Macrophage polarization: convergence point targeted by *Mycobacterium tuberculosis* and HIV

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In the arms race of host–microbe co-evolution, macrophages (Mφs) have been endowed with strategies to neutralize pathogenic challenge while preserving host integrity. During steady-states conditions, Mφs perform multiple house-keeping functions governed by their differentiation state, tissue distribution, and signals from the microenvironment. In response to pathogenic challenge and host mediators, however, Mφs undergo different programs of activation rendering them either pro-inflammatory and microbicidal (M1), or immunosuppressants and tissue repairers (M2). An excessive or prolonged polarization of either program may be detrimental to the host due to potential tissue injury or contribution to pathogenesis. Conversely, intracellular microbes that cause chronic diseases such as tuberculosis and acquired immunodeficiency syndrome exemplify strategies for survival in the host. Indeed, both *Mycobacterium tuberculosis* (Mtb) and human immunodeficiency virus (HIV-1) are successful intracellular microbes that thrive in Mφs. Given these microbes not only co-circulate throughout the developing world but each has contributed to prevalence and mortality caused by the other, substantial insights into microbe physiology and host defenses then rest in the attempt to fully understand their influence on Mφ polarization. This review addresses the role of Mφ polarization in the immune response to, and pathogenesis of, Mtb and HIV.

**Keywords:** macrophage, *Mycobacteria*, tuberculosis, HIV, AIDS, polarization

### INTRODUCTION

Pathogens have evolved ingenious strategies to circumvent the host immune response as part of the constant evolutionary process taking place in all living organisms. Chief among these strategies is the prevention of the inflammatory response or seizure of the anti-inflammatory mechanism in place to protect tissue integrity. The manipulation of macrophage (Mφ) polarization is one of the main targets to accomplish this, since this antigen presenting cell represents the first line of an active defense system in the host, and if successfully done, it can then undermine adaptive immunity (Benoit et al., 2008). Mφ polarization is a dynamic process governed by mechanisms dictating their tissue distribution and functional capacities in response to endogenous and exogenous signals (Martinez et al., 2009). Polarized Mφs are broadly classified into two groups: classical (M1) and alternative (M2) activated. On one hand, M1 program is a direct response to type-1 inflammatory conditions (e.g., IFN-γ) and pathogen challenge, and it has been associated to resistance to intracellular pathogens and to some form of tumors. On the other hand, the M2 program is driven by type-2 inflammatory signals such as IL-4 and IL-13 (M2α); immune complexes, toll-like receptors (TLRs) agonists, or IL-1 receptors (M2β); and immunosuppressants including IL-10, transforming growth factor-β (TGF-β) or glucocorticoids (M2c; Table 1). M2 Mφs participate in diverse activities including the suppression of inflammation, enhancement of phagocytosis, promotion of tissue remodeling and repair, elimination of parasites, and unwanted tumor angiogenesis (Sica et al., 2008; Martinez et al., 2009; Murray and Wynn, 2011). Furthermore, it is becoming clear that Mφ polarization supports different, and in some cases, opposing biological functions, that influences tissue homeostasis, and numerous pathological situations, including infectious diseases (Benoit et al., 2008; Cairo et al., 2011). Given the pivotal role Mφs play as sentinels of the immune system, they represent ideal cell targets for subversion by successful intracellular pathogens.

The purpose of this short review is not to provide a comprehensive summary of Mφ polarization; others have recently reviewed this growing research area (Martinez et al., 2009; Murray and Wynn, 2011). Also, we will not address the multiple ways by which the pathogens in question circumvent the immune system, as there are excellent reviews covering this subject (Deretic et al., 2004; Carter and Ehrlich, 2008; Meena and Rajni, 2010; Hajishengallis and Lambris, 2011). Instead, we will focus exclusively on the significance of Mφ polarization in the context of pathophysiology caused by *Mycobacterium tuberculosis* (Mtb) and human immunodeficiency virus (HIV).

