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The Plasmacytoid Dendritic Cell as the Swiss Army Knife of the Immune System: Molecular Regulation of Its Multifaceted Functions

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Plasmacytoid dendritic cells (pDC) have been regarded as the “professional type I IFN–producing cells” of the immune system following viral recognition that relies on the expression of TLR7 and TLR9. Furthermore, pDC link the innate and adaptive immune systems via cytokine production and Ag presentation. More recently, their ability to induce tolerance and cytoxicity has been added to their “immune skills.” Such a broad range of actions, resembling the diverse functional features of a Swiss army knife, requires strong and prompt molecular regulation to prevent detrimental effects, including autoimmune pathogenesis or tumor escape. Over the last decades, we and other investigators have started to unravel some aspects of the signaling pathways that regulate the various functions of human pDC. In this article, we review aspects of the molecular regulatory mechanisms to control pDC function in light of their multifaceted roles during immunity, autoimmunity, and cancer. The Journal of Immunology, 2014, 193: 5772–5778.

Plasmacytoid dendritic cells (pDC), a subset of the dendritic cell (DC) family, develop from hematopoietic stem cells in the bone marrow. The intermediate progenitor cell stages of human pDC are to be defined, but mouse pDC differentiate from either common DC progenitors or lymphoid-primed multipotent progenitors (1). Human and mouse pDC development depend on Flt3 ligand (2, 3); expression of the transcription factor Spi-B, an Ets-family member controlling expression of the antiapoptotic gene Bcl2A1 (4–7); and the basic helix-loop-helix protein E2-2 (8, 9). pDC are key mediators of innate immunity, mainly against viruses, by sensing their nucleic acids via TLR7 and TLR9. Furthermore, pDC also produce the proinflammatory cytokines IL-6 and TNF-α, which regulate T, B, and NK cell and conventional DC (cDC) responses, together with IFN-α/β (10). Further, pDC play a role in T cell activation because TLR ligation induces pDC maturation into so-called “pDC-derived DC” that exhibit DC morphology and Ag-presentation capacity (11). Over the past years, the molecular pathways involved in controlling pDC activation and maturation are being unraveled, uncovering new aspects of pDC functions, such as cytotoxic and tolerogenic abilities. Such pleiotropic immune abilities, similar to the features of a Swiss army knife (Fig. 1), may have detrimental effects when uncontrolled, as seen in autoimmune diseases. We review the main molecular mechanisms that should keep activated pDC “on physiological track” and highlight some aspects of deregulated pathways as observed in disease, with a particular focus on human pDC.

TLR signaling

During the first 6 h following TLR7/9 activation, pDC devote up to 60% of their transcriptome to expression of type I IFN genes (IFN-α, -β, and -ω) and type III genes (IFN-λ1–3) (12, 13). Such robust secretion capacity requires specific cellular and molecular mechanisms; as such, their “plasmacytoid” secretory morphology resembles Ab-secreting plasma cells. The rapid and substantial IFN-α/β production by pDC in response to TLR ligation is mediated by constitutive expression of the master regulator IFN response factor (IRF)7 (reviewed in Ref. 14) (Fig. 2). The signaling cascades downstream of TLR7/9 depend on the adaptor protein MyD88, which complexes with IL-1R–associated kinase (IRAK)1 and IRAK4, TNFR-associated (TRAF)6 and TRAF3, and IRF7 and IRF5 (reviewed in Ref. 14). Both TLR7/9 signaling pathways activate NF-κB depending on phosphorylation of inhibitory (I)kB proteins by the kinases IkBα and IkBβ and...

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Abbreviations used in this article: BDC2, blood DC Ag 2; BLK, B lymphoid tyrosine kinase; cDC, conventional DC; DCIR, DC immunoreceptor; GC, glucocorticoid; GrB, granzyme B; HCV, hepatitis C virus; IL-77, Ig-like transcript 7; IRAK, IL-1R–associated kinase; IRF, IFN response factor; pDC, plasmacytoid dendritic cell; SLE, systemic erythematosus lupus; Treg, regulatory T cell; VitD, vitamin D.

