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Review

Dendritic cells and monocyte-derived cells: Two complementary and integrated functional systems

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ABSTRACT

Dendritic cells (DC) are professional antigen sensing and presenting cells that link innate and adaptive immunity. Within the DC population multiple subpopulations exist, each possessing distinct phenotypic and functional properties, together forming a complex cellular network capable of integrating multiple environmental signals and determining immunity or tolerance. Inflammatory monocyte-derived DC are considered a subtype of DC generated upon inflammation. However, we now know that rather than being a *bona fide* DC subtype, these monocyte-derived cells (MC) more likely represent a distinct type of highly plastic cell that is able to acquire a multitude of functional capabilities, some of which are shared with DC. In this review, we will first discuss the latest developments in our understanding of the organization of the DC and MC networks in both mouse and human and of the functional specializations of their subpopulations. Finally, we will discuss how DC and MC form two complementary and integrated functional systems.

Contents

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1. Introduction

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Dendritic cells (DC) form a heterogeneous group of antigen sensing and presenting cells that are critical agents in the induction and regulation of immune responses, and therefore potential targets for therapeutic intervention in immune-mediated conditions.

DC were originally described as cells with a stellate morphology capable of efficiently activating naïve T-cells. Although true, we now know that this description is too simple: within the DC population multiple subpopulations exist, each possessing distinct phenotypic and functional properties, together forming a complex cellular network capable of integrating multiple environmental signals and determining immunity or tolerance. In addition, a complementary system of monocyte-derived cells (MC) coexists with the DC network. MC can be found in tissue in steady state but are most readily generated upon inflammation and exhibit high plasticity and versatility in their functions, which are heavily influenced by the microenvironment orchestrated and generated by local DC.

DC subsets can be classified by various parameters and at different levels, which will be discussed below, including localization, phenotype, ontogeny, gene expression profile and specialized function. Historically, the broadest division was made between DC resident in lymphoid organs and migratory DC that exist in all non-lymphoid tissues and can be detected migrating through the lymphatics to draining lymph nodes (LN). Lymphoid-resident DC were also termed conventional dendritic cells (cDC) to distinguish them from plasmacytoid DC (pDC), known for their unique capacity to produce massive amounts of type I interferons in response to viral stimulation. Additional key features of cDC are their dependence on the growth factor fms-like tyrosine kinase 3 ligand (FLT3L) and its receptor FLT3 [1], as well as granulocyte macrophage colony stimulating factor (GM-CSF) and its receptor GM-CSFR [2,3]. They also exhibit a unique ontogeny, arising from common DC precursors present in the bone marrow (BM) [4], and expressing the transcription factor Zinc Finger and BTB Domain Containing 46 (ZBTB46) as they mature [5]. These criteria are important, as several other cell types including MC and Langerhans cells (LC) share features of DC, and it has been challenging to understand their relationship to the DC population at large. LC, described as the DC population of the epidermis, were long considered part of the DC family, until recent data demonstrating their unique embryonic ontogeny and FLT3-independence revealed that they are in fact an unusual type of tissue-resident macrophage that acquires DC-like functions upon maturation [6,7]. Additionally, during inflammation, MC are generated and recruited into tissues by microbial and/or inflammatory stimuli. These cells were initially classified as inflammatory DC as they can present antigen and exhibit an overlapping phenotype with cDC. However, we now know that MC arise independent of both FLT3 and GM-CSFR [2], and so more likely represent a distinct type of highly plastic cell able to acquire a multitude of functional capabilities, some of which are shared with cDC, rather than a *bona fide* DC sub-type [8].

In this review, we will first discuss the latest developments in our understanding of the organization of the DC and MC networks and of the functional specializations of their subpopulations. We will consider the newly recognized parallels between DC and MC populations in both mouse and human, focusing on cDC. The distinct pDC system has been recently reviewed elsewhere, and we refer the reader to these publications for further information [9,10]. Finally, we will give an overview of the flexible integration of the DC and MC populations and how this system is shaped by ontogeny or "central programming", as well as by microenvironmental stimuli or "peripheral programming" within a given tissue during health and disease.

2. Mouse dendritic cell subsets

Expression of the integrin CD11c (integrin alpha X) and major histocompatibility complex (MHC) class II molecules (MHC-II) was classically thought to characterize all *bona fide* DC subsets during both the steady state and inflammation. However this definition is now known to be an over-simplification as is does not reflect the true diversity of DC and MC subpopulations. In mouse lymphoid organs, DC can be separated into several phenotypically and functionally distinct subsets and were originally segregated according to mutually exclusive expression of the surface markers CD8α and CD4 in lymphoid tissues. In non-lymphoid tissues, the dividing markers are the integrins CD103 (integrin alpha E) and CD11b (integrin alpha M), while in the intestine an atypical additional DC subset co-expressing CD103 and CD11b exists (Fig. 1). The entity formed from these subpopulations of cells across the various tissues collectively constitutes the cDC compartment.

2.1. Conventional DC (cDC) compartment

The genetic and functional studies that will be discussed below have revealed that lymphoid organ resident CD8α$^+$ and non-lymphoid organ CD103$^+$ DC subsets on one side, and lymphoid organ resident CD4$^+$ and non-lymphoid organ CD11b$^+$ DC subsets on the other side, constitute two distinct DC lineages. Each lineage, irrespective of their lymphoid/non-lymphoid localization and distinct phenotypes, possesses unique characteristics and properties. Based on these advances, it was recently proposed that murine cDC are most appropriately divided into only two main subtypes: classical type 1 DC (cDC1) for CD8α$^+$/CD103$^+$ DC, and type 2 DC (cDC2) for CD4$^+$/CD11b$^+$ DC [8]. Accordingly we will use the denominations cDC1 and cDC2 hereafter.

2.1.1. CD8α$^+$ and CD103$^+$ DC subsets (cDC1)

DC expressing CD8α (in lymphoid organs) or CD103 (in peripheral organs and the migratory fraction of LN) represent a unified lineage according to their functional capacities and transcription factor requirements. These cDC1 exhibit a strict dependence on FLT3L for their differentiation [11] and require GM-CSFR for

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