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Review article

Plasmacytoid dendritic cell role in cutaneous malignancies

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ABSTRACT

Plasmacytoid dendritic cells (pDCs) correspond to a specialized dendritic cell population that exhibit plasma cell morphology, express CD4, CD123, HLA-DR, blood-derived dendritic cell antigen-2 (BDCA-2), and Toll-like receptor (TLR)7 and TLR9 within endosomal compartments. Through their production of type I interferons (IFNs) and other pro-inflammatory cytokines, pDCs provide anti-viral resistance and link the innate and adaptive immunity by controlling the function of myeloid DCs, lymphocytes, and natural killer (NK) cells. While lacking from normal skin, pDCs are usually recruited to the skin in several cutaneous pathologies where they appear to be involved in the pathogenesis of several infectious, inflammatory/autoimmune, and neoplastic entities. Among the latter group, pDCs have the potential to induce anti-tumour immunity; however, the complex interaction of pDCs with tumor cells and their micro-environment appears to contribute to immunologic tolerance. In this review, we aim at highlighting the role played by pDCs in cutaneous malignancies with special emphasis on the underlying mechanisms.

Contents

Abbreviations: BDCA-2, blood dendritic cell antigen-2; CD123, interleukin-3 receptor α chain; CTL, cytotoxic CD8 T lymphocyte; DC, dendritic cell; GZMB, granzyme B; IFN, interferon; IL, interleukin; ILT7, immunoglobulin superfamily receptor immunoglobulin-like transcript 7; IRF, interferon-regulatory factor; mDC, myeloid dendritic cell; MyD88, myeloid differentiation primary responsive gene 88; MxA, myxovirus protein A; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cell; NK, Natural killer; pDC, plasmacytoid dendritic cell; TLR, Toll-like receptor; TNF, tumor necrosis factor; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; Treg, T-regulatory cell.

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1. Introduction

Plasmacytoid dendritic cells (pDCs) are unique DCs that are being extensively studied in recent years. They exhibit plasma cell morphology and express CD4, HLA-DR, CD123, blood-derived dendritic cell antigen-2 (BDCA-2), and Toll-like receptor (TLR)7 and TLR9 within endosomal compartments. They contribute to innate immunity by sensing nucleic acids via TLR7 and TLR9. Upon TLR7/9 triggering, pDCs become activated leading to the production of large amounts of type I interferons (IFNs) [1,2]. In fact, pDCs are the most potent type I IFN producers, secreting up to 1000 times more IFNα/IFNβ than other cell types [3–6]. Signalling through a common receptor (IFN-α/βR), type I IFNs usually induce the expression of multiple genes through a complex process that involves different pathways that mainly lead to an antiviral state [7–9]. pDCs also produce pro-inflammatory cytokines including interleukin (IL)-6 and tumor necrosis factor (TNF)-α which, along with type I IFNs, contribute to the regulation of other immune cell function such as myloid DCs, T, B, plasma and natural killer (NK) cells [1,2,10].

While lacking from normal skin, pDCs are recruited to the skin in wound healing and several pathologies such as infectious, inflammatory, and neoplastic entities [3,5,6,11–15]. In this review, we present the available evidence on pDCs' role in cutaneous malignancies.

2. pDC characteristics and identification

pDC develop from bone marrow hematopoietic stem cells. Mouse pDCs differentiate from common DC progenitors or lymphoid-primed multipotent progenitors [16], while human pDCs' intermediate progenitor cell stages have not been identified yet. pDC development depends on multiple factors such as transcription factor Spi-B expression [17], Flt3 ligand [18,19], and the basic helix-loop-helix protein E2-2 [20,21].

The most important characteristic of pDCs is their extraordinary ability to secret type I IFNs following TLR7/9 activation [1,3–6]. TLR are pattern recognition receptors that respond to pathogen-associated molecular patterns [22,23]. TLR7 interacts with guanosine- or uridine-rich single-stranded RNA (ssRNA) from viruses, the synthetic imidazoquinoline compounds and guanosine analogues [5,23], while TLR9 detects ssDNA molecules that contain unmethylated CpG-containing motifs commonly found in viral genomes [5,23]. TLR activation induces multiple signaling pathways including adaptor molecule MyD88 (myeloid differentiation primary responsive gene 88). The latter recruits signaling mediators to activate the transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and IFN-regulatory factors (IRFs) [1,5]. These ultimately induce transcription of genes encoding immunomodulatory and proinflammatory molecules [24].

pDCs function as antigen presenting cells remains to be controversial. Immature mouse pDCs are able to take up soluble antigen though less efficient than conventional DCs [25]. At least in vitro, human pDCs have been shown to be able to internalize, process, and present antigen to CD8+ and CD4+ T cells [26,27]. pDCs appear to have an efficient machinery that allows cross-presentation to CD8+ T cells [27,28].

