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Cytokines and Chemokines in *Mycobacterium tuberculosis* Infection

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ABSTRACT Chemokines and cytokines are critical for initiating and coordinating the organized and sequential recruitment and activation of cells into *Mycobacterium tuberculosis*-infected lungs. Correct mononuclear cellular recruitment and localization are essential to ensure control of bacterial growth without the development of diffuse and damaging granulocytic inflammation. An important block to our understanding of TB pathogenesis lies in dissecting the critical aspects of the cytokine/chemokine interplay in light of the conditional role these molecules play throughout infection and disease development. Much of the data highlighted in this review appears at first glance to be contradictory, but it is the balance between the cytokines and chemokines that is critical, and the "goldilocks" (not too much and not too little) phenomenon is paramount in any discussion of the role of these molecules in TB. Determination of how the key chemokines/cytokines and their receptors are balanced and how the loss of that balance can promote disease is vital to understanding TB pathogenesis and to identifying novel therapies for effective eradication of this disease.

INTRODUCTION

Cytokines are soluble, small proteins that are produced by cells and act in a largely paracrine manner to influence the activity of other cells. Currently, the term "cytokine" describes proteins such as the tumor necrosis factor family, the interleukins, and the chemokines. Virtually every nucleated cell can produce and respond to cytokines, placing these molecules at the center of most of the body's homeostatic mechanisms (1). Much of our knowledge of the function of cytokines has been derived from studies wherein homeostasis has been disrupted by infection and the absence of specific cytokines results in a failure to control the disease process. In this context, infection with *Mycobacterium tuberculosis* has proven to be very informative and has highlighted the role of cytokines in controlling infection without promoting uncontrolled and damaging inflammatory responses (2–4). Herein, we focus on the key cytokine and chemokines that have been studied in the context of human TB using experimental medicine as well as *M. tuberculosis* infection of various animal models, including non-human primates (NHPs), mice, and rabbits. Perhaps the most important message of this review is that in a complex disease such as TB the role of any one cytokine cannot be designated either "good" or "bad" but rather that cytokines can elicit both protective and pathologic consequences depending on context.

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Why is TB such an informative probe allowing for detailed investigation of the function of cytokines and chemokines in immunity? One recent development in our understanding of TB stems from theories of coevolution between modern humans and *M. tuberculosis* (5). Evolutionary patterns based on genetic analyses suggest that *M. tuberculosis* and humans coexisted for tens of thousands of years in Africa but that, when humans left Africa and developed a more urban lifestyle, TB developed into a substantial health problem (6). During coevolution between humans and *M. tuberculosis*, *M. tuberculosis* likely evolved tools and stratagems with which to manipulate the human immune response to ensure effective transmission (7); this manipulation has been so successful that it is thought that over one-third of the world's population harbors some form of *M. tuberculosis* infection (8).

Two facts illustrate the focus of *M. tuberculosis* on manipulating the human immune response. First, *M. tuberculosis* is the major active constituent of complete Freund's adjuvant, which has been used for decades to stimulate long-lived cellular immune responses in vertebrate animals. Second, we have exploited the strong and sensitive T-cell-based inflammatory response to *M. tuberculosis* antigens as a skin test to indicate infection with *M. tuberculosis*. Thus, teleologically speaking, we may suggest that *M. tuberculosis* does not fail to induce immunity, it simply manipulates it such that its need to be transmitted is met. This manipulation occurs from the start of the human *M. tuberculosis* interaction when immune surveillance cells of the lung recognize danger through binding of their pattern recognition receptors to exquisitely refined *M. tuberculosis* pathogen-associated molecular molecules. It is this initial interaction that results in production of chemokines and cytokines, which then recruit and activate inflammatory cells (9). Following this initial interaction, bacteria migrate to the draining lymph node where they initiate (quite effectively) antigen-specific T cells that differentiate into cytokine-producing cells capable of expressing a variety of chemokine receptors that allow them to traffic away from the lymph node and into sites of tissue inflammation (7, 9). These antigen-specific T cells must then migrate via chemokine gradients, colocate with *M. tuberculosis*-infected phagocytic cells, and release cytokines that activate the infected cells to kill the *M. tuberculosis* (7, 9). If this induction of immunity is not met by *M. tuberculosis*, then the host dies rapidly with no effective transmission of the bacterium to further hosts.

The need for communication between cells both for efficient migration and for specific instruction during expression of immunity is where the critical role of cytokines and chemokines in controlling TB lies. Indeed, for the majority of those infected with *M. tuberculosis*, the efficient expression of immunity via competent cytokine and chemokine expression results in no sign of disease other than an ability to exhibit an inflammatory response to *M. tuberculosis* antigen (i.e., the skin test response). However, for *M. tuberculosis* to be efficiently transmitted, a degraded inflammatory lesion capable of delivering live bacteria to the airways must develop, and it is this evolutionary need that likely drives the development of the disease process in the lung. *M. tuberculosis* expresses molecules that promote inflammatory responses, which then need to be regulated to avoid tissue damage. If the bacterial burden is large or if the bacteria proliferate rapidly, then the coordination between cells mediated by cytokines and chemokines cannot occur quickly enough and immunity cannot be expressed, despite the presence of all of the required components. Understanding the functions and interactions between cytokines and chemokines is therefore critical to our attempts to limit TB. Herein, we discuss the roles of specific cytokines (Table 1) and chemokines (Table 2) in the context of *M. tuberculosis* infection and how they function to stop the development of TB, and also how they might contribute to the progression of disease.

CYTOKINES

Tumor Necrosis Factor Alpha

Tumor necrosis factor alpha (TNFα) is a cytokine that is released following activation of the immune system. Although it is primarily produced by macrophages, TNFα can also be secreted by lymphocytes, mast cells, endothelial cells, and fibroblasts (10). Because most cells exhibit responsiveness to TNFα, it is considered a major proinflammatory mediator. It is produced as a type II transmembrane homotrimeric protein (mTNF) that can become released into the extracellular milieu through the proteolytic action of TNFα-converting enzyme (TACE) (11). Soluble TNF (sTNF) exists as a 51-kDa trimeric protein that is unstable on reaching nanomolar concentrations (12), but which on binding to cognate TNF receptors (TNF-R) induces activation of proinflammatory responses mediated by NFκB, JNK, and p38, as well as promotion of apoptosis (10, 13–16). There are two TNF receptors, TNF-R1 and TNF-R2. Both TNF-R1, also known as CD120a and p55/60, and TNF-R2, also known as CD120b and p75/80, can

TABLE 1 The positive and negative roles of cytokines in TB

Cytokine	Receptor/signal	Role in TB
TNFα	TNFR1, TNFR2 JNK, p38, NFκB	Positive: Essential for survival following *M. tuberculosis* infection. Initiation of innate cytokine and chemokine response and phagocyte activation. Negative: Mediator of tissue damage.
IFNγ	IFNGR1, IFNGR2 JAK/STAT	Positive: Essential for survival following *M. tuberculosis* infection. Coordinates and maintains mononuclear inflammation. Expressed by antigen-specific T cells. Negative: Potentially pathogenic.
IFNα/IFNβ	IFNAR1, IFNAR2 JAK, TYK, ISG, ISRE	Positive: Required for initial recruitment of phagocytes to the lung. Negative: Overexpression of IFNα/IFNβ results in recruitment of permissive phagocytes and regulation of T-cell accumulation and function.
IL-6	IL-6R, gp130 JAK, STAT3, MAPK	Positive: Potentiates early immunity – nonessential unless a high-dose infection.
IL-1α/IL-1β	IL-1R1, IL1RAcP MyD88, IRAK4, NFκB	Positive: Essential for survival following *M. tuberculosis* infection. Induction of IL-17. Promotes PGE_2 to limit type I IFN.
IL-18	IL-18Rα, IL-18Rβ MyD88, IRAK, NFκB	Positive: May augment IFNγ – nonessential. Regulator of neutrophil and monocyte accumulation, optimal induction of IFNγ by T cells.
IL-12 p40,p35	12Rβ1, IL-12Rβ2 JAK2, TYK2, STAT4	Positive: IL-12p40 and IL-12p35 essential for survival following *M. tuberculosis* infection. Mediate early T-cell activation, polarization, and survival. Negative: Overexpression of IL-12p70 is toxic during *M. tuberculosis* infection.
IL-23 p40,p19	IL-23R, IL-12Rβ1 JAK2, TYK2, STAT3	Positive: Required for IL-17 and IL-22 expression during *M. tuberculosis* infection. Nonessential in low-dose challenge required for long-term control. Negative: Mediates increased pathology during chronic challenge.
IL-27 EBI3,p28	IL-27Rα, gp130 JAK1/2, TYK2, STAT1/3	Positive: May control inflammation and reduce pathology. Negative: Regulates protective immunity to *M. tuberculosis* infection by limiting the migration and survival of T cells at the inflamed site.
IL-35 p35,EBI3	IL-12Rβ2, gp130 STAT1/4	Positive: Regulate the availability of subunits of IL-12, IL-27. Negative: Potential immunoregulatory role.
IL-17A/F	IL-17RC, IL-17RA	Positive: Essential for survival following infection with some strains of *M. tuberculosis*. Induction and maintenance of chemokine gradients for T-cell migration. Negative: Drives pathology via S100A8/A9 and neutrophils.
IL-22	IL-22R1, IL-10R2 TYK2, JAK1, STAT3	Positive: Induces antimicrobial peptides and promotes epithelial repair, inhibits intracellular growth of *M. tuberculosis* in macrophages.

bind either the membrane or the soluble form of TNFα (17–19). An important regulator of activation is localization of receptor expression, as TNF-R1 is ubiquitously expressed, whereas TNF-R2 expression is restricted to subsets of neuronal cells, T cells, endothelial cells, microglia, oligodendrocytes, cardiac myocytes, thymocytes, and human mesenchymal stem cells (20). Signaling through TNF-R2 can only be activated through mTNF, and not sTNF. This complex interplay between positive and negative regulators of TNF activity reflects the potential disruptive power of TNFα, and this regulation of immunity provides tempting targets for manipulation by *M. tuberculosis*.

Originally described for its ability to promote necrosis of tumors (21), TNFα has since been implicated in proliferation and differentiation of immune cells, as well as multiple inflammatory processes including migration (20) and apoptosis of *M. tuberculosis*-infected cells *in vitro* (22, 23). Upon initial *M. tuberculosis* infection, the interaction between immune surveillance cells such as phagocytes in the lung and the invading *M. tuberculosis* results in the production of multiple proinflammatory cytokines, including TNFα (4) (Fig. 1). Although both virulent and avirulent *M. tuberculosis* are able to induce comparable levels of TNFα by human alveolar macrophages, TNFα produced in response to infection with virulent *M. tuberculosis* strains has less bioactivity (24). This is an example of the ability of the bacterium to manipulate the host response, because the decreased TNFα bioactivity has been attributed to the induction of IL-10 by the virulent strain, which then results in release of soluble TNF-R2 that binds the induced TNFα, thereby inhibiting its function (24). As infection progresses, TNFα plays a role in coordinating the chemokine response within the lung and in facilitating the development of the granuloma; it is also produced by both CD4 and CD8 T cells and plays an important role in optimal macrophage activation (25).

