Review

Central role of dendritic cells in the regulation and deregulation of immune responses

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Received 7 January 2008; received after revision 18 January 2008; accepted 25 January 2008

Abstract. Dendritic cells (DCs) play a critical role in orchestrating the innate and adaptive components of the immune system so that appropriate, coordinated responses are mounted against infectious agents. Tissue-resident DCs interact with microbes through germline-encoded pattern-recognition receptors (PRRs), which recognize molecular patterns expressed by various microorganisms. Antigens use PRR activation to instruct DCs for the appropriate priming of natural killer (NK) cells, followed by specific T-cell responses. Due to the central role of DCs in regulating the activation and progression of immune responses, minor imbalances in the feedback control of Toll-like receptor (TLR)-activated cells have been associated with autoimmunity in genetically prone individuals. We review here recent findings on the role of DCs in the priming of innate and adaptive immune responses and the possible involvement of DCs in inducing and maintaining autoimmune reactions.

Keywords. Dendritic cells, innate immunity, adaptive immunity, pattern recognition receptors, CD14, natural killer cells, autoimmunity.

Introduction

Dendritic cells (DCs) were initially described as the ‘natural adjuvants’ inducing adaptive immune responses [1–3]. DCs are special leukocytes capable of alerting the immune system to the presence of infections and responsible for the activation and control of both innate and adaptive immune responses [4, 5]. DCs are particularly frequent in tissues forming an interface with the external environment, such as the skin, gut and lungs [6–8], where they perform a sentinel function – detecting incoming pathogens – and can recruit and activate cells of the innate immune system [9–11]. DCs take up antigens and efficiently process them for presentation in association with major histocompatibility complex (MHC) molecules. These cells must be sensitive to the amount of antigen present and the persistence of antigens if they are to fulfill their role as sentinels correctly. They use a repertoire of non-clonal receptors to signal downstream to the nucleus, conveying information about what is present in the environment (quality and quantity) and the duration of this signal. This complex activity is revealed by transcripational responses involving the differential expression of thousands of genes and the integration of a number of signaling pathways. The active transcripational response leads to...
the acquisition of diverse DC functional phenotypes, orchestrating the appropriate immune response [12, 13].

DCs are highly plastic. The signals determining a particular DC function and, consequently, the type of adaptive immune response therefore depend mostly on the local microenvironment and on the interaction between DCs and microbes. DCs are the critical link between innate and adaptive immune responses, and the deregulation of DC activation via Toll-like receptors (TLRs) has been associated with autoimmunity in susceptible individuals, particularly through the production of type I interferons (IFNs). In this review, we summarize recent findings on the role of DCs in priming innate and adaptive immune responses and the possible involvement of DCs in deregulated autoimmune reactions.

**DC heterogeneity**

DCs are of hematopoietic origin and have been found in many different organs and tissues, including heart, liver, thyroid, pancreas, bladder, kidney, ureter, gut, lungs and skin. Fully developed DCs have also been observed in the circulatory networks of the body, including blood and afferent lymphatic vessels. DCs display a high degree of plasticity within organs and lymphoid tissues, and DC effector functions are often regulated by tissue microenvironment [14]. As superbly described by Shortman [15, 16], DCs can be subdivided into conventional DCs, cells having phenotypic and functional characteristics of DCs, and pre-DCs, cells requiring a further step of development to acquire phenotypic and functional DC features. Conventional DCs can, in turn, be subdivided in migratory and lymphoid tissue-resident DCs. Migratory DCs are the sentinels of non-lymphoid tissues and migrate to the draining lymph nodes after the encounter of inflammatory stimuli. Migration to lymph nodes can also occur at low rate in steady-state conditions. Lymphoid tissue-resident DCs do not reach the lymphoid organs through the lymphatics but capture the antigen directly inside the lymphoid organ. Most of thymic, spleen and around half of lymph node DCs are lymphoid tissue-resident cells. Migratory and lymphoid tissue-resident DCs can be further divided into subtypes. For migratory DCs the division is based on the tissue origin, while for lymphoid tissue-resident DCs it is based on the expression of particular markers [17–20]. For instance, six different DC populations have been identified in skin-draining lymph nodes all expressing CD11c; CD8\(^+\)DEC205\(^+\) resident DCs, CD8\(^-\)DEC205\(^+\) (both CD4\(^-\) and CD4\(^+\))- resident DCs, CD8\(^{low}\) CD205\(^{int}\) DCs (migratory dermal DCs) and CD8\(^{low}\) DEC205\(^{high}\) DCs (migratory Langerhans cells, LCs) [20, 21]. In general, in mouse lymph nodes and spleen DCs are characterized by the expression of CD11c and are classified based on the expression of CD4, CD8 and the two uptake receptors DEC205 and DCIR2, recognized by the 33D1 antibody. Thus, CD4^+CD8^-, CD4^+CD8^+ and CD4^+CD8^- have been identified. Moreover, a subpopulation of CD8^+ DCs expressing DEC205 and a subpopulation of CD8^- DCs expressing DCIR2 have also been described [22]. In the spleen, CD8^- DCs are mostly found in the marginal zone, whereas CD8^- DCs are mostly found in the T-cell area [19]. CD8^- DCs migrate to the T-cell areas following stimulation with microbial stimuli [23]. In steady-state conditions, DCs resident in lymphoid and non-lymphoid tissues are phagocytic cells and express low levels of the costimulatory molecules CD80 and CD86, and low levels of MHC class II. Upon activation following microbial stimuli encounter, both migratory and lymphoid tissue-resident DCs downregulate phagocytic activity, increase processing capacity, and upregulate MHC and costimulatory molecules at the cell surface [21]. In addition, migratory DCs acquire the capacity to migrate to lymph nodes. When they reach the lymph nodes, they have a mature phenotype [15].

Finally, a DC population producing large amounts of type I interferons (IFNs) following microbial infections – IFN-producing plasmacytoid DCs (pDCs) – has been described in mouse blood and lymph nodes [24]. In steady-state conditions, these cells can be classified as preDCs [15]. Upon activation they acquire not only the capacity to produce large amounts of type I IFNs but also some DC antigen-processing and -presentation properties [25]. Human DC phenotypes have been less well typed. DCs expressing CD11b, CD11c and CD4 have been described in the spleen and tonsils [19]. No CD8^-expressing DCs have been identified. Human IFN-producing pDCs are CD45RA^-CD123^+ and CD11c^- [26].

Migratory and lymphoid tissue-resident DCs can sense the presence of a pathogen through a large innate receptor repertoire. The signal transmitted by these receptors is crucial for DC maturation and possible migration to secondary lymphoid tissues, leading to the initiation of adaptive immune responses.

**How do DCs sense pathogens?**

DCs interact with microbes through germline-encoded pattern-recognition receptors (PRRs) [27], which recognize molecular patterns expressed by various micro-