Review

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Trafficking properties of plasmacytoid dendritic cells in health and disease

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Plasmacytoid dendritic cells (PDCs) represent a subset of circulating leukocytes characterized by the ability to release high levels of type I interferon (IFN). Under homeostatic conditions PDCs are confined to primary and secondary lymphoid organs. This is consistent with the restricted profile of functional chemotactic receptors expressed by circulating PDCs (i.e. CXCR4 and ChemR23). Accumulation of PDCs in non-lymphoid tissue is, however, observed in certain autoimmune diseases, allergic reactions and tumors. Indeed, PDCs are now considered to be involved in the pathogenesis of diseases characterized by a type I IFN-signature and are considered as a promising target for new intervention strategies. Here, current knowledge of the molecular mechanisms involved in the recruitment of PDCs under homeostatic and pathological conditions are summarized.

Background on PDCs: history and function

The cell now recognized as a plasmacytoid dendritic cell (PDCs) was originally described as a "lymphoblast" on the basis of its morphological features. It was subsequently renamed "T-associated plasma cell" due to the abundance of rough endoplasmic reticulum, "plasmacytoid T cell" by reason of CD4 expression, and "plasmacytoid monocyte" for the expression of some myelo-monocytic markers in the absence of B- and T-cell specific antigens [1]. The function of PDCs remained completely unknown until it was reported that PDCs represent a subset of dendritic cells (DCs) [2], and that they correspond to the natural type I interferon (IFN)-producing cells [3,4].

PDCs originate in the bone marrow, from both myeloid and lymphoid precursors, although myeloid derivation is predominant, where a dendritic cell (DCs) progenitor gives rise to PDCs and classical "myeloid" DCs (MDCs) [5,6]. PDCs can differentiate into MDCs after stimulation and genome-wide analysis showed that the gene expression profile of PDCs is closer to MDCs than to other hematopoietic cells [7,8]. The development of both PDCs and MDCs depends on Fms-like kinase 3 ligand (Flt3L), but the E2-2 transcription factor is uniquely required for PDCs differentiation [9,10].

Peripheral human PDCs have a unique cell surface phenotype: they lack B cell, T cell, myeloid cell, and NK cell lineage markers, and express CD4, CD123 (IL3Rα), CD303 (BDCA2), ILT3 and ILT7 [9]. Among these molecules, BDCA2 and ILT7 are highly specific for PDCs. These cell surface receptors use the transmembrane adaptor protein FcεRIγ chain, inhibit type I IFN and PDCs inflammatory chemokine production upon engagement by antibodies or ligands, and are down-regulated upon PDCs activation [11]. In addition, an anti-CD303 monoclonal antibody currently represents the most specific marker to detect PDCs on tissues sections (Figure 1) [12].

The dichotomous function of PDCs, i.e. production of type I IFN and DCs differentiation [13], is associated with distinct morphological and structural changes, as well as a shift of the transcriptional machinery [14,15]. In particular, as PDCs differentiate to DCs they lose the capacity to produce type I IFN and upregulate MHC class I and II and the T-cell costimulatory molecules CD40, CD80 and CD86 [2,16,17]. PDCs are the major cellular source of type I IFN (especially IFN-α) [3], which induces a strong antiviral state [17,18]. The main PDCs pathogen recognition receptors reside in the endosomes and consist of Toll-like receptors (TLR)-7 and -9, whose engagement leads to powerful type I IFN secretion, followed by DCs differentiation [15,19,20]. TLR-7 and TLR-9 respond to viral RNA and DNA that reach endosomes upon cell infection or autophagy [15]. In addition, these receptors can detect self-DNA in the context of autoimmunity, especially in combination with proteins (such as the natural antimicrobial peptide LL37, anti-self DNA antibodies and the High mobility group box 1/HMGB1 protein), that form complexes with extracellular self-DNA, preventing its degradation and promoting the intracellular transport and prolonged association with endosomes [15,21]. The master mediator of type I IFN production, occurring downstream of TLR-7/9 signalling, is the transcription factor IRF7, whose constitutive expression by PDCs may also explain their robust production of this cytokine upon activation [9]. In addition to BDCA2 and ILT7, other surface receptors (e.g. NKp44, DCIR) negatively regulate the amplitude of the type I IFN response by PDCs, while others behave as activators (e.g. FCγRIIa/CD32 and CD300a/c).

