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# A Study of Immunological Activity of Alveolar Macrophages In Tuberculosis Infection

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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/-Ddeficient mice. While both SP-A- and SP-D-deficient mice exhibited evidence of immunopathologic defects, the CD11bhigh CD11chigh 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.

## 1. Introduction

Inhaled Mycobacterium tuberculosis is taken up by local alveolar macrophages, which provide the first line of defence for the infected individual. Infected alveolar macrophages release a panel of antimicrobial effector molecules, cytokines, and chemokines, which govern innate immune responses (fig 1) and initiate specific immunity. This complex network of mediators induces activation of antimicrobial activity in macrophages, migration of antigen laden phagocytes to the draining lymph nodes, and finally the influx of antigen specific T lymphocytes to the site of infection (fig 2). Optimally, this results in the formation of a well organised granuloma consisting of central macrophages with surrounding lymphocytes. This cellular microenvironment provides a physical and immunological barrier for the entrapped bacilli thereby preventing multiplication and spread of the mycobacteria. Nevertheless the granuloma contains viable bacilli—most likely throughout the lifetime of the host—and the maintenance of the granuloma is a prerequisite to keep the bacilli in check. Factors disrupting the fine-tuned balance between the low level mycobacterial metabolism and the steady cellular influx to the granuloma will inevitably expose the risk of tipping the balance infavour of the pathogen and result in reactivation of disease. TNF plays a key role in these processes and mice deficient in TNF fail to control a primary challenge with M. tuberculosis. TNF is also essential for maintaining the state of dormancy in mice and humans. The precise mechanisms underlying these findings are yet to be defined but several functions attributed to TNF are potentially relevant for preventing reactivation of tuberculosis.

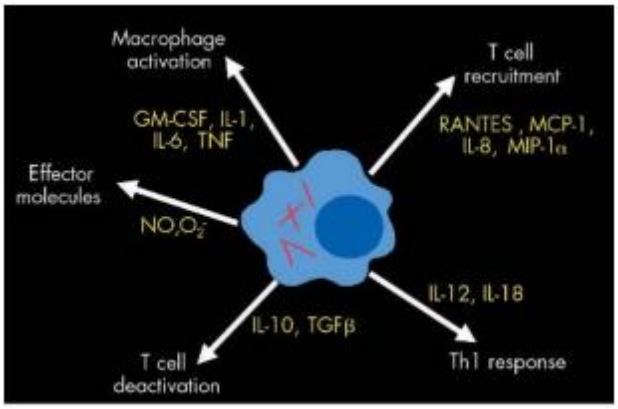


**Figure 1 Innate immunity in tuberculosis**

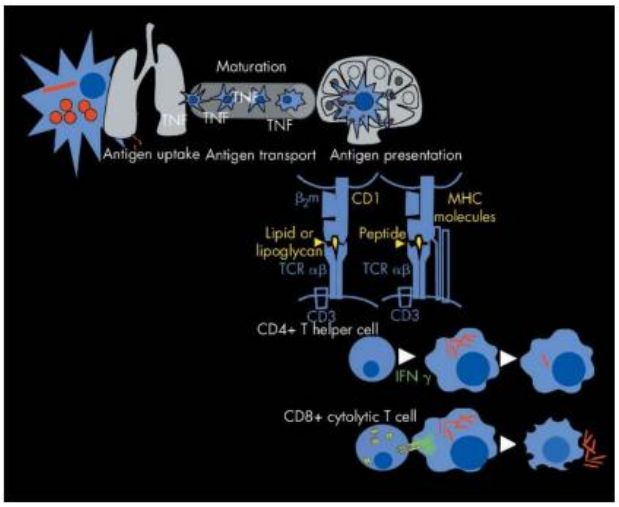


**Figure 2 Initiation of adaptive immunity**

## 2. Tuberculosis

Alveolar macrophages infected with M. tuberculosis undergo apoptosis, a process that is at least partially mediated by TNF. Virulent M. tuberculosis prevents apoptosis via the suppression of TNFand neutralization of TNF in cultures of avirulent mycobacteria restores the ability to induce apoptosis in the host cells. This implicates that the prevention of TNF mediated apoptosis is an evasion strategy of virulent mycobacteria. To date there is no clear consensus on whether apoptosis of infected macrophages is beneficial or harmful for the infected organism. The induction of apoptosis could contribute to protection by directly killing the mycobacteriaor by strengthening adaptive immunity by inducing the cross-presentation of mycobacterial antigens by dendritic cells (DCs). On the other hand massive apoptosis of macrophages in TNF receptor deficient mice has been described without beneficial effects on mycobacterial killing. Taken together, these reports suggest that TNF supports apoptosis of macrophages infected with M. tuberculosis, thereby contributing to the clearance of the pathogen.