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subsequent degradation (15, 16). Known NF-κB members are RelA/p65, RelB, cRel, p52, and p50, which form homo- or heterodimers. The RelA/p50 heterodimer is most frequently activated after TLR signaling (15). RelA/p50 dimers are directly responsible for expression of costimulatory molecules (i.e., CD40, CD80, CD86), whereas IRF5, together with NF-κB and MAPK activation, is crucial for the production of IL-6 and TNF-α (reviewed in Ref. 14). Phosphorylation of IRF7, likely mediated by PI3K activation, leads to IRF7 nuclear translocation with the help of osteopontin, which, in turn, leads to IFN-α/β gene transcription (17, 18). Auto/paracrine production of IFN-α/β promotes pDC survival via induction of antipapoptotic genes, whereas TNF-α supports pDC maturation. It is believed that ligation of TLR in the early endosomal/lysosome-related compartment will preferentially turn on IFN production, whereas late endosomal/lysosomal engagement regulates proinflammatory cytokine production and maturation (reviewed in Ref. 14) (19).

Counterregulation of TLR signaling

TLR7/9 signaling needs to be counterregulated to prevent ongoing cytokine production, because this is deleterious for the host. Cell surface receptors on human pDC that dampen TLR-induced responses include the C-type lectin blood DC Ag 2 (BDCA2), DC immunoreceptor (DCIR), Ig-like transcript 7 (ILT7), FcεRI, NK protein 44, adenosine diphosphate P2Y receptors, a NO-induced cGMP-dependent receptor, and PGE2 receptors (20–22). Viruses can hijack the signaling pathways downstream of such receptors and escape from immune recognition (Fig. 2). For example, the hepatitis C virus (HCV) envelope glycoprotein E2 binds to BDCA2 and DCIR, which inhibits IFN-α production in pDC when exposed to HCV-infected hepatocytes (23). Moreover, exposure of pDC to HCV-infected hepatoma cells prevents NF-κB phosphorylation via an endocytosis-dependent mechanism, resulting in a lack of cell surface expression of CD40, CCR7, CD86, and TRAIL, as well as of TNF-α and IL-6 secretion (24). Another example is HIV, which induces production of IFN-α via TLR7 signaling to elicit antiviral activity in acute infection (25). In addition, HIV gp140 binds to DCIR (26) to recruit phosphatases (e.g., SHP1 and SHP2) and tyrosine kinases (e.g., Src, Fyn, Hck, Syk) to the ITIM domain of DCIR (27, 28). Recruitment of this signalsome is important for DCIR activity with regard to HIV binding/entry and enhanced HIV replication (26). It is possible that DCIR activation via gp140 inhibits IFN-α production in pDC, thereby increasing HIV replication. Following HIV-induced IFN-α secretion is expression of IFN-stimulated genes, such as MxA and BST2/Tetherin (29) in surrounding cells. Although increased expression of BST2 on leukocytes, including CD4+ T cells, may play a role in decreasing HIV virion release from infected cells in acute HIV infection (30), BST2 binding to its inhibitory receptor ILT7 expressed on pDC may dampen IFN production (31) and increase viral replication, at least during the acute phase. During chronic HIV infection, sustained levels of IFN-α return, likely as a result of persistent immune activation, leading to HIV pathogenesis. During chronic infection, pDC express increased levels of IRF7 (32) and lower levels of ILT7 (33), which may contribute to persistent IFN-α secretion as well. In addition to IFN-α, TNF-α may be responsible for persistent immune activation, because treatment of SIV-infected rhesus macaques with an Ab to TNF-α reduced expression of proinflammatory cytokines and immunopathology in lymphoid tissues (34).

A new layer of regulation involved in fine-tuning immune responses is provided by microRNAs (35), which are also involved in posttranscriptional regulation of protein expression in pDC. miR-155 and miR-155* have an opposite role in controlling TLR-induced IFN production by human pDC (36). miR-155* augments IFN-α/β expression by suppressing the negative TLR7 signaling mediator IRAKM (37). miR-155 inhibits IFN expression by targeting the adaptor TAK1-binding protein 2 (38). We showed that mir-146a is induced in human pDC by TLR7/9 agonists, but not IL-3, thereby interfering with cytokine production, maturation, and survival (39). Together with similar data in the mouse (34, 40) mir-146a is recognized as a “brake of the immune response” by downregulating IRAK1 and TRAF6 expression and, hence, dampening of TLR-induced responses.