In addition to type I IFN, PDCs produce other cytokines, including TNF-α IL-6, and CXCL8 [17,22], and inflammatory chemokines such as CXCL9, CXCL10, CCL3, CCL4, and CCL5 [20,23]. Thus, PDCs influence cells of both innate and adaptive immune responses [17]. Type I IFN

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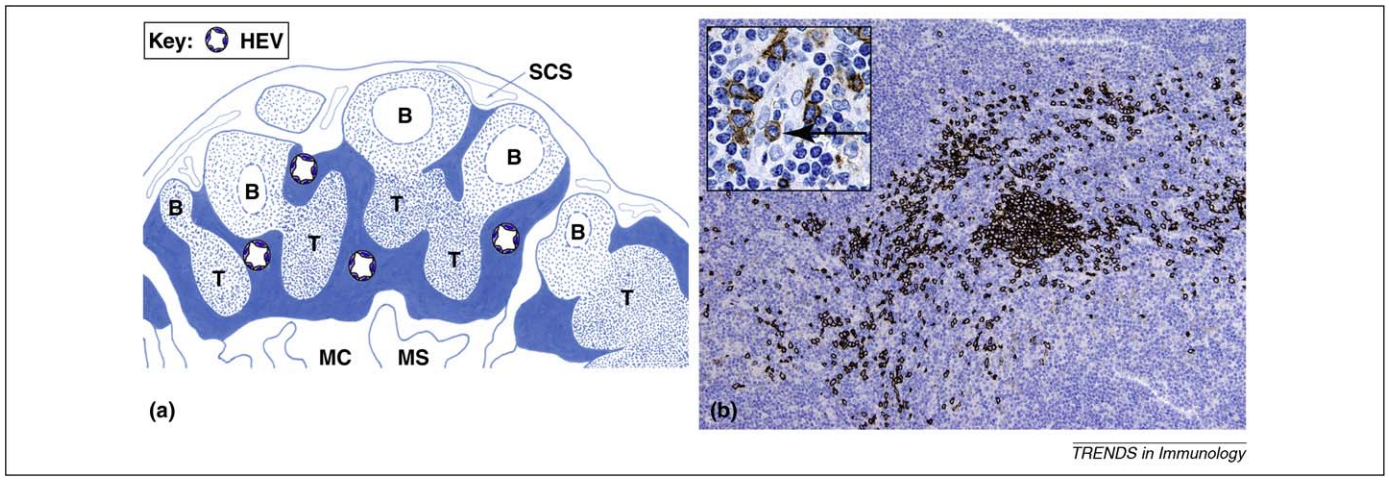

Figure 1. Localization and detection of PDCs in human lymph nodes. **(a)** PDCs localize in lymph node compartments (filled blue) typically located in areas surrounding B follicles (B) in the cortex and T nodules (T) in the paracortex. In these areas, PDCs localize in proximity to high endothelial venules (HEV); (SCS: subcapsular sinuses, MC: medullary cord; MS: medullary sinuses). **(b)** PDCs are specifically detected in formalin fixed and paraffin embedded tissues using an anti-BDCA2/CD303 monoclonal antibody (moAb). The figure shows BDCA2-positive PDCs distributed as clusters and dispersed cells; the inset shows a single PDCs within the lumen of a high endothelial venule. BDCA-2 is not expressed by other cells, and this completely circumvents the issue of specificity encountered when other antigens are targeted. For instance, anti-CD123 moAb, largely used in the past to stain PDCs in tissue sections, cross-reacts with other cell types, such as endothelial cells, sinus lining cells and activated macrophages (e.g. epitheliod macrophages in granulomas).

