Optimization of inhaled therapies for tuberculosis: The role of macrophages and dendritic cells

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Summary

Inhaled therapies in the form of drugs or vaccines for tuberculosis treatment were reported about a decade ago. Experts around the world met to discuss the scientific progress in inhaled therapies at the international symposium “Optimization of inhaled Tuberculosis therapies and implications for host–pathogen interactions” held in New Delhi, India on November 3–5, 2009. The meeting was organized by the Central Drug Research Institute (CDRI) Lucknow, India. The lung is the main route for infection with *Mycobacterium tuberculosis* bacilli and the primary site of reactivation of latent disease. The only available vaccine BCG is relatively ineffective at preventing tuberculosis disease and current therapy requires prolonged treatment with drugs which results in low patient compliance. Consequently, there is a need to design new vaccines and therapies for this disease. Recently there has been increased interest in the development of inhaled formulations to deliver anti–mycobacterial drugs and vaccines directly to the lung and many of these therapies are designed to target lung macrophages and dendritic cells. However, the development of effective inhaled therapies requires an understanding of the unique function and immunosuppressive environment of the lung which is driven, in part, by alveolar macrophages and dendritic cells. In this review, we will discuss the role of alveolar macrophages and dendritic cells in the host immune response to *M. tuberculosis* infection and the ways in which inhaled therapies might enhance the anti–microbial response of phagocytes and boost pulmonary immunity.

Keywords: Tuberculosis; Macrophage; Dendritic cell; Inhaled therapy

stimulate innate bactericidal responses and/or antigen presenting functions more efficiently and will ameliorate drug toxicity due to reduction in dose/duration of treatment.¹² However, the development of successful inhaled therapies in general will depend on the confounding characteristics of the lungs, in addition to the multiple variables added by alterations in its structure and damage inflicted by the inflammatory process, and needs to take into account factors such as aeration of the lungs, deposition and lung function, formation of biofilms and resistance in the face of treatment.^[12] and ^[13]

The role of alveolar macrophages and dendritic cells in the immuneresponse to *Mycobacterium tuberculosis*

M. tuberculosis infection in the lungs

Tuberculosis is mainly a disease of the lung and is characterized by a long chronic stage of infection and progressive pathology that compromise the respiratory system. The bacteria enter through the respiratory route and infect macrophage cell populations in the lung.¹⁴ If the bacteria are not eliminated right away by innate mechanisms of immunity then they multiply and enter the blood stream reaching other organs. M tuberculosis also infects macrophages in the blood, spleen, lymph nodes, liver, kidney, and intestine; in these other organs the pathology can differ significantly from the lung.¹⁴ In a way, it is the special environment of the lung described above that sustains a chronic infection with M. tuberculosis and subsequent pathology found in tuberculosis disease.

Once inside the lungs, to establish infection, M. tuberculosis need to traverse the airways and settle in the alveolar spaces where the phagocyte macrophage populations [AM and DCs] are located. The fate of the bacillus within the infecting cell depends on the state of activation of the phagocyte [alternative or classical state of activation] encountering the bacillus. As explained above, the lungs' macrophage populations can be found in multiple phenotypes and stages of differentiation and the survival of the bacillus in the lungs "is a lottery", its fate depending on the type and activation state of the phagocytic cell found in its way. It is believed that the bacillus is able to survive within the macrophage if the phenotype of the phagocytic cell interacting with M. tuberculosis displays an anti-inflammatory phenotype also known as "alternative activation state". Thus, these cells have increased expression of pattern recognition receptors such as the mannose and scavenger receptors facilitating cell and bacillus interaction but they also have a reduced oxidative burst and they are unable to eliminate the bacillus. In Schlesinger's words "They eat but do not influence".^[15] and ^[16]

Activation state of phagocytes, influence of the lung environment and current studies of dry powder formulations affecting phagocyte activation state

The activation state of the phagocytes within the alveolar spaces appears to be governed by a highly regulated alveolus immune environment. Thus, surfactants found in the alveolar spaces in tuberculosis disease are believed to influence the environment in which the bacilli may establish infection in the lung and are responsible for the maintenance of an alternatively activated alveolar macrophage.^[2] and ^[4] Surfactants, predominately A and D, are released by type II epithelial cells in the alveoli and are routinely taken up and recycled by alveolar macrophages. Surfactant A is taken up by the mannose receptor, dampens the oxidative burst by inhibiting translocation of NADPH oxidase to the phagosome and increases expression of TLR2 and TLR4 on the cell surface. Surfactant protein D on the other hand, inhibits phagocytosis but promotes phagolysosomal fusion of those bacilli that are phagocytosed.^{[2], [17], [18], [19], [20], [21], [22]} and ^[23] Using mathematical modelling Schlesinger's group has calculated the time required for alternatively activated macrophages to be replaced by classically activated macrophages in the M. tuberculosis infected lung; termed "switching time". From this study it was estimated that in mice infected with M tuberculosis it takes approximately 50 days to convert to classically activated macrophages.²⁴

From the therapeutic viewpoint switching from alternative to classical activation of macrophages in the infected lung may be achieved by inhalation of microparticles prepared as a dry powder formulation.^{[13], [25]} and ^[26] This procedure has been demonstrated by Misra's group at CSIR, India to drive infected macrophage towards a more "classical macrophage activation pathway".²⁵ Poly(lactic acid) (PLA) microparticles formulated to carry anti-

tuberculosis drugs to macrophages in the lung were used as one type of inhaled therapy.²⁶ Unexpectedly, as well as the anti-microbial effects of the antibiotics contained in the microparticles, the particles themselves also triggered innate macrophage microbicidal activity including increased production of reactive oxygen species, nitric oxide and pro-inflammatory cytokines that is more reminiscent of classical macrophage activation compared to that induced by *M. tuberculosis* alone. The microparticles also augmented infected macrophage cell death which displayed a phenotype more similar to classical apoptosis (i.e. activation of caspases). Moreover, macrophage activation by blank microparticles was also associated with reduced mycobacterial survival compared to untreated macrophages.

Development of the adaptive immune response against *M. tuberculosis* infection and current immunotherapeutic approaches to delivery into the lungs

Adaptive immunity to *M. tuberculosis* infection is dependent on the emergence of specific sub-populations of T cells. It is well known that CD4 T cell populations are critical for overcoming this infection^{[27], [28], [29]} and ^[30] but other cell populations such as CD8 T cells,^{[31], [32]} and ^[33] $\gamma\delta$ T cells^[34] and ^[35] and NK cells respond to pulmonary infection with *M. tuberculosis*.³⁶ Priming of adaptive immunity towards a Th1 cytokine response (IL-12, IL-23, IFN γ , TNF α , IL-17) is an essential step to limit multiplication of *M. tuberculosis*.^{[37], [38], [39], [40], [41]} and ^[42] Evidence suggests that the mediastinal lymph node cluster draining the lungs is the first organ where priming of a Th1 response against pulmonary infection with *M. tuberculosis* occurs⁴³ and is mediated by DCs carrying bacteria to this organ via lymphatic vessels or directly by free bacteria reaching the lymphoid tissues through the lymph fluid or blood.⁴⁴ Primed T cells then are recruited to the lung driven by chemokine gradients where they interact with infected cells and deliver IFN γ which ultimately will activate production of microbicidal substances by AM and DCs. In summary, if bacteria are not eliminated by innate mechanisms of immunity then they multiply within the infected cell and it is not until adaptive immunity develops, and provides a supply of IFN γ , that the bacterial multiplication is eliminated or contained. The latter leads to a chronic stage of infection characterized by a persistent source of mycobacterial antigens in the lung, sustaining a chronic inflammatory response with a continuous recruitment of monocytes, macrophages (MO) and DCs^[7] and ^[45] as well as T and B lymphocytes^[46] and^[47] along with a sustained production of several inflammatory cytokines and chemokines.^[27] and ^[48] This inflammatory process develops into a granuloma lesion which helps restrain the surviving bacteria.

