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Dendritic cells in cancer: the role revisited

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Dendritic cells (DCs) with their potent antigen presenting ability are long considered as critical factor in antitumor immunity. Despite high potential in promoting antitumor responses, tumor-associated DCs are largely defective in their functional activity and can contribute to immune suppression in cancer. In recent years existence of immune suppressive regulatory DCs in tumor microenvironment was described. Monocytic myeloid derived suppressor cells (M-MDSCs) can contribute to the pool of tumor associated DCs by differentiating to inflammatory DCs (inf-DCs), which appear to have specific phenotype and is critical component of antitumor response. Here we examine the role of inf-DCs along with other DC subsets in the regulation of immune responses in cancer. These novel data expand our view on the role of DCs in cancer and may provide new targets for immunotherapy.

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Introduction

DCs are professional antigen presenting cells (APCs) that sample the microenvironment and provide antigens and co-stimulatory signals to cells of the adaptive immune system [1]. In steady state, DCs are largely present as an immature and weak APC characterized by the high capacity to capture antigens, low expression of costimulatory molecules and limited secretion of cytokines [2,3]. Different stimuli associated with bacteria, viruses, and damaged tissues can induce the activation and maturation of DCs. Activated DCs are characterized by a down-regulated antigen capture activity, increased expression of mayor histocompatibility complex II (MHC class II), costimulatory molecules and C-C chemokine receptor type 7 (CCR7), high ability to produce cytokines and active migration to draining lymph nodes (dLNs). These DCs are potent inducers of T cell responses and are long considered as a critical component of antitumor immunity. However, it is also known that DCs do not effectively function in cancer. Recent advances in the understanding of the biology of different populations of DCs allow for better characterization of the nature of tumor associated DCs and provide new avenues for their therapeutic regulation.

Overview of the origin and types of dendritic cells in tumor-bearing hosts

DCs differentiate in bone marrow (BM) via sequential steps involving common myeloid progenitors (CMP) and macrophage/DC progenitors (MDPs). MDPs give rise to common monocyte precursors (cMOP) and common DC precursors (CDPs) [4,5]. cMOPs then give rise to monocytes [6], which in tissues can differentiate to DCs under certain conditions, such as in cancer [7]. In steady state conditions practically all DCs in tissues differentiate from CDPs [8].

Currently, several subsets of DCs are recognized (Table 1) and the development of each subset of DCs is driven by specific transcriptional factors [9]. E2-2 favors the differentiation of plasmacytoid (pDCs) [10], while Id2 expression drives the differentiation of conventional (cDCs). Among cDCs, $CD8\alpha^+$ cDC in lymphoid organs and $CD103^+$ cDCs in non-lymphoid organs depend on interferon regulatory factor 8 (Irf8) and basic leucine zipper transcriptional factor ATF-like 3 (Batf3) [11,12], and $CD11b^+$ DCs depend on interferon regulatory factor 4 (Irf4) and RbpJ [13,14]. Zing finger and BTB domain containing 46 (Zbtb46) is selectively expressed by cDC lineages, but not by pDCs, macrophages, or monocytes. Zbtb46 is not necessary for DC development but it might influence DC subset composition [15,16].

Fms-like tyrosine kinase 3 ligand (Flt3L) and granulocyte-macrophage colony stimulating factor (GM-CSF) are major cytokines involved in DC differentiation. The development of pDCs and cDCs but not monocyte derived DC is dependent on Flt3L and on its receptor Flt3 [17–19]. GM-CSF signaling is required for the development of non-lymphoid tissue-resident DCs in steady state and for the induction of $CD8^+$ T cell immunity against particulate antigens. Mice lacking GM-CSF or their receptors showed normal monocyte [20] and lymphoid tissue DC differentiation, but an impaired development of $CD103^+$ DCs and $CD11b^+$ DCs in intestine, lung and dermis [21]. GM-CSF was also implicated in the acquisition of the capacity to cross-present antigens by cDCs [22,23].