Cytotoxicity

TLR7/9 stimulation of pDC also induces the expression of TRAIL (Apo-2L) (41, 42), which mediates cell death of TRAIL-sensitive infected cells and tumor cells expressing either TRAIL-R1 or TRAIL-R2 (43). Because TRAIL-expressing pDC accumulate in basal cell carcinoma lesions topically treated with the TLR7 agonist imiquimod, this suggests that pDC may be involved in imiquimod-induced regression of tumor lesions (41, 44). In response to HIV, pDC express TRAIL (45), which is present in peripheral blood and lymph nodes of HIV-infected individuals and may directly kill death receptor 5 (+) CD4+ T cells via the TRAIL/ death receptor 5 pathway (46, 47), although this is questioned by other investigators (48). We identified NGFI-A–binding protein 2, which is induced by TLR7/9 signaling in pDC, as a regulator of TRAIL expression (49). Autocrine IFN-α/β signaling also regulates TRAIL expression in human and mouse pDC (41, 49–51). pDC may kill target cells via the serine protease granzyme B (GrB) as well, which is constitutively expressed in human pDC (52). pDC-derived GrB lyses the erythroleukemic cell line K562 in a perforin-independent,
but caspase-dependent, manner (53). However, this could not be recapitulated when using primary T cells as targets (54).

**Ag uptake**

The ability of pDC to induce adaptive immunity through direct Ag presentation to T cells remained controversial for a long time. Most research focused on cDC, because they are more efficient as APC. Immature mouse pDC are able to take up soluble Ag, but less efficiently than cDC, possibly due to a lower macropinocytosis activity (55). Human pDC express several receptors to detect and endocytose pathogens that can be processed and presented to T cells. Ags coupled to Abs that target the endocytic receptors DEC-205 (56), DCIR (57), FcγRIIA (58), and BDCA2 (59) efficiently induce Ag-specific CD4+ T cell activation. Although BDCA2 (60) and DCIR (57) are downregulated after TLR activation, DEC-205 expression is induced after TLR activation and continues to function as an Ag-internalization receptor (56).

**Tolerance**

In the immature state, pDC have a poor ability to support T cell proliferation (67) and even suppress T cell responses indirectly through the induction of regulatory T cells (Treg) (68, 69). pDC contribute to peripheral T cell tolerance in...
Despite the low frequency of pDC in blood and lymphoid tissues, because human CD4+ and NK T cells are the main pro-
a negative-feedback loop to terminate adaptive-immune respon-
T cell activation (54, 77). IL-21 may be involved in mediating
or IDO impair T cell proliferation (54, 71, 77). GrB is in-
subset has yet to be identified, but pDC expressing either GrB
TLR triggering, correlating with reduced ability to prime
and mucosal tolerance (73). “Tolerogenic” pDC may be
transplantation (70), tumor escape (71), oral tolerance (72),
and mucosal tolerance (73). “Tolerogenic” pDC may be
in mouse gut and thymus (74–76). Such pDC may
present in mouse gut and thymus (74–76). IL-21 may be involved in mediating
response. 
response.

Melanoma progression in humans may be associated with
tumor-infiltrating pDC promoting pproinflammatory Th2 and Treg through OX40L and ICOSL, respectively (79), although this conflicts with the observation that patients with metastatic melanoma receiving intranodal injections of pDC mount anti-
tumor responses (80). In addition, a subset of pDC expressing
lymphocyte activation gene 3 negatively regulates T cell acti-
which increases the intracytoplasmic pH and prevents
FcR
by SLE immune complexes can be inhibited by blocking the
autoantibody-secreting plasma cells (10). IFN-
and bacteria through TLR7/9 activation. pDC are not only
pDC are major inducers of immune responses against viruses
in autoimmune diseases.

Autoimmune diseases

Despite the low frequency of pDC in blood and lymphoid tissues, their high potential to also produce IFN-α in response to self–nucleic acids raised questions about their putative role in autoimmunity. Unwanted IFN-α production by pDC is involved in autoimmune pathogenesis, including systemic lupus erythematosus (SLE) (84, 85), Sjögren’s syndrome (86), and psoriasis (87). Blood and tissue cells of these patients have an IFN signature indicating that IFN-inducible upregulation of IFN-stimulated genes can be used as a disease biomarker (87). In addition to the deleterious effects of IFN, pDC differentiate into mature pDC with an Ag-presenting capacity that is able to steer T cell responses, adding to the patho-
genesis of autoimmune diseases.

