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MONOCYTES AND INFECTION: MODULATOR, MESSENGER AND EFFECTOR

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Abstract

Monocytes are a subset of circulating blood cells with remarkable plasticity. They can develop into a wide range of terminally differentiated cells and perform versatile functions during infection, tumor formation and in the setting of chronic inflammation. This review focuses on the role of monocytes during microbial infection and summarizes our understanding of the diverse roles that monocytes play in defense against different pathogens.

Monocytes are a subset of circulating blood cells with remarkable plasticity. They can develop into a wide range of terminally differentiated cells and perform versatile functions during infection, tumor formation and in the setting of chronic inflammation. This review focuses on the role of monocytes during microbial infection and summarizes our understanding of the diverse roles that monocytes play in defense against different pathogens.

Overview: subsets of monocytes and their functions

Although circulating monocytes and their potential role as macrophage progenitors have a long history that extends to the early decades of the last century, it was not until much later, with the advent of flow cytometry, monoclonal antibody generation and murine genetic engineering, that the complexity and plasticity of circulating monocytes could be explored and increasingly defined (Geissmann et al., 2003). Since then, comprehensive phenotypic and functional analyses have been carried out, which demonstrate that monocytes play important and at times divergent roles in various pathological conditions.

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Conflict of Interest

The authors claim no conflict of interest.

Monocytes are a heterogeneous population, which quickly respond to stimuli including TLR signaling following exposure to pathogens and to inflammatory cytokines (Auffray et al., 2009). Murine monocytes are divided into two categories. Ly6C^{hi} inflammatory monocytes express high levels of CC chemokine receptor 2 (CCR2) but low levels of CX3CR1 (Geissmann et al., 2003), and circulate between blood and bone marrow under homeostatic conditions. They infiltrate tissue upon infection and serve as precursors of different kinds of effector cells, including TNF-and-iNOS Producing Dendritic Cells (TipDCs) during *Listeria monocytogenes* infections (Serbina et al., 2003b). The diverse role of monocyte-derived cells, which includes secreting cytokines, transporting antigens and priming/polarizing T cells has been demonstrated following infection with different microbial pathogens. (Hohl et al., 2009; Rivera et al., 2011; Samstein et al., 2013) The function of recruited monocytes is highly dependent on the context of infection, the site and the microenvironment. In other settings, such as chronic inflammation or in tumors, monocytes differentiate into so-called myeloid-derived-suppressive cells (MDSC) or macrophages and produce a complex spectrum of cytokines and growth factors, such as IL-10, Arginase, TGF-β and M-CSF, that can suppress immune responses and promote tumor growth (Gabrilovich et al., 2012; Motz and Coukos, 2013).

An interesting subset of circulating monocytes expresses high levels of CX3CR1 and low levels of Ly6C and CCR2 (Geissmann et al., 2003). This subset is characterized by “patrolling” the luminal endothelium. Patrolling by this monocyte subset depends on LFA-1 and ICAM-1 interaction between CX3CR1^{hi} monocytes and the endothelial cells, and experimental studies demonstrate that monocytes contribute to surveillance, wound healing and vascular-endothelial growth (Auffray et al., 2007; Nahrendorf et al., 2007). CX3CR1^{hi} monocytes can differentiate into CX3CR1^{+} intestinal LP macrophages (Geissmann et al., 2010; Medina-Contreras et al., 2011). Their roles in infections are less well understood, although it has been suggested that they are involved in very early defense against *Listeria monocytogenes* (Auffray et al., 2009). Recent studies of the two monocyte subsets suggest that CX$_3$CR1^{int}Ly6C^{+} inflammatory monocytes are precursors for CX3CR1^{+}Ly6C monocytes in the intestine under homeostasis (Yona et al., 2013). With inflammation, however, CX$_3$CR1^{int}Ly6C^{+} monocytes develop into pro-inflammatory DCs and prime Th1 responses (Rivollier et al., 2012).

