Monocytes and the Host Response to Fungal Pathogens

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Monocytes and their derivatives, including macrophages and dendritic cells, play diverse roles in the response to fungal pathogens. Sensing of fungi by monocytes triggers signaling pathways that mediate direct effects like phagocytosis and cytokine production. Monocytes can also present fungal antigens to elicit adaptive immune responses. These monocyte-mediated pathways may be either beneficial or harmful to the host. In some instances, fungi have developed mechanisms to evade the consequences of monocyte activation and subvert these cells to promote disease. Thus, monocytes are critically involved in mediating the outcomes of these often highly fatal infections. This review will highlight the roles of monocytes in the immune response to some of the major fungi that cause invasive human disease, including *Aspergillus*, *Cryptococcus*, *Candida*, *Histoplasma*, *Blastomyces*, and *Coccidioides*, and discuss potential strategies to manipulate monocyte responses in order to enhance anti-fungal immunity in susceptible hosts.

Keywords: monocyte, macrophage, dendritic cell, fungal infections, innate immunity

INTRODUCTION

Monocytes are innate immune cells that may be generated in the bone marrow from two different precursors, either a granulocyte-monocyte progenitor (GMP) or a monocyte-dendritic cell progenitor (MDP) (Yanez et al., 2017; Wolf et al., 2019; **Figure 1**). Monocytes derived from either of these lineages consist of two main types: (1) classical "inflammatory" monocytes that are CCR2$^+$ Ly6C^{hi} in mice and CD14$^+$ CD16$^-$ in humans, and (2) non-classical "patrolling" monocytes that are CCR2^{lo} Ly6C^{lo} in mice and CD14^{lo} CD16$^+$ in humans. Lineage tracing studies suggest that non-classical monocytes develop directly from classical monocytes (Yona et al., 2013). During homeostatic conditions, non-classical monocytes patrol the circulation to engage in tissue repair and clearance of dead cells (Auffray et al., 2007). During inflammation or infection, classical monocytes are mobilized from bone marrow reserves in response to chemokines that bind to the CCR2 receptor, such as CCL2 and CCL7 (Shi and Pamer, 2011). Upon entering affected tissues, classical monocytes can further differentiate into macrophages and monocyte-derived dendritic cells (MoDCs). Macrophages that differentiate from monocytes in the adult bone marrow are distinguished from tissue resident macrophages (e.g., alveolar macrophages, glial cells) that originally derive from fetal yolk sac progenitor cells or monocytes from the fetal liver (Hoeffel and Ginhoux, 2018). However, there is evidence that bone marrow-derived monocytes can help replenish the tissue-resident macrophages of specific organs including the gut, the skin, and the heart (Ginhoux and Guilliams, 2016). MoDCs are also distinct in origin from conventional dendritic cells (cDCs) and plasmacytoid dendritic cells (pDCs) that are derived from a common dendritic cell progenitor (CDP). The ontogeny of monocytes and ongoing controversies about their origins and development are reviewed in further detail elsewhere (Jakubzick et al., 2017; Murray, 2018; Wolf et al., 2019).
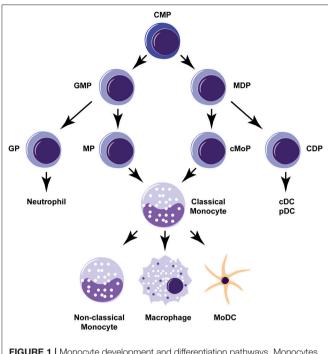
FIGURE 1 | Monocyte development and differentiation pathways. Monocytes can develop from either a granulocyte-monocyte progenitor (GMP) or a monocyte-dendritic cell progenitor (MDP). Classical "inflammatory" monocytes can give rise to non-classical "patrolling" monocytes or further differentiate into macrophages or monocyte-derived dendritic cells (MoDCs). Common myeloid progenitor (CMP), granulocyte progenitor (GP), monocyte-committed progenitor (MP), common monocyte progenitor (cMoP), common dendritic cell progenitor (CDP), conventional dendritic cell (cDC), plasmacytoid dendritic cell (pDC).

