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At Once Friends and Foes: Myeloid-Derived Suppressor Cells in Human Tuberculosis

Abstract

Mycobacterium tuberculosis (Mtb) is the causative agent of human tuberculosis (TB) disease. In chronic infections such as TB, consistent pro-inflammatory signalling promotes the generation of myeloid-derived suppressor cells (MDSCs). MDSCs are innate immune cells that are further divided into polymorphonuclear (PMN-MDSC) and monocytic (M-MDSC) subtypes on the basis of their morphology. These cells exert immunosuppressive effects on other immune cell types, thereby protecting the integrity of the lung tissue from damage caused by dysregulated *Mtb*. However, this comes at the expense of containing the *Mtb* infection. MDSCs' unique double-edged role makes them an attractive target for host-directed TB therapeutics. This review aims to summarize current knowledge on the role of MDSCs in TB.

Introduction

Before the COVID-19 pandemic, *Mycobacterium tuberculosis (Mtb)* was the deadliest single infectious agent worldwide. In 2021, 1.6 million people died from tuberculosis (TB)[1,2]. *Mtb* is transmitted from person to person through aerosolized droplets that travel through the respiratory tract to the alveoli of the lungs, where it begins to replicate[3]. If the host's immune system can contain the infection without eliminating it, this is considered a latent TB infection (LTBI); *Mtb* will not cause symptoms nor spread to others[4]. There are two types of active TB disease: primary TB and TB reactivation. In the former, the host will produce an inadequate immune response to control bacterial replication. They will then become symptomatic and may spread *Mtb*[5,6]. In the latter, immunosuppression will allow a previously contained infection (LTBI) to spread. This could be due to physical damage to the lung tissue, taking immunosuppressant drugs, or HIV co-infection[7,8]. Standard treatment for TB disease is a combination of antibiotics and usually lasts 4-9 months[9]. First-line treatment has an 85% success rate with strict adherence to the regimen[9]. As patients initiate second- and even third-line therapy, the risk of their infection becoming drug-resistant increases[9]. Drug-resistant cases of TB are difficult to treat, and the financially and physically taxing treatment regimen can engender compliance issues among patients, leading to worse health outcomes[10].

With antimicrobial resistance on the rise and precious few antibiotics in development, new strategies to combat TB are necessary. A better understanding of the immune response to *Mtb* could lead to the development of host-directed therapeutics such as vaccines. An emergent immune cell type in TB disease is the myeloid-derived suppressor cell (MDSC)[11]. Originally studied in cancer, these cells have potent immunosuppressive activity[12]. This review aims to describe an updated understanding of MDSCs' role in TB as both a protective and pathogenic cell type, at once limiting tissue damage and preventing *Mtb* clearance.

Methods

This review was conducted on PubMed and Google Scholar with the search terms, ("Tuberculosis" OR "*Mtb*") AND ("myeloid-derived suppressor cell" OR "MDSC"). The most recent review in the field of MDSCs in TB was published in April 2019 by Magcwebeba et al.[11]. Thus, the search period was adjusted to include papers published since 2019. Primary research articles were vetted for relevance to the topic, and additional background information on immunology and/or *Mtb* was located in primary research articles' citations, reputable reviews, or public health/government organizations' websites.

Myeloid-derived suppressor cells

MDSCs are a heterogeneous collection of immature neutrophils and monocytes[13]. As implied by their name, MDSCs originate in the bone marrow (myeloid) and have potent immunosuppressive activity[13]. Myeloid cells are a part of the innate immune response, which is typically activated in response to danger-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) through a series of pattern-recognition receptors (PRRs), of which the most prominent are toll-like receptors (TLRs)[14].

Innate immune cells are recruited to the site of immunological threats by the release of attractant cytokines by damaged cells. Myeloid cells will then help clear pathogens through degranulation or phagocytosis[15].

Macrophages, dendritic cells (DCs), and monocytes are all phagocytes; they will ingest target particles into the phagosome, a specialized vacuole, which will then mature to become the phagolysosome[16]. This organelle contains digestive enzymes to degrade the ingested particles[16].