## 3. Alveolar macrophages in tissue damage control

Whether tissue damage is of infectious or inflammatory origin, Aφs must reduce the inflammation in first instance to limit the extent of injury. To do so, Aφs have been described to develop different anti-inflammatory strategies (Figure 3). Aφs are effectors of the resolution of inflammation through phagocytosis of apoptotic cells (efferocytosis), preventing dying cells from releasing pro-inflammatory and toxic contents into the environment while triggering the release of anti-inflammatory and repair factors. In vivo and in vitro studies have shown that apoptotic cell clearance induces the secretion of transforming growth factor β1 (TGF-β1), prostaglandin E2 (PGE2), and platelet-activating factor (PAF), with associated suppression of pro-inflammatory cytokines, chemokine's, and leukotriene C4. These findings have been confirmed in human. Indeed, defective lipopolysaccharide (LPS)-stimulated uptake of apoptotic cells by Aφs from patients with severe asthma has been associated with failure to induce the synthesis of PGE2 and 15-hydroxyeicosatetraenoic acid (15-HETE). Moreover, defective phagocytosis has been observed in several respiratory pathologies. In severe asthma in children, macrophage function is abnormal and characterized by reduced phagocytic function and excessive apoptosis. In addition to asthma, defective phagocytic function has been described in chronic obstructive pulmonary disease, cystic fibrosis, and idiopathic pulmonary fibrosis and also has been attributed a role in sustained/chronic inflammation.

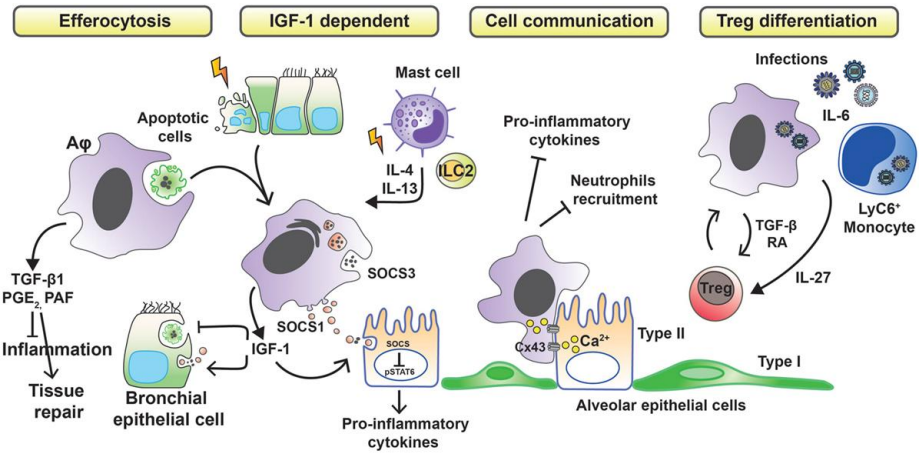


**Figure 3. Anti-inflammatory strategies of alveolar macrophages favoring tissue damage control**

Allergens, such as house dust mite, can cause apoptotic epithelial cell death and trigger the synthesis of IL-4 and IL-13 from mast cells and type-2 innate lymphoid cells (ILC2s). These events lead to the production of insulin-like growth factor 1 from Aφs that enhances the uptake of anti-inflammatory macrophage-derived microvesicles by airway epithelium. Bourdonnay et al. report that Aφs can secrete suppressors of cytokine signaling SOCS1 and -3 in exosomes and microparticles, respectively, for uptake by alveolar epithelial cells and subsequent inhibition of STAT activation. Notably, airway epithelial cells can use $PGE_2$ as a signal to evoke SOCS3 release from Aφs to dampen their endogenous inflammatory responses in an LPS inflammation model. Contact-dependent communication between Aφs and alveolar epithelium has been described also to modulate immunity through gap junction-like connections and the propagation of calcium waves. The consequence of this intercellular communication was immunosuppressive. The binding of CD200R and TGF-βR, expressed by Aφs, with their ligands (CD200 and TGF-β, respectively) present on the cell membrane of epithelial cells is a negative regulator of Aφ activation.

