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Plasmacytoid pre-dendritic cells (pDC) from molecular pathways to function and disease association.

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Abstract: Plasmacytoid pre-dendritic cells (pDC) are a specialized DC population with a great potential to produce large amounts of type I interferon (IFN). pDC are involved in the initiation of antiviral immune responses through their interaction with innate and adaptive immune cell populations. In a context-dependent manner, pDC activation can induce their differentiation into mature DC able to induce both T cell activation or tolerance. In this review, we described pDC functions during immune responses and their implication in the clearance or pathogenicity of human diseases during infection, autoimmunity, allergy and cancer. We discuss recent advances in the field of pDC biology and their implication for future studies.

pDC: a history of mysteries

Plasmacytoid pre-dendritic cells (pDC) were first described in 1958 by pathologists Lennert K, and Remmele W, as a plasmacytoid cell (i.e harboring morphological/cytological features similar to plasma cells) located in the T cell areas of secondary lymphoid tissue[1]. The long road from that seminal discovery to our current understanding of pDC biology was paved with mysteries. Many of them have been solved in the past 20 years[2], the most important of which being their ability to produce large amounts of type I interferon (IFN) [3,4], and to differentiate into bona fide dendritic cells (DC) capable of stimulating T cells [5–7]. Some of them still remain, at least partially, unsolved: What is the respective contribution of innate versus adaptive functions of pDC in physiology and pathology? Which are the factors evoking immune activating versus immunoregulatory functions of pDC? Are PDC protective or pathogenic in some diseases, and is there a therapeutic potential in targeting pDC?

In this review, we will describe established features of pDC biology, and also discuss more recent and sometimes controversial work on pDC function. As the field has significantly moved towards the study of pDC in human diseases, we will devote approximately half of this review to pathological settings, such as infection, autoimmunity, allergy, and cancer. Focusing a review on human pDC is an additional reason to discuss more in depth the link with human pathology, which may differ in many aspects from mouse disease models. Also, there are a number of phenotypic and functional differences between human and mouse pDC, which may significantly impact their contribution to immune regulation in health and disease: i) mouse pDC express the B-cell marker B220, and the DC marker CD11c, both lacking from human pDC; ii) mouse pDC produce IL-12 in response to microbial stimulation, which is not the case for human pDC ([8] and see below). In most of the chapters below, we will essentially discuss studies specifically performed in the human system. We refer the

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readers to other reviews on pDC biology for more thorough information on mouse pDC (References [9,10]).

Defining features of human pDC

The pDC field has been very confusing at times, as illustrated by the number of names that pDC have been given (T-associated plasma cells, plasmacytoid T cells, plasmacytoid monocytes, pre-DC2/pDC2, IPC: Interferon-Producing Cells, plasmacytoid pre-dendritic cells, plasmacytoid dendritic cells). This, together with the morphological, phenotypical, and functional plasticity of pDC, extended the confusion to even their very nature, in particular their link to DC [11]. Since their discovery, pDC have been defined by a combination of characteristics, none of them being sufficient individually to discriminate them from other immune cells. PDC-defining features should clearly differentiate those that are absolutely required, and are linked to pDC "identity", and those that represent characteristics of lower specificity and sensitivity, depending on activation state, and/or anatomical location.

The first defining feature for pDC is their plasmacytoid morphology that is very easily recognized by any cyto-pathologist: round shape, eccentric nucleus, strongly basophilic peripheral cytoplasm, and a pale Golgi zone named the acroplasm[11]. This very peculiar morphological feature was the basis for the initial description of pDC in secondary lymphoid tissue[1], and should be seen as a required defining criterion, as illustrated by its presence in naming pDC ("plasmacytoid"). However, it is far from being 100% specific (and hence sufficient), since normal and malignant B cells can adopt a plasma cell like morphology[12], and so are some rare urothelial malignancies[13].

The second defining feature is the ability of pDC to produce very large amounts of type I IFN[14]. This should really be seen as a "potential", since the actual triggering of IFN production is highly dependent on the nature of the activating signals received by pDC ([14] and see below), i.e some stimuli strongly activate pDC without evoking their IFN production ability [5,6,15]. However, immune cells not having the potential to produce type I IFN in large amounts under the appropriate stimulatory conditions are not pDC.

The third feature is their ability to differentiate into bona fide DC, which was historically their first identified functional feature [5,6], hence their name of DC precursor or pre-DC [14,16]. The plasmacytoid and dendritic morphologies are mutually exclusive, and can be viewed as the two "faces" of pDC [11].

The fourth type of defining criteria are molecular markers. MHC class II molecules are always constitutively expressed by pDC, and are upregulated following activation[14], this being shared by all antigen-presenting cells (APC). Granzyme B was shown to be one of the most pDC-specific markers in normal peripheral blood[17], although this marker is not specific in other contexts, in particular during inflammation, when other cells may express it. CD303 (BDCA-2) was identified as a pDC-specific marker in healthy donors peripheral blood[18], but was recently shown to be also expressed by rare DC subsets, the preDC and DC5/AS DC, as revealed by single cell mRNAseq [17,19]. CD304 (BDCA-4, Neuropilin-1) is expressed by resting blood pDC[18], as well as preDC and DC5/AS-DC [17,19] and It can also be expressed by activated T cells and DC [20,21]. CD123 is often used to identify pDC, and is a very sensitive but poorly specific marker, shared by other DC and immune cell subsets [17,19,22].

