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REVIEW

A pathogenic role of plasmacytoid dendritic cells in autoimmunity and chronic viral infection

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Following the discovery of plasmacytoid dendritic cells (pDCs) and of their extraordinary ability to produce type I IFNs (IFN-I) in response to TLR7 and TLR9 stimulation, it is assumed that their main function is to participate in the antiviral response. There is increasing evidence suggesting that pDCs and/or IFN-I can also have a detrimental role in a number of inflammatory and autoimmune diseases, in the context of chronic viral infections and in cancers. Whether these cells should be targeted in patients and how much of their biology is connected to IFN-I production remains unclear and is discussed here.

Introduction

The existence in the blood of cells with high capacity to secrete type I IFN (IFN-I) was first documented in the 1950s (Lennert and Remmele, 1958). It was only in the late 1990s and early 2000s that these IFN-producing cells were defined and characterized in both humans and mice and called plasmacytoid dendritic cell (pDC) precursors (Cella et al., 1999; Siegal et al., 1999; Asselin-Paturel et al., 2001; Nakano et al., 2001). The extraordinary ability to secrete IFN-I by pDCs has driven most of our understanding about the biology of these cells, in particular how they participate in antiviral immunity and their adjuvant properties via the IFN-dependent activation of many innate and adaptive immune cells. Indeed, depletion of pDCs in mice either by targeted toxin (Swiecki et al., 2010) or E2-2 mutations (Cervantes-Barragan et al., 2012) leads to uncontrolled viral infections. Following their stimulation, these cells mature quickly from a plasmacytoid morphology into a more classic DC with the associated antigen presentation capability. These cells then stop producing IFN-I (Duramad et al., 2003; Colonna et al., 2004; Ito et al., 2006) and can then activate T cells, becoming key players in the adaptive response. The role of pDCs in linking innate and adaptive immunity to control viral infections has been well documented and reviewed (Colonna et al., 2004; Reizis, 2019). Because of their ability to contribute to both innate and adaptive responses, pDCs have been a cell type of great interest (Reizis et al., 2011), and numerous trials are underway to activate these cells in various disease indications (Reizis, 2019). However, there is strong evidence, although much of it indirect, that persistent or uncontrolled activation of pDCs through the nucleic acid–sensing TLRs contributes to a number of inflammatory and autoimmune diseases, including cancers, as well as in the context of chronic viral infections, and strategies to inhibit these cells are being tested in clinical trials (Table 1).

A key question that has raised significant debate is how much of the contribution by pDCs to immunity and/or diseases is solely due to their production of IFN-I. This is a timely question as many drugs targeting either the IFN pathway or pDCs directly are currently being evaluated in large clinical trials with various amounts of success (Table 1). The discovery and initial characterization of pDCs have been discussed in multiple review articles (Liu, 2005; Guiducci et al., 2009; Tang et al., 2010; Reizis et al., 2011; Vermi et al., 2011; Swiecki and Colonna, 2015; Reizis, 2019), so we will focus on discussing the role that they may play in promoting autoimmunity and then describe novel findings linking pDC activation and IFN-I production during chronic infectious diseases. We will also summarize the various approaches currently in clinical development that target pDCs or the IFN-I pathway, and discuss how much extrapolation can be made from recent clinical trials targeting IFN-I.

pDCs, a key cell type that links innate and adaptive immunity

pDCs have a unique role in linking innate and adaptive immunity. These cells have a lymphoid shape and a plasma cell morphology with an extensive endoplasmic reticulum, multiple mitochondria, and a small Golgi apparatus. pDCs have poor antigen presentation ability, in particular for exogenous antigens, but can acquire antigen-presenting cell function following activation with the expression of co-stimulatory molecules that can instruct T cells toward specific functional subsets. It is worth noting that phenotype mapping of human DCs suggests potential heterogeneity within the described pDC subset (Alcántara-Hernández et al., 2017; Reizis, 2019), and current markers used to identify and purify pDCs in human blood are shared by a small population of preDC that can evolve into classical DCs and may thus account for some of the observations made with pDCs (See et al., 2017). However, once activated by TLRs, the expression of co-stimulatory molecules is induced in all pDCs,

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Table 1. **Therapeutic approaches targeting the IFN/pDC pathway**