Several immunosuppressive diseases or drug immunotherapies have provided additional information about a very important aspect of chronic infection with *M. tuberculosis*, namely that the containment of *M. tuberculosis* growth within the granuloma requires a continuous expression of the Th1 cytokines IL-12, IFN γ and TNF α at all times.^{[49], [50]} and ^[51] If any of these cytokines are absent or blocked, TB disease reactivates. In this scenario, the continuous production of inflammatory cytokines during the chronic stage would lead to extreme inflammation-associated pathology as happens in IL-10 deficient mice⁵² but for the fact that the immune system uses the production of immunosuppressive cytokines e.g. IL-10 and TGF β to counteract this. Thus, in chronic disease strong and sustained activation of a Th1 cytokine response against latent *M. tuberculosis* infection is responsible for the anti-microbial activity against this bacillus but this strong anti-microbial response elicited by the host is unable to completely clear the bacteria. The “halted anti-microbial capacity” of the host has two concomitant origins: first; the highly inflammatory character of the Th1 response and activation of immunosuppressive mechanisms elicited by the host to counterbalance inflammation, and second, the expression of bacterial antigens that are capable of causing immunosuppression in the host. As result of both, host inflammation and bacterial antigens, the anti-microbial activity provided by the Th1 response is intercepted and diminished [but not

abolished]. Altogether, to survive this infection, the host must keep a tight balance between both, the Th1 response and the immunosuppressive mechanisms; otherwise it will become a diseased host. From this perspective and with the objective of enhancing/recovering the host anti-microbial activity during the latent stage of infection several strategies are being studied to modulate the lung environment including intrapulmonary delivery of cytokines [IFN γ , M-CSF],[\[10\]](#) and [\[53\]](#) chemokines [XCL1][\[54\]](#) or their inhibitors [antibodies, XCL1 siRNA, TGF β siRNA].[\[55\]](#) In summary, these studies show when small concentrations of cytokines, chemokines or inhibitors of these (siRNA, antibodies, drugs) are delivered by the intrapulmonary route it is possible to change the course of the lung immune response and pathology. The main goal of these studies is to learn how and when we need to target the latently infected host to fully recover the anti-microbial activity of the infected cell and how we can use this information in the context of current chemotherapeutic treatments. With the purpose of enhancing pulmonary immunity and host anti-microbial capacity several antigen formulations and vaccines are currently being studied.[\[56\]](#), [\[57\]](#), [\[58\]](#), [\[59\]](#) and [\[60\]](#) These studies have benefited by recent advances in spray drying and aerosol delivery, and its application to the preparation of vaccine for inhalation.[\[12\]](#), [\[58\]](#), [\[59\]](#) and [\[61\]](#) Thus, aerosol delivery of BCG vaccine prepared as a spray-dried nanomicroparticle aerosol,[\[57\]](#), [\[58\]](#) and [\[59\]](#) or liposome, chitosan and PLGA-PEI DNA vaccine[\[56\]](#) and [\[62\]](#) have also been used in mice and guinea pigs to enhance pulmonary anti-microbial activity against *M. tuberculosis* infection. Aerosol delivery of the BCG nanomicroparticle to normal guinea pigs subsequently challenged with virulent *M. tuberculosis* significantly reduced bacterial burden and lung pathology both relative to untreated animals and to control animals immunized with the standard parenteral BCG.[\[57\]](#) and [\[59\]](#) Similarly, the immunogenicity of a DNA vaccine encoding the *M. tuberculosis* latency antigen Rv1733c and the effect of pulmonary delivery and co-formulation with poly (d,l-lactide-co-glycolide) (PLGA)-polyethyleneimine (PEI) nanoparticles on host immunity is also being studied. Rv1733c DNA adsorbed to PLGA-PEI nanoparticles and applied to the lungs increased T cell proliferation and IFN γ production more potently compared to the same vaccinations given intramuscularly. The strongest immunogenicity was obtained by pulmonary priming with nanoparticle-adsorbed Rv1733c DNA followed by boosting with Rv1733c protein. These results confirm that PLGA-PEI nanoparticles are an efficient DNA vaccine delivery system to enhance T cell responses through pulmonary delivery in a DNA prime/protein boost vaccine regimen.[\[56\]](#) In other studies, an HLA-A2 transgenic mouse model have been used to investigate the effects of pulmonary delivery of a new DNA plasmid encoding eight HLA-A*0201-restricted T cell epitopes from *M. tuberculosis* formulated in chitosan nanoparticles. In these studies, it was shown that the chitosan-DNA formulation was able to induce the maturation of DCs while chitosan solution alone could not, indicating the DNA was released from the particles and able to stimulate DCs. Pulmonary administration of the DNA plasmid incorporated in chitosan nanoparticles was also demonstrated to induce increased levels of IFN γ secretion compared to pulmonary delivery of plasmid in solution or the more frequently used intramuscular immunization route. These results indicate that pulmonary delivery of DNA vaccines against tuberculosis may provide an advantageous delivery route compared to intramuscular immunization, and that increased immunogenicity can be achieved by delivery of this DNA encapsulated in chitosan nanoparticles.[\[62\]](#) Finally, a powder vaccine intended for aerosol delivery was formulated by spray drying the Adenovirus [Ad35]-vectored tuberculosis AERAS-402 vaccine with mannitol-based stabilizers and is being studied in a non-human primate animal model of TB infection.[\[60\]](#) These studies have demonstrated good CD4 and CD8 T cell response in the bronchoalveolar spaces.