Last, there are a number of "negative" pDC markers that help differentiate them from other related cells, for example CD11c (negative on pDC, and positive on other human DC and monocyte/macrophages), and AXL (negative on pDC and positive on DC5/AS DC) [17]. In summary, morphology and function are the most robust and conserved defining features of human pDC. These should be systematically assessed before concluding on the nature of any cell type suspected to correspond to pDC. Surface markers have been very useful to purify and quantify pDC in different settings, but should be used very cautiously because of their promiscuity, and variable expression levels during inflammation. We believe that the combined evaluation of several parameters is required to undoubtedly define a cell as pDC, and the selection of pDC-defining surface markers should be done very carefully, and integrate the latest single cell level studies in the field [17,19,22].

A specialized sensing machinery links innate stimuli to function

To understand pDC functions during immune responses, it is essential to characterize their sensing abilities. We will distinguish two main categories of receptors: i) pathogen sensors, located in intracellular compartments and; ii) innate receptors located on the cell surface.

Intracellular receptors for pathogen sensing

Although not exclusive to other functions, intracellular receptors have evolved for their ability to detect intracellular pathogens, such as viruses. High baseline expression of the endosomal Toll-Like Receptor (TLR)7 and 9 is one of the main features of human pDC [23,24]. Through TLR7, pDC recognize single-stranded viral RNA, synthetic imidazoquinolines (imiquimod, resiquimod, i.e R848) [25,26] and endogenous (self) RNA [27]; TLR9 allows the sensing of single stranded (ss)DNA viruses rich in CpG motives, such as herpes simplex virus 1 (HSV-1), HSV-2, as well as synthetic oligodeoxinucleotides (ODN) rich in unmethylated CpG motives [28]. The ability to sense ssDNA viruses through TLR9 distinguishes human pDC from other DC subsets [24], and this is a shared ability with the recently described blood "preDC" that were shown to express TLR9, and respond to TLR9 stimulation [19]. In contrast, human pDC lack TLR3 expression, a feature of blood conventional DC (cDC) 1 ($CD141^+$ DC), impeding recognition of double stranded RNA viruses through the endosomal pathway. Triggering of TLR7 and 9 from early endosomes activates the MyD88-IRF7 pathway, leading to the production of large amounts of type I IFN [28]. Constitutive high expression of the transcription factor IRF7 [29] is one of the mechanisms that endow pDC with their strong rapid type I IFN production potential [14,17]. Alternatively, TLR-ligand recognition from late endosomes, induces the activation of the MyD88-NFkB pathway, stimulating the production of pro-inflammatory cytokines and chemokines, as well as upregulation of costimulatory immune checkpoints [28]. In addition to the TLR-dependent sensing of nucleic acids, pDC can sense cytosolic DNA through the helicases DHX36 and DHX9 [30], members of the RIG-I-like receptors superfamily. This response is MyD88-dependent and can trigger both IFN and pro-inflammatory cytokines production [30]. It has been suggested as well that upon activation through TLR ligands, pDC can upregulate the expression of the cytosolic dsRNA sensor RIG-I and respond to 5'-triphosphate dsRNA [31]. PDC can sense cytoplasmic RNA from replicating viruses in yellow fever live vaccine YF-17D infection through RIG-I leading to IRF3 activation and IFN production [32]. In addition, it has been proposed for mouse [33] and human pDC [34] the presence of a functional cGAS-STING pathway sensing cytosolic DNA and inducing type I IFN production. Both TLRs and cytosolic sensors have the potential to initiate a strong type I IFN response by pDCs, and require prior internalization of the microbial nucleic acids

by mechanisms such as endocytosis [9], autophagy [35], or LC3-associated phagocytosis (LAP) [36]. The use of intra-cellular microbial sensing receptors in human pDC has several implications: i) it restrains the IFN production to specific intracellular pathogens, mostly viruses, which are themselves a target of IFN anti-viral effects; ii) it creates a specialization of pDC among other innate immune cells; iii) it prevents pDC activation by extra-cellular nucleic acids, which can be produced physiologically in certain forms of inflammatory cell death, especially from neutrophils [37]. Access of autologous nucleic acids to endosomal pDC compartments contributes to breaking tolerance to self-antigens, and development of auto-immunity [28] (*See below*)

Environmental sensing by surface receptors

PDC surface receptors can induce pDC activation and differentiation into mature DC capable of T cell priming, or can modulate pDC responses to TLR ligands. PDC express the IL-3R, whose specific α-chain CD123 has been largely used as a very sensitive (albeit non-specific) pDC marker [14]. PDC activation through IL-3 induces the upregulation of costimulatory checkpoint molecules such as CD80 and CD86 and their differentiation into mature DC capable of stimulating CD4+ T cell proliferation [5]. PDC also express the GM-CSFR, which shares the common β chain with the IL-3R, and respond to GM-CSF activation in a similar manner [15]. Both IL-3 and GM-CSF promote pDC survival and activation, without inducing IFN secretion. At a different level, autocrine/paracrine TNF-α can increase pDC maturation into DC when it is present in combination with a pDC survival factor [38]. PDC also express other cytokine receptors that can modulate their responses but do not function as a primary activating stimulus. PDC-derived IFN-α/β act through the IFN receptor (IFNAR) in an autocrine manner, establishing a positive feedback for IFN production [39]. On the other hand, IL-10 and TGF-β have been shown to diminish pDC-IFN secretion in response to TLR ligands [40,41]. Other cytokines that modulate pDC functions are IL-2, increasing TNF-α secretion on CD40L-activated pDC [42], and IL-18 promoting pDC chemotaxis [43].

