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The involvement of plasmacytoid cells in HIV infection and pathogenesis

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ABSTRACT

Plasmacytoid dendritic cells (pDCs) are a unique dendritic cell subset that are specialized in type I interferon (IFN) production. pDCs are key players in the antiviral immune response and serve as bridge between innate and adaptive immunity. Although pDCs do not represent the main reservoir of the Human Immunodeficiency Virus (HIV), they are a crucial subset in HIV infection as they influence viral transmission, target cell infection and antigen presentation. pDCs act as inflammatory and immunosuppressive cells, thus contributing to HIV disease progression. This review provides a state of art analysis of the interactions between HIV and pDCs and their potential roles in HIV transmission, chronic immune activation and immunosuppression. A thorough understanding of the roles of pDCs in HIV infection will help to improve therapeutic strategies to fight HIV infection, and will further increase our knowledge on this important immune cell subset.

1. Introduction

Plasmacytoid dendritic cells (pDCs) are one of the two principal subsets of human dendritic cells (DCs). The term “plasmacytoid” refers to their plasma cell-like morphology, due to an abundant cytoplasm with a well-developed endoplasmic reticulum. They differ in morphology, phenotype and function from myeloid DCs (mDCs, also referred to as conventional or classical DCs). Several pDCs-specific surface markers have been established, in particular human blood dendritic cell antigen (BDCA)-2 and BDCA-4, immunoglobulin-like transcript 7 (ILT7) and IL3Rα (CD123).

The discovery and identification of pDCs is the result of converging studies that date back to 1950s. In 1958, a specific cell type with a plasma cell-like morphology was identified in T cell areas of reactive human lymphoid tissue. They were shown to express the T cell-associated marker CD4, MHC-II, but lacked CD3, B cell lineage (CD19 and CD21) or myeloid (CD13, CD14, CD11c) markers [1]. Several decades after their initial description, Facchetti and colleagues termed them as either “plasmacytoid T cells” or “plasmacytoid monocytes” based on their morphology and location [2]. Independently, Alm and colleagues [3,4], Fitzgerald-Bocarsly and colleagues [5,6], and Trinchieri and colleagues [7,8] identified a specific minor subset of human peripheral blood leukocytes capable of producing high-level of interferon alpha (IFN-α). These cells were labelled as “natural IFN-producing cells” (NIPC) and, like plasmacytoid monocytes, they did not express markers of T, B, monocyte, or natural killer (NK) cells. The identity of these cells as dendritic cells came from Liu and colleagues in 1997, when they identified a subset of $CD4^+CD3^-CD11c^-$ cells with plasmacytoid morphology in the T cell area of human tonsils; they called these cells type 2 DC precursor (pre-DC2) based on their maturation into Th2-inducing DC upon culture with IL-3 and CD40L [9]. However, it was clear that these cells were distinct from mDCs, which were not the main producers of IFN-α. It was only in 1999 that Siegal and colleagues demonstrated that plasmacytoid monocytes, NIPC and pre-DC2 were the same cellular entity now known as plasmacytoid dendritic cells [10,11].

Numerous studies elucidate pDCs functions in different types of infection, autoimmune diseases and in maintenance of tolerance. This review will be focused on the recent advances in the understanding of the pDCs role in Human Immunodeficiency Virus type 1 (HIV-1) infection. We begin by introducing the pDCs biology, including their development, localization and trafficking in the body and their role as effectors at the interface between innate and adaptive immunity.