Approach	Target	Drug (name)	Company	Indication	Status
pDC depletion/ inhibition	ILT7	VIB7734	Viela Bio	Myositis	Active
	BDCA2	BIIB-059	Biogen	SLE, cutaneous LE	Active
	CD123 and CD3	XmAb-14045	Xencor	AML	Active
	CD123	IMGN632	Immunogen	AML, BPDCN, MDS, B-cell acute lymphocytic leukemia, and other CD123-positive malignancies	Active
	CD123	Talacotuzumab	Johnson & Johnson	MDS, LE, systemic cancer, AML	Active
	CD123 and CD3	Flotetuzumab	MacroGenics	AML and MDS	Active
	CD123	Elzonris (tagraxofusp)	Stemline Therapeutics, Inc.	BPDCN, AML, CMML, chronic MF, multiple myeloma in combination with pomalidomide	Approved by the FDA in 2018, for the treatment of BPDCN
IFN pathway	IFNAR1	MEDI546, anifrolumab	AstraZeneca/ MedImmune	SLE	Active
	IFN-α	MEDI545, sifalimumab	AstraZeneca/ MedImmune	SLE, dermatomyositis, and polymyositis	Inactive
	IFN-α	IFNa Kinoid	Neovacs	SLE, dermatomyositis, type I diabetes, HIV/AIDS	Active
	IFN-α and IFN-ω	JNJ-0839, JNJ-55920839	Johnson & Johnson	SLE	Active
	IFN-β	PF-06823859	Pfizer Inc.	Dermatomyositis, SLE	Active
	IFN-I antagonist	RSLV-601	Resolve	Preclinical autoimmune	Active
	Tyk2	BMS-986165	Bristol Myers Squibb Co.	SLE, psoriasis, Crohn's disease	Active
	Tyk2	NDI-031232, NDI-031301, NDI-031407	Nimbus Therapeutics LLC	Preclinical	Possibly inactive; new allosteric inhibitors in development
	Tyk2/JAK-1	PF-06700841	Pfizer Inc.	Ulcerative colitis, plaque psoriasis, and alopecia areata	Active
	Tyk2/JAK-1	SAR-20347	Sareum Holdings plc/ SRI International	IBD, MS, SLE, psoriasis, RA	Active
	JAK-3/JAK-1	Tofacitinib	Pfizer Inc.	RA, psoriatic arthritis, ulcerative colitis, ankylosis spondylitis, juvenile arthritis, dry eye syndrome	Active
	JAK kinase	Baricitinib	Eli Lilly	RA, atopic eczema, SLE, GVHD, psoriatic arthritis, alopecia areata	Active
Nucleic acid sensors	STING antagonist	TBD	Nimbus Therapeutics LLC/Cellgen	SLE, interferonopathies	Active
	TLR7/9 antagonist	IMO-3100	Idera	Psoriasis	Active
	TLR7/8/9 antagonist	IMO-8400	Idera	Cancer: Waldenström's; DLBCLMyD88(L265P); psoriasis	Active
	TLR7/9 antagonist	DV1179	Dynavax	SLE	Inactive
Immune complex digestion	RNA/immune complexes	RSLV-132	Resolve	SLE, Sjogren's syndrome	Active

AML, acute myeloid leukemia; BPDCN, blastic pDC neoplasm; CMML, chronic myelomonocytic leukemia; FDA, US Food and Drug Administration; GVHD, graft-versus-host disease; IBD, inflammatory bowel disease; LE, lupus erythematosus; MDS, myelodysplastic syndrome; MF, myelofibrosis; MS, multiple sclerosis; RA, rheumatoid arthritis; TBD, to be determined.

which confers T cell priming properties to these cells (Duramad et al., 2003; Guiducci et al., 2006). Although pDCs can be activated through different cell surface receptors and cytosolic nucleic acid sensors (Kim et al., 2010), the sensing of nucleic acids through TLR7 and TLR9 seems to be the dominant mode of activation of these cells with respect to IFN production (Liu, 2005; Guiducci et al., 2009; Swiecki and Colonna, 2015; Reizis, 2019). Signaling through these two TLRs leads to the rapid and massive production of all type I and type III IFNs, which triggers the induction of IFN-stimulated genes (ISGs), many of them with antiviral properties. Remarkably, within 10 h following the sensing of nucleic acids, >80% of all induced genes in pDCs are IFNs or ISGs (Duramad et al., 2003; Ito et al., 2006).

Because of these properties, it is postulated that the key function of pDCs is to act as antiviral cells. Consistently, pDCs have been reported to play a critical role in controlling early virus infections, as summarized in a number of reviews over the years (Colonna et al., 2004; Reizis, 2019). It is clear, however, that pDCs constitute only one of the many layers involved in antiviral responses (Wang et al., 2011). Because of their significant evolutionary pressure on the immune system, viruses can be sensed by a series of nucleic acid sensors, as well as through other pathways, that are present in most cells, including nonimmune cells. It has been extensively reported that IFN-I, in particular IFN-β, can be produced by most cell types, such as epithelial cells, in response to multiple pathogen-sensing receptors including TLRs, NOD-like receptors (NLRs), RIG-I–like receptors (RLRs), and cyclic GMP-AMP synthase (cGAS)/stimulator of interferon genes (STING), as reviewed recently (Ioannidis et al., 2013; Tan et al., 2018; Ablasser and Chen, 2019; Swanson et al., 2019). Interestingly, although potentially damaging mutations in nucleic acid–sensing TLRs are extremely rare as compared with the other cell surface TLRs (Barreiro et al., 2009; Casanova et al., 2011), patients with mutations in key elements of the TLR signaling pathways such as MyD88 or IRAK4 whose pDCs do not produce IFN in response to TLR7 or TLR9, do not show drastic susceptibility to viruses (Yang et al., 2005; Ku et al., 2007; von Bernuth et al., 2008). These findings suggest that immunity to most viruses does not depend solely on pDCs or on the TLR7/TLR9-MyD88-IRAK4 pathway (von Bernuth et al., 2012).

One of the key challenges with our ability to characterize the role of pDCs in vivo results from the inherent differences between human pDCs and their mouse counterpart. Two differences are particularly problematic. First, while the expression of TLR7 and TLR9 is restricted mostly to pDCs and B cells in human blood cells, these two TLRs are also expressed by most of the myeloid cells in the mouse (Hattermann et al., 2007; Forsbach et al., 2008; Janke et al., 2009; Guiducci et al., 2013), which contributes to some of the key differences observed between mice and humans. Second, although mouse pDCs can produce IFN-I and contribute to antiviral response (Boonstra et al., 2003; Asselin-Paturel et al., 2005; Reizis, 2019), these cells also produce pro-inflammatory cytokines such as IL-12 in quantities unseen in human pDCs (Boonstra et al., 2003; Duramad et al., 2003). The consequence of these differences is that the in vivo activation of TLR9 in humans yields a very strong IFN-I response (Friedberg et al., 2005), whereas the TLR9 response in the mouse is predominantly IL-12, IL-6, etc. One should thus be careful in extrapolating data gathered studying the mouse pDC biology to that in humans. Human pDCs can develop in humanized mice with normal phenotype and function in lymphoid organs (Zhang et al., 2011), which could prove to be relevant to studying human pDC biology in vivo.