### MACROPHAGE POLARIZATION IN Mtb INFECTION

The world health organization reports tuberculosis (TB) is still one of the leading causes of death due to a single infectious agent (Mtb) with 1.7 million deaths and 9.4 million new cases in 2009, and estimates that about one-third of the human population may be latently infected (WHO Global Tuberculosis Control Report 2010, 2010). Active TB may occur directly after infection or through the reactivation of latent infection that is confined in granulomas. The
elaboration and maintenance of granulomas depends on a dedicated immune response, which is not fully understood. Recently, however, it was demonstrated mycobacteria exploits Mφ activation to turn the granuloma into an effective tool for pathogenesis (Davis and Ramakrishnan, 2009; Volkman et al., 2010). Therefore, a better understanding of Mφ polarization during Mtb infection might yield further clues about how Mtb circumvents the immune system.

As aforementioned, Mφ polarization is mainly driven by type-1 and type-2 inflammatory signals (Table 1). Type-1 inflammatory cytokines are essential in the defense against Mtb since their expression often correlates with efficient anti-Mtb immune responses, and genetic deficiencies of these factors lead to increased TB susceptibility (Quintana-Murci et al., 2007). IFN-γ drives the M1 program characterized by Mφ capacity to kill most mycobacteria and restrict the replication of the remainder (Ehrt et al., 2001). The early phase of the anti-Mtb immune response is marked by M1 Mφ polarization in multiple animal models and reminiscent of the clinical data collected from patients with active TB (Figure 1; Benoit et al., 2008). At the transcriptional level, the gene modulation induced by Mtb in Mφs highly overlaps, and in some cases synergizes, with that induced by IFN-γ to establish the M1 phenotype (Ehrt et al., 2001). At the granuloma level in mice, M1 Mφ polarization is evident in mice between 7 and 30 days after Mtb infection when high levels of IFN-γ and iNOS are also detected within this structure and around the alveolar compartment (Redente et al., 2010). All in all, polarization of M1 Mφs is part of the “common host response” against intracellular bacteria characterized by high expression of iNOS and consequent nitric oxide (NO) production (characteristic of murine models), secretion of pro-inflammatory cytokines and chemokines, release of proteolytic enzymes and anti-microbial peptides, enhanced phagocytosis, and development of a toxic intracellular environment reflected in the fusion of microbial phagosomes with acidic and hydrolyase-rich lysosomes (Ehrt et al., 2001; Deretic et al., 2004; Martinez et al., 2009; Cairo et al., 2011; Murray and Wynn, 2011). It remains to be demonstrated whether transcription factors [e.g., p65 and interferon regulatory factor (IRF5)] or regulators (e.g., SHIP1) that dictate the M1 program of macrophage polarization also play a role in TB infection (Martinez, 2011). Considering this hostile environment created by M1 Mφs, it is not surprising Mtb has evolved strategies to interfere with M1 polarization. Indeed, Mtb inhibits IFN-γ activation of Mφs by secreting virulence factors such as lipoarabinomannan that halters phagosome maturation, or early secretory antigenic target-6 (ESAT-6) that prevents the activation of NF-κB and IFN-γ regulatory factors downstream of TLR-2 (Deretic et al., 2004; Benoit et al., 2008). Indirectly, Mtb blocks M1 polarization by the transcriptional inhibition of IFN-γ-responsive genes through a bystander effect involving IL-6 (Sibley et al., 1996; Benoit et al., 2008).