Abbreviations: AIDS, Acquired Immune Deficiency Syndrome; APC, antigen presenting cells; CDP, common DC progenitor; DCs, dendritic cells; Env, envelope; HEV, high endothelial venules; HIV-1, Human Immunodeficiency Virus type 1; IDO, indoleamine-pyrrole 2,3-dioxygenase; IFN, interferon; IPC, interferon producing cells; IRF, interferon regulatory factor; ISG, interferon-stimulated genes; LN, lymph node; mDCs, myeloid dendritic cells; NK, natural killer; pDCs, plasmacytoid dendritic cells; SIV, Simian Immunodeficiency Virus; TLR, toll like receptor; T_{regs}, regulatory T cells

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2. PDCs origin and development

Originally described in humans, pDCs have also been characterized in other mammalian species including mice, rats and monkeys [12–16]. The characterization of pDCs in mice was of particular importance to garner data regarding developmental origin and transcriptional control of the pDCs lineage (reviewed in ref. [17]). Ever since the identification of pDCs as a distinct cell type, their origin and lineage affiliation has been controversial, in part because these cells show features of both lymphocytes and dendritic cells. One of the earliest investigation placed pDCs in the myeloid lineage due to their expression of the receptor for GM-CSF [18], whereas others proposed a lymphoid lineage based on their expression of gene products associated with lymphocytes including pre-T cell receptor α, SpiB and a partially rearranged immunoglobulin heavy chain [19]. However, the current view is that these cells can be derived from either myeloid or lymphoid precursors. Notably, the depletion of lymphoid progenitors by estrogen treatment does not affect pDCs, suggesting that the latter develop largely from non-lymphoid cell sources [20].

A common DC progenitor (CDP, or pro-DC) that generates both pDCs and mDCs, but not other cell lineages, has been identified in the bone marrow. The CDP is characterized by the expression of some cytokine receptors, in particular: Fms-like tyrosine kinase 3 (Flt3, also known as CD135), macrophage colony-stimulating factor receptor (M-CSFR; also known as CD115) and by low levels of the receptor tyrosine kinase KIT (CD117) [21–23]. The development program directing pDCs vs mDCs differentiation starts at the CDP stage through two developmental systems. Flt3 and its ligand (Flt3L) are essentials for pDCs and DCs development, controlling the expansion of common progenitors and peripheral DC homeostasis [24]. It is noteworthy that pDCs are more dependent on Flt3 signalling than most mDCs, as in its absence pDCs population is selectively reduced in the lymphoid organs and bone marrow of mice [25,26]. This suggests a crucial role of Flt3 signalling in pDCs development, possibly promoting their differentiation or mature survival after the common progenitor stage. Flt3L acts through the activation of signal transducer and activator of transcription 3 (STAT3) and phosphoinositide 3-kinase (PI3K)-dependent activation of mammalian target of rapamycin (mTOR) [27,28]. Recently, it was shown that Flt3L and type I IFN act synergistically to promote pDCs development from common lymphoid progenitors by inducing upregulation of Flt3 [29]. In addition to Flt3 signalling, M-CSF (also known as CSF-1) supports the generation of pDCs, while the growth factor GM-CSF inhibits it. The latter induces STAT5-mediated signalling abolishing pDCs related gene expression in $Flt3^+$ progenitors and inhibiting the interferon regulatory factor 8 (IRF8), which is crucial for pDCs development [13,30]. Another transcriptional factor, whose upregulation is reported to be essential for committing CDP to the pDCs lineage is E2-2, the basic helix-loop-helix E protein that directly binds to the promoters of several pDCs expressed genes such as *BDCA2*, *ILT7*, *IRF7*, *IRF8* and *SPIB* [31–33]. E2-2 is expressed abundantly in murine and human pDCs and scarcely in mDCs and other cell types. Consistent with this, the deletion of E2-2 results in the loss of pDCs-associated markers, spontaneous differentiation into mDC-like cells, upregulation of MHC class II and an increase in the ability to prime T cells [32]. On the contrary, other cell types (including mDCs and B cells) developed normally. The activity of E2-2 is antagonized by the repressor Id2, essentially absent in CDP, pre-pDCs and pDCs but prominently expressed in mDCs [34]. Thus, continuous E2-2 expression and low levels of Id2 are required to maintain the lineage identity of pDCs and to prevent their spontaneous differentiation into mDC-like cells. However, E2-2 represents only one of several transcription factors and other regulatory molecules (e.g., microRNAs) that are implicated in different aspects of pDCs development and expression program (reviewed in ref. [17,35]).

