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The Innate and Adaptive Immune Response during *M. tuberculosis* Infection

Abi-Rizk A*, El Beyrouthy M and Hanna-Wakim L

Faculty of Agricultural and Food Sciences, University of the Holy Spirit of Kaslik B.P 446 Jounieh, Lebanon

***Corresponding author:** Abi-Rizk A, Faculty of Agricultural and Food Sciences, University of the Holy Spirit of Kaslik, Lebanon, Tel: 961 9 600 876; E-mail: alainabirizk@usek.edu.lb

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Abstract

Mycobacterium tuberculosis, the causative agent of tuberculosis is a facultative intracellular pathogen that infects and resides in humans and is a leading infectious cause of death in many parts of the world with a worrying increase in transmission and resistance to drugs. Surfactant proteins A and D (SP-A and -D) play a role in many acute bacterial, viral, and fungal infections and in acute allergic responses. *In vitro*, human SPs bind *Mycobacterium tuberculosis* and alter human and rat macrophage-mediated functions. Here we report the roles of SP-A and SP-D in *M. tuberculosis* infection following aerosol challenge of SP-A-, SP-D-, and SP-A/-D-deficient mice. These studies surprisingly identified no gross defects in uptake or immune control of *M. tuberculosis* in SP-A-, SP-D-, and SP-A/-D-deficient mice. While both SP-A- and SP-D-deficient mice exhibited evidence of immunopathologic defects, the $CD11b^{high}$ $CD11c^{high}$ dendritic cell populations and the gamma interferon (IFN-γ)-dependent CD4+ T cell response to *M. tuberculosis* were unaltered in all genotypes tested. Together, these data indicate that SP-A and SP-D are dispensable for immune control of *M. tuberculosis* in a low-dose, aerosol challenge, murine model of tuberculosis (TB).

This pathogen is generally transmitted by inhalation of infectious aerosols into the lung with deposition in the terminal bronchioles and alveoli. Most affected persons stand an effective immune response that might controls this pathology but does not totally eradicate the primary tuberculosis infection and the reactivation of persistent *M. tuberculosis* later in life occur frequently in active tuberculosis cases . Many studies are still running up in order to better understand the interactions between *M. tuberculosis* and the immune environment of the lung. In this review, we describe initial interactions between the lung environment and *M. tuberculosis* and we summarize the normal surfactant turnover by alveolar macrophages and AEC II in to the uptake of *M. tuberculosis* in alveolar epithelial cells and macrophages during the innate immune response followed by the T cells initiation of the adaptive immunity in the lung.

Keywords: *Mycobacterium tuberculosis; Pathogen;* Macrophages; AEC II; Lung

Early Innate Immune Response to *M. tuberculosis*

One of the first interactions *M. tuberculosis* encounters in the lung is its binding with the pulmonary surfactant molecules. AEC II

Alveolar epithelial cells type II] and Club cells [Clara cells] secrete pulmonary surfactant, while alveolar macrophages are involved in its catabolism. Alveolar macrophages are the initial and most critical sites of infection with *M. tuberculosis* and one of the first interactions *M. tuberculosis* encounters in the lung is the binding of pulmonary surfactant molecules. [1]

Pulmonary surfactant are multimolecular complexes composed of 90% lipids and 10% proteins secreted by AEC II cells and Club cells in distal bronchioles and alveoli [2,3]. The main function of this surfactant is to reduce the surface tension of alveolar fluid and to facilitate reversible expansion. Saturated dipalmitoyl phosphatidylcholine is the most abundant phospholipid accounting for 45–55% of surfactant lipid, and Cholesterol comprises 8–10% of surfactant lipid. The rest are various species of PC (Phosphatidylcholines), PE (Phosphatidylethanolamines), phosphatidylglycerols and phosphatidylinositols replaced with saturated and/or unsaturated chains of palmitic and/or oleic acids. In addition to lipids, surfactant consists of four well-characterized proteins called Surfactant Protein A [SP-A], Surfactant Protein B [SP-B], Surfactant Protein (SP-C), and Surfactant Protein D (SP-D) [4]. SP-B and SP-C are small highly hydrophobic proteins with an essential role in compression, expansion, and formation of the surface active phospsholipid monolayer at the air–liquid interface [4]. SP-A and SP-D are large hydrophilic proteins that bind phospholipid components to preserve surfactant ultrastructure and formation of surfactant vesicles that influence lipid monolayer formation at the air/liquid interface and metabolism of pulmonary surfactant by alveolar macrophages and AECII [4].