Perhaps the best strategy to avoid the challenges posed by M1 Mφs is to shift their program into M2 Mφs. TB susceptibility parallels with elevated levels of type-2 inflammatory signals (e.g., IL-4, IL-13; Kahnert et al., 2006; Raju et al., 2008; Almeida et al., 2009; Schreiber et al., 2009). Likewise, high levels of IL-10 (mostly derived from Mφs) correlate with active TB patients (Barnes et al., 1993; Verbon et al., 1999). Interestingly, the predominant type-2 inflammatory environment shifts back to type-1 after successful treatment of pulmonary TB in infected patients (Verbon et al., 1999; Raju et al., 2008). These observations in humans parallel with those reported in Mtb-infected mice; that is, there is an early type-1 immune response characterized by IFN-γ during the first 3 weeks after infection, followed by a type-2 immune response that contains high levels of IL-4 (Figure 1; Orme et al., 1993). A type-2 inflammatory environment drives the M2 program that renders Mφs immunomodulatory and poorly microbicidal (Raju et al., 2008; Martinez et al., 2009). At the transcriptional level, this seems to be the case in mice since M2 Mφs displayed a diminished inflammatory response to Mtb as reflected by a reduced NO production and increased of iron availability, suggesting these phagocytes offer a permissive intracellular environment for bacterial replication (Kahnert et al., 2006). Indeed, IFN-γ-induced NO production is essential for host survival with respect of experimental TB, while iron-starvation is key to bacteriostasis (Ehrt et al., 2001; Forbes and Gros, 2001; Cairo et al., 2011). It remains to be seen if Mtb also influences the expression level of Kruppel-like factor 4 (KLF4) or any other transcription factor/regulator recently shown to be critical for both the establishment of the M2 program and the inhibition of M1 polarization (e.g., STAT6, Cot/tpl2; Liao et al., 2011; Martinez, 2011). At the functional level, it has been demonstrated that both IL-4 and IL-13 inhibit autophagy in M1 Mφs resulting in enhanced survival of Mtb, an impairment that might also extend to M2a Mφs (Harris et al., 2007). At the granuloma level in mice, iNOS continues to be expressed within this structure but a significant shift from M1 toward M2 Mφs [iNOS^{mso} Arginase-1 (ARG1)] occurs around the alveolar compartment starting at day 35 and continuing up to day 60 after Mtb infection, accompanied by high levels of type-2 inflammatory signals (Ly et al., 2007; Redente et al., 2010). Given the development of fibrosis is a key characteristic of caseous granulomas during Mtb dissemination, and that M2 Mφs have been implicated in the inhibition of fibrosis development, the shift from M1 into M2 program might represent an attempt by the host to halt the pathophysiology caused by Mtb or a microbial strategy to shield from immune attack (Dorhoi et al., 2011).

Table 1: Priming stimulus for the classical (M1) and alternative (M2a-c) activation of macrophages.

| M1 program | M2 program |
|------------|------------|
| M2a        | M2b        | M2c       |
| Priming stimulus | IFN-γ+ LPS or TNF | IL-4     | Immune complexes | IL-10 |
|            | IL-13      | TLR ligands | TGF-β           |
|            | IL-1R ligands | Glucocorticoids | MCSF |

