides
TLR-9	Unmethylated CpG oligodeoxyribonucleotides
CD40	CD40L
DHX36, DHX9	CpG-A and CpG-B
IFI16	DNA

pDC: Setting the tune between innate and adaptive immune response

Under normal conditions pDC are found in small numbers in peripheral blood and in T cell areas of lymph nodes, spleen, thymus, mucosal-associated lymphoid tissues and liver. pDC secrete large amounts of type-I interferon, which induces augmented expression of many antiviral molecules, leading to an efficient antiviral response [20,21]. Besides producing type-I interferon, pDC are also able to secrete inflammatory cytokines, mainly IL-12, IL-6 and TNF-α. Through secretion of these cytokines, pDC serve as a bridge between innate and adaptive immune responses [1]. Among the main functions of pDC over this complex network, are the induction of long-term survival T cells mediated by type I interferon and IL-12 [22,23]; CD8+ T cells cytotoxicity, as well as IFN-γ production [24] and NK cytotoxicity [25]. Moreover, as feedback response, type-I interferon induces the maturation of pDC, allowing them to become professional antigen presenting cells increasing the surface expression of co-stimulatory molecules [26]. Also, IL-6 and type-I interferon promote the differentiation of B cells into immunoglobulin secreting plasma cells, and isotype switching, demonstrating cooperation between both cytokines. IFNα induces differentiation of activated B cells into nonsecreting plasmablasts which in response to IL-6 become Ig secreting plasma cells [27]. In summary, by acting on many different immune cells, pDC can influence the innate and adaptive immune responses.

LL37: A novel potent trigger of pDC activation

Lande et al. identified the only human cathelicidin LL37, it belongs to the cationic antimicrobial peptide family and has been identified as a key mediator of pDC activation in autoimmune diseases, such as psoriasis. They found by real-time PCR analysis that LL37 was highly expressed in psoriatic skin lesions and neutralization of LL37 completely inhibited the capacity to induce IFN-α [28]. Although it is clear that LL37 associated with self-DNA activates pDC, the precise mechanism is not completely understood until now.

LL37 is responsible for a breach in innate tolerance to self-DNA by forming a complex that is retained within early endocytic compartments of pDC to trigger TLR9 signaling and induce IFN production. In the absence of LL37 human DNA is unable to induce IFN production, indicating that LL37 induces IFN-α by converting non-stimulatory self-DNA into a potent trigger of pDC activation. Binding of LL37 to DNA induces the formation of complexes with structural changes in the DNA that can be reversed by salt-induced dissociated peptide, indicating important ionic interactions between anionic phosphate groups of DNA and cationic amino acids of LL37 in terms of the pathogenicity of self-antigens.

TLR-7 and TLR-9: Key players in pDC activation

TLRs are transmembrane receptors that have a luminal domain with leucine rich repeats and a cytoplasmic domain for downstream signaling [29]. The TLRs mainly involved in viral responses are: TLR2, TLR3, TLR7, TLR8 and TLR9. pDC recognize viral nucleic acids mainly via TLR7 and TLR9, which reside in the endoplasmic reticulum and are transported to the endosomal compartment