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Major review

Role of dendritic cell subsets in immunity and their contribution to noninfectious uveitis

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ABSTRACT

Dendritic cells (DCs) are a heterogeneous population. Murine DCs consist of conventional DCs (cDCs) and plasmacytoid DCs (pDCs). In humans, the analogous populations are myeloid DCs (mDCs) and pDCs. Though distinct in phenotypes and functions, studies have shown that these DC subsets may interact or "crosstalk" during immune responses. For example, cDCs may facilitate pDC maturation, and pDCs may enhance antigen presentation of cDCs in certain pathogenic conditions or even take on a cDC phenotype themselves. The role of DCs in noninfectious uveitis has been studied primarily in the experimental autoimmune uveitis mouse model and to a more limited extent in patients. Recent evidence shows that the number, phenotype, and function of DC subsets are altered in this disease. We provide an overview of selected recent developments of pDCs and cDCs/mDCs, with special attention to their interaction and the dual roles of DC subsets in noninfectious uveitis.

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1. Introduction of dendritic cells and noninfectious uveitis

Dendritic cells (DCs) were discovered in the late 1970s by Ralph Steinman of Rockefeller University,[58] leading to his Nobel Prize in Physiology or Medicine in 2011.[42] DCs are professional antigen-presenting cells (APCs) that connect the innate and adaptive immune responses with critical roles in immune tolerance and defense against pathogens.[59] Although DCs all share the ability to activate naïve T-cells, they are a heterogeneous population in terms of their further phenotypic and functional characteristics.[57] Categorizations include: conventional (also known as classical or myeloid) DCs vs plasmacytoid DCs; "steady-state" DCs (present at all times) vs "inflammatory" DCs (develop in response to inflammation); and anatomical location (e.g., lymphoid tissue "resident" DCs vs nonlymphoid tissue peripheral "migratory" DCs).

The study of DC biology has elucidated these subsets in both mouse and human, identifying some degree of interspecies correspondence between subsets, but also important differences. Murine and human DCs are both comprise two major subsets, the key distinction being between

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conventional (also known as classical or myeloid DCs) and plasmacytoid DCs (pDCs). There is some variation in the terms used in the literature, but for the purposes of this review we will use the terms conventional DCs (cDCs) to describe the nonplasmacytoid DCs in mice and myeloid DCs (mDCs) to describe the equivalent group in humans.[8,18,37] In both species pDCs are the more homogeneous group, being distinguished by a nondendritic plasma cell-like morphology in their resting state and an ability to rapidly secrete type I interferons (IFNs) in response to viral infection. The cDC/mDC grouping contains a number of different subsets with a range of functions directed towards directing T-cell responses.[31] Classification of DCs and their discrimination from other mononuclear phagocytes (monocytes and macrophages) is made more challenging by plasticity, especially under inflammatory conditions, which means that surface phenotype is not always a reliable guide to ontogenic relationship.

Human noninfectious uveitis is a potentially blinding condition characterized by intraocular inflammation. There is considerable evidence that most noninfectious uveitis is autoimmune (or at least autoinflammatory) in origin.[32] The immune dysregulation observed in patients can be modeled and interrogated in animal models of uveitis, notably with the immunization of uveitogenic antigens supplemented with complete Freund adjuvant in experimental autoimmune uveitis (EAU).[62] Such models provide evidence of loss of tolerance to important intraocular antigens, such as S-antigen and interphotoreceptor retinoid-binding proteins (IRBPs), and enable elucidation of the immune processes leading to the generation of autoreactive $CD4^+$ T-cells and their pathological function within the eye.[11] Critically, EAU has also been successfully induced by intravenous injection of mature DCs pulsed with uveitogenic antigens.[61]

Data in humans are less complete, but still compelling. There is histological evidence of T-cell infiltrates at sites of inflammation in eyes with uveitis,[3] which is supported by flow cytometric studies of intraocular fluid samples from patients with active inflammation.[10,44] With regard to the role of autoantigens in human disease, De Smet et al noted lymphocyte stimulation responses to peptide determinants of retinal S antigen in a range of uveitis conditions, being most frequent in uveitis associated with Behçet disease or sarcoidosis.[12,13] Our recent work has been directed towards determining the role of DCs in the pathogenesis of noninfectious uveitis.[A] In this review, we discuss recent advances in the understanding of DC subsets in both mice and human and explore the implications of these recent findings to noninfectious uveitis.