In SLE, autoantibodies directed to nuclear Ags are aberrantly produced and deposited in tissues, causing inflammation. Nucleic acid–containing immune complexes trigger IFN-α release from pDC upon FcγR-I mediated uptake into endo-
somes and local engagement of TLR7/9 (89, 90). pDC num-
bbers in blood of SLE patients are reduced, but pDC infiltration is found in skin and renal lesions (91). The IFN signature correlates with disease activity and severity (84, 92) but is independent of the relative TLR7 gene copy number (93). SLE pathogenesis can be linked to increased IL-6 production by activated pDC, which, together with IFN-α, promotes survival and differentiation of autoreactive B cells into autoantibody-secreting plasma cells (10). IFN-α production by SLE immune complexes can be inhibited by blocking the FcγR-I mediated uptake of IgG (94) by hydroxychloroquine, which increases the intracytoplasmic pH and prevents acidification and maturation of endosomes (95), or by C-reactive protein, which binds apoptotic cells and nucleo-
protein autoantigens (96). Reduced miR-146a expression is
found in PBMC of SLE patients and may add to elevated IFN-α and IL-6 levels (97). Accordingly, SLE is associated with miR-146a polymorphisms (98–100). Lower expression of miR-146a may be linked to a miR-146a promoter variant binding less efficiently to Ets1 (99). Not all studies support an association between SLE and miR-146 polymorphisms (101). BDCA2 and ILT7, which complex with FcεRΙγ, are other negative regulators of TLR-induced IFN-α production in pDC that inhibit SLE pathogenesis (102, 103). This involves a BCR-like signaling mechanism relying on activa-
tion of adaptors, such as Syk, B cell linker, and B lymphoid
tyrosine kinase (BLK). Reducing BLK levels in mouse pDC
increased TLR9-induced IFN-α production (104). Given that
genetic variants in the BLK locus are identified in SLE
patients by genome-wide association studies, it is notable that
certain polymorphisms correlate with reduced BLK levels
(105). Consequently, this may increase IFN-α secretion and,
therefore, contribute to SLE predisposition. SLE patients are
generally treated with glucocorticoids (GC) that exert an anti-
inflammatory effect, likely by inhibition of NF-κB activation.
However, these drugs do not convey maintenance of disease
control in the majority of patients as a result of inefficient
NF-κB inhibition in pDC (106), thereby preventing GC-induced
pDC death and, consequently, ongoing IFN-α production.
An improved therapeutic advantage may be gained by treating
SLE patients with inhibitors of Syk (107), BTK (108), or
TLR (109). Future intervention may aim at altering ex-
pression of miR-29b/c, which is involved in TLIR-inhibited
GC-induced pDC apoptosis, by directly targeting Mcl-1 and
Bcl-2 (110).

In psoriasis, a disease of chronic skin inflammation, lesions contain activated pDC that secrete IFN-α/β (87, 111) as a result of the presence of cathelicidin peptides, including LL-
37, which are produced by activated keratinocytes (112). LL-
37 complexes with self-DNA/RNA released by dying cells and engages TLR7/9, leading to chronic IFN-α production (112, 113). Psoriatic lesions are effectively treated with vitamin D (VitD) analogs, which have anti-inflammatory properties (114). pDC may contribute to the tolerance induction, because VitD impairs the ability of pDC to induce T cell proliferation and secretion of the Th1 cytokine IFN-γ (115). It remains unresolved how VitD programs the tol-
erogenic properties in pDC, but this is not due to altered expression of costimulatory molecules, MHC class II, or produc-
tion of IFN-α. Despite the pathological role of pDC in autoimmune skin diseases, the physiological importance of
pDC in initiating skin wound healing is also reported. Follow-
ing skin injury, pDC are rapidly recruited to the site of tissue damage to sense self–nucleic acids released by dying
cells in combination with cathelicidins, as well as to initiate
tissue repair via TLR-induced IFN-α production (116).

Conclusions

pDC are major inducers of immune responses against viruses
and bacteria through TLR7/9 activation. pDC are not only capable of linking the innate and adaptive immune system via
rapid and sustained production of cytokines, including type I
IFN, IL-6, and TNF-α, they can activate T cells through direct
Ag presentation in vitro and, likely, in vivo. In addition, pDC
are able to directly kill bystander tumor cells, thereby particip-
in cancer-induced immune responses. Although the
beneficial role of pDC in immunity is undisputable, their recently discovered “tolerogenic” face in different tumors suggests their involvement in tumor-escape mechanisms. Such a broad range of action requires tight regulation, both at the transcriptional and posttranscriptional level, to control development.

Disclosures

The authors have no financial conflicts of interest.

References


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BRIEF REVIEWS: REGULATION OF pDC FUNCTIONS IN HEALTH AND DISEASE


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