HHS Public Access

Author manuscript

Immunol Rev. Author manuscript; available in PMC 2016 March 01.

Published in final edited form as:

Immunol Rev. 2015 March ; 264(1): 167–181. doi:10.1111/imr.12276.

B cells and Antibodies in the Defense against *Mycobacterium tuberculosis* infection

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Summary

Better understanding of the immunological components and their interactions necessary to prevent or control *Mycobacterium tuberculosis* (Mtb) infection in humans is critical for tuberculosis (TB) vaccine development strategies. While the contributory role of humoral immunity in the protection against Mtb infection and disease is less defined than the role of T cells, it has been well established for many other intracellular pathogens. Here we update and discuss the increasing evidence and the mechanisms of B cells and antibodies in the defense against Mtb infection. We posit that B cells and antibodies have a variety of potential protective roles at each stage of Mtb infection, and postulate that such roles should be considered in the development strategies for TB vaccines and other immune-based interventions.

Keywords

Tuberculosis; immunity; antibodies; immunoglogulins; B-lymphocytes

Introduction

A more complete picture of the correlates of protection against *M. tuberculosis* (Mtb) infection and disease is critical for effective vaccine development. An estimated third of the world's population is infected with Mtb but merely ~10% develop the disease, active tuberculosis (TB) during their lifetime (1). The immunological components and their interactions necessary to prevent or control Mtb infection in humans remain incompletely understood. The currently available *M. bovis* Bacillus Calmette-Guerin (BCG) vaccine, based on an attenuated *M. bovis* strain, has been in use for many decades but does not prevent Mtb infection and provides insufficient protection against disease (reviewed in (2, 3)). Many promising vaccines have been and are currently being developed (reviewed in (4)) but efficacy in humans remains to be proven. In 2013, there were an estimated 9 Million

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people who developed TB, and around 1.5 Million died from the disease emphasizing the urgency for better vaccines and other preventive measures (1).

Tuberculosis vaccine development strategies have been guided by the paradigm that protection against intracellular pathogens is based on cell-mediated immunity (CMI) while humoral immunity is relevant in the defense against extracellular pathogens. We note that almost two decades ago Rook and Hernandez-Pando (5) wrote: 'Almost all the current review literature on the mechanism of immunity to tuberculosis states that antibody plays no role. We have found no evidence for this statement. Although antibody alone is certainly not sufficient, it may well be necessary", at least in some hosts. Although cell-mediated immune mechanisms, predominantly based on T cells and mononuclear phagocytes, are the cornerstone in the defense against Mtb at most stages of the infection (reviewed in (6-11)), increasing evidence over the past years suggests that innate (12-14) and humoral immunity also play a role (reviewed in (15-18). Furthermore, the interactions and complementing effects between the different arms of the immune system will likely be needed for optimal protection against infection and development of disease.

Although antibodies (Abs) were previously believed to have little role in the defense against intracellular pathogens that view has changed in recent decades (reviewed in (19)). Abs to intracellular pathogens can mediate protection through various mechanisms extending from classical functions such opsonization and complement activation to non-classical functions such as signaling through Fc receptors (FcR) and modulation of the inflammatory host response (reviewed in (19-21)). In fact, the plethora of Ab functions against intracellular pathogens is likely to remain elusive unless specifically studied. A good example for this is the tremendous variety of Ab mechanisms which we have demonstrated in our experimental *in vivo* and *in vitro* studies with *C. neoformans* (reviewed in (22)). Humoral immunity as well as the synergistic effects between humoral and other arms of the immune system have become apparent for the protection against many intracellular pathogens (reviewed in (19, 23)). The list of intracellular pathogens that have been shown to be vulnerable to humoral immunity is long and has kept growing over the past decade (*Table 1*). As of today, it includes Gram negative bacteria such as *Salmonella* (24, 25), *Yersinia* (26-29), *Ehrlichia* (30, 31), *Brucella* (32-34), *Coxiella* (35, 36), *Legionella* (37-39), *Neisseria* (40, 41), and *Chlamydia* spp. (42-44); Gram positive bacteria such as *Listeria* spp. (45); fungi such as *Cryptococcus* (reviewed in (22)) and *Histoplasma* (46, 47) spp.; and parasites such as *Plasmodium* (48-52), *Leishmania* (53-55), and *Toxoplasma* (56, 57) spp. (57). More importantly, for several of these organisms vaccines with protective efficacy based on either Abs alone or the combination of humoral and CMI have been or are being developed (*Table 1*). We here review and update the evidence, functions and mechanisms of B cells and Abs in the protection against Mtb infection and disease, and discuss their potentially critical interactions with other arms of the immune system. Just as for other intracellular pathogens, we believe that these data should also be taken into consideration for TB vaccine development strategies.