might have an autocrine role on PDCs, consequently amplifying type I IFN secretion and inducing a state refractory to viral infections [16,20]. PDCs-derived type I IFN also regulates T-cell function including long-term T-cell survival and memory T-helper 1 polarization, CD8+ T-cell cytolytic activity and IFN-γ production [20]. PDCs also increase NK cell-mediated cytotoxicity and IFN-γ production, induce differentiation and maturation of MDCs and, together with IL-6, induce the differentiation of B lymphocytes into immunoglobulin-secreting plasma cells. Finally, inflammatory chemokines can attract activated T cells to sites of inflammation [20]. Interestingly, it has been shown that PDCs can induce apoptosis of tumour and virus-infected cell lines, either directly by secreting TRAIL (TNF-related apoptosis-inducing ligand) upon activation, or indirectly via the effect of type I IFN on other cytotoxic cells [24,25]. PDCs contain abundant granzyme B, but the role of this enzyme as a cytotoxic molecule remains elusive, because PDCs, in contrast to other cytotoxic cells, lack the pore-forming perforin [1,26].

Freshly isolated human PDCs are poor antigen-presenting cells, but upon activation by viruses, CpG, IL-3 and CD40L they acquire full DCs morphology and phenotype, presenting antigen to CD4+ T cells, and cross-priming of CD8+ T cells, albeit less efficiently than classical MDCs [17,27–29]. The DCs features of PDCs *in vitro* are not demonstrated easily on tissue PDCs [1], possibly results from loss of specific PDCs markers (e.g. BDCA-2/CD303) upon activation and differentiation, or the lack of a complete maturation state by tissue PDCs. More recent data have shown that PDCs, especially when unstimulated or alternatively stimulated, or in certain anatomical locations, act as tolerogenic instead of immunogenic cells. This may occur via different mechanisms, such as secretion of granzyme B (GrB) to impair T-cell proliferation [30] or by production of indoleamine-2,3-dioxygenase (IDO) to promote regulatory T-cell generation [31,32].

Taken together, these observations indicate that PDCs are flexible in directing T cell responses and support the idea that PDCs and MDCs are not just quantitatively different, but complementary, exerting coordinated and independent control of T cell proliferation and differentiation that may provide fine tuning and plasticity to immune responses [27,29].

Molecules involved in PDCs trafficking

Pioneering work by Cella and colleagues suggested that PDCs could migrate directly from the blood compartment into lymph nodes, across high endothelial venules (HEV) [3] (Figure 1). This hypothesis was subsequently confirmed, in the mouse. Indeed, PDCs express lymph node homing molecules such as L-selectin and PSGL1, the counter-ligand of P- and E-selectins [33,34]. In addition, PDCs express CXCR4, the receptor for CXCL12, which is a homeostatic chemokine expressed by HEV [3,33,35–37]. L-selectin and CXCL12 are apparently central in inducing PDCs migration, as shown by the reduced number of PDCs in the secondary lymphoid organs of mice defective for L-selectin and DOCK2, a molecule involved in CXCR4 signalling in PDCs [34,38]. CXCL12 may also have a role in the development of PDCs in bone marrow stromal cell niches [39]. Under reactive conditions, additional molecules are involved in mouse PDCs homing to lymph nodes, such as E-selectin and the chemokine receptors CCR5 and CXCR3 [36,37,40]. Consistent with *in vivo* data, mouse PDCs migrate *in vitro* in response to CCL3 and CCL5, and to CXCL9 and CXCL10, the respective CCR5 and CXCR3 ligands. PDCs also express the chemokine receptor CCR9 and migrate to the CCR9 ligand CCL25 to home to the small intestine [41] (Figure 2).

PDCs purified from human blood express an extensive profile of chemotactic receptors including the CC chemokine receptors, CXCR3 and CXCR4 [35]. However, with the exception of CXCR4, these receptors are apparently non-functional in transwell-based chemotaxis assays [35,42,43]. Although unable to directly induce PDCs migration, CXCR3 ligands increase the chemotactic response to CXCL12 [42,43]. Furthermore, CXCR3 ligands