In humans, monocytes can be divided into three subsets based on CD14 and CD16 expression. CD14^{+}CD16^{+} and CD14^{+}CD16 monocytes resemble mouse inflammatory monocytes and express CCR2 and traffic to the site of infection or inflammation to carry out antimicrobial or pro-inflammatory functions (Geissmann et al., 2003; Serbina et al., 2008). Human CD14^{lo}CD16^{+} cells express CX3CR1 and are involved in endothelial patrolling similar to mouse CX3CR1^{hi} monocytes(Cros et al., 2010).

Monocyte recruitment to the site of infection

Inflammatory monocytes traffic between the bone marrow and bloodstream and constitute a small population of white blood cells under steady state conditions. Upon infection, however, egress of monocytes from the bone marrow to the bloodstream is enhanced and mediated by CCR2-CCL2 interaction. CCR2 is highly expressed on Ly6C^{+} monocytes and

CCL2 (MCP1) expression is induced on PDGFR-b^{+}Nestin^{+} bone marrow mesenchymal stromal cells (MSCs) and CD31^{+} bone marrow endothelial cells in a TLR-dependent manner (Serbina and Pamer, 2006; Shi et al., 2011). CCR2-CCL2 interaction is believed to drive inflammatory monocytes migration towards endothelial cells, followed by trafficking into the bloodstream. In the absence of TLR-MyD88 signaling, inflammatory monocyte emigration from the bone marrow can be induced by TNF and type I IFN (Jia et al., 2009), suggesting that inflammatory cytokines may play a compensatory and partially overlapping role with TLR-MyD88 signaling to drive CCR2-CCL2-mediated monocyte trafficking. In addition to CCL2, a second CCR2 ligand, CCL7, is also involved in monocyte trafficking (Jia et al., 2008; Tsou et al., 2007). CCR2KO animals have a profound deficiency in monocyte circulation whereas CCL2KO and CCL7KO mice have a partial reduction under homeostatic conditions and after *L.monocytogenes* infection (Jia et al., 2008; Shi et al., 2011). Consequently, CCR2KO animals are more susceptible to *L.monocytogenes* infection than CCL2KO or CCL7KO mice (Jia et al., 2008). These findings suggest that CCL2 and CCL7 make parallel contributions to monocyte trafficking. It is notable that CCL7, but not CCL2, is upregulated in the kidney post infection, suggesting a possible tissue-specific role of CCL7 in antimicrobial defense (Jia et al., 2008). On the other hand, neither CCL2 nor CCL7 seems to be required for circulating monocytes to enter the infected tissue or to differentiate to effector cells. This is illustrated by the finding that CCR2KO monocytes traffic efficiently to sites of infection following adoptive transfer into the bloodstream (Bosschaerts et al., 2010; Serbina and Pamer, 2006; Shi et al., 2010) and differentiate to TipDCs (Jia et al., 2008; Serbina and Pamer, 2006). ICAM-1 has been suggested to mediate monocyte infiltration to target organs. (Shi et al., 2010).

Monocytes directly exert microbicidal effects through TNF and iNOS

As demonstrated in the *L.monocytogenes* model, monocytes are swiftly recruited and activated at the site of infection. Importantly, activated monocytes can secrete TNF and produce inducible nitric oxide synthase (iNOS, also termed NOS2)(Serbina et al., 2003b). Production of TNF and iNOS by monocytes requires infection by live, virulent bacteria, is dependent on TLR-MyD88 signaling and IFN-γ, and is negatively regulated by Th2 cytokines such as IL-10, IL-4 or IL-13(Bosschaerts et al., 2010; De Trez et al., 2009; Serbina et al., 2003a). TNF and iNOS play an important role in clearing *Listeria* infection (MacMicking et al., 1995; Nakane et al., 1988; Pfeffer et al., 1993) through distinct mechanisms. TNF functions mainly through TNFR1 during infections, as TNFR1KO animals are highly susceptible and succumb to *L. monocytogenes* infection (Rothe et al., 1993). TNF-TNFR1 binding activates NF-κB signaling, leading to transcription of inflammatory genes (Chen and Goeddel, 2002; Micheau and Tschopp, 2003), stimulation of IFN-γ production (Tripp et al., 1993) and enhancement of macrophage listericidal activity (Bancroft et al., 1989; Nakane et al., 1988). Membrane-bound TNF has been shown to partially protect infected mice, indicating the requirement for cell-cell interactions (Torres et al., 2005). iNOS production leads to the production of nitric oxide (NO)in phagocytic cells, including monocytes, which likely kills bacteria by inducing DNA damage and disrupting bacterial metabolism. (Nathan and Shiloh, 2000)

Similar to the *L.monocytogenes* infection model, TNF and/or iNOS produced by monocyte-derived DCs has been implicated in the control of infections caused by *Toxoplasmagondii* (Dunay et al., 2008; Mordue and Sibley, 2003; Robben et al., 2005), *Salmonella typhimurium* (Rydstrom and Wick, 2007) *Trypanosomabrucei* (Bosschaerts et al., 2010), and *Influenza* virus infections(Aldridge et al., 2009; Lin et al., 2008). In some of these diseases, monocyte functions in addition to TNF and iNOS have been implicated, such as IL-12 production (Dunay et al., 2008). In some cases, monocyte-produced TNF and iNOS can be deleterious. For example, following influenza virus infections, monocyte responses can exacerbate inflammation, causing tissue damage and suppression of wound healing (Karupiah et al., 1998; Lai et al., 2009; Lin et al., 2008).

Monocytes transport antigens to T cells

In addition to differentiating into TipDCs, inflammatory monocytes play versatile and active roles in modulating the development, recruitment and activation of other immune cells during infection. Monocytes can differentiate into dendritic cells and prime $CD4^+$ T cells in various infection models including fungal (Hohl et al., 2009), bacterial (Samstein et al., 2013) and viral infections (Aldridge et al., 2009). The mechanism by which monocytes prime T cell responses has been intensively investigated. Recently, it has been demonstrated, by using a murine *Mycobacterium tuberculosis* model, that monocytes transport live bacteria to the draining lymph node. (Samstein et al., 2013) Depletion of $Ly6C^{hi}$ monocytes in CCR2-DTR mice at the early and late stages of infection results in distinct outcomes, and that monocyte depletion at early time points significantly reduces the number of live bacteria in mediastinal lymph nodes, which leads to decreased proliferation of *M.tuberculosis* -specific T cells and thus hampers bacterial clearance. This indicates that live bacterial trafficking to the LN is mediated by inflammatory monocytes and is required for efficient T cell priming. This process does not require MHCII expression on the monocytes, but rather, requires MHCII expression on classical dendritic cells (cDC) in the LN. Taken together, these observations suggest a model in which monocytes carry antigen to lymph nodes and transfer it to cDCs, which present antigens and activate antigen-specific T cells (Samstein et al., 2013). This was similarly observed in a dermal fungal infection model, where monocyte-derived DCs carry attenuated yeast to skin-draining lymph nodes but fail to present the fungal antigen in the node. Instead, dermal and lymph node-resident DCs present fungal antigen and prime naive antigen-specific T cells (Ersland et al., 2010).

Monocytes orchestrate functions of other cells

In addition to antigen transportation, inflammatory monocytes modulate T cell responses. In a pulmonary infection model using the fungal pathogen *Aspergillus fumigatus*, monocytes are involved in both T cell priming at early time points and T cell polarization at later time points (Hohl et al., 2009; Rivera et al., 2011). Inflammatory monocytes induce Th1 polarization by inducing T-bet expression in responding CD4 T cells (Rivera et al., 2011). Th1 polarization depends on IL-12 and IFN-γ and monocyte-derived cells can produce IL-12 to facilitate priming and expansion of Th1 CD4 T cells in response to infection (Kim et al., 2011; Leon et al., 2007; Schreiber et al., 2013; Wuthrich et al., 2012).