Invasive fungal infections represent a significant cause of human disease, with an estimated 1.5 million people dying each year (Bongomin et al., 2017). Unfortunately, the incidence of these infections is increasing with the expanded use of immunosuppressive therapies, broad-spectrum antibiotics, and invasive medical devices (Pfaller and Diekema, 2010; Clark and Drummond, 2019). Invasive infections are commonly caused by fungi of the genera *Aspergillus, Candida*, *Cryptococcus*, *Blastomyces*, *Coccidioides*, and *Histoplasma* (**Table 1**). Except for *Candida* species, which are commensal organisms found on the skin and mucosal surfaces, these fungi are environmental microorganisms that are typically acquired after inhalation into the lungs. All of these fungi can cause invasive disease in a wide-spectrum of immunocompromised patients, such as those with genetic immunodeficiencies, HIV/AIDS, cancer, solid organ, and hematopoietic stem cell transplantation, autoimmune diseases, immunosuppressive treatments, and other predisposing states like diabetes and pregnancy. However, apparently immunocompetent patients can also be affected by many of these fungi, including *Candida, Cryptococcus gattii,* and the endemic fungi *Blastomyces, Coccidioides*, and *Histoplasma*. Unfortunately, the morbidity and mortality from invasive fungal infections remains quite high despite current drug regimens, some of which utilize multiple antifungal agents. Therefore, the

development of novel therapeutic approaches to fungal infections is imperative to improving clinical outcomes.

Monocytes and their derivatives have been found to play critical roles in the outcomes of fungal infections (**Table 1**). For example, monocyte-deficient mice are more susceptible to infections with *Aspergillus fumigatus* (Hohl et al., 2009; Espinosa et al., 2014), *Candida albicans* (Ngo et al., 2014; Dominguez-Andres et al., 2017b), and *Histoplasma capsulatum* (Szymczak and Deepe, 2009). On the other hand, the absence of monocytes during *Cryptococcus neoformans* infection can either be detrimental or beneficial to host outcomes, depending on the infection model (Traynor et al., 2000; Osterholzer et al., 2008, 2009; Charlier et al., 2009; Heung and Hohl, 2019). This plasticity of monocytes in the regulation of immune responses to fungi makes these cells ideal targets for immunomodulatory therapies. Indeed, strategies to target monocyte development and function are already under investigation as potential cancer therapies given their roles in facilitating both pro-tumor and anti-tumor effects (Olingy et al., 2019). This review will highlight the key mechanisms by which monocytes regulate innate immunity to fungi, including fungal sensing, phagocytosis, cytokine production and cellular crosstalk, and antigen presentation and T cell priming. Recent developments in understanding the role of trained immunity in monocyte responses to fungal pathogens will also be discussed.

FUNGAL SENSING AND ORCHESTRATION OF THE IMMUNE RESPONSE

Monocytes express a variety of receptors to facilitate detection of fungal cells. Pattern recognition receptors (PRRs), including C-type lectin receptors (CLRs), Toll-like receptors (TLRs), and NOD-like receptors (NLRs), can detect pathogen-associated molecular patterns (PAMPs) like β-glucan, chitin and mannose in the fungal cell wall and trigger downstream signaling pathways to coordinate the innate immune response (Lionakis et al., 2017). Complement receptors (CRs) and Fc receptors also assist in fungal sensing by detecting complement or antibody-bound fungal cells (Erwig and Gow, 2016). These receptors can have individual effects or work in collaboration with each other. For example, cytokine production by macrophages and DCs is regulated by the CLR Dectin-1 and complement receptor 3 (CR3) during *H. capsulatum* infection and by Dectin-1 and TLR2 in *Coccidioides* infection models (Viriyakosol et al., 2005, 2013; del Pilar Jimenez et al., 2008; Lin et al., 2010; Huang et al., 2015). The activation of the NLRP3 inflammasome during histoplasmosis is coordinated by Dectin-1 and Dectin-2 signaling (Chang et al., 2017). During *C. albicans* infection, Dectin-1, Dectin-2, and Mincle collectively contribute to host defenses by regulating monocyte cytokine production and phagocytosis of the fungus (Thompson et al., 2019). Additionally, the balance between Dectin-1 and TLR signaling in MoDCs can determine the Th1 and Th17 responses to *A. fumigatus* (Rivera et al., 2011).