In addition to its physical functions, several protein components of pulmonary surfactant have been shown to exercise immunomodulatory actions that increase immune control of respiratory pathogens and help in reducing inflammatory damages [4,3]. These immunoregulatory properties are mainly mediated by the Surfactant Proteins A and D [SP-A and SP-D] [2,3]. In fact, SP-A and SP-D present a collagen-like domain in the N terminus that mediates oligomerization, a coiled-coiled area [neck], and a globular Ca^{+-} dependent carbohydrate recognition domain at the C terminus [3]. The C-terminal lectin-binding domain of these proteins [SP-A and SP-D] is important in some antimicrobial functions and varies in specificity for glycosylated targets [2,3], and have the ability to bind exposed carbohydrate residues on the surface of *M. tuberculosis* [4,5].

SP-A forms a bouquet structure of 6 trimers [octadecamer] that associates with surfactant lipids and tubular myosin and can also bind to the CD93 [C1q Receptor], the TLR2 and TLR4 [toll-like receptors 1 and 4], the CD91/calreticulin complex, the SIRP-alpha [Signal Inhibitory Regulatory Protein], and the SP-R210 (specific MYO18A receptor). SP-D, forms a cross-like dodecamer of 12 chains that resides in the aqueous phase of the alveoli and can bind MFAP4 (Microfibril-Associated Protein 4), CD14, defensins, decorin, C1Q complex (A, B and C), TLR2, TLR4, and some glycoprotein of unknown function.

Both SP-A and SP-D are members of the collectin family of innate immune proteins with characteristic collagen-like and carbohydrate recognition domains (CRD). The CRD domains of collectins bind glycoconjugates on the surface of pathogens in a calcium dependent manner [3,6]. The interaction of pulmonary collectins with bacteria modulates the uptake and subsequent fate of microbes in alveolar macrophages. [2,7-10] bacterial viability,[11] and transcriptional programming [12].

It has been shown that both SP-A and SP-D bind mycobacterial cell wall LAM (Lipoarabinomannan)[2,13] In the case of *M. tuberculosis*, SP-A enhances its uptake by overexpressing of a a C-type lectin, the macrophage mannose receptor, which may have a permissive pathogenic role in mycobacterial invasion of macrophages [14]. Specifically, SPA binds a wide range of mycobacterial targets, including ManLam [from virulent and avirulent mycobacterial strains] [15,16], lipomannan [13], a 60-kDa glycoprotein [17], and Apa [*M. tuberculosis* surface glycoprotein] [18]. Furthermore, SP-A is able to enhance expression of other innate immune receptors that have a partial role in mycobacterial uptake by macrophages including the scavenger receptor SR-A**30** and the complement receptor CR3 [19-21]. Regarding SP-D, it has been shown that this protein binds also with ManLam (Mannosylated Lipoarabinomannan) from the Erdman strain [7] and can enhance phagolysosomal fusion in macrophages leading to increased intracellular killing of *M. tuberculosis* [9].

I*n vitro* studies showed that SP-A and SP-D are capable of modulating the antituberculosis [anti-TB] response with both negative and positive consequences on bacterial control. Both SP-A and SP-D seems to play a major role in the agglutination of bacteria [9,22]. In fact, Ex vivo studies shows that SP-A-mediated agglutination enhance of *M. tuberculosis* association with alveolar epithelium [15] and internalization in human and murine macrophages [23-25]. This potential of agglutination, seems not associated with bacterial killing, since SP-A signaling has also been reported to reduce the production of reactive nitrogen [25] and oxygen intermediates [26] and "SP-D-mediated opsonization", seems to agglutinate bacteria, postpone phagocytosis, and ease the phagolysosomal fusion and control of *M. tuberculosis* [9-11].

The ability of SP-A and SP-D to modulate the expression and inflammatory activity of toll-like receptors could shape the inflammatory activity of macrophages in response to *M. tuberculosis* infection [27-29].