Mycobacterium tuberculosis also reprograms M2 Mφs through secretion of immunosuppressants such as IL-10. For instance, Mtb might influence all TLR-dependent signaling by targeting DC-SIGN to induce IL-10 and counteract the pro-inflammatory response, as shown in dendritic cells (Geijtenbeek et al., 2003; Hajishengallis and Lambris, 2011). Likewise, the mannosylated
lipoarabinomannan from Mtb enhances the production of IL-10 and other immunosuppressants through recognition by the mannose receptor (MR) in immature dendritic cells (Chieppa et al., 2003). Although alveolar Mφs express DC-SIGN and MR, their role in M2 Mφs has yet to be demonstrated (Chroneos and Shepherd, 1995; Taillieux et al., 2005). Nevertheless, Schreiber et al. (2009) reported Mtb-induced IL-10 in Mφs promotes the M2 polarization program displaying diminished anti-mycobacterial effector mechanisms. Indeed, Mφ-specific overexpressing IL-10 transgenic mice were indeed susceptible to Mtb infection, displayed a specifically suppressed IL-12 in infected tissues, and were characterized by lung Mφs with a M2 phenotype permissive to Mtb infection (Schreiber et al., 2009). These observations correlate well with another study in mice where Mtb was shown to promote its survival and ability to cause disease through a MyD88-dependent induction of ARG1. ARG1 inhibits NO production by Mφs by competing with iNOS for arginine (the common substrate), thus rendering these cells permissive to Mtb infection (El Kasmi et al., 2008; Hajishengallis and Lambris, 2011). Taken together, these observations suggest the reprogramming toward M2 Mφs by IL-10, and other immunosuppressants such TGFB and glucocorticoids (Hernandez-Pando et al., 2006), might be yet another adaptation by Mtb to survive and thrive inside of Mφs (Figure 1). However, it should be noticed that this phenomenon might also represent a control mechanism by the host to preserve the integrity of mucosal sites as uncontrolled type-1 inflammatory responses against Mtb result into lung immunopathology (Hernandez-Pando et al., 2006; Ordway et al., 2006).

**MACROPHAGE POLARIZATION IN HIV INFECTION**

Human immunodeficiency virus-1 is another successful intracellular pathogen responsible for a worldwide pandemic. According to 2009 estimates by the United Nations, there were about 33.2 million people worldwide living with HIV-1 infection and 2.6 million individuals had been newly infected (Cohen et al., 2011). In the absence of antiviral therapy, HIV-1 infection progresses through acute and asymptomatic stages leading to the eventual failure of the host immunological functions and acquired immunodeficiency syndrome (AIDS). A reason is that HIV-1 targets cells from the mononuclear phagocyte lineage that drive an effective antiviral response and simultaneously serve as reservoirs of latent or productive infection (Goodenow et al., 2003). Among these cells,
MΦs are critical to pathogenesis because they contribute to early transmission, systemic dissemination, and persistence of HIV-1. Indeed, HIV-1 evades immune surveillance by hiding and thriving inside MΦs despite anti-retroviral treatment, and when infected, they persist for months displaying insensitivity to viral cytopathic effects. In addition, MΦs continuously secrete high level of viral particles over prolonged time periods by storing assembled virus in specialized endosomal compartments (Orenstein et al., 1988; Benaroch et al., 2010). Thus, they represent powerful long-term viral reservoirs (Goodenow et al., 2003; Carter and Ehrlich, 2008; Herbein and Varin, 2010; Cohen et al., 2011).

In light of recent evidence suggesting that M1 and M2 MΦs influence HIV-1 pathogenesis, there is a surging interest to study the viral effects in MΦ polarization. In vitro, HIV-1 infection drives MΦs toward a M1 program. This MΦ response includes production of type-1 pro-inflammatory cytokines (IFN-γ, IL-2, IL-12, TNFα, IL-1β, IL-6, IL-18) and chemokines (CCL3, CCL4, MIP-α, MIP-β, RANTES), increased NO and respiratory burst, up-regulation of MHC-II molecules, and down-regulation of HIV-entry receptors (e.g., CD4, CCR5, CXCR4), and endocytic receptors (e.g., CD163, CD206; Swingler et al., 1999; Cassol et al., 2009, 2010; Herbein and Varin, 2010). Although few studies have examined thoroughly HIV-induced polarization of MΦs in vivo, there is a predominance of MΦs displaying a M1 phenotype during the acute stage (Figure 1; Cassol et al., 2010; Herbein and Varin, 2010; Cohen et al., 2011). Whether M1 MΦs are beneficial to the host during HIV-1 infection remains an open question since MΦ functions vary according to the experimental context. For instance, in vitro infection of M1 MΦs in the presence of IFN-γ and TNFα is associated with a suppression of HIV-1 replication, a sharp decrease in HIV-1 DNA synthesis at 48 h, and a decrease in the accumulation of HIV-1 proteins (Cassol et al., 2009). In addition, other studies demonstrate that M1 MΦs inhibit viral entry, assembly, and budding, suggesting the M1 program can be beneficial to the host (Cassol et al., 2010; Herbein and Varin, 2010). However, it is also known that pro-inflammatory signals derived from M1 MΦs favor the formation of viral reservoirs with increased transcription of HIV-1 LTR (long terminal repeat), alluding M1 MΦs might benefit HIV pathogenesis (Cassol et al., 2010; Herbein and Varin, 2010).