An interesting facet of PRR expression by monocytes is the capacity to discern different morphologic forms of fungi. *C. albicans* exists in yeast and filamentous forms, which can

	Organism	Typical clinical presentations	Key roles of monocytes and derivatives
Mold	*Aspergillus* spp. (*A. fumigatus*, *A. terreus*)	Pneumonia and other respiratory tract infections, systemic infections in immunocompromised patients	**Beneficial:** Phagocytize and kill conidia, cytokine production to enhance fungicidal activity of neutrophils, transport conidia to the lymph nodes and facilitate adaptive CD4^{+} T cell responses **Harmful:** Reservoir of viable conidia
Yeast*	*Cryptococcus* spp. (*C. neoformans*, *C. gattii*)	Pneumonia, meningitis in immunocompromised patients and apparently immunocompetent patients (*C. gattii*)	**Beneficial:** Phagocytize and kill conidia, T cell priming **Harmful:** Reservoir of viable yeast that aids in dissemination
Polymorphic fungus	*Candida albicans*	Blood stream infections, deep infections often related to medical devices or surgical interventions, disseminated disease, skin and mucosal infections	**Beneficial:** Cytokine production and cellular crosstalk with NK cells to enhance fungicidal activity of neutrophils, elicit Th1 and Th17 immune responses, innate immune memory
Dimorphic fungi	*Blastomyces dermatitidis*	Pneumonia, disseminated disease	**Beneficial:** T cell priming **Harmful:** Reservoir in which spores convert into proliferative yeast forms
	Coccidioides spp. (*C. immitis*, *C. posadasii*)	Pneumonia, meningitis, disseminated disease	**Beneficial:** Phagocytize and kill arthroconidia and endospores, pro-inflammatory cytokine production
	Histoplasma capsulatum	Pneumonia, disseminated disease	**Beneficial:** Phagocytize and kill yeast, antigen processing/presentation to T cells **Harmful:** Reservoir of viable yeast (resting macrophages and monocytes)

Exhibits filamentous growth in the environment during the mating cycle.

be present at different stages of the infection process (Noble et al., 2017). The morphogenesis of *C. albicans* from yeast to hyphae at mucosal surfaces activates the NLRP3 inflammasome in macrophages, which can stimulate Th17 responses that are important for mucosal defense (Joly et al., 2009; Gow et al., 2011). Dectin-1 on macrophages can bind to β-glucan that is exposed at budding sites on the yeast form of *C. albicans* which triggers phagocytosis and reactive oxygen species (ROS) production (Gantner et al., 2005). Additionally, DCs exposed to *C. albicans* yeast can induce Th1 immune responses, while exposure to hyphal forms elicits Th2 responses (d'Ostiani et al., 2000). The mold *A. fumigatus* forms airborne spores called conidia. Under permissive conditions, these resting conidia can be induced to swell, germinate, and form hyphae that can invade underlying tissues. Germination involves shedding of the immunosuppressive outer rodlet layer of conidia and exposure of PAMPs in the fungal cell wall, including β-glucan and α-mannan (Aimanianda et al., 2009). These PAMPs are detected by Dectin-1 and Dectin-2, resulting in the activation of NF-κβ and pro-inflammatory cytokine production by macrophages and moDCs (Hohl et al., 2005; Steele et al., 2005; Gersuk et al., 2006; Carrion Sde et al., 2013). Different receptors also mediate phagocytosis of the different forms of *A. fumigatus*. Mannose receptor can regulate the uptake of conidia by DCs, while FcγRII and FcγRIII assist with uptake of hyphal forms (Bozza et al., 2002). Similar to *C. albicans*, the sensing of different morphotypes of *A. fumigatus* can affect the adaptive immune response. Metabolically active, live *A. fumigatus* conidia induce beneficial Th1 CD4^{+} T cell responses, while inactive, heat-killed conidia and hyphae can stimulate a Th2-skewed response (Bozza et al., 2002; Hohl et al., 2005; Rivera et al., 2005). Thus, the ability to sense different morphologies of fungi may enable monocytes and their derivatives to distinguish potentially invasive forms

from non-invasive forms, as well as different stages of fungal infection, so that the immune system can respond accordingly.

PHAGOCYTOSIS: HOST OR PATHOGEN ADVANTAGE?

Phagocytosis of fungal cells by monocytes and their derivative macrophages and DCs is another key element of the immune response. Fungi can be eliminated in these cells in the phagolysosome, an acidified compartment that can sequester nutrients and contains various enzymes, ROS generated by NADPH oxidase (NOX2), and reactive nitrogen species (RNS) produced by inducible nitric oxide synthase (iNOS or NOS2) in response to pro-inflammatory stimuli (Uribe-Querol and Rosales, 2017). This fungal killing may be sufficient to halt the progression of infection, but it can also provide fungal antigens that can be used to initiate the adaptive immune response to ensure sterilizing immunity. Fungal uptake is not always beneficial to the host, however, as some fungi have adapted to the harsh environment in the phagolysosome or can subvert monocytes to enable fungal persistence and proliferation.

Macrophages are the prototypical phagocyte and are conventionally described as polarizing into either pro-inflammatory, classically-activated (M1) macrophages or anti-inflammatory, alternatively-activated (M2) macrophages (Lawrence and Natoli, 2011). This M1/M2 classification is based on the expression of particular markers. For example, M1 macrophages typically express NOS2. M2 macrophages express markers like transglutaminase 2 (TGM2), arginase 1 (ARG1), resistin-like molecule-alpha (RETNLA/FIZZ1), chitinase-like 3 (CHIL3/YM1), and chitinase-like 4 (CHIL4/Ym2), the latter four being murine-specific. M1 macrophage polarization can be

induced by IFNγ, GM-CSF, or lipopolysaccharide (LPS), while M2 polarization can be induced by IL-4 or IL-13. Despite this binary designation, macrophages are actually quite heterogenous along the spectrum from M1 to M2, so other classification schemes have been proposed but have not yet been used consistently in the literature (Mosser and Edwards, 2008; Martinez and Gordon, 2014; Murray et al., 2014).

M1 macrophages are typically fungicidal cells. For example, while *H. capsulatum* can replicate within resting (M0) macrophages and monocytes, activation of these cells with cytokines, including IFNγ and GM-CSF, restricts the intracellular growth of *H. capsulatum*, in part by sequestering nutrients like zinc ions that are needed for fungal growth (Howard, 1964; Wu-Hsieh and Howard, 1987; Newman et al., 1991; Subramanian Vignesh et al., 2013). Similarly, *Coccidioides immitis* arthroconidia (the spore form) can survive within unstimulated macrophages *in vitro*, but the addition of IFNγ or TNF enables fungal killing (Beaman et al., 1983). Human monocytes do have an innate ability to take up and kill *C. immitis* arthroconidia, however killing of endospores (the replicating form within the host) requires stimulation by pro-inflammatory cytokines (Ampel and Galgiani, 1991; Beaman, 1991; Ampel et al., 1992). *A. fumigatus* induces M1 polarization and ROS production by macrophages, and mice that lack NOX2 activity in monocytes and macrophages are highly susceptible to *A. fumigatus* infection (Gersuk et al., 2006; Grimm et al., 2013; Zhang et al., 2019). M1 macrophages are more fungicidal against *C. neoformans* than M2 macrophages *in vitro* (Davis et al., 2013). *In vivo*, a shift in macrophage polarization from M2 to M1 correlates with the fungal clearance phase in a murine model of chronic cryptococcosis, and M1 polarization has been associated with host protection against *C. neoformans* in vaccination models (Osterholzer et al., 2011; Hardison et al., 2012). Interestingly, *C. neoformans* has been able to take advantage of the dynamic process of macrophage polarization. In a fatal infection model of cryptococcosis, the fungus induces monocytes to assume an M2 macrophage phenotype that is permissive for fungal proliferation and dissemination (Heung and Hohl, 2019). However, disrupting IL-4 and IL-13 signaling can improve murine outcomes after *C. neoformans* challenge (Stenzel et al., 2009; Muller et al., 2013).

MoDCs can also have direct fungicidal effects. For instance, MoDCs take up and kill *A. fumigatus* conidia, a process mediated in part by NOX2 (Espinosa et al., 2014). They have been shown to engulf and kill both *C. neoformans* and *C. gattii*, although this leads to different outcomes in the adaptive immune responses to the two species (Wozniak and Levitz, 2008; Huston et al., 2013). Additionally, MoDCs kill and process *H. capsulatum* for subsequent antigen presentation to T cells (Gildea et al., 2001).

Fungi have developed counteractive mechanisms to avoid or survive within the phagolysosome. *Cryptococcus* species produce a large polysaccharide capsule to avoid phagocytosis in the first place, but they also can survive within the phagolysosome of monocytes and macrophages (Feldmesser et al., 2000; Alvarez and Casadevall, 2006; Ma et al., 2006; Alvarez et al., 2008, 2009; Heitman et al., 2010; Nicola et al., 2011). *C. immitis* endospores and arthroconidia have been shown to block the fusion of phagosomes with the lysosome in monocytes and macrophages

(Beaman and Holmberg, 1980; Beaman et al., 1981). *H. capsulatum* blocks phagosome-lysosome fusion in macrophages and can inhibit acidification of the phagolysosome (Eissenberg et al., 1993; Newman et al., 1997). *Aspergillus terreus*, which can be more refractory to treatment than other *Aspergillus* species, persists as viable conidia in the phagolysosome of macrophages and MoDCs, in addition to dampening the expression of pro-inflammatory cytokines and markers of transmigration by DCs (Slesiona et al., 2012; Hachem et al., 2014; Hsieh et al., 2017). *B. dermatitidis* spores are readily taken up by lung macrophages, but this step promotes the conversion of spores into the yeast form of the fungus with subsequent proliferation (Sterkel et al., 2015). The yeast form of *B. dermatitidis* has also been found to reduce nitric oxide production by macrophages by inhibiting NOS2 activity (Rocco et al., 2011). These studies clearly indicate that the regulation of phagocytosis and maturation of the phagolysosome in monocytes and their derivatives play key roles in the outcomes of fungal infections and, therefore, may be important targets for enhancing host antifungal immunity.

CYTOKINE PRODUCTION AND CELLULAR CROSSTALK

The inflammatory milieu generated by monocyte-derived cytokine and chemokine secretion is important for the development of both the innate and adaptive immune response to fungal pathogens. Human susceptibility to blood stream infections with *Candida* has been correlated to single-nucleotide polymorphisms in monocyte-derived cytokines (Jaeger et al., 2019). Monocytes and their derivative cells can produce pro-inflammatory cytokines like TNF, IL-1, and IL-12, anti-inflammatory cytokines like IL-10 and TGF-β, pleiotropic cytokines like IL-6 and IL-15, and chemokines like CXCL1, CXCL2, CCL5, CXCL9, and CXCL10 (Carson et al., 1995; Arango Duque and Descoteaux, 2014). These molecules can influence the activation and recruitment of other immune cells and the polarization of the adaptive immune response.

The secretion of pro-inflammatory cytokines is typically associated with beneficial host responses. Monocytes and their derivatives are an important source of TNF and other pro-inflammatory cytokines and chemokines during infection with *A. fumigatus* and *C. albicans* (Kim et al., 2005; Cortez et al., 2006; Gersuk et al., 2006; Espinosa et al., 2014). In response to *H. capsulatum*, macrophages and DCs secrete pro-inflammatory TNF, IL-6, and IL-12 that inform the adaptive immune response (Lin et al., 2010; Huang et al., 2015). Anti-inflammatory cytokines are more often correlated with poor antifungal immunity. For instance, during *Coccidioides* infection, the susceptibility of C57BL/6 mice is strongly correlated with IL-10 secretion (Jimenez Mdel et al., 2006; Fierer, 2007). DBA/2 mice that are more resistant to *Coccidioides* have DCs that produce less IL-10 and both macrophages and DCs that produce more pro-inflammatory cytokines compared to C57BL/6 mice (del Pilar Jimenez et al., 2008). Additionally, IL-1RA is secreted by human whole blood samples and murine bone marrow-derived DCs upon stimulation with coccidioidal antigens, and it may play a

role in blocking IL-1R1 signaling that is host protective (Ampel et al., 2018; Viriyakosol et al., 2018).

Monocyte-derived cytokines can also mediate crosstalk with other innate effector cells. During systemic *C. albicans* infection, IL-15 secreted by monocytes and IL-23p19 produced by DCs induce natural killer (NK) cells to secrete GM-CSF that is required for neutrophil fungicidal activity (Whitney et al., 2014; Dominguez-Andres et al., 2017b). Additionally, monocytes and moDCs promote the fungicidal activity of neutrophils against *A. fumigatus* conidia through the production of pro-inflammatory cytokines (Espinosa et al., 2014). Therefore, manipulation of cytokines produced by monocytes and their derivative cells can have a significant impact on both the innate and adaptive immune response.

ANTIGEN PRESENTATION AND THE ADAPTIVE IMMUNE RESPONSE

Monocytes and their derivatives are capable of serving as antigen presenting cells (APCs) to prime T cells and induce adaptive immune responses that promote fungal clearance (Roy and Klein, 2012). DCs are the main professional APCs and can pick up fungal antigens by scavenging apoptotic infected cells and antigens shed by fungal cells or by ingesting and processing fungal pathogens directly (Bozza et al., 2002; Lin et al., 2005). After antigen acquisition, DCs mature, as evidenced by upregulation of surface markers including major histocompatibility complex I (MHC I) and II (MHCII) molecules that present antigen to $CD8^+$ and $CD4^+$ T cells, respectively, and co-stimulatory molecules such as CD80 and CD86. The mature DCs then migrate to lymphoid tissues where they encounter and prime T cells (Eisenbarth, 2019).

In a murine model of chronic cryptococcosis, monocytes can differentiate into DCs that mediate the generation of a Th1 adaptive response that aids in clearance of the fungus (Osterholzer et al., 2009). DCs have been shown to ingest *C. neoformans* or bind cryptococcal antigens, resulting in DC maturation and the subsequent activation and proliferation of T cells (Syme et al., 2002; Mansour et al., 2006; Wozniak et al., 2006; Wozniak and Levitz, 2008). MoDCs that present *H. capsulatum* antigen can dampen harmful Th2 responses by reducing IL-4 production by $CD4^+$ T cells (Szymczak and Deepe, 2010). Additionally, MoDCs can cross-present *H. capsulatum* antigen acquired from apoptotic macrophages to promote $CD8^+$ T cell cytotoxic responses under conditions where $CD4^+$ T cells are absent or low, as might be found in HIV/AIDS patients (Lin et al., 2005). In vaccination models for *B. dermatitidis* and *H. capsulatum*, robust $CD4^+$ T cell priming is dependent on monocyte recruitment to the immunization site (Wuthrich et al., 2012). Human MoDCs exposed to *C. immitis* antigen can induce T cell proliferation and IFNγ secretion (Richards et al., 2001). During respiratory aspergillosis, monocytes differentiate into DCs that traffic *A. fumigatus* conidia to the draining mediastinal lymph nodes and trigger beneficial $CD4^+$ T cell responses (Bozza et al., 2002; Hohl et al., 2009). Interestingly, it appears that fungi can also subvert DC antigen presentation pathways. As noted

earlier, MoDCs can kill *C. gattii*, but concurrently, the fungus is able to prevent further DC maturation that would lead to a robust adaptive immune response (Huston et al., 2013). Hence, there are multiple steps in antigen presentation by moDCs that can be optimized to generate more effective adaptive immune responses to fungi.

TRAINED IMMUNITY: A SECOND MEMORY BANK FOR THE IMMUNE SYSTEM

The adaptive immune response, which includes the generation of memory T and B cells, is the classic mechanism by which the immune system retains memory of foreign antigens to ensure a rapid and specific response upon re-exposure. However, recent studies indicate that monocytes and other innate immune cells can also contribute to immunological memory through the process of trained immunity (Netea et al., 2011, 2016). Trained immunity is established when innate immune cells exposed to microbial antigens undergo sustained epigenetic and metabolic modifications that can enhance their response to a subsequent non-specific stimulus. This innate immune memory is typically maintained over a shorter period of time (weeks to months) compared to adaptive immune memory (years). Notably, the life span of innate immune cells can be quite short, but there is evidence to suggest that hematopoietic stem cells and progenitors of innate immune cells can undergo trained immunity, thereby extending the duration of innate immune memory (Yanez et al., 2013).

