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Plasmacytoid dendritic cells: development, regulation and function

Boris Reizis

Department of Pathology and Department of Medicine, New York University School of Medicine, New York, NY 10016, USA

Abstract

Plasmacytoid dendritic cells (pDCs) are a unique sentinel cell type that can detect pathogen-derived nucleic acids and respond with rapid and massive production of type I interferon. This review summarizes our current understanding of pDC biology, including transcriptional regulation, heterogeneity, role in antiviral immune responses, and involvement in immune pathology, particularly in autoimmune diseases, immunodeficiency and cancer. We also highlight the remaining gaps in our knowledge and important questions for the field, such as the molecular basis of unique interferon-producing capacity of pDCs. A better understanding of cell type-specific positive and negative control of pDC function should pave the way for translational applications focused on this immune cell type.

Introduction

2019 marks the 20th anniversary of the definitive description of plasmacytoid dendritic cells (pDCs) as a unique cell type by the Liu and Colonna groups (Cella et al., 1999; Siegal et al., 1999). This description was based on extensive prior research by multiple groups (reviewed in (Colonna et al., 2004; Liu, 2005)) that collectively defined the essential properties of pDCs: secretory “plasmacytoid” morphology akin to that of plasma cells, rapid and massive production of type I interferons (IFN-I) in response to viruses, and the ability to differentiate into conventional dendritic cells (cDCs) in vitro. The last 20 years produced extraordinary insights into all aspects of pDC biology, including their development, mechanism of activity and role in the immune system. At the same time, this progress brought us to fundamental unanswered questions about the role and mechanism of pDC function. Solving these questions would hasten the translation of accumulated knowledge into clinical applications focused on pDCs.

Accordingly, the goal of this review is both to summarize the current understanding and to highlight the gaps in our knowledge of pDC biology. Rather than an extensive listing of all pDC-related topics, it focuses on several key areas and concepts, and also emphasizes the

Correspondence: Boris.Reizis@nyumc.org.

studies of the last several years that have not been covered in the previous reviews. I sincerely apologize to the researchers whose important original contributions could not be cited due to the limited time frame and scope of this review.

Development and transcriptional regulation of pDCs

pDCs primarily reside in and recirculate through lymphoid organs, where they typically comprise 0.1-0.5% of nucleated cells. They have the round morphology of a secretory lymphocyte and express low levels of MHC class II that can be upregulated upon activation. pDCs express high levels of endosomal nucleic acid-sensing Toll-like receptors (TLRs) TLR7 and TLR9, which recognize single-stranded RNA and unmethylated CpG DNA, respectively. pDCs respond to these nucleic acids with massive secretion of IFN-I, which commences within 1-3 hours and involves IFN-β and most IFN-α subtypes. pDCs also produce type III interferon (IFN-λ or IL-28/IL-29) and additional cytokines (e.g. TNF-α) and chemokines (Gilliet et al., 2008; Reizis et al., 2011; Swiecki and Colonna, 2015). The speed, magnitude and broad spectrum of interferon production by pDCs are reflected in the original definition of these cells as “natural interferon-producing cells” (Colonna et al., 2004; Liu, 2005). This and other key genetic and functional features of pDCs are shared between humans and mice (Crozat et al., 2010; Guilliams et al., 2016), highlighting evolutionary conservation of this immune cell type. This review will primarily focus on IFN-I production as the most prominent, unique and well-established feature of pDCs, even as other aspects of pDC function such as antigen presentation are undoubtedly important (Villadangos and Young, 2008).

pDCs are continuously produced in the bone marrow (BM) and emerge as mature cells into the periphery, where they remain non-proliferative and have a relatively short lifespan of several days (Zhan et al., 2016). Similar to cDCs, pDC express cytokine receptor Flt3 (CD135) and are strictly dependent on its ligand Flt3L for their development. Conversely, Flt3L in the absence of other signals is sufficient to drive the development of pDCs and cDCs from myeloid and lymphoid progenitors (Sathe et al., 2013), consistent with the potential of both progenitor types to produce pDCs in vivo (Shigematsu et al., 2004). The myeloid pathway to pDCs includes a potential common dendritic cell (DC) progenitor (CDP) (Naik et al., 2007; Onai et al., 2007) and pDC-biased DC progenitors (Onai et al., 2013; Schlitzer et al., 2011). The identity of lymphoid progenitors of pDCs has been recently studied in greater detail (Herman et al., 2018; Rodrigues et al., 2018). Notably, relative rarity and quiescence of pDC-committed lymphoid progenitors (Rodrigues et al., 2018) are not consistent with these cells being a major source of much more abundant pDCs. Indeed, lineage tracing using the CDP marker Csf1r showed that the vast majority of pDCs became labeled (Loschko et al., 2016); in contrast, recently deposited results of B cell progenitor tracing suggest that a minor distinct population of pDCs is derived from these progenitors (Dekker et al., 2018). Furthermore, pDCs develop from stem cells in vivo with the same kinetics as myeloid cells including cDCs (Sawai et al., 2016), and progenitors with transcriptomic features of pDCs emerge prior to lymphoid progenitors (Upadhaya et al., 2018). Collectively, the results so far suggest that pDCs develop primarily through a Flt3L-driven pathway shared with cDCs, with a potential additional contribution of lymphoid progenitors. Importantly, clonal tracing of transplanted or cultured progenitors (Dursun et

al., 2016; Lee et al., 2017; Lin et al., 2018; Naik et al., 2013) suggest that the commitment to produce pDC and/or cDC subsets may be determined at early stages of differentiation, i.e. prior to the emergence of phenotypically defined DC progenitors.

The fact that Flt3L alone is sufficient for pDC development suggests the existence of a robust transcriptional program that drives spontaneous pDC differentiation and pDC vs cDC lineage bifurcation, unless subverted by competing stimuli. Transcription factors such as PU.1 control the entire Flt3L-driven program of DC development (Carotta et al., 2010), whereas the subsequent specification of pDCs requires the E protein transcription factor TCF4 (E2-2) (Cisse et al., 2008; Nagasawa et al., 2008). TCF4 is expressed in all hematopoietic progenitors and can amplify its own expression in developing pDCs through a BRD protein-dependent feedback loop, underlying a self-sustained program of pDC development (Grajkowska et al., 2017). The pDC expression program appears to be initiated in progenitors that express IRF8 (Upadhaya et al., 2018), which is required for pDC development in vitro (although surprisingly, not in vivo (Sichien et al., 2016)). TCF4 acts jointly with its protein cofactor MTG16 (Ghosh et al., 2014) and additional factors such as BCL11A (Ippolito et al., 2014; Wu et al., 2013) to promote pDC development (Fig. 1A). Conversely, E protein inhibitor ID2 may “break” the TCF4-driven transcriptional program to channel the development into cDCs, particularly the ID2-dependent cDC1 subset. Thus, the loss of MTG16 or of transcriptional repressor ZEB2 (Scott et al., 2016; Wu et al., 2016) causes de-repression of ID2 and impairs pDC development, whereas the development of cDC1 is enhanced. A milder reduction of TCF4 activity by the deletion of pDC-specific “long” isoform $TCF4_L$ (Grajkowska et al., 2017) reduces pDC development but facilitates the development of the non-canonical DC subset discussed below. TCF4 is a close homolog of other E protein transcription factors TCF3 (E2A) and TCF12 (HEB), the key regulators of lymphocyte development. All three E proteins bind to the same consensus sequence and share target genes; accordingly, TCF4 in pDCs binds to and activates many genes that are activated by E2A/HEB in developing lymphocytes (Ceribelli et al., 2016; Ghosh et al., 2014). This unique feature of transcriptional control distinguishes pDCs from cDCs and likely accounts for their transcriptomic similarity to lymphoid progenitors (Herman et al., 2018). For instance, Dntt (TdT) and Ccr9 are canonical targets of E proteins in lymphoid progenitors and are also among the most TCF4-dependent genes in pDCs (Cisse et al., 2008), even though Dntt has no obvious function in these cells. Furthermore, deletion of TCF4 from mature pDCs induces the switch to dendritic morphology and expression of cDC gene signature (Ceribelli et al., 2016; Ghosh et al., 2010). Additional “resolution” between pDC and cDC expression programs is provided by transcription factor ETV6, which represses the cDC gene signature in pDCs and vice versa (Lau et al., 2018). Altogether, these studies underscore a close relationship between pDC and the cDC lineages and reveal a unique transcriptional program that maintains pDCs in a “lymphoid-like” state and opposes alternative cDC fates.