Supporting Data for a Role of B cells and Abs in the Defense Against Mtb Infection

The limited appreciation of Abs as being a heterogeneous group of proteins that vary in protective and non-protective functions combined with the paradigm that they have little to no role in the defense against intracellular pathogens and the contradictory results of older serum transfer studies (58), has made it challenging to make a convincing case for their role in the defense against Mtb. The evidence for a role of B cells and Abs in the defense against Mtb infection was recently reviewed by us in detail (15-18), and is summarized and updated in *Table 2*. An important element of this evidence includes studies from various groups demonstrating that the passive transfer of monoclonal Abs (mAbs) against some Mtb antigens, ranging from surface-associated polysaccharides to proteins (59-66), as well as human polyclonal IgG or homologous immune sera (67-69), improve the outcome of mycobacterial infection in mice (*Table 2*). However, these studies have various limitations (reviewed in (15, 16), and well-designed *in vitro* and *in vivo* studies are warranted to expand such experiments and further identify the mechanisms of potentially protective Abs and their efficacy in various animal models. Other critical parts of the evidence are observational and experimental studies in humans and animal models showing inverse relationships between titers of Abs against certain mycobacterial antigens and susceptibility to infection and disease in humans and animals (70-73); and studies demonstrating increased TB susceptibility in animal models with deficits in B cell function and humoral immunity (74-79) (*Table 2*). Just as for mAbs, further research in these areas is now needed to elucidate the underlying mechanisms of these results.

Ab Functions Contributing to the Protection Against Mtb

In considering the various mechanisms by which Abs could contribute to host defense against mycobacterial infection it may be worthwhile to separate them depending on whether the effect is direct or indirect.

Classical mechanisms of Ab action

A variety of studies have provided data supporting that several of the classical functions associated with Ab mediated immunity could potentially be effective against Mtb (*Fig. 1*). These include mechanisms such as opsonization and complement activation. Other direct mechanisms of Ab-mediated immunity such as toxin neutralization do not apply as Mtb does not produce toxins although it is conceivable that Ab binding and Ab-mediated clearance of mycobacterial antigens that are immunomodulatory would provide a comparable function. Ab-dependent cellular cytotoxicity (ADCC) could potentially enhance host resistance to Mtb but we are not aware of studies reporting this mechanism. With regards to opsonization, Ab-mediated phagocytosis has been shown to promote phagolysosomal fusion (80) and thus overcome the inhibition of lysosomal fusion, which is a major mechanism by which mycobacteria survive after ingestion by macrophages. In addition, FcγR engagement triggers signal transduction that results in increased macrophage Ca2+ and intracellular killing (81), and FcR engagement by Abs subverts the evasion of lysosomal degradation of BCG (38). Also indicative of a direct effect was the report that IgG coated compared to

uncoated BCG resulted in an increased oxidative burst in the phagosomes of macrophages with enhanced mycobacterial killing (82). With regards to complement activation, TB patients with IgG2 (but not IgM) to LAM manifested increased complement activation on BCG (83). Similarly, human Ab (IgG > IgM) was reported to result in enhanced complement deposition on BCG (84), and human IgG was also reported to trigger complement activation resulting in increased phagocytosis of Mtb by macrophages (85).

Non-classical mechanisms of Ab action

In recent years other mechanisms of Ab-mediated protection that could contribute to host defense against Mtb have been described (*Fig. 1*). The discovery of activating and inhibitory FcRs has added a rich new layer of possibilities to mechanisms for Ab action against Mtb. In this regard, modulation of the different receptors can have effects on macrophage function that affect their susceptibility to mycobacteria (74). For example, Mtb infection of mice lacking the activating FcγR γ-chain results in disease with more severe immunopathology that was associated with higher levels of IL-10 (74). Since TB is a disease characterized by an intense inflammatory response differences in the relative engagement of activating and inhibitory functions by the various Ab isotypes could have profound effects on whether the tissue response is effective at clearing mycobacteria or promotes mycobacterial persistence through immune damage. Indirect evidence to support such scenarios comes from the observation that individuals with TB had significantly higher gene expression of the activating FcγRIA (CD64) in whole blood than those with LTBI irrespective of HIV co-infection status (86). Consistent with this result, TB patients had a significant reduction in whole blood FcγRIA RNA expression after treatment relative to the levels before therapy was initiated (87). The FcγRIA receptor may be particularly important in the pathogenesis of TB because it is expressed in cells of the monocytic lineage, is involved in immune complex clearance, and its expression is induced by IFN-γ. Thus, these results provide intriguing hints for the importance of FcγR activation in the outcome of Mtb infection. Another receptor that has been potentially associated with resistance to Mtb is FcεRII-CD23. Activation of FcεRII-CD23 can trigger the killing of intracellular pathogens such as *Leishmania major* (55), and *Toxoplasma gondii* (57), and also enhance anti-mycobacterial activity (88).

Another indirect mechanism by which Ab-mediated immunity can affect host susceptibility against Mtb is through the effects of Ab on CMI and the inflammatory response (*Fig. 1*). Evidence for the potential of Abs against Mtb to mediate synergy by the different immune arms in humans comes from the observation that BCG vaccinated individuals have Abs that enhance both innate and cell-mediated immunity to Mtb (71). Furthermore, Abs from individuals who have presumably been exposed to Mtb as a result of contact with TB patients block the proliferation of monocyte cultures after tuberculin stimulation if they have high but not low IgG to tuberculin (89). Abs are further involved in antigen clearance by forming Ag-Ab complexes that can then be disposed by cells of the reticuloendothelial system (90). For example, Abs to Mtb could potentially modify the outcome of infection by promoting the clearance of mycobacterial components that influence the immune response. In this regard, Abs to LAM have been shown to promote the clearance of this mycobacterial product that is known to have immunomodulatory effects which could promote disease by

causing dysregulation of effective responses (90). Recent data further confirm the influence of mycobacterial surface-associated lipoproteins on the host's response to Mtb. For example, the lipoproteins LprG and LpqH participate in regulating cell-mediated responses against Mtb (91), and LprG is further relevant for the surface expression of LAM on macrophages, which in turn is essential for the virulence of Mtb (92). Thus, it is not surprising that vaccination with Mtb membrane vesicles induces both cell-mediated and Ab responses against LprG and LpqH that protect mice against infection with Mtb (93). Again, further studies are critical to prove the causality of such associations, and to further study the specific mechanisms by which Abs against highly immunogenic antigens participate in the defense against Mtb infection.

Studies with other microorganisms suggest additional mechanisms by which Abs to Mtb could modify the outcome of the infection. For example, Abs to the fungus *Cryptococcus neoformans* and the Gram positive bacterium *Streptococcus pneumonia* can alter the metabolic state of these organisms by simply binding to their surfaces (94, 95). For *C. neoformans* Ab binding to the capsule altered lipid metabolism making the fungal cell more susceptible to antifungal agents (94). For *S. pneumonia* Ab binding led to agglutination that mimicked conditions where quorum sensing effects occurred leading to activation of competence and fratricidal mechanisms resulting in bacterial lysis (95). Direct Ab-mediated bactericidal effects have also been described for an Ab that binds outer surface protein B of *Borrelia burgdorferi* and disrupts the bacterial surface (96). Although these mechanisms have not been investigated with mycobacteria, the fact that they occur with such phylogenetically distant microbes suggests that Ab binding to the surface of Mtb could also modify the metabolic state of the microbe in a manner that is beneficial to the host and/or mediate direct antimicrobial effects. In this regard, an anti-idiotypic mAb mimicking the action of killer toxin was reported to directly kill mycobacteria (97).

Molecular characteristics of effective Abs against Mtb

Experience with other systems has established that the efficacy of Ab is determined by the structural characteristics of the immunoglobulin molecule, the amount of Ab available and the immunological state of the host (21). Hence, it is reasonable to expect that the efficacy of Ab-mediated immunity against Mtb will also depend on the same characteristics. Structural features of immunoglobulins that are effective against individual pathogens are generally gleaned from studies with mAbs. However, for Mtb only a few protective mAbs have been described and the database is too small to make firm statements. To date, four murine isotypes, IgM, IgG1, IgG3 and IgA have been represented among protective Abs against Mtb (59-66), suggesting that these constant regions can help mediate protection when coupled with variable regions that confer certain specificities. The amount of Ab is a critical parameter in determining whether protection occurs. With too little antibody there may be an insufficient amount to confer protection. However, too much Ab may be equally detrimental to efficacy once the amount is sufficient to produce a prozone effect (98). For Mtb there is evidence that prozone effects can occur (99), and there is currently no information available on the optimal Ab concentrations needed for protection. The complexity of these parameters together with the complexity of the response to Mtb suggests

caution in concluding from negative experiments that a given mAb or Ab response is not protective unless the system is extensively explored.

Interactions of B Cells with Other Immunocytes in the defense against Mtb

Accumulating evidence suggest that B cells also play a role in the orchestration of an immune response against Mtb by interacting with various immune cells (reviewed in (17, 18) (*Fig. 1*). The functional versatility of B cells is remarkable and this lymphocyte subset can shape the development of an immune response through multiple mechanisms. B cells are proficient antigen presenting cells, a rich source of a wide array of cytokines, and the only generator of immunoglobulins. Each of these attributes can impact the differentiation and functions of a wide variety of immune cells such as T cells, neutrophils, macrophages, and dendritic cells (reviewed in (17, 18). Due to the highly active and dynamic interaction among various cells in the immune network, prediction of the relative contribution of a specific cell type is not currently possible or straightforward.

Interactions of B cells with macrophages

It has been observed that B cells exist in aggregates in the tuberculous lungs of a number of host species including humans, non-human primates and mice (100-104). Various immune cells are present in the aggregates, and immunophenotyping of these cells suggest that the structures represent ectopic germinal centers (GC) (75, 105). It is thus possible that in the GC-like aggregates, B cells interact with the other immune cells present to significantly regulate the local immune response. Because of the close proximity between B cells and macrophages in the tuberculous lungs of mice (101), and the regulation of this topological relationship by tumor necrosis factor-α (TNF) (106), a cytokine known to play an essential role in defense against Mtb, the implication of B cell-macrophage interaction will be discussed herein.

It is well established that macrophage subsets with distinct immunological functions can differentially regulate the immune response (107, 108). Indeed, evidence exists that M2 macrophages are conducive to microbial persistence (109) as well as tumor progression (110, 111). Relevant to tuberculosis, it has been shown that *Nippostrongylus brasiliensis* (a gastrointestinal nematode) infection in mice promotes Th2 immunity that in turn, compromises host defense against the tubercle bacillus through induction of the development of alternatively activated (M2) macrophages (112). One mechanism underlying M2 differentiation is based on the effect of B1 cells by way of IL-10 production (113). The role of this regulation in the progression of melanoma has been demonstrated in adoptive transfer experiments involving B1 cells (113). Whether B cells play a similar regulatory role in the M2 differentiation, thereby diminishing host defense against *M. tuberculosis* as observed in co-infection with *N. brasiliansis* remains to be determined.

Interactions of B cells with T cells

Emerging evidence indicates that B cells can also modulate T cell response to mycobacteria (*Fig. 1*). For example, the development of optimal BCG-induced Th1 response requires B cells to regulate T cell response in Mtb-infected mice during chronic infection, thereby

modulating the level of immunopathology (114). B cells can further indirectly regulate T cell function through the production of Abs. Mice unable to signal through the inhibitory FcγRIIB receptor (FcγRIIB−/−), relative to wild-type, display enhanced resistance to the tubercle bacillus (74). The enhanced resistance in the FcγRIIB−/− mice is associated with a more robust pulmonic Th1 response, as assessed by the level of IFN-γ-producing CD4+ T cells (74). Together, these data suggest that B cells can regulate Th1 responses by the production of Abs, which, upon reacting with antigens, generate immune complexes that then initiate FcR signaling. Furthermore, immunohistochemical studies conducted on the lungs of Mtb-infected mice, non-human primates, and humans have revealed the presence of CXCR5+ T cells in the GC-like structures (104). This CXCR5+ T cell subset, a major interacting partner of B cells, may play a role in Mtb control by contributing to the formation of the lymphoid nodule and perhaps macrophage activation.

Interactions of B cells with Neutrophils

Mice deficient in B cells (the μMT strain) have provided further evidence that this lymphocyte is required for the development of optimal immune response to Mtb. B cell-deficiency results in enhanced tuberculous lung inflammation, tissue neutrophilia, and increased local production of IL-10 (75). The influence on a neutrophil phenotype is supported by the observation that B cell-deficiency is associated with neutrophils with enhanced mobility (115). This neutrophil phenotype can also adversely affect vaccine efficacy in B cell-deficient mice (114, 115). Tissue neutrophilia in B cell-deficient mice could be due to the ability of B cells to regulate the IL-17/neutrophilic response (114). Together, results of these latter two studies strongly suggest a role for B cells in modulating neutrophil function. The B cell-specificity for the phenotypes observed in the μMT strain is supported by the reversal of these aberrancies by B cell adoptive transfer experiments. In addition, the depletion of B cells in wild-type animals recapitulate the immunopathology and neutrophilia phenotypes observed in μMT mice (114). Worthy of note, the adoptive transfer studies revealed that in μMT tuberculous mice receiving B cells transplant reversal of the B cell-deficient phenotypes is associated with partial replenishment of serum Ig but not with homing of the transferred cells to the lungs (75). These latter results suggest that the ability of the transferred B cells to reverse the aberrant phenotypes observed in Mtb-infected μMT mice is at least partially due to the immune regulatory attributes of Abs, and that the humoral immune response in a tuberculous host significantly shapes the protective immunity against the tubercle bacillus. Indeed, administration of immune sera procured from Mtb-infected animals reverses tissue neutrophilia in tuberculous μMT mice (114).

Interestingly, humans with pulmonary TB have lower peripheral blood B cell counts than subjects without or with Mtb infection but no disease (116, 117). These observations are consistent and supportive of experimental studies demonstrating the role of B cells and Abs in the defense against Mtb infection. Collectively, the data suggest that B cells and Abs can also shape the immune response to Mtb through interaction with other immune cells. These interactions further highlight the complexity of the mechanisms underlying the development of an efficient protective immune response against Mtb, and as a result, the relative significance of specific immunological elements in host defense against the tubercle bacillus might be difficult to ascertain.

Role of Humoral Immunity at Different Stages of Mtb Infection

The relevance of defense mechanisms against Mtb infection has to be viewed in the context of the various states that lie between initial infection and established disease. In that respect, it is important to distinguish whether the goal of a vaccine or other immune-based intervention is a) to prevent or rapidly clear initial infection; b) to protect against the development of disease/reactivation in already latently infected individuals; or c) to treat already established disease. These goals will likely require different balances between involving the various elements of the immune defense, and Abs could have a different role at each level (*Fig. 1*). However, the diversity of Ab functions, the complex interplay between B-cells and other immunocytes, and the limitations of animal models (reviewed in (118)) pose major challenges to decipher the parts of the various immune arms and their specific balance relevant for optimal protection at each stage of infection. To complicate matters further, the heterogeneity of the human immune response as well as the level of immune competency of individuals (reviewed in (15, 119)) will have to be taken into account when developing vaccines and other immune-based interventions against Mtb infection.