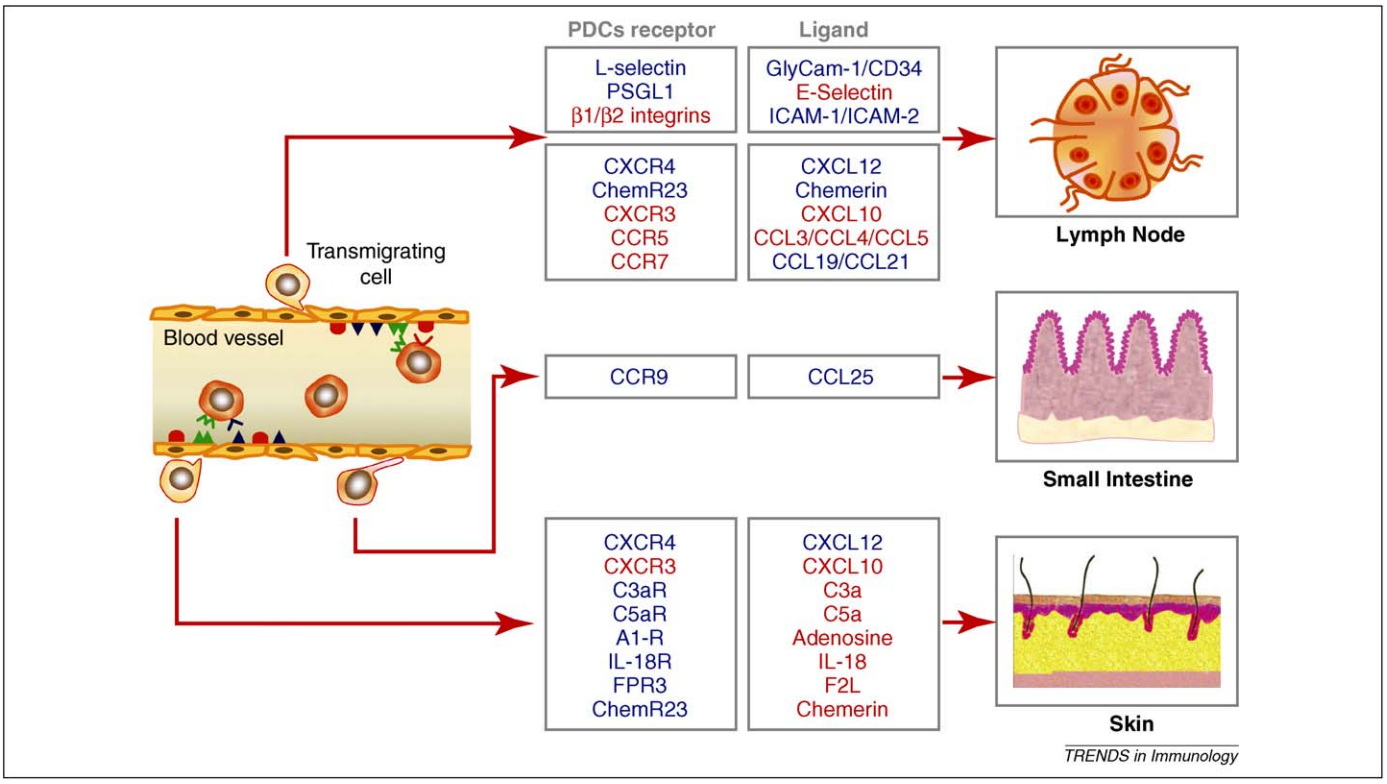

Figure 2. Trafficking properties of circulating PDCs. Blood PDCs constitutively express high levels of L-selectin, CXCR4 and ChemR23. The ligands for these receptors are expressed by high endothelial venules (HEV); therefore, these molecules may account for the homeostatic recruitment of circulating PDCs to lymph nodes. Under inflammatory conditions other molecules become involved in this process, such as PSGL-1, the ligand for E-selectin, β1 and β2 integrins and the chemokine receptors CCR5 and CXCR3. CCR7 is upregulated following activation, and is likely to be involved in the migration of mature PDCs through the engagement of its ligands CCL19 and CCL21, presented by HEV. Under pathological conditions, PDCs are also recruited to peripheral tissues; the molecules involved in this process have not been characterized directly. However, PDCs are known to migrate in response to chemokines and other chemotactic factors that are produced, or upregulated, during inflammation. In the mouse, CCR9 and its ligand CCL25, are responsible for the recruitment of PDCs to the small intestine both under homeostatic and inflammatory conditions. The different colors indicate the molecules involved in homeostatic (blue) and inflammatory (red) PDCs trafficking; also, constitutive molecules may be upregulated during inflammatory reactions. In the blood vessel, adhesion molecules and their respective counter-receptors are indicated in red or blue, chemotactic factors and their receptors in green. Evidence for the involvement of the different molecules is sometimes related only to mouse or human work; see the text for details and related references.