Aφ plasticity associated to the control of tissue damage is an important factor in pathogen persistence. The prevalence of the so-called M2 phenotype has been often associated with a positive outcome because of its ability to control tissue damage. However, M2 macrophages represent a permissive niche for the persistence of many intracellular pathogens. Indeed, persistence of bacteria has been described for several human diseases including Legionnaires' disease and tuberculosis. Alarmins, such as IL-33, IL-25, and TSLP, play an important role in macrophage polarization during tissue damage. The synthesis of IL-33 by epithelial cells, characteristic of the lung environment after birth, triggers the release of IL-13 by ILC2s and induces an anti-inflammatory M2 phenotype. Such an environment has been associated with the delayed response to *Streptococcus pneumoniae* infection in mice.

Decreased antimicrobial activity and augmented oxidative metabolism of M2 macrophages compared to glucose-dependent metabolism of M1 cells represent the main factors contributing to pathogen persistence in the host. The decreased production of nitric oxide following IL-4-driven arginase-1 expression facilitates the survival of pathogens sensitive to this reactive species and perhaps explains why *Chlamydia pneumoniae* has been reported to prefer the M2 than M1 macrophage for its proliferation *in vitro* . In this scenario, pathogens not only benefit from but also drive macrophages toward the M2 phenotype that better suits their own requirements, as suggested by recent publications. A mathematical model has been proposed to facilitate the investigation of M1 to M2 switching following infection of macrophages with *M. tuberculosis* .

*Mycobacterium tuberculosis* upregulates the expression of peroxisome proliferator-activated receptor-γ in infected macrophages leading to increased lipid droplet formation, expression of M2 markers and downregulation of the M1 response, including the respiratory burst and nitric oxide production. In this way, *M. tuberculosis* not only circumvents the protective host response but may also guarantee the nutrient rich environment required for its growth and survival. Indeed, *M. tuberculosis* secretes a hydrolase to catalyze host lipid hydrolysis. This capacity of pathogens to use cell metabolism to persist in the airspaces seems unavoidable. Further, M2 macrophages demonstrate an iron metabolism of benefit for pathogens. M2 macrophages have reduced iron storage and increased iron and heme uptake resulting in a high iron label pool, thus favoring the growth and survival of pathogens. For instance, *M. tuberculosis* can use macrophages as an iron source and produce siderophores able to sequester iron from host transferrin and lactoferrin, leading to augmentation of iron concentrations in infected macrophages and favoring its growth. Other metal metabolism can be "highjacked" by pathogens, such as zinc. Vignesh et al. have shown that IL-4, a well-known M2-polarizing signals, alters macrophage zinc homeostasis *via* metallothionein 3 and the zinc transporter SLC30A4, promoting pathogen persistence in M2 macrophages.

**4. Tissue damage control may drive pathogen persistence**

The environment created by the tissue damage control may favor the persistence of pathogens in the airways. Indeed, the immunosuppressive properties of Aφs during the process of the control of tissue damage are presumably key in leading to immune evasion. Evasion from immune surveillance is an important parameter leading to the persistence of pathogens. The incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia in otherwise healthy individuals is increasing. These bacteria persist in lower airways by surviving within Aφs. An *in vitro* study found that *S. aureus* persists and replicates inside a murine Aφ cell line. Among the mediators used by Aφs to control tissue damage, we previously mentioned that $PGE_2$ is produced after efferocytosis and exerts anti-inflammatory effects. $PGE_2$ is known to suppress natural killer cell activity by increasing cellular cyclic adenosine monophosphate and downregulates MHC class II expression on dendritic cells to decrease antigen presentation. More recently, it has been shown that the anti-inflammatory action of $PGE_2$ in the lung is mediated only by the prostaglandin E receptor 4 (EP4). In this way, it seems pathogens can take advantage of $PGE_2$. Indeed, $PGE_2$ can inhibit bacterial killing by Aφs by inhibiting NADPH oxidase. In macrophages infected by *M. tuberculosis*, $PGE_2$ generated by TLR2 stimulation/p38 MAPK phosphorylation triggers EP4 to produce increased amounts of $PGE_2$. Then $PGE_2$ provides protection against necrosis *via* EP2. Production of $PGE_2$ by the host is a protective mechanism against *M. tuberculosis* by inhibiting type I IFN as well as inducing apoptosis in macrophages. Similarly, Influenza virus induces $PGE_2$ to suppress type I IFN subverting innate immunity. Taken together, it seems that pathogens have developed mechanisms to induce $PGE_2$ production by macrophages to suppress inflammation and better survive within the host. A recent study by Roquilly et al. shows that dendritic cells and macrophages developing in the lungs after the resolution of a severe infection acquire tolerogenic properties that contribute to persistent immunosuppression and susceptibility to secondary infections.

