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Dendritic cell development—History, advances, and open questions

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ABSTRACT

Dendritic cells (DCs) are uniquely potent in orchestrating T cell immune response, thus they are indispensable immune sentinels. They originate from progenitors in the bone marrow through hematopoiesis, a highly regulated developmental process involving multiple cellular and molecular events. This review highlights studies of DC development—from the discovery of DCs as glass-adherent antigen presenting cells to the debate and resolution of their origin and lineage map. In particular, we summarize the roles of lineage-specific cytokines, the placement of distinct hematopoietic progenitors within the DC lineage and transcriptional programs governing DC development, which together have allowed us to diagram the current view of DC hematopoiesis. Important open questions and debates on the DC development and relevant models are also discussed.

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1. Introduction

Dendritic cells (DCs) are uniquely potent in orchestrating T cell immune response, thus they are indispensable immune sentinels. They originate from progenitors in the bone marrow through hematopoiesis, a highly regulated developmental process involving multiple cellular and molecular events. This review highlights studies of DC development—from the discovery of DCs as glass-adherent antigen presenting cells to the debate and resolution of their origin and lineage map. In particular, we summarize the roles of lineage-specific cytokines, the placement of distinct hematopoietic progenitors within the DC lineage and transcriptional programs governing DC development, which together have allowed us to diagram the current view of DC hematopoiesis. Important open questions and debates on the DC development and relevant models are also discussed.

2. Identification of the DC—a mononuclear phagocyte uniquely potent in initiating T cell immunity

2.1. Discovery of DCs

The discovery of DCs resulted from the effort to understand the cellular initiator of adaptive immune response. Macrophages, monocytes and their bone marrow precursors, comprising the mononuclear phagocyte system (MPS), were long appreciated for their capacity to adhere to, engulf and degrade infectious pathogens reviewed in Ref. [1]. Importantly, some MPS cells retain antigens that are not entirely degraded and present them on the cell surface in the context of the MHC-peptide complex, resulting in T cell activation [2,3]. MPS cells adhere to glass readily, thus glass-adherence was recognized as a characteristic feature of MPS cells and widely used for their isolation. In the 1960s it was recognized that glass-adhering cells from mouse spleen could prime adaptive immune response, *i.e.*, induce antibody production from naïve lymphocytes *in vitro* [4]. It was speculated that antigen-presenting cells (APCs) initiated the response by activating T cells, which subsequently stimulated antibody production from B cells, thereby bridging innate immunity and adaptive immunity. However, the exact identity of such immunity-initiating APC within the MPS was unclear. In 1973, Ralph Steinman and Zan Cohn, during microscopic study of the glass-adhering mouse splenocytes, discovered a small population of cells with unique stellate morphology, and named them dendritic cells (DCs) [5]. It was soon found that DCs express high level of MHC II and are uniquely potent in stimulating T cell proliferation—orders of magnitude more potent than macrophages and other APCs examined [6]. Thus DCs were discovered as the T cell-activating member of MPS.

The early studies of DC origin and *in vivo* dynamics utilized cell surface markers, bone marrow chimeras, ^{3}H-thymidine injection, GM-CSF culture and colony formation assays (reviewed in Ref. [7]). Glass-adhering DCs in mouse spleen express characteristic myeloid markers such as CD33 and CD11b and are replenished by rapidly proliferating bone marrow progenitors. These progenitors produce DCs together with granulocytes, monocytes and macrophages. Based on these studies, DCs were considered to be of myeloid origin.

2.2. DCs, macrophages and monocytes are separate lineages

Because monocytes were originally considered to be the migratory bone marrow precursor to all MPS cells, scientists understandably reasoned DCs also descend from monocytes. This reasoning was supported by the fact that both human and mouse monocytes can acquire typical DC features. When cultured with GM-CSF *in vitro*, monocytes up-regulate MHC II and accessory molecules, develop dendrites and become immune-stimulatory to T cells [8,9]. Similarly, *in vivo*, monocytes can develop DC features during inflammation [10,11]. However, it is now clear that neither DCs nor tissue resident macrophages descend from monocytes in the steady state (reviewed in Ref. [12]). As demonstrated from genetic fate mapping and adoptive transfer experiments, tissue resident macrophages derive from a yolk-sac-derived erythroid-myeloid progenitor ([13,14]), whereas DCs descend from progenitors distinct from monocytes (discussed in Section 3). Thus, despite belonging to the same MPS, DCs, macrophage and monocytes have distinct origins.

3. DC subsets

DCs control many aspects of immunity. Broadly, they initiate T cell immunity and tolerance [15]. Specifically they can regulate differentiation of T cells toward Th1, Th2, Th17 or Treg subsets. DCs can also indirectly skew T cell subset differentiation by activating innate lymphocytes to produce conditioning cytokines for T cell subset specification [16]. Such diverse functions of DCs are unlikely executed by one type of cell. Indeed, multiple DC subsets have been identified, each displaying distinct phenotype, carrying out distinct functions, and collaboratively enabling adaptive T cell immune response (reviewed in Ref. [17]). As growing numbers of DC subsets were identified, one question arose: do these DC subsets share the same origin? This question has generated heated and ongoing debate, tantalizing hypotheses, and surprising findings that provide deeper insights and more questions about DC development and hematopoiesis as a whole.

3.1. From glass-adhering DCs to CD11c^{+} DCs

Although the morphologic and functional differences between DCs and other leukocytes were striking, few immunology laboratories in the 70s were equipped to perform the purification procedures required to study DCs until monoclonal antibodies to DC markers became available. A series of mouse DC-restricted monoclonal antibodies were produced by Steinman and others starting in the 1980s, including 33D1 (specific for the cell surface receptor DCIR2/Clec4a4), NLDC-145 specific for the adsorptive endocytosis receptor,

DEC205/cluster of differentiation (CD205), and N418 (specific for the integrin, CD11c). These monoclonal antibodies were used