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Review

Monocyte-derived dendritic cells: targets as potent antigen-presenting cells for the design of vaccines against infectious diseases

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SUMMARY

Monocytes play important roles in the inflammatory response, which is essential for the innate response to pathogens. Monocytes are able to differentiate to dendritic cells (DCs) under inflammatory situations. In recent decades, the heterogeneity of monocytes and their different traffic pathways have been identified in both human and murine systems. Different monocyte subsets show distinct inflammatory cytokine profiles and differentiation potential under steady-state and inflammatory situations. We discuss the biology of monocytes, their relationship with DCs, and the potential of monocyte-derived dendritic cells (moDCs) in the design of vaccines against certain chronic infectious diseases.

1. Introduction

Monocytes are circulating blood leukocytes with a fundamental capacity to differentiate into macrophages. In the right environment, monocytes can also differentiate into specialized antigen-presenting dendritic cells (moDCs). In the human and in mice, monocytes have some typical morphological features: irregular cell shape, oval- or kidney-shaped nucleus, cytoplasmic vesicles, and a high cytoplasm-to-nucleus ratio. However, they are still very heterogeneous in size and shape and are difficult to distinguish by morphology or by light scatter analysis alone from blood DCs, activated lymphocytes, and natural killer (NK) cells. In recent decades, with the help of flow cytometry and different transgenic mouse models, monocytes have been divided into two to three subsets.[1–3]

Monocytes play important roles in the inflammatory response, which is essential for the innate response to pathogens. They are distinct from polymorphonuclear cells (PMNs) and NK cells, which also belong to the innate arm of the immune system, as well as from lymphoid T and B cells, which represent the adaptive arm of the immune system. Monocytes represent about 10% of leukocytes in human blood and 4% of leukocytes in mouse blood. In recent years, studies using murine models have clearly demonstrated that monocytes are distinct from conventional dendritic cells (cDCs), which are derived from dendritic cell precursors present in the bone marrow and circulating blood.[4,5] Monocytes are also distinct from plasmacytoid dendritic cells (pDCs), the type I interferon-producing cells, which are differentiated from the hematopoietic precursors in the bone marrow and traffic into lymphoid organs via high vein endothelium cells.

In some infections, monocyte numbers increase in peripheral blood, and they infiltrate into the inflammatory sites. Studies on monocytes have broadened our horizons on dendritic cell biology in relation to the induction of innate and adaptive immune responses. In recent decades, heterogeneity among monocytes and their different traffic pathways have been identified. The inflammatory cytokine profiles and differentiation potentials of different monocyte subsets under steady-state and inflammatory situations in response to distinct microbial products are recognized. This progress has provided opportunities for novel designs of new treatments against pathological inflammation, as well as prophylactic and therapeutic vaccines against some chronic diseases.

2. Monocyte phenotypic heterogeneity: human PBMCs

More than 20 years ago, Passlick et al. demonstrated that human monocytes in the blood are heterogeneous.[6] In addition to

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the classical $CD14^{++}$ monocytes, which comprise the major subset in the circulation, a subset of $CD14^{+}CD16^{+}$ monocytes is readily identified, which make up 2.2% of the whole peripheral blood mononuclear cells (PBMCs) and form about 13% of all CD14-positive cells.[6] The $CD14^{++}CD16^{-}$ monocytes represent 80% to 90% of blood monocytes. Recently, new nomenclature has been suggested by an expert panel in Brescia, Italy, to define three subsets of monocytes according to the cell surface expression of CD14 and CD16. The major subset of monocytes consists of CD14-high CD16-negative ($CD14^{++}CD16^{-}$). The CD16 expressing monocytes are usually divided into CD14-high CD16-low ($CD14^{++}CD16^{+}$) and a CD14-low CD16-high ($CD14^{+}CD16^{++}$) subsets.[3]

Human $CD14^{++}$ $CD16^{-}$ monocytes express high levels of CCR2 (C-C chemokine receptor 2) and CD62L (L-selectin), but lower CX_3CR1 (C-X_3-C chemokine receptor 1) on their surface. They have higher phagocytic and myeloperoxidase activity, and superoxide release. When stimulated with lipopolysaccharide (LPS), the cells produce higher levels of interleukin (IL)-10, but lower levels of tumor necrosis factor alpha (TNF-α) and IL-1. In contrast, human $CD16^{+}$ monocytes express high levels of CX3CR1, but lower CCR2, and are responsible for the production of TNF-α in response to LPS stimulation.[7–10] Several studies have reported that $CD16^{+}$ monocytes are found in larger numbers in the blood of patients with acute inflammation and infectious diseases.[11,12] The numbers of $CD16^{+}$ cells have been found to increase greatly in the organs involved in some autoimmune diseases, such as rheumatoid arthritis and systemic lupus.[13,14]

