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Macrophages and control of granulomatous inflammation in tuberculosis

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The granuloma that forms in response to *Mycobacterium tuberculosis* must be carefully balanced in terms of immune responses to provide sufficient immune cell activation to inhibit the growth of the bacilli, yet modulate the inflammation to prevent pathology. There are likely many scenarios by which this balance can be reached, given the complexity of the immune responses induced by *M. tuberculosis*. In this review, we focus on the key role of the macrophage in balancing inflammation in the granuloma.

INTRODUCTION

Tuberculosis remains a serious health threat worldwide. There were 9.4 million new cases of tuberculosis and 1.7 million deaths in 2009.[1] Although this disease can be cured by drug treatment, the regimens involve several drugs and at least 6 months of therapy; obstacles to treatment include timely diagnosis, access to health care, compliance, side effects, and drug interactions. A vaccine, BCG (Bacillus Calmette-Guerin), which is an attenuated *Mycobacterium bovis* strain, has been used for nearly a century, but efficacy against adult disease is questionable. In fact, most of the deaths from tuberculosis occur in countries where BCG vaccination of infants is routine.[1] Clearly, better diagnostic, preventive, and therapeutic strategies are necessary to gain control of this disease.

Tuberculosis is caused by *Mycobacterium tuberculosis* (Mtb). This bacterium has a complex cell wall, composed of long-chain fatty acids, glycolipids, peptidoglycan, and proteins, and a slow doubling time (18–24 h). It is primarily a respiratory pathogen, and usually transmitted by the cough of a person with active disease. Primary tuberculosis can occur within the first year or so after exposure, and is the result of an uncontrolled initial infection. This could be because of an extremely virulent bacillus, large or repeated exposures, an immune response that is insufficient to control bacterial replication, or the induction of excessive pathology. The majority (90%) of infected humans effectively contain, but do not eliminate, the bacteria and are defined as having "latent" infection. This is a clinical term, meaning a person is infected (as evidenced by T-cell reactivity to mycobacterial antigens) but is asymptomatic and not contagious. However, a latently infected human has a 10% lifetime risk of reactivating the infection and presenting with active tuberculosis. Thus, the estimated 2 billion latently infected humans are an enormous reservoir of potential disease.

The factors that lead to containment of infection or progression to disease are not well understood and are multifactorial. Typically, tuberculosis presents as pulmonary disease, but with systemic manifestations, including anorexia and wasting. The old name for tuberculosis was "consumption," as this disease appears to consume the patient. The wasting is partly because of production of inflammatory cytokines, such as tumor necrosis factor (TNF), known to cause cachexia.[2,3] Thus, the disease is driven by host and mycobacterial factors. A new complication in the setting of human immunodeficiency virus/Mtb co-infection also points to inflammation as an important contributor to tuberculosis: antiretroviral therapy that restores CD4 T-cell responses can occasionally have the paradoxical effect of unmasking or reactivating tuberculosis.[4–6] This immune reconstitution inflammatory syndrome also supports that modulation of inflammation may be an essential component of management of tuberculosis.

We hypothesize that the balance of pro- and anti-inflammatory immune responses at the site of infection (the granuloma) is crucial to control of infection. Although there are numerous inflammatory mediators in tuberculosis, a key cell in the granuloma is the macrophage. Here, we focus on the macrophage as a major player in the balance of inflammation in the granuloma, necessary for inhibiting bacterial replication and for control of pathology.

