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Plasmacytoid Dendritic Cells in Cutaneous Disorders

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Abstract Skin immune surveillance is granted by a complex contingent of sentinel innate immune cells with antigen-presenting function. The latter include Langerhans cells (LCs), multiple subsets of dermal dendritic cells (DDCs), and dermal macrophages (DMs). As for other peripheral non-lymphoid tissues, the microenvironment of the normal skin is lacking plasmacytoid dendritic cells (PDCs), a circulating DCs subset that mainly populates primary and secondary lymphoid organs. PDCs accumulation in the skin is observed in different cutaneous inflammatory disorders, including autoimmunity and viral infection. This review will summarize current knowledge on the biology of skin DCs and will highlight the functional role of PDCs in the complex microenvironment of well-characterized cutaneous disease models.

Keywords Plasmacytoid dendritic cells · Psoriasis · Lupus erythematosus · IFN-DC · Interferon · TLR · Molluscum contagiosum virus · Blastic plasmacytoid dendritic cell neoplasm

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Abbreviation

DCs	Dendritic cells
DDCs	Dermal dendritic cells
DMΦ	Dermal macrophages
PDCs	Plasmacytoid dendritic cells
IFN	Interferon
IFN-I	Type I interferon
TLR	Toll-like receptor
BPDCN	Blastic plasmacytoid dendritic cell neoplasm

Introduction

The skin-associated immune system protects the host against a different array of external and endogenous insults. Immune cells of the skin have a significant role in the organization of the first line of defense by triggering microbicidal mechanisms and activating the inflammatory response. Among innate components of the immune system, dendritic cells (DCs) consist of a heterogeneous population of leukocytes that can direct adaptive T- and B-cell immune responses to different antigens. With some potential exception, human DCs are mostly bone marrow derived $CD45^{+}MHC\text{-}II^{+}$ cells lacking markers of lineage, such as CD3, CD14, CD16, CD19, and CD56. Different DCs populations have been classified based on their dominant location (lymphoid organs DCs, intraepithelial and interstitial DCs in nonlymphoid peripheral tissues), presumed origin (myeloid DCs and plasmacytoid DCs [PDCs]), or functional properties (e.g., regulatory, tolerogenic). In the skin, different resident DCs subsets can be identified in the epidermis and dermis. In addition, circulating DCs can be recruited to the site of inflammation in various skin disorders. We revise the recent discoveries on the DCs repertoire of the normal human skin and highlight the role of PDCs in cutaneous diseases.

Dendritic Cell Populations in Normal Skin. What's New on the Shelf?

DCs are important sentinels of skin immune system. Expression of MHC-II molecules in normal skin identifies a complex contingent of professional antigen-presenting cells, including DCs and dermal macrophages (DMs; Fig. 1). Intraepidermal DCs correspond to the unique Langerhans cells (LCs) population that can be easily identified on section by the expression of a panel of markers (e.g., S100 protein, CD1a, E-caderin), including the recently identified Birbeck granules associated protein Langerin (Fig. 1). In the skin, stellate LCs are regularly found in the suprabasal layers of the epidermis in close contact with keratinocytes.