Since IFNs are pleiotropic cytokines that can potentially induce exacerbated inflammation, their production should be tightly regulated. PDC express several inhibitory surface receptors that regulate type I IFN production by interfering with TLR7 and 9 signaling. Human pDC express the ITAM-associated receptors ILT7 [44,45], CD303 (BDCA-2) [46], FcεRIα[47] and, upon activation with IL-3, NKp44[48]. The ITAM receptors need association with an adapter molecule for signal transduction, and human pDC express the adapters DAP12 and the γ chain of Fc receptor ε (FcεRIγ). Another group of inhibitory receptors contain the intracellular ITIM domain, and human pDC express CD300 [49] and DCIR [50]. The presence of C-type lectin receptors as CD303 and DCIR may allow surface sensing of pathogen glycoproteins but their known functions is mostly associated to the modulation of pDC response to TLR triggering [9].

Although pDC activation in response to pathogens depends mainly on intracellular sensing, its function can be regulated by numerous surface receptors sensing self and non-self-derived signals. This allows controlling pDC responses by secreted host-derived factors, in order to support an orchestrated and properly regulated immune response.

PDC modulate immune responses through type I IFN

PDC have been named “Professional type I IFN producing cells” [14]. Within 6 hours of viral activation, 60% of human pDC transcriptome corresponds to type I IFN genes [8]. They can

produce up to 1000 times more IFN than any other blood cell [3,4]. Along with their robust production of type I IFNs, including IFN-α, IFN-β and IFN-ϖ, pDC can also express type III IFNS IL-28a (IFN-λ2), IL-28b (IFN-λ3) and IL-29 (IFN-λ1) in response to TLR7 or 9 ligands [51].
During viral infections, pDC-derived IFNs can directly act on infected cells, as well as surrounding neighbors through the ubiquitously expressed IFNAR. Downstream signaling from IFNAR induce the expression of IFN-stimulated genes (ISGs) participating in the control of viral replication and spread [52]. Furthermore, pDC-derived type I IFN has a critical role in modulating the innate and adaptive immune responses by inducing activation and maturation of several immune cell populations. IFN type I stimulates cDC maturation, as well as monocyte-derived DC differentiation promoting a Th1 type of immune response [53,54]. IFN enhances NK cell maturation and cytolytic activity, as well as IFN-γ secretion [55] and, together with pDC-secreted IL-6, promotes B cell differentiation into plasma cells [56]. In addition, pDC-derived type I IFN stimulates cDC and pDC antigen cross-presentation to CD8+T cells [57,58], and promotes CD4+ T cell polarization into Th1 cells [38,7] (Figure 1)

PDC differentiation into mature DC

Before the association between pDCs and "the natural type I IFN-producing cells" [14], pDC were shown to differentiate into mature DC in response to IL-3, or IL-3+CD40L [5]. Since then, this pDC functionality has been largely studied and brought us to the understanding that pDC role as APC is absolutely dependent on the type of stimulation and surrounding microenvironment.
Steady state pDC express intermediate levels of MHC II molecules that are highly upregulated upon activation, together with costimulatory molecules, and allow antigen presentation to CD4+T cells [7]. In the presence of IL-3, pDC-derived DC upregulate the costimulatory molecules CD40, CD80, CD86, CD83, and OX40L, among others, and preferentially drive regulatory Th2 responses from naïve CD4+ T cells [6]. GM-CSF- activated pDC induced a similar pattern of T cell-derived cytokines although producing more IFN-γ and less IL-10 [15]. In contrast, viral or CpG ODN-mediated pDC activation promotes a strong naïve CD4+T cell polarization towards Th1 cells [38,7,6]. This Th1 priming was shown to be promoted by type I IFN, in an IL-12-independent manner [14]. Furthermore, TLR-activated pDC can induce the generation of T regulatory (Treg) cells, a process favored by the expression of ICOSL [59,60]. This tolerogenic response has emerged as a way to prevent excessive inflammation that could be detrimental to the host during infection, but may also be involved during thymus Treg development [61] (Figure 1).
When studding rare immune populations, the possible contamination with other cell subsets has created confusion for the adjudication of specific immune functions. Human pDC where thought to produce IL-12 until clear demonstration that a contaminating myeloid population was the source of this production[8], a subject that has been confirmed at the single cell level [19]. Recent studies using single-cell mRNA sequencing and cytometry by time of flight (CyTOF) technologies described a rare circulating DC population named preDC or AS DC/DC5 [17,19]. This population appeared to shared commonly used pDC surface markers as CD123 (IL3R), CD303 and CD304 [17,19]; and was shown to be more potent T cell activator than pure pDC at the steady state and under certain types of activation. These data have raised concerns on the T cell activation potential of pDC. In order to interpret a possible contamination of pDC by preDC or AS DC/DC5, several points should be considered: i) preDC or DC5 only corresponds to a minor proportion among total blood APC, and could not