The granuloma

There is no doubt that containment of bacillary spread coincides with granuloma formation however the number, type and size of granulomas varies even within the same patient and the

same lung lobe⁶³ suggesting each granuloma is a single entity governed by its own environment. Once the granuloma is formed, this may remain as an active and well formed structure able to contain the bacilli for the rest of the patient's life, it may achieve localized sterilization of the infection and mineralization of the lesion or, in the worst case scenario, it may progress into a localized caseation and necrosis that eventually will break down and release the bacteria into the airways.

The complexity of pulmonary macrophage cell populations during a chronic M. tuberculosis infection reach its climax at the granuloma level. At this location, these cells can be found as monocytes, macrophages, dendritic cell^[45] and ^[64] multinucleated cells giant cells, epithelioid cells and foamy cells.^[45], ^[63], ^[65] and ^[66] As the granuloma matures, many macrophages cells within the granuloma engulf large quantities' of lipids,^[63], ^[66], ^[67], ^[68], ^[69]and ^[70] express high levels of intracellular immunosuppressive and pro fibrotic cytokines IL-10, IL-4, TGF β and anti-apoptotic markers [TRAF].^[45] and ^[64] These cells are eventually driven into the core of the granuloma protected/strangled [depending on the outcome of disease] by a fibrotic envelope that excludes the T cells [source of IFN γ and responsible for anti-microbial activation] and large numbers of B cells [of unknown function]. During this process the center of the granuloma progressively becomes very hypoxic in nature^[71] and ^[72] and the predominant macrophage phenotype in the core of the granuloma becomes the multinucleated and foamy cell also expressing immunosuppressive cytokines IL-10 and IL-4 but not TGF β [mouse model Gonzalez-Juarrero unpublished data]. In humans, non-human primates and guinea pigs the center of the granuloma may progress into a caseum and necrotic lesion that eventually collapses and fails to retain the infectious bacilli.^[63], ^[73] and ^[74]

Lipids within the granuloma and foamy cells appear to be of both host and bacterial origin.^[63], ^[67] and ^[68] In humans the developmental process leading to caseation at the core of the granuloma appears to be correlated with the content and accumulation of lipids.⁶⁸ Russell's group exploited genome-wide microarray analysis to show that within the caseous granuloma there is sequestration of low density lipids droplets and high levels of ceramides which influences cell morphology (foamy cell appearance), cholesterol sequestration and cell death.

Role of mycobacterial antigens in persistence of M. tuberculosis

The role of mycobacterial mannosylated lipids as a potential factor involved in persistence of M. tuberculosis within infected cells have been supported by multiple studies.^[4], ^[75], ^[76], ^[77], ^[78] and ^[79] Bloom's group in 1991⁸⁰ reported a potential role for lipoarabinomannans [LAM] as factors in the persistence of M. tuberculosis in infected cells, and other studies also attributed this capacity specifically to manLAM.^[81] and ^[82] Most recently, Schlesinger and Torrelles have demonstrated that M. tuberculosis clinical isolates vary in their degree of surface mannosylation and they suggest these differences may have great impact on the outcome of the disease.⁷⁸ There is direct evidence manLAM affects DC maturation and function^[79], ^[83] and ^[84] and the same antigen either as a cell wall component of M. tuberculosis or as a free antigen, drives DCs into IL-10 production.^[76], ^[85], ^[86], ^[87], ^[88] and ^[89] Thus, mycobacterial mannosylated lipids are believed to play an important role in bacterial persistence by modulating the host response during the course of chronic infection with M. tuberculosis.⁹⁰ Several groups have demonstrated that manLAM binds to the mannose receptor [MR], and the dendritic cell-specific intercellular adhesion molecule-3 grabbing nonintegrin [DC-SIGN] molecule present on the surface of AM and DCs.^[88], ^[89], ^[90] and ^[91] Schlesinger's group demonstrated that binding

of ManLAM to MR or DC–SIGN molecules activates different pathways of phagosomal traffic.[76](#) Other mycobacterial antigens may act in a similar manner; for instance, M. tuberculosis secretory antigen (MTSA)–differentiated DCs and MTSA–matured DCs were shown to down–regulate inflammatory responses of M. tuberculosis primed T cells.[92](#) This collectively demonstrates that mycobacterial lipids can accumulate in the granuloma, down–regulate protective immune responses to the bacillus, and lower anti–microbial expression by stimulating immunosuppressive mechanisms and/or alternative pathways of cell activation in AM and DCs.

The role of cell death in the immune response to M. tuberculosis

M. tuberculosis is an intracellular pathogen and its survival within the host requires living cells. Cell suicide is an important innate defence against intracellular pathogens. Host cell death not only inhibits bacterial replication by depriving the pathogen of its niche but also stimulates innate and adaptive immune responses; the latter vary depending on the mechanism of cell death; apoptosis or necrosis. Until recently, apoptosis (characterized by the activation of caspases and the formation of apoptotic bodies which are phagocytosed before the loss of membrane integrity) was deemed to be immunologically silent. On the contrary, necrosis was thought to be an accidental event resulting in rapid cell lysis and inflammation. It is now known however, that apoptosis can be either tolerogenic or immunogenic depending on the context in which it occurs.[93](#) Thus, during development or maintenance of homeostasis the interaction of apoptotic cells with dendritic cells results in the proliferation of regulatory T cells[94](#) and when apoptosis is accompanied by expression of damage–associated molecules such as calreticulin,[93](#) or occurs in the context of a bacterial infection with exposure of pathogen–associated molecules, interacting dendritic cells can stimulate protective immune responses.[94](#) Conversely, necrosis can occur in a highly regulated fashion and does not necessarily evoke an immunogenic reaction in responding cells.

Several lines of evidence suggest that macrophage apoptosis is beneficial for the host response to tuberculosis by having direct bactericidal effects on intracellular mycobacteria and also in the stimulation of protective immunity. For example, the induction of apoptosis of cultured macrophages by exogenous apoptotic stimuli such as Fas ligand reduces the survival of intracellular M. tuberculosis[95](#) whereas necrosis does not prevent bacillary growth. In addition, macrophages from an inbred strain of mouse (C3HeB/FeJ) that is susceptible to M. tuberculosis infection undergo necrosis when infected while macrophages from the less susceptible strains of mice undergo apoptosis.[96](#) Furthermore, apoptotic vesicles released by dying, infected macrophages are taken up by dendritic cells and cross prime CD8+ T cells via MHC1 and CD1 molecules.[\[97\]](#) and [\[98\]](#) The resulting antigen–specific cytotoxic T cells can then kill infected macrophages via the perforin–granzyme pathway.