In *M. tuberculosis* infection models, the importance of TNFα is exemplified by mice deficient in the TNF receptor or following TNF neutralization (26). In these models, TNFα deficiency results in increased suscep-

TABLE 2 The positive and negative roles of chemokines in TB

Chemokine	Receptor	Role in TB
CCL-3,-4,-5	CCR1	Positive: Upregulated during infection. Nonessential in mouse model
CCL-2,-7,-12	CCR2	Positive: Maximizes and organizes early macrophage and T-cell accumulation in the lung Negative: Mediates recruitment of permissive phagocyte accumulation into the lung
CCL-17,-22	CCR4	Positive: Mediates optimal granuloma formation to mycobacterial antigen Negative: May limit T-cell proliferation via T_{REG}
CCL-3,-4,-5	CCR5	Positive: Regulation of pulmonary infiltrates – nonessential. May mediate early dendritic cell accumulation in the lymph node. May augment macrophage *M. tuberculosis* killing via CCL5?
CCL-20	CCR6	Positive: Expression of CCR6 on T cells specific for *M. tuberculosis* antigens Negative: CCL-20 seen at high levels in active TB
CCL-19,-21,	CCR7	Positive: Mediates efficient migration of dendritic cells and *M. tuberculosis*-specific T-cell activation.
CXCL-1,-2,-3,-5,-6,-7,-8	CXCR1	Positive: Expressed on neutrophils mediates accumulation
	CXCR2	Negative: Absence of CXCR2 or CXCL5 results in improved bacterial control and reduced neutrophil accumulation
CXCL-9, -10,-11	CXCR3	Positive: Required for optimal granuloma formation. Expressed on *M. tuberculosis*-specific T cells. Use of CXCL9-11 levels to indicate disease level? Required for early recruitment of T cells to lung
CXCL-13	CXCR5	Positive: Required for correct location of T cells within granulomas. Required for B-cell follicle formation in *M. tuberculosis*-infected lungs. Required for optimal protection.

tibility with mice succumbing to infection within 2 to 3 weeks, while harboring a high bacterial burden (26). Critically, although inflammatory cells accumulate at the site of *M. tuberculosis* infection in TNFα-deficient mice, they do not coalesce to form granulomas (26–29). Granulomas are considered to be a hallmark of TB and are composed of macrophages, multinucleated giants cells, $CD4^+$ and $CD8^+$ T cells, B cells, and neutrophils (30). In one of the earliest studies of the role of TNFα in mycobacterial disease, it was shown that TNFα neutralization following BCG infection led to the loss of granulomas (31). Neutralization of TNFα also leads to decreased expression of key chemokines such as CCL5, CXCL9, and CXCL10. CXCL9 and CXCL10 both bind to the receptor CXCR3 (32, 33), expressed on activated T cells, while CCR1 and CCR5, expressed on both innate (i.e., macrophages and neutrophils) and adaptive cells (i.e., T and B cells), bind to CCL5 (34). Thus, TNFα sits at the crossroads where innate immunity and acquired immunity, as well as cytokines and chemokines interact. In the absence of TNFα, T cells expressing CXCR3 fail to encounter the ligands CXCL9 and CXCL10 required to recruit these cells into the granuloma. Thus, the required communication between infected phagocytes and the instructive T cells does not occur, resulting in loss of immunity.

The importance of the granuloma in restricting the movement of *M. tuberculosis* to more immunoprivileged sites has long been appreciated (35). Indeed, inhibition of TNFα promotes dissemination of *M. tuberculosis* to sites such as the central nervous system (CNS) (36, 37) wherein adverse events are profound and often irreversible. It is thought that *M. tuberculosis* migrates to the CNS secondarily from a primary site elsewhere in the host (38, 39), although how it crosses the blood-brain barrier is not clear. Although TNFα is produced in the CNS and is thought to exacerbate progression of TB-related damage in the CNS in a rabbit model (40), use of neuron-specific TNFα-deficient mice has shown that neuron-derived TNFα production is dispensable for protection against CNS-TB (41). These data support the notion that TNFα is critical for the initiation and coordination of cellular responses, but that it has the potential to be pathogenic when expressed in the absence of immunity.

TNFα is required throughout the life of the infected host because reactivation of pulmonary TB occurs in latently infected mice upon neutralization of TNFα (42). Upon neutralization, less defined granuloma formation is seen along with increased bacterial burden in the lung and extrapulmonary sites such as the liver and spleen (42) (Fig. 2). Enhanced histopathology is also observed in TNFα-neutralized mice, supporting the importance of a regulated cellular interaction during *M. tuberculosis* infection. The protective role of TNFα is further highlighted in those patients with autoimmune and chronic diseases who are undergoing anti-TNFα-neutralizing therapies, including infliximab, adalimumab, and etanercept (43, 44). Although this therapy is successful at treating the autoimmune disease, a significant correlation between reactivation of latent TB in patients undergoing anti-TNFα therapy has been reported (45–52). Patients using infliximab and/or adalimumab have a higher incidence of TB reactivation in extrapulmonary sites compared with etanercept (50). While a mechanism for this has not been determined, mathematical modeling and bioinformatic analysis suggest that reactivation is related to drug tissue penetration, drug half-life,

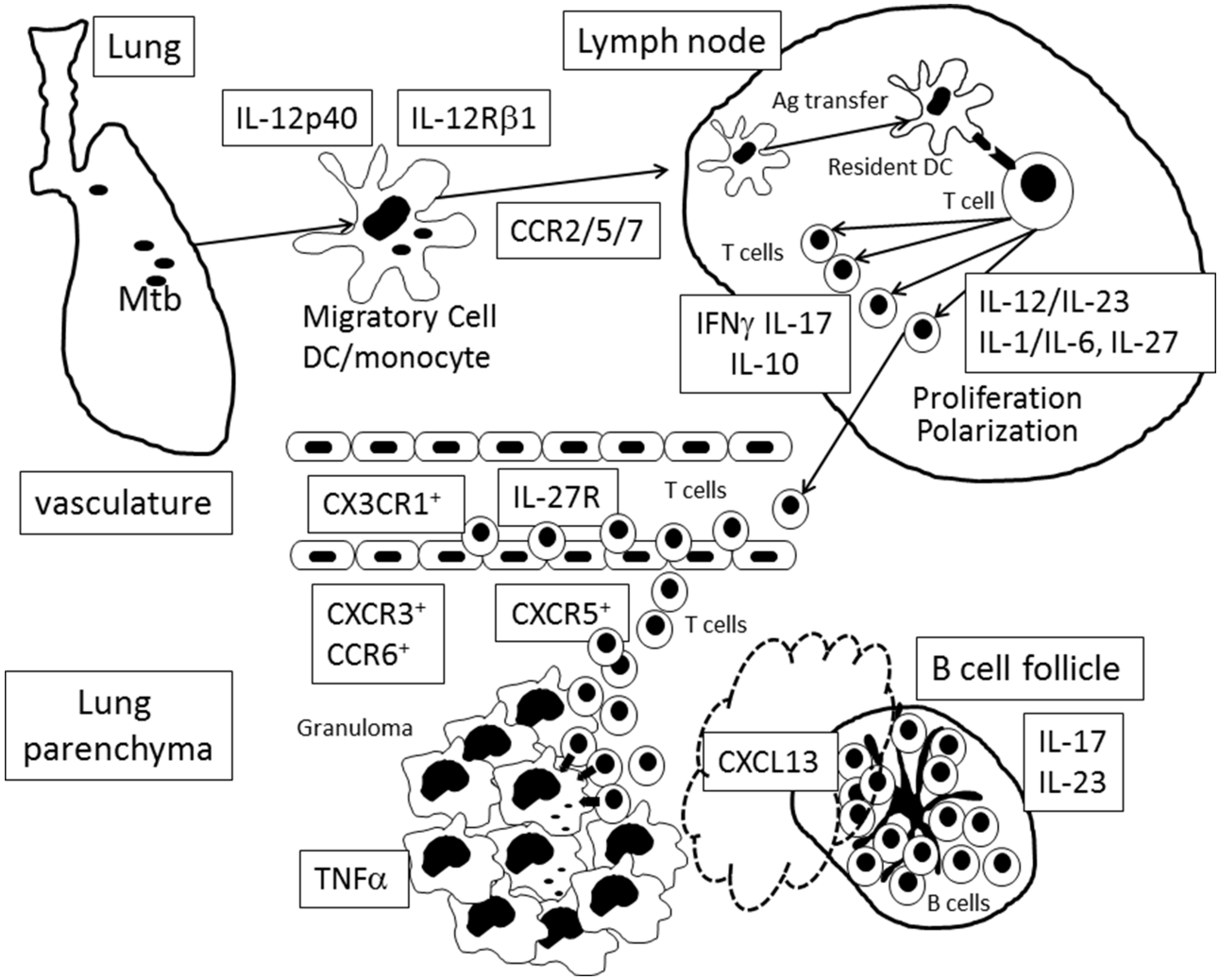

FIGURE 1 The role of chemokines and cytokines in the innate response to *M. tuberculosis* infection. Upon early infection of the lower airways, *M. tuberculosis* encounters alveolar macrophages and lung epithelial cells. Alveolar macrophages are a major source of proinflammatory cytokines (TNFα), although stromal cells can produce cytokines and chemokines that will also modulate immune responses. During early infection, dendritic cell trafficking from the lungs to the lymph node via CCR7 results in primed naive T cells and initiation of adaptive immune responses. Replicating bacteria generate a fulminant reaction that results in the mobilization and recruitment of both neutrophils and monocytes from the bone marrow via the induction of proinflammatory cytokines and chemokines. Regulation of cellular recruitment occurs via coordinated cytokine and chemokine induction. While initial recruitment of monocytes requires type I IFN, overexpression of this cytokine results in high levels of CCR2-expressing monocytes with limited ability to control bacterial growth. Type II IFN (IFNγ) regulates the recruitment of neutrophils, which is promoted by IL-17. CXCL5 and CXCR2 mediate the recruitment of damaging neutrophils. Mtb, *M. tuberculosis*.

and relative specificity for membrane-bound TNFα or soluble TNFα (53). An intriguing mechanism for the effect of infliximab on immunity to *M. tuberculosis* infection has been suggested by the observation that this antibody-based drug binds to mTNF expressed on effector memory CD8 T cells, thereby facilitating complement-mediated lysis and likely loss of *M. tuberculosis*-specific CD8 T cells (54). In a cynomolgus macaque model of TB, latently infected primates were given either soluble TNFα or adalimumab and exhibited increased reactivation

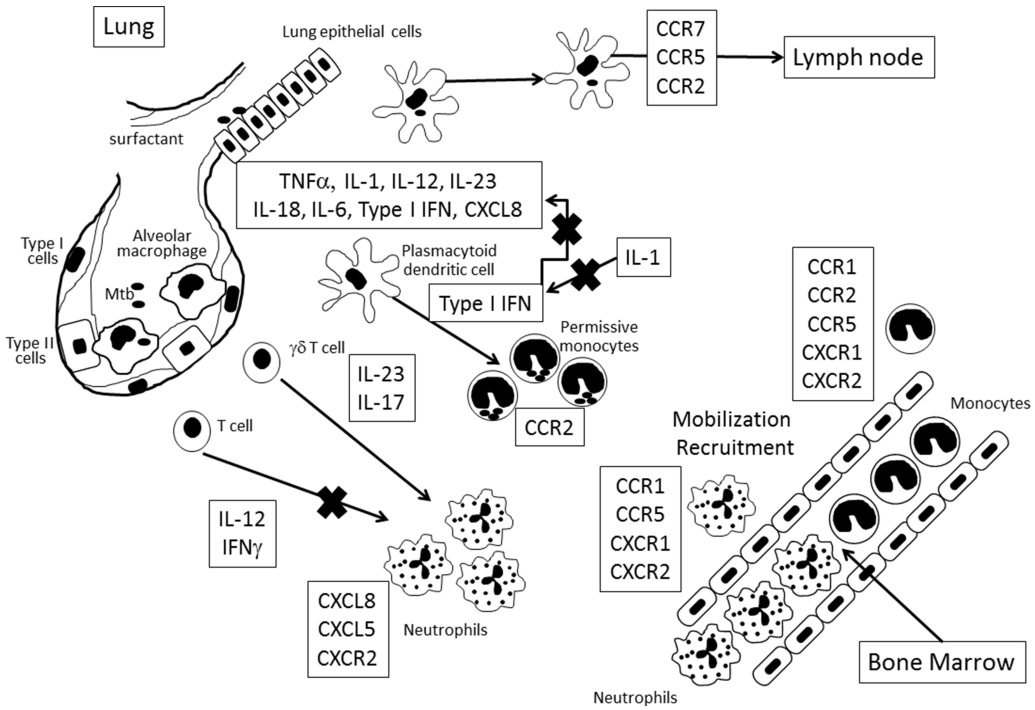

FIGURE 2 The role of chemokines and cytokines in the adaptive response to *M. tuberculosis* infection. Following *M. tuberculosis* infection of the lung, migratory cells take the bacteria to the draining lymph node likely using both cytokine (IL-12p40) and chemokine (CCR2, CCR7) pathways. Antigen is then transferred to antigen-presenting cells that stimulate naïve T cells via MHC class I and class II. Antigen-presenting cells make cytokines and chemokines to potentiate T-cell proliferation and polarization. Activated T cells migrate from the draining lymph node through the vasculature to the inflamed site. Some T cells remain in the vasculature ($CX3CR3^+$) while others migrate into the parenchyma ($CXCR3^+CCR6^+$). Expression of CXCR5 on antigen-specific T cells allows them to respond to IL-23- and IL-17-dependent CXCL13 and locate effectively within the granuloma, where they activate *M. tuberculosis*-infected macrophages. T cells express a variety of cytokines in the lung including IFNγ, TNFα, IL-17, and IL-10 that have both protective and negative effects depending upon the context.

and harbored higher bacterial burdens than their latently infected untreated counterparts (55). As would be expected because of the higher bacterial burden and the role of TNFα in limiting bacterial spread, there were more granulomas in the lungs of the treated monkey (26, 55). In the zebrafish model of *Mycobacterium marinum* infection, TNFα is required for control of mycobacterial growth and to regulate macrophage necrosis (56).

