Mini Review

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The Biology of Plasmacytoid Dendritic Cells and Their Role in Pathogenesis of Erythema Multiforme and Other Inflammatory Dermatoses: A Mini Literature Review

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Abstract

Plasmacytoid Dendritic Cells (pDCs) are a unique dendritic cell population with both innate and adaptive immune functions. When pDCs get activated by various pathogens or self-DNA, they are able to produce massive amount of interferon type I and play an essential role in immune defense mechanisms. Plasmacytoid DCs are generally absent from the normal skin. In the past decade, their involvement in pathogenesis of different inflammatory dermatoses has been widely explored. Plasmacytoid DCs' excessive sensing of non-self or self-DNA (upon skin injury) was addressed as a primary trigger for many cutaneous pathologies. Recently, we have also shown significant amount of pDCs in erythema multiforme lesions and hypothesized that these cells are central to EM pathogenesis as well. However, neither EM pathogenesis nor pDCs' actual role in this entity is well studied. In this mini review, our goal is to outline recent updates on pDCs and their role in particular inflammatory skin diseases such as psoriasis. Our focus will also be the highlights of our recent study and our perspective regarding relationship between pDCs and EM.

Keywords: Plasmacytoid dendritic cell; pDCs; Erythema multiforme; Inflammatory dermatoses

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Introduction

Plasmacytoid Dendritic Cells (pDCs) were initially described as a specialized DC subset that responds to viruses with massive production of type I interferon and play a crucial role in antiviral immune response [1,2]. However, accumulated evidence indicated that pDCs have many other functions including linking innate and adaptive immune system, recognizing various pathogens and tolerance induction [1,3,4]. It was also shown that pDCs can be involved in the initiation and development of many autoimmune and inflammatory conditions [1].

Plasmacytoid DCs mainly reside in lymphoid tissues and represent approximately 0.1% to 0.5% of peripheral blood mononuclear cells [1,2]. Although pDCs are not normally present in peripheral tissues, they can accumulate in inflammatory sites and contribute to ongoing inflammation [3]. Hence, PDCs have been implicated in various inflammatory dermatoses such as psoriasis [2]. Our recent study also demonstrated that pDCs are important in the pathogenesis of etiologically different variants of erythema multiforme, especially the virally-induced variant [5]. In this mini review, we aim to summarize the recent advances in PDCs' biology, functions as well as their unique role in EM and other certain inflammatory dermatoses.

Development, Identification and Functions of pDCs

Plasmacytoid dendritic cells are constantly produced from hematopoietic stem cells in the bone marrow *via* both myeloid and lymphoid pathways [1,4]. Upon their production and activation of the CXCR4–CXCL12 signaling pathway, mature PDCs migrate to the primary and secondary lymphoid organs *via* peripheral blood [1, 4]. Naive PDCs manifest a plasmacytoid morphology and express low levels of major histocompatibility complex (MHC) [1,3]. In contrast, activated PDCs gain dendritic cell-like morphology and up-regulate their MHC, and T-cell costimulatory molecule expressions [1,3].

Plasmacytoid DCs were initially identified by their selective expression of CD303 (BDCA2), CD304 (BDCA4), Immunoglobulin-like Transcript 7 (ILT7), CD4, CD45RA, CD68, ILT3 and CD123 [1]. They were shown to be negative for the lineage-associated markers CD3, CD19, CD14, CD16 and CD11c [1]. Later, a specific subset of CD2hi CD5+CD81+ pDCs was discovered to express the pDC markers CD123, CD303 and CD304 [1]. Upon activation,

instead of IFN-I, these cells secrete IL-12 and potently boost T- and B-cell responses [1]. After the advance in single-cell analysis, pDCs were divided into two subsets: 1- Canonical IFN-I-producing pDCs; 2- Axl+ DCs, which are the non-canonical pDCs and inefficient at IFN-I production. Moreover, activated canonical pDCs were divided into three subpopulations based on their CD80 and PD-L1 expression [6]. P1-pDCs (PD-L1+CD80-) show a plasmacytoid morphology and are specialized in type I interferon production [6]. The P3-pDCs (PD-L1- CD80+) display a dendritic morphology and promote T cell activation and Th2 differentiation [6]. Lastly, the P2-pDCs (PD-L1+CD80+) adopted a phenotype and morphology between the P1- and P3-pDCs with both innate and adaptive functions [6]. On the other hand, the immune functions of Axl+ DCs has been much less elucidated due to their more recent discovery [1].