are fully competent in inducing PDCs adhesion and migration when immobilized on heparan sulphates expressed by endothelial cells [33]. Two recent reports showed that PDCs purified from patients with chronic hepatitis C, or exposed *in vitro* to IFN-α, acquire the ability to respond to CCR2, CCR5 and CXCR3 ligands [44,45]. These results suggest that under appropriate stimulatory conditions, additional chemokine receptors may be involved in human PDCs recruitment. In line with this hypothesis, leukemic PDCs express a wider profile of functional chemokine receptors than the normal circulating counterpart [46]. In addition to chemokines, adenosine and F2L, two agonists released by damaged tissues at the site of inflammation, have the ability to induce PDCs migration through the engagement of the adenosine receptor A1 and FPR3 (the formyl peptide receptor formerly known as FPRL2), respectively [47,48]. It was also reported that like MDCs, PDCs have functional receptors for the anaphylatoxins C3a and C5a [49]. Finally, IL-18 induces the migration of PDCs and promotes the differentiation of Th1 lymphocytes [50]. All these data suggest that, in addition to chemotactic cytokines, signals associated with inflammation and tissue damage may contribute to recruitment of PDCs to pathological tissues.

Recruitment of PDCs to non-lymphoid tissues is observed in certain pathological conditions, such as autoimmune diseases (i.e. lupus erythematosus disease, psoriasis and rheumatoid arthritis) [1,51,52], allergic diseases (i.e. contact dermatitis and nasal mucosa polyps) [53] and in tumors [2,54] (Table 1). However, the mechanisms underlying this effect are elusive. Recently, we and others have characterized chemerin, the ligand of ChemR23, as a new chemotactic factor for PDCs (Box 1) [55,56]. Chemerin is expressed by HEV in reactive lymph nodes and by activated dermal blood vessels in autoimmune skin lesions [55,57,58]. Therefore, current evidence strongly implicates the ChemR23/chemerin axis in the regulation of human PDCs trafficking to lymph nodes and to pathological tissues.

Of note, although the migration of blood PDCs to secondary lymphoid organs and to peripheral tissues has so far attracted the most attention, there is evidence that PDCs may also enter lymph nodes via the lymphatic route [59]; further studies are needed to address this issue in humans.

Accumulation of PDCs in human diseases: recent advances

Similar to other human leukocytes, PDCs can undergo neoplastic transformation (Box 2) and accumulate during some inflammatory pathological conditions [1,27]. Pathologists can easily detect human PDCs on archival tissues using anti-CD303 as a marker and can screen for their

Table 1. Pathological conditions characterized by PDCs tissue infiltration[1,12,27].

Disease	Tissues
Accumulation of ''pathogenetic'' PDCs with increased function	
Lupus erythematosus	Skin and kidney
Lichen planus	Skin and mucosa
Psoriasis	Skin
Rheumatoid arthritis	Synovial tissue
Nasal allergy	Nasal mucosa
Accumulation of PDCs with defective function	
Melanoma	Primary and metastatic tumor site
Carcinomas (ovary, breast, head and neck)	Primary tumor site
Accumulation of PDCs with anti-viral/ anti-tumor response	
Human Herpes Virus infection	Skin
Human Papilloma Virus infection	Skin
Molluscum Contagiosum Virus infection	Skin
EBV-infection (Hydroa vacciniformis)	Skin
Imiquimod-treated carcinomas, melanoma and viral infection	Skin
Accumulation of PDCs (function unknown)	
Kikuchi's lymphadenitis	Lymph node, skin
Hodgkin's lymphoma	Lymph node
Castleman's disease, hyalin vascular type	Lymph node
Granulomas (infectious, sarcoidosis)	Lymph node
Cutaneous Pseudolymphomas	Skin
Cutaneous Marginal Zone Lymphomas	Skin
Decrease in number/function of PDCs	
Human Immunodeficiency Virus infection	Peripheral Blood
Hepatitis C Virus infection	Peripheral Blood
Solid tumors and haematologic malignancies	Peripheral Blood