Following the initial lineage commitment, pDCs undergo an elaborate differentiation program that ensures their functionality (Fig. 1B). Thus, transcription factor SPIB facilitates the retention of immature pDCs in the BM (Sasaki et al., 2012); conversely, RUNX2 facilitates the exit of mature pDCs from BM to the periphery (Chopin et al., 2016; Sawai et al., 2013). The IFN-I-producing capacity of pDCs is dependent on interferon response

family (IRF) transcription factors including IRF7 (Honda et al., 2005b), IRF5 (Dai et al., 2011; Yasuda et al., 2013) and IRF8 (Sichien et al., 2016). Consistent with the key role of IRF7, several factors were shown to regulate its activity in pDCs: for instance, SPIB (Sasaki et al., 2012) and NFATC3 (Bao et al., 2016) interact with IRF7 and facilitate the activation of IFN-I genes. Furthermore, RUNX2 was proposed to directly activate IRF7 expression (Chopin et al., 2016) whereas MYC may repress it to limit IFN-I production (Kim et al., 2016). Finally, pDC-enriched epigenetic regulator CXXC5 together with DNA demethylase Tet2 was shown to promote *Irf7* expression by maintaining the hypomethylation of its promoter in pDC (Ma et al., 2017). Collectively, these studies begin to reveal a complex transcriptional network that maintains the capacity of pDCs for rapid response while limiting unwanted hyperactivation. Key parts of this network, including epigenetic mechanisms and *cis*-regulatory elements that facilitate pDC functionality, still remain to be identified.

Heterogeneity and post-activation fate of pDCs

Recent single-cell analysis of human DC population revealed a subset with some phenotypic features of pDCs that was incapable of IFN-I production but efficiently primed T cells (Alcantara-Hernandez et al., 2017; See et al., 2017; Villani et al., 2017). Together with other reports on human pDC heterogeneity (Matsui et al., 2009; Zhang et al., 2017), these results suggest the existence of a “non-canonical” DC population that is intermediate between the canonical pDCs and cDCs. Further analysis of this population, defined by several markers including AXL, revealed that it is heterogeneous and comprises “pDC-like” as well as “cDC-like” cells (Alcantara-Hernandez et al., 2017; Villani et al., 2017). Importantly, “non-canonical” DC subsets have been described previously in the mouse, most notably the distinct $Cx3cr1^{+}$ subset of $CD8^{+}$ cDCs (Bar-On et al., 2010; Lau et al., 2016). These cells manifest the surface phenotype and functionality of cDCs, lack IFN-I production, yet have a transcriptional profile related to pDCs and require TCF4 for development. Furthermore, a recently deposited study proposed a distinct minor subset of Axl+ murine pDCs that are derived from lymphoid progenitors, lack IFN-I production but show increased antigen-presenting capacity (Dekker et al., 2018). Preliminary comparison of expression profiles and/or phenotypes of these subsets suggests a concordance between human and murine “non-canonical” pDC and cDC subsets, which potentially comprise an evolutionarily conserved spectrum (Fig. 2). Notably, non-canonical pDCs and cDCs co-express TCF4 and ID2, consistent with their intermediate position between $TCF4^{high}$ pDCs and $ID2^{high}$ cDCs. This proposed cross-species alignment of DCs is supported by high-dimensional DC phenotyping in humans and mice (J. Idoyaga, personal communication), and remains to be comprehensively tested in future studies. Most importantly, the developmental origin and function of non-canonical subsets need to be elucidated in both species.

Within the canonical mature pDC subset, heterogeneity is evident in the expression of surface markers such as murine CD4, CD8 (O’Keeffe et al., 2002) or Ccr2 (Sawai et al., 2013), yet its significance remains unclear. The question of pDC heterogeneity is directly tied to a broader question of pDC function and eventual fate upon TLR-mediated activation. While activated pDCs are capable of cytokine production as well as antigen presentation and cross-presentation, these processes may either occur sequentially in the same cells, or

represent separate fates of different pDCs. The latter appears more likely because only a fraction of pDCs produce IFN-I irrespective of the stimulus, as confirmed using IFN-I reporter strains (Bauer et al., 2016; Kumagai et al., 2007; Tomasello et al., 2018). Furthermore, pDC activation results in the massive pDC apoptosis caused by IFN-I (Swiecki et al., 2011). It is therefore conceivable that the majority of IFN-producing pDCs die in vivo, whereas the surviving ones remain capable of antigen presentation. Indeed, in vitro activated human pDCs generate distinct populations with preferential IFN-producing or antigen-presenting capacities (Alculumbre et al., 2018). These populations were proposed to diversify spontaneously through paracrine cytokine signaling; however, pre-existing commitment towards these fates within the pDC population cannot be ruled out. Importantly, the observed differentiation into cDC-like cells represents an intrinsic property of activated pDCs (Grouard et al., 1997) that cannot be explained by contamination with AXL^+ DCs (Alcantara-Hernandez et al., 2017; Alculumbre et al., 2018). The analysis of such activation-induced differentiation in vivo, as well as the broad characterization of pDC cell fate during immune responses, represent important challenges for future studies.

Mechanism of interferon production by pDCs

Signaling by endosomal TLRs through the adaptor MyD88 and transcription factor IRF7 appears to be a major (albeit not exclusive) mechanism of pDC activation that results in IFN-I production (Honda et al., 2005a; Honda et al., 2005b). Another consequence of TLR/MyD88 signaling is the activation of NF-κB and the ensuing induction of cytokines such as TNF-α and costimulatory molecules; this pathway is very important but not unique to pDCs and will not be further discussed here. Non-endosomal MyD88-dependent TLRs such as TLR2 may also be functional in pDCs in response to certain stimuli (Dasgupta et al., 2014). The cGAS/STING and RIG-I pathways of intracellular sensing may be functional in pDCs in response to replicating DNA (Li et al., 2013) and RNA (Bruni et al., 2015; Kumagai et al., 2009) viruses, respectively. Alhtough it has been suggested that intracellular sensing pathways such as cGAS/STING and MDA5/MAVS may restrict IFN-I response of pDCs (Yu et al., 2016), this model is not supported by other studies (Spaulding et al., 2016). Importantly, endosomal TLR-induced IFN-I production represents a very specific feature of pDCs: for example, in vivo administration of TLR9 ligand CpG induces a rapid systemic IFN-I response that is mediated exclusively by pDCs (Asselin-Paturel et al., 2003; Blasius et al., 2004; Cervantes-Barragan et al., 2012).