3. Localization and trafficking of pDCs

Initial studies showed that pDCs migration is quite different from that of mDCs. The latter, following their development, leave the bone marrow to give rise to resident and migratory DCs. Instead, pDCs are mostly confined to primary and secondary lymphoid organs (lymph nodes, spleen), and they are found in rare numbers in peripheral tissues under homeostatic conditions. Moreover, unlike mDCs that reach lymph nodes (LNs) via afferent lymphatic vessels, pDCs circulate through the body via the bloodstream and enter lymphoid tissues directly via high endothelial venules (HEV) [36]. In inflammatory conditions, pDCs leave the bloodstream and accumulate at the site of infection, where they can secrete IFN-α, take up antigens and migrate to draining LNs for antigen presentation [37]. pDCs can also accumulate in inflammatory sites, as in the case of systemic lupus erythematosus (SLE) or psoriasis, and infiltrate primary and malignant melanoma, ovarian and breast carcinoma [38]. The recruitment into these sites suggests that pDCs may contribute to the ongoing inflammatory response through the release of cytokines and chemokines [39] or, alternatively, to the induction of tolerogenic responses [40].

Which factors influence pDCs migration? CD62L (L-selectin), PSGL1, β1 and β2 integrins and multiple chemokines receptors, such as CXCR4, CCR7, CXCR3, CCR5, CCR2 and CCR6 [41,42] are involved and promote recruitment in steady-state and during inflammation. The migration of pDCs to lymphoid tissue is promoted by expression of L-selectin (non-inflamed states) or E-selectin (inflamed states) in HEV [43], while pDCs egress from the bone marrow into the blood is dependent on CCR5 and CCR2. The high expression of CCR7 at the surface of pDCs promotes the migration toward increased concentration gradient of its ligand CCL9 and CCL21 abundantly secreted by LNs, thus contributing to pDCs homing in LNs [42]. Moreover, pDCs employ both CCR7 and CXCR4 as critical chemokine receptors to migrate into the splenic white pulp under steady-state conditions [44]. CXCR4 also promotes pDCs recruitment to tumors that produce CXCL12 [40].

pDCs express CD62L, PSGL-1, β1/β2 integrins and the chemokine receptors CCR5, CXCR3 and CCR7, which mediate adhesion and chemotaxis to peripheral LNs and the splenic white pulp under normal and/or inflammatory conditions [45,46]. CCR6 and CCR10 are expressed by a subset of human tonsil pDCs and enable migration to inflamed epithelia producing CCL20 and CCL27 [47]. CCR9 and its ligand CCL25 promote trafficking of peripheral pDCs to the thymus and are required for pDCs recruitment to the small intestine under both normal and inflammatory conditions [48,49]. MAdCAM-1, β7 integrin and CD103 also influence pDCs trafficking to the gut [50]. In addition to chemotactic chemokines, pDCs can be recruited also in response to signals associated with inflammation and tissue damage, such as IL-18, thanks to the engagement of receptors for chemerin (ChemR23), adenosine (A1-R) as well as the anaphylatoxins C3a and C5a [51,52]. We discuss later on the crucial role of pDCs recruitment at the site of HIV entry, where the presence of inflammatory pDCs at the site of viral transmission seems to fuel HIV spread rather than limit it even if the secretion of the CCR5 ligands CCL3 and CCL4 by HIV-activated pDCs could limit viral spreading.

4. PDCs: effectors at the interface of innate and adaptive immunity

PDCs are key players in the early antiviral response thanks to the substantial production of type I and III IFN in response to viral RNA or DNA through activation of Toll like receptor (TLR)-7 and -9. In addition to their role in antiviral immunity, recent studies suggest that pDCs also play an important role in antifungal immunity (for a comprehensive review see ref. [53]). Furthermore, pDCs can act as antigen-presenting cells (APCs), a process typically referred to as “priming”. Although pDCs are generally thought to be less efficient compared to mDCs, they can efficiently induce memory $CD4^+$ and $CD8^+$ responses when