Well-established and the most prominent feature of pDCs is the massive secretion of type I interferon following Toll-like receptor (TLR)7 and TLR9 activation [7]. TLR7 has been shown to detect guanosine- or uridine-rich Single Stranded RNA (ssRNA) viruses (such as influenza virus). While TLR9 responds to ssDNA molecules that consist of unmethylated CpG-containing motifs (such as herpes simplex virus 1 and some bacteria) [7]. The activation of TLRs induces multiple signaling pathways and transcription factors which results in the production of immunomodulatory and prionflammatory molecules, like IFN-α [7]. To a much lesser extent, pDCs also produce IL-6, IL-8, tumor necrosis factor-α and IFN-λ in response to viruses [1,3].

Plasmacytoid dendritic cells are important immunomodulatory cells that have a wide variety of effects on both innate and adaptive immunity [3]. They play a central role in the activation and recruitment of Natural Killer (NK) cells [3]. Additionally, pDCs are involved in the differentiation of cytotoxic CD8+ T cells and effector CD4+ T cells that secrete IFN-γ, maturation of IL-4 secreting T cells, and plasma cell differentiation [3,8]. Besides having direct anti-viral effects, IFN-I secretion also promotes the function of myeloid DCs [3]. Although *in vitro* studies have proven that the human pDCs are able to present antigens, this has yet to be demonstrated *in vivo* [7,9].

Plasmacytoid DCs have been shown to induce CD4+ T cell anergy, CD8+ T cell deletion, and Treg differentiation, thus display tolerogenic functions [8]. It was also suggested that recirculating pDCs might help the inactivation or deletion of autoreactive T cells through presenting self-antigens in the thymus [8].

Role of pDCs in Pathogenesis of Different Inflammatory and Autoimmune Dermatoses

Under normal conditions, pDCs are not present in the skin and other peripheral non-lymphoid tissues. However, upon viral skin infections or skin injury, as well as during certain inflammatory skin disorders, pDCs can migrate from the blood into the affected area [2]. Many studies revealed the pDCs' functions in the initiation, progression and aggravation of cutaneous dermatoses [7]. It was shown that pDCs do not always defend the host against harmful insults and sometimes play a pathologic role instead.

Regardless of the initiating factor, the immune reaction is suggested to play a key role in the skin's response to a variety of injuries [10]. The keratinocytes are shown to be central to the initiation of immune-mediated skin injury [10]. They recognize pathogen-associated molecular patterns (PAMPs) of microbial origin and Danger-Associated Molecular Patterns (DAMPs), such as toxins through TLRs. Subsequently, cytokines and chemokines produced by keratinocytes activate DCs and pDCs. These cells further recruit and activate T lymphocytes [10].

Normally, host-derived self-DNA released into the extracellular environment by damaged cells cannot activate TLR9 in pDCs. However, due to the error in certain protective mechanisms, pDCs may recognize self-nucleic acids and contribute to many autoimmune and/or inflammatory dermatoses [7]. Here, we will briefly review psoriasis, lupus erythematosus and lichen planus and their association with pDCs.

Psoriasis and pDCs

Psoriasis is a common T-cell mediated chronic inflammatory disease that is characterized by the abnormal proliferation and differentiation of keratinocytes. In the early stages of psoriatic lesions, large numbers of activated pDCs are present in the dermis (**Figure 1**). In a study where pDCs were targeted by using anti-BDCA-2 antibody that inhibits their ability to produce IFNs, it further blocked the activation of autoimmune T-cell and development of skin lesions [2]. This study clearly shows that pDC activation and IFNs in the psoriasis lesion drives autoimmunity and contributes to the development of this disease.

Persistently high antimicrobial peptide LL37 was described as a central mediator of pDC activation in psoriasis [2, 7]. The overexpression of this peptide causes an excessive formation of LL37/DNA complexes that trigger pDCs to produce IFNs. Subsequently, IFNs cause an uncontrolled maturation of myeloid DCs, which are the main stimulators of autoreactive T-cells, such as Th1 and Th17 cells. These cells secrete IFN-γ, IL17 and IL22, which increase the expression of cationic antimicrobial peptides including LL37 in keratinocytes. This pathway potentially explains the persistently high level of LL37 in patients with psoriasis. In contrast, common epidermal damage induces LL37 expression transiently. The Koebner phenomenon, the appearance of new psoriatic lesions on previously unaffected skin secondary to trauma, can also be explained by this pathway [2, 11].