account for the global cell maturation observed as upregulation of costimulatory molecules when analysed at the single cell level; ii) the nature of the stimulus used to trigger pDC activation can switch from almost purely IFN secretion to pure DC maturation, iii) steady state non-activated pDC lack the intrinsic ability to induce T cell activation as well as to secrete IFN; iv) Last, when pDC are sorted using a gating strategy that excludes preDC or DC5, the ability of pDC to mature into DC and induce T cell activation is maintained, indicating that it is not due to a contamination [62,22]. In addition, we have recently shown that, after stimulation, only a fraction of the initial pDC population differentiates into a complete mature DC (P3-pDC) [62], probably diluting the effect on T cell proliferation. Ultimately, while under certain activation conditions pDC induce lower T cell proliferation and maturation than other DC subsets, its potential relevance in shaping the T cell responses should be considered. Its role as mature DC may be central depending on the nature of the pathogen and the pathways leading to pDC activation.

PDC express MHC I and MHC II and are capable of presenting both endogenous and virus-derived antigens to CD4+ and CD8+ T cells [63]. However, their low antigen internalization ability mediated by micropinocytosis and phagocytosis, together with their lower MHC II expression, make them less efficient than cDC with regard to presentation of exogenous antigens [63]. Several studies on human pDC indicated that they are effective in cross-presenting antigens to CD8+ T cells [64,65], to a similar extent as cDC2 (CD1c+) and cDC1 (CD141+) subsets [66].
Hence, pDC harbor key functions in both innate and adaptive immunity, controlled by complex, and highly context- and stimulus-dependent mechanisms. This has led to some controversies on whether adaptive pDC functions are being evoked in vivo in different physiopathological contexts, as opposed to IFN production being the main function of pDC [67,68]. We believe this is mainly due to the various contexts, stimuli, and disease models studied, rather than a cell-intrinsic exclusive involvement of pDC in innate versus adaptive immunity.

The multiple roles of pDC in infection

PDC are involved in different types of infections (such as virus, bacteria and fungi), their response being tightly linked to the underlying sensing mechanisms and downstream functional impact (*See above*).
PDC function against viruses is extremely important in the acute phase of the infection, to inhibit viral replication and prevent viral spreading, as for example in herpes simplex virus infection [69]. As the infection progresses, other host cell types, such as DC, monocytes, and macrophages, take part in IFN production [70]. Remarkably, individuals carrying mutations in the IRF7 gene, resulting in impaired pDC responses, are more susceptible to influenza virus infection [71]. However, type I IFN production by pDC may not be always beneficial during influenza infection, as shown by a mouse model wherein pDC over-activation induced massive and deleterious inflammation [72]. Whether this may contribute to pathology in severe forms of human influenza virus infections is not known.

In chronic viral infections, the role of pDC is more debated. During HIV infection, pDC may contribute to disease progression by recruiting T cells through chemokines, such as CCL3 and CCL4 [73], and producing Type I IFN [74]. Notably, *in vitro* HIV-stimulated pDCs induce T cell

apoptosis trough TRAIL expression, and promote Treg development through the IDO pathway [75]. However, recent studies also highlight the beneficial role of pDC-derived IFN in the early stages of HIV infection in the simian model, and their recruitment in the gut of elite controllers during HIV infection, suggesting a contribution to protective anti-viral immunity [76,77]. PDC were also studied in the context of other chronic viral infections. A common feature is the absence or low IFN levels induced by hepatitis B (HBV) [78,79] and C (HCV) viruses [80,81], as well as human papilloma virus[82]. The amount of type I IFN induced by a given virus may be critical to promote viral control versus chronic infection (Figure 2A), in addition to virus-related features.

The role of pDC has been less characterized in bacterial infection. PDC are recruited to the lymph node T-cell zone in Mycobacterium tuberculosis patients where they are producing granzyme B [83]. The pathological role of Type I IFN observed in mycobacterial infections [84] point to a possible detrimental role of pDCs. However, the link between pDC, type I IFN, and mycobacterial infection was not specifically addressed. Various reports indicate that pDC are present in human tonsils where they are in contact with bacteria [85]. Moreover, pDCs are able to sense and respond to Gram-positive and negative bacteria, with an upregulation of co-stimulatory molecules, and IFN production [85]. They can interact directly with B cells to induce IL-10 production in response to Staphylococus aureus. [86]. Hence, pDC influence both innate and adaptive immunity in bacterial infection, but their impact on the outcome of the infection remains unclear.

Intriguingly, latest studies highlight a role for pDCs in fungal infections. In the presence of *Aspergillus fumigatus hyphae*, pDCs play a protective role indirectly by producing IFN and TNF-α[87], and directly by killing fungi through the secretion of calprotectin and lactoferrin, capable of chelating divalent cations necessary for fungal growth[88]. Furthermore, in the presence of *A. fumigatus,* pDC secreted "pDC extracellular traps" (pETs) formed by DNA and citrullinated histone H3, with a structure similar to neutrophil extracellular traps (NETs)[89]. These traps are generally assembled with antimicrobial peptides leading to the killing of microbes that cannot be phagocytosed.