Although pDCs clearly contribute to early antiviral immunity, it is important to distinguish their impact in acute versus chronic situations. The activation of pDCs and the production of IFN-I can be important to the antiviral response and can promote tissue repair. However, the chronic or long-term persistent activation of these cells, which can be seen in autoimmunity and persistent viral infections, can lead or contribute to impaired immunity and disease progression, as discussed below.

pDCs are chronically activated in patients with autoimmunity and contribute to disease pathogenesis

The contribution of IFN-I to mediating immune responses to infections has been well documented (McNab et al., 2015). In the late 1970s and early 1980s, a series of studies discovered increased levels of IFN-α in the sera of lupus patients (Hooks et al., 1979; Ytterberg and Schnitzer, 1982). The chronic presence of elevated levels of IFN-α in lupus and multiple autoimmune diseases has since been well documented (Baechler et al., 2003; Bennett et al., 2003; Kirou et al., 2004; Banchereau et al., 2016), and it is believed that chronic high levels of IFN-I can contribute to autoimmunity (Crow et al., 2019). The two critical questions relevant to the development of efficacious therapeutic strategies appear to be: (1) what biological effect of IFN-I can explain the promotion of autoimmunity? and (2) what are the signaling pathways involved leading to IFN production and the cellular origin of IFN-I in patients?

Biological impact of IFN-I in autoimmune disease

IFN-I has pleiotropic activities and can impact almost every cell type in the body. IFN-I consists of 13 IFN-α subtypes, IFN-β, IFN-ω, IFN-κ, and IFN-ε, and it is still unclear how the effect of these various IFNs differs on immune and/or nonimmune functions and whether this large number of genes reflects strong evolutionary pressures on the IFN pathway due to its role in antiviral immunity or underlines different biological functions. The presence of an IFN-I signature with chronic expression of ISGs is a hallmark of many autoimmune diseases, which is both striking and somewhat confusing. Indeed, it is difficult to rationalize how a common IFN-I–dependent inflammatory response can yield diseases that have very different clinical manifestations. One potential explanation is that IFNs act as adjuvants to elevate the level of inflammation in patients, thus promoting an underlying preexisting immune response to autoantigens (Fig. 1). The direct effect of IFNs on most immune cells, such as T cell differentiation and B cell activation and differentiation into plasma cells (Jego et al., 2003; Rodero and Crow, 2016; Crow et al., 2019), and on the myeloid cell compartment certainly argues for this hypothesis (Fig. 1). IFN-induced epigenetic modifications leading to increased immune activation likely play a role as well (Park et al., 2017). However, some of the commonly measured ISGs are extremely sensitive to IFN, and the ease of