Table 1

DC subsets and their basic functions

Subsets	Transcriptional factor	Mouse	Human	Functions
pDC	E2-2	CD11c, Ly6C, B220, Siglec-H	CD4, HLA-DR, CD123, BDCA2, TLR7 AND 9	Type I IFN production, tumor killing, antigen presentation,
Lymphoid tissues Resident cDC	Irf4, Rbpj	CD11b, CD11c, CD172a	CD11b, CD11c, CD172a, CD1c	Antigen presentation, induction of Th2 T cell responses
Lymphoid tissues Resident cDCs	Batf3, Irf8	CD11c, CD8α, Clec9a/DNGR1, XCR1	CD11c, CD141, Clec9a/DNGR1, XCR1	Antigen cross presentation, induction of anti-tumor responses
Non Lymphoid tissues Migratory cDC	Batf3, Irf8	CD11c, CD103, Clec9a/DNGR1, XCR1	CD11c, CD141 (BDCA3), Clec9a/DNGR1, XCR1	Antigen cross presentation, migration, induction of anti-tumor responses
Inflammatory DCs		MHC II, CD11b, F4/80, Ly6c, CD206, CD115/GM-CSFR, Mac-3/CD107b FcεRI, CD64	HLA-DR, CD11c, CD1c (BDCA1), CD1a, FcεRI, CD206, CD172a, CD14, CD11b	Antigen presentation, migration, induction of anti-tumor responses, production of TNF and NO, tumor rejection
Intratumoral DCs (DC2)	Baft3, Irf8, Zbtb46	MHCII, CD11c, CD24, CD103	CD45,HLA-DR, CD141 (BDCA3)	Antigen cross presentation, induction of anti-tumor responses, production of IL-12, tumor rejection,
Intratumoral (DC1)	Irf4	MHCII, CD24, CD11b	CD45,HLA-DR, CD1c (BDCA1)	Unknown

The characterization is based on the most recent transcriptional factors and phenotypic markers used to distinguish different population of myeloid cells in TME and periphery.

Plasmacytoid DCs

pDCs is a multifunctional population of BM derived DCs [24,25] specializing in the production and secretion of type I interferons (IFNs). In mice, pDCs express Siglec-H, B220, Ly6c, and low amount of CD11c along with variable amounts of CD8α and CD4. In the periphery, mouse pDCs express CC-chemokine receptor 9 (CCR9), LY49Q and SCA1 [26–28]. Human pDCs exhibit plasma cells morphology and express CD4, HLA-DR, CD123, and blood derived cell antigen-2 (BDCA-2), as well as Toll-like receptor (TLR) 7 and 9 within endosomal compartments but not CD11c [26,28,29]. Under homeostatic conditions, pDCs are found in small numbers in T cell areas of LNs and spleen, mucosal-associated tissues, thymus and liver. Upon TLR7/9 triggering, pDCs secrete high amount of type I IFN and produce interleukin-12 (IL-12), IL-6, tumor necrosis factor α (TNF-α), and other pro-inflammatory chemokines. pDCs can act as antigen presenting cells, but they are much less efficient than cDCs and depending on the context, antigen presentation by pDCs can induce immunogenic responses or tolerance [28].

pDCs represent small population of DCs and there is rather limited information about their involvement in antitumor responses. In mouse B16 melanoma, pDCs stimulated with TLR agonists were able to mediate tumor killing by the expression of TNF-related apoptosis-inducing ligand (TRAIL) and granzyme B and C and further exert their antitumor effects via production of type I IFN and subsequent activation of cytotoxic T and NK cells [30–32]. The initiation of immune responses leading to melanoma regression could be linked to the presence of pDC and their production of IFN-α [32]. In an orthotropic murine mammary tumor model, the administration of TLR7 ligands resulted in pDC activation and a potent antitumor effect [33]. The administration of activated pDCs loaded with tumor associated antigens to melanoma patients induced the specific $CD4^+$ and $CD8^+$ T cells responses [34].

Conventional DCs

In mice, cDCs can be divided into two main subpopulations: $CD11b^-$ and $CD11b^+$ cells. $CD11b^-$ DCs include lymphoid tissue $CD8\alpha^+CD11b^-$ DCs and non-lymphoid tissue $CD103^+CD11b^-$ DC. Lymphoid-tissue resident $CD11c^+CD8\alpha^+$Clec9a/DNGR-1^+XCR1^+ DCs and migratory $CD11c^+CD103^+$Clec9a/DNGR-1^+XCR1^+DCs are considered the most effective cross-presenting DCs *in vivo* [35]. Contrary to other subsets, Baft3-dependent $CD103^+$ and $CD8^+$ DCs have specific properties favoring cross-presentation. They limit the antigen degradation by maintaining an alkaline pH in their phagosomes through the production of reactive oxygen species (ROS). A recent study showed that the lectin family member Siglec-G negatively controlled ROS production by inhibiting NOX2 on DC phagosomes. This resulted in an excessive hydrolysis of exogenous antigens which led to a decreased formation of MHC class I-complexes for cross-presentation. Cross presenting $CD8^+$ DCs showed lower expression of Siglec-G than $CD8^-$ DCs, and Siglec-G deficient mice generated stronger cytotoxic T cells (CTL) than wild type mice [36•]. $CD11b^+$ DCs are an IRF4-dependent subset of lymphoid resident DCs characterized by the expression of CD11c, CD11b, CD172a. $CD11b^+$ DCs have a dominant role in presenting antigens on MHC class II to $CD4^+$ T cells. $CD11b^+$ DCs, contrary to $CD103^+$ DCs, induced Th2 cell priming in lung during