Role of humoral immunity in preventing or rapidly clearing initial Mtb infection

Abs could play a substantial role in preventing or rapidly clearing initial Mtb infection. During its initial encounter with the host Mtb would still be in a predominantly extracellular phase where Abs could rapidly bind to Mtb and augment macrophage phagocytosis and killing through the engagement of FcR, a mechanism that has been effective in clearing other intracellular pathogens (*Table 1*). At this level pathophysiologic processes in the respiratory system have to be taken into particular consideration (reviewed in (120)). Although some doubts remain whether Abs could play a role at the alveolar level during initial infection (Orme I, Tuberculosis 2014, in press), systemic mAbs have shown to protect against other intracellular, respiratory pathogens. For example, intraperitoneal injection of mAb targeting a lipopolysaccharide of the Q fever producing facultative intracellular organism *Coxiella burnetii* has shown to protect mice against aerosolized infection (36). Also in accordance with these notions, vaccines based on the induction of Abs that promote phagocytosis of respiratory, intracellular pathogens such as *Yersinia pestis* and *Francisella tularemia* have recently been developed and shown protection against Plague and Tularemia (28, 29, 121). Furthermore, alveolar macrophages and epithelial cells produce several proteins of the classical and alternative pathways of complement (122, 123), and complement proteins have been detected in the bronchoalveolar lavage (BAL) fluid from various different mammalian species including humans (124-127). Thus, Abs activating complement (83) which would enhance phagocytosis and cellular recruitment further to the site of Mtb infection, could also contribute to the rapid clearing of Mtb.

Role of humoral immunity in containing Mtb infection

Mtb causes a spectrum of infectious states, and development of disease as well as disease manifestations are dependent on the immune competency of the host (reviewed in (119, 128-130). The role of the granuloma in containing Mtb infection is considered critical (131), although there are ongoing debates about this relevance (132-134). Abs could contribute to

the control of Mtb infection and prevention of reactivation through various mechanisms at the granuloma level. For example, IgM was shown to enhance granuloma formation in BCG infected mice by promoting an early inflammatory response (135), a mechanism that could be relevant in both the immunologically naive and the latently infected host. Just as during the initial infection, FcR-mediated phagocytosis could also play a role in maintaining control over Mtb infection. This function would likely play a role when Mtb has left it's predominantly "dormancy" state but has not yet reached a sufficient burden to cause disease. At this level, it would also be critical whether Abs function as pro- or anti-inflammatory proteins (reviewed in (15, 16)), which would depend on their ability to activate certain FcR with different beneficial or potentially harmful effects depending on the immune competency of the host.

Role of humoral immunity in improving disease manifestations

During disease, considerable amounts of Mtb are located in the extracellular space, especially in cavities and necrotic lesions (136, 137), and thus Abs could improve disease manifestations through their capability for FcR-mediated phagocytosis and killing of Mtb. Abs could further promote clearance of immunomodulatory antigens, such as polysaccharides and lipopolysaccharides which can hinder the development of an efficient immune response. Importantly, since Abs can be pro- and anti-inflammatory depending on their isotype and the type of receptor that they interact with (reviewed in (21)), the effect of Abs on disease manifestations could be very different depending on the type of Ab present. The damage-response framework posits that host damage is a function of the immune response producing a U-curve (138). Evidence supporting this view in animal models comes from experiments in zebra fish showing that control of mycobacterial infection requires the right balance between too little and tissue-damaging immune responses (139). Similar, in experimental Mtb infection of mice excessive pulmonary accumulation of the innate myeloid-derived suppressor cells resulted in TB lethality while targeted depletion ameliorated disease (140). In humans, such concept is supported by the beneficial effects of withdrawing anti-inflammatory drugs such as corticosteroids or TNF-alpha blocker in disease associated with drug-induced immunosuppression (141, 142) while such anti-inflammatory drugs are beneficial in disease manifestations associated with a profound and potentially fatal inflammatory response such as tuberculous pericarditis, pleurisy, meningitis, or pulmonary cavities (reviewed in (143-146). In this construct pro-inflammatory Abs are likely to be helpful to individuals with insufficient tissue response while the same Abs could be deleterious to individuals mounting a strong tissue response. Conversely, anti-inflammatory Ab responses could be helpful in down-regulating the florid tissue-damaging inflammatory response that accompanies pulmonary infection and produces the classical lesions of casseous necrosis. By this hypothesis such Abs would protect through reduced inflammation that in turn could promote clearance of mycobacteria from tissues and reduce person-to-person spread by preventing cavity formation. However, anti-inflammatory Ab responses would be expected to be deleterious in individuals with weak tissue responses, such as observed in milliary tuberculosis where an inadequate tissue response results in a high mycobacterial burden. Influencing the inflammatory balance will likely be particularly complex in certain forms of disseminated TB such as TB meningitis. This form of extrapulmonary TB results from hematogenous spread of Mtb likely due to a

lack of sufficient immune and inflammatory response which could be worsened by anti-inflammatory effects, and yet steroids are presumed to be beneficial by reducing the sequelae of the local inflammatory response and have shown to reduce mortality (147-149). At this time we do not understand enough about the effects of Ab on the inflammatory response to predict if certain patients would benefit from specific immunomodulating Abs. Such knowledge and understanding would be especially critical when considering and developing post-exposure and therapeutic vaccines, as well as adjunctive Ab-based therapy, an approach that has been successful in other infectious and respiratory diseases such as those caused by *Pseudomonas aeroginosa* (150-152) and respiratory syncytial virus (153, 154), and might offer an alternative for difficult to treat multi-drug resistant TB cases.

View of Relevance for Abs in TB Vaccine and Treatment

The complexity of the mycobacterial pathogenesis, which involves intracellular and extracellular phases together with strong inflammatory responses that can contribute to tissue damage suggest that successful defense requires a layered approach where the various components of the immune system work synergistically to control the infection. Given the numerous observations that both Abs and B cells can contribute to host defense it is reasonable that future vaccine strategies include the goal of eliciting protective Ab responses in addition to inducing T cell immunity. In fact, it is possible that BCG vaccination mediates its modest protective effects by eliciting both T and B cell responses. Evidence for the importance of the B cell component comes from the observations that BCG was not effective in eliciting protective responses against Mtb in B cell-deficient CBA/xid mice (115). Furthermore B cells may also contribute by enhancing the T cell response given that these were impaired in when B cell-deficient μMt mice were vaccinated with BCG. Consequently there are both theoretical and experimental reasons to support the development of new vaccines that simultaneously elicit protective B and T cell responses including protective Abs. Since effective humoral responses require Abs of certain specificity and isotype it will be important that future vaccines include epitopes known to elicit protective Abs. Given the antigenic complexity of mycobacteria it is possible that for the full expression of Ab-mediated protection vaccines will need to elicit responses to multiple epitopes, such that those Abs can function in cooperative and synergistic manner. This has recently been demonstrated for HIV, where a broad diversity of neutralizing Abs has been isolated from HIV-infected patients with high Ab titers (155), and passive transfer of a combination of neutralizing Abs targeting different epitopes controlled HIV infection in humanized mice and SHIV infection in nonhuman primates more effectively that single Ab transfer (156, 157). One of the probably most promising targets to include in TB vaccines would be the mycobacterial capsular polysaccharide AM, as we and others have shown protection of mAbs targeting AM in passive transfer studies (61, 64), and have shown BCG comparable or superior protective efficacy of conjugate vaccines containing this antigen ((72) and Prados-Rosales, unpublished data).

Adjunctive Ab-based therapy would be another attractive option that could be particularly beneficial in difficult to treat TB cases. The benefit could lie in both improved cure rates as well as shortened therapy, and this approach might offer an attractive alternative for treating multi-drug resistant TB cases. Ab-based therapies are becoming more common, and have

led to major improvements in the treatment of several malignancies and autoimmune diseases (reviewed in (158, 159)). This approach has had a slow development in infectious diseases (reviewed in (160)), but is currently gaining more ground in the treatment of diseases such as those caused by *P. aeroginosa* (150-152) and respiratory syncytial virus (153, 154), and could potentially revolutionize the treatment of HIV (156, 157). Given the unpredictable heterogeneity of polyclonal serum preparations, Ab-based therapy in TB, just as for other infections, would most likely have to be based on mAbs. Another aspect to consider is that combinations of mAbs targeting different epitopes could enhance (or decrease) their efficacy against infections (161, 162). These emerging properties will have to be further taken into consideration and their careful evaluation will be critical when developing Ab-based therapy against TB.

Summary and Conclusions

The majority of the TB vaccine field considers CMI the essential or even sole component of the immune response necessary for the defense against Mtb infection. The contributory role of B cells and Abs in the protection against Mtb infection is less defined than the role of T-cells. However, this role has been established for many intracellular pathogens by now, and the evidence that Abs can play an adjunctive or synergistic role with cellular immunity is a fact that should be considered in development strategies for TB vaccines and other immune-based interventions. The diversity of Ab functions, the complex interplay between B-cells and other immunocytes, the limitations of animal models, and the heterogeneity of the human humoral immune response to Mtb pose major challenges to decipher the parts of the various immune arms and their specific balance relevant for optimal protection at each stage of infection. Therefore, further studies of B cell and Ab functions in the defense against Mtb, their influence on the pathogenesis of the various states of infection, and their role in the outcome of mycobacterial infections are urgently needed.

Acknowledgements

This work was supported by funds from the National Institute of Health (NIH)/National Institute of Allergy and Infectious Diseases (NIAID; AI-096213 to J.M.A., AI-063537 and AI-094745 to J.C., and AI-033774, AI-052733, AI-033142 to A.C.) and the National Heart, Lung, and Blood Institute (NHLBI; HL-059842 to A.C.), the Center for AIDS Research (CFAR) at the Albert Einstein College of Medicine (AI-51519; J.M.A.), the Aeras TB vaccine foundation (J.M.A. and A.C.) and the Food and Drug Administration (FDA; 1U18 FD004012/01 to J.M.A.). A.C. is also the recipient of a Bill & Melinda Gates Grand Challenge award and TB Vaccine Accelerator Program award. We thank Tingting Chen for her graphic assistance with the figure.