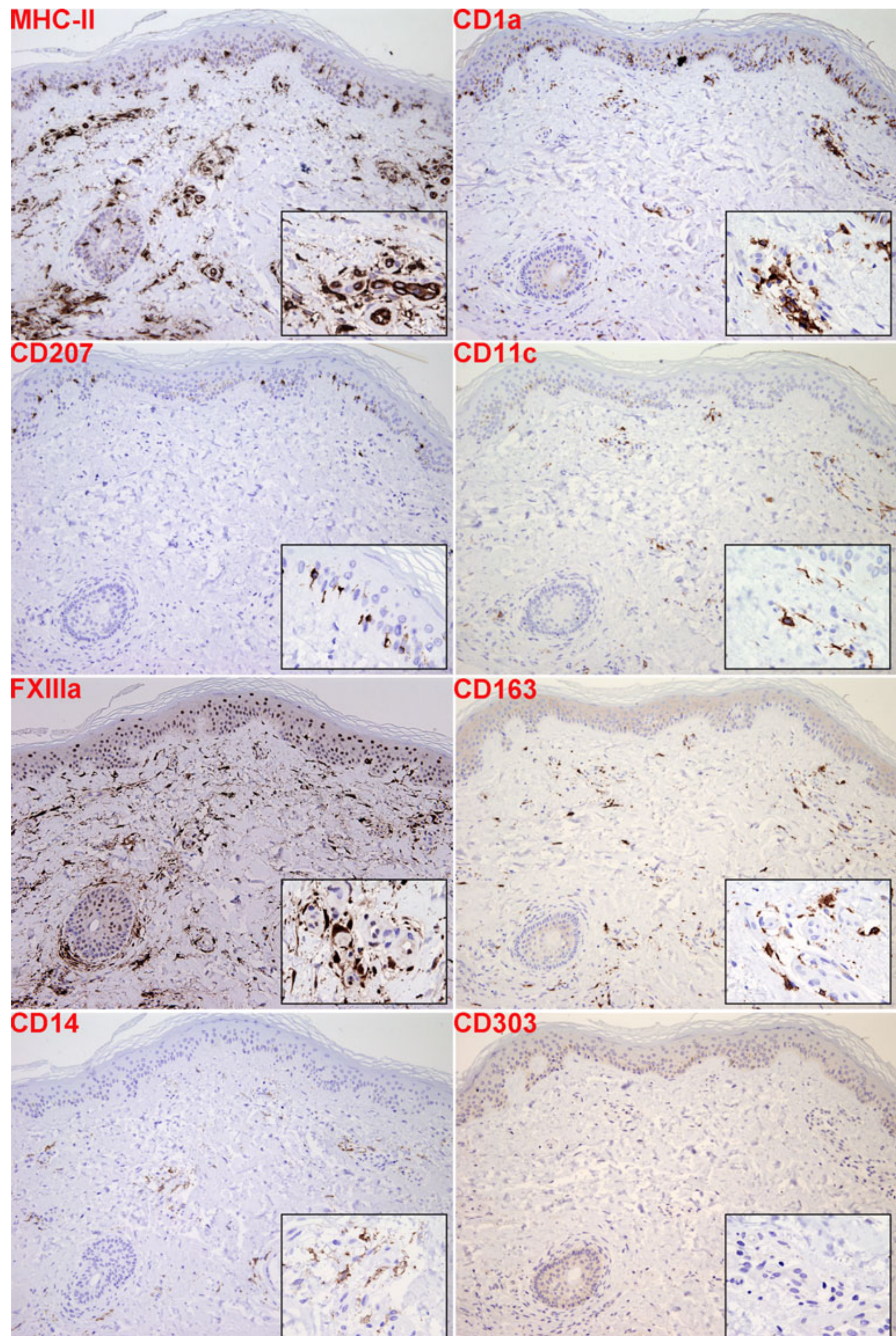

Fig. 1 DCs markers in human normal skin. Formalin-fixed human skin sections are stained as labeled (revealed by DAB, brown). Sections are counterstained with Meyer's hematoxylin. Magnification 100× and 400× (insert)

Upon antigen encounter, they migrate via lymphatics to the T-cell area of draining lymph nodes to regulate skin adaptive T-cell immune responses to different pathogens. Although LCs represent one the most well studied antigen-presenting cell population, it is still not completely understood whether they elicits T-cell activation or tolerance [1, 2]. We recently reported that interleukin (IL)-34, the alternative CSF1R ligand, is abundantly produced by skin keratinocytes and selectively directs the developmental program of LCs [3]. Significantly, IL-34-deficient mice lack LCs and show an attenuated contact hypersensitivity reaction, supporting the hypothesis that LCs more likely promote T-cell activation.