Regarding the relationship to moDCs, both subsets of monocytes can differentiate into dendritic cells (DCs) in the presence of granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-4 when cultured in vitro. They internalize soluble and particulate antigens similarly, and both are able to stimulate T cell proliferation in autologous and allogeneic cultures.[7,15,16] However, $CD16^{+}$ moDCs express higher levels of CD86, CD11a, and CD11c, and show lower expression of CD1a and CD32 compared to $CD16^{-}$ moDCs. LPS-stimulated $CD16^{-}$ moDCs express increased levels of IL-12 p40 mRNA and secrete greater amounts of IL-12 p70 than $CD16^{+}$ moDCs, whereas levels of transforming growth factor beta 1 (TGF-β1) mRNA are higher in $CD16^{+}$ moDCs. Moreover, $CD4^{+}$ T cells stimulated with $CD16^{+}$ moDCs secrete increased amounts of IL-4 compared to those stimulated by $CD16^{-}$ moDCs.[7] Using an in vitro transendothelial migration model, Randolph et al. showed that monocytes can migrate across an endothelial barrier in vitro and differentiate into DCs, which reverse-migrate back across the endothelial layer, or into macrophages, which remain in the subendothelial matrix.[17] In this model, the $CD14^{+}CD16^{+}$ monocytes were found to be more likely to become DCs than the $CD14^{+}CD16^{-}$ monocytes,[8] indicating that the $CD14^{+}CD16^{+}$ monocytes might be precursors of DCs. There appears to be a developmental relationship in that the classical $CD14^{+}$ monocytes develop the non-classical $CD14^{+}CD16^{+}$ monocytes. $CD14^{+}CD16^{+}$ monocytes may represent a more mature version.[8]

3. Monocyte phenotypic heterogeneity: mouse PBMCs

To study the roles and functions of different monocyte subsets under physiological or pathological situations, CD14 does not serve as a practical marker for identifying mouse blood monocytes, as in humans, because CD14 levels are very low on the cell surface of mouse monocytes.[1] The expression of macrophage colony-stimulating factor receptor (M-CSFR, CD115), a key factor in driving the development of macrophages,[18] selectively delineates monocytes in the blood of mice. The use of CD115 alone or in combination with F4/80 identifies the same subsets of monocytes in wild-type C57BL/6 mice[19] as does the use of GFP knocked into the CX3CR1 locus,[20] a popular model for tracing monocytes through an endogenous fluorescent tag. Currently murine peripheral blood monocytes are divided into at least two subsets: the Gr1 (Ly6C) high and Gr1 (Ly6c) low monocytes. The mouse $Ly6C^{high}$ monocytes are also $CCR2^{+}CD62L^{+}CX_3CR1^{low}$, and correspond to $CD14^{++}CD16^{-}$ (classic) human monocytes. $Ly6c^{low}$ monocytes express higher levels of CX_3CR1, and the $CX_3CR1^{high}CCR2^{+/-}CD62L^{-}Ly6c^{low}$ mouse monocytes correspond to $CD14^{+}CD16^{+}$ human monocytes.[19,21,22] A subset expressing Gr1 $(Ly6C)^{int}$ has also been reported.[19,23] BM monocytes are $Ly6c^{high}$ and that Ly6c expression is rapidly lost during in vitro development into macrophages or DCs.[24] When sorted $Ly6c^{high}$ blood monocytes were cultured in vitro, expression of Ly6C was lost within 3 days. On depleting mouse blood monocytes, the $Ly6c^{high}$ cells had repopulated in 3–4 days, with $Ly6c^{low/int}$ cells appearing in significant numbers from 7 days after the depletion.[24] This possibly mimics the developmental relationship in the maturation process of monocytes.

4. Differentiation of the DC progenitor: origin of DC subsets

DCs comprise several subsets, and their roles in the presentation of antigens derived from pathogens, vaccines, and self-tissues are now being elucidated (see the review by Villadangos and Schnorrer[25]). Different DC types have distinct roles in initiating immunity to specific pathogens. There are two main categories of DCs: pDCs and conventional DCs (cDCs). They both originate from hematopoietic stem cells in the bone marrow via intermediate progenitors.

pDCs generate high amounts of type I interferon (IFN-I) and acquire the typical DC morphology after activation. Their activation and IFN-I production are critical for the initiation of antiviral immune responses. It has been shown that the basic helix-loop-helix protein E2-2/TCF4 is a required transcription factor for pDC development in both the human and the mouse[26] and for the maintenance of mature pDCs.[27] Recently, a population identified in the bone marrow as Lin^{-} c-$Kit^{int/lo}Flt3^{+}$M-$CSFR^{-}$ and expressing high amounts of E2-2 has been described as the pDC progenitor. These cells are derived from either common DC progenitors (CDPs) or lymphoid-primed multi-potent progenitors, with prominent pDC differentiation potential.[28] The pDC-committed progenitors are different from the macrophage and DC progenitors (MDP), which express the phenotypic markers as Lin^{-} $CX_3CR1^{+}CD11b^{-}$ c-$Kit^{int/lo}Flt3^{+}$M-$CSFR^{+}$ and produce many more cDCs than pDCs.[29,30]

cDCs present in the thymus, spleen, and lymph nodes and can be grouped into two main categories that are distinguished by the paths they follow to access the lymphoid organs.[31] One major category of lymphoid organ DCs is the blood-derived or resident DCs. With their surface expression of CD4 and CD8, the lymphoid organ resident DCs can be subdivided into three types: $CD4^{+}$ DCs, $CD8^{+}$ DCs, and $CD4^{-}CD8^{-}$ (double-negative) DCs. They develop from bone marrow precursors within the lymphoid organs without previously trafficking through peripheral tissues.[32–35] The migratory DCs are the second category of lymph node DCs, and these develop from earlier precursors in the peripheral tissues and travel through the afferent lymphatics to reach the local draining lymph nodes. This group of DCs is largely absent from the spleen and thymus because these organs do not receive afferent lymph.[25] Migratory DCs follow the lifecycle described by the Langerhans cell paradigm: they traffic from peripheral tissues to the lymph nodes, where they exhibit a mature phenotype.[31] They are present in peripheral tissues in an immature state that is specialized for sampling the environment using various endocytic mechanisms, but are characterized by low levels of expression of MHC molecules and T cell co-stimulatory molecules (see the review by Steinman[36]).