In parasitic infection, the role of pDCs was mostly studied in malaria, where pDCs were not activated in the context of *Plasmodium falciparum* blood-stage[90]. However, TLR7-dependent induction of IFN showed a protective role in early infection stages in the mouse[91]. More studies are needed to clarify the role of pDC and IFN in malaria and other parasitic infections.

In conclusion, the complexity of pDC functions in innate and adaptive immunity is reflected in their intricated beneficial or detrimental roles in infection. Factors such as pDC activation state, microbial and tissue context, and timing (early/acute versus late/chronic stages) all influence the ultimate impact on the outcome of the infection.

PDC are major players in autoimmune and allergic diseases.

Through their ability to secrete high amounts of type I IFN, pDC have been identified early on as a potential player in SLE, and other inflammatory and auto-immune diseases[92,93]. Important studies shed light on the signals that may induce pDC activation in such non-

microbial/sterile inflammation. In SLE, circulating immune complexes (IC), formed by auto-antibodies (Ab) and autologous DNA/RNA, are internalized into pDC endosomes through FcγRII (CD32) and sensed by TLR7 and TLR9[94]. In psoriasis, antimicrobial peptides such as LL-37 trigger IFN production after binding extracellular DNA to form molecular complexes that are shuttled to, and retained within, early endocytic compartments in pDCs to trigger TLR-9[95]. Through these mechanisms, pDC may break tolerance to self-antigens in SLE and psoriasis (Figure 2B).

PDC can be actively recruited to inflamed tissues[96,97]. In early psoriasis plaques, fibroblasts, mast cells, and endothelial cells express chemerin and promote pDC recruitment through chem23R[98]. PDC interact with other immune cells to promote and exacerbate inflammation. Circulating neutrophils from SLE patients may release NETs and induce pDC activation[37] (Figure 2B). NK cells may promote pDC activation via MIP-1β secretion and LFA-mediated cell-cell contact[99]. In SLE, pDC-derived IFN-α and CD40 expression increase plasmablast differentiation, auto-antibody production, and fail to induce regulatory B cells[100].

PDC pathogenicity may also be influenced by genetic predisposition to deregulation in the type I IFN pathway. Susceptibility loci to SLE and autoimmune diseases have been identified by genome-wide association studies[101]. Some of them could promote pDC activation and type I IFN production by alteration of immune complex clearance (FCGR2A, FCGR3A, ITGAM, CRP, C4A, C4B, C2, C1Q) and increased TLR7-9/IFN pathway (IRAK1, IRF5, IRF7, SPP1, STAT4, TREX1, ATG5). Studies have shown that some of these polymorphisms, in particular in the IRF-5, IRF-7, and ILT3 genes, may have a direct functional impact on type I IFN secretion by pDC[102–104].

Besides SLE, an “interferon signature” is associated to other active autoimmune diseases: Sjögren’s syndrome, dermatomyositis and systemic sclerosis[105]. PDC have been involved in dermatomyositis lesional skin[106]. Circulating IC with auto-Ab to topoisomerase I, Jo-1, and Ro 52/60 may act as endogenous type I IFN inducers production in pDC[107,108]. In pDC from patients with systemic sclerosis, an upregulation of miR-618 influence pDC development and increase the expression of mRNA encoding IFN-responsive gene[109]. Future studies may reveal additional pDC-activating mechanisms underlying a dysregulation of innate immunity. Interestingly, pDC adaptive functions have been less studied in the context of autoimmunity, and it remains unclear whether they may also contribute to disease pathogenesis through excessive T cell activation.

Because of their clear disease association and pathogenic role, pDC are an important therapeutic target in autoimmunity. Hydroxychloroquine, an antimalarial agent, which inhibits type I IFN production by pDC, is the cornerstone of SLE management [110,111]. Development of drugs targeting the IFN pathway, such as the monoclonal antibody anifrolumab (anti type I IFN receptor Ab), or Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathway inhibitors, are promising compounds in SLE and autoimmune diseases associated with IFN signature and pDC dyregulation[112,113].

Besides auto-immunity, pDC are implicated in allergic diseases such as asthma, atopic dermatitis and allergic rhinitis, all being associated with chronic and dysregulated inflammation. They are characterized by an increased Th2 polarization, allergen-induced production of IgE by plasma cells and hypersensitivity mediated by basophils and FcεRI/II. PDC are being recruited in nasal mucosa and sputum from allergic patients, and involved in allergic inflammation[114,115]. In children with atopy, relative deficiency of circulating pDC appears to be a risk factor for future development of asthma[116] (Figure 2B). In asthma, pDC express higher CD40, CD62L, CD64 and FcεRIα, but TLR7-mediated IFN-α secretion is significantly reduced[117,118]. Interestingly, in healthy individuals, pDC-derived IFN-α selectively constrain Th2 cytokine synthesis following rhinovirus exposure[119]. This negative regulatory mechanism between IFN-α and Th2 polarization may be defective in allergy, explaining the possibility of a viral infection triggering or aggravating asthma exacerbations[120] (Figure 2B). Overall, evidence from human studies mostly points at a pathogenic role of pDC in allergy through Th2 priming. Mouse models in that context have brought controversial results, supporting either a protective effect through Treg induction[121], or a pro-allergic effect through Th2 (V. Andreakos et al, unpublished). It will be important to specifically study pDC in a diversity of clinico-pathological forms of allergy, based on age, anatomical site, co-infections, chronicity, which may dictate opposite pDC functions through a different inflammatory micro-environment. This may have direct implications on designing relevant pDC-targeting strategies in allergy.