In the dermis, antigen-presenting cell populations are far more complex. Dermal DCs (DDCs) are considered the skin counterpart of interstitial DCs found in the interstitium of solid organs. Although DDCs have long been defined as a homogeneous population based on the expression of the transglutaminase factor XIIIA (FXIIIA) [4], it is now clear that there is no single feature (morphology or localization) or marker that allows a correct distinction between DDCs and DMs. In analogy to other tissues, most of the markers used for the identification of cutaneous myeloid DCs and macrophages significantly overlap (Fig. 1). In the past 5 years, the usage of classical DDCs markers combined with antibodies to blood dendritic cell antigens (BDCA1-3) either on dermal single cell suspensions and on sections, significantly changed the scenario of skin DCs [5, 6, 7••, 8–14]. In addition to DMs, it can be now possible to distinguish at least three major DDCs subsets in the dermis (Table 1). The most abundant DDCs subset is represented by CD1c + (BDCA-1) immature mDCs. These cells coexpress CD11c, CD209, and low levels of CD1a. They likely migrate to draining lymph nodes via CCR7 where they can potently stimulate T cells, although at lesser extent compared with mature DCs [12]. In addition to CD1c + DCs, reports from different groups indicated that CD14+ DCs normally occur in the dermis; this DCs subset is more closely related to blood monocytes and *in vitro* derived DCs, as indicated by their transcriptomic profile [7••]. Finally, a third DCs subset is characterized by high expression of CD141 (BDCA-3). CD141 identify thrombomodulin, an integral membrane protein expressed on the surface of endothelial cells, blood monocytes, and circulating DCs that serves as a cofactor for thrombin. The occurrence of $CD141^{+}$ DDCs was originally reported more than a decade ago by Cuzzi-Maya and colleagues [15]. Interestingly, the recent phenotypic (expression of XCR1, TLR3, CLEC9A, and CADM1) and functional analysis of $CD141^{high}$ DCs indicate that they are capable to efficiently cross-present antigens to T cells [14]. Recently, also SlanDCs, which were initially described as large population of circulating proinflammatory DCs, have been identified among resident DDCs [16]. Although it is conceivable that circulating PDCs can occasionally home to normal skin and be detected by fluorescence-based *in situ* strategies, as previously reported [12, 17], an extensive analysis of formalin-fixed normal human skin sections performed in our laboratory indicates that BDCA2+ PDCs are not part of the resident skin DCs contingent (Fig. 1).

Brief Overview of Human PDCS

More detailed overview covering different areas of PDCs history and biology can be found elsewhere in the literature [18–20]. From the identification as “lymphoblasts” by Karl Lennert in 1958 [21], PDCs were given a number of different names [22, 23]; however, when *in vitro* data provided evidence that they represent a subset of DCs [24] and produce high amount of type I interferon [25, 26], a functional terminology has been adopted defining these cells either as to plasmacytoid dendritic cells or interferon-producing cells.

PDCs originate in the bone marrow from a dendritic cell progenitor common to PDCs and conventional “myeloid” DCs [27, 28]. In the blood, they are defined by the HLADR +/CD11c-/lin-/CD123+/BDCA-2+ phenotype. In tissues, PDCs mainly reside in the peripheral lymph nodes and tonsils [29, 30] but also can be found in the thymic medulla, bone marrow, spleen (at the boundary between white and red pulp), and mucosa-associated lymphoid tissue. Although different reagents have used in the past, CD123 and BDCA-2/CD303 represent the most specific and sensitive markers for PDCs [31•, 32]. It should be keep in mind, however, that CD123 can be detected with lower intensity on other cell types, such as endothelial cells [33], activated macrophages, and subsets of dendritic cells [31•]. BDCA-2/CD303 can be partially lost upon PDCs activation in inflammatory processes [32, 34], but no other cells are known to express this antigen. Interestingly, PDCs express granzyme B but not perforin and TIA-1 [35, 36]. PDCs show distinctive profile of pathogen recognition receptors, mainly expressing the endosome-associated Toll-like receptors (TLR)-7 and 9. Their engagement (viral RNA and DNA sequences) in PDCs leads to powerful type I interferon (I-IFN) secretion and differentiation to DCs [37–39]. The master mediator of I-IFN production occurring downstream of TLR-7/9 signaling is the transcription factor IRF7, whose constitutive expression by PDCs also may explain their robust production of this cytokine upon activation [40].