This is supported by multiple observations that immune activation driven by MΦs correlates with HIV-1 pathogenesis (Goodenow et al., 2003; Lamers et al., 2009; Cohen et al., 2011). Recently, Brown et al. (2008) characterized the HIV-1-induced polarization of MΦs as “M1HIV” since it displays a pro-inflammatory state with increased production of cytokines independently of TLR-pathway. The authors argue that while HIV-1 stimulates MΦs through a variety of signaling pathways to promote a “tailored” inflammation in its favor, the TLR recognition of viral replication is impaired and could serve as a viral evasion strategy. Given that prolonged pro-inflammatory MΦ activation during chronic HIV-infection contributes, not only to a permissive environment for the formation of viral reservoirs with strong transcriptional activity, but also to disease progression and HIV-induced tissue damage, the proposed M1HIV polarized state may render MΦs detrimental to the host (Goodenow et al., 2003; Brown et al., 2008; Lamers et al., 2009).

As HIV-disease progresses from the acute to asymptomatic stage, there is a switch from a type-1 toward a type-2 inflammatory environment (Figure 1; Vasilescu et al., 2003; Becker, 2004). At the transcriptional level, lymphatic tissue microarray analyses from HIV-1-infected subjects at different clinical stages revealed that each stage has a unique gene profile (Li et al., 2009). The acute phase is characterized by gene expression involved in innate and adaptive immunity. The asymptotic phase, however, down-regulates the acute phase gene profile to baseline level while it displays an increased expression of immunosuppressive genes (Li et al., 2009). Based on these immunological systemic changes, it is likely that a polarization switch occurs in MΦs from a M1 program during the acute phase to the M2 programs through later stages. Although there is no overwhelming evidence confirming the abundance of M2 MΦs in either the asymptotic or AIDS phase in vivo, the fact CD163 (a M2 MΦ cell surface marker) is considered as a potential biomarker for HIV-1 disease progression may allude to the presence of M2 MΦs in HIV-1-infected individuals (Burdo et al., 2011; Tippett et al., 2011). Similar to M1 MΦs, it is not known whether M2 MΦs benefits the host during HIV-1 infection. In vitro activation of M2a (IL-4-treated) MΦs results in inhibition of virus replication (Cassol et al., 2009). Other studies have demonstrated that both IL-4 and IL-13 down-regulate viral entry receptors and HIV-1 reverse transcription in MΦs (Cassol et al., 2010). Furthermore, activation of M2c (IL-10-treated) MΦs strongly inhibits reverse transcription, transcription of HIV-1 LTR and viral assembly (Herbein and Varin, 2010). Based on these observations, it might be tempting to conclude that M2 MΦs are beneficial to host immunity against HIV. However, the progression of AIDS is characterized by the loss of IL-2 and increase of IL-10 correlating with HIV viremia (Brockman et al., 2009; Sandanger et al., 2009). Moreover, the haplotypes of both IL-4 and IL-10 genes have been associated recently with AIDS progression (Vasilescu et al., 2003). Therefore, the switch toward a M2 MΦ program might simply be part of a defensive mechanism by the host to control HIV-induced tissue damage since they participate in suppression of inflammation and promotion of tissue repair (Figure 1; Martinez et al., 2009; Murray and Wynn, 2011).

Recently, a functional proteomic analysis of HIV-infected MΦs in the presence of regulatory T cells showed that a deviation of M1 to M2 MΦ program is associated with neuroprotection in the case of HIV-associated neurocognitive disorders, suggesting M2 MΦs may curtail the M1HIV polarized activity resulting in tissue damage (Huang et al., 2010). Conversely, the switch toward the M2 MΦ program might also occur as an evasion strategy by HIV to promote its own survival. A recent study demonstrated that HIV up-regulates both programmed cell death ligand 1 (PD-L1) and PD-L2 expression, members of the B7-CD28 family, and PD-1 ligands, in MΦs (Porichis et al., 2011). Given the importance of these molecules in T cell exhaustion during HIV infection, the ability of IL-10 to both activate the M2c MΦ program and induce PD-L1, and the fact that IL-10 production and increased expression of PD-L1 correlate in HIV-infected patients, the authors propose the manipulation of PDL expression in MΦs as a strategy to evade immune responses (Trabattoni et al., 2003; Porichis et al., 2011).

Whatever the true role of M2 MΦs in HIV infection, it is clear they...
influence the establishment of HIV pathogenesis, and more studies are needed to examine thoroughly HIV-induced polarization of Mφs in vivo.

CONCLUSION

Tuberculosis is the most common opportunistic infection in AIDS and often used as a clinical parameter for undiagnosed AIDS cases (Deretic et al., 2004). While the synergy between Mtb and HIV is evident at the clinical level, the mechanisms accounting for it are poorly understood. Deretic et al. (2004) proposed the interference with endosomal sorting machine as a molecular mechanism contributing to the synergy between these two pathogens. Likewise, we envision the pathogenic modulation of Mφ polarization as a cellular mechanism that might influence this synergism. As aforementioned, it is estimated that about one-third of the human population may be latently infected with Mtb (WHO Global Tuberculosis Control Report 2010, 2010), suggesting that one in three of the 2.6 million people newly infected with HIV-1 in 2009 (Cohen et al., 2011), for example, would also be coinfected with Mtb. Latent Mtb is confined in solid granulomas composed of mainly by Mφs and T cells that maintain their stability. The coinfection with HIV-1 results in a dramatic increase in the odds of latently infected people progressing into overt TB to a staggering annual risk of 10% (Deretic et al., 2004; Swaminathan et al., 2010). HIV-driven immune perturbation, reflected in the loss of CD4+ T cells and abnormal low levels of TNFα causes the loss of granuloma integrity and efficiency in anti-microbial containment leading to post-primary reactivation state (Paige and Bishai, 2010). These events may increase both Mφ necrosis and release of intracellular bacilli accounting for the extrapulmonary TB manifestation diagnosed in patients with HIV-driven immunosuppression (Swaminathan et al., 2010). The awakened Mtb then might induce M1 Mφs to drive an excessive TNFα response (together with other mechanisms such as MMP secretion) to deliberately promote parasitic granuloma formation, resulting in the recruitment of additional naïve Mφs and the tissue pathology (Davis and Ramakrishnan, 2009; Paige and Bishai, 2010; Volkman et al., 2010). Excessive levels of TNFα may not only contribute to the classical symptoms of cachexia in TB, but also to the augmentation of HIV-1 transcription and accelerated formation of viral reservoirs (Deretic et al., 2004). In the absence of an efficient adaptive immune response due to HIV-driven impairment, uncontrolled inflammation can result in lung immunopathology, and consequently, the host may induce tissue repair responses. The shift from M1 to M2 Mφ program may become pronounced and prolonged in the sterile attempt to restore tissue integrity, elevating the level of IL-10 that is typical of disease progression by both pathogens, and thus contributing to the failure of all immunological functions and clinical collapse. While highly speculative, this scenario highlights the importance to understand Mφ polarization in the context of immune activation and pathogen-driven disease, and its potential to be yet another convergence point targeted by Mtb and HIV to circumvent the host immune system.

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