In its battle to survive within the host it appears that M. tuberculosis can also inhibit host cell death or manipulate the mechanism of death. Indeed, it has been suggested that virulent strains of mycobacteria inhibit macrophage apoptosis[\[99\]](#), [\[100\]](#), [\[101\]](#) and [\[102\]](#) but cause necrosis and that this promotes the survival of M. tuberculosis. This is supported by recent data indicating that the genome of M. tuberculosis encodes for genes that actively inhibit macrophage apoptosis and enhance intracellular survival, including nuoG,[103](#) pknE[104](#) and secA.[105](#) Deletion mutants of some of these genes have been found to induce more apoptosis than the wild type bacilli. In fact, the secA deletion mutant, which is attenuated in mice, stimulates a more robust pathogen–specific CD8+ T cell response.[106](#)

Despite its ability to (at least partially) inhibit apoptosis there is no doubt that *M. tuberculosis* causes macrophage cell death both in vivo and in vitro although the mechanism is not fully understood.¹⁰⁷ The effect that *M. tuberculosis* and its components exert on macrophage viability appears to be multifaceted. TNF, released by macrophages infected with *M. tuberculosis*, can signal in an autocrine fashion to cause cell death. It has been reported that TNF-mediated apoptosis of infected murine macrophages is dependent on the MAP kinases p38 and ASK1; p38 phosphorylates the anti-apoptotic protein FLIP which is also phosphorylated by c-ABL, tagging it for degradation by the proteasome and thus allowing autoactivation of procaspase 8 and apoptosis.¹⁰⁸ However, there is also evidence that *M. tuberculosis* can inhibit the extrinsic^[109] and ^[110] and intrinsic pathways of apoptosis in vitro^[111] and^[112] by interfering with TNF signalling and upregulating anti-apoptotic host cell mediators such as Mcl-1 and A1. In addition, foamy macrophages in granulomas in the lungs of mice infected with *M. tuberculosis* have been found to express high levels of TNFR-associated factors (TRAFs) 1–3 which are associated with resistance to apoptosis.⁴⁵ In keeping with these data human and murine macrophages have been reported to undergo TNF- and caspase-independent cell death which is associated with activation of cathepsin and serine proteases.^[113] and ^[114] Given the influence that cell death has in shaping the immune response to *M. tuberculosis* infection and the ability of the pathogen to subvert this process, it is not surprising that infected macrophages might activate multiple redundant cell death pathways. Inhaled therapies that stimulate caspase activity in infected macrophages and drive the cell death mechanism towards apoptosis rather than necrosis could be beneficial in the treatment of tuberculosis.^[115] and ^[116] Understanding the precise cell death mechanism(s) induced by *M. tuberculosis* in macrophages and the subsequent consequences for the innate and adaptive immune response may aid in the development of new therapies and vaccines for tuberculosis.

In summary, the outcome of an infection with *M. tuberculosis* is determined by the balance between a series of host- and pathogen-driven events. The host attempts to eliminate or contain the infection within the granuloma by inducing macrophage apoptosis, activation of macrophages, maturation and migration of dendritic cells and the stimulation of a protective Th1 adaptive immune response. On the other hand, the pathogen seeks to subvert this host response by strategies such as inhibiting apoptosis, inhibiting lysosome maturation and hijacking host cell lipid metabolism to survive the hostile environment of the phagosome and promoting a regulatory T cell response. In addition, the immunosuppressive environment of the alveolus aids the pathogen in its task, in the early and late stages of infection. In the design of effective inhaled drug delivery systems to treat or prevent *M. tuberculosis* infection the complex interplay between all of these elements will need to be taken into consideration.

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Competing interests

None declared.

Ethical approval Not required.

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