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Monocyte-mediated defense against bacteria, fungi, and parasites

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ABSTRACT

Circulating blood monocytes are a heterogeneous leukocyte population that contributes critical antimicrobial and regulatory functions during systemic and tissue-specific infections. These include patrolling vascular tissue for evidence of microbial invasion, infiltrating peripheral tissues and directly killing microbial invaders, conditioning the inflammatory milieu at sites of microbial tissue invasion, and orchestrating the activation of innate and adaptive immune effector cells. The central focus of this review is the *in vivo* mechanisms by which monocytes and their derivative cells promote microbial clearance and immune regulation. We include an overview of murine models to examine monocyte functions during microbial challenges and review our understanding of the functional roles of monocytes and their derivative cells in host defense against bacteria, fungi, and parasites.

1. Introduction

Circulating monocytes arise from pluripotent hematopoietic stem cells through a series of progressively committed oligopotent progenitors in the bone marrow [1,2]. The common monocyte progenitor (CMoP) represents a committed proliferative progenitor that is restricted to monocytes and monocyte-derived macrophages under homeostatic conditions [3]. Beyond their steady-state function in seeding mononuclear phagocytes in peripheral tissues during post-natal life [4], monocytes are increasingly recognized as critical cellular constituents of innate and adaptive immune responses against a wide range of microbes [5]. This review summarizes the role of monocytes against major bacterial, fungal, and parasitic organisms and associated human clinical syndromes (Table 1).

Human and murine monocytes express the receptor for monocyte colony-stimulating factor (M-CSF receptor; CD115) and the integrin CD11b. Monocytes are classified into two major subsets on the basis of chemokine, adhesion, pattern recognition, and Fc receptor expression [5–7]. In mice, Ly6C^{hi} monocytes, often termed inflammatory or CCR2^{+} monocytes, express high levels of the chemokine receptor CCR2 and low levels of CX3CR1. Conversely, murine Ly6C^{lo} monocytes, often termed resident monocytes, express low levels of CCR2 and high levels of CX3CR1. Murine Ly6C^{hi} and Ly6C^{lo} monocytes are present in similar numbers in the blood under steady state conditions. Murine Ly6C^{hi} monocytes seem functionally equivalent to human CD14^{hi}CD16^{-} monocytes, often termed CD14^{+} monocytes, while Ly6C^{lo} monocytes seem functionally equivalent to human CD14^{lo}CD16^{+} monocytes, often termed CD16^{+} monocytes. While the similarities between murine and human subsets were initially established on the basis of a limited set of surface antigens, in-depth transcriptional analyses support the notion that murine Ly6C^{hi} and human CD14^{+} monocytes as well as murine Ly6C^{lo} and human CD16^{+} monocytes form broadly conserved counterparts [8]. Several excellent reviews cover important species-specific differences between murine and human monocyte subsets in more detail and discuss minor monocyte subsets as well [2,5].

During microbial tissue invasion, Ly6C^{hi} monocytes mobilize in the bone marrow, enter the circulation, and extravasate into the periphery at portals of infection. Ly6C^{hi} monocytes and their derivative cells condition the local inflammatory milieu, activate innate effector cells through cellular crosstalk, engulf and kill microbes, and play critical roles in naïve T cell activation and in directing CD4 T cell differentiation. Recent work indicates that murine Ly6C^{hi} and human CD14^{+} monocytes can acquire features

Abbreviations: Ab, antibody; Ag, antigen; BM, bone marrow; CCR2, CC-chemokine receptor 2; CDP, common DC progenitor; CLR, C-type lectin receptor; cMoP, common monocyte progenitor; DC, dendritic cell; DT, diphtheria toxin; LSL, lox-stop-lox; MDP, macrophage-DC progenitor; M-CSF, monocyte colony-stimulating factor; Mo, monocyte; NO, nitric oxide; NOS, nitric oxide synthase; ROS, reactive oxygen species; Tg, transgene; TLR, toll-like receptor.

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Table 1
Bacterial, fungal, and parasitic diseases and important monocyte functions.