In addition to I-IFN, PDCs produce other cytokines, including tumor necrosis factor (TNF)-α, IL-6, and CXCL8 [41, 42], and proinflammatory chemokines, such as CXCL9, CXCL10, CCL3, CCL4, and CCL5 [43], thus participating to the organization of a panoply of innate and

Table 1 Dominant phenotype of DDC and DMs in human normal skin based

Marker	MΦ (IS/FC)	$CD1c^+$ DC (IS/FC)	$CD141^{high}$ DC (IS/FC)	CD14 DC (IS/FC)
CD11c	[12] Negative / [9, 12]Positive^L	[11, 13]Positive / [12]Positive^H	ND/ [7••, 13] Positive$^{L\ to\ I}$	ND/ [6]Positive
CD1a	[9]Negative / [6]Negative	[11, 13]Positive/ [6]Positive	ND/ [7••]Positive^L	ND/ [5, 8]Negative
CD163	[6, 12]Positive / [6, 12]Positive^H	[12]Negative / [6]Negative	ND/ND	ND/ [6, 16]Positive ^{L}
FXIIIa	[6]Positive / [12]Postive^H	[12] Negative/[12]Positive^L	ND/ND	[11]Positive/ [6, 8]Positive
CD68	[9]Positive/ND	Positive [12]/ ND	ND/ND	[5]Positive/ ND
CD206	[9, 12]Positive/ ND	[12]Positive /ND	ND/ND	[5]Positive/ ND
CD209	[9, 12]Positive/ ND	[12, 13]Positive/ ND	ND/ ND	[5]Positive/ [8]Positive
CD207	[9]Negative/ ND	[12]Negative/ ND	ND/ [7••]Negative	ND/[5, 8]Negative
CD1c	[6]Negative/[12]Negative	[12]Positive/[12]Positive^H	ND/ [7••]Positive	ND/[8]Negative or [6]Positive
CD303	[12]Negative/ ND	[12, 13]Negative/ ND	[13]Negative/ND	[13] Negative/ ND
CD141	ND/ND	ND/ [7••, 12]Positive^L	ND/ [12]Positive^H	ND/ [7••]Negative
CD14	[9]Positive/ [6]Positive	[11, 13]Negative/ ND	ND/ [7••]Negative	[5]Positive/ [5]Positive^H

IS in situ technique (immunohistochemistry and immunofluorescence); *FC* flow cytometry; *L* low; *I* intermediate; *H* high; *ND* not done

adaptive immune responses [42]. I-IFN regulates many T-cell functions, including long-term T-cell survival and memory T-helper 1 polarization, CD8+ T-cell cytolytic activity, and interferon (IFN)-γ production [39]. PDCs also potentiate NK cell-mediated cytotoxicity and IFN-γ production, induce differentiation and maturation of myeloid DCs and, together with IL-6, cooperate in the differentiation of B lymphocytes into immunoglobulin-secreting plasma cells [44]. It has been shown that PDCs also can kill tumors and virus-infected cell lines, either by secreting TRAIL (TNF-related apoptosis-inducing ligand) upon activation or indirectly by activating other cytotoxic cells via I-IFN [45, 46].

Cutaneous Migration of PDCS to Inflamed Skin

Details on the mechanisms guiding PDCs to human tissues have been extensively reviewed elsewhere by our group [19]. Although mostly absent in peripheral nonlymphoid tissue, blood PDCs can accumulate in inflamed tissues [18–20], particularly in the skin. This propensity might reflect the expression of skin homing molecules by PDCs. Circulating PDCs express multiple chemotactic receptors; however, only CXCR4 and ChemR23 are biologically active receptors in healthy donors [19, 47]. Because CXCL12 is widely expressed in tissues, the CXCR4/CXCL12 axis might account for PDCs accumulation in many pathological conditions. Significantly CXCR3 ligands increase the chemotactic response of PDCs to CXCL12 [48, 49]. Recently, we have proposed chemerin and its cognate receptor, ChemR23, as a crucial chemotactic factor for human PDCs in different skin inflammatory disorders [50]. In the following sections, we will summarize data supporting the role of PDCs in the pathogenesis of some of the most relevant skin disorders. It is well established that PDCs are capable of organize the local immune response in inflamed tissues. In particular, they represent a relevant source of proinflammatory chemokines, including CCL3, CCL4, CCL5, CXCL9, and CXCL10, which can attract activated CD4+ and CD8+ T cells to sites of inflammation [19, 43].