This, however, opens up a truly challenging question: what makes the TLR7/9-induced IFN-I response so specific for pDCs? The expression of TLR7 and TLR9 is a distinct but not unique property that is shared with B cells and several myeloid cell types (particularly in the mouse). Additional important mechanisms of TLR-induced IFN-I production include the PI3K/mTOR pathway activation (Cao et al., 2008; Guiducci et al., 2008), prolonged retention of TLR ligands in early endosomes (Guiducci et al., 2006; Honda et al., 2005a), and regulation of endosomal TLR signaling by the AP-3 adaptor complex and the AP-3-interacting cation transporter Slc15a4 (Blasius et al., 2010; Sasai et al., 2010). However, none of these mechanisms or molecules is specific for pDCs; conversely, candidate pDC-specific signaling mediators such as endocytic adaptor Pacsin1 contribute to IFN-I response but are not essential for it (Esashi et al., 2012). Finally, fundamental differences may exist in

the response of pDCs to synthetic TLR agonists and to viruses: for instance, AP-3 was recently shown to be required for the former but not the latter (Tomasello et al., 2018).

In most cell types, the expression of IRF7 is normally low or absent, and is induced by the first wave of IFN-β production through an IFN-I receptor (IFNAR)-mediated feedback loop. Quiescent pDCs express high levels of IRF7, and therefore were proposed to secrete IFN-I rapidly and independently of the IFNAR-based feedback signaling (Barchet et al., 2002; Dalod et al., 2002). Indeed, IFNAR was shown to be dispensable for pDC response to viruses such as vesicular stomatitis virus (VSV) (Barchet et al., 2002) and murine cytomegalovirus (MCMV) (Tomasello et al., 2018). Surprisingly, IFNAR-deficient pDCs manifested normal response to MCMV despite expressing low baseline levels of IRF7 (Tomasello et al., 2018). On the other hand, IFNAR appears necessary for full-strength IFN-I response to TLR ligands in vivo (Asselin-Paturel et al., 2005; Blasius et al., 2010; Tomasello et al., 2018) and to certain viruses in vitro (Kumagai et al., 2009), and for optimal functionality of human pDC in vitro (Laustsen et al., 2018). These data suggest that IFNAR-independent signaling does not require high IRF7 levels and may promote pDC responses to certain viruses, although full pDC functionality still requires intact IFNAR signaling.

In contrast to the traditional “cell-intrinsic” view of pDC activation, recent studies highlighted its unexpectedly cooperative nature (Fig. 3A). It has been observed early on that pDC form tight clusters within hours of activation by TLR ligands in vivo (Asselin-Paturel et al., 2005), although the functional significance of such clustering remained unclear. In vitro, the magnitude of IFN-I response to TLR ligands was shown to be facilitated by cell density (Kim et al., 2014), as confirmed recently by single-cell activation assay (Wimmers et al., 2018). These studies ascribed the observed cooperativity to autocrine/paracrine IFN-I signaling, which may indeed be important in these settings as discussed above. However, another potentially important mechanism is cell-cell interaction and the associated polarization of IFN-I production and sensing, as observed upon pDC activation in vitro (Saitoh et al., 2017). This study showed that pDC response to TLR ligands and to the influenza virus is impaired in the absence of integrin LFA-1 and of downstream regulators of intracellular trafficking that localize TLRs and secreted IFN-I to the sites of cell-cell contact (Saitoh et al., 2017). The contribution of LFA-1 expressed on pDCs to IFN-I production in response to MCMV and to TLR9 ligand has been recently confirmed in vivo (Tomasello et al., 2018). These recent studies highlight cell-cell interactions (including homotypic clustering of pDCs) and the associated profound polarization of TLR sensing, IFN-I production and IFN-I-mediated feedback signaling as important features of pDC response. Collectively, the unique IFN-I-producing capacity of pDCs cannot be easily explained by any single known mechanism or molecule. Instead, it appears to integrate multiple pathways and cellular processes, in a manner that still remains to be fully elucidated.

Negative regulation of IFN-I production by pDCs

The IFN-I-producing capacity and “trigger-happy” state of pDC must have necessitated the need for counterbalancing inhibitory mechanisms. Some of these act through broadly expressed surface receptors such as CXCR4 and CD44, which inhibit pDC activation in response to natural monoamines (Smith et al., 2017) and galectin-9 (Panda et al., 2018),

respectively. Some of the inhibitory receptors are shared with lymphocytes and seem to be "re-purposed" for inhibitory function in pDC, such as murine Lag3 (Workman et al., 2009) and CD28 (Macal et al., 2016). Yet other receptors are relatively specific for pDCs, such as murine SiglecH and human BDCA-2 (CD303) and ILT-7 (CD85). Additional members of this class are likely to exist, as illustrated by the recent description of mouse pDC-specific inhibitory receptor CD300c (Kaitani et al., 2018). These receptors inhibit pDC response when engaged with agonistic antibodies and are thought to signal through a common pathway involving ITAM-containing adaptors such as Fc receptors and DAP12 (Gilliet et al., 2008). SiglecH is a sialic acid-binding lectin whose exact ligands are poorly understood, although its deletion causes enhanced IFN-I response by pDCs (Puttur et al., 2013; Schmitt et al., 2016). SiglecH-deficient mice also develop autoimmunity several weeks after viral infection (Schmitt et al., 2016), although it is unclear if this striking phenotype emanates from pDCs. Unless some pDCs acquire a long lifespan after infection, the delayed autoimmunity is likely mediated by long-lived SiglecH$^+$ cells such as macrophages. BDCA-2 is a C-type lectin that binds multiple glycoproteins including serum immunoglobulins (Kim et al., 2018), raising the possibility that antibody responses inhibit pDC activation through BDCA-2-mediated homeostatic mechanism. ILT-7 is an immunoglobulin-like receptor whose single known ligand is BST2 (tetherin), an interferon-inducible antiviral membrane protein that may provide a negative feedback signal to IFN-I-producing pDC (Cao et al., 2009). Murine pDCs lack an obvious ortholog of ILT-7 but specifically express Bst2 (Blasius et al., 2006b), which paradoxically facilitates IFN-I production (Swiecki et al., 2012) and may contribute to pDC resistance to infection.

The species-specific nature of above-mentioned inhibitory pathways likely reflects separate evolutionary pressures from pathogens. On the other hand, a distinct and evolutionarily conserved pDC-specific pathway involves a receptor-type protein tyrosine phosphatase PTPRS, which is expressed in multiple tissues but is highly pDC-specific within the immune system of humans and mice (Bunin et al., 2015). The deletion or ligation of PTPRS (along with the homologous pDC-specific phosphatase PTPRF in the mouse) respectively enhanced or inhibited pDC activation. The ligands of PTPRS likely involve diverse heparan sulfate proteoglycans, suggesting a potential way for pDC to monitor the integrity of extracellular matrix. The intracellular substrates of PTPRS are unknown, but the inhibitory activity of a tyrosine phosphatase mirrors the recently identified positive roles of tyrosine kinases SYK (Aouar et al., 2016), LYN and FYN (Dallari et al., 2017) in pDC activation. Global or dendritic cell-specific deletion of PTPRS/PTPRF in the mouse caused spontaneous IFN-I production and colitis (Bunin et al., 2015), highlighting the inherent danger posed by even mild pDC hyperactivation. Overall, negative regulation of pDC responses appears fundamental to pDC biology and is responsible for the most prominent cell type-specific molecular features including the hallmark surface markers such as SiglecH and BDCA-2. Further analysis of these pathways may provide attractive opportunities for therapeutic targeting of pDC activation, e.g. inhibition in autoimmune diseases or activation in cancer.

The nature of virus recognition by pDCs

pDCs were defined by their ability to respond to the purified influenza virus added to cultures, and this certainly represents an important mode of pathogen recognition by these

cells (Fig. 3A). Direct recognition of internalized virions through endosomal TLRs is indeed strongly supported by the ability of pDC to respond to viruses that have been rendered replication-deficient, e.g. by physical inactivation (Asselin-Paturel et al., 2001; Deal et al., 2010; Kumagai et al., 2009; Lund et al., 2003). It is also consistent with the relative resistance of pDCs to infection by many viruses to which they are capable of responding with IFN-I production.

Other viruses such as VSV elicit IFN-I production only when replication-active (Hornung et al., 2004; Lee et al., 2007), and productive infection of pDCs by IFN-I-inducing viruses has been described in vitro (Cervantes-Barragan et al., 2007; Dai et al., 2011; Manuse et al., 2010) and in vivo (Macal et al., 2012). Notably, these experimental settings utilized high viral doses in vitro, and the resulting infection of pDCs was still lower than of other cell types. Autophagy may represent one mechanism whereby a virus replicating inside the pDC would get access to the endosomal compartment and induce IFN-I production (Lee et al., 2007) (Fig. 3B). On the other hand, single-cell analysis of response to several viruses (including VSV) demonstrated that viral replication and IFN-I production occurs in different cells within the pDC population (Deal et al., 2010; Doring et al., 2014; Frenz et al., 2014). This may reflect the heterogeneity of IFN-I response by pDCs as noted above – in this scenario, IFN-I-producing pDCs would suppress viral replication while those lacking IFN-I production would sustain it. Another possibility, however, is that pDCs spontaneously "divide the labor" - some get infected and others recognize the virus replicating in the infected pDCs (Fig. 3B). This scenario is consistent with the highly cooperative nature of pDC activation as discussed above, as well as with the emerging unique feature of pDCs - the ability to recognize virus-infected cells.

This new paradigm of virus recognition by pDCs (Fig. 3C) was introduced in a study of hepatitis C virus (HCV), an RNA virus with a strict tropism for hepatocytes. It showed that pDCs produce IFN-I by interacting with and recognizing HCV-infected hepatocytes rather than the free HCV (Takahashi et al., 2010). This recognition is TLR7-dependent, requires physical contact between pDCs and live infected cells, and was initially proposed to occur via the short-range transfer of viral RNA in exosomes (Dreux et al., 2012; Takahashi et al., 2010). Subsequent studies have demonstrated the same phenomenon for multiple diverse RNA viruses including retroviruses (Lepelley et al., 2011; Rua et al., 2012), lymphocytic choriomeningitis virus (LCMV) (Wieland et al., 2014), hepatitis A virus (Feng et al., 2015), Dengue and West Nile viruses (Decembre et al., 2014) and yellow fever vaccine virus (Bruni et al., 2015). These studies also showed that RNA of a replicating virus may be transferred between infected cells and pDCs within immature viral particles or enveloped virions. In cells latently infected with the DNA herpesvirus Epstein-Barr virus (EBV), EBV-derived RNA can be transferred to pDCs through exosomes and can elicit the expression of IFN-I and interferon-stimulated genes (ISG) (Baglio et al., 2016). In addition to human pDCs, this phenomenon was also observed in murine (Frenz et al., 2014) and porcine (Garcia-Nicolas et al., 2016) pDCs. It may also be applicable to non-viral pathogens, as suggested by the close interactions of pDCs with macrophages during TLR7-mediated activation of pDCs in malaria-infected mice (Spaulding et al., 2016).

The recognition of virus-infected cells by pDCs has multiple potential advantages. First, it helps pDCs detect the virus during the main intracellular events of its life cycle including replication and possibly even latency, rather than during the often transient and rare extracellular transit. Indeed, the recognition of a free virus such as VSV, even at a high multiplicity of infection, appears less efficient than the recognition of cells infected with the same virus (Frenz et al., 2014). Second, it makes pDCs resistant to multiple evasion mechanisms used by viruses to prevent recognition and IFN-I secretion by the infected cell. Third, it allows the detection of viruses with a very narrow tropism (e.g. HCV) and facilitates precise tissue localization of responses towards infected cells. This mode of recognition also offers a potential explanation for the above-mentioned cases where pDCs themselves get infected: in this scenario, infected pDCs may elicit TLR-driven production of IFN-I from uninfected pDCs (Fig. 3B). Thus, pDCs appear to have evolved a unique ability to monitor the intracellular compartment in a manner resembling other sentinel cells such as NK cells and cytotoxic T cells.

Fundamental questions still remain about this emerging mechanism of virus recognition by pDCs. Is the recognition of virus-infected cells a special case of certain viruses recognized through TLR7, or a “default” mode applicable to the majority of RNA and DNA viruses? TLR9-mediated recognition of infected cells has not been demonstrated yet, although the transfer of the virus and cellular material from cells infected with the DNA virus herpes simplex virus (HSV) to pDCs has been described (Megjugorac et al., 2007). Recent histological analysis of IFN-I-producing pDCs during MCMV infection suggests that they are indeed localized in proximity to virus-infected cells (Tomasello et al., 2018). However, the recognition of primary infected cells by pDCs still remains to be documented in vivo, ideally by intravital microscopy. Perhaps most importantly, we need to understand how the virus-derived material is being transferred and why it can be recognized so efficiently compared to the free virus. The role of LFA-1-mediated adhesion in the process would be consistent with the analysis of homotypic pDC interactions (Saitoh et al., 2017), and is supported by blocking studies in vitro (Assil et al., 2018; Garcia-Nicolas et al., 2016) and by genetic deletion in vivo (Tomasello et al., 2018). These and other data support the formation of integrin-mediated “interferogenic synapse” between the infected cell and a pDC, as proposed in a recently deposited study (Assil et al., 2018). Future studies should elucidate molecular mechanisms that mediate the formation and function of this synapse at both sides, particularly those responsible for its specificity for pDCs.

The role of pDC in immune responses to infections

Studies of pDC activation in vitro typically produce satisfyingly robust and specific responses of pDCs to the majority of viruses. However, in vivo testing of pDC function during infections has been frequently disappointing: for instance, pDCs are not strictly required for the in vivo control of such “model” murine viruses as influenza, VSV, MCMV or acute LCMV (Cervantes-Barragan et al., 2012; Swiecki et al., 2010; Wolf et al., 2009). These results may reflect the notoriously multilayered nature of immune responses - for instance, conventional DC were shown to compensate for the absence of pDCs in infections with ectromelia virus (Kaminsky et al., 2015) or MCMV (Puttur et al., 2016). Additional reasons may include peculiarities of laboratory mice as a model, such as the mutations of

key antiviral ISG in common strains. Conversely, the role of pDCs has to be rigorously assessed by genetic ablation, as depleting or inactivating antibodies (Table 1) are not fully pDC-specific: for instance, the commonly used depletion target Bst2 (120G8, CD317, mPDCA-1) is also expressed on plasmacytes in the steady state and is induced on many cell types during infection (Blasius et al., 2006b). Ultimately, genetic models using human BDCA2-driven diphtheria toxin receptor (DTR) for acute depletion (Swiecki et al., 2010) or *Tcf4* targeting for constitutive pDC loss (Cervantes-Barragan et al., 2012) (Table 1) revealed several viral infections in which pDCs play a major role. Although these tools implicated pDCs in response to certain non-viral pathogens such as bacteria (Crother et al., 2012) and apicomplexan parasites (Spaulding et al., 2016; Yu et al., 2016), the net activity of pDCs in these models appears complex and incompletely understood.

Mouse hepatitis virus (MHV) causes an acute infection that is normally controlled in TLR7- and IFNAR-dependent manner. A strict requirement for pDCs in the control of MHV infection has been demonstrated using both antibody-mediated and genetic pDC depletion (Cervantes-Barragan et al., 2012; Cervantes-Barragan et al., 2007). Within 2 days post-infection, pDCs produce nearly all detectable IFN-I, which is critical for the survival of cDCs and macrophages (Cervantes-Barragan et al., 2009). Another prominent example of pDC dependence is systemic (but not local) HSV infection, in which pDC are required for early production of IFN-I within 8-12 hours, NK cell activation and ultimately for survival (Swiecki et al., 2013). Using a complementary genetic approach in which IRF7-dependent IFN-I production was restricted to pDCs, it was shown that pDCs are sufficient to control acute infection with Dengue and Chikungunya viruses (Webster et al., 2018). In all these models, a very rapid production of IFN-I by pDCs appears critical for protection against cytopathic effects of the virus, NK cell activation, amplification of cytokine response and overall innate control of viral replication. Notably, systemic IFN-I production is not always detectable (Webster et al., 2018), suggesting that close-range IFN-I production by pDCs may be particularly important. Given that coronaviruses, herpesviruses and flaviviruses (exemplified by MHV, HSV and Dengue virus, respectively) exerted major evolutionary pressures on mammalian immune systems, these results emphasize the critical role of pDCs in immunity and explain their emergence and evolutionary conservation.

In addition to their innate protective function, pDCs also play a key role in shaping the adaptive responses to viruses. This was first illustrated by impaired survival and accumulation of VSV-specific cytotoxic T cells upon pDC depletion (Swiecki et al., 2010). Moreover, pDC-deficient mice are unable to control persistent LCMV infection due to impaired $CD4^+$ T cell priming, which in turn impairs CD8+ T cell response to LCMV (Cervantes-Barragan et al., 2012). The role of pDCs in T cell priming may be mediated at least in part through their cooperation with cDC (Rogers et al., 2017), particularly the recruitment of $XCR1^+$ cDC1 that mediate $CD8^+$ T cell cross-priming (Brewitz et al., 2017). The effect of pDC on T cell responses is not limited to cytotoxic T cell priming and may exert broader effects on virus-induced pathology. For example, pDCs contribute to IFN-I response and control of respiratory syncytial virus (RSV) infection in the lung (Davidson et al., 2011; Lynch et al., 2018). In addition, they dampen RSV-induced Th2 responses, lung inflammation and asthma (Cormier et al., 2014), at least in part through the induction of regulatory T cells (T_{regs}) (Lynch et al., 2018). Likely reflecting the role of pDCs in long-

term adaptive responses, persistent viruses such as LCMV impair the IFN-I producing capacity of pDC (Lee et al., 2009; Zuniga et al., 2008). This “exhausted” state of pDCs was recently shown to result from a combination of impaired development, enhanced self-renewal in the periphery and persistent signaling through TLR7 (Macal et al., 2018). The role of pDCs in human persistent viral infections has been largely studied in the HIV infection, where pDCs mount vigorous IFN-I response that is protective at early stages but may drive immune pathology later in the course of infection (Aiello et al., 2018). Collectively, these results highlight the critical dual function of pDCs in antiviral responses: rapid protection through innate mechanisms such as cytoprotective effects and NK cell activation, and fine-tuning of adaptive responses through enhanced T cell differentiation. Both phenomena are likely to involve IFN-I production (both local and systemic) as well as other mechanisms such as production of additional cytokines and chemokines and possibly antigen presentation; elucidating these mechanisms represents an important challenge for years to come.

The role of pDC activation in autoimmunity

Soon after pDCs were conclusively identified as a distinct IFN-I-producing cell type, their potential role in excessive cytokine production in autoimmune disease was proposed (Ronnblom and Alm, 2001). In subsequent years, excessive or aberrant pDC activity has been implicated in almost every autoimmune or inflammatory disease. As in the case of infections, rigorous testing in genetic models appears critical to establish immune pathologies with a particularly prominent role of pDCs. For instance, genetic ablation of pDCs revealed only a mild stage-specific role of pDCs in a genetic model of psoriasis (Glitzner et al., 2014) and no role in a chemically induced model (Wohn et al., 2013). In other examples, genetic impairment of pDCs had no effect in two genetic models of colitis (Sawai et al., 2018), and exacerbated the disease in an antibody-mediated model of arthritis (Nehmar et al., 2017). Even genetic approaches occasionally produce conflicting results as illustrated by studies in atherosclerosis, where constitutive or inducible pDC ablation was shown to impair (Sage et al., 2014) or promote (Yun et al., 2016) the disease, respectively. On the other hand, recent genetic studies strongly support the role of pDCs in several autoimmune diseases.

The pathogenic role of pDC in type I diabetes was proposed based on the expansion of pDC at the onset of human diabetes (Allen et al., 2009) and pDC infiltration into islets in the NOD mouse model (Diana et al., 2013). Indeed, constitutive genetic depletion of pDCs was shown to ameliorate insulitis and significantly reduce the incidence of diabetes in NOD mice (Hansen et al., 2015). In scleroderma (systemic sclerosis, SSc), an antibody-mediated autoimmune disease that targets connective tissue including the skin, patients manifest the elevated expression of ISG (“interferon signature”) and the pathogenic immune complexes induce IFN-I production in pDCs (Eloranta et al., 2010; Kim et al., 2008). Moreover, pDCs from SSc patients produce high levels of proinflammatory cytokine CXCL4, which correlates with the risk and progression of the disease (van Bon et al., 2014). The most recent study connected the aberrant CXCL4 production to increased IFN-I expression in pDCs from SSc patients, and showed that transient pDC depletion could prevent and even revert skin fibrosis in a chemically induced animal model (Ah Kioon et al., 2018). In both

diabetes and SSc, pDC likely act locally at the sites of inflammation (pancreatic islets and skin, respectively) and/or in the regional lymphoid organs to promote inflammation through the production of IFN-I and other mediators such as CXCL4.