PDC function in cancer: from physiopathology to immunotherapy

The clinical benefit of type I IFN therapy in hematologic malignancies and melanoma, and the observation of pDC infiltrating multiple tumor types [122–126], have raised the question of the role of pDC in cancer.

Considering the innate-sensing receptors expressed by pDC, an important question was their possible ligands in the context of the tumor microenvironment (TME). Necrotic tumor cells release damage associated molecular patterns (DAMPs), such as high-mobility group box-1 protein (HMGB1) and mitochondrial DNA, which stimulate TLR9[127], and may activate pDC. The presence of GM-CSF in the TME is well documented in multiple cancers, supporting an activation of tumor-infiltrating (TI)-pDC through constitutively expressed GM-CSF receptor[128]. However, the expression of maturation markers such as CD40 and CD80 on TipDC obtained from human tumor biopsies seems to vary among tumor types, either absent in lung cancer [129] or upregulated as compared to blood pDC in melanoma [126], breast[130], or ovarian cancer[124], making it unclear whether endogenous tumor-derived signals are effectively activating pDC.

Interestingly, the same studies all showed that TI-pDC have a decreased capacity to produce IFN under TLR stimulation in vitro as compared to blood or healthy tonsil pDC, regardless of the expression of maturation markers before stimulation. This impairment in IFN production suggested a tolerogenic phenotype of TI-pDC, further supported by an ability to expand Treg cells and induce a Th2 differentiation, through the ICOSL and OX40L pathways, respectively [126,128]. In melanoma, the expression of Indoleamine 2,3-dioxygenase (IDO), another well-known immunosuppressive molecule, has been predominantly detected in pDC among the different DC subsets[131]. The importance of this mechanism was confirmed by the

enhancement of Ag presentation and Ag-specific cytotoxic T lymphocyte induction, following IDO inhibition by Toho-1 in a human leukemic pDC line[132].

Studies have shown that IFN production under TLR stimulation of pDC was significantly decreased by the addition of head and neck[122] or breast tumor-derived supernatants[130]. Since then, an ever-growing list of molecules, such as TGF-β, TNF-α[133], IL-10[134], Prostanglandin E2 (PGE2)[135] or IL-3[125], were shown to contribute to this tolerogenic phenotype of TI-pDC. The role of TGF-β and IL-10 suggests a potential paracrine loop between pDC and regulatory T cells (Figure 2B). Another mechanism that could reduce TipDC activation is the tumor-induced down-regulation of TLR9[122] . The induction of a Th2 differentiation of tumor infiltrating T cells by TI-pDC may be induced by GM-CSF, as shown in breast cancer[128] or TARC/CCL17, MDC/CCL22 and MMP-2, as suggested in melanoma[126].

Beside their tolerogenic effect, in vitro cytotoxicity assays with blood pDC acting on tumor cell lines suggested that TI-pDC may also have a direct cytotoxic effect on tumor cells in a TRAIL-dependent manner, but also via Granzyme B secretion, and Fas-Fas ligand interaction[136]. However, in these studies, blood pDC were artificially stimulated with TLR ligands and outnumber by 20 to 100 fold their targets, two conditions that do not reproduce the TME context and limit the extrapolation of these data. Hence, although pDC expression of Granzyme B and TRAIL was shown by many studies[137], and confirmed on “pure pDC”, defined as HLA-DR+CD123+AXL-CD2- DC[17], the role of these molecules in the tumor context remains controversial.

Despite pDC functional plasticity, and their expression of death molecules, most studies suggest that pDC may function predominantly as promoting tumor development through Treg induction [138]. These mechanistic observations are in line with the clinical correlation of high levels of TI-pDC with bad prognosis in several cancer types, such as breast cancer[123], ovarian cancer[124], multiple myeloma[125], and melanoma[126]. Thus, TI-pDC may be considered as a potential target for anti-cancer therapy. A first approach would be to deplete pDC. SL-401 targets IL-3 receptor (IL-3R) and efficiently depletes pDC in a mouse model of multiple myeloma[125].

A second approach would be to reprogram pDC phenotype from tolerogenic to anti-tumoral pDC through TI-pDC stimulation. It is one of the modes of action of the TLR7 agonist Imiquimod, which is routinely used to treat basal-cell carcinoma and HPV-associated cutaneous tumors, and under investigation in melanoma[139] (Figure 2B). However, apoptosis induction of tumor cells in a Bcl-2[140] or p53-dependent manner[141], has been described.