Autoimmune Inflammatory Dermatoses

PDCs accumulate in some inflammatory dermatoses where they participate to the organization of the local immune responses [51]. The most characterized examples are lupus erythematosus (LE) [52] and psoriasis (PS) [53••]. In LE and PS, cutaneous accumulation of PDCs is dependent on the local activation of the chemerin/ChemR23 axis [32, 50, 54••]. In particular, chemerin is strongly produced in the inflamed skin by keratinocytes, dermal vessels, and fibroblasts, whereas skin-infiltrating PDCs express ChemR23. In this context, it should be considered that the release of proteolytic enzymes, such as cathepsin G, elastase, and tryptase by activated neutrophils and mast cells is instrumental to convert inactive prochemerin to functional chemerin. Remarkably, the kinetics and distribution of cutaneous PDCs infiltration as well as mechanisms of PDCs activation are different in these two conditions.

In LE skin lesions, PDCs generally persist during the entire spectrum of the disease [32]. By studying the immune cell repertoire in a large cohort of LE skin biopsies, we could confirm cutaneous infiltration of $BDCA2^+$ PDCs as

hallmark of LE. However, PDCs were more frequently observed and numerous in cutaneous LE compared with systemic LE, suggesting a broader tissue distribution of this cells in the systemic form of the disease. Remarkably, the distribution of cutaneous PDCs showed two distinct patterns. More commonly, PDCs were observed within perivascular inflammatory nodules in the dermis, associated with mature DCs, whereas a second component was observed along the dermal-epithelial junction (junctional PDCs; Fig. 2). A large body of preclinical models and clinical evidences (reviewed in [52]) has suggested a fundamental role of PDCs in the pathogenesis of LE, mainly via IFN-I production. Accordingly, we could document that type I IFN-inducible gene MxA is abundantly produced in LE skin by keratinocytes, dermal inflammatory cells and vessels. In LE, IFN-I is induced in response to nucleic acid-containing immune complexes internalized through FcγRII-mediated endocytosis. Immune complexes reach the endosomal compartment and activate TLR9. PDCs activation is further prolonged by the HMGB1-RAGE interaction [55•]. HMGB1, a nuclear DNA-binding protein, is passively released from damaged (i.e., necrotic) cells or secreted by monocyte-derived cells including macrophages and myeloid DCs exposed to inflammatory cytokines [56, 57]. Significantly, both keratinocytes and dermal mononuclear inflammatory cells in the skin samples from patients with LE showed strong induction of HMGB1 [58]. HMGB1 also is secreted by PDCs stimulated with CpG ODN and might regulate the production of IFN-I in an autocrine fashion [59]. All of these findings suggest that HMGB1 may contribute significantly to the persistent local activation of PDCs in LE, where immune complexes deposition, tissue damage, and recruitment of myeloid DCs and macrophages co-occur. LE PDCs also express the cytotoxic molecule granzyme B and, remarkably, the junctional PDCs contingent is found in association with perforin-expressing cytotoxic T cells in areas of severe epithelial damage. These findings suggest a potential contribution of junctional PDCs to the generation epithelial cell death not only as adjuvant (via IFN-I) but also as effector cells via secretion of cytotoxic molecules. Granzyme B production by PDCs requires IL-3 and is enhanced by the immunosuppressive cytokine IL-10 [60]. However, it remains to be clarified which proinflammatory stimuli in LE PDCs can execute the granzyme B effector program. Cytotoxic damage is a major pathological event in the "interface" dermatitis found in LE, and similar changes, albeit to a lesser extent, can be observed in lichen planus, where PDCs colocalize at the dermoepidermal junction with NK cells [61].