2. Characteristics of murine dendritic cell subsets

As introduced earlier, murine DC subsets consist of two main populations: cDCs and pDCs. In terms of surface phenotype, cDCs are $CD11c^+$ and pDCs are $PDCA1^+$[66] (Table 1). Conventional DCs are found in lymphoid tissues including spleen, lymph nodes, and bone marrow, but are also widely distributed among non-lymphoid tissues. The major cDC subsets are defined according to the presence of CD8α and CD11 b. The $CD8^+$ cDC subset is a well-characterized lymphoid tissue based subset with important roles in cross-presentation of exogenous antigens to $CD8^+$ T-cells,[14] and interleukin (IL)-12 secretion. Interestingly, transcriptome profiling identified that there is an equivalent subset in non-lymphoid tissues which is $CD8^-$ and is defined by the integrin $CD103^+$;[43] the lymphoid $CD8^+$ subset and the non-lymphoid $CD103^+$ subset share a number of features including responsiveness to TLR3 stimulation and expression of the chemokine receptor XCR1.

The CD11 b^+ ($CD8^-$) subset is less well characterized. They are the most abundant cDCs in lymphoid tissue and are also found in non-lymphoid tissues. This is a highly heterogeneous group. Further segregation has been attempted on the basis of surface markers such as CD4, but this has not been supported by transcriptome profiling.[26] CD11 b^+ DCs differ functionally from $CD8^+$ DCs, being more effective in inducing $CD4^+$ T-cell responses, and capable of producing IL-6 and IL-23, while being poor at cross-presentation and the production of IL-12.

Plasmacytoid DCs are found in the blood and periphery. The term "plasmacytoid" refers to their appearance when resting of a non-dendritic plasma cell-like morphology. Their key function is the detection of virus by toll-like receptor (TLR) 7 or TLR9, with production of high levels of type I IFNs. They are characterized by being $PDCA\text{-}1^+$, but also express DEC-205 and B220.

DCs may also arise from monocytes, both *in vivo* and *in vitro*. *In vivo*, such monocyte-derived "inflammatory" DCs (infDCs) arise secondary to infection or inflammation. *In vitro*, they may be generated from bone marrow cells (bone marrow–derived DCs; BMDCs) under the stimulation of recombinant granulocyte macrophage-colony stimulating factor (GM-CSF).[25,36] A key function of infDCs is to produce large amounts of TNF-α and iNOS (so-called TNF-iNOS–producing DCs). They have a critical role in pathogen clearance, with an important influence in the appropriate polarization of a T-cell response.

A challenge to the study of DC biology in the eye is the limitation that DC numbers *in vivo* are too low to isolate enough for performing the functional and mechanistic studies. For this reason, most functional studies in mouse and human have depended on the use of *in vitro* cultures of bone marrow–/monocyte-derived DCs. Although we, among others, have found these model systems useful, the extent to which these *in vitro* BMDCs reflect cDCs and/or infDCs is not yet fully established. Gene expression profiles have been shown to differ significantly between cDCs (in which development is Flt3-ligand dependent) and BMDCs (in which development is GM-CSF–dependent).[67] Conversely, cDCs and BMDCs do share expression of the transcription factor Zbtb46.[52]

3. Characteristics of human dendritic cell subsets

As outlined earlier, there are shared features, but also important differences, between murine and human DC systems. Interspecies comparison based purely on surface phenotype of DC subsets is generally unhelpful, whereas more recent studies based on gene expression have been more rewarding. The key distinction of conventional DCs (hereafter