A wide spectrum of human diseases including infection, cancer and autoimmunity is associated with accumulation of PDCs in lymphoid and peripheral tissues, or reduction of PDCs in peripheral blood. For many of these diseases, compelling evidence supports a pathogenic role of PDCs accumulation, mainly related to either the increase or the reduction of PDCs function. Alternatively, PDCs accumulation might exert an adjuvant immune function, as in viral infection, and in Imiquimod-treated cancers. In many other pathologies, information available is still limited and PDCs function largely unknown.

occurrence in large-scale clinical studies. A number of pathological conditions can be characterized by the presence of PDCs (Table 1). In this section we summarize findings for several of these pathologies where abnormalities in PDCs are thought to contribute to disease.

Autoimmune inflammatory dermatoses as a paradigm of PDCs-associated disease models

PDCs are normally absent from the skin. However, they accumulate in some inflammatory dermatoses, where they organize local immune responses [60]. The best characterized examples of these conditions are lupus erythematosus (LE) [61] and psoriasis [62]. Conversely, in other skin diseases, such as atopic dermatitis, PDCs are not recruited to the inflamed tissue [53]. In LE and psoriasis, cutaneous accumulation of PDCs is associated with the local activation of the chemerin/ChemR23 axis (Box 1) [55,57,63]. In particular, chemerin is strongly induced in keratinocytes, dermal vessels and fibroblasts, whereas skin infiltrating PDCs strongly express ChemR23. The kinetics and distribution of cutaneous PDCs infiltration is different in these two pathological conditions. In psoriasis, PDCs infiltration is restricted largely to the dermis, and predominantly found in early phases of the disease [57,62]. In contrast, in LE skin lesions PDCs persist during the entire spectrum of the disease [63] and are located, not only in the dermis, but also at the dermo-epidermal junction in areas of epithelial cell damage. These findings suggest a novel view of the role of these cells in skin autoimmunity, where PDCs might coordinate the dermal immune reaction and sustain epithelial damage via secretion of cytotoxic molecules. In fact, cytotoxic damage is a major pathological event in the "interface" dermatitis found in LE, and similar changes,

Box 1. The chemerin/ChemR23 axis in inflammation

ChemR23 is a serpentine Gi-coupled receptor originally cloned by Parmentier and colleagues [91]. ChemR23 is expressed by antigen-presenting cells, such as MDCs, PDCs and macrophages, and by blood monocytes and NK cells [55,58,92]. In contrast to other chemotactic receptors, human ChemR23 maps to chromosome 12, and shows little homology with other receptors of the same family (e.g. 38%, 36% and 35% with C3aR, C5aR and FPR1, respectively). *In vivo*, ChemR23 is expressed in the lymph node by interfollicular MDCs and PDCs, by sinus macrophages and by germinal center macrophages. In inflamed skin, ChemR23 expression is mostly restricted to MDCs and PDCs [55]. Chemerin, the only natural ligand so far identified for this receptor, was originally purified from ovarian cancer ascites and rheumatoid synovial fluids, and corresponds to the product of the Tig-2 gene. This protein contains a cystatin fold, and, similar to other family members, it is produced as an inactive precursor that is activated through proteolytic cleavage of the C-terminus by proteases released from neutrophils and proteases generated by the coagulation cascade or produced by bacteria [93]. *In vivo*, chemerin is produced by HEV and sparse perivenular spindle cells in the interfollicular area of the lymph node, and in inflamed skin, by activated blood endothelial cells, fibroblasts, and epithelial and mast cells. The anti-inflammatory lipid Resolvin E1 was shown to exert its function through interaction with ChemR23. In addition, chemerin proteolytically generated peptides possess anti-inflammatory activity *in vivo* [94,95]. Therefore, ChemR23 may also possess anti-inflammatory activities, as recently suggested in experiments testing a mouse model of lung inflammation [96]. CCRL2, an orphan serpentine receptor binds chemerin at the N-terminal in the absence of receptor signalling and internalization, and presents chemerin to ChemR23-positive cells *in vitro* [56]. This finding discloses a new potential role of chemerin in leukocyte recruitment. Chemerin was recently shown to be produced by adipocytes and to act as an autocrine differentiation and activation factor. Therefore the potential role of chemerin in the metabolism of adipose tissue represents a new area of active research [97].