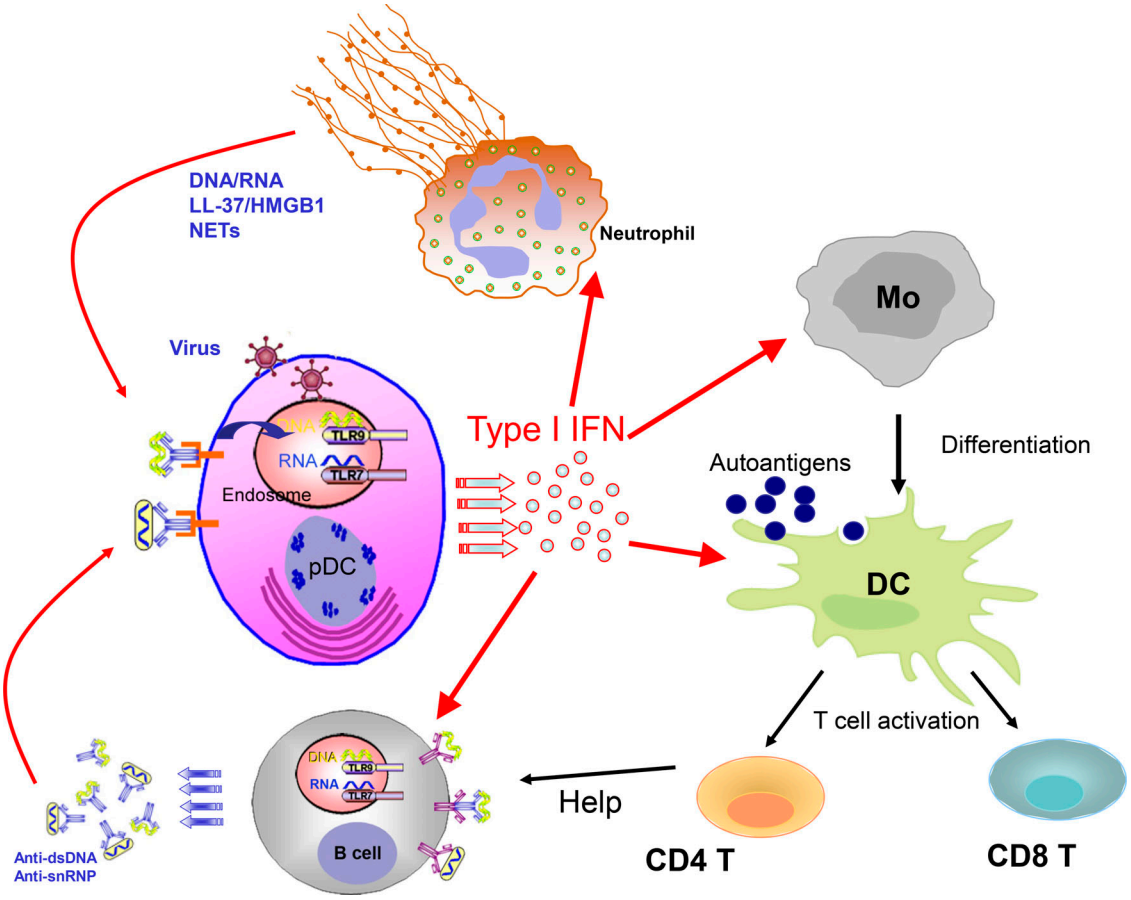

Figure 1. **The central role of pDCs and the produced IFN-I in promoting inflammatory and autoimmune diseases.** IFN-I and IFN-III are produced by pDCs in response to signals delivered by TLR7 and/or TLR9 in response to the sensing of self–nucleic acids. The accumulation of self-DNA and -RNA in the endosomes can be mediated by complexing with antimicrobial peptides, often induced by tissue injury, by anti–double stranded DNA (dsDNA)/anti–small nuclear ribonucleoproteins (snRNP) or via the uptake of DNA released by NETosis. The secreted IFN will promote the induction of many ISGs and will directly impact immune cells to promote the generation of autoantibody-producing plasma cells and autoreactive T cells. Mo, monocyte; NET, neutrophil extracellular traps.

detection might mask the fact that most of the ISGs cannot easily be functionally connected to autoimmunity.

Origin and source of IFN-I in patients

Although it is likely that the IFN response in patients with autoimmune diseases is due to difficulties in controlling or regulating immune responses to nucleic acids (Barrat et al., 2016), the identity of the cells responsible for the elevated levels of IFN-I during autoimmune diseases is unclear, and the key sensors and/or receptors that trigger IFN in these cells are also not well defined. Many genetic studies have identified mutations in DNase or genes associated with DNA and/or RNA recognition in patients with lupus-like syndrome or clearly defined interferonopathies such as Aicardi-Goutières syndrome (Rodero and Crow, 2016). This is also consistent with numerous mouse studies where deletion of nucleic acid sensors can ameliorate autoimmune diseases. It is worth noting, however, that the data are not consistent across the models tested, and mice deficient for the TLR9 gene surprisingly show exacerbated disease in many mouse models of lupus, even though the level of anti–double stranded DNA autoantibodies can in some cases be decreased (Christensen et al., 2006; Sindhava et al., 2017).

The role of TLR7 and TLR9 has been particularly well studied because of their expression on pDCs, but also due to the ability of nucleic acid–containing immune complexes to induce IFN by human pDCs through these two receptors (Fig. 1; Barrat et al., 2005; Means et al., 2005; Vollmer et al., 2005). Furthermore, the observation that lupus patients treated with a high dose of glucocorticoids still express an IFN signature due to survival signals in pDCs via TLR7 and TLR9 clearly suggests that pDCs are an important cell type involved in the sustained IFN levels in patients (Guiducci et al., 2010a), although these data do not formally exclude the possibility that other cells could contribute to the IFN, as glucocorticoids have pleiotropic activities. The contribution of pDCs to disease has also been clearly demonstrated in multiple mouse models of lupus using genetic approaches (Rowland et al., 2014; Sisirak et al., 2014), further suggesting a critical role of pDCs in lupus. The presence of pDCs in patients' skin has also been described in a series of related cutaneous autoimmune diseases including lichen planus, dermatomyositis, lichen sclerosis, and cutaneous graft-versus-host disease, which share a common pathological feature named "interface dermatitis" (Wenzel and Tüting, 2008). The close association between IFN-producing pDCs and granzyme B–positive

T cells, together with accumulation of nucleic acid–containing immune complex at the junction of dermis and epidermis (McCauliffe, 1996), suggests that the chronic presence of pDCs producing IFN-α may play a central role in disease development (Blomberg et al., 2001; Farkas et al., 2001; Wenzel and Tüting, 2008). It is tempting to speculate that the infiltration of the skin by pDCs and their activation likely by self–nucleic acids is part of the natural function of pDCs, leading to rapid secretion of IFN-I, which is important for wound healing and for initiating host immunity (Gregorio et al., 2010; Guiducci et al., 2010b). However, the presence of pDCs in the skin weeks after the initial injury suggests that these cells become chronically activated, leading to pathogenic lesions (Guiducci et al., 2010b). Whether the cells are chronically activated in the skin or are recruited to the skin over many weeks will be important to understand. The contribution of pDCs to psoriasis is less clear, as pDCs and IFN-I are not involved in the imiquimod-induced psoriasis model in mice (Wohn et al., 2013). However, the role of pDCs and IFN-I has been shown in a xenograft model (Nestle et al., 2005) and recently in a subset of TNF-treated paradoxical psoriasis patients (Conrad et al., 2018), suggesting that pDCs may contribute to psoriasis in some patients.

One key question is thus to better understand the factors that control the qualitative and quantitative response by pDCs in the skin as well as the mechanism responsible for the shutting down or resolution of the response in vivo, which we know very little about but could create some novel therapeutic approaches. Taken together, these studies in diseases with interface dermatitis as well as recent work in skin fibrosis (Ah Kioon et al., 2018) suggest that pDCs may have a dominant role in the IFN response observed in the skin, and studies aimed at targeting pDCs in patients should focus on disease indications that involve the skin. Although trials targeting TLRs have yielded inconclusive results, a recent study looking at the attenuation of pDC response using an antibody that targets the human pDC-specific BDCA2 in systemic lupus erythematosus (SLE) patients suggests that pDCs are responsible, at least partially, for the presence of the chronic IFN signature in the blood of patients (Furie et al., 2019). Interestingly, blocking pDCs in these patients had a dramatic effect on the skin, with a sustained inhibition of IFN-inducible markers in the skin of patients that correlated with amelioration of symptoms (Furie et al., 2019).

