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Review

Dendritic cells in the regulation of immunity and inflammation

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ABSTRACT

As potent antigen-presenting cells, dendritic cells (DCs) comprise the most heterogeneous cell population with significant cellular phenotypic and functional plasticity. They form a sentinel network to modulate immune responses, since intrinsic cellular mechanisms and complex external, environmental signals endow DCs with the distinct capacity to induce protective immunity or tolerance to self. Interactions between DCs and other cells of the immune system mediate this response. This interactive response depends on DC maturation status and subtype, as well as the microenvironment of the tissue location and DC-intrinsic regulators. Dysregulated DCs can initiate and perpetuate various immune disorders, which creates attractive therapeutic targets. In this review, we provide a detailed outlook on DC ontogeny and functional specialization. We highlight recent advances on the regulatory role that DCs play in immune responses, the putative molecular regulators that control DC functional responding and the contribution of DCs to inflammatory disease physiopathology.

1. Introduction

Dendritic cells (DCs) are specific antigen-presenting cells that function as messengers between innate and adaptive immune responses. DCs are very few in number, but they have a ubiquitous distribution in the body to serve as sentinels for foreign and dangerous material [1]. Immune system activation in response to pathogens or sterile inflammation involving both innate and adaptive immunity is a double-edged sword [2]. Full activation of an inflammatory response is essential for the initial host defense, particularly against most infections; however, inappropriate activation or overactivation of inflammatory responses may elicit damaging inflammation to the host [3]. A proper response to maintain immune homeostasis occurs through a precise, complex network of regulatory mechanisms [4]. So, DCs emerge as key players for the immune system. Research efforts continually refine our knowledge on DC functions to initiate both protective pro-inflammatory and tolerogenic immune responses [5].

Typically, DCs recognize a wide range of 'danger signals' both from invading microbes and injured host cells through binding either pathogen-associated molecular patterns (PAMPs) or damage-associated molecular pattern molecules (DAMPs) to specialized pattern recognition receptors (PRRs) [6]. Antigen recognition by DCs induces phagocytic processing of antigens and antigen presentation, increases expression of costimulatory molecules and cytokine production, and ultimately primes naïve T cells to activate adaptive immunity [7]. DCs can also regulate immune responses by generating both central and peripheral tolerance and controlling inflammatory responses by various mechanisms, such as inducing apoptosis of autoreactive T cells and T cell anergy, expanding regulatory T cells and limiting other effector cell responses [8]. Through interactions with other immune system cells accompanied by cytokine release or cell–cell contact, DC subsets with significant phenotypic and functional plasticity perform these complicated tasks. Recent efforts to characterize the regulators that program the function of DCs suggest that complex environmental signals and intrinsic cellular mechanisms direct DC functions [9]. Since alterations in DC biology underlie various inflammatory immune disorders[10], understanding how different subsets of DCs regulate immunity and inflammation is vital to develop new intervention strategies to target the immune system in various pathologies. In this review, we summarize the current knowledge about the differentiation and functional classification of DCs. We highlight recent advances on DC biology through extrinsic regulators from the local tissue microenvironment, such as cell–cell contact, soluble mediators, and intrinsic regulators, like membrane-associated receptors, intracellular enzymes and epigenetic factors. We also describe the dual role of DCs in the pathogenesis of inflammatory diseases and immunomodulatory strategies used in therapeutic interventions.

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2. Differentiation and functional classification of DCs

2.1. Ontogeny of DCs

Traditionally, DCs arise from hematopoietic stem cells (HSCs). DC differentiation from HSCs is a multistep process that varies spatiotemporally [11]. In bone marrow, $CD34^+$ HSCs can generate multipotent progenitors (MPPs), which can then differentiate into common myeloid progenitors (CMPs) and common lymphoid progenitors (CLPs). Adoptive transfer of CMPs and CLPs populations into irradiated animals revealed that these early precursors have almost similar efficiency to produce conventional DCs (cDCs) and plasmacytoid DCs (pDCs) in mice. An analogous potential can occur in human CMPs and CLPs cultured *in vitro*. However, the ability of CMPs or CLPs to differentiate into these two major categories of DCs is confined to only those subsets expressing fms-related tyrosine kinase 3 (Flt3). $Flt3^+$ CMPs differentiate into macrophage-DC progenitors (MDPs), the common precursor for monocytes, macrophages and DCs. Common DC progenitors (CDPs) are derived from MDPs and produce a DC-restricted progenitor that exclusively generates a precursor DC population (pre-DCs) but not monocytes or macrophages. The terminal differentiation of cDCs from a cascade of bone marrow DC-committed precursors occurs locally in lymphoid organs and peripheral tissues throughout the body [12]. Compared to cDCs, pDCs can rapidly secrete significant type I IFN quantities in response to foreign nucleic acids [13]. The ontogeny of pDC differs significantly from cDCs. pDCs develop from a continuum of $Flt3^+$ c-Kit^{low} progenitors, including CLPs and CDPs, and fully develop in the bone marrow [14]. Transcription factor E2-2 is an essential and specific regulator of pDC development [15]. Following development in the bone marrow, pDCs circulate in the blood and then enter peripheral and lymphoid tissues.