Concerning their identification, pDCs are lineage negative, $CD11c^{-}$, IL-3 receptor α chain $(CD123)^{+}$, $HLA\text{-}DR^{+}$ and $CD4^{+}$ cells. Specific pDC markers include BDCA-2 and BDCA-4 [1,3–6,29]. Human pDCs also express cell surface receptors that allow counter-regulation of TLR7/9 signaling in order to prevent ongoing cytokine production. In addition to C-type lectin BDCA2, these receptors include Ig-like transcript 7 (ILT7), DC immunoreceptor, NK protein 44, adenosine diphosphate P2Y receptors, and PGE2 receptors [5,29,30].

3. pDCs and malignancy

On one hand, pDCs can exert their anti-tumor effect through type I IFN production and the subsequent activation of cytotoxic T and NK cells [6,31,32]. In one study, *in vitro* functional assessment of pDC present at the periphery of melanomas showed that these pDCs are capable of initiating a Th1 response with proliferation of CD8+ T cells specifically directed against melanoma cells [31]. In another study evaluating pDC role in melanoma regression, it was shown that the initiation of the immune response leading to tumour regression could be linked to pDC presence and their secretion of IFN-α, which induced IP-10 expression and the subsequent recruitment of cytotoxic T cells [32]. On the other hand, pDCs have the potential for direct cytotoxic killing of susceptible

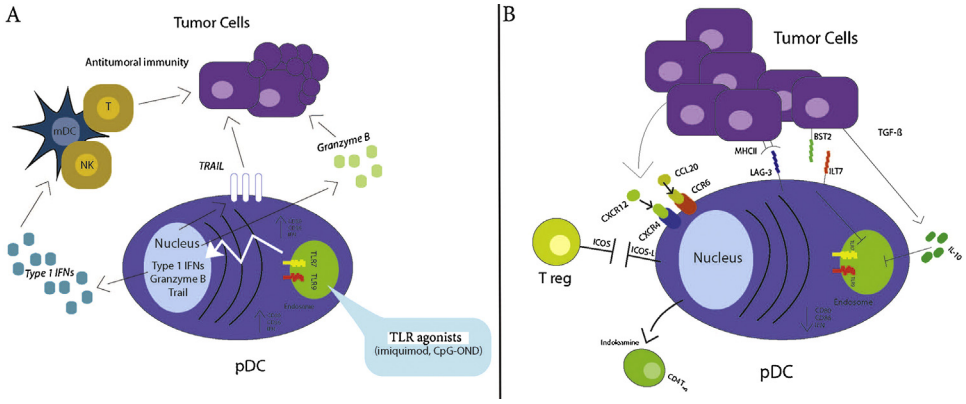

Fig. 1. pDC role in tumor inhibition and tolerance. A. pDC activation by TLR 7 and/or 9 agonists leads to MyD88-dependent production of type I IFNs and pro-inflammatory cytokines as well as expression of costimulatory molecules such as CD80, CD83 and CD86. pDCs have direct (granzyme B and TRAIL) and indirect (activation of NK cells by type I IFN) tumoricidal activities. B. Mechanisms of tumour-associated pDC contribution to immunologic tolerance include recruitment (through CCR6/CCL20 and CXCR12/CXCR4 pathways) of immature pDCs (lack costimulatory molecule expression), lack of pDC activation, active suppression of type I IFN production by pDCs (by BST2- ILT7 interaction or pDC-secreted immunosuppressive cytokines such as IL10), alternate pDC activation (such as through LAG-3+ pDC interaction interaction with HLA-DR+ tumor cells), and/or pDC tolerance promotion by activating Tregs (through ICOSL/ICOS interaction and indoleamine 2,3-dioxygenase) and expressing anti-inflammatory cytokines.

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