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Review

Human mononuclear phagocyte system reunited

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ABSTRACT

The human mononuclear phagocyte network comprises dendritic cells (DCs), monocytes and macrophages with a range of immune functions including antigen presentation linking innate and adaptive immunity. A number of DC, monocyte and macrophage subsets have been described in lymphoid and non-lymphoid tissue of mouse and human, with increased understanding of their distinct functional properties and genetic and cellular pathways of development. More recently, through comparative biological studies, a unified nomenclature of mononuclear phagocytes has begun to emerge with the identification of homologous subsets in several species. In this review, we discuss the recent developments in the classification of human mononuclear phagocytes and the parallel organization of this network in the mouse, the origin and genetic control of their differentiation and the immunological functions of the distinct subsets in health and the dynamic changes that occur during inflammation.

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1. Introduction

Dendritic cells (DCs), monocytes and macrophages are a heterogeneous population of mononuclear cells that are specialized in antigen processing and presentation to initiate and regulate immune responses (reviewed in [1–3]). In addition to their afferent sentinel functions, DCs and macrophages are also coordinators and effectors of homeostasis and inflammation in peripheral tissues [4–6]. There has been a paradigm shift in our understanding of mononuclear phagocytes beyond the traditional view of DCs and macrophages as functional variations of monocytes. Significant progress has been made in understanding human and mouse mononuclear phagocyte biology in tandem, including a number of important recent conceptual advances concerning their ontogeny and development (reviewed in [7–11]). An exceptionally fruitful strategy to integrate these findings has been comparative analysis of mouse and human, which has identified homologous subsets and facilitated a unified classification of mononuclear phagocytes across species [12–20].

While harnessing DCs and macrophages for therapeutic purposes has major implications for infectious disease, vaccine science, transplantation, tolerance induction, inflammation and cancer immunotherapy, the use of monocyte-derived DCs in therapy has so far been underwhelming (reviewed in [21,22]). A thorough understanding of the origin and immune function of human mononuclear phagocytes *in vivo* may direct our attentions to more effective therapeutic strategies. In this review, we will discuss the recent developments in our understanding of the developmental origins and function of the human mononuclear phagocyte network.

2. The mononuclear phagocyte family

Mononuclear phagocytes, in contrast to polymorphonuclear granulocytes (originally known as *micro*phages), are leukocytes with specialized antigen processing and presentation function. They are found in almost all tissue compartments, including peripheral blood and are often referred to as antigen presenting cells (APCs). The 'mononuclear phagocyte system' was proposed in the late 1960s by van Furth to include circulating monocytes and tissue macrophages [23], the latter assumed to be differentiated state of monocytes. In 1973, the late Nobel Laureate, Ralph Steinman, working in Zanvil Cohn's laboratory, discovered the dendritic cell (DC), a new type of mononuclear leucocyte with probing morphology, endocytic function and potent activation capacity of naïve T cells, in the mouse spleen [24]. In the late 1970s, DCs were included into the family of mononuclear phagocytes [23]. Although DCs were shown to have unique properties to macrophages, their independence from monocytes and macrophages as a distinct lineage has attracted controversy over many years [25,26]. Recent advances have revealed the intimate connection between these cells reuniting the focus on mononuclear phagocytes as a unified system.

Mononuclear phagocytes are found in all tissue compartments including peripheral blood circulation. Macrophages may be considered as fixed tissue residents but peripheral tissue DCs have the capacity to migrate to draining lymph node *via* lymphatics. In addition, lymphoid tissues are also populated by blood-derived resident DCs [27,28]. In draining lymph nodes, migratory DCs and resident DCs contribute to the collective DC population and can be distinguished by the differential expression levels of CD11c and MHC Class II [17,29].

2.1. Relationships between DCs, monocytes and macrophages

The developmental and functional relationships of monocytes, macrophages and DCs have been the subject of much study and debate. In the 1990s, it was found that blood monocytes could be differentiated into dendritic-like cells (mo-DCs) or macrophages-like cells (mo-Macs) under the influence of cytokines including GM-CSF, TNFα, and IL-4 or M-CSF, respectively [30–33]. The difficulty of accessing human peripheral tissue leukocytes such as resident macrophages and the rarity of DCs in blood (<0.1% of mononuclear cells) meant that most studies relied experimentally on the use of mo-DCs and mo-Macs. These *in vitro* models have allowed us to gain enormous insights into the function of these cells but their relationship to *in vivo* equivalents is still obscure [34,35].

The distinct developmental pathways of monocytes and DCs from hematopoietic stem cells (HSCs) were defined in mouse, showing that DCs arose independently, through progenitors with restricted DC potential, reliant on specific genes [36–42]. Ontogeny studies have demonstrated the non-redundant role of CSF-1R for macrophage differentiation from embryonic or HSC/monocyte-precursors (reviewed in [9]) and FLT3 for steady-state DC differentiation (reviewed in [3,43]). More recently, transcriptional profiling has enabled the separation of DCs from monocytes and macrophages in both human and mice overcoming the limitations posed by restricted surface markers which may overlap between cell types and show idiosyncratic species differences [17,19,44,45].

2.2. *Steady-state* versus *inflammation*

Peritoneal macrophages elicited in animals using inflammatory stimuli have been widely studied over many years [46]. Seminal work from the 1960s showed that macrophages in *Listeria monocytogenes* infected lesions in mice ingested the bacterium and provided cellular resistance to infection [47]. It is clear that inflammatory tissue contains mononuclear phagocyte populations, which are not present in steady-state [48–53]. The origin and nature of these cells is now a focus of intense study in both mouse and human.

3. Classification of human mononuclear phagocytes

3.1. *Non-lymphoid tissue*

Although epidermal Langerhans cells (LCs) were first described in 1868[54], their identity as a member of the mononuclear phagocyte system was not appreciated until 1973, when they were found to express MHC Class II and complement receptors [55–57]. A notable property of some mononuclear phagocytes and lymphocytes from the skin is their ability to migrate spontaneously from skin explants cultured *ex vivo* [58–61]. Spontaneous migration which occurs over 1–3 days from explanted skin was assumed to recapitulate lymphatic migration lending the use of skin explant culture as a convenient tool to study human tissue migratory DCs, with epidermal LCs studied as the prototype migratory tissue DCs. Dermal DCs, the exemplars of human interstitial DCs, were first identified within migrated cells from dermal explants [60,61]. Two subsets were defined by the expression of CD1a and CD14, the latter being FXIIIA^{lo}, and CD1c negative; both expressing CD11c ([60,61] and reviewed in [62]). In contrast to DCs, dermal macrophages do not migrate spontaneously from skin explants, are highly autofluorescent and contain dense melanin granules within their cytoplasm [63,64]. Dermal macrophages are CD14^{+}, CD11b^{+}, MHCClassII^{lo} *in situ*, FXIIIa^{br} and are spindle-shaped by whole mount immunostaining corresponding to the previously described dermal dendrocytes or melanophages [64,65].

Dermal CD1c^{+} DCs, co-express CD1a but are distinct from LCs which express langerin, EpCAM and higher amounts of CD1a [63,66,67]. Recently, CD141 (thrombomodulin)^{hi} DCs were identified in human peripheral tissues [17], resolving the tissue myeloid DC compartment into two fractions analogous to human blood

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