**5. 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 [SPB], 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 SPD 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 SPD] 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 (MicrofibrilAssociated 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].

## 6. 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. 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 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. 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. 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. 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. 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, 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, while IL-4 is elevated and its gene expression seems correlating with both the M. Tuberculosis severity in infected patients and the risk of subsequent disease in healthy but highly exposed people. 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.

## 7. 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.

## References


1. Chroneos ZC, Midde K, Sever-Chroneos Z, Jagannath C (2009) Pulmonary surfactant and tuberculosis. Tuberculosis (Edinb) 89 Suppl 1: S10-14.
2. Torrelles JB, Azad AK, Henning LN, Carlson TK, Schlesinger LS (2008) Role of C-type lectins in mycobacterial infections. Curr Drug Targets 9: 102-112.
3. Wright JR (2005) Immunoregulatory functions of surfactant proteins. Nat Rev Immunol 5: 58-68.
4. Pérez-Gil J (2008) Structure of pulmonary surfactant membranes and films: the role of proteins and lipid-protein interactions. BiochimBiophysActa 1778: 1676-1695.
5. Ferguson JS, VoelkerDR, McCormack FX, Schlesinger LS (1999) Surfactant protein D binds to Mycobacterium tuberculosis Bacilli and Lipoarabinomannan via carbohydrate-lectin interactions resulting in reduced phagocytosis of the bacteria by macrophages1. J. immunol 163: 312-321.
6. Kuzmenko AI, Wu H, McCormack FX (2006) Pulmonary collectins selectively permeabilize model bacterial membranes containing rough lipopolysaccharide. Biochemistry 45:2679-2685.
7. Ferguson JS, Voelker DR, McCormack FX, Schlesinger LS (1999) Surfactant protein D binds to Mycobacterium tuberculosis Bacilli and Lipoarabinomannan via carbohydrate-lectin interactions resulting in reduced phagocytosis of the bacteria by macrophages1. The J Immunol 16: 312-321.


 

8. Gaynor CD, McCormack FX, Voelker DR, McGowan SE, Schlesinger LS (1995) Pulmonary surfactant protein A mediates enhanced phagocytosis of Mycobacterium tuberculosis by a direct interaction with human macrophages. The J. Immunol 155: 5343-5351.
9. Ferguson JS, Martin JL, Azad AK, McCarthy TR, Kang PB, et al. (2006). Surfactant protein D increases fusion of Mycobacterium tuberculosiscontaining phagosomes with lysosomes in human macrophages. Infection and immunity 74: 7005-7009.
10. Ferguson JS, Voelker DR, Ufnar JA, Dawson AJ, Schlesinger LS (2002) Surfactant protein D inhibition of human macrophage uptake of Mycobacterium tuberculosis is independent of bacterial agglutination. J Immunol 168: 1309-1314.
11. Wu H, Kuzmenko A, Wan S, Schaffer L, Weiss A, et al. (2003) Surfactant proteins A and D inhibit the growth of Gram-negative bacteria by increasing membrane permeability. J Clin Invest 111: 1589-1602.
12. Zhang S, Chen Y, Potvin E, Sanschagrin F, Levesque RC, et al. (2005). Comparative signature-tagged mutagenesis identifies Pseudomonas factors conferring resistance to the pulmonary collectin SP-A. PLoS pathogens 1: e31.
13. Sidobre S, Nigou J, Puzo G, Rivière M (2000) Lipoglycans Are Putative Ligands for the Human Pulmonary Surfactant Protein A Attachment to Mycobacteria critical role of the lipids for lectin-carbohydrate recognition. J. BiolChem 275: 2415-2422.
14. Beharka AA, Crowther JE, McCormack FX, Denning GM, Lees, J, et al (2005). Pulmonary surfactant protein A activates a phosphatidylinositol 3-kinase/calcium signal transduction pathway in human macrophages: participation in the up-regulation of mannose receptor activity. Immunol 175: 2227-2236.
15. Hall-SL, Watts G, Crowther JE, Balagopal A, Torrelles JB, et al. (2006). Mycobacterium tuberculosis binding to human surfactant proteins A and D, fibronectin, and small airway epithelial cells under shear conditions. Infect Immun 74: 3587-3596.

 