Perhaps the strongest case for the pathogenic role of pDCs has been built in systemic lupus erythematosus (SLE), a systemic disease driven by immune complexes of autoantibodies and nucleic acid-containing nuclear antigens (reviewed in (Panda et al., 2017)). More than half of SLE patients manifest interferon signature that correlates with clinical disease, and IFNAR deletion ameliorates SLE in experimental models. Clinical SLE is associated with the reduction of pDCs in the peripheral blood and their concomitant accumulation in tissue lesions. pDC can be induced to produce IFN-I by multiple SLE-associated molecular features including nucleic acid-containing immune complexes, complexes of DNA with antimicrobial peptides, neutrophil extracellular traps (NETs) and as shown most recently, oxidized mitochondrial DNA (Caielli et al., 2016; Lood et al., 2016). Consistent with the predominant occurrence of SLE in females, female pDC have higher IFN-I-producing capacity than male pDC, due to both cell-intrinsic and extrinsic factors (Griesbeck et al., 2015; Laffont et al., 2014). Importantly, even a transient DTR-based ablation of pDCs ameliorated SLE in two genetic models (Davison and Jorgensen, 2015; Rowland et al., 2014). Furthermore, a constitutive impairment of pDCs by monoallelic deletion of *Tcf4* strongly reduced autoantibody production and all disease manifestations in two different spontaneous models of SLE (Sisirak et al., 2014). The magnitude of the effect was particularly striking, given that *Tcf4* haplodeficiency causes only a partial reduction of pDC numbers and IFN-I-producing capacity. These data confirmed an essential role of pDCs in SLE pathogenesis as well as revealed its systemic nature: pDC are required not only for inflammation triggered by immune complexes, but also for the production of autoantibodies. This emerging role of pDC in both innate and adaptive immune responses to self is reminiscent of their dual role in antiviral responses as discussed above, and poses major questions about its mechanism. It remains to be determined what initial molecular signals cause pDC hyperactivation, and how they are sensed; the issue is particularly challenging because TLR9, the proposed major sensor of self-DNA in pDC, appears to have a net tolerogenic activity in experimental SLE. Interestingly, the mechanism of sensing in some cases may resemble the recognition of virus-infected cells, e.g. the recognition of microRNA transferred via exosomes (Salvi et al., 2018). Another question is whether pDCs act primarily through IFN-I secretion (local or systemic), the production of other soluble mediators such as IL-6 (Jego et al., 2003), or other functions such as antigen presentation. Finally, pDCs may act directly on the differentiation or maintenance of autoreactive B cells, and/or promote autoreactivity indirectly through T cells or other cell types; the former possibility is supported by studies in human cells in vitro (Jego et al., 2003; Menon et al., 2016) and remains to be confirmed and analyzed in vivo.

The role of impaired pDC activity in immunodeficiency and cancer

Mirroring pDC hyperactivation in autoimmunity, impaired pDC activity has been implicated in immunodeficient states or inefficient immune responses, e.g. to tumors. pDCs in neonates have a significantly reduced capacity to produce IFN-I in response to viruses such as RSV (Cormier et al., 2014; Zhang et al., 2014) and rhinovirus (Barlow-Anacker et al., 2017). This

reduced pDC function may contribute to increased susceptibility to infections in neonates and in particular may underline the ability of RSV to promote lung inflammation and asthma later in life (Lynch et al., 2018). On the other end of the age spectrum, pDCs from aged mice showed a significant impairment of IFNI production in vitro and during viral infection in vivo, potentially due to increased oxidative stress (Stout-Delgado et al., 2008); a similarly impaired function was observed in pDCs from elderly humans (Jing et al., 2009). Together with pDC impairment by persistent viruses as discussed above, the likely cell-extrinsic effect of aging on pDCs may contribute to impaired responses to infections and vaccines in the elderly.

Finally, studies in cancer patients showed a profoundly aberrant and/or hypofunctional state of tumor-infiltrating pDCs: in particular, pDC in breast and ovarian tumors produce IFN-I poorly yet have an increased capacity to induce T_{reg} differentiation (Conrad et al., 2012; Labidi-Galy et al., 2011; Sisirak et al., 2012). This aberrant function may be imparted by tumor-derived soluble factors such as TGF-β (Sisirak et al., 2013) and is thought to promote tumor growth as suggested by animal models (Le Mercier et al., 2013). The role of TGF-β and the tumor-promoting properties of pDCs have been recently confirmed using genetic pDC depletion in mice (Terra et al., 2018). Although activated pDCs can be administered to elicit anti-tumor T cell responses in vivo (Liu et al., 2008; Tel et al., 2013), the data so far suggest a net tumor-promoting effect of endogenous pDCs that manifest impaired IFN-I production and immunosuppressive properties. The molecular basis of pDC reprogramming in the tumor environment remains to be fully elucidated and may represent a target for immunotherapy.

Concluding remarks

Based on the knowledge of pDC biology accumulated over the last two decades, it should now be possible to address major outstanding issues, such as the molecular basis of IFN-I-producing capacity of pDCs, the nature and consequences of pathogen recognition, and the mechanisms whereby pDCs contribute to protective and pathogenic immune responses. Moreover, the field seems to be rapidly crossing the “bottleneck” towards translation of the basic knowledge into clinically relevant applications. For example, the study of pDC development helped elucidate a highly aggressive leukemia type, the blastic plasmacytoid dendritic cell neoplasm (BPDCN) - from its initial identification as the leukemic counterpart of pDCs (Chaperot et al., 2001) to better diagnostic tools and potential therapeutic approaches targeting pDC-specific transcriptional machinery (Ceribelli et al., 2016). Furthermore, the analysis of pDC function led to the development of antibodies that deplete pDCs or inhibit their function (Table 1). Further dissection of pDC regulation should facilitate the development of nondepleting reagents to modulate pDC function in the long term, e.g. dampen pDC hyperactivation in autoimmunity or reverse their dysfunction in cancer. The observations that even a partial functional modulation (Hansen et al., 2015; Sisirak et al., 2014) or a transient ablation (Ah Kioon et al., 2018; Rowland et al., 2014) of pDCs have a dramatic effect on chronic disease bode well for the utility of this cell type as a therapeutic target.