Persistent pDC activation during chronic HIV-1 infection

Intimate interaction of HIV-1 with pDCs during acute infection

Interestingly, human pDCs express high levels of CD4, the major receptor of HIV-1, and the co-receptors CCR5 and CXCR4 (Siegal et al., 1999). Indeed, HIV-1 proviral DNA is detected in HIV-infected patients' pDCs (Donaghy et al., 2003; Schmidt et al., 2004). Productive HIV-1 infection of pDCs is efficient at similar levels as T cells during acute HIV-1 infection in humanized mice in vivo (Zhang et al., 2011). However, pDCs appear to be relatively resistant to HIV-1 infection in vitro, suggesting intrinsic restriction factors that suppress productive HIV-1 replication in pDCs in vitro (Bloch et al., 2014). On the other hand, in the absence of productive HIV-1 infection, $CD4^+$ pDCs efficiently bind and endocytose HIV-1 virions to the endosome, where HIV-1 genomic RNA is recognized by TLR7, leading to the signaling cascade to activate IRF7 and the downstream IFN-I genes (Beignon et al., 2005; O'Brien et al., 2013). Reverse transcription inhibitors or fusion inhibitors fail to prevent HIV-induced pDC activation. When CD4 binding is blocked with mAb, sCD4, or anti-CD4 mAb, or when inhibitors of endocytosis are used, HIV-mediated pDC activation is efficiently abrogated (Reszka-Blanco et al., 2015). Therefore, CD4-mediated endocytosis of HIV-1 is sufficient to activate human pDCs via the TLR7 receptor in the endosome (Fig. 2). Not surprisingly, the co-receptor CCR5 or CXCR4 is not required for the process. Interestingly, CD4 seems to deliver HIV-1 virions or RNA to a unique site in the early endosome, where it preferentially and persistently activates IFN-I expression (O'Brien et al., 2016).

Regarding its role in controlling early HIV-1 or simian immunodeficient virus (SIV) infection in vivo, a number of correlative studies have been reported that indicate their immediate and efficient activation during acute infection, correlated with early induction of IFN-I and elevation of ISGs (Loré et al., 2005; Killian et al., 2006; Fitzgerald-Bocarsly and Jacobs, 2010; Lehmann et al., 2010). However, several reports also indicate that pDCs are activated during early HIV/SIV infection to recruit HIV/SIV target T cells to the gut to promote early HIV/SIV infection (Reeves et al., 2012; Lehmann et al., 2014). Due to the intrinsic limitations of mechanistic investigation in HIV-infected humans or in SIV-infected nonhuman primates (NHPs), most correlations are established between HIV or SIV infection and pDC activation in various tissues. Their exact role in controlling or promoting HIV or SIV infection in vivo is not clearly defined.

Humanized mice transplanted with human immune tissues or cells have been developed to study HIV-1 infection (McCune et al., 1988, 1991; Namikawa et al., 1988; Bonyhadi et al., 1993). We and others have reported that human pDCs with normal percentage and function are developed in lymphoid tissues in humanized mice (Traggiai et al., 2004; Zhang et al., 2011; Tanaka et al., 2012). Importantly, HIV-1 infection results in T cell depletion, correlated with immune activation in lymphoid organs of humanized mice as in human patients (Zhang et al., 2011). Human pDCs are rapidly activated by HIV-1 infection, and the level of pDC activation is correlated with $CD4^+$ T cell depletion (Zhang et al., 2011), which is consistent with the observation from HIV-1–infected patients (Buimovici-Klein et al., 1983, 1986; Meier et al., 2009) and SIV-infected monkeys (Campillo-Gimenez et al., 2010; Harris et al., 2010). An mAb to human CD303 (BDCA-2) that specifically and efficiently depletes human pDCs in all lymphoid organs in humanized mice has been used to characterize the role of human pDCs in HIV-1 infection and immunopathogenesis during HIV-1 infection (Li et al., 2014, 2017; Zhang et al., 2015; Zhao et al., 2018). When pDCs were depleted before infection and during acute HIV-1 infection, HIV-1 replicated to significantly higher levels in all tissues, and no IFN-I or ISGs were detected. Remarkably, human CD4 depletion was reduced by pDC depletion in the presence of higher HIV-1 viremia. Therefore, pDCs are the major source of IFN-I during acute HIV-1 infection, which suppress HIV-1 replication but contribute to CD4 T cell depletion (Li et al., 2014; Cheng et al.,