Neutrophils are the most abundant type of granulocytes, but they are also capable of phagocytosis[17]. In addition, they may release a neutrophil extracellular trap (NET), composed of the DNA contents of the neutrophil coated in cytoplasmic and granular proteins, with the goal of containing pathogens[17].

MDSCs develop in prolonged states of inflammation, such as in cancer, persistent infections (e.g., active TB), sepsis, and autoimmunity[13]. In these

conditions, bone marrow precursors are consistently exposed to myeloid growth factors and inflammatory signals, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage colony-stimulating factor (M-CSF), IL-1β, IL-6, and cellular stress signalling[18]. MDSCs are mainly classified into two subtypes: granulocytic/polymorphonuclear MDSC (PMN-MDSC) and monocytic MDSC (M-MDSC), which have granulocytic and monocytic myeloid precursors, respectively[18]. PMN-MDSCs share cell surface markers with neutrophils (CD11b+CD14−CD15+/CD66b+) but PMN-MDSCs have lower density than neutrophils and distinct functionality[19]. M-MDSCs are CD14+CD15−HLA-DRlo/−, and they are distinguished from monocytes by low major histocompatibility complex class II (MHC-II) expression[18]. These methods of differentiating MDSCs from their brethren cell types are not infallible, however, and more accurate ways of characterizing MDSCs is an active area of research.

In patients with TB, MDSC subtype frequency has been found to be associated with disease severity; MDSCs generally are found more frequently in peripheral blood of patients with active TB versus LTBI[20]. Within the group of patients with active TB, however, those with lower disease severity score had increased proportions of PMN-MDSCs compared to those with high disease severity score[20]. These findings imply that MDSCs are not strictly pathogenic, and the PMN-MDSC subtype in particular may have a protective role in active TB[20,21].

Insults in the lung will induce the activation of an inflammatory state termed the inflammasome[22]. In its acute form, this state aids in the clearance of insults and preservation of lung function[23]. In a prolonged *Mtb* infection, immune activation can be pathogenic. The inflammasome is first induced by PRR sensing of PAMPs or DAMPs, then leading to the cleavage of pro-Interleukin-1β (pro-IL-1β) to its active form, Interleukin-1 (IL-1β)[22]. IL-1β is highly inflammatory and drives fibrosis in the lung; excessive fibrotic tissue will impair respiration[24]. As well, *Mtb*-infected macrophages release inflammatory cytokines tumour necrosis factor (TNF) and Interleukin-6 (IL-6), as well as attractant chemokines which recruit other inflammatory cell types, including monocytes, neutrophils, natural killer cells, and T cells[25]. All of these cell types have been shown to produce matrix metalloproteinases (MMPs)[26]. Excessive production of MMPs will degrade the extracellular matrix (ECM) to the point of outpacing tissue regeneration and lead to the formation of cavities in the lung (cavitation)[26]. The induction of MDSCs, particularly PMN-MDSCs, is likely a homeostatic mechanism to limit inflammation and preserve lung function. Conversely, the dampened immune response might compromise the containment of *Mtb* and result in TB reactivation.

Human immunity against *Mtb*

In the typical response to *Mtb*, DCs encounter and phagocytose *Mtb* at the site of infection, then migrate to the lymph node to present *Mtb* antigens to naïve CD4+ T cells with T cell receptors (TCRs) specific to the *Mtb* antigen. Once activated by this interaction, *Mtb*-specific CD4+ T cells expand and mature and begin to produce pro-inflammatory cytokines; IFN-γ is of particular importance in anti-*Mtb* immunity, as it is responsible for activating macrophages[27]. Alveolar macrophages (AMs) reside in the lung and are one of the first points of immune contact for *Mtb*. However, they are less effective in clearing *Mtb* via phagocytosis than interstitial macrophages (IM), which are recruited later in the response to infection[28].

