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REVIEW

Plasmacytoid dendritic cells of the gut: Relevance to immunity and pathology

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Abstract Plasmacytoid dendritic cells (pDCs) are bone marrow-derived immune cells with the ability to express copious amounts of type I and III interferon (IFN) and can differentiate into antigen-presenting dendritic cells as a result of stimulation by pathogen-derived nucleic acid. These powerful combined functionalities allow pDCs to bridge the innate and adaptive immune systems resulting in a concerted pathogen response. The contribution of pDCs to gastrointestinal immunity is only now being elucidated and is proving to be a critical component in systemic immunity. This review will explore the immunology of pDCs and will discuss their involvement in human disease and tolerance with an emphasis on those in the gastrointestinal lymphoid tissue.

Contents

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1. Introduction

1.1. Note from the authors

Since the identification of pDCs as a discrete class of immune cells, significant progress has been made in understanding their developmental process and the mechanisms by which they respond to pathogens. Although we will briefly discuss these subjects, the primary purpose of this review is to emphasize the role of pDCs in gastrointestinal immunity and gut-related pathology. Therefore, we would refer the reader to a number of excellent reviews such as Reizis et al. [1], Fitzgerald-Bocarsly et al. [2], or Lande and Gilliet [3], which provide a comprehensive summary of the development and mechanisms of pDC functionality.

1.2. Identification of pDCs as unique populations of immune cells

Dendritic cells (DCs) are antigen-presenting cells that sense pathogens and present pathogen-derived peptides to T and B cells, thus triggering and influencing adaptive immune responses. In humans, dendritic cells are most commonly divided into two classes: plasmacytoid dendritic cells (pDCs) and conventional dendritic cells (cDCs) [4,5]. cDCs can be further subdivided into five populations based upon their expression of the surface markers CD1c, CD16, or BDCA-3 [6]. Each subtype of cDC has been reported to display significant transcriptional differences, likely reflective of their differences in antigen-uptake, signaling, and migration [7]. pDCs are a unique population of bone-marrow-derived immune cells that upon activation by pathogen-derived nucleic acid produce large amounts of type I and type III IFN as well as proinflammatory cytokines [8,9]. Accordingly, pDCs play a pivotal role in bridging the innate and adaptive immune systems. Although the first unequivocal characterization of pDCs was relatively recent, Lennert and Remmele first described pDCs in 1958 as a subset of cells with plasma cell-like morphology observed in lymph nodes (LNs) [10]. In consideration of their morphology, and their expression of the T cell marker CD4 [11] and monocyte markers such as CD123 and CD68 [10,12], these cells came to be known as plasmacytoid T cells or plasmacytoid monocytes. Twenty years after Lennert and Remmele first described the plasmacytoid T cells, Trinchieri and colleagues identified a subset of non-T cell lymphocytes by their antiviral activity and their ability to activate natural killer (NK)-cell-mediated cytotoxicity through the production of IFN-α [13]. Those cells were subsequently referred to as natural IFN-producing cells. Ultimately, independent research conducted in the laboratories of Liu [14] and Colonna [8] confirmed that the plasmacytoid T cells identified by Lennert and Remmele and the natural IFN-producing cells identified by Trinchieri and colleagues were one and the same.

2. Development, distribution and morphology

2.1. Classic dendritic cells vs. plasmacytoid dendritic cells

pDCs share many key features with cDCs, to which they are related; therefore, it is useful to use cDCs as a point of reference when discussing pDCs. Both pDCs and cDCs originate from a common hematopoietic progenitor and differentiate through a pathway that involves FMS-related tyrosine kinase 3 (FLT3L)-induced signaling [15,16]. Although the two cell populations may originate from a common bone marrow precursor, pDCs diverge down an alternative developmental path in a process that likely requires the constitutive expression of the pDC-specific transcription factor E2-2 as well as the Runt family transcription factor Runx2 [17–20]. The migration and distribution patterns also differ between the two classes of dendritic cells. cDC precursors travel via the bloodstream to the lymphoid organs and peripheral tissue where they develop into immature resident and migratory DCs, respectively [4]. These immature cDCs are committed to antigen sampling and are characterized by low-level expression of T cell costimulatory molecules and major histocompatibility complex (MHC) class II [5]. They may remain in the resident tissue until they encounter an activation signal, typically as a result of the engagement of Toll-like receptors (TLRs) [21]. TLRs are transmembrane receptors that recognize repeating molecular motifs conserved within a specific class of microbe, such as the lipopolysaccharide of Gram-negative bacteria or the unmethylated CpG DNA common to many microbial genomes [22,23]. Upon microbial activation, these immature cDCs will migrate to the LNs where they undergo significant changes that result in the development of their