Lupus erythematosus and pDCs

Lupus erythematosus (LE) is a complex autoimmune disease with a broad spectrum of clinical presentations ranging from isolated cutaneous lesions to systemic multi-organ involvement. Pathogenesis of LE is well established and IFNs as well as pDCs are widely involved in this matter (**Figure 2**) [7].

LE is characterized by the production of antibodies to self-nucleic acids. Depending on the underlying subtype, different antibodies can be involved in the pathogenesis [7]. The autoantibodies

bind to self-nucleic acids released by apoptotic cells and form immune complexes [2]. Subsequently, these immune complexes are accumulated in the skin and other target organs [2]. Autoantibodies bind to low-affinity Fc receptor FcγRII and mediate the internalization of immune complexes [2]. By this method, self-nucleic acids become enabled to activate TLR9 and TLR7 in pDCs, which leads to IFN-driven inflammation and disease development [2].

Lichen planus and pDCs

Lichen planus (LP) is another chronic, inflammatory disease of the skin and mucous membranes where pDCs play a central role in the pathogenesis (**Figure 3**) [2,7]. Initially, high levels of IFN-α inducible protein MxA was identified in the LP lesion [2]. Later, many studies revealed the presence and activation of pDCs which produce IFN-I [2]. However, the trigger for pDCs in LP remains a mystery [2]. It was suggested that LL37/DNA complexes may be the trigger for pDC activation due to the Koebner phenomenon [2]. Upon showing human herpes virus type 7 (HHV-7) in LP lesions, researchers proposed that pDCs can get activated through TLR9 [7]. However, HHV-7 is not present in the majority of cases of LP and thus, cannot serve as the sole attribution [12].

Role of pDCs in Pathogenesis of Erythema Multiforme

Erythema Multiforme (EM) is an immune-mediated reaction that involves skin (EM minor) and/or mucosal surfaces (EM major). EM is associated with variety of agents i.e. viral (herpes simplex virus), bacterial (mycoplasma pneumonia), drugs, etc [13]. As oppose to well-defined etiologic factors, the pathophysiology of EM is still not completely understood. In Herpes-Associated EM (HAEM), it is believed that the HSV DNA fragments are transported to the distant skin areas by mononuclear cells; hence, the keratinocytes are shown to express viral genes [14]. Thereafter, CD4+ Th1 cells infiltrate the lesion and secrete IFN-γ to recruit more inflammatory cells [14]. Intriguingly, autoreactive T-cells carry on the main inflammatory response, which suggests

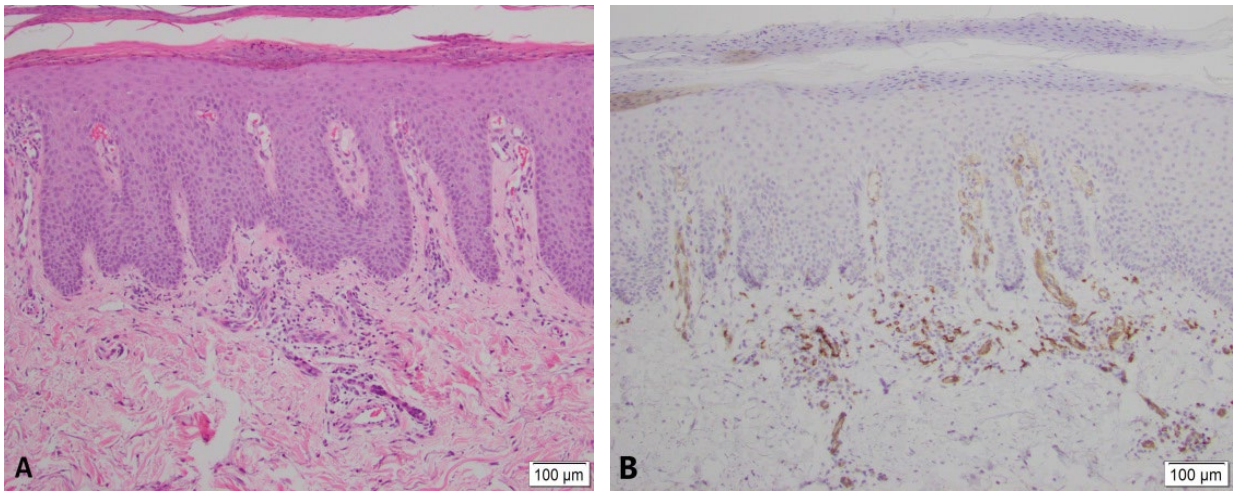

Figure 1: H&E and CD123. This figure shows epidermal hyperplasia with dermal lymphocytic infiltrate (A) and presence of pDCs (B) in psoriasis.