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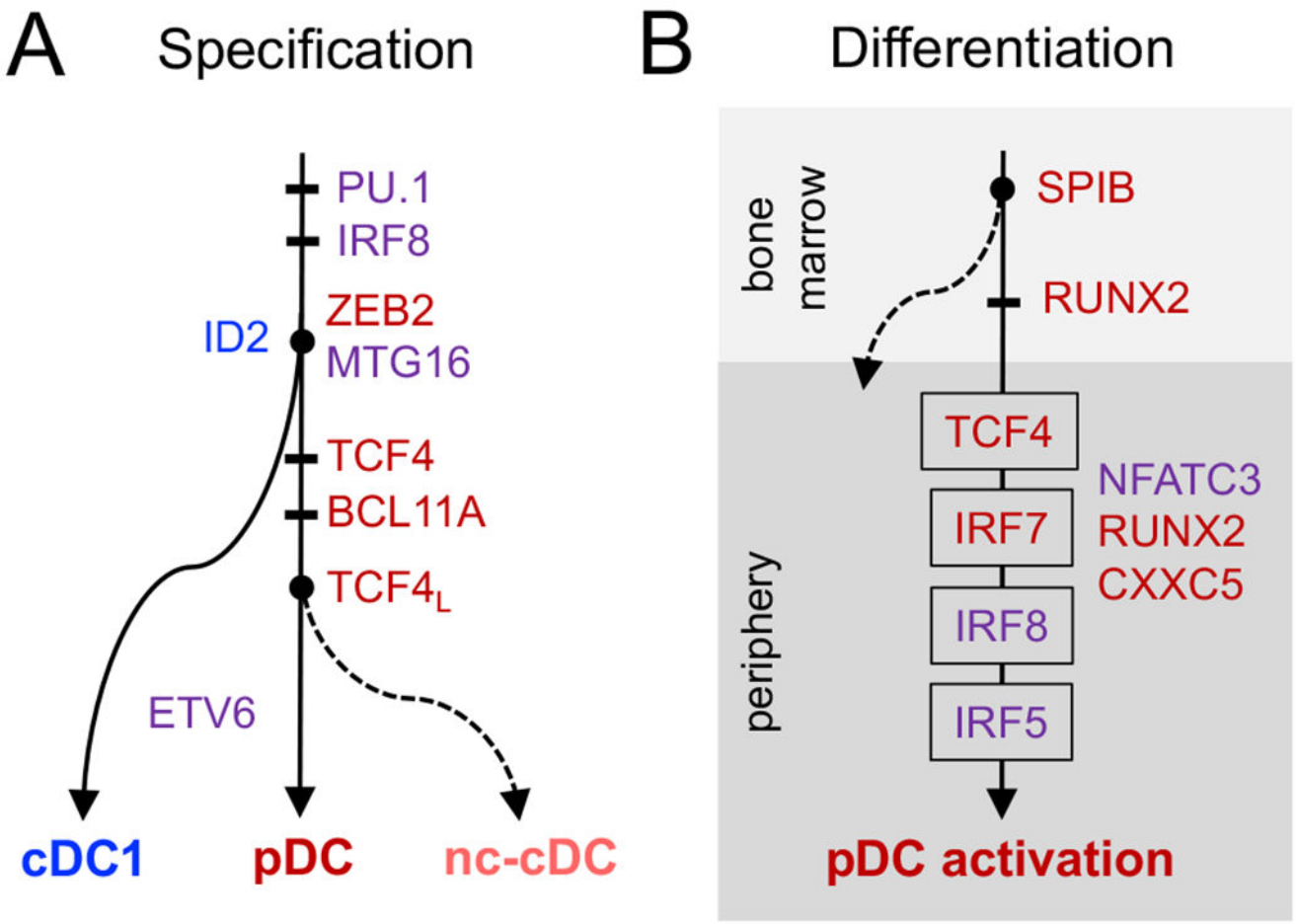

Figure 1. Transcriptional control of pDC lineage.

Transcription factors with enriched expression in pDCs, cDCs or all DCs are shown in red, blue or violet, respectively.

(A) Transcription factors that regulate pDC specification in the bone marrow. Lineage splits leading to alternative cell fates including cDC1s and non-canonical DCs are highlighted. $TCF4_L$ denotes the pDC-specific long isoform of TCF4.

(B) Transcription factors that regulate the differentiation of committed pDCs in the bone marrow and pDC functionality in the periphery.

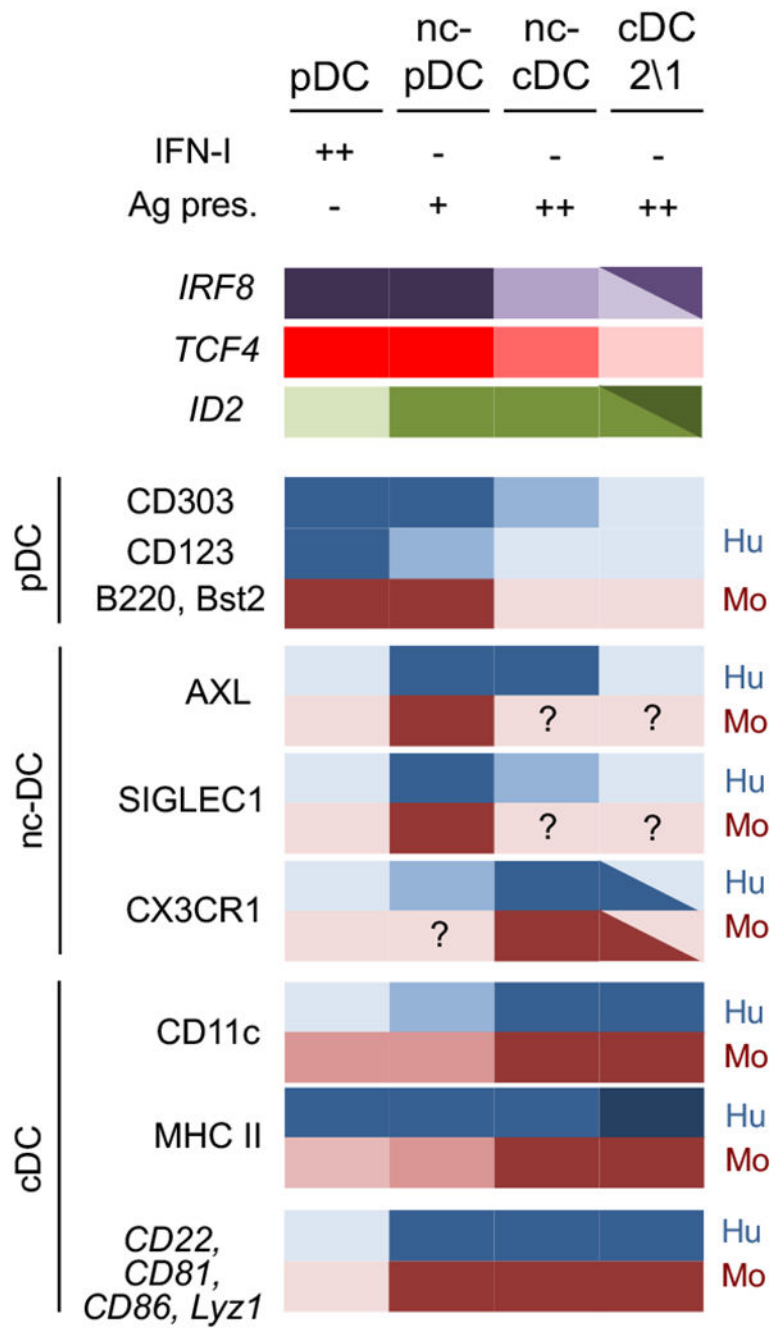

Figure 2. The proposed spectrum of dendritic cell subsets.

Shown on this hypothetical scheme are canonical pDCs and cDCs (including cDC1 and cDC2) and the intermediate "non-canonical" populations including non-canonical pDCs (nc-pDC) and cDCs (nc-cDC). Shown are functional properties including the IFN-I production capacity and antigen presentation capacity in the steady state; expression of key transcription factors; and surface markers in the human (Alcantara-Hernandez et al., 2017; Villani et al., 2017) and mouse (Bar-On et al., 2010; Lau et al., 2016; Dekker et al., 2018). Italicized genes and markers denote expression based on reported transcript levels.

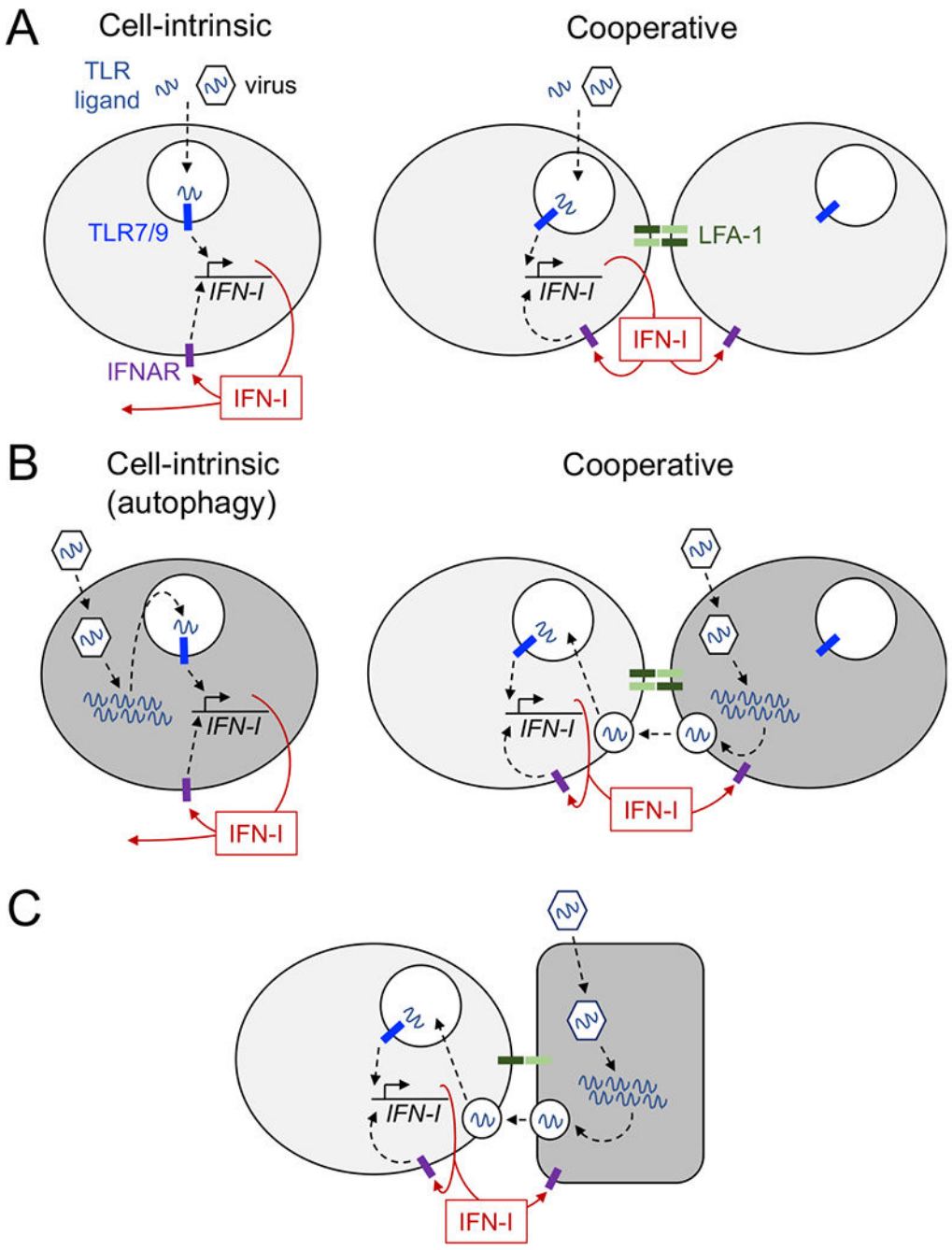

Figure 3. The mechanism of pDC activation.

(A) Activation by TLR ligands or viruses that do not infect pDCs. Shown is the traditional "cell-intrinsic" model and the emerging "cooperative" model that highlights homotypic interaction between pDCs and directional signaling and IFN secretion.

(B) Activation by viruses that infect and replicate in pDCs. Shown is the "cell-intrinsic" model based on autophagy-mediated TLR signaling, and the proposed "cooperative" model whereby virus replication and TLR signaling occur in different cells, and TLR ligands are transferred via exosomes or viral particles. An infected cell is highlighted in dark grey.

(C) Activation by viruses that infect cells other than pDCs. TLR ligands are transferred from infected cells (highlighted in dark grey) to pDCs during polarized contact via exosomes or viral particles.

Plasmacytoid dendritic cells (pDCs) are innate immune sentinels that play important roles in immunity to infection and autoimmunity. This review by Boris Reizis highlights recent progress and emerging areas of interest in pDC biology as well as translational applications.

Table 1.

In vivo depletion and functional modulation of pDCs

Driver/target	Targeting strategy	Advantages	Caveats	References
Genetic (mouse)				
Tcf4 (E2-2)	DC-specific deletion using Itgax-Cre	Constitutive specific depletion of peripheral pDCs	Complex allele combination; depletion incomplete on C57BL/6 background	(Cisse et al., 2008) (Cervantes-Barragan et al., 2012)
Tcf4 (E2-2)	Monoallelic germline deletion	Constitutive functional impairment of pDCs; single allele	Partial reduction of pDC numbers and functionality; effects in non-pDCs formally possible	(Cisse et al., 2008) (Sisirak et al., 2014)
Ikzf1 (Ikaros)	Germline hypomorphic mutation on Rag2-null background	Specific absence of peripheral pDCs	Complex allele combination; requires lymphocyte reconstitution; effects in non-pDCs formally possible	(Allman et al., 2006) (Guillerey et al., 2012)
CLEC4C (BDCA-2)	Human transgene driving DTR	DT-inducible depletion; efficient; repeated DT injections used for several weeks; single allele	Depletion of non-pDCs formally possible; side effects of DT	(Swiecki et al., 2010) (Rowland et al., 2014)
SiglecH	knock-in of DTR	DT-inducible depletion; efficient; based on endogenous mouse gene	Nonspecific - effects in non-pDCs demonstrated; concomitant SiglecH deletion; side effects of DT	(Takagi et al., 2011) (Swiecki et al., 2014)
Antibody-mediated (mouse)				
Bst2 (CD317)	Depleting mAb (clones 120G8, mPDCA-1, 927)	Rapid depletion	Short-term; can be used only in the steady state; targets other cells (e.g. plasma cells)	(Asselin-Paturel et al., 2003) (Krug et al., 2004) (Blasius et al., 2006b)
SiglecH	Agonistic mAb (clone 440c)	Rapid functional impairment	Short-term; may affect other cells (e.g. macrophages)	(Blasius et al., 2004) (Blasius et al., 2006a)
Antibody-mediated (human, primate)				
IL-3Rα (CD123)	Depleting mAb (clone CSL362)	Efficient depletion	Depletes other CD123+ cells (e.g. basophils); blocks IL-3 signaling	(Oon et al., 2016)
CLEC4C (BDCA-2, CD303)	Agonistic mAb (clone 24F4A)	Specific; causes functional impairment	Efficiency to be demonstrated in human subjects	(Pellerin et al., 2015)

DT, diphtheria toxin; DTR, diphtheria toxin receptor; mAb, monoclonal antibody