"SP-A-mediated attachment" of *M. tuberculosis* to macrophages was associated by the suppression of nitric oxide synthesis, suggesting that SP-A may decrease the mycobactericidal activities of alveolar macrophages [30] SP-A may also have differential effects depending on whether SP-A acts on infected or uninfected macrophages in tuberculosis *in vivo* [22] SP-A could modulate adaptive immunity being able to suppress the recall response to mycobacterial antigen in PBMC from tuberculin-positive individuals. [22]

The ligation of the SP-A receptor (SP-R210) decreased synthesis of IFNγ, [Interferon gamma] suppressing lymphocyte proliferation in response to mycobacterial cell wall antigen via a mechanism that involves the elaboration of the anti-inflammatory IL-10 (Interleukin-10) and TGF- β (Transforming growth factor beta)[31]. Beside immunological interactions with surfactant, mycobacterial cell wall lipids, particularly TDM [trehalose, 6,6-dimycolate or cord factor], inhibit the biophysical activity of surfactant in lowering surface tension [32,33]. Also, TDM may contribute to the spreading of virulent mycobacteria along air–water interfaces and surfactant monolayers. The interaction of whole lung surfactant, rather than individual components, with *M. tuberculosis* leads to significant transcriptional adaptation in *M. tuberculosis* characterized by expression of cell wall lipases that could degrade surfactant phospholipids [34]. Given these initial interactions between the pulmonary surfactant and *M. tuberculosis*, normal surfactant turnover by alveolar macrophages and AEC II may contribute to the uptake of *M. tuberculosis* in alveolar epithelial cells and macrophages and subsequent initiation of adaptive immunity in the lung [1].

The Adaptive Immune Response after Infection with *M. tuberculosis*

The modulation of alveolar epithelial cells and macrophages responses the M tuberculosis infection goes beyond intracellular trafficking. In fact, if phagocytes are not activated by the exposure to IFN-g and/or tumor necrosis factor [TNF] before the infection, the ability of M tuberculosis to inhibit phagosome maturation and function by upregulating the production of reactive oxygen and nitrogen derivatives is increased [35-40]. Most patients respond initially to *M. tuberculosis* infection by producing IFN-g. The unconventional T-cell subsets (gd, NK-T and CD-1 restricted cells [41,42] largely proliferate at the early phases of *M. tuberculosis* infection, and bound between the innate and the adaptive immune responses by starting the cytokine production [42,43]. By secreting IFN-g, the unconventional T-cell subsets induce the activation of APCs and amplification of IL-12 and IL-18 production, which will clearly induce a positive feedback loop for the production of IFN-g [44]. The control of IL-12 expression seems essential for the activation and expansion of the IFN-g-secreting CD4T cells, which is crucial for immunity against *M. Tuberculosis* [44,45].

While CD4T cells seems essential at the early IFN-g response against M.tuberculosis, CD8T cells become more important in the later phases of disease via there cytotoxic activity and/or IFN-g production [46-48]. But, *M. tuberculosis* seems to have developed the ability to challenge the host's immune response, by refuting Th1 [T helper 1 cells] function and development. Im fact, *M. tuberculosis* cell wall extracts seems to inhibit some of the downstream effects of IFN-g [49-52], so that even if it's produced, IFN-g activity becomes much reduced. Adding that IFN-g responses are generally reduced in patients with advanced M.Tuberculosis infection [53], while IL-4 is elevated [53-55] and its gene expression seems correlating with both the *M. Tuberculosis* severity in infected patients [53,54] and the risk of subsequent disease in healthy but highly exposed people [55,56]. The increased ratio of IFN-g/IL-4 in most patients during therapy and its increase in early infected persons suggest that this state is directly related to the disease [55,56].

Notice that a poor prognosis of *M. Tuberculosis* is directly associated with a low IFN-g/IL-10 ratio similar to what is seen in IFN-g/IL-4 ratio [55-58] and shifting the balance between IFN-g and IL-4

or IL-10 production and function seems to be also a major survival strategy for *M. tuberculosis*. Another important molecule for the protection against *M. Tuberculosis* is TNF- α [necrosis factor alpha] [59], as shown by the rapid reactivation of latent *M. tuberculosis* infection in people treated with TNF-a receptor antagonists [60-62]. But due to the high levels of IL-4, TNF- α seems to induce tissue damage rather than protection.

Conclusion

Nowadays, most patients present an effective immune response that might control *M. Tuberculosis*, but does not totally eradicate the primary tuberculosis infection and the reactivation later in life occurs frequently. Even though not all the interactions between the lung environment and *M. tuberculosis* are fully understood, many studies are still running up in order to better understand the interactions between this pathogen and its host, so possible total eradication becomes finally a reality.

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