The ability to rapidly diagnose active disease from latent infection would be highly beneficial in identification and prompt treatment of TB. TNFα has recently been proposed as a biomarker to distinguish between active pulmonary disease and latently infected individuals who do not exhibit disease symptoms (57). Using polychromatic flow cytometric analysis, patients with pulmonary TB disease have a higher proportion of single positive TNFα-producing *M. tuberculosis*-specific $CD4^+$ T cells compared with individuals with latent infection (57). This was further confirmed in a blinded study whereby this parameter was the sole diagnostic for pulmonary TB disease (57). TNFα lies at the crux of the TB conundrum. It is critical for control of infection with both phagocyte-activating and granuloma-organizing functions, but too much TNFα can mediate tissue damage and promote transmission (Table 1).

The Interferons

The interferon family demonstrates the potential for similar cytokines to play protective and pathologic roles in TB disease. Based on receptor specificity and sequence homology, the interferons (IFNs) are classified into two types (58). IFNγ is the only type II interferon and, while structurally related to the type I interferons IFNα and IFNβ, these cytokines use different receptors and have

distinct chromosomal locations (58). Unlike type I IFNs that bind to a common heterodimeric receptor composed of IFNAR1 and IFNAR2 chains, IFNγ binds to the IFNγ receptor (IFNGR) which comprises two ligand-binding IFNGR1 chains that associate with two signal-transducing IFNGR2 chains (58). In addition, while IFNγ is essential for survival following *M. tuberculosis* infection the type I IFNs appear to be largely detrimental to the host during TB and may be coopted by the bacterium for its own ends (Table 1).

Type II interferon (IFNγ)

IFNγ-IFNGR binding induces signaling within the cell primarily through the Janus kinase/signal transducers and activators of transcription (JAK-STAT) pathways and results in changes in both the migratory and functional capacity of multiple cell types such as macrophages, NK cells, and T cells (59–61). Innate production of IFNγ by phagocytes stimulated through their pattern recognition receptors results in early proinflammatory responses to infection (58, 62) and, unlike TNFα, which is regulated tightly by highly related molecules, production of IFNγ is regulated by cytokines such as IL-12 and IL-18, which are also secreted by immune surveillance cells upon ligation of their pattern recognition receptors (58, 63, 64).

Genetic deficiency in the IFNγ pathway in humans is associated with increased risk for mycobacterial disease and Mendelian susceptibility to mycobacterial disease (MSMD) (65, 66). Autosomal complete recessive IFNγR1-deficient patients exhibit a predisposition for mycobacterial infections manifesting early in life and with poor prognosis (67). IFNγR2 deficiency (either total protein loss or loss of function) has also been observed and results in a similar outcome to IFNγR1 deficiency (68, 69). Similarly, mice that do not express IFNγ because of targeted gene disruption are severely susceptible to both low-dose aerosol (70) and intravenous infection (71, 72) and exhibit poor macrophage activation and exacerbated granulocytic inflammation (70, 71).

The classic function of IFNγ is as a phagocyte-activating cytokine which instructs macrophages and other cells to change function. In particular, in the absence of IFNγ *M. tuberculosis* occupies an intracellular environment wherein there is little reactive radical production; the phagosome does not fuse with lysosomes and remains at neutral pH. There is also an ample supply of iron due to the location of the phagosome in the early endosomal pathway (73). While innate sources of IFNγ can activate macrophages, there is very little control of *M. tuberculosis* growth in the absence of α/β T cells or major histocompatibility complex (MHC) class II following aerosol infection (74), suggesting that both IFNγ and antigen-specific T cells are required for control of this infection. However, whether it is T cells producing IFNγ that are critical has not been definitively demonstrated, but the strongest support of a critical need of $CD4^+$ T cells to make IFNγ is from a transfer model in mice (75). In contrast, memory T cells can mediate protection in the absence of either IFNγ or TNFα, suggesting other functions need to be identified (76). Both $CD4^+$ and $CD8^+$ T cells produce IFNγ and accumulate within the infected lung and, while absence of $CD4^+$ T cells results in rapid susceptibility to *M. tuberculosis* infection, the absence of $CD8^+$ T cells results in susceptibility later in the infection (77). The organization of the granuloma is also disrupted in the absence of $CD4^+$ T cells with predominantly perivascular cuffing of lymphocytes observed (78), suggesting that, in the absence of $CD4^+$ T cells, chemokine gradients are not established for T-cell migration. It is also the case that, while $CD8^+$ T cells can make IFNγ during *M. tuberculosis* infection, they require $CD4^+$ T cells to do so optimally (79).

The induction of IFNγ-producing T cells has been the focus of anti-TB vaccine design but has not been particularly fruitful. It is clear that humans need antigen-specific T-cell responses to control TB (because those with human immunodeficiency virus [HIV]/AIDS develop TB readily) and that absence of IFNγ promotes mycobacterial disease in humans, so why have we not progressed? Again, we come back to the issue of the communication between the T cells and the infected phagocytes. If the T cells are unable to colocate with the phagocytes and/or the phagocytes are unable to respond to the signals delivered by the T cells, then the number of IFNγ-producing T cells circulating throughout the body is meaningless. It is therefore the case that IFNγ production by activated T cells is not a correlate of protection, rather the ability of antigen-specific T cells to penetrate and survive within the infected site may be. In this regard, recent studies demonstrate that not all cytokine-producing antigen-specific T cells are able to penetrate the TB granuloma and some remain in the vasculature or cuff around the vessels and this is related to their expression of transcription factors, chemokine receptors, and differentiation state (80–82); these markers should perhaps be considered as correlates of protection.

IFNγ can act on cells other than macrophages; indeed, its most critical function in TB may not be to activate macrophages but rather to limit polymorphonuclear

(PMN) inflammation (Fig. 1). Most susceptible mouse strains exhibit high PMN infiltration in the lungs once infected (83–86), and inhibition of this infiltration improves survival (83). Mice that lack IFNγ exhibit high PMN infiltration as do mice lacking $CD4^+$ T cells (70, 78). Neutrophils that lack the IFNγR fail to undergo apoptosis and accumulate in the lungs of *M. tuberculosis*-infected mice, and their removal improves survival without altering bacterial burden (87). Similarly, chimeric mice lacking IFNγR on their radio-resistant cells overexpress IL-17 and have excessive neutrophil recruitment and reduced survival (88). It is possible that the high IFNγ-producing $CD4^+$ T cells that populate the vasculature (80, 82) are located in such a position to reduce neutrophil accumulation.

Production of IFNγ is a very useful diagnostic tool that has been developed to be more selective than the older skin test assay. In this prominent test for *M. tuberculosis* exposure, *M. tuberculosis* antigens (selected to be unique for *M. tuberculosis* versus other mycobacteria) are used to stimulate IFNγ release (89–91). While this test selects for those who are exposed, it is not optimized to distinguish between those individuals who are infected but healthy and those in the process of developing active disease. Recently, studies have shown that patients that have more IFNγ-producing T cells are actually more likely to progress to active disease, suggesting that this test may be optimized to identify those progressing toward disease (92).

Type I interferon (IFN)

The interferons were first identified more than half a century ago for their antiviral activity (93). Type I IFNs represent the largest group, with at least 13 gene products identified in humans and mice, with IFNα and IFNβ being the best classified and the focus of this section. For clarity, IFNα and IFNβ will be collectively referred to as IFNα/β throughout this section. The innate response to pathogens occurs via Toll-like receptor (TLR) engagement resulting in a complex cytosolic cascade of signal transduction toward IFN-regulatory factor3/7 (IRF3/7)-mediated transcription of IFNα/β genes (94). Secreted IFNα/β engages IFN subunit receptors 1 and 2 (IFNAR1/2) at the cell surface, which then activate dimers of the tyrosine kinases JAK and tyrosine kinase (TYK) (94, 95). The end result is activation of IFN-stimulated gene factor (ISG) that then interacts with IFN-stimulated response elements (ISRE) at the promoters of IFNα/β-regulated genes (94, 95).

The type I IFNs were not thought to play a major role in *M. tuberculosis* infection and indeed infection of IFNAR-deficient mice with a low-dose aerosol of *M. tuberculosis* Erdman strain did not indicate any major impact of the loss of this receptor (96). However, use of strains with increased virulence, such as the W-Beijing strain HN878, has revealed an important strain-dependent outcome in relation to type I IFNs. The pathogenesis of *M. tuberculosis* strain HN878 is associated with IFNα/β-dependent reduction in the activity of the proinflammatory cytokines IFNγ, TNFα, IL-6, and IL-12, as well as in the anti-inflammatory IL-10 (97, 98) (Fig. 1). Intranasal delivery of IFNα/β also results in increased bacterial burden and reduced survival in contrast to IFNγ-treated mice (97). Furthermore, IFNα/β signaling interferes with IFNγ-mediated killing of *M. tuberculosis* (99). One hypothesis regarding the role of type I IFNs during chronic *M. tuberculosis* infection is that the accumulation of plasmacytoid dendritic cells in the lung provides a source of excess type I IFN which then inhibits the accumulation of $CD4^+$ and $CD8^+$ T cells in the lung (98) (Fig. 1). Finally, transcriptional analysis of peripheral blood cells from those exposed to TB shows that both IFNγ and type I IFN signatures occur, but that the type I IFN signature is predominantly associated with neutrophils (100).

In a mechanistic analysis of the function of IFNα/β in TB, polyinosinic-polycytidylic acid and poly-L-lysine and carboxymethylcellulose (poly-IC) were used to induce elevated levels of IFNα/β during *M. tuberculosis* infection (101). This poly-IC treatment results in elevated bacterial burden and increases the recruitment of an apparently permissive $CD11b^+GR1^{int}$ cell phenotype recruited via chemokine (C-C motif) ligand 2 (CCL2) and C-C chemokine receptor type 2 (CCR2) (101) (Fig. 1). Similarly, careful analysis of the cells recruited to the lungs of mice lacking either type I or type II IFN receptors demonstrates a protective function for type I IFN signaling in that, in its absence, initial recruitment of target host cells for *M. tuberculosis* does not occur and immunity is compromised (102).

IFNα/β is another perfect example of a "goldilocks" cytokine in TB (Table 1). Just enough is required to initiate recruitment of phagocytes that provide activatable host cells for *M. tuberculosis* to invade; however, production of too much IFNα/β results in large numbers of permissive cells that cannot be effectively activated. Also, too much of this cytokine can limit the activation state of the infected phagocytes and potentially limit the accumulation and function of the T cells required to regulate the mononuclear structure of the granuloma.