A last approach is to exploit the T cell priming capacity of pDC. A vaccine, consisting of intranodal injections of pDCs previously activated and loaded with tumor antigens[142] has been tested in melanoma patients and was able to induce specific CD4 and CD8 responses. However, clinical response rates were limited to a small proportion of patients. To overcome this limited efficacy, the most recent approach is to combine DC-based vaccines, which include both pDC and myeloid DC, with targeted therapies[143], or to directly deliver intravenously RNA lipoplexes, which are internalized by pDC but also CD11c+ conventional DC and macrophages[144] (Figure 2B).

In summary, pDC are actively explored as targets for cancer immunotherapy, despite a complex function, and remaining controversies on their contribution to tumor development versus control. As for allergy, we propose that specific studies of pDC in various tumor types and stages, may uncover clinical settings and patient groups which would predominantly benefit from pDC targeting.

Conclusions and perspectives

Although major progress was made in our understanding of pDC biology, many aspects remain unclear, and the complexity of pDC functions constitute a future challenge. A clear pDC definition needs to be used, putting at the forefront cytological and functional features, surface markers being essential tools to identify and purify pDC but difficult to use as defining criteria because of their variable sensitivity, specificity and stability in different steady state and inflammatory microenvironments. In that area, important new knowledge was recently generated by single cell RNAseq studies, which now needs to be integrated in pDC purification and monitoring protocols.

Systems, large scale approaches are contributing to the characterization as well as functional understanding of pDC biology and multiple signal integration. We have developed a high-resolution analysis framework to analyze the integration of endogenous and microbial signals by human pDC based on large-scale transcriptomics data[145]. This established the concept of multimodality in signal integration, meaning that the two same signals can be integrated according to multiple modes for different cellular outputs. Our study also revealed that a microbial stimulus (influenza virus) may inhibit the response to an endogenous factor (IL-3).

Because of the complex physiopathology of autoimmune diseases, large scale data analysis approaches have been broadly carried out[146]. The analysis of pDCs from lupus mice with RNAseq technology led to conclude that pDC present an altered transcriptional signature in early stages of the disease[147,148]. Using RNAseq technology, gene loci were associated with IFN production in human pDC in systemic lupus erythematosus patients[102]. Gene expression profile of human primary pDC stimulated with CpGB showed overexpression of MYC via TLR9 agonist, which is a novel target that modulates human pDC[149]. Large-scale proteomics analysis was used to elucidate the role of pDC in priming the immune response upon viral challenge. The shift of pDC response upon TLR stimulation from type I IFN to IL-1b may avoid disproportionate inflammation response[150].

A number of molecular mechanisms have been identified and characterized regulating pDC function: how they work together is now the challenge. How multiple signals are being integrated? Which of activating versus inhibitory receptors are dominant when co-triggered? The implication of pDC in several human diseases is well established, but the detailed understanding of their contribution to disease pathogenesis and physiopathology is lacking in most cases. The complexity here rises from the several ways pDC may adapt to various and dynamic inflammatory microenvironments. This is complicated by additional genetic factors.

Addressing all these levels of complexity is expected to derive exciting new biology, and to help deciphering inflammatory diseases, because of the numerous interactions between pDC and other molecular and cellular inflammatory players. Ultimately, this will be the only way to rationale pDC-targeting strategies, which may rarely be of general benefit in a given

disease entity, but should most of the time benefit only a subset of patients with specific disease characteristics.

Figure legends

Figure 1. PDC activation and modulation of the immune response

PDC activation through endosomal TLR7/9 ssRNA or dsDNA viruses, or CpG ODNs leads to high type I IFN secretion and pDC maturation into mature DC. PDC-derived IFN-I induce an antiviral response on immune and non-immune cells through the upregulation of interferon stimulated genes (ISGs) that prevent viral replication and spread. IFN-I induces NK cells cytotoxic activity and IFN-γ secretion; APC functions by stimulating cDC maturation and crosspresentation and, monocyte differentiation into DC and; favors B cell differentiation into plasma cells. pDC-derived DC and IFN-I can prime naïve CD4+T cells differentiation into regulatory Th1 cells and crosspresent Ag to CD8+Tcells. Alternatively, TLR-independent pDC activation through IL-3 or GM-CSF, induces their differentiation into mature DC capable of priming Th2 responses without IFN secretion.

Figure 2. PDC involvement in human diseases

A. During acute viral infections, pDC-derived type I IFN plays a critical role in the viral clearance by preventing replication and spread. IFN-I induces innate and adaptive immune cells activation. Viral-induced pDC-derived DC prime naïve CD4+T cells to differentiate into Th1 and T regs. During chronic viral infections, pDC may be reduced in the circulation or producing low IFN-I, failing in controlling the viral spread. Bacteria can trigger pDC activation. In Mycobacterial infections, pDC-derived IFN-I has a negative impact on the disease severity. Both Gram+ and Gram- bacteria can induce pDC activation, IFN-I secretion and upregulation of costimulatory immune checkpoints. Fungal infections, as A. fumigatus, can stimulate IFN-I and TNF-α secretion as well molecules acting in directly killing the fungi as calprotectin, lactoferrin and pDC extracellular traps (pETs). It has been proposed that pDC may produce IFN-I upon triggering by parasites as malaria. B. In autoimmune diseases, as systemic lupus erythematosus (SLE), the presence of autoantibodies and neutrophils extracellular traps (NETs) complexes with self-nucleic acids induce pDC activation and type I IFN secretion that contributes to increase inflammation and disease pathology. Treatments include hydroxychloroquine, a drug inhibiting endosomal acidification and TLR activation; and anti IFNAR antibodies. In psoriasis, pDCs are recruited to the skin plaques by chemerins, where cationic antimicrobial peptides such as LL37 can complex with self-DNA and activate pDC though TLR9 to induce IFN-I secretion. In cancer, the presence of Treg cytokines as IL-10 and TGF-β can stimulate a tolerogenic pDC state that contributes to the generation of Tregs through the expression of ICOSL and IDO, constituting a pDC-Treg feedback. Treatments with imiquimod aim to induce pDC activation through TLR7 to rescue their IFN-producing capacity. The use of RNA-lipoplexes (RNA-LPX) can trigger pDC IFN secretion and DC maturation and antigen presentation. In allergy, pDC role is debated, some studies showing a pDC contribution to the allergic inflammation by the induction of Th2 cells and, others suggesting a beneficial effect by the induction of Tregs contributing to the tolerance.

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Figure 1

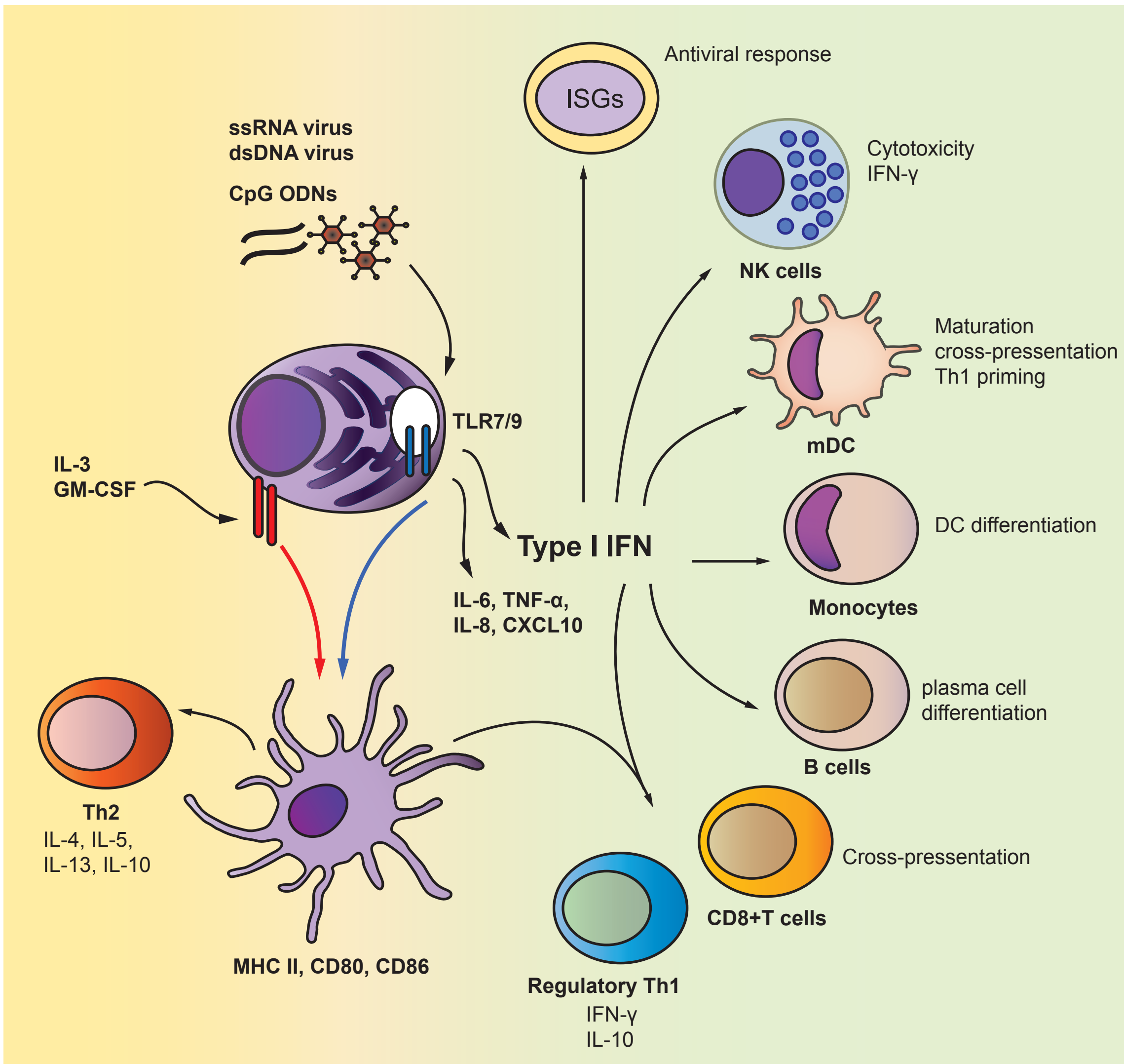

Figure 2