Box 2. Tumors derived from PDCs

Proliferation of PDCs in tumors occurs under two distinct clinicopathological conditions: one is composed of morphologically mature PDCs that are barely distinguishable from their normal counterparts; the other, defined as blastic PDCs neoplasms (BPDCN) [98], consists of PDCs showing an immature morphology. *De novo* expression of antigens such as CD2, CD5 and CD7 has been reported in both conditions, but a more profound aberrant phenotype is typically found in BPDCN, with frequent loss of classical PDCs markers (such as CD68 and GrB) and expression of CD56 and TdT proteins [12]. Both conditions can be associated with myeloid neoplasms. In mature PDCs, proliferation is a constant finding [99], and the myeloid neoplasm is generally represented by chronic myelomonocytic leukemia. The clonal relationship between PDCs and myeloid leukaemia is supported by FISH analysis that demonstrated identical cytogenetic abnormalities in the two cell populations [99,100]. On the other hand, only ten to twenty per cent of BPDCN cases are associated with a myeloid neoplasm, generally consisting of an acute or chronic leukemia with monocytic differentiation that may be associated with an underlying myelodysplastic syndrome. This myeloid leukemia can precede, coexist or develop subsequently to BPDCN.

Mature PDCs tumors manifest as nodular accumulations of PDCs, especially in lymph nodes and bone marrow, while BPDCN typically presents with multiple skin lesions that rapidly spread to bone marrow and multiple organs. The peculiar skin tropism of PDCs in BPDCN has been related to their expression of the neural cell adhesion molecule CD56 and of the skin homing receptor CLA. In addition, leukemic PDCs express the chemokine receptors CXCR3, CXCR4, and CCR7, whose respective ligands CXCL9, CXCL12, and CCL19 are concomitantly found in cutaneous sweat glands and follicle epithelium [46].

albeit to a lesser extent, are found in lichen planus, where PDCs co-localize at the dermo-epidermal junction with NK cells [58]. These observations point toward a role for PDCs as effector cells. In all these dermatoses, production of high levels of type I IFN by PDCs is pathogenic. In LE, type I IFN is induced in response to nucleic acid-containing immunocomplexes internalized through Fc receptors. In psoriasis, a recently reported mechanism of PDCs activation is based on the production of the endogenous antimicrobial peptide LL37 by damaged keratinocytes. LL37 is able to bind and convert self-DNA or self-RNA into potent TLR-dependent PDCs triggers [64,65]. Remarkably, LL37 is induced strongly in the lesional epidermis of psoriasis biopsies [66]. Therefore, locally activated PDCs acquire the ability to release large amounts of type I IFN, that in turn sustains B and T cell autoimmune responses.

Tumor-associated PDCs: new players in cancer immunity

Type I IFN plays a prominent role in limiting tumor cell growth, and several human cancers are treated with type I IFN [67]. However, the role of PDCs in the control of tumor cell proliferation is still questionable. In a clinical study, TLR-dependent activation of PDCs contributed to rejection of cutaneous tumors. In this condition, PDCs produced type I IFN, expressed TRAIL and localized together with T cells and NK cells [25]. Interestingly, a new cell population of $CD11c^+$ myeloid DCs endowed with tumoricidal potential was identified in these lesions [25]. The relevance of PDCs in cancer immunosurveillance has been recently shown in mice [68,69], where TLR9-activated PDCs lead to the regression of subcutaneous B16 melanoma tumors, by orchestrating the sequential activation of NK cells, MDCs and $CD8^+$ T cells.