	Organism	Common Clinical Syndromes	Features of monocyte-mediated defense
Bacteria	*Listeria monocytogenes*	Gastroenteritis; bacteremia and meningitis in pregnant women, neonates, and immune compromised hosts	• Identification and functional characterization of "Tip-DCs" as monocyte-derived effector cells • Memory CD8 T cell and NK cell activation and tissue recruitment • CD4 T cell polarization
	Mycobacterium tuberculosis (Mtb)	Pneumonia; extrapulmonary disease following dissemination	• *Mtb* transport to lung-draining LNs • *Mtb* Ag transfer to LN DCs
	Klebsiella pneumoniae	Pneumonia; bacteremia in immune compromised patients	• Essential for pulmonary clearance of specific human clinical isolates
Fungi	*Aspergillus fumigatus*	Pneumonia and systemic disease in immune compromised hosts; Allergenic disease in atopic hosts	• Transport of conidia to lung-draining LNs • Direct conidial killing • Innate immune crosstalk with neutrophils to regulate killing • Regulation of Th1/Th17 CD4 T cell differentiation
	Blastomyces dermatiditis	Pneumonia and mucocutaneous disease	• Monocyte recruitment subverted by fungus-induced chemokine proteolysis
	Candida albicans	Mucositis, dermatitis and vulvovaginitis; systemic disease primarily in immune compromised hosts	• Monocytes contribute to renal and CNS fungal clearance • Fungal Ag trafficking from mucosal sites
	Cryptococcus neoformans	Pneumonia and meningitis, usually in immune compromised hosts	• Monocyte-derived exudative macrophages protect hosts against serotype A strains
	Histoplasma capsulatum	Pneumonia and systemic disease in immune compromised hosts	• CCR2 signaling prevents detrimental T helper 2 cytokine environment in lung
Parasites	*Schistosoma* spp.	Acute and chronic schistosomiasis; Urinary tract or portal fibrosis is associated with tissue injury and organ failure	• Differentiate into macrophages with M2 phenotypic characteristics • Induction of Tregs and regulation of Th2 responses
	Toxoplasma gondii	Cervical lymphadenopathy, chorioretinitis, congenital toxoplasmosis; disseminated disease and encephalitis in immune compromised patients	• Parasite killing in the intestine • Regulation of neutrophil activation
	Plasmodium sp.	Malaria	• Blood stage parasite elimination

of "trained immunity", a functional attribute with memory-like features that may facilitate pathogen clearance in subsequent encounters. In addition to these antimicrobial activities, murine Ly6C^{lo} and human CD16^{+} monocytes exhibit exquisite vascular and endothelial surveillance functions and can detect microbial nucleic acids and viruses via Toll-like receptor (TLR) 7 and 8 signaling pathways [9,10].

Our understanding of the contribution of monocytes and their derivative cells to vascular and endothelial surveillance, pathogen clearance in peripheral tissues, and to resolution of tissue damage following infectious challenges has extended to a wide range of microbes. The aim of this review is to summarize recent literature and highlight new insights on the role of monocytes and their derivative cells in innate and adaptive host defense against prokaryotic and eukaryotic pathogens. While the primary emphasis focuses on *in vivo* studies in murine experimental infection models, with an overview of genetically engineered mouse models to investigate monocyte functions *in vivo*, we discuss some relevant human examples as well. Monocyte development and monocyte trafficking during homeostasis, inflammatory states, and antimicrobial immunity has been reviewed extensively elsewhere [2,11,12].

2. Murine models to study monocyte function during microbial challenges

Researchers have developed a number of experimental strategies to trace and manipulate murine monocyte subsets and functions, primarily based on their expression of specific chemokine or adhesion receptors and transcription factors as well as susceptibility to toxin-loaded liposomes (Table 2).

First among these was the development of CCR2$^{(-/-)}$ mice in which the frequency of circulating Ly6C^{hi} monocytes is ~50–80% lower than in CCR2$^{(+/+)}$ mice [13]. *Ccr2*$^{-/-}$ Ly6C^{hi} monocytes fail to emigrate from bone marrow stores during experimental infections, notably *Listeria monocytogenes*. CCR2$^{(-/-)}$ mice are highly susceptible to systemic listeriosis due to a deficiency of Ly6C^{hi} monocyte-derived effector cells that produce TNF and express inducible nitric oxide synthase, best known as TNF/iNOS-producing dendritic cells (Tip-DCs), at sites of listerial tissue invasion [14]. This mouse strain is particularly well suited to study CCR2-dependent monocyte functions during microbial challenges and its role in mobilizing monocytes to portals of pathogen infection. Gene knockout and fluorescent reporter mouse strains for CCR2 ligands (i.e. CCL2/MCP-1, CCL7/MCP-3, and CCL12/MCP-5) are available [15–17] and have been utilized in pathogenesis studies, primarily to decipher the relative contribution of individual CCR2 ligands to monocyte trafficking [18] and to identify their cellular sources [17].

The development of CX3CR1 and CCR2 fluorescent reporter mice enabled the identification of circulating murine monocyte subsets and bone marrow progenitors on the basis fluorescent transgene expression [1,7]. These strains have facilitated numerous adoptive transfer studies of highly purified bone marrow or circulating monocytes to examine monocyte differentiation and effector functions during infectious challenges. The promoters for these chemokine receptors have been harnessed to drive a human