CD8+ T cells, or cytotoxic T cells, may also directly kill *Mtb* by producing the cytolytic protein granulysin[29]. CD4+ and CD8+ T cells are both typically activating cell types. T regulatory cells (Tregs) are key players in negative immune regulation[30]. In short, Tregs release anti-inflammatory cytokines and bind other immune cells' receptors to diminish or completely shut down their function[31].

When the immune system cannot clear *Mtb* infection, the next best thing is to limit bacterial spread by walling it off. Innate and adaptive immune cells will aggregate into a structure called the granuloma[32]. The granuloma is duplicitous as it prevents *Mtb* from spreading further, but also provides a niche which cannot be accessed by incoming immune cells, thus allowing *Mtb* to replicate within[32]. This structure is common in LTBI[33]; the patient may continue without symptoms indefinitely, provided a lapse in immunity does not occur, in which case *Mtb* may be reactivated[7].

MDSCs' suppression of T helper function

In persistent *Mtb* infection, the frequency of MDSCs in peripheral blood correlates negatively with T cell responsiveness to *Mtb* antigens[34]. An emerging body of evidence favours a causal relationship, as MDSCs produce factors that impede T cell functionality.

M-MDSCs, like macrophages, can produce nitric oxide (NO). However, where macrophages' NO production acidifies the phagolysosome and promotes *Mtb* lysis, MDSCs' NO production also mediates T helper cell suppression, and thus can promote *Mtb* survival[35]. In patients with active TB, MDSCs highly express inducible nitric oxide synthase (NOS2), an enzyme that synthesizes NO[36,37]. High levels of NO will nitrosylate the TCR and promote the degradation of its zeta-chain. Without a complete TCR, T cells have impaired antigen recognition and, because of this, will not effectively respond to immunological threats[38]. PMN-MDSCs express reactive oxygen species (ROS) to a similar effect[37,39]. However, in chronic infection, PMN-MDSCs' anti-immune function may be beneficial to curb tissue damage inflicted by the prolonged immune response[20].

MDSCs from active TB patients also express arginase-1 (ARG1), an enzyme that depletes L-arginine[37,40]. The amino acid L-arginine is essential to T cell fitness and survival—without it, T cells have diminished cytokine production, proliferation, and expression of the TCR[41,42].

TB patients' MDSCs have also been shown to increase CD62L expression in T helper cells, although the mechanism is unclear[43]. CD62L is a cell surface marker that promotes T cell trafficking to the lymph nodes[44]. This marker is usually found on naïve T cells, and shedding CD62L is a critical step in their maturation, i.e., activation[44]. This finding could either imply that MDSCs are preventing T cell maturation or that they are inducing mature T cells to begin expressing CD62L once again, impeding their ability to localize to the lung.

In a nonhuman primate study of TB, researchers found that MDSCs from macaques with active TB expressed interleukin-10 (IL-10) and programmed death-ligand 1 (PD-L1) at significantly higher levels than MDSCs from healthy controls and macaques with LTBI[45]. IL-10 is an anti-inflammatory cytokine that can act on many cell types[46]. It can first prevent dendritic cells from trafficking to the lymph node, which is a crucial step to T cell activation[46]. Further, IL-10 can directly impact CD4+ T cells by inhibiting proliferation and inflammatory cytokine production, one of which is IFN-γ—as a downstream effect of MDSCs' IL-10 production, macrophage activation will be hindered[46]. IL-10 will also act more immediately on macrophages by inhibiting a bactericidal phenotype and antigen presentation capabilities[46]. The same effect of IL-10 is seen in monocytes[46]. Upon TCR stimulation, T helper cells express programmed cell death protein 1 (PD-1), which binds PD-L1[47]. The PD-L1/PD-1 interaction inhibits the activation, proliferation, and survival of all T helper cells. In the CD8+ subset, this interaction inhibits cytotoxic secretion[48]. In a healthy individual, this mechanism serves to prevent pathological immune activation, where T cells continue to respond to and generate inflammatory signals to an immunological threat that no longer exists and thereby cause damage to the host. Additionally, MDSCs' PD-L1 expression could be directed at maintaining the hypoxic environment of the granuloma; when peripheral blood mononuclear cells (PBMCs) were infected with *Mtb* and then treated with anti-PD1 immunotherapy, TNF-α was secreted in excess, and this increased *Mtb* growth[49].