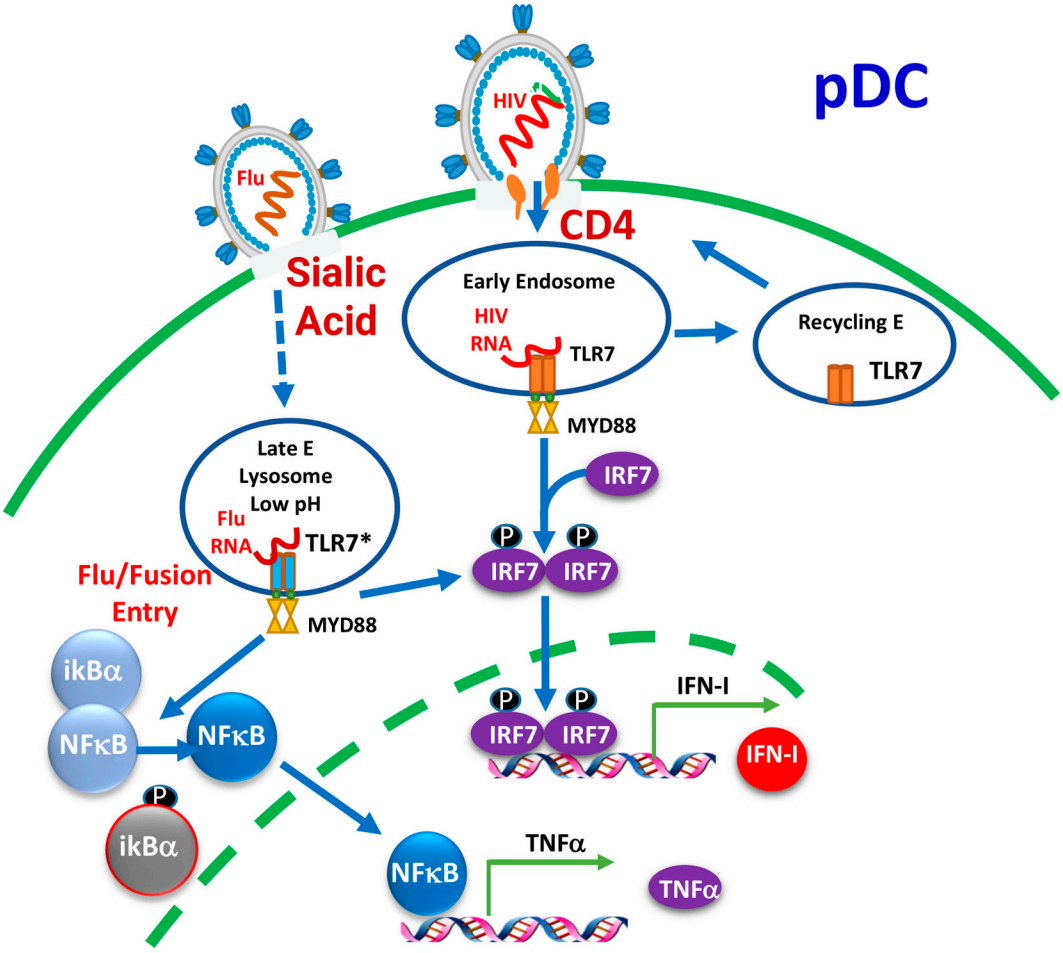

Figure 2. **CD4-mediated endocytosis of HIV-1 leads to persistent/repeated IFN-I induction in pDCs.** HIV-1/CD4 traffics predominantly to early and recycling endosomes, where HIV-1 genomic RNA interacts with TLR7 to activate MYD88, NFκB, IRF7, and IFN-I, leading to repeated response to TLR7 stimulation and persistent IFN induction. In contrast, influenza virus is endocytosed further to late endosomes or lysosomes, where the cleaved TLR7* responds to the flu genomic RNA more rapidly and transiently to activate IRF7 and NFκB. The low pH–induced fusion of flu is critical for flu entry and infection. P, phosphorylation; E, endosome.

2017a, 2018a; Su, 2019. To define the role of IFN-I in HIV-1 pathogenesis, blocking IFNAR1 during chronic HIV-1 infection in humanized mice also reduced CD4 T cell deletion in the presence of higher viral replication (#29750; Cheng et al., 2017a). Consistently, blocking IFN-I signaling in NHP with a recombinant human antagonistic IFN-β with IFN-α/β receptor (IFNAR) binding activity but diminished IFN-I activity led to elevated SIV replication, although elevated SIV diseases were observed during later years of infection (Sandler et al., 2014).

pDCs are persistently activated during chronic HIV-1 infection

Persistent hyperinflammation has been associated with pathogenesis in HIV-1 and SIV infection, but the underlying cellular and molecular effectors remain elusive (Deeks, 2011). In the years before highly active antiretroviral therapy (HAART), persistent IFN-α production was reported to correlate with HIV-1 disease progression, and IFN-α was used as a vaccine to induce IFN-α–neutralizing antibodies in HIV-1 patients (Gringeri et al., 1999). Although interrupted by the HAART enrollment of the trial patients, the subgroup of immunized patients with a rise in anti–IFN-α antibodies showed a significantly lower rate of HIV-1–related diseases (Gringeri et al., 1999). When pDCs were first characterized in the peripheral blood of HIV-infected patients, it was reported that pDCs were severely depleted during HIV-1 infection (Siegal et al., 1999; Soumelis et al., 2001). Later studies have demonstrated that, following HIV-1 infection, activated pDCs migrate to lymphoid and inflammatory tissues (Lehmann et al., 2010). Persistently activated pDCs in lymphoid tissues seem to be linked with HIV-1 disease progression (Liu, 2005; Sabado et al., 2010; Zhang and Su, 2012; Miller and Bhardwaj, 2013). First, IFN-I and ISG responses persist in HIV-1 infection and pathogenic SIV infections in Asian macaque species, but resolve to baseline in nonpathogenic SIV infections of sooty mangabeys and African green monkeys (Bosinger et al., 2009; Jacquelin et al., 2009). Second, pDCs from sooty mangabeys exhibited more rapid resolution of IFN-α production in response to SIV than rhesus macaques (Bosinger et al., 2013) and exerted lower IFN-α response in response to TLR triggering (Mandl et al., 2008). Third, HIV-infected patients who do not exhibit disease despite high

plasma virus loads have paradoxically low levels of ISG expression (Rotger et al., 2011). However, the functional role of pDCs in HIV-1 in patients or SIV in monkeys is not clearly defined.

To test the role of persistent pDC activation in HIV-1 diseases, several reports have documented efforts to modulate pDC activity with endocytosis inhibitors in human patients, or with TLR7/9 antagonist or TLR7 agonist in SIV-infected NHP. To block pDC endocytosis/activation, HIV-1 patients were treated with clinical doses of chloroquine used for treating malaria, with unclear effects on HIV-1 diseases (Routy et al., 2015; Jacobson et al., 2016). Similar efforts have been made to define the role of IFN-I signaling in SIV-infected NHP models. In a recent report, administration of recombinant IFN-α in SIV-infected NHP treated with HAART showed no significant effect on SIV persistence (Palesch et al., 2018). Similarly, blocking IFN-I induction with a TLR7/TLR9 antagonist in SIV-infected monkeys showed no significant beneficial effect on early SIV infection (Kader et al., 2013). A recent study with an mAb that neutralizes most IFN-α (but not other IFN-I subtypes) in SIV-infected NHP showed only slightly elevated SIV replication but no significant effect on T cell function or pathogenesis (Carnathan et al., 2018). Although generally interesting, the reported findings regarding the role of pDC/IFN-I from HIV-infected patients or SIV-infected NHP are not definitive, due to the limitation of reagents and experimentation in human and nonhuman primates.