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INITIATION OF INFECTION

Transmission occurs when droplet nuclei of Mtb expectorated via cough from someone with active tuberculosis are inhaled. The battle between pro- and anti-inflammatory signals begins in the airways with the initial contact of bacillus with host cells. Ingestion of intracellular bacteria by airway antigen-presenting cells (macrophages and dendritic cells) initiates the first important immune responses. Mtb induces proinflammatory cytokines interleukin (IL)-12, IL-1β, and TNF (reviewed in ref. 7). IL-12 plays a critical role in initiating a T helper 1 (TH1) T-cell response.[8] TNF induces cytokine and chemokine production by macrophages, activates macrophages for killing, and modulates macrophage apoptosis.[9–13] The anti-inflammatory cytokines such as IL-10 and TGF-β can also be produced by Mtb-infected macrophages, which downregulate proinflammatory cytokines and T-cell proliferation and activation, balancing the response between bacterial eradication and host survival.[7,14]

The alveolar macrophages, which line the airways, have been described as deficient in their interaction with Mtb;[15] however, most humans who encounter Mtb do not become infected (as determined by immunologic reactivity), suggesting that in fact, the cells in the airways are quite robust in deterring productive infection with this bacillus. Alveolar macrophages have been considered to be anti-inflammatory in nature,[15] which contributes to suppressing inflammation in the airways. How these cells, or other cells in the airways, are so successful at warding off infection, then, remains to be determined.

GRANULOMA FORMATION

After the encounter of bacillus and macrophage in the airways, the infected macrophage may facilitate the spread of disease first by cellular necrosis to disseminate extracellular bacteria and by migration to distal sites in the lungs. Once in the parenchyma, the bacilli set off a slow inflammatory process by infected macrophages. These infected macrophages recruit uninfected macrophages to ultimately form a granuloma.[16–18]

Dendritic cells in lungs or airways are also infected by Mtb, and migrate to thoracic lymph nodes, where a T-cell response is primed.[19] This process is quite slow; studies in various animal models suggests that priming of T cells does not occur until 12–21 days postinfection.[20–23] Pulmonary inflammation due to interaction of bacillus with macrophages and other cells results in recruitment of monocytes, neutrophils, and primed T cells and B cells to lungs, culminating in formation of a granuloma. A granuloma is an organized and structured collection of immune cells that forms in response to chronic antigenic stimulation, in the context of macrophage-mediated factors. The granuloma is the classic pathologic feature of tuberculosis, and functions both as a niche in which the bacillus can grow or persist and an immunologic microenvironment in which cells with antimycobacterial functions interact to control and prevent dissemination of the infection.

Granulomas are observed in active, latent, and reactivation tuberculosis. Thus, the mere formation of a granuloma is insufficient for control of infection—rather, the granuloma must be functioning properly. In active tuberculosis, the host often has numerous granulomas that are incapable of controlling infection; bacteria, either extracellular or within macrophages or dendritic cells, then spread throughout the lung or disseminate to other organs, initiating new granuloma formation. In latent infection, there are usually one or a few granulomas in lungs and lymph nodes, although our knowledge of the true nature of latent infection in humans is limited, and these granulomas are capable of limiting the growth and spread of Mtb. One of the major gaps in our understanding of tuberculosis is what factors define a "functioning" granuloma, i.e., the type of granuloma that eliminates or exerts long-term control over the infection. Based on the variety of immune responses shown to contribute to control or exacerbation of tuberculosis, we assume that multiple combinations of responses may constitute a functioning granuloma (**Figure 1**), and these likely differ among individuals and even among granulomas in a single individual.

Although granulomas are composed of a variety of cell types, the primary cellular component of the structure is the macrophage. The macrophage is the initiating cell for granuloma formation[17,18] and the major cell type in most granulomas. Macrophages both harbor the majority of Mtb and have the effector functions to kill these bacilli. There are a variety of macrophage phenotypes in granulomas with various functions, including antimycobacterial effector mechanisms, pro- and anti-inflammatory cytokine production, and secretion of chemokines and proteins associated with tissue remodeling. Thus, this cell contributes to most aspects of inflammation and control of infection within the granuloma. This review will focus on the roles of the macrophage in promoting or controlling inflammation in tuberculosis granulomas, directly and through its interaction with other cells in the granuloma.

