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Review

Warfare and defense: The host response to *Cryptococcus* infection

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ABSTRACT

Cryptococcus neoformans and *Cryptococcus gatti* are the etiological agents of cryptococcosis, a life-threatening mycosis affecting the central nervous system. Cryptococcal meningoencephalitis is the most fatal mycosis in AIDS patients, resulting almost 200 000 deaths annually. High cost, side effects and drug resistance are constant elements during treatment of cryptococcosis, encouraging the development of novel therapeutic strategies including immunomodulatory protocols. Thereby, to understand how the host responds to *Cryptococcus* is essential. In this review, we discuss the immune response against *Cryptococcus* and immunoevasion strategies.

1. Introduction

Cryptococcosis is a life-threatening fungal infection most often caused by *Cryptococcus neoformans* and *Cryptococcus gattii*. These human encapsulated pathogens are able to cause damage not only to immunocompromised patients but also to immunocompetent individuals. Inhalation of fungal particles are the first stage of *Cryptococcus* infection. After the fungus reaches the lung, infection may progress to fatal meningoencephalitis. Recent estimates suggest 223 000 cases of cryptococcal meningitis annually, resulting in 181 100 deaths. Sub-Saharan Africa is the region with highest incidence (73 % of cases), followed by Asia and the Pacific (19 % of total) (Rajasingham *et al.*, 2017). Cryptococcosis remains the most fatal fungal disease among AIDS patients worldwide (Denning, 2016, Park *et al.*, 2009) and is the second most common cause of AIDS-related mortality, behind tuberculosis only.

There are no vaccines to prevent cryptococcosis and currently available antifungals are inefficient, expensive and toxic (Casadevall, 2017). Hence, immunotherapy has been considered as a promising tool for the development of

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future anticryptococcal agents. In this context, review overviews the host immunity against *Cryptococcus* and highlights aspects of both innate and adaptive immune responses.

2. Innate and adaptive immunity in cryptococcal infection

Host immunity to Cryptococcus

The immune response to *Cryptococcus* spp. may be separated into two phases: the afferent phase, which involves innate immune responses and the development of the link to adaptive immune responses, and the efferent phase, which is orchestrated by the adaptive immune system. Although innate immune cells are critical for eliminating and restraining fungi, such as *Candida* spp. and *Aspergillus* spp., *Cryptococcus* spp. are resistant to phagocytosis and possess several mechanisms that prevent killing inside phagocytes (Erwig and Gow, 2016). Thus, innate immunity is not sufficient to eliminate the pathogen, and the major functions of the afferent phase during cryptococcosis are the recognition of fungal cells and the production of signals that will promote adaptive immunity (Eastman *et al.*, 2015). In this context, resident macrophages and dendritic cells are essential for the afferent phase. While dendritic cells are essential for cryptococcal antigen presentation to T helper lymphocytes, both cell types produce cytokines that will influence the effector mechanisms of T lymphocytes (Eastman *et al.*, 2015).

Once activated, dendritic cells migrate to the lung associated lymph nodes (LALN), where they interact with T lymphocytes, inducing the proliferation and polarization of different effector mechanisms by antigen-specific T cells (Xu *et al.*, 2016). The efferent phase develops through the migration of *Cryptococcus*-specific T cells to the sites of infection (Lindell *et al.*, 2006). There, the T cells will produce cytokines that will influence the macrophage response to infection. The major CD4+ T cell phenotypes involved in the immunity and pathogenesis of cryptococcosis are denominated Th1 and Th2 cells. Th1 cells develop in the presence of IL-12, and produce large amounts of IFNγ and TNF, which induce the classical activation of macrophages (M1) (Sica and Mantovani, 2012). These macrophages have an increased ability to phagocytose and eliminate cryptococci (Wager *et al.*, 2014). Th2 cell development is influenced by IL-4, IL-25, IL-33 and thymic stromal lymphopoietin (TSLP), and these cells produce cytokines such as IL-4, IL-5 and IL-13 (Zhu *et al.*, 2010). The cytokines produced by Th2 cells are involved in several inflammatory reactions in the lung, such as mucus production and airway hyperresponsiveness, which can be increased by the activity of eosinophils and basophils (Endo *et al.*, 2014). Moreover, IL-4 and IL-13 induce macrophage polarization into alternatively activated macrophages (M2), which do not exhibit anti-fungal activity and are thus susceptible to *Cryptococcus* proliferation (Sica and Mantovani, 2012, Wager *et al.*, 2015). Therefore, while Th1 cells generate a protective environment against *Cryptococcus* spp., Th2 responses make the host susceptible to fungal proliferation and immunopathology.

An efficient immune response to *Cryptococcus* spp. will lead to the generation of granulomas, which are characterized as immune structures formed by macrophages, multinucleated giant cells (fused macrophages) and CD4+ lymphocytes (Shibuya *et al.*, 2005). The primary function of this structure is to contain the infection and prevent pathogen dissemination. It is believed that in healthy individuals, granulomas will resolve without clinical manifestations. In fact, clinical studies of antibody profiles suggest that cryptococcal infection is common in immunocompetent individuals (Deshaw and Pirofski, 1995, Abadi and Pirofski, 1999, Goldman *et al.*, 2001). In this context, infection probably proceeds to a latent stage in which disease is rare. However, immune deficiency or immune suppression can trigger the reemergence of a latent cryptococcal infection, leading to active disease (Garcia-Hermoso *et al.*, 1999). In fact, the number of patients presenting with cryptococcosis increased as a result of the AIDS pandemic and the more frequent use of transplant drugs to induce immune suppression (Molez, 1998, Singh *et al.*, 2005). Immune impairment may result in uncontrolled infection and dissemination to the central nervous system (CNS), leading to inflammation in this tissue, which is associated with high mortality rates (Sloan and Parris, 2014). Although *C. neoformans* infection is frequently associated with immune impairment, *C. gattii* is believed to cause disease in healthy individuals (Galanis *et al.*, 2009).

Macrophages

Alveolar macrophages are resident lung cells that interact with cryptococcal spores or yeast cells soon after they enter the alveolar spaces. This interaction leads to phagocytosis, and the fate of this fungus is related to the host immune status. While healthy individuals contain the yeasts and block their dissemination, immunocompromised hosts may produce an inflammatory environment that favors pathogen replication, even inside macrophages. In this context, the balance between cytokines and the presence of specific virulence factors from pathogens regulates the final macrophage phenotype.

Natural killer (NK) cells (afferent phase) and Th1 lymphocytes (efferent phase) are important producers of IFNγ, which can stimulate M1 macrophage activation in a signal transducer and activator of transcription 1 (STAT1)-dependent manner (Fig. 1). In fact, STAT1 is essential for M1 polarization and fungal elimination during cryptococcal infection (Wager *et al.*, 2015). M1 macrophages express high levels of TNF and IL-12, which are essential for the development of Th1 responses against *Cryptococcus* (Fig. 1) (Decken *et al.*, 1998, Huffnagle *et al.*, 1996, Xu *et al.*, 2016, Herring *et al.*, 2002). Furthermore, this phenotype is associated with ROS and NO production (Fig. 1). Although inside the macrophage, *Cryptococcus* cells are resistant to ROS (Zaragoza *et al.*, 2008), this fungus is sensitive to the NO produced by M1 macrophages (Aguirre and Gibson, 2000, Rivera *et al.*, 2002, Hardison *et al.*, 2010). However, *Cryptococcus* protects itself from NO by inhibiting the expression of iNOS (K *et al.*, 1997). This effect can contribute to the polarization of the non-protective M2 phenotype, down-regulating anti-cryptococcal activity and enhancing host susceptibility (Naslund *et al.*, 1995, Arora *et al.*, 2005, Xiao *et al.*, 2008, Wager *et al.*, 2015). In humans, it is possible to find iNOS–expressing macrophages in granulomas, which suggests that this mechanism of

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