Fungal antigens have been found to induce trained immunity in monocytes and their derivative cells. Exposure to β-glucan and to heat-killed or sublethal doses of the commensal fungus *C. albicans* can cause histone modifications and metabolic changes in monocytes and macrophages (Quintin et al., 2012; Saeed et al., 2014). Upon rechallenge with a lethal infection of *C. albicans*, these trained monocytes and macrophages had enhanced cytokine production and improved survival of the infected mice (Browder et al., 1984; Quintin et al., 2012). These host protective effects were confirmed to take place in the absence of T and B cells (Bistoni et al., 1986; Leonhardt et al., 2018). The trained cells also had stronger responses upon restimulation with other microbial antigens and pathogens, including lipopolysaccharide (LPS) and *Staphylococcus aureus* (Di Luzio and Williams, 1978; Quintin et al., 2012; Marakalala et al., 2013). Blocking epigenetic modifications or inhibiting glycolysis can disrupt trained immunity and these beneficial effects (Dominguez-Andres et al., 2017a, 2019). Fungal antigens other than β-glucan may also be able to induce trained immunity. For example, chitin isolated from the commensal yeast *Saccharomyces cerevisiae* can enhance monocyte responses to *C. albicans* as well as gram-positive and gram-negative bacteria (Rizzetto et al., 2016).

There is some evidence that DCs may also have memory-like capabilities. Studies using a vaccine strain of *C. neoformans* indicate that splenic DCs undergo histone modifications that enhance cytokine responses upon rechallenge with a virulent

strain of *C. neoformans* (Hole et al., 2019). However, these DCs did not have a robust response to other secondary stimuli including LPS, *S. aureus*, and *C. albicans*. The fungal component of *C. neoformans* that may be involved in stimulating this DC memory also remains to be identified.

Strides are being made to further enhance the effects of trained immunity. For example, deleting SHIP-1 in trained macrophages increases their production of pro-inflammatory cytokines and improves their protection against lethal *C. albicans* infection (Saz-Leal et al., 2018). However, priming innate immune cells with microbial antigens does not always result in beneficial host responses. Trained immunity may play pathologic roles in conditions involving chronic inflammation, and LPS has previously been shown to induce tolerance in monocytes and macrophages to secondary stimuli (Dobrovolskaia and Vogel, 2002; Fan and Cook, 2004; Netea et al., 2016). Thus, as with any immunomodulatory strategies, it will be important to evaluate the full effects of trained immunity on the overall immune response.

CONCLUSIONS AND FUTURE PERSPECTIVES

The multiple roles of monocytes and their derivative cells in the host response to fungal pathogens highlight their importance in mediating the outcomes of infection. Dissecting the specific mechanisms by which monocytes carry out these functions may enable us to develop novel therapeutics that can target these pathways to improve the mortality rates from invasive fungal infections. With the current intense focus on the role of the microbiome in human health, it will be interesting to further uncover the roles that commensal organisms may play in the trained immunity of monocytes as a key defense mechanism

against pathogenic fungi. There is ongoing work to determine whether the heterogeneity of monocyte responses may be tied to their origins in the hematopoietic tissues. For instance, there is evidence that the fate of monocytes is predetermined in the bone marrow and may originate from differences in expression of the transcription factor PU.1, which can dictate their eventual differentiation into iNOS$^+$ macrophages vs. moDCs (Menezes et al., 2016). Whether the development of monocytes from different progenitors (i.e., from an MDP vs. GMP progenitor) can influence their ultimate role in the response to fungal pathogens also remains to be determined (Wolf et al., 2019). Besides the pathogens discussed in this review, there are other medically important fungi in which the role of monocytes and monocyte-derived cells is unknown or has only begun to be explored, such as *Pneumocystis jirovecii*, *Fusarium* spp., the Zygomycetes like *Rhizopus* spp. and *Mucor* spp., and emerging pathogens like *Candida auris* (Friedman and Schwartz, 2019). Therefore, the study of monocytes and immunity to fungal pathogens remains a burgeoning and critical area of research.

AUTHOR CONTRIBUTIONS

LH conceptualized, wrote, and edited the manuscript.

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