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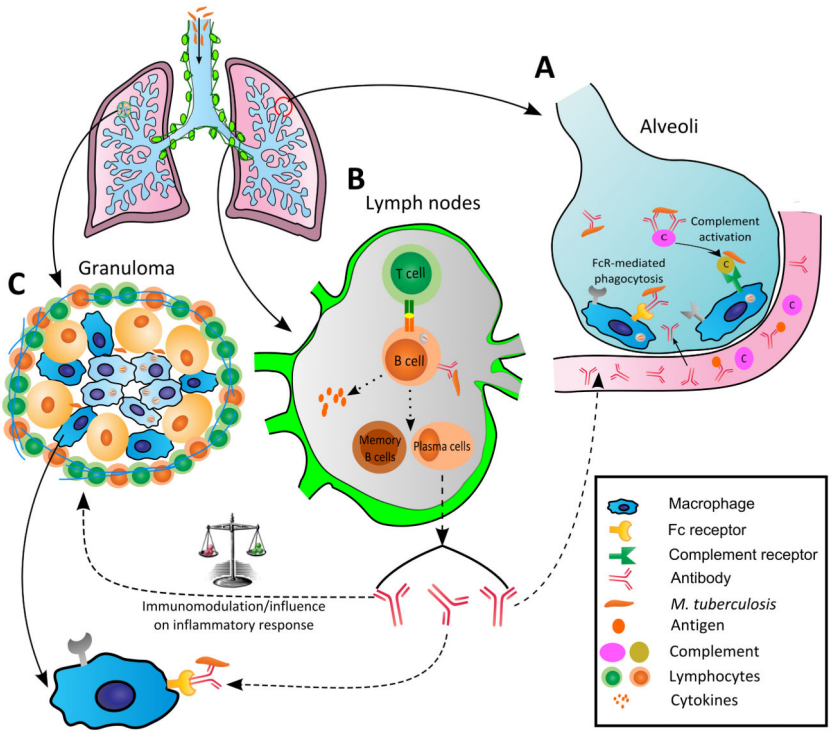

Fig. 1.

Scheme showing the pathogenesis of tuberculosis and steps where antibody (Ab) and B cells could conceivably provide protection based on literature reports of B cell and Ab action against *M. tuberculosis* (Mtb) infection. A) Ab could potentially affect the outcome of infection in the alveolar space through opsonization, complement activation, and FcR-mediated enhanced Mtb phagocytosis and killing. Ab could contribute defense mechanisms at the alveolar level during the initial state of infection when inflammation would increase serum permeability and allow the transfer of Abs and complement into the alveolar space; B) B cells located at the germinal center of lymphoid organs could play a role in the defense against infection through i) their function as antigen presenting cells and activation of T cells, ii) production of cytokines that could influence the development of the T helper response, and iii) production of Abs which could modulate various aspects of the innate and adaptive immune response, and clear immunomodulatory Mtb antigens by forming immune complexes; and C) Influence of B cells and Ab on the Abs on the inflammatory response, FcR-mediated phagocytosis and killing of extracellular Mtb within the cavity. Ab could affect granuloma formation through its intrinsic pro- and anti-inflammatory effects. Formation of better organized granulomas in the presence of Ab could potentially translate into reduced dissemination and local control of infection.

Table 1

A selection of studies demonstrating a role for B cells and antibodies in the protection against intracellular pathogens

Pathogen	Disease	Mechanisms & Effects	Ref
Gram negative bacteria			
Salmonella enterica serovar Typhi	Typhoid	Live oral vaccine is protective against typhoid in humans and induces anti-LPS IgG that correlates significantly with increased opsonophagocytosis of *S. enterica*	(25)
Neisseria meningitidis	Meningitis	Nasal vaccination of mice with surface exposed protein NadA of *N. meningitidis* serotype B induces strong cellular responses (Th1&Th2) and bactericidal Abs in the respiratory tract	(41)
Yersinia pestis	Plague	mAb against LcrV promotes PMN phagocytosis of *Y. pestis*	(26)
		Protection of mice against pneumonic plague by intranasal vaccination with inactivated *Y. pestis* is partially dependent on FcRs and can be transferred to naive mice with immune sera	(27)
		Vaccine induced antibodies against *Y. pestis* antigens F1 and LcrV protect mice against pneumonic plague	(28, 29)
Ehrlichia chaffeensis	Ehrlichiosis	MAb against an outer membrane protein of *E. chaffeensis* protects mice against *E. chaffeensis* infection	(31)
Brucella abortus	Brucellosis	MAb targeting a polysaccharide protects mice against *B. abortus* infection, likely through macrophage killing of opsonized *B. abortus*	(34)
Coxiella burnetti	Q fever	Ab against Coxiella membrane protein/invasin OmpA inhibit internalization of Coxiella by non-phagocytic cells	(35)
		mAb against Coxiella phase I lipopolysaccharide protects mice against Coxiella infection by increasing macrophage phagocytosis via FcR	(36)
Francisella tularensis	Tularemia	Intranasal immunization of *F. tularensis*-mAb immune complexes enhances IgA production, protects mice against infection, and is FcyR dependent	(163)
		MAb opsonizes F. tularensis and leads to FcR-dependent enhancement of T cells and dendritic cells	(121, 164)
Legionella pneumophilia	Legionnaire's disease/pneumonia	Engagement of FcR by Abs results in lysosomal fusion	(38)
		Mice immunized with single B cell antigens or antigen combinations were protected against *L. pneumophilia* infection	(39)
Chlamydia ssp.	Trachoma, urethritis, pelvic inflammatory disease, lymphogranuloma venerum, pneumonia	IgG2a and IgA enhance rapid Th1 response via FcR	(165)
		Abs enhance Th1 activation	(42)
		Vaccination of koalas with chlamydial outer membrane protein induces specific neutralizing antibodies, and protects koalas against infection by eliciting strong cellular and humoral immunity	(43)
Gram positive bacteria			