A VARIETY OF GRANULOMA TYPES IN HUMAN TUBERCULOSIS

In humans, a spectrum of granulomas is observed in active tuberculosis and even latent infection. The classic granuloma in tuberculosis is the caseous granuloma, so called because the center of this granuloma has a "cheese-like" appearance grossly. Histologically, this granuloma consists of epithelioid macrophages surrounding an acellular necrotic region, with a lymphocytic cuff, comprising both B and T cells.[24] Neutrophils can also be observed within caseous granulomas. Caseous granulomas can range in size from 1 mm to >2 cm. In chronic or latent infection, this type of granuloma can become calcified, with the calcification process beginning within the caseous center. A calcified granuloma generally represents a successful immune response and is associated with fewer inflammatory cells than other granulomas. Other types of granulomas include non-necrotizing granulomas, composed primarily of macrophages with a few lymphocytes, necrotic neutrophilic granulomas, and completely fibrotic granulomas. Peripheral fibrosis can be observed in some caseous granulomas. With all of these granulomas types, it is easy to imagine several microenvironments within and among granulomas for the microbe, as well as a range of immune microenvironments.

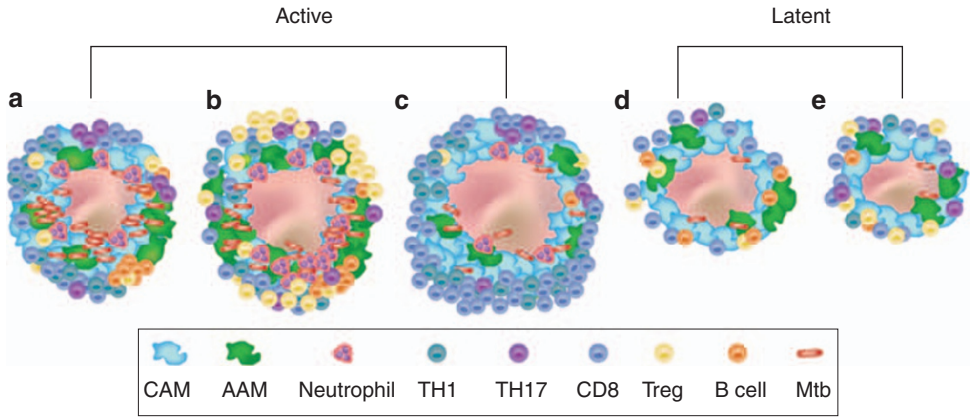

Figure 1 Balance of responses in the granuloma dictate bacterial control and pathology. There are a variety of combinations that can lead to an inflammatory granuloma in active tuberculosis (TB). Three possibilities are shown: (**a**) Active granuloma with high bacterial numbers, many classically activated macrophages (CAMs) and alternatively activated macrophages (AAMs), T helper 1 (TH1) cells, some neutrophils, and few regulatory T cells (Tregs). (**b**) Active granuloma with too many Tregs, AAMs, not enough TH1 and CAMs, high neutrophils, and high bacterial load. (**c**) Active granuloma with fewer bacilli, but overabundance of CAMs and TH1 cells, and not enough Tregs. Two possible latent granulomas are shown, although there are likely many combinations. (**d**) Latent granuloma with CAMs and AAMs in balance, with relatively few T cells. (**e**) Latent granuloma with more Tregs to balance the higher TH17 and TH1, but a balance of AAMs and CAMs.

TUBERCULOSIS MODEL SYSTEMS

Tuberculosis is a human disease, but obtaining lung tissue (with granulomas) from people with tuberculosis is difficult. Thus, animal model systems are necessary for detailed studies of tuberculosis. Mice develop a chronic, progressive infection with Mtb; the granulomatous infiltration in lungs lacks the structured and organized appearance of human granulomas.[25] There have been reports of mouse strains developing granulomas that more closely represent human lesions,[26] and these may be useful for a focused approach to granuloma biology in a system that is rich in reagents. In Guinea pigs and rabbits, some granulomas are more human-like and studies in these species have yielded important insights on the development and structure of granulomas.[25] Infection of zebrafish with *Mycobacterium marinum*, an aquatic mycobacterial species, recapitulates a human caseous granuloma.[27] Studies in zebrafish embryos have allowed dynamic observation of granuloma formation and spread,[16–18] and the use of genetic tools has enabled dissection of some of the factors important in granuloma formation and maintenance.[9,28] Non-human primates (primarily macaques) have been used as models for human tuberculosis.[21,29–33] A full spectrum of granuloma types identical to human granulomas can be observed in Mtb-infected macaques, and immunologic tools are available for this model. Finally, computational models of granulomas provide the unique ability to study factors involved in tuberculosis that are not possible to study in experimental systems.[12,34] Here, we draw on data from all the model systems in our discussion of granulomas in tuberculosis.

CLASSICALLY AND ALTERNATIVELY ACTIVATED MACROPHAGES IN TUBERCULOSIS

Monocytes migrate to the site of infection from blood, in response to inflammatory signals (cytokines and chemokines) that are often produced by macrophages as well.[12] Only a fraction of macrophages in the granuloma are actually infected with Mtb, although this proportion is likely to be higher in a granuloma that is poorly functioning and not controlling the infection. It is difficult to estimate the fraction of cells infected in human granulomas, or the number of bacilli per cell because acid-fast staining for the microbe is notoriously inefficient in human and non-human primate tissues. Nonetheless, we consider the macrophage populations to consist of both infected and uninfected cells, both of which can be influenced by other factors (cells and soluble factors) in the granuloma. Mtb can have effects on macrophages from within by interacting with host receptors, such as Toll-like receptors in the phagosome.[35–42] It has been suggested that under some circumstances Mtb can escape the vacuole to reside in the cytoplasm,[43,44] and that mycobacterial molecules can exit the phagosome and interact with cytoplasmic receptors to induce responses.[45–48] Mycobacteria and microbial factors can interact with cells from the outside as well, again through Toll-like receptors or other receptors. The variety of cytokines induced by interaction of Mtb with macrophages can then act on other cells within the granuloma, including macrophages, to induce various functional and phenotypic changes in cells that then modulate the environment of the granuloma.

In recent years, the complexity of macrophage populations has gained appreciation.[49,50] For ease of discussion, macrophages differentiated in response to cytokine signals have been termed either classically activated macrophages (CAMs) or alternatively activated macrophages (AAMs).[49–52] CAMs arise in response to TH1 T-cell signals (interferon-γ and TNF). These macrophages produce proinflammatory cytokines (TNF and IL-12) and chemokines and are capable of killing bacilli; in mice, a marker for CAM is inducible nitric oxide synthase (iNOS). iNOS uses arginine as a substrate for production of nitric oxide that can kill Mtb. In mice, iNOS is essential for control of Mtb infection.[53–55] iNOS expression in human tuberculous lung macrophages has been reported,[56,57] and we have detected iNOS expression

in macrophages in macaque granulomas (J.T. Mattila and J.L. Flynn, personal communication).

AAMs are anti-inflammatory in nature, and were initially described as arising in response to TH2 cytokines IL-13 and IL-4.[50,51] These macrophages can produce IL-10, TGF-β, and IL-6. In a TH2 environment, induction of the AAM phenotype is STAT-6 (signal transducer and activation of transcription 6) dependent.[51] There are a set of genes and proteins used to characterize AAMs, with the primary marker being arginase.[51] Arginase also uses arginine as a substrate and directly competes with iNOS for arginine, making the relative expression of these genes in a macrophage an important balancing feature for whether the macrophage will be pro- or anti-inflammatory, and directly affects the ability of a macrophage to kill Mtb (**Figure 1**).

There are several recent studies of AAMs in tuberculosis. Unlike parasitic and worm diseases, or asthma, where AAMs have been predominantly studied, tuberculosis induces a TH1-mediated immune response. It is difficult to measure IL-4 or IL-13 in tuberculous granulomas, and interruption of these genes in mice has little effect on Mtb infections, although there are a few reports that these cytokines can interfere with adequate control of tuberculosis.[58–60] The generation of AAMs in tuberculous (TH1) granulomas appears to have a different mechanism. Mtb induces arginase (*Arg1*) gene expression in a MyD88-dependent but STAT-6-independent fashion in murine macrophages.[36] This *Arg1* induction by mycobacteria was mediated by Toll-like receptor-induced IL-6, IL-10, and granulocyte colony-stimulating factor production by macrophages.[61] However, only a subset of AAM markers were induced by these cytokines, suggesting perhaps an intermediate AAM phenotype compared with a TH2 environment. Other studies using a mouse that overexpressed IL-10 from macrophages supported that IL-10 can strongly induce arginase expression in the lungs of Mtb-infected mice.[61] The latter study also suggested that IL-10 enhanced the sensitivity of macrophages to IL-4, exacerbating induction of AAMs even in the presence of very low IL-4 levels, as might occur in a granuloma. These mice had higher numbers of Mtb in the lungs, which was correlated with increased AAMs. Mice lacking arginase specifically in macrophages controlled Mtb infection better than wild-type mice, and *Arg1* −/− macrophages had enhanced iNOS expression and increased killing of Mtb *in vitro*. Thus, although Mtb appears to have a different mechanism for induction of arginase than a TH2-mediated disease, arginase and AAM appear to inhibit control of Mtb infection.

Some studies have suggested that alveolar macrophages are inherently alternatively activated, and may allow Mtb bacilli to gain a foothold immediately upon entering the airway, as they are impaired in their ability to kill bacilli.[15] Gordon and Martinez[51] have suggested that true AAMs require a signal of "activation" to attain the qualities of AAMs, and hence although alveolar macrophages before infection are not classically activated, they may not be true AAMs, either. There is clearly a spectrum of activation for macrophages, and incompletely activated cells may possess some but not all qualities of AAMs or CAMs, depending on the local cytokine environment.

BACTERIAL KILLING VS. PATHOLOGY: BALANCE OF RESPONSES IN THE GRANULOMA

The battle for control of Mtb infection occurs in granulomas, and the mechanisms that contribute to bacterial killing can also contribute to pathology. Excessive pathology also results in disease exacerbation. With a focus on macrophages, one can consider the balance of CAMs and AAMs to be crucial to the successful granuloma (**Figure 1**). Whereas CAMs are required for killing bacilli, the production of proinflammatory mediators and the continued recruitment and stimulation of T cells can lead to tissue damage and poor resolution of granulomas. Conversely, mouse data suggest that a granuloma with a substantial representation of AAMs would impair killing of bacteria, even while dampening inflammation and T-cell proliferation. The balance of CAMs and AAMs in a granuloma may be necessary to control infection and tissue damage. It also may be that CAMs and AAMs are spatially located differently in the human granuloma and play both roles—microbial killing and T-cell recruitment and activation where bacteria are more plentiful and downregulation of the T-cell environment where necessary to prevent tissue damage. Changes to location or numbers of macrophage types could affect the balance of the granuloma and lead to increased pathology or decreased bacterial killing (**Figure 1**). Location differences would not be apparent from the murine studies, as these granulomas have little of the organized structure of human granulomas.

WHAT FACTORS MIGHT CONTRIBUTE TO THE BALANCE OF AAM AND CAM?

Macrophages can differentiate in response to many factors, including cytokines, direct cell-to-cell contact with T cells, antibodies from B cells, and microbial factors (interacting through pattern recognition receptors). These factors in aggregate likely affect the balance of inflammation in a single granuloma. Because the factors that control inflammation are dynamic, each granuloma in a host could act independently in terms of inflammation and bacterial numbers; data from the macaque model supports this (P.L. Lin and J.L. Flynn, unpublished data).

T cells

T-cell responses are primary players in the inflammatory balance in the granuloma.[62,63] This includes cytotoxic T cells (which can kill infected cells), TH1 T cells that produce combinations of IL-2, interferon-γ, and TNF,[64] TH17 cells producing IL-17, and regulatory T cells (Tregs) that can produce IL-10 or TGF-β and inhibit proliferation and cytokine production by other cells. It is not clear what controls the balance of T cells within a granuloma, and how dynamic the changes are over the course of infection. There is a strong TH1 response in most people infected with Mtb, regardless of whether they develop active disease or latent infection. Recent intriguing data demonstrated that the immunodominant T-cell epitopes are conserved in Mtb strains,[65] leading to speculation that it is to the advantage of the bacillus to induce strong T-cell responses. Mtb heat-shock protein 70 can interact with the CD40 receptor on dendritic cells, leading to increased IL-12 production and TH1 responses,[66] again supporting that

Mtb has evolved mechanisms for driving strong T-cell responses.[67] Robust T-cell responses are linked to cavitary disease,[68–70] a form of tuberculosis in which a granuloma is in direct contact with an airway, allowing bacteria to be more easily transmitted to a new host. Thus, regulation of TH1 responses may be necessary for optimal control of the infection and pathology.

TH17 responses in mice precede a strong TH1 response in the lungs, and increased TH17 cells can lead to enhanced recruitment of TH1 cells.[71–73] This appears to be important in vaccine-induced control of Mtb in mice,[73] but the long-term role for TH17 cells in inducing or recruiting TH1 cells, and the effect this may have on the inflammatory balance in the granuloma in humans is not known. IL-17 also contributes to neutrophil recruitment in other systems, and neutrophils can increase the inflammatory nature of a granuloma. Excessive neutrophils have been implicated in active tuberculosis in humans.[74] The data for the importance of TH17 cells in human tuberculosis are scarce so far (reviewed in ref. 75); BCG immunization does induce both TH1 and TH17 cells,[76] but whether these are necessary for protection or contribute to pathology is not clear.

CD4 + Foxp3 + Treg cells are important contributors to dampening inflammation. These cells are present in the granuloma of humans, non-human primates, and mice.[77–79] The loss of Foxp3 + Tregs in mice leads to higher bacterial loads.[79] However, modulation of the Treg population in certain mice leads to increased mortality because of enhanced inflammation in the lungs.[80] Tregs are good candidates for balancing immune responses through their interactions with T cells and necessary for preventing autoimmune diseases. Although Tregs are often only considered in their capacity to downregulate effector T-cell responses, and therefore exacerbate the infection, in chronic or persistent infections, these cells may be crucial players in preventing pathology. In macaques, Tregs rapidly left the blood and appeared in the airways following Mtb infection.[78] Surprisingly, those monkeys with high levels of Tregs in blood before infection (presumably resulting in higher levels in lungs postinfection) were more likely to develop latent, rather than active tuberculosis. Thus, these cells may modulate the granuloma environment, and downregulate inflammation, which somehow contributes to the success of the granuloma in containing the infection (**Figure 1**).

The importance of regulating the T-cell response to control granulomatous inflammation is also demonstrated by the phenotype of programmed death-1 (PD-1) knockout mice. PD-1 is an exhaustion marker for T cells and engagement of PD-1 inhibits T-cell responses. In PD-1-deficient mice, the effector CD4 T-cell response was substantially enhanced, but the mice succumbed quickly because of increased pathology and higher bacterial load.[81,82] The mechanisms by which this occurs in the PD-1 knockout mice are not clear, and may be because of enhanced necrosis in the lungs due to strong T-cell responses, providing the right environment for robust growth of the bacilli. These data support that increased CD4 TH1 cells do not necessarily enhance control of infection, and that the lack of regulation of T cells by several different mechanisms exacerbates pathology.

B cells

B cells are a major cellular component of granulomas in humans, non-human primates, and mice infected with *Mtb*[83–86] (J.L. Flynn, J. Chan and J. Phuah, unpublished data). In *Mtb*-infected mice, B cells constitute 5–7% of total leukocytes present in lungs.[84] They form discrete aggregates suggestive of tertiary lymphoid tissues with features of germinal center B cells,[87,88] which are in close proximity to macrophages[84] (**Figure 1**). Emerging evidence in mice indicates that B cells are required for optimal immunity against *Mtb*, modulating susceptibility, cytokine production, histopathology, neutrophilic infiltration, as well as T-cell responses.[89] How B cells regulate the immune response to *Mtb* is just beginning to be addressed. B cells can produce antibodies, cytokines, and present antigens,[89] which potentially regulate other immune cells in the granuloma in a direct or indirect fashion. In particular, the macrophage is subject to regulation by B cells.

There are B-cell subsets with distinct immunologic function,[90–92] including signature cytokine profiles, much like in the T-cell TH1/TH2 paradigm.[90,92] The functional relevance of the different cytokine profiles is underscored by the ability of distinct effector B-cell subsets to bias the development of T cells along the TH1 or TH2 lineage.[90,92] In infectious diseases model, AAM macrophages are conducive to persistence of certain pathogens.[93] Recently, B1 cells, a subset of B lymphocytes, have been shown to promote the polarization of macrophages to a unique phenotype, including upregulation of IL-10 production, downregulation of TNF, IL-1β, and CCL3 (chemokine (C-C motif) ligand 3), as well as expression of typical AAM markers such as *Ym1* and *Fizz1*.[94] The key factor mediating polarization is IL-10.[95] It is possible that by regulating macrophage functions, B cells can affect immune responses to the tubercle bacillus.

By virtue of their ability to produce antibodies, B cells are requisite to formation of immune complexes with potent immunoregulatory roles. For example, ligation of Fcγ receptors (FcγRs) on macrophages by immune complexes can have remarkable immunological effects. Ligation of FcγRs by antibody-coated *Leishmania* results in increased IL-10 and decreased IL-12 production by macrophages,[96] enhancing leishmanial growth in macrophages. As a result, the phenomenon has been termed "antibody-dependent enhancement (ADE) of microbial infection."[96] ADE was originally observed in viral pathogens, most notably the Dengue virus,[97–101] and can be dependent on the nature of the immune complex.[102] Whether ADE is applicable to *in vivo Mtb* infection, where immune complexes are known to exist,[103,104] remains to be determined. Plasma cells, B cells that produce large quantities of antibodies, are found in macaque granulomas (J. Phuah and J.L. Flynn, unpublished data). Mice infected with monoclonal antibody-coated *Mtb* displayed improved outcome.[105] The FcγRIIB-deficient knockout strain has increased control of *Mtb* infection, concomitant with an enhanced Th1 T-cell response.[106] Furthermore, although immune complex engagement of activating FcγR has been reported to a major mechanism underlying IL-10-enhancing ADE, immune complex-treated Mtb-infected FcγRIIB knockout macrophages produce enhanced IL-12p40.[106]

Thus, through antibody production, B cells can modulate host immune responses by different mechanisms, one of which could be regulation of macrophage via FcgR engagement with immune complexes.

Through antibody production and modulation of macrophages, modulation of T cells,[89,91] as well as direct cytokine production, B cells have the ability to contribute to the inflammatory balance in the granuloma (**Figure 1**). Although neglected to date, the role of B cells in regulating the immune response during Mtb infection warrants further investigation.

CONCLUSIONS

Mtb orchestrates a complex set of immune responses in humans, with the most common outcome being lifetime control of the infection. However, when the balance of immune responses is disturbed, primary tuberculosis or reactivation of latent infection can occur. Here we explored the macrophage as a key mediator of inflammatory control in the granuloma, as it is the cell that interacts most frequently with the bacillus and the other key cells within the granuloma. Thus, it acts as the central control cell for events within the granuloma, dictating the outcome of infection. Strategies for modulating the macrophages may be useful in preventing disease, but must be approached carefully, as we do not understand the balance of cells and mediators necessary to kill bacilli, yet prevent lung pathology. These are important areas for further study.

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DISCLOSURE

The authors declared no conflict of interest.

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