Role of pDC in HIV-1 infection and pathogenesis in humanized mice

Depletion of pDCs with the anti–BDCA-2 mAb in humanized mice could diminish IFN-I production during early HIV-1. Additionally, the depletion of pDCs could protect human immune cells in the presence of increased HIV-1 replication (Li et al., 2014; Zhang et al., 2015). To test the role of IFN-I signaling in humanized mice with persistent HIV-1 infection, the HIV-1 replication levels in the IFNAR1-blocked group were also enhanced, which is associated with suppression of ISG expression. Interestingly, human T cells were rescued in number and functions in anti-IFNAR1 mAb–treated mice. Hence, blocking IFNAR1, like pDC depletion (Li et al., 2014; Zhang et al., 2015), also enhanced HIV-1 replication but reversed HIV-1 diseases during persistent HIV-1 infection in humanized mice (Cheng et al., 2017a,b, 2018a). When an mAb against IFNAR2 was used in humanized mice, however, HIV-1 replication was suppressed, which is associated with reduced immune hyperactivation (Zhen et al., 2017). It is not clear how blocking IFNAR1 or IFNAR2 had a distinct impact on HIV-1 replication, ISG induction, or immune activation. Other factors that are different in the two reports also include different HIV-1 isolates and different strains of immunodeficient mice.

As in human patients, combination antiretroviral therapy (cART) or HAART could efficiently inhibit HIV-1 replication, but HIV-1 reservoirs persist and rebound rapidly after cART discontinuation (Choudhary et al., 2009; Denton et al., 2012; Kalscheuer et al., 2012; Marsden et al., 2012; Cheng et al., 2017a). As in HIV-1 patients, cART fails to fully suppress HIV-induced inflammation, including ISG induction. When cART is stopped, HIV-1 rebounds rapidly to pre-cART levels. Therefore, humanized mice provide a highly relevant model to study HIV-1 reservoir persistence, immunopathogenesis, and therapy, as reported with broadly neutralizing antibodies (Halper-Stromberg et al., 2014), therapeutic vaccines (Cheng et al., 2018b) and IFNAR-blocking mAb (Cheng et al., 2017a; Zhen et al., 2017) for HIV-1 reservoir reduction or elimination.

Human T cells are partly rescued by cART in number in humanized mice. However, IFNAR blockade is needed to fully reverse inflammation and T cell exhaustion (PD1/TIM3 induction) in CD8 T cells. Blocking IFNAR during chronic HIV-1 infection in humanized mice led to complete rescue of T cell number, reversion of T cell immune exhaustion, and anti-HIV T cell activity. Most importantly, anti-IFNAR mAb has rescued anti-HIV T cell immunity (Zhen et al., 2017; Cheng et al., 2018b). Consequently, HIV-1 reservoirs, as measured by both cell-associated HIV DNA and cells with infectious HIV-1, are reduced in the IFNAR-blocking mice. Furthermore, when cART is stopped, a significant delay of HIV-1 rebound is observed (Cheng et al., 2017a). Therefore, pDC depletion or IFNAR blockade provides a new strategy to reduce or control HIV-1 reservoirs (Cheng et al., 2017a,b, 2018a; Deeks et al., 2017; Zhen et al., 2017) (Fig. 3).

Therapeutic approaches targeting the pDC/IFN-I axis

There are multiple therapeutic approaches currently targeting either one or more IFN-I, their receptors, the TLRs or other nucleic sensors that can induce IFNs, or the pDCs themselves (Table 1). Each of these approaches offers some advantages, but all have limitations as well. The key questions are to understand (1) whether success or failure of any of these approaches in one disease would predict the outcome in other related diseases; and (2) how redundant these pathways are, in particular whether the outcome of a trial targeting the IFNAR, is predictive of a pDC-depleting strategy. We would argue that this is not the case for both questions. As discussed above, it is unclear how the elevated serum levels of specific IFN-I subtypes or of ISGs can lead to autoimmune diseases with different affected organs, different serological markers, and different overall pathogenesis. The challenge is thus to determine the direct link between specific IFN-Is, ISGs, and specific organ damage, and untangle the direct and dominant contribution of IFN to disease. Furthermore, it is expected that approaches as different as blocking the JAKs or IFN itself or depleting pDCs would impact the IFN or host immune responses in such a different way, at the mechanistic level, that it is not possible to translate the efficacy of drugs targeting one pathway to predict the effect of others.

The recent report that a phase III trial testing the effect of anifrolumab, an mAb that blocks the IFNAR in SLE, did not meet its primary endpoint was disappointing news, in particular in light of the promising data of the phase II trials. Although we still have much to learn from this and other trials that are still under way using the IFNAR-blocking antibody, it begs to question as to how much these data would help predict the impact of a pDC-targeted approach. First, there are inherent differences in both strategies. The approach of blocking the IFNAR, which is expressed in most cells of the body, must assume that the effect will be partial, as it is improbable to reach a complete block in every cell at the dose tested. Further data looking at the