Compared with LE, the role of PDCs and INF-I in the pathogenesis of PS has been envisaged only recently [62]. Relevant to the pathogenesis of PS is the combination of events involving both keratinocytes and immune cells [63]. It is widely accepted that a skin immune reaction to still unknown antigens is central to PS. Th1- or Th17-polarized infiltrating T-cells are skewed to produce IFN-γ, TNF-α, IL-17, and IL-22. Also, innate immune cells, including neutrophils, monocytes, macrophages, and natural killer T cells, have been implicated in the pathogenesis of PS. Infiltration of IFN-I producing PDCs in PS has been recently demonstrated by different groups and appear to be predominantly found in early phases of the disease (Fig. 2) [53••, 54••]. Significantly, xenograft models indicate that blocking of IFN-I production by PDCs or IFN-I signalling inhibits expansion of pathogenic T-cells and PS development [53••]. However, based on the kinetics of the PDCs distribution in human PS skin [53••, 54••] (presence only in early active plaque but not in the chronic phase), it seems that only transient production of IFN-I is required for PS to develop. PDCs activation in PS is linked to the cationic endogenous antimicrobial peptide LL37. The bioactive form of LL37—a member of the cathelicidins family produced by keratinocytes and neutrophils—results from cleavage of the hCAP18 propeptide by serine proteases [64]. LL37 is able to bind and convert extracellular self-DNA fragments into aggregated particles that are resistant to DNase. These complexes enter PDCs by lipid-raft mediated endocytosis and once delivered to the early endocytic compartments potently trigger TLR9-dependent IFN response [65•, 66•]. Significantly, binding of HMGB1/RAGE to these complexes might prolong their association with TLR9. It has been recently demonstrated that also self-RNA forms complexes with LL37 [65•] capable to induce TLR7 activation in PDCs leading to IFN-I secretion. In PS lesions [67] LL37 is

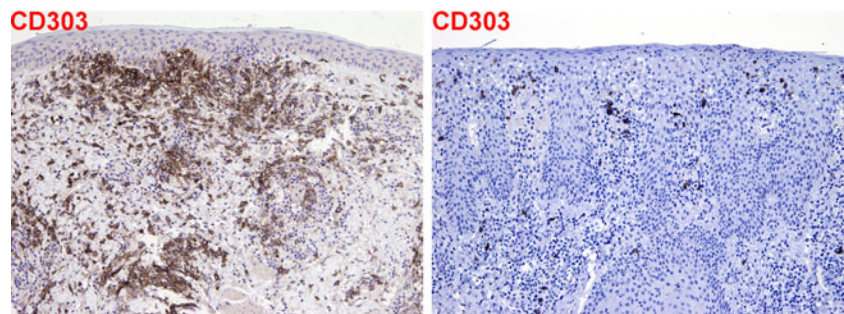

Fig. 2 PDCs in LE and PS. Formalin-fixed human skin sections are from LE (left) and PS (right) patients and stained for anti-CD303 (revealed by DAB, brown). Sections are counterstained with Meyer's hematoxylin. Magnification 100×

strongly induced in keratinocytes throughout the development of the lesion. An additional source of LL37 that might sustain PDCs activation is represented by neutrophils that might represent a significant fraction of the immune cell repertoire in PS. A very recent finding by Tohyama et al. suggests a new connection between IFN-I and PS by showing that this cytokine specifically up-regulates the expression of IL-22R on keratinocytes [68•]. This data strongly support the hypothesis that PDCS cross-talk with IL-22 producing T cells might contribute to regulate epidermal remodeling in PS [69].

Role of PDCS in Immune Surveillance to Skin Tropic Viruses

PDCs can detect viral RNA and DNA through TLR7 and TLR9 and secrete large amounts of IFN-I in response to a variety of viruses in vitro and in vivo [37]. It is well established that IFN-I confers resistance to viruses by different mechanisms (reviewed by [39]) However, PDCs may contribute to antiviral defence through additional mechanisms including direct- or cross-presentation of viral antigens to T cells [70, 71] and T helper 1 (Th1) cell polarization of CD4+ T cells by secreting IL-12 [72, 73]. In addition, PDCs can directly exert effector function and kill virus-infected cells through FasL- and TNF-related apoptosis inducing ligand (TRAIL)-dependent mechanisms [45, 74]. When tested *in vivo* in the optimal experimental system, specific PDCs depletion impacts on the amplitude of virus-specific NK cell or CD8+ T-cell responses in a fashion that is dependent on the infecting agent and viral burden [75••].