At steady state, mouse cDCs are broadly divided into two classes: lymphoid DCs and migratory DCs [16]. Lymphoid DCs, encompassing subclasses $CD8\alpha^+$ and $CD11b^+$ DCs, reside mainly in spleen and tissue-draining lymph nodes and rapidly take up antigens from the bloodstream and lymph for T cells presentation. Migratory DCs can further separate into $CD103^+$ and $CD11b^+$ cDCs, which traffic from peripheral tissues, such as skin, lung, liver, kidney and intestinal tract, to draining lymph nodes charged with tissue antigens [17]. Transcription factors, Batf3 and IRF-4, control cDC differentiation into $CD8\alpha^+$/$CD103^+$ and $CD11b^+$, respectively [18]. Recently, studies made significant progress to elucidate mouse DC development. Much less is known about the ontogeny of human DCs, because of the scarcity in blood and the difficulties to isolate them from other human tissues. Most of our knowledge about human DC biology comes from experiments using cells derived *in vitro* from monocytes or from $CD34^+$ hematopoietic progenitors [19]. However, recent studies show that steady-state human blood and secondary lymphoid organs contain at least three DC subsets [20]: $CD141^+$ myeloid DCs, $CD1c^+$ myeloid DCs and pDCs, which differ considerably from monocyte- and $CD34^+$-derived DCs *in vitro*. Classification of DC subset functional homology across species shows that $CD141^+$ myeloid DCs (also known as thrombomodulin$^+$ or $BDCA3^+$) and $CD1c^+$ myeloid DCs (also known as $BDCA1^+$) are homologous to mouse lymphoid $CD8^+$ and $CD8^-$ DC subsets, respectively [21]. Only human pDCs express typical pDC markers like CD123 and BDCA2, while murine pDCs uniquely express BST2 and Siglec H [22].

2.2. Inflammatory DCs

pDCs and cDCs arise via pre-DCs, which exit the bone marrow and travel through the blood stream to lymphoid and non-lymphoid tissues under steady state and inflammatory conditions (Fig. 1). Different subtypes of immature DCs either populate the skin, mucosal surfaces and most solid organs or circulate in the blood to act as sentinels for PAMPs and DAMPs [23]. This activation by “danger signals” induces a coordinated and complex process of DC maturation. However, recent studies revealed new insights into the ontogeny and development of a third DC population, so-called “inflammatory DCs”, which only form in response to inflammatory stimuli, not at steady state [24]. Most inflammatory DCs share common features with cDCs, such as morphology, phenotype, migratory properties and ability to activate $CD4^+$ and $CD8^+$ T cells. However, they differ in their lineage of origin [25]. cDCs can be modeled *in vitro* by monocytes in the presence of IL-4 and GM-CSF, while inflammatory DCs develop from bone marrow-derived DCs cultured with GM-CSF in vitro [26]. Inflammatory DCs may initially derive from $Ly6C^{hi}$ monocytes, which emigrate from the bone marrow depending on CCR2 and travel to inflamed/infected tissues to fully differentiate at the site of inflammation [27,28]. Under different inflammatory conditions, early hematopoietic precursors such as HSCs, CLP and CDPs were also identified as the direct precursors of inflammatory DCs to bypass normal lineage commitment steps [29]. These inflammatory DCs, which produce TNF-α and nitric oxide (NO), play a major role to clear infectious agents, such as *Listeria monocytogenes, Brucella melitensis*, *Leishmania major* and *Trypanosoma brucei* [30,31]. It is interesting that a myeloid population accumulating within the tumor after adoptive cell therapy is phenotypically similar to inducible NO synthase- and TNF-producing inflammatory DCs, which is important for adoptively transferred $CD8^+$ cytotoxic T cells to destroy tumors, providing a rationale for switching the balance between pro- and anti-tumor myeloid cells in the tumor microenvironmen [32]. Inflammatory DCs then migrate to lymphoid nodes and present antigens to naive $CD4^+$ T cells to induce TH1 [33,34], TH2 [35,36] or TH17 [37] cell differentiation depending on the inflammatory environment. Human inflammatory DCs are found in two different inflammatory environments, ascites from untreated ovary and breast cancer patients and synovial fluid from RA patients, which are derived from monocytes and are involved in the induction and maintenance of Th17 cell responses through the release of Th17 cell-polarizing cytokines [38]. So, inflammatory DCs appear not only during pathogenic inflammation, but also in experimental models of inflammatory diseases like asthma [39] and psoriasis [40], rheumatoid arthritis patients and cancer patients. This prevalence and pattern suggests inflammatory DCs are an important target for optimal vaccine design [41].

2.3. Regulatory DCs

DCs are critical to regulate the subtle balance between immunity and tolerance [42]. Aside from their unique capacity to present antigens and prime T-cell responses, DCs may have an important immune-regulatory function essential for both central and peripheral tolerance [43]. Growing evidence suggests regulatory DCs can contribute to immunological tolerance by inhibiting T cell responses, inducing T cell unresponsiveness and apoptosis and generating regulatory T (Treg) cells [44].

Thymic DCs are generally classified into three subtypes: resident $CD8\alpha^+$ $SIRP\alpha^-$ cDCs, migratory $CD8\alpha^-CD11b^+SIRP\alpha^+$ cDCs and $CD11c^{int}CD45RA^{int}$ pDCs [45]. All three thymic DC subsets can mediate central tolerance through different mechanisms [46]. Recent cell lineage tracing studies using fluorescent reporter mice show that intrathymic precursors of thymic resident cDCs develop intrathymically from thymic-homing, bone marrow progenitors via CCR7- and CCR9-mediated chemokine signals [47]. Although thymic resident cDCs comprise the most abundant thymic DC subset, they do not have efficient exchange with circulating peripheral DCs and the chemokine XCL1 produced predominantly by medullary thymic epithelial cells mediates medullary accumulation of thymic dendritic cells that express the chemokine receptor XCR1 [48]. They can provide immature T cells with a distinct self-antigenic repertoire and cross-present both blood-derived and tissue-specific antigens from medullary thymic epithelial cells to educate thymocytes. As shown in parabiosis experiments, thymic migratory DCs arrive from the peripheral circulation, where