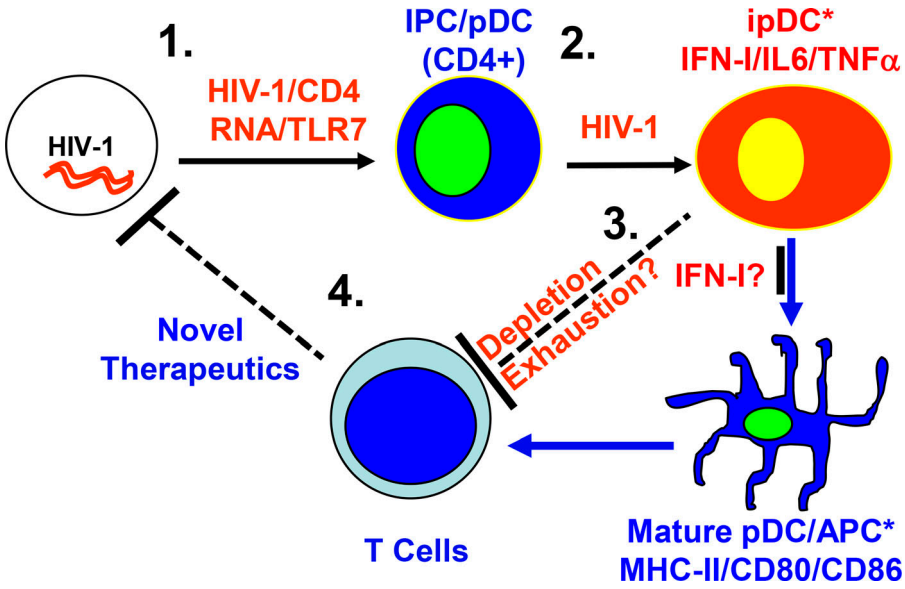

Figure 3. **Induction of inflammatory or immature pDCs (ipDCs) during chronic HIV-1 infection.** HIV-1 activates pDCs via CD4-dependent endocytosis and HIV-1 RNA-mediated TLR7 activation (1). Persistent activation of pDCs by HIV-1 leads to accumulation of ipDCs (2). ipDCs deplete and impair T cells via unclearly defined IFN-dependent mechanisms (3). Targeting the ipDC/IFN-I axis can rescue anti-HIV T cells to help control HIV-1 (4). IPC, IFN-producing cell; ipDC, immature pDC.

pharmacology of anifrolumab outside blood cells, where the effect is by definition maximal, would be very informative. It is predicted that targeting pDCs will also lead to a partial effect on IFN production, but for different reasons. All the IFN-Is and IFN-IIIs would be reduced but only from a single source and likely following the engagement of the TLRs. Pathways involving other nucleic acid sensors in other cells would not be impacted. Second, it is abundantly clear that pDCs have many other biological functions outside of the IFN that they produce. The kinetics of IFN production is very limited to the first hours after TLR triggering, and pDCs then exert strong antigen presentation capabilities. In addition, pDCs secrete cytokines such as IL-6, TNF, and IL-12 and control directly or indirectly the expression of many proinflammatory cytokines and chemokines, suggesting that the inhibition or depletion of pDCs could have a wider impact than just targeting IFN-I. These cells are also activated through other TLR-independent ways and produce critical chemokines that help direct the immune response. However, their role in the skin appears critical, while their contribution to the inflammatory response in other organs is less clear. Thus, focusing on the skin to evaluate pDC-targeting drugs would take advantage of a strong scientific rationale and less complex clinical designs. The recent report showing that attenuation of pDCs using BIIB059, a humanized mAb that binds the pDC marker BDCA2, led to reduced IFN signals and cellular infiltration in skin lesions with decreased CLASI-A score (Furie et al., 2019) is a strong indication that an organ-specific approach with a primary focus on the skin may be a promising strategy with such drugs. One can argue that pDCs can be defined as "professional adjuvant cells," which would explain the potent adjuvant effect of CpG-containing oligonucleotides in humans. Targeting pDC is thus predicted to impact IFN production but importantly to directly inhibit immune responses to autoantigens (Fig. 1).

Tumor-associated pDCs (TA-pDCs) are detected in multiple human cancers. In human breast cancers (Treilleux et al., 2004) and ovarian cancers (Conrad et al., 2012), infiltration of pDCs is significantly associated with worse prognosis in survival and metastasis. In human patients with multiple myeloma, TA-pDCs are shown to suppress antitumor CD8 T cells, associated with tumor growth (Chauhan et al., 2009; Ray et al., 2017). Therapeutic strategies that eliminate or reprogram TA-pDCs will likely provide a novel immunotherapeutic approach to treating human cancers with high levels of TA-pDCs.

Concluding remarks

The contribution by IFN-I produced by pDCs to antiviral immunity has been well described. Evidence suggests that similar pathways may drive the pathogenesis of autoimmune and autoinflammatory diseases but also chronic infections and cancer. Trials targeting the IFNs, their receptor or signaling components of IFNAR, the nucleic acid sensors, or the pDCs are underway, and initial results have been mixed. It is possible that a key issue is that the IFN response in the context of an autoimmune disease mirrors the situation of antiviral responses where multiple cell types and pathways are involved, depending on the kinetics of the response, the organ, the pathogen, or the mode of infection. This creates a situation where targeting specific organs or symptoms might be preferable, rather than aiming at reducing the overall disease. Carefully designed clinical studies targeting specific sensors or cell types will be required to untangle this question. The concept of blocking the IFN/pDC axis in chronic infectious diseases is not intuitive due to the key role of IFN in antiviral response, but the recent findings in diseases such as HIV and other diseases with common pathogenic mechanisms of persistent activation suggest that IFN-I and pDCs play a detrimental role. The safety of targeting the IFN pathways should be carefully evaluated, in particular in patients who often receive immunosuppressive drugs, and whether the risk/ratio of such treatment will be to the benefit of patients. Finally, it remains to be determined whether blocking IFN/pDC will lead to transient amelioration of symptoms or could lead to a disease-modifying scenario that would reduce the treatment cycle and the overall risk of adverse events for patients.

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