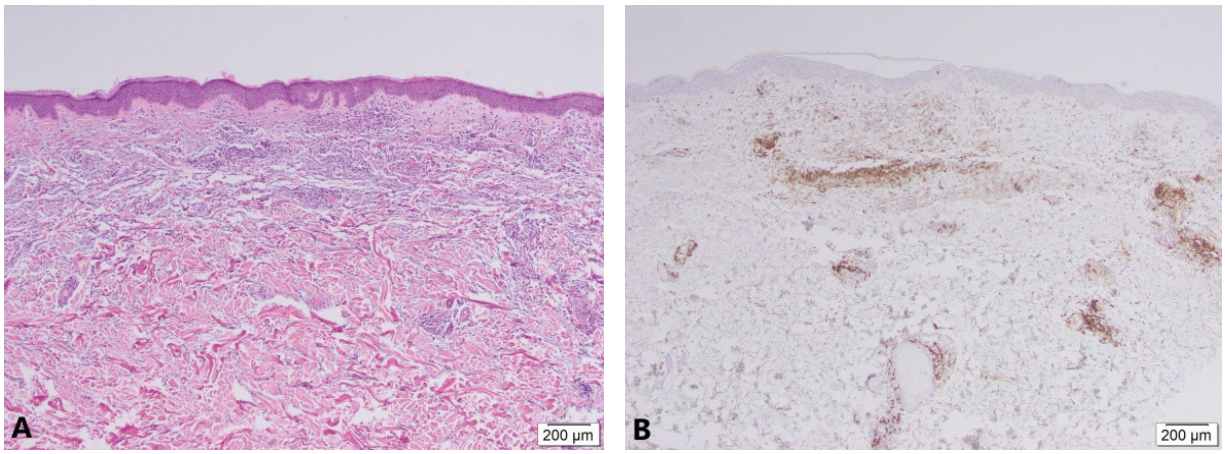

Figure 2: H&E and CD123. This figure depicts superficial and deep dermal inflammation (A) and involvement of pDCs (B) in subacute cutaneous lupus erythematosus.

that HAEM may have an autoimmune component. In Drug Induced Erythema Multiforme (DIEM), TNF-α was shown to be a major cytokine which is mainly produced by monocytes [14]. This data suggest that HAEM and DIEM are mechanically distinct syndromes.

There is only scattered information in the literature about pDCs' presence and role in EM [15,16]. In our recent study, we aimed to investigate their density and distribution by using a CD123 ImmunoHistoChemical (IHC) stain in etiologically different variants of EM. We grouped the biopsies diagnosed with EM based on their etiology and the percentage of CD123 positive pDCs in the dermal inflammatory infiltrate [5]. In all cases of erythema multiforme, we observed a significant amount of CD123 positive cells within both the dermal inflammatory infiltrate and the epidermal inflammatory cells (**Figure 4**) [5]. This observation suggests that the pathophysiology of etiologically different EMs might have a common pathway involving pDCs. We proposed that in EM, infectious pathogens or certain drugs activate the keratinocytes through PAMPs and DAMPs and recruit pDCs for a further inflammatory response. However, additional studies are needed to support our hypothesis and to explain how the trigger is transferred to the affected skin.

We correlated the epidermotropic abilities of pDCs with T-lymphocytes and concluded that the epidermal pDCs most likely have immunogenic functions. Regardless of the underlying etiology, these cells possibly sense non-self or "masked" self-DNA and accelerate the immunologic response. We think that pDCs located in the upper dermis might be of both immunogenic and tolerogenic types and maybe the dominance of one over the other determine the severity and outcome of the disease. However, a sole analysis of IHC patterns of CD123 expression was insufficient to distinguish these two populations. We believe that their precise role should be identified in EM, as it may have therapeutic implications.

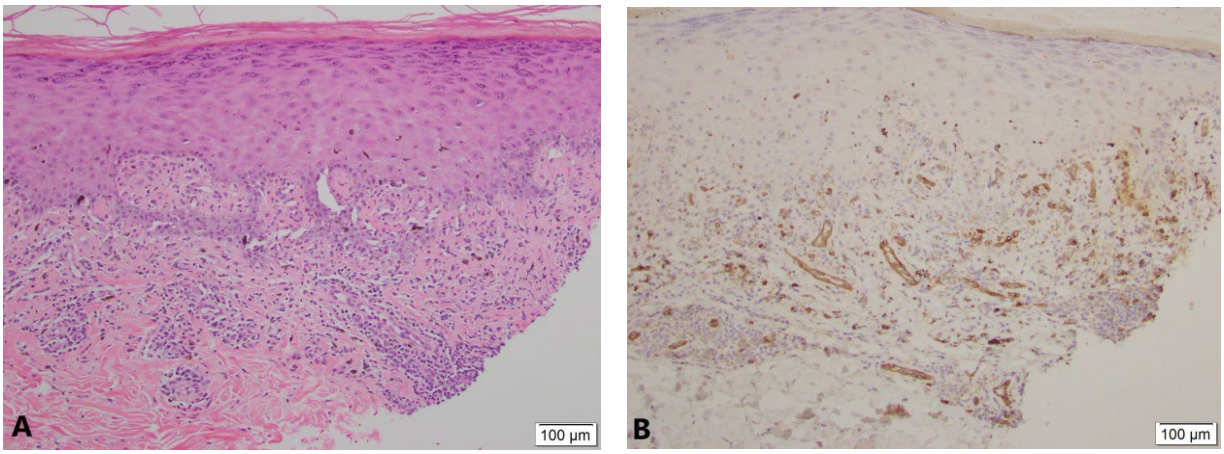

Figure 3: H&E and CD123. This figure demonstrates lichenoid inflammation (A) and associated CD123 positive pDCs (B) in lichen planus.

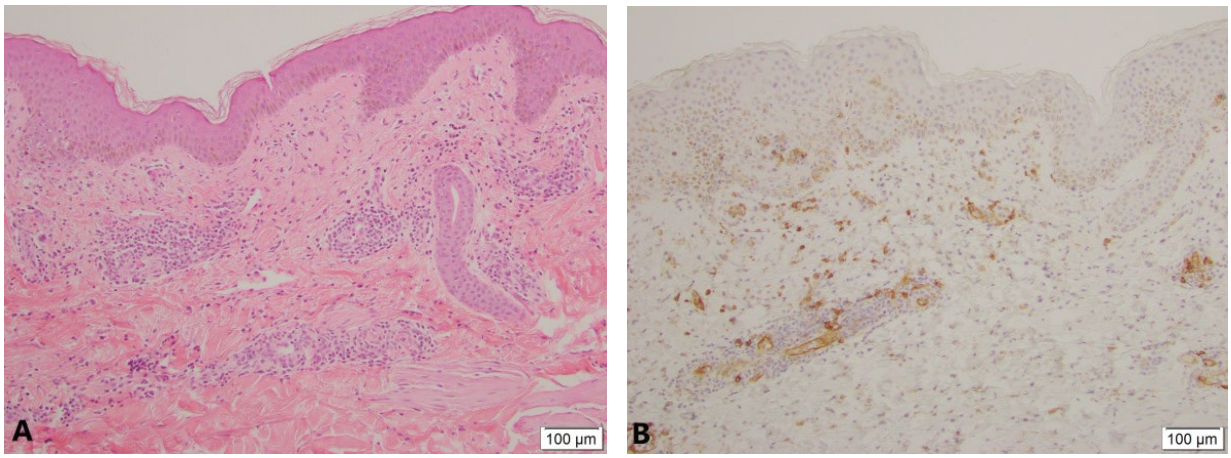

Figure 4: H&E and CD123. This figure shows perivascular inflammation (A) and dermal and epidermal distribution of pDCs (B) in erythema multiforme.

Conclusion

Our study also revealed that the cases of virally induced EM display a higher number of pDCs in the dermal infiltrate compared to non-virally induced EMs (p-value<0.05). This observation indicates that pDCs may be more involved in virally induced EMs and may play an additional role in the pathogenesis. This information may be even used in histologic differentiation of the various etiologic types of EM. However, our results are only weakly significant due to the limited number of cases. A larger study would be necessary in order to confirm this observation.

As our understanding of pDCs has advanced; their involvement in the pathogenesis of different inflammatory skin diseases has been better recognized. Plasmacytoid DCs' unregulated sensing of pathogenic or self-nucleic acids upon skin damage has been found to be a major initiator of many inflammatory dermatoses. Unfortunately, there are only a few studies regarding the presence and role of pDCs' in EM. In our study, we were able to demonstrate the extensive involvement of pDCs in EM regardless of etiology. However, further investigation is called for to clarify their importance in EM pathogenesis.

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