MDSCs would require close proximity to T cells to inhibit them through the PD-L1/PD-1 interaction, as well as through production of NO, NOS, ARG1, and IL-10[50]. A non-human primate model of TB showed that T cells surround the granuloma, and a similar model placed MDSCs at the same location[45,51]. This localization both supports MDSCs' ability to exert immunosuppressive functions on T cells, as well as their support of the hypoxic granuloma.

On the basis of similar findings in cancer, MDSCs have also been proposed to induce Tregs in TB[12]. Tregs are present in significantly higher frequencies in the blood of patients with active TB and LTBI than in healthy controls, but MDSCs have yet to be proven to be implicated in this phenomenon[52].

Phagocytosis and metabolic changes

Mtb may evade immune detection by persisting intracellularly in the phagosomes of macrophages, particularly in the granuloma[53]. Once infected with *Mtb*, macrophages in the granuloma switch from glycolysis to lipid metabolism—this shift promotes the accumulation of intracellular lipid droplets (LD), which then favours further differentiation into "foamy" macrophages. *Mtb* can then use the fatty acids (FAs) and cholesterol contained in foamy macrophages' LDs as an energy source[54]. Whether this metabolic shift is a protective mechanism to curb *Mtb* growth or is somehow induced by *Mtb* to provide itself with an energy source is contentious, as the molecular mechanism of this change during TB is unknown[55].

As M-MDSCs share phagocytic abilities and a myeloid ancestor with macrophages, it has been hypothesized that they may also harbour *Mtb* and undergo similar metabolic changes. A recent study with M-MDSCs from TB patients showed that this cell subset had increased expressions of soluble proteins and cell surface markers involved in phagocytosis and that these proteins and markers significantly decreased after disease treatment, suggesting that M-MDSCs have increased phagocytic abilities in *Mtb* infection[56].

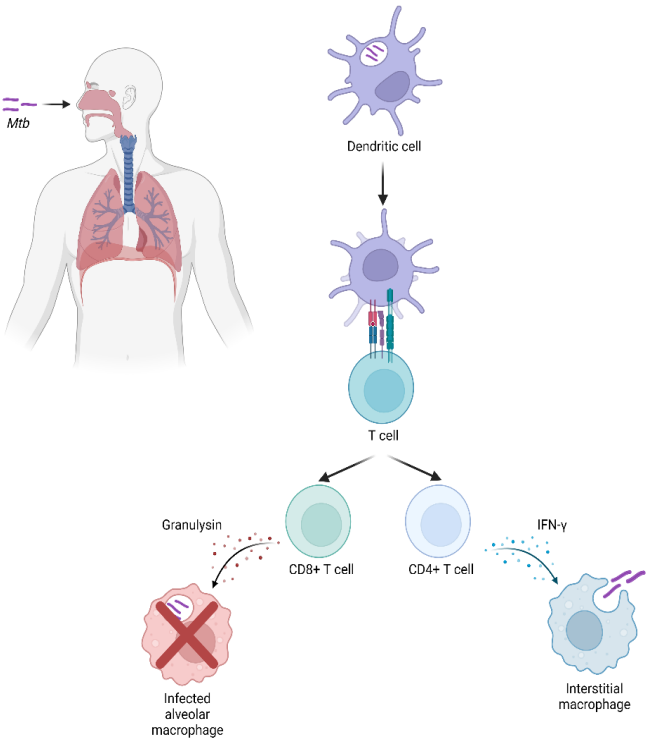

Figure 1. Summary of successful response to *Mtb* threat. *Mtb* enters the host's respiratory tract and travels to the lungs. DCs will phagocytose the bacteria, and present antigens to T cells in the lymph node. Once activated, CD8+ T cells can kill infected macrophages by releasing granulysin, and CD4+ T cells can activate uninfected macrophages to properly lyse bacteria by releasing IFN-γ. Created with Biorender.com.

Moreover, proteins in the signalling pathway regulating the metabolic switch and LD formation are also upregulated in TB, and research in cancer found that immunosuppressive MDSCs rely primarily on lipid metabolism for their energetic demands[39]. This evidence suggests a metabolic dimension of MDSCs' pathogenicity, but no study has shown either *Mtb's* inhabitation of M-MDSCs or MDSCs' switch to lipid metabolism in TB.

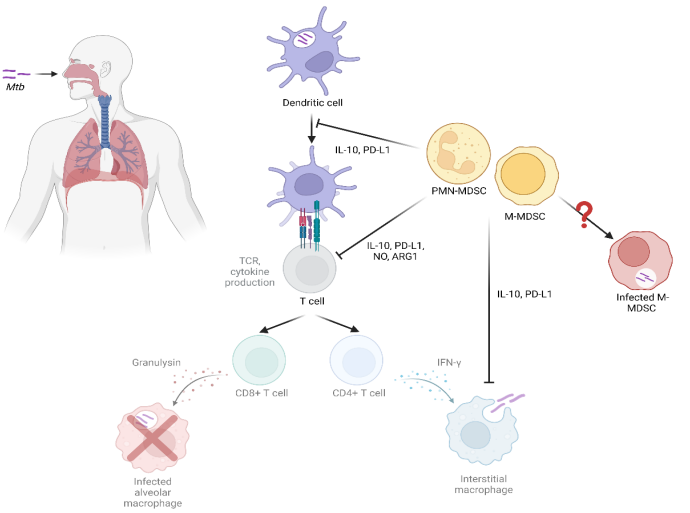

Figure 2. Summary of proposed mechanisms of MDSC intervention in chronic *Mtb* infection. MDSCs are proposed to interfere in the immune response at many levels. Expression of IL-10 and PD-L1 may inhibit DC antigen presentation as well as macrophage activation. In addition, NO and ARG1 production can inhibit T cells' cytokine production as well as TCR stability. M-MDSCs are also suspected reservoirs for *Mtb*. Created with Biorender.com.

Conclusion

The interplay between *Mtb* and the immune system is multifaceted and complex. Myeloid-derived suppressor cells have surfaced as important players in this interaction in recent years, after their discovery in cancer. These cells of myeloid origin are induced in response to chronic inflammation and dampen T helper cell function through the sequestration of L-arginine and the release of NO, ROS, and soluble factors. This homeostatic balance is delicate, and if the infection is not resolved, long-term immunosuppression enables *Mtb* growth. Although intended to preserve lung function, MDSC induction can be ultimately detrimental to the host. To add another shade of nuance to this picture, MDSC subtypes, PMN-MDSCs and M-MDSCs, seem to have differing pathogenicity; PMN-MDSCs have been implicated in a more protective role, while M-MDSCs are hypothesized to alter their metabolism to provide nutrients for intracellular *Mtb* bacteria, promoting their growth and sheltering them from immune detection.

The picture, however, is not complete. On the basis of findings in cancer, additional immunosuppressive mechanisms of MDSCs have been proposed, such as killing DCs and inducing Tregs, but they have not been validated in TB[39]. As well, no research has probed MDSCs' interactions with other TB-relevant members of the innate immune compartment, that is, macrophages, natural killer cells, DCs, and neutrophils[57]. Finally, the hypothesized intracellular infection with *Mtb* and altered metabolism of M-MDSCs, although well-supported, remains a hypothesis. More research is required before M-MDSCs can be seriously considered as a target for therapeutic intervention to limit niche availability for *Mtb*, be that through inhibition of phagocytosis or of their hypothesized metabolic reorganization. PMN-MDSCs would be less immediately effective in *Mtb* clearance, but their immunoregulatory abilities could be harnessed to improve outcomes of chronic infections.

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