In humans, the role of PDCs in viral infections has been suggested in the setting of HIV and hepatitis [76–78]. In the human skin, accumulation of PDCs has been reported only in acute varicella infection [79] and in HPV-associated *Verruca vulgaris* [80]. Our group recently characterized the local immune cell repertoire in *Molluscum contagiosum* virus (MCV) infection of the skin [31•]. In immune competent host MCV, induces self-limiting tumor-like cutaneous lesions that can undergo spontaneous regression preceded by local inflammation. The cellular mechanisms underling this event are still incompletely understood. In our study, we analysed 36 cases of MCV-induced skin lesions. By histology and immunohistochemistry, we identified highly immunogenic MCV-induced lesions showing a dense and composite immune reaction associated with cell death in keratinocytes. Immune cell infiltration consisted of numerous cytotoxic T cells admixed with natural killer cells and IFN-I producing PDCs. Among IFN-I target cells infiltrating regressing MCV lesions we could identify a cell population resembling the so-called “IFN-DCs” characterized by the expression of CD123, CD11c, CD16, and CD14. IFN-DCs represent recently identified DCs populations that can be generated in vitro by type I IFN conditioning of peripheral blood monocytes [81–86]. In vitro generated IFN-DCs are effective in taking up antigens and produce several chemokines and cytokines that can induce Th1 and Th17 polarization [87, 88•]. In addition, IFN-DCs also might exert direct effector function via TRAIL and Granzyme B [89]. These and additional series of data [90•] have suggested clearly that IFN-DCs might represent promising adjuvants for cancer immunotherapy. In our study, we showed that MCV-infiltrating IFN-DCs strongly reacted to IFN-I inducible genes. In addition, these cells were strategically located in close proximity to apoptotic keratinocytes, suggesting their direct involvement in the rejection process. It has been reported that IFN-DCs can contribute in different ways to the local immune surveillance to viruses. IFN-DCs can cross-present viral antigen to $CD8^{+}$ T cells, increase the immunogenicity of infected cells by producing IFNs or exert effector functions through GrB and TRAIL [84, 91]. In our study, we could document GrB and TRAIL expression by MCV-associated IFN-DCs and, accordingly, our in vitro generated IFN-DCs showed a strong induction of TRAIL and FasL. It is still unclear how PDCs get activated in MCV-lesions [92]. In addition to a direct sensing of MCV through TLR9, PDCs can be activated by contact with MCV-infected keratinocytes. A third hypothesis suggests PDCs might sense self-DNA or self-RNA complexed to LL-37 secreted by keratinocytes and surrounding polymorphonuclear cells. To our view, PDCs and IFN-DCs might significantly also contribute as effector cells to clear MCV from the skin of infected patients. It is highly likely that IFN-DCs can be generated in other clinical settings, including autoimmune disorders, such as LE, PS, and lichen planus [87]. In the latter cases, it will be of worth to establish how IFN-DCs impact skin pathology.

Blastic Plasmacytoid Dendritic Cell Neoplasm

Tumoral proliferations of plasmacytoid dendritic cells (PDCs) are rare hematological neoplasms, which may occur in two clinically and pathologically different forms, respectively derived from mature and immature PDCs. The former mainly involves lymph nodes and bone marrow and is invariably associated with a clinically dominant myeloid neoplasm [93], whereas blastic plasmacytoid dendritic cell neoplasm (BPDCN) derives from immature precursors of PDCs and shows a distinctive cutaneous tropism, with rapid and progressive systemic extension [94]. The striking tendency of BPDCN tumor cells to localize to the skin has been related to the expression of antigens that favour skin migration, such as CLA and CD56 [95], as well as to the local

production of ligands of chemokines expressed by tumor cells (CXCR3, CXCR4, CCR6, CCR7) [96]. BPDCN occur in approximately 75 % of cases in males and the median age at diagnosis is 66.0 years, but 13 % of cases have been reported in individuals younger than age 20 years. There are currently no clues to the etiology of BPDCN, and Epstein-Barr virus (EBV) as well as other viruses (HIV, HCV, HHV6, HHV8, CMV, and HTLV-1 or 2) are generally negative [97•].