The characterization of PDCs has been performed in a variety of human neoplasms [54,70–72]. However, the potential impact of PDCs for cancer immunity is based largely on *in vitro* studies of circulating PDCs, while PDCs detectable at the tumour site (tumor-associated PDCs, TA-PDCs) are poorly characterized. Available data on TA-PDCs indicate that they are defective in type I IFN production, and secrete indoleamine 2, 3-dioxygenase (IDO) [73]. It should be noted, however, that the possibility that PDCs may produce IDO has been questioned [20]. The production of type I IFN *in vitro* can be inhibited by cross-linking surface receptors such as CD303, NKp44 and ILT7 [20]. The identity and tissue source of the natural ligands for CD303 and NKp44 remain elusive. In contrast, ILT7 ligands, including BSTA2, are expressed by several human cancer cell lines, and inhibit strongly the production of type I IFN by activated PDCs [11,74]. A novel mechanism was proposed recently, where PDCs may exert tolerogenic, instead of immunogenic, functions. In fact, it was reported that IL-10 can induce human circulating PDCs to suppress T-cell proliferation through the secretion of GrB [30]. This finding is of interest given the high amounts of IL-10 produced in the tumour microenvironment and might explain the pro-tumorigenic effect of this cytokine observed in some experimental conditions [75].

In summary, properly activated PDCs are naturally endowed with anti-tumor activity, but the tumor microenvironment can subvert this property. There are some data on the migration mechanisms adopted by TA-PDCs, with the CXCR4/CXCL12 axis being involved in the migration to ovarian cancer and melanoma [54,71]. The availability of new experimental models and new strategies for depleting PDCs *in vivo* will be extremely helpful in defining the trafficking properties and the role of PDCs in tumour growth.

Modulation of leukocyte recruitment by PDCs

The production of chemokines by DCs subsets represents an important level of immuneregulation [76,77]. As mentioned, the potential of PDCs to regulate leukocyte recruitment is mostly related to the ability of these cells to respond to viral infection with high levels of type I IFN production. HSV1-activated PDCs recruit T and NK cells through the production of CXCL9, CXCL10 and CCL4, and CD40-engagement further strengthens this response [78,79]. Exposure of PDCs to HIV-1 surface components triggers the secretion of the CCR5 ligands CCL3 and CCL4, suggesting a role of PDCs in limiting viral spreading [80]. In the lung, PDCs are among the earliest inflammatory cells to enter the bronchoalveolar space following influenza A virus infection [81], and support the recruitment of $CXCR3^+$ and $CCR5^+$ effector T cells through the local secretion of CXCL10 and CCL5 [82]. A protective role for C5a in allergic asthma has been linked to a shift in the MDC/PDCs ratio toward PDCs, with an accompanying decrease in CCL17 production [83]. Furthermore, PDCs depletion exacerbates respiratory syncytial virus lung immunopathology [84]. In indirect acute lung injury, PDCs are thought to control the recruitment of inflammatory

monocytes through the regulation of lung CCL2 production [85]. Also, PDCs-induced CXCL8 secretion might impact the recruitment of neutrophils into the lung during chronic obstructive pulmonary disease [86]. PDCs-derived CXCL10 was also shown to be responsible for recruiting $CXCR3^+$ T cells to cutaneous LE lesions [51], and the cerebrospinal fluid of patients with neuropsychiatric lupus [87]. In this context, PDCs have also been implicated in autoimmune diseases by promoting Th17 immune responses through the production of IL1β and IL23p19 [88,89]. Moreover, by secreting CCL4, PDCs might be involved in regulatory T cell recruitment to the tumor site, representing an additional mechanism for controlling immune function [90].

Concluding remarks

More than fifty years since the first description of the "enigmatic" cell population now known as PDCs, many aspects of PDCs biology still await clarification. The mechanisms that govern the *in vivo* distribution of these cells under homeostatic conditions remain elusive, and the biological role of PDCs in many diseases in which they are regularly detected is poorly understood. Paradoxically, more information is available on the involvement of PDCs in human inflammatory and neoplastic conditions than in experimental models, hampering the correct understanding of the molecular basis of PDCs activation. The new and more specific reagents now available to detect PDCs in human and mouse tissues will be instrumental in defining the role of PDCs in immune responses. Furthermore, the possibility to generate mice selectively depleted of PDCs will allow conceptual models about PDCs function to be probed *in vivo*. Therefore, it is likely that in the next few years we will be able to evaluate in a critical manner the available literature and to advance our current knowledge on the biological function of PDCs.

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