Pathogen	Disease	Mechanisms & Effects	Ref
Listeria monocytogenes	Meningitis, gastroenteritis, sepsis	MAb against listeriolysin O reduces intracellular growth of *L. monocytogenes* and blocks passage from phagosome to cytosol	(45)
Fungi			
Cryptococcus neoformans	Meningitis, pneumonia	IgG1 mAb against the capsular polysaccharide GXM of *C. neoformans* enhanced granulomatous inflammation in the lungs of *C. neoformans* infected mice, prolonged survival and reduced CFU	(166)
		IgG switch variants of an mAb against the GXM protect mice against *C. neoformans* independent of complement	(167)
		MAb against GXM induces increases of granulocytes among lung leukocytes, cytokine responses and may function by down-gegulating the inflammatory response in *C. neoformans* infected mice	(168)
		MAb against *C. neoformans* inhibits the release of capsular antigen	(169)
		Human IgG2 & IgG4 but not IgG1 & IgG4 protect mice against *C. neoformans* infection in passive transfer studies	(170)
		Binding of mAb against GXM to *C. neoformans* alters gene expression and modulates fungal metabolism	(94)
		Binding of protective mAbs against GXM impairs yeast budding	(171)
Histoplasma capsulatum	Histoplasmosis	MAbs against a surface protein of *H. capsulatum* protect mice against *H. capsulatum* infection and were associated phagocytosis and lung cytokine levels	(46)
		Opsonization of *H. capsulatum* with mAb against a surface protein reduced the ability of *H. capsulatum* to regulate the phagosomal pH and resulted in more efficient T cell activation	(47)
Parasites			
Plasmodium falciparum	Malaria	Passive transfer of mAbs and imune sera inhibit liver-stage infection of *P. falciparum* in mice	(51)
		Vaccination with a fusion protein of circumsporozoite induces Ab-mediated protection against malaria in mice	(50)
		Introduction of genes encoding the mAb against the surface circumsporozoite protein protected mice against malaria	(49)
Leishmania major	Leishmaniasis	IgE immune complexes via binding to the FcεRII-CD23 promote killing of *L. major* by inducing nitric oxide synthase in human macrophages	(55)
L. amazonensis		B cells promote macrophage killing of *L. amazonensis*	(54)
		Non-specific IgG2a soluble immune complexes activate infected macrophages via the FcRy-common chain to kill of *L. amazonensis* in a NADPH oxidase dependent process	(53)
Toxoplasma gondii	Toxoplasmosis	B cell deficient mice are more susceptible to *T. gondii* infection that wild type mice and can be protected by passive transfer of immune sera	(56)
		IgE/FcεRII-CD23 mediated killing of intracellular *T. gondii* by human macrophages	(57)

mAb: monoclonal antibody

Table 2

Supporting data for a role of humoral immunity in the defense against Mtb infection

Studies	Results	References
Passive transfer of mAbs and polyclonal IgG	MAbs against AM, LAM, HBHA, 16 kDa α-crystalin and MPB83 improve the outcome of mycobacterial infection in mice	(59-66)
	Human polyclonal IgG or homologous immune sera improve the outcome of mycobacterial infection in mice	(67-69)
	Transfer of immune sera from Mtb-infected mice reverses tissue neutrophilia in B cell deficient mice with TB	(114)
High Ab titer associated with reduced susceptibility	AM-containing conjugate vaccine elicits Ab response that reduces susceptibility to infection	(72, 172)
	BCG as well as Mtb antigen-containing conjugate and DNA/RNA vaccines elicit cellular and humoral immune responses and improve outcome of infection	(71, 72, 172-181)
Increased susceptibility in hosts with deficits in humoral immunity	Peak of childhood TB is temporally correlated with nadir in maternal Ab	(182-184)
	Lack of Abs against certain mycobacterial antigens is associated with TB dissemination in children and adults	(70, 185-188)
	Lack of early humoral immune response in Mtb infected nonhuman primates predicts high likelihood for reactivation disease	(73)
	B cell deficient mice are more susceptible to TB	(74-76)
	Humans with pulmonary TB have lower peripheral blood B cell counts than subjects without or with Mtb infection but no disease	(116, 117)
	Polymeric IgR-deficient mice loose mycobacterial antigen-specific IgA response in saliva and are more susceptible to respiratory BCG infection	(79)
	IgA deficiency increases susceptibility to mycobacterial infection in mice	(77, 78)
Other	FcR-mediated phagocytosis promotes phagolysosomal fusion	(80)
	IgG bound to BCG enhances oxygen release in phagosomes and antimycobacterial activity of alveolar macrophages	(82)
	Existence of mycobactericidal Abs	(97)
	FcR-mediated phagocytosis increases macrophage Ca2+ signaling and intracellular killing	(81)
	Enhanced Mtb resistance of mice lacking the inhibitory FcγRIIB receptor is associated with a more robust polmonic Th1 response	(74)
	Optimal BCG-induced Th1 response	(114)

Studies	Results	References
	requires B cells	
	Higher FcyRIA expression in i) subjects with TB compared to LTBI; and ii) subjects pre compared to post antituberculous treatment	(86) (87)

mAb: monoclonal Ab; AM: arabinomannan; LAM: lipoarabinomannan; HBHA: heparin-binding haemaglutinin; Mtb: *M. tuberculosis*; Table modified and updated with permission from Achkar and Casadevall (15)