There are no specific karyotypic abnormalities in BPDCN. BPDCN belongs to the wide spectrum of myeloid neoplasms that display *TET2* mutations [98]. Nevertheless, the genetic as well as the gene expression profile [99] in BPDCN is fundamentally distinct from that in myeloid leukemias; in particular, *JAK2* or *NPM* mutations are regularly lacking [98, 100], whereas tandem duplication of *FLT3* (TD-*FLT3*) are very rarely observed [97•]. Overall, the complex genetic anomalies encountered in BPDCN have been shown to result in losses of factors involved in the G1/S transition pathway and on the cell-cycle checkpoint controlling proteins (e.g., *CDKN2A, CDKN2B* genes, *RB1, LATS2, TP53, CDKN1B,* and *ETV6*) [101, 102] that could represent a crucial and early oncogenic event in BPDCN, providing a basis for the phenomenon of chemoresistance that frequently develops, despite an initial favorable response to chemotherapy.

The overall health of patients at presentation is generally good, and the main reason for seeking medical advice is cutaneous lesions. The interval between the first symptoms and the diagnosis ranges from 1 to 18 months [103]. The clinical presentation of skin lesions is extremely heterogeneous: they can be solitary, grouped in one area, or generalized, and appear as flat maculae, plaques or nodules; the size ranges from few millimeters to several centimeters, and the appearance may be erythematous, hyperpigmented, reddish, bluish, purpuric, erosive, or even necrotic [104, 105]. BPDCN is characterized by a rather monomorphous and dense infiltrate composed of cells with blastic features resembling myeloblasts or lymphoblasts [94, 97•]. Diagnosis of BPDCN inevitably relays on immunophenotyping: the expression of CD4 and CD56 (the latter representing an antigen not expressed on normal PDCs) in the absence of lineage specific markers for myelomonocytic, NK cells, T cells, or B cells, has defined the majority of cases of BPDCN. BPDCN diagnosis has been greatly improved with the development of more specific PDCs-associated markers, such as CD123, TCL1, BDCA-2/CD303, CD2AP [97], and BAD-LAMP BPDCN [106]. Due to their blastic nature, aberrant expression of antigens related to immaturity like TdT and CD117, but not CD34, can be observed.

BPDCN may show a deceptively indolent clinical presentation, with initial resolution of symptoms in most cases using a variety of intensive chemotherapy regimens or steroids, but the course is almost invariably aggressive, with early relapses and rapid extracutaneous dissemination, with or without overt leukemia. The median survival varies from 10 to 16.7 months. At present, there is no consensus for optimal treatment of BPDCN, but sustained clinical remission or cure has been reported in patients who received acute leukemia chemotherapy regimens and allogeneic stem cell transplantation in first complete remission [103, 107–109]. Although allogeneic stem cell transplantation is now advocated for BPDCN treatment in adults, its role in pediatric cases is unclear, and it has been recommended that treatment of children with BPDCN would include ALL-type therapy with central nervous system prophylaxis, reserving SCT for second complete remission or for cases in which initial treatment does not induce a rapid or complete remission [110].

Conclusions

PDC are absent in healthy skin. However, a series of preclinical and clinical observations have confirmed that they are recruited to inflamed skin in different disorders, mainly via Chemerin/ChemR23 axis. Although it is still largely unknown how PDCs interact with other resident immune cells, it is now clear that activated PDC sustain autoimmunity in predisposed individuals but might also eradicate cutaneous-tropic viruses. In skin autoimmunity, PDCs amplify and polarize local adaptive immune responses *via* production of IFN-I and exert direct effector functions at the dermoepidermal interface. This set of valuable information is forming the groundwork for targeting cutaneous PDC infiltration and activation in these disorders.

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- • Of importance
- •• Of major importance

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