In addition to T cells, monocytes also regulate the function of other cell types. In the case of *A. fumigatus* infection, inflammatory monocytes optimize the function of neutrophils in clearing the infection in the lung by augmenting neutrophil conidiacidal activity (Espinosa et al., 2014). At the mucosal level, TipDCs regulate B cell class switching and promote mucosal IgA production under steady state conditions. (Tezuka et al., 2007)

Conclusion Remarks

Since their discovery, our understanding of the development and function of monocytes in infections has greatly advanced. Monocytes are highly sensitive and reactive to pathogen-derived molecules, and can quickly respond to microbial-stimuli to inhibit pathogens at early stages of infection. Monocyte differentiation and functionality are highly dependent on the context of the infection. They can enhance microbicidal activities by producing TNF and iNOS, in some settings they transport live microbes to the draining LN for presentation to T cells by DCs and, in other infections, they participate T cell priming and Th1 polarization in draining lymph nodes and at the site of infection. The influence of monocytes on neutrophils and B cells are also being increasingly appreciated. The pathways of monocyte development and differentiation into a wide range of distinct effector cells are being defined. It is likely that this new knowledge will eventually be exploited to enhance defense against infectious pathogens and to limit deleterious inflammatory conditions.

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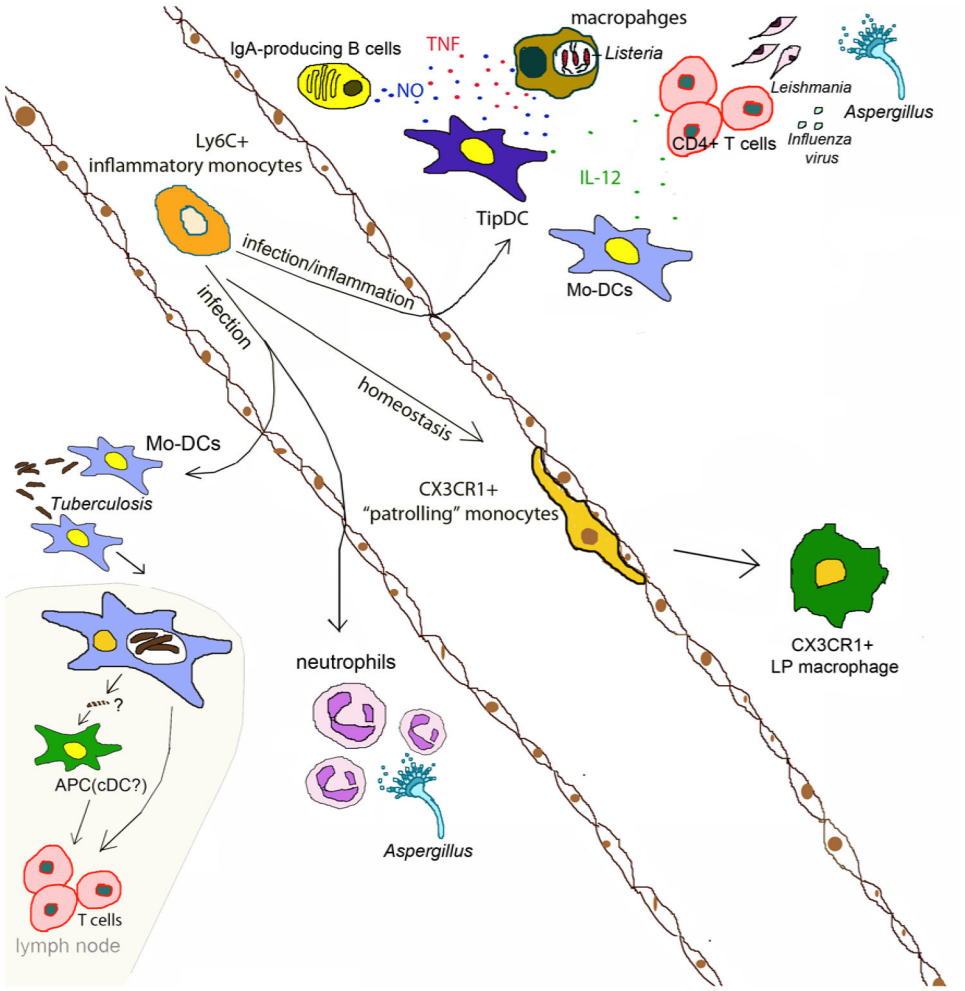

Fig. 1.
Differentiation and effector mechanism of monocytes