Interleukin-6

Interleukin-6 (IL-6) is a pleiotropic cytokine produced in response to inflammatory stimuli (103) and is involved in the essential cellular processes of differentiation, proliferation, and apoptosis. Many cell types express IL-6, including those of lymphoid and nonlymphoid origin (103), and expression can be induced by other cytokines including IL-1, TNFα, and IFNγ (104, 105). IL-6 signals through soluble and membrane-bound IL-6R of which the glycoprotein 130 dimer (gp130) is an essential component (106). Downstream signaling is mediated by a phosphorylation cascade involving JAK, mitogen-activated protein kinase (MAPK), and STAT pathways (106, 107). The pluripotency of IL-6 warrants regulation and this is mediated by suppressor of cytokine signaling (SOCS), which inhibits STAT signaling (106, 107).

The relative importance of IL-6 during TB depends upon the route and dose of infection. As we have discussed, communication between cells is critical for successful expression of immunity and, if the dose is low or bacteria are slow to grow, then the kinetics of the cellular response are not critical. However, if the dose is high and systemic, then the kinetics of the response becomes critical. This concept is illustrated by IL-6, because in its absence (either by antibody treatment or by gene deletion) there is increased susceptibility to intravenous challenge with a large dose of mycobacteria (108, 109). In contrast, in a low-dose aerosol *M. tuberculosis* challenge model, while modestly increased bacterial burden occurs in the lungs of IL-6-deficient mice, the impact is not lethal (110). In both the low- and high-dose challenge models, increased IL-4, as well as reduced or delayed T-cell accumulation and IFNγ expression, is observed, suggesting that IL-6 can act to potentiate IFNγ expression at the site of infection (108, 110). It appears also that IL-6 is required for optimal induction of protective responses during vaccination, because, in its absence, both BCG and a subunit vaccine are less effective (109, 111).

Interpretation of the role of IL-6 in TB is complicated by the fact that the soluble IL-6 receptor can mediate *trans*-signaling and is implicated in inflammatory diseases such as inflammatory bowel disease (112). To address the role of IL-6 further, a gp130 construct capable of sequestering IL-6 in the blood (sgp130FC) was delivered to mice during *M. tuberculosis* infection, but no impact on disease progression was seen. In contrast, when mice are made to overexpress this construct, a temporary but significant increase in bacterial burden occurs during acute infection (113). This observation is consistent with an early role of IL-6 in potentiating immunity during early *M. tuberculosis* infection.

In vivo data support a protective role for IL-6 in the induction of early protective responses mediated through IFNγ (108, 110). Human studies also give us considerable insights into the role of IL-6 during TB. Cavitary TB is the most destructive form of caseous TB whereby necrosis liquefies cellular material and results in compromised lung function. Humans with cavitary TB express lower levels of IL-6 and the chemokine IP-10 in their bronchial alveolar lavage (BAL) fluid in comparison with TB patients without cavitary disease, thereby indicating IL-6 and IP-10 as potential markers of controlled (noncavitary) TB (114). As would be expected, elevated neutrophils were observed in BAL from cavitary TB patients, while noncavitary TB patients presented with elevated alveolar macrophages (114); interestingly, there was no correlation between cytokine expression in BAL fluid and serum cytokine production (114). In contrast, an earlier study identified elevated blood plasma levels of IL-6 from TB patients with developed lung lesions (115). Based on the mechanistic data from animal studies and the human data, IL-6 appears to be associated with effective early expression of immunity in the lung via the combination of regulated mononuclear inflammation and rapid accumulation of lymphocytes. Its effects are modest but may be critical following high-dose exposure or during immunodeficiency.

IL-1 Cytokines

The proinflammatory cytokines IL-1α, IL-1β (collectively called IL-1 here), and IL-18 are members of the IL-1 family (116). IL-1 was first identified in the 1940s as an endogenous pyrogen (117–119). IL-1 and IL-18 as well as their respective receptors (IL-1R1 and IL-18R) are widely expressed by all nucleated cells of the body including endothelial cells, monocytes, macrophages, and neutrophils (116). Expression of IL-1 and IL-18 is mediated in part by the canonical pathway of inflammasome activation, which involves the sensor (e.g., TLR), an adaptor molecule such as myeloid differentiation primary response gene 88 (MyD88), and caspase-1 (120–122). Alternatively, IL-1β and IL-18 can also be induced by the noncanonical inflammasome pathway that is distinguished by the activation of caspase-8 and -11 on the precursor of the cytokines in the cytosol (123, 124). MyD88 is an important cytosolic mediator linking TLR signaling to the transcription of inflammasome components (122).

IL-1α is mostly associated with sterile cell injury (e.g., cigarette smoke), but is also induced during nonsterile cell injury (e.g., bacterial) where it functions locally as an alarmin (125–130). IL-1β is induced during infection and is primarily produced by monocytes, macrophages, and dendritic cells (131–134). IL-1 signals through the IL-1R1 receptor present on a number of cells including endothelial cells, monocytes, macrophages, and T lymphocytes (116, 128, 135, 136). IL-18 is expressed constitutively in the cytosol at low levels as a precursor, which is activated by caspase-1 activity following bacterial stimulation, stimulation by neutrophils or by IL-4 or IFNγ (137–139). IL-18 activity results from colocalization of IL-18 receptor alpha (IL-18Rα) and IL-18 receptor beta (IL-18Rβ) on host cells including monocytes and epithelial cells (140).

IL-1R/IL18R/MyD88

Signaling through MyD88 is shared between TLR, IL-1R, and IL-18R (141–143). MyD88 is an essential component in innate signaling in response to TB, because MyD88 gene-deficient mice exhibit profound susceptibility to *M. tuberculosis* infection (143). Importantly, following mycobacterial stimulation, MyD88 gene-deficient macrophages and dendritic cells exhibit reduced IL-6, TNF, and IL-12p40 production, suggesting a critical role for MyD88 in pattern recognition responses to *M. tuberculosis* infection (143). Aerosol infection results in dramatically increased lung burden coinciding with increased inflammation and accumulation of neutrophils and macrophages (143). Despite the poor innate response to *M. tuberculosis* infection in the MyD88 gene-deficient mice, the accumulation of IFNγ-producing T cells was not affected. It is likely that these antigen-specific cytokine-producing T cells were unable to mediate protection because of failures within the phagocytes accumulating at the site or as a result of being unable to communicate with the infected phagocytes (143). That BCG vaccination results in protection against *M. tuberculosis* infection in MyD88-deficient mice suggests that it is a failure of T cells to accumulate rapidly enough in naive mice that contributes to their susceptibility (143).

What then is MyD88 signaling doing? Comparison of the phenotype of IL-1-deficient mice and MyD88-deficient mice is suggestive in this regard, because both exhibit increased susceptibility with focal necrosis despite generation and accumulation of cytokine-producing T cells (144). These observations suggest that induction of IL-1 is likely Myd88 dependent and that this pathway plays a critical role in protective immunity to TB.

IL-1

IL-1α and IL-1β are interdependent proinflammatory cytokines critical to defense against TB (145–149). Mice lacking either IL-1α or IL-1β or both are susceptible to acute and chronic infection, respectively, following challenge with *M. tuberculosis* (145–148). IL-1 α/β double-deficient mice share a similar susceptibility to infection as IL-1R1KO and MyD88KO mice (143, 144, 148, 150). Deficiencies in the IL-1 pathway (IL-1 α/β or IL-1R1) have no impact on the protection against BCG delivered intravenously, suggesting that virulence of the pathogen is a factor in the role of the IL-1 pathway (146). Anti-IL1α and anti-IL-1α/β antibodies delivered subcutaneously to *M. tuberculosis*-infected mice have also been shown to result in loss of body weight and lethality (148). Furthermore, lung sections from anti-IL-1α-treated mice exhibit lung parenchyma consumed by cellular infiltrates (148). During sterile mediated inflammation, IL-1α appears to be involved in the expression of proinflammatory cytokines such as IL-6 in primary fibroblasts (151), which may be associated with mobilization of neutrophils (152). It has also recently been observed that, upon activation of the inflammasome, IL-1β and IL-18 are capable of inducing expression of the neutrophil-recruiting cytokine IL-17 (153–155). IL-17 responses are essential in the protection against some *M. tuberculosis* strains, such as HN878 and for recall responses to H37Rv (149, 156, 157). Consistent with this, IL-1R1 gene-deficient mice infected with the *M. tuberculosis* strain HN878 produce decreased levels of IL-17 and decreased populations of IL-17-producing cells *in vitro* and *in vivo* (149).

IL-1 is produced by $CD11b^{+}Ly6G^{-}$ cells following *M. tuberculosis* infection (145), and rescue of the lethal phenotype in IL-1α mice can be accomplished by directed viral expression of IL-1α in $CD11c^{+}$ cells transplanted in IL-1α gene-deficient mice (147). It would seem, therefore, that a primary function of the IL-1/IL-1R pathway is to mediate the recruitment and coordination of cellular responses by the induction of proinflammatory cytokines from the stroma (145, 147). One critical aspect of IL-1 function is in promotion of prostaglandin E_2 (PGE_2), which in turn mediates inhibition of type I IFN-induced accumulation of permissive macrophages at the site of infection (158) (Fig. 1). Prostaglandins such as PGE_2 are produced by the action of cyclooxygenase (COX) enzymes on arachidonic acid, and, in the absence of inducible COX enzymes, mice are highly susceptible to *M. tuberculosis* infection, and delivery of PGE_2 during *M. tuberculosis* infection results in a partial rescue of the lethal phenotype in IL-1α/β-

infected mice (158). Taken together, the underlying function of IL-1 in *M. tuberculosis* appears to be in regulating type I IFN function and helping to maintain the balance between sufficient phagocytes to mediate control of the intracellular pathogen, while inhibiting the overrecruitment of permissive macrophages mediated by type I IFN (102).

IL-18

IL-18 is essential for the production of IFNγ from T cells under some conditions (159–163), and, in some instances, its absence can result in increased susceptibility to *M. tuberculosis* (150), although, in other conditions, increased susceptibility to *M. tuberculosis* infection is not observed (162, 163). Interestingly, when susceptibility is observed, the accumulation of neutrophils and inflammatory chemokines CXCL1 and CXCL2 is elevated, and depletion of neutrophils and monocytes from the lung results in decreased bacterial burden (150). In *M. tuberculosis*-infected IL-18-deficient mice, an increased frequency of IFNγ-producing $CD4^+$ and $CD8^+$ T cells in the lungs is seen, but total IFNγ production by these T-cell populations is decreased, suggesting that IL-18 could contribute to optimal IFNγ induction during TB (150, 162, 163). It would appear, therefore, that IL-18 plays a role in inducing high IFNγ production in T cells, but that this is not required for protection, and that its more critical role (perhaps when dose or virulence of the *M. tuberculosis* strain is high) is that of regulator of phagocyte accumulation, possibly mirroring the role of IL-1 and MyD88.

Our working model of immunity to TB places the emphasis on rapid and correct accumulation of both phagocytes (macrophages and neutrophils) and T cells to the site of infection. This accumulation is initiated by the innate sensors within the lung and results in the induction of TNF, IFNs, and IL-1 family members. The correct ratio of these cytokines is essential for the balance of permissive and nonpermissive phagocytes and for the development of a granuloma such that infected phagocytes and antigen-specific T cells can communicate effectively to stop *M. tuberculosis* growth. How the antigen-specific T cells develop and are regulated is covered below.

IL-12 Cytokine Family

The IL-12 family of cytokines belongs to the IL-6 superfamily and is the only family composed of heterodimeric cytokines (164, 165), and this unique feature bestows diverse and pleiotropic functions because of promiscuous chain pairing (166). The alpha chains of the IL-12 family (p19, p28, and p35) contain four-helix bundle structures and pair with one of two beta chains (either p40 or Epstein-Barr virus-induced gene 3 [Ebi3]) (164–166). IL-12 is composed of the subunits p35/p40, IL-23 of p19/p40, IL-27 of p28/Ebi3, and IL-35 of p35/Ebi3 with expression of the distinct subunits being regulated independently (166). In addition, IL-12p40 can also be secreted both as a homodimer (IL-12p80 or IL-12p$(40)_2$) and as a monomer (IL-12p40) (167). Both macrophages and dendritic cells are major producers of IL-12p40, IL-12, IL-23, and IL-27 (168). These cytokines are largely associated with the induction and regulation of cytokine expression within antigen-stimulated T-cell populations.

IL-12

IL-12 plays an important role as a link between innate and adaptive immune responses, and is produced by and influences multiple effector cells (169, 170). Composed of IL-12p35 and IL-12/23p40, IL-12 (IL-12p70) is primarily secreted by macrophages, dendritic cells, and B cells (166, 171, 172). The importance of IL-12 in TB is dramatically illustrated by several experiments of nature wherein humans with IL-12p40 deficiency display an inherent predisposition to *M. tuberculosis* infection (173–178). Furthermore, patients with MSMD harbor deficiencies in IL-12Rβ1, IFNγR1, and IL-12p40, and exhibit susceptibility to *M. tuberculosis* and develop BCGosis following delivery of the BCG vaccine (66, 178–181). Genetic etiology for MSMD is associated with mutations in the autosomal genes *IFNGR1*, *IFNGR2*, *STAT1*, *IL12B*, *IL12BR1*, and X-linked gene *IKKBG*, encoding NF-κB essential modulator (NEMO) (66). All these autosomal genes are associated with IL-12/IFNγ-dependent signaling and the IFNγ-mediated activation of macrophages. Mutations in *IKKBG* impair CD40-dependent IL-12 production in monocytes and dendritic cells, despite normal CD40-mediated induction of costimulatory molecules on dendritic cells (182). These human data highlight the importance of this pathway to TB control.

IL-12 is expressed within the lung at the site of TB (183) and delivery of IL-12 to *M. tuberculosis*-infected mice decreases bacterial burden, while reduction of IL-12 by antibody increases bacterial burden (184). Interestingly, delivery of IL-12 also modestly improves the outcome for mice lacking acquired cellular immunity, suggesting that it can mediate immunity via direct action on innate cells (184). Mice genetically deficient for the IL-12p40 subunit are acutely susceptible to *M. tuberculosis* infection (185, 186), whereas those

lacking IL-12p35 exhibit prolonged survival relative to the IL-12p40-deficient mice (186). This, in turn, is dependent on the availability of the IL-23p19 subunit (187). The absence of IL-12p40 results in the substantial loss of antigen-specific IFNγ production (185, 186) (Fig. 2), while the presence of IL-23p19 in the IL-12p35-deficient mice appears to promote sufficient antigen-specific IFNγ production to increase protection relative to the IL-12p40-deficient mice (187). It also appears that stable and prolonged IL-12 production is required to maintain IFNγ production and to limit bacterial growth long term (188). This requirement for long-term function may also apply in humans, because absence of the IL-12R1 results in poor accumulation of IFNγ-producing memory T cells (189). The innate pattern recognition receptors, TLR2 and TLR9, are necessary for optimal production of IL-12p40 in response to *M. tuberculosis* exposure (190), while the *M. tuberculosis* lipoarabinomannans have been shown to negatively regulate TLR-mediated IL-12 production by inducing an inhibitor of TLR signaling, IRAK-M (191). In contrast, mycobacterial LprA is a TLR2 agonist and promotes IL-12p40 production (192), reflecting the need for *M. tuberculosis* to both induce and regulate IL-12p40 for its own ends.

IL-12 signals through interactions between IL-12/23p40, and IL-12p35 with IL-12Rβ1 and IL-12Rβ2, respectively (193–195), with the IL-12p40 interacting with IL-12Rβ1 on the target cell surface, thereby allowing the IL-12Rβ2 to induce JAK and STAT signaling and activate STAT4 homodimers (166). The homodimer IL-12p40, IL-12$(p40)_2$, antagonizes IL-12-mediated immune responses through competitive binding of IL-12Rβ1 (196–198). However, in TB, it appears that IL-12$(p40)_2$ can also function as an agonist (199), and supports dendritic cell migration to the draining lymph nodes (200, 201), to promote T-cell priming and differentiation (200). Specifically, following *M. tuberculosis* infection, dendritic cells are thought to be the first immune cells to traffic to the draining lymph node (202), and this may occur in an IL-12p40- and IL-12Rβ1-dependent manner (200, 203). Bone marrow-derived dendritic cells from mice deficient in IL-12p40 are unable to activate naive T cells in the draining lymph node following delivery to the lung and fail to confer protective adaptive responses (200). However, treatment of the IL-12p40-deficient dendritic cells with the homodimer IL-12$(p40)_2$ is sufficient to restore migration of the dendritic cells to the draining lymph node and for activation of naive T cells to occur (200). Expression of IL-12Rβ1 is also required to facilitate dendritic cell migration to the draining lymph node (203) and, indeed, $CD11c^+$ cells in the *M. tuberculosis*-infected lung express an alternative splice variant of IL-12Rβ1 that augments IL-12Rβ1-mediated effects (203). In particular, dendritic cells expressing the splice variant exhibit enhanced migration from the infected lung to the draining lymph nodes and supported activation of *M. tuberculosis*-specific T cells (203) (Fig. 2). In an interesting example of cytokine cross talk, mice lacking the p75 receptor for TNF (TNFRp75) exhibit increased IL-12p40 and enhanced IL-12p40-mediated dendritic cell trafficking to draining lymph nodes (204). Thus, IL-12Rβ1 is important for the effector function of IL-12p40 on dendritic cells, as well as mediating recruitment and function of CD4 T cells in response to TB.

IL-23

IL-23 utilizes the p40 beta subunit paired with the alpha chain p19 (205). Before the discovery of IL-23, the interpretation of data from IL-12p40- and IL-12p35-deficient models of disease had been difficult (206). Specifically, studies found that the outcome of IL-12p35 deficiency was not always the same as in IL-12p40-deficient models (207–209). The discovery of IL-23 led to the reassessment of the role of IL-12p40 (205, 206, 208, 209), and disease models previously associated with IL-12 were, in fact, shown to be primarily driven by IL-23 and not IL-12 or they clarified unique disease-driving features of the two cytokines (206, 208–211). Currently, IL-23 and IL-23 pathway antagonists are in phase 2 and phase 3 clinical trials for treating patients with moderate to severe psoriasis (207), making the determination of the role of IL-23 in TB a critical undertaking. IL-23 stabilizes the induction of the T_H17 cell subset, which produces IL-17A, IL-17F, and IL-22, and it is also required for the double expression of IL-17 and IFNγ (212). However, IL-23 alone is not sufficient to drive differentiation of T_H17 cells, which requires the key cytokines transforming growth factor β (TGFβ) and IL-6 (213). In addition, IL-23 can also induce IFNγ production in human T cells as well as support the proliferation of mouse memory T cells (205, 214). The interaction with its receptor, composed of IL-23R and IL-12Rβ1 subunits, activates the downstream signaling molecules, JAK and STAT, for production of its signature cytokines (166, 205, 214–216). IL-23 primarily signals through STAT3, while IL-12 can signal through STAT1, 3, 5, and 4, but preferentially signals through STAT4 (166). Upon infection with *M. tuberculosis*, lung dendritic cells produce IL-23, likely mediating the induction of IL-17 production (187, 217, 218).

Although IL-23 is important for generation of *M. tuberculosis*-specific IL-17-producing T cells (Fig. 2), mice deficient in IL-23p19 control *M. tuberculosis* effectively for up to 90 days whereupon bacterial growth increases relative to intact mice (187, 219). In addition, treatment of *M. tuberculosis*-infected mice with adenovirus-expressing IL-23 reduces *M. tuberculosis* burden and increases cellular responses (220). In the absence of IL-23p19, *M. tuberculosis*-infected mice did not develop well-organized B-cell follicles, and this was associated with a complete absence of IL-17 and IL-22 in the lung. In addition, there was very little expression of the B-cell follicle-associated chemokine CXCL13 resulting in increased accumulation of lymphocytes around the vessels rather than within the granulomatous regions (219) (Fig. 2). Thus, in support of our working model, coordinated communication between lymphocytes and infected macrophages is inefficient in the absence of specific cytokines/chemokines (in this case, IL-23-dependent CXCL13) and bacterial growth occurs in the absence of this efficient communication.

IL-23 also plays a chemokine-dependent role in the efficient expression of vaccine-induced mucosal immunity. This role was first highlighted in mice subcutaneously vaccinated with an adjuvant-paired I-A^b-restricted $ESAT6_{(1-20)}$ peptide, which induces both IFNγ- and IL-17-producing antigen-specific $CD4^+$ T cell responses (157). Critically, the improved kinetics of the vaccine-induced IFNγ-producing T cells is lost in the absence of IL-23, because this cytokine is required for the generation of lung resident IL-17 producing $CD4^+$ memory T cells that generate a chemokine gradient facilitating the accelerated IFNγ response. In the absence of IL-23, vaccine-induced protection to *M. tuberculosis* challenge is lost (157). Coimmunization of mice with a DNA vaccine composed of *M. tuberculosis* antigen 85B (Ag85B) and an IL-23-expressing plasmid also confers enhanced protection through the induction of augmented T-cell proliferation and IFNγ production in comparison with Ag85B alone (217). Other studies also support an important role for IL-17-producing $CD4^+$ T-cell subsets in mediating mucosal vaccine-driven protection (156, 221–223). Specifically, adoptive transfer of *M. tuberculosis*-specific IL-17-producing T cells into unchallenged mice confers protection following exposure to *M. tuberculosis* (156). Furthermore, use of adjuvants capable of driving lung-resident IL-17-producing cells is able to initiate early CXCL13 expression, thereby promoting appropriate accumulation of $CXCR5^+$ T cells within the *M. tuberculosis*-induced inflammatory site (221). These IL-17-producing T cells are long lived (222) and are associated with improved protection when recombinant BCG vaccines are used (223).

IL-27

IL-12 and IL-23 are proinflammatory cytokines with the capacity to drive cytokine production in T cells (168, 224, 225). In contrast to this clear role for IL-12 and IL-23, IL-27 is pluripotent and has a complex and sometimes apparently contradictory capacity to influence inflammation and lymphocyte function (166, 226–228), indicating a pleiotropic nature for IL-27. IL-27 is composed of the p28 alpha and Ebi3 beta chains, and signals through the IL-27Rα (WSX-1 or TCCR) and gp130 receptor subunits (166, 229, 230). IL-27 can mediate suppression of IL-17-production by T cells (231) via STAT1 signaling to promote IL-10-producing Tr1cell-like regulatory populations (232). It also promotes proliferation (229) and polarization via T-bet (233) in naive T cells (Fig. 2).

In the context of *M. tuberculosis* infection, IL-27R-deficient mice challenged with *M. tuberculosis* exhibit lower bacterial burden in the lungs and increased granuloma-localized lymphocytes (234, 235), but these mice succumb to disease earlier than control animals (235). Thus, while IL-27R activity appears to limit expression of immunity locally, it may actually protect from undue pathologic damage. Because of the pleiotropic nature of IL-27 it is very difficult to dissect out its specific function in TB. The absence of the gp130 component of the IL-27R on phagocytes during *M. tuberculosis* infection results in loss of the increased inflammatory consequences of IL-27R deficiency but does not impact the reduced bacterial burden seen in mice lacking IL-27R on all cells, suggesting that these two aspects of IL-27R deficiency are independent (236). In contrast, mice lacking IL-27R only on T cells exhibit the improved ability to control bacterial burden over the long term (82). This improvement was associated with enhanced localization and reduced differentiation (i.e., reduced T-bet expression) of IL-27R-deficient $CD4^+$ T cells within the infected lung parenchyma. *M. tuberculosis*-specific $CD4^+$ T cells lacking IL-27R are also intrinsically fitter than IL-27R-sufficient $CD4^+$ T cells in mice within the same environment (82) (Fig. 2). The importance of IL-27 is further confirmed in human patients, wherein IL-27 is significantly increased in patients with active TB compared with latently infected individuals (82). In our working model of TB immunity, IL-27 appears to play the role of mediator of increased inflammation within the phagocyte population while also serving to limit the efficacy of the T-cell population

by driving them to a state of differentiation that limits their ability to locate to, and persist within, the inflamed granuloma.

IL-35

IL-35, a dimeric protein encoded by IL-12α and IL-27β chains, has been shown to suppress $CD4^+$ T-cell responses (237). It is thought to be primarily expressed by regulatory T (T_{REG}) cells (238) and is required for optimal function both *in vivo* and *in vitro* (239). IL-35 is important for the generation of human and mouse T_{REG} cells, termed iT_R35 cells (239), which function independently of IL-10 and TGFβ. While a specific function for IL-35 in *M. tuberculosis* infection has not been directly addressed, the relative availability of IL-35 in the presence and absence of the other IL-12 family subunits makes consideration of this cytokine an important part of any interpretation of outcome in mice or humans lacking IL-12 family subunits.

IL-23-Dependent Cytokines

IL-17

The IL-17 cytokine family is composed of six members, IL-17A to IL-17F, with IL-17A and IL-17F being the most studied. Production of IL-17 is conventionally attributed to T cells, but other lymphocytes as well as innate immune cells can produce this cytokine (240). IL-17 cytokines are proinflammatory and can be protective or pathogenic depending on the nature of the challenge faced by the host (241, 242). It is at mucosal sites that IL-17 plays its most important regulatory and protective role against invading pathogens.

Following mycobacterial infection, lung-resident γδ T cells are a primary source of early IL-17 (218), and likely support early neutrophil accumulation (243) (Fig. 1). Following BCG infection, IL-17 expression can be detected as early as day 1 postinfection and is dependent on IL-23 expression (243). One recently identified capacity of IL-17 is to regulate mycobacterially induced IL-10 (244). Following vaccination with BCG, dendritic cells produce PGE_2, which is required for the induction of both IL-10 and IL-23 with the IL-23 being required for IL-17 production (244). This IL-17 is then thought to downregulate IL-10 production, thereby allowing increased IL-12 that subsequently promotes IFNγ production. In the absence of IL-10, the IL-23-mediated IL-17 is not required and, in the absence of IL-23, BCG fails to effectively induce protective IFNγ-producing T cells (244). This study was the first to show that PGE_2 induction of IL-17 was sufficient to overcome the inhibitory effects of IL-10 and support the generation of antigen-specific and cytokine-producing T cells during mycobacterial vaccination and challenge.

As with IL-23, low-dose challenge with some strains of IL-17A (i.e., H37Rv and CDC1551) in the absence of IL-17 results in no obvious phenotype (149, 187, 245) until late in disease (219). In contrast, following infection with the W-Beijing strain HN878 of *M. tuberculosis*, IL-17R expression on radio-resistant cells (likely fibroblasts) of the lung is required to coordinate the rapid accumulation of cells within the lung via the induction of CXCL13 and recruitment of $CXCR5^+$ T cells to lymphoid follicles within the tissue (149) (Fig. 2). Importantly, the W-Beijing HN878 *M. tuberculosis* strain induces high levels of IL-1β and IL-17 relative to other *M. tuberculosis* strains (149) and also induces excess type I IFN (97), which is capable of bringing in permissive macrophages in a CCR2-dependent manner (101) (Fig. 1). HN878 induces an environment that is highly permissive for its growth, and it is this environment that results in the need for the optimum expression of immunity wherein IL-17 promotes rapid accumulation and the correct localization of the T cells needed to change the permissive macrophages to ones that limit bacterial growth (149).

The role of IL-17 in initiating early coordination of cellular responses in naive mice is apparent when the challenge is significant as in the case of HN878; however, the concept of IL-17 as a coordinator of early mucosal responses in TB actually stems from vaccine work. Initial studies using a defined subunit vaccine determined that lung-resident IL-17-producing cells induced by vaccination are vital for the induction of the chemokines (CXCL9, CXCL10, and CXCL11) required for the accumulation of IFNγ-producing memory T cells (157). Further studies have shown that adoptive transfer of *M. tuberculosis*-specific IL-17-producing T cells into naive mice is able to mediate protection in an aerosol challenge model, thereby identifying these types of cells as valid targets for vaccine-mediated induction (156). Finally, mucosal immunization with *M. tuberculosis* antigens induces potent IL-17 responses that improve upon BCG vaccine-induced protection in mice (221). Interestingly, in mucosal vaccine models, IL-17 rather than IFNγ appears to be most important for vaccine-induced protection against *M. tuberculosis*, providing support for the model that it is the coordination of the cellular response that is the determining factor in the success of vaccination (221, 246). Critically, antigen-specific IL-17-producing memory T cells are induced by vaccination and respond up to 2 years postvaccination

(222). These memory T cells appear to be metastable and become IFNγ producers within the lung (222), probably as a result of the action of IL-23 (212). In fact, pluripotent memory T cells capable of producing not only IL-17 but also TNF and IL-2 may be the most appropriate target T cells for vaccination (247). Manipulation of BCG can also result in increased induction of IL-17-producing memory cells, and this is associated with improved protection as in the case of the recombinant BCG strain rBCGΔureC:Hly (223). Thus, IL-17 drives the induction of CXCL9-11 to recruit protective antigen-specific T cells, as well as CXCL-13 to localize $CXCR5^+$ cytokine-producing T cells within TB granulomas. Despite the protective outcome of IL-17 discussed above, IL-23-dependent IL-17 production is also associated with damaging neutrophil accumulation during a chronic restimulation model of TB (248). Indeed, exacerbated production of IL-17 appears to drive pathology by inducing S100A8/A9 proteins that recruit neutrophils into the lung (249). Thus, IL-17 also fits the bill as a "goldilocks" cytokine in TB (Table 1).

IL-22

IL-22 is primarily produced by $CD4^+$ T cells as well as γδ T cells, natural killer (NK) cells, and innate lymphoid cells following exposure to innate or infectious stimuli (250). IL-22 can have dual effects in the context of inflammation, and this has been attributed to its coexpression along with IL-17 (250, 251). The major functions of IL-22 are the regeneration and survival of the intestinal, airway, and external epithelium, as well as stimulating the secretion of antimicrobial peptides such as lipocalin and β-defensin (245, 250, 252). In the context of *M. tuberculosis*, IL-22 is expressed at higher levels than IL-17 at the site of infection and within granulomas from TB patients and NHP models (253, 254). Furthermore, in NHPs infected with *M. tuberculosis*, $CD4^+$ T cells expressing membrane-bound IL-22 limit *M. tuberculosis* intracellular growth in macrophages (255). IL-22 can also inhibit intracellular growth of *M. tuberculosis* in human monocyte-derived macrophages by promoting phagolysosomal fusion and induction of Calgranulin A, a heterodimer of S100A8 and S100A9 proteins (256). Moreover, human NK cells cultured with *M. tuberculosis*-infected macrophages produce IL-22 and mediate macrophage activation (257). Finally, IL-22 increases as patients receive anti-TB treatment, and this has been associated with a decrease in a regulatory B-cell population ($CD19^+CD1d^+CD5^+$ B cell), the *in vitro* depletion of which results in enhanced IL-22 production by T cells (258).

Animal studies using low-dose aerosol challenge indicate that, in uncomplicated infection models, IL-22-producing T cells accumulate in the lung and express IFNγ (259). In the absence of this cytokine, however, there appear to be no significant consequences (260). However, in a BCG vaccine model, $NK1.1^+$ cells appear to make IL-22, which contributes to protection by regulating T_{REG} cells (261). Taken together, the current data suggest a protective role for IL-22 in TB disease progression, possibly via antimicrobial peptide production, cellular function, and promotion of epithelial repair.

Regulatory Cytokines

IL-4, IL-5, IL-13

IL-4 was first described as a product of $CD4^+$ T lymphocytes that are now known as T_H2 T cells (262, 263). T_H2 responses inhibit T_H1 responses (264–266). IL-4, IL-5, and IL-13 are the signature cytokines associated with T_H2 responses; they are induced in response to helminth infections and contribute to diseases such as asthma and allergy (267–270); they mediate expulsion of multicellular parasites occupying mucosal tissues. IL-4R signaling requires heterodimerization of IL-4Rα (shared with IL-13) and the common gamma chain (shared with IL-2) (271). The IL-4 receptor (IL-4R) is the primary mediator of action, and ligation of IL-4R results in signal transduction via STAT-6 and subsequent GATA-3 transcription (272–275). Both STAT-6 and GATA-3 distinguish T_H2 cells from other T_H cells, including T_H1 and T_H17 (270). IL-4 expression is, in part, regulated by IL-2 and is associated with the differentiation of T_H2 cells, which then express and maintain IL-4 and IL-5 in a positive feedback loop (276, 277). IL-4R is expressed on many cell types, including lymphocytes, epithelial cells, and fibroblasts (278, 279). IL-5 is primarily associated with recruitment of eosinophils (280) and basophils (281) and the development of antibody-producing B cells (282, 283). The IL-5 receptor comes in both low- and high-affinity forms whose activity is context dependent when expressed on the surface of lymphocytes, eosinophils, and basophils (284).

During TB, IL-4 levels are quite variable, with mRNA detectable in peripheral blood mononuclear cells (285) and IL-4-producing T cells isolatable from TB patients (286); however, peripheral blood mononuclear cells from active, *M. tuberculosis* culture-positive patients show decreased IL-4 expression (287–289). While a significant increase in IL-4 is observed in the plasma of TB patients compared with household contacts (290), IL-4 plasma levels are not different between HIV

patients and non-HIV patients with TB (290, 291), and anti-TB treatment is associated with decreased plasma IL-4 levels (290). IL-4 mRNA has been shown to be upregulated in the necrotic areas in the lungs of HIV$^+$ patients with pleural TB (292) and is consistent with increased CD4$^+$ cells expressing IL-4 in TB patients exhibiting cavitary disease (293). In an NHP model, IL-4-expressing T cells are increased transiently at week 6 post-*M. tuberculosis* infection; however, this population is not sustained (294). One reason for the variable association of IL-4 expression with disease profile may lie in the fact that infection with *M. tuberculosis* is associated with expression of the IL-4 antagonist IL-4δ2, and it may be the relative levels of IL-4 and its splice variant that define the impact of the cytokine on disease outcome (295–297).

Aerosol *M. tuberculosis* infection of mice deficient in IL-4, IL-4/IL-13, IL-4Rα, or STAT-6 fails to result in early differences in bacterial burden (298, 299) despite increased levels of IFNγ (110); however, during chronic infection, bacterial burden increases in IL-4Rα and STAT-6 gene-deficient mice (298). IL-4 can influence *M. tuberculosis*-induced granulomas, because overexpression of this cytokine by adenovirus results in increased accumulation of monocytes and eosinophils within the granuloma (300). This demonstrates that IL-4 has the potential to deviate the *M. tuberculosis*-induced granuloma from its mononuclear to a more granulocytic characteristic (35, 301), but that its impact on disease is not strong.

Information regarding the role of IL-5 in TB is limited; however, following intranasal infection of IL-4- or IL-5-deficient mice with BCG effective clearance is observed with no differences in bacterial burden or lung pathology among IL-4- and IL-5-deficient mice (302). One area where this cytokine may play a role, however, is in HIV coinfection, because IL-5 is not observed in NHP monocytes infected with *M. tuberculosis*, but, during coinfection with simian immunodeficiency virus (SIV), IL-5 and IL-13 are increased (303). NHP models coinfected with SIV and *M. tuberculosis* show disrupted CD4$^+$ T-cell levels (303), and the mechanism of loss appears to be related to monocyte-derived IL-5 that was induced following SIV infection (303).

IL-13 was originally described as a T-cell-derived cytokine capable of inhibiting proinflammatory cytokine production (304, 305); IL-13 function has since been extended to include regulating airway restriction and antihelminth responses (306–308). Furthermore, IL-13 is not only produced by T_H2 cells, but can also be generated by invariant NK T cells (iNKT), granulocytes (e.g., basophils, eosinophils, and mast cell), murine group 2 innate lymphoid cells (ILC2s), and human "chemoattractant receptor-homologous molecule expressed on T_H2 lymphocytes" (CRTH2)-type 2 ILCs (309–313). It is structurally similar to IL-4 and signals through cell surface receptor heterodimers composed of IL-4Rα and IL-13Rα1 subunits to activate STAT6 (313).

Although not much is known regarding IL-13 in *M. tuberculosis* infection, whole blood mRNA from latently infected children shows increased IL-13 compared with uninfected controls (314), although IL-13 levels are not different between actively and latently infected children (314). IL-13 may play a modulatory role in autophagy, which is an important homeostatic mechanism for intracellular degradation and has a protective function during mycobacterial infection (315–317). Indeed, in both murine and human macrophages, IL-13 and IL-4 are independently capable of inhibiting autophagy as well as IFNγ-induced autophagy-mediated killing of *M. tuberculosis* (317). Transgenic mice overexpressing IL-13 succumb to infection with *M. tuberculosis* sooner than control mice and have more necrotic granulomas within the lung (318), and this is associated with delayed expression of IFNγ and IL-17-producing CD4$^+$ T cells and increased arginase production by macrophages within the necrotic granulomas (318). While this overexpression of IL-13 represents an artificial situation, it highlights the potential for disruption of the T-cell response to have a profound effect on TB development. Studies utilizing IL-13 gene-deficient mice are necessary to truly uncover the distinct role for IL-13 in TB.

Transforming Growth Factor β

TGFβ is a pleiotropic cytokine and regulates hundreds of genes (319–322) to modulate inflammation, cell proliferation, and differentiation, as well as cell migration (323–325). TGFβ can be made by various cell types, including all leukocytes (e.g., lymphocytes, macrophages, monocytes, dendritic cells) (325, 326). Not surprisingly, the impact of TGFβ on disease outcomes is dependent on cell type and stage of cellular differentiation, as well as the cytokine milieu (327).

TGFβ levels are increased in blood monocytes isolated from TB patients compared with uninfected individuals (328), and TGFβ localizes primarily to multinucleated Langhans giant cells within the granulomas of TB patients (328). TGFβ is induced in human blood monocytes by *M. tuberculosis* lipoarabinomannans (329), and human monocytes treated with TGFβ allow for increased intracellular *M. tuberculosis* sur-

vival, suggesting that TGFβ can play a regulatory role and potentially negative role in the context of *M. tuberculosis* infection (330). T cells and monocytes from TB patients cocultured with natural inhibitors of TGFβ, such as decorin and latency-associated peptide, exhibit restored T-cell proliferation and monocytic control of *M. tuberculosis*, again suggesting that TGFβ is a regulatory inhibitor of both T-cell responses and antibacterial activity (331). TGFβ is also able to induce IL-10 and to synergize with this cytokine to suppress IFNγ production (332). The contribution of TGFβ polymorphisms to TB susceptibility is not clear (333, 334). The polymorphism +869T/C does not correlate with increased susceptibility in a Chinese population (334), whereas the same polymorphism in an Indian population reveals a significant susceptibility to *M. tuberculosis* in patients harboring this polymorphism. Our knowledge of the importance of context in the function of TGFβ suggests that other genetic or indeed cultural differences may mask the contribution of this polymorphism. Taken together, the data suggest that TGFβ plays an inhibitory role in host responses to *M. tuberculosis* infection.

IL-10

IL-10 was initially identified as a "cytokine synthesis inhibitory factor" produced by Th2 cells (335). However, IL-10 can be produced by other T-cell subsets including T_H1 and T_H17 cells, macrophages, some dendritic cell subsets, myeloid-derived suppressor cells, B cells, and neutrophils (336). In addition, T_{REG} cells are also a major source of IL-10 and serve to limit potentially pathogenic immune responses (336). IL-10 signals through the IL-10R, which comprises IL-10R1 and IL-10R2 (337). IL-10R1 is induced on hematopoietic cells, while IL-10R2 is expressed constitutively on most tissues and immune cells (336). In myeloid cells, IL-10 production can occur via TLR-MyD88-dependent pathways (338), as well as TLR-independent C-type lectin receptor engagement (339).

In the context of TB, meta-analyses suggest that polymorphisms in the IL-10 gene, specifically –1082G/A polymorphisms in Europeans and –592A/C polymorphisms in Asians, are significantly associated with TB risk (340). Furthermore, antigen-specific IL-10 production is found in pulmonary TB patients (341, 342) and, along with TNFα production, can be used to reliably distinguish between latent TB and pulmonary TB (342). In addition, increased accumulation of T_{REG} cells expressing IL-10 correlates with increased bacterial burden and more severe TB in an Indian population (343, 344), and a high level of IL-10 at the end of treatment in pulmonary TB patients is associated with TB recurrence (345). Finally, infection with helminths in TB patients results in decreased antigen-specific IFNγ and IL-17 responses, which are dependent on IL-10, because IL-10 blockade significantly increases frequencies of IFNγ-producing cells (346, 347).

Following mycobacterial stimulation, dendritic cells and macrophages both produce IL-10 (338, 348). In macrophages, IL-10 can block phagosome maturation and macrophage activation in a STAT3-dependent manner, thus allowing a niche for *M. tuberculosis* to replicate and survive within the phagosome (349). In addition, IL-10 can inhibit aspects of IFNγ-mediated macrophage activation (350). In dendritic cells, mycobacterially induced IL-10 production can inhibit antigen presentation through the downregulation of MHC class II molecules, decreased IL-12 production, and inhibition of dendritic cell trafficking to the lymph nodes for T-cell priming (351, 352). In keeping with this regulatory role for IL-10, studies have shown that IL-10 gene-deficient mice infected with *M. tuberculosis* exhibit increased T_H1 and T_H17 responses, and this coincides with improved *M. tuberculosis* control during chronic infection (336) (Fig. 2). The effect is not dramatic and indeed some challenge models fail to show an impact of IL-10 gene deficiency (299, 353, 354). Interestingly, CBA mice generate significant early macrophage IL-10 production correlating with increased susceptibility to *M. tuberculosis* infection (355). This increased susceptibility also coincides with reduced expression of TNFα and IFNγ in T cells and can be reversed by blocking IL-10R signaling very early in infection (355). In CBA IL-10 gene-deficient mice, *M. tuberculosis* infection results in development of fibrotic granulomas with similarity to lesions seen in humans (356). In vaccine models, blocking IL-10 at the time of BCG vaccination (336), or using IL-10 gene-deficient mice in BCG vaccination and *M. tuberculosis* challenge experiments (244), demonstrates that IL-10 limits IFNγ and IL-17 responses during priming and decreases vaccine-induced protection against *M. tuberculosis* challenge. Computational modeling also highlights the pleiotropic role for IL-10 (357). Importantly, there are differences in the role of specific cytokines depending on the nature of the *M. tuberculosis* strains being examined. Indeed, the W-Beijing HN878 strain induces robust IL-10 production to inhibit the induction of a Th1 response (98). In the future, therefore, addressing the role for IL-10 in the context of infection, a variety of *M. tuberculosis* strains will likely provide novel insights into the function of IL-10 in TB.

THE CHEMOKINES

Limiting bacterial spread and containment of inflammation within discrete sites are hallmarks of disease control in TB and dovetail with the establishment of the TB granuloma. The TB granuloma is a multicellular immune bolus consisting of a number of cell types including macrophages, neutrophils, lymphocytes, and B cells, among others (358). Formation of the TB granuloma is governed by coordinated expression of the chemotactic cytokines referred to as chemokines. Chemokine expression establishes a chemical gradient that drives mobilization and recruitment of cells from peripheral organs to the site of infection and within the granuloma. The importance of this coordination has recently emerged to be critical in disease control with proper localization of CD4 T cells in the lung parenchyma being paramount (80–82).

Since the discovery of the first chemokine, now known as CXCL8 (i.e., IL-8), numerous chemokines have been identified, resulting in the need for a uniform nomenclature currently based on primary sequences of chemokine ligands (359–361). These chemokine ligands modulate biological processes through interactions with seven transmembrane G protein-coupled receptors (360, 362). Chemokines are divided into four families (C, CC, CXC, CX3C) based on the presence of cysteine(s) and the presence or absence of nonconserved amino acids between those cysteines (360, 361). The CC chemokine receptors (CCR) are involved in the recruitment of monocytes, neutrophils, lymphocytes, and macrophages (34). During bacterial infection, signaling via pattern recognition receptors drives the expression of CC chemokine ligands (CCL) and the development of gradients that are responded to by specific cell surface chemokine receptors (34) with functional recruitment involving monomeric or dimeric forms in the respective chemokine ligands (363). CXC chemokine ligands, denoted as CXCL, contain a nonconserved amino acid between the two cysteines, unlike CCL chemokines (360, 361). The number of chemokine ligands outnumbers the chemokine receptors, suggesting redundant or highly refined roles for the receptors as in the case for CCR4 expression mediating the migration of both T_H1 and T_H2 responses (363). This is further exemplified by CXC receptors (CXCR), which are capable of binding multiple CXCLs to promote the migration of specific cells along a chemokine gradient (360). Because development of the granuloma and communication between the cells within the granuloma are so critical for control of disease, this section will explore the roles chemokines play in modulating TB disease outcome. In accordance with the most recent chemokine nomenclature, CCRs and CCLs as well as CXCRs and their ligands, CXCLs, are numbered (e.g., CCR2, CCL2) in a manner that avoids the previous random naming system (364) (Table 2).

CC Receptors and Their Ligands

CCR1

CCR1 is expressed by T lymphocytes, neutrophils, dendritic cells, monocytes, and macrophages (365–369). Under normal conditions, CCR1 is constitutively expressed at low levels, but it is upregulated during stimulation of neutrophils with granulocyte-macrophage colony-stimulating factor (GM-CSF) and during the differentiation of monocytes to macrophages (369, 370).

In TB patients, $CD4^+$ T lymphocytes expressing CCR1 are elevated in the pleural fluid (371), and, in the blood, increased levels of $CCR1^+$ T lymphocytes, natural killer (NK) cells, and neutrophils are seen (372). *In vitro*, human neutrophils express both CCR1 and produce CCL3 upon infection with *M. tuberculosis* (373). Infection with *M. tuberculosis* induces the expression of the CCR1 ligands CCL3, CCL4, and CCL5 in the lung (374, 375); however, CCR1 deficiency in mice does not impact control or disease progression following *M. tuberculosis* infection (35). Thus, it is likely that, while CCR1 correlates with cellular activation during TB, it does not appear to play a strong role in protection.

CCR2

CCR2 has a similar distribution pattern as CCR1 on hematopoietic cells (376, 377). Expression of CCR2 on monocytes and its interaction with CCL2 and CCL7 are essential for mobilization of monocytes from the bone marrow into the circulation and into sites of inflammation (378). Increased levels of CCL2 in the serum of pulmonary TB and TB patients with disseminated disease have been reported (379) and are associated with the damaging influx of inflammatory cells during TB pleurisy (371, 372). At a minimum, the presence of CCR2 and its ligands is a potential indicator of disease severity in TB patients.

Low-dose aerosol *M. tuberculosis* infection of mice elicits increased expression of CCL2, CCL7, and CCL12 in the lung during the acute stages of *M. tuberculosis* infection (380). Accordingly, mice deficient in CCR2 or CCL2 are defective in macrophage and T-lymphocyte recruitment following *M. tuberculosis* infection (380–383) (Fig. 1). Consistent with defects in recruitment of immune cells, granuloma formation in CCR2 gene-deficient mice is delayed, and is associated with perivascular cuffing and loosely formed granulomas (380).

Similarly, *M. tuberculosis*-infected CCL2 gene-deficient mice also exhibit decreased granulomatous inflammation in *M. tuberculosis*-infected lungs (382, 383), despite these innate and adaptive immune defects, CCR2 gene-deficient mice are not more susceptible to low-dose *M. tuberculosis* infection using either the aerosol or intravenous route (380). When taken in the context of the role of the type I IFNs in recruiting just enough (102) but not too many phagocytes (101), it may be that using a simple gene deficiency model to dissect the role of each chemokine or chemokine receptor will not be informative (Fig. 1).

CCR4

CCR4 is expressed on T-cell subsets including T_H17, T_H2, and T_{REG} cells that mediate allergic responses and protection against extracellular pathogens (384–386). T lymphocytes expressing CCR4 are mobilized via a chemokine gradient established by dendritic cells in the context of both allergic and parasite-induced inflammation (387–392). In the context of *M. tuberculosis* infection, T_{REG} cells are increased in the peripheral blood of TB patients and inhibit production of IFNγ by *M. tuberculosis*-specific $CD4^+$ T cells (393, 394), and CCR4 antagonists promote proliferation of T cells during MVA85A vaccination (395). The ligand for CCR4, CCL17, but not CCL22 has also been shown to be elevated in the serum of active TB patients (396). These data suggest that CCR4-mediated regulation of T-cell responses to *M. tuberculosis* antigens may occur during TB and that antagonism of CCR4 maybe a target for therapeutic use or as an adjuvant during vaccination. Mechanistic analysis of CCR4 function during mycobacterially induced granuloma responses demonstrates that, despite delivery of mycobacterial and helminth antigens inducing both CCL17 and CCL22 in mouse lungs, the absence of CCR4 results in reduced granuloma formation in following mycobacterial but not helminth antigen challenge (397). Further investigation of the role of CCR4 in the development of immunity and immunopathology is likely warranted.

CCR5

CCR5 is expressed on monocytes, macrophages, T lymphocytes, neutrophils, and dendritic cells (34, 376, 377, 398) and responds to CCL3, CCL4, and CCL5 (374, 375). CCR5 is most notable in the study of HIV infection, where CCR5 facilitates viral entry into T lymphocytes and macrophages (398, 399). HIV infection dramatically compromises immunity to TB, and this is thought to be largely as a result of compromised T-cell function; however, blocking CCL5 in cultures of *M. tuberculosis*-infected alveolar macrophages from HIV patients results in enhanced *M. tuberculosis* growth (374), suggesting that CCL5 can directly promote bacterial killing by *M. tuberculosis*-infected macrophages. Interestingly, analysis of single-nucleotide polymorphisms in *CCL5* has identified two risk haplotypes, A-C-T and G-C-C, that are associated with susceptibility to TB (400). What remains unclear is whether this haplotype is associated with increased or decreased CCL5 production.

In the mouse model of *M. tuberculosis* infection, all three CCR5 ligands are upregulated in the lungs, with CCL5 being induced to the highest level (375, 401). Upon *M. tuberculosis* infection, CCL5 gene-deficient mice exhibit transient early impairment in granuloma formation and delayed T-cell recruitment (401), while CCR5 deficiency results in increased inflammation in the lung (375) (Fig. 1). The observed delayed T-cell recruitment into the lungs of CCL5-deficient mice (401) is not entirely surprising, because CCR5-CCL5 are important for dendritic cell trafficking to the lymph nodes, facilitating T-cell activation and accumulation during TB (375, 401). The difference between the outcome for the CCR5- and CCL5-deficient mice in terms of inflammatory outcome may reflect the action of other CCR5 ligands acting in the absence of CCL5. The increased accumulation of $CD4^+$ and $CD8^+$ T lymphocytes, myeloid cells, neutrophils, and macrophages in the lungs of chronically infected CCR5-deficient mice suggests, however, that any compensating ligand is not optimal at limiting pathologic consequences (375). Whether the models are showing true redundancy in the chemokine or our failure to appreciate the subtle nature of the function of each chemokine is still an issue for debate (402).

CCR6

CCR6 has only one known ligand, CCL20 (403), and is expressed on effector and memory T cells, myeloid dendritic cells, and B cells. CCR6 is important for the recruitment of CCR6-expressing cells to mucosal surfaces and their localization at sites of inflammation in epithelial tissues (403, 404). While CCR6 plays a vital role under both homeostatic and inflammatory conditions, it has been implicated in pathologic conditions, particularly in cancer and rheumatoid arthritis models (405, 406). Although few studies have investigated the role of CCR6 in *M. tuberculosis* infections, emerging data support a protective role for CCR6 (407). Specifically, memory $CD4^+$ T cells specific for *M. tuberculosis* antigens coexpress CXCR3 and CCR6 and these

$CXCR3^+CCR6^+$ $CD4^+$ T cells are associated with an IFNγ response (386). Following *ex vivo* expansion, those $CD4^+$ T cells that produced IL-17A in response to *M. tuberculosis* coexpressed CXCR3 and CCR6 (408). In a detailed analysis of reactivity to mycobacterial antigens it was found that $CXCR3^+CCR6^+$ IFNγ-producing $CD4^+$ T cells from latently *M. tuberculosis*-infected individuals responded to three immunodominant antigenic islands within the *M. tuberculosis* genome that were all associated with bacterial secretion systems (409) (Fig. 2). The CCR6 ligand, CCL20, appears at high levels in peripheral blood mononuclear cells, myeloid-derived macrophages, and bronchoalveolar lavage samples from TB patients (410, 411) and increased CCL20 mRNA is seen in murine and NHP lung (412, 413). It is likely therefore that CCR6 mediates the localization of memory cells to sites of *M. tuberculosis*-induced inflammation. Mouse studies have identified a critical role for CCR6 in the innate immune-mediated control following acute BCG infection (407). Innate cell types, such as CD1b-restricted iNKT cells, are impacted by the absence of CCR6, in that they fail to accumulate effectively in the lung, and this is associated with poor bacterial control and increased susceptibility to *M. tuberculosis* infection (407). Collectively, the current literature suggests that there is a correlation between CCR6 expression and bacterial control; however, mechanistic studies investigating the function of CCR6 in innate immune responses as well as its role in directing memory T-cell migration are required.

CCR7

Correct localization of dendritic cells and T and B cells is critical for the function of secondary lymphoid tissues (414). CCR7 ligation by CCL19 and CCL21 is vital for the positioning of T cells and dendritic cells in the paracortical region of these secondary lymphoid organs (SLO) (415) (Figs. 1 and 2). CCL19 and CCL21 are constitutively expressed by SLO stromal cells, while CCL21, but not CCL19, is expressed on lymphatic endothelial and high endothelial venules (415–418). CCR7 has also been implicated in thymic function and development, as well as homeostatic and inflammation-induced migration of dendritic cells to draining lymph nodes via the afferent lymphatics. In *M. tuberculosis* infections, it is thought to be necessary for dendritic cells from the lungs to relocate in the SLOs, activate naive T cells, and elicit recruitment of T cells into the site of infection for bacterial control. Early migration of mature dendritic cells to the mediastinal lymph node is supported by CCR7 (419), and CCR7-deficient mice exhibit impaired dendritic cell migration to this node (420) (Fig. 2). Similarly, *plt* mutant mice, which lack expression of CCL19 and CCL21-Ser in SLO, also have poor dendritic cell migration (421), and proliferation of adoptively transferred *M. tuberculosis*-specific $CD4^+$ T cells is delayed in mice deficient of CCR7 (420) and *plt* mice (422). Interestingly, the CCR7 chemokine ligand, CCL19, is present within granulomas containing B-cell aggregates that resemble lymphoid structures, and in the absence of CCR7 these B-cell follicles are also absent (416). While these mice display disorganized B-cell aggregation, the enhanced lymphocytic infiltrations observed in the lungs of CCR7 gene-deficient mice are sufficient to control *M. tuberculosis* to levels comparable to CCR7-sufficient mice (416). Similarly to CCR7-deficient mice, *plt* mutant mice fail to develop B-cell follicles and have disorganized granulomas (422). However, unlike CCR7-deficient mice, *plt* mutant mice also have delayed accumulation of IFNγ-producing T cells and maintain higher bacterial burden (422). Thus, it seems that CCR7 plays an important role in the proper migration of dendritic cells to the draining lymph node for priming and activation of T cells, as well as the migration of $CD4^+$ T cells into lymphoid follicles following *M. tuberculosis* infection.

CXC Receptors and Their Ligands

CXCR1 and CXCR2

CXCR1 and CXCR2 share the binding partners, CXCL6 and CXCL8, while CXCR2 can exclusively bind to CXCL1-3, CXCL5, and CXCL7 (423). All these CXCLs contain the ELR motif, corresponding to a Glu-Leu-Arg tripeptide motif at the amino terminus region, adjacent to their CXC sequence. The functional role of this ELR motif is to confer angiogenic activity to the ELR-containing chemokine (424) and this motif is important for ligand-receptor binding interactions on neutrophils (425, 426). Ligand binding to CXCR1 and CXCR2 causes degranulation, intracellular calcium mobilization, and phosphorylation of MAPK (427).

Although most notably expressed on neutrophils in TB patients, both CXCR1 and CXCR2 can also be expressed on NK cells, T cells, and monocytes (423, 428). Comparison of CXCR1 expression on peripheral blood from TB patients shows that individuals with pulmonary TB have increased CXCR1, whereas latent TB patients have increased CXCR2 in whole blood (429). Moreover, increased CXCR1 correlates with impaired oxidative function in leukocytes, suggesting a possible regulatory role for CXCR1 on oxidative stress

(429). CXCR2-deficient mice infected intraperitoneally with *Mycobacterium avium* have decreased neutrophil accumulation and increased bacterial burden (430). However, following pulmonary infection with *M. avium*, no difference in cellular infiltrate or bacterial burden is observed, which highlights the importance of route and dose on identifying the function of the highly redundant chemokines.

CXCL8 has been the most studied CXCR1/2 ligand in the context of TB and this important neutrophil chemoattractant is expressed by multiple cell types, including alveolar epithelial cells, monocytes, macrophages, and fibroblasts upon *M. tuberculosis* infection *in vitro* (431–434) (Fig. 1). Following *in vivo M. tuberculosis* infection, pulmonary granulomas containing fibroblasts are also capable of secreting CXCL8 (431), and TB sputum samples contain elevated CXCL8 levels (435). CXCL8 is present at high levels at positive tuberculin skin reaction sites and is associated with high levels of neutrophils at this site (436). Furthermore, neutrophils isolated from pulmonary TB patients have increased expression of CXCL8, which is further increased following *ex vivo* infection with H37Rv but not the clinical strains, S7 and S10, suggesting strain-specific regulation of CXCL8 production in neutrophils (373). Whether CXCL8 is associated with a protective or pathologic response remains controversial (437, 438). Serum CXCL8 levels from pulmonary TB patients following treatment with antibiotics decreased, suggesting that CXCL8 could be a marker for treatment efficacy (439). Whether disease improvement is directly correlated to reduced CXCL8 levels or simply a reflection of reduced neutrophil accumulation is unclear (Fig. 1).

CXCL5, which is also a CXCR2 ligand, plays an important role in host responses against *M. tuberculosis* (440), because both CXCR2 and CXCL5 gene-deficient mice display lower bacterial burden following *M. tuberculosis* infection, which correlates with reduced neutrophil accumulation to the lung (440). In this model, alveolar epithelial secretion of CXCL5, mediating the recruitment of neutrophils, is dependent on TLR2 engagement with *M. tuberculosis* and blocking of neutrophil recruitment improves outcome in the lung (440) (Fig. 1). It appears that CXCR2 plays an important role in the pathologic granulomatous response during TB, and this could be an important target for host-directed therapy.

CXCR3

CXCR3 binds to its chemokine ligand partners, CXCL9, CXCL10, and CXCL11, also known as MIG, IP-10, and I-TAC, respectively (428, 441). It is expressed primarily by activated $CD4^+$ and $CD8^+$ T cells, and is detected on B cells and innate lymphocytes such as NK cells and NKT cells (428). CXCR3 expression is associated with supporting localization of cells to the site of infection (442, 443). Most notably, CXCR3 expression on effector T cells plays an important role in the migration of T cells both *in vitro* and *in vivo* (33, 441, 444–446) and the transcription factor T-bet transactivates CXCR3 on T cells to promote this migration (441) (Fig. 2). It is characterized as an inflammatory chemokine receptor on T cells and is significantly enhanced on T cells from inflamed tissues in human inflammatory reactions and has been implicated in various human and murine disease models, including idiopathic pulmonary fibrosis and asthma (441, 443, 447).

In response to *M. tuberculosis* infection, CXCR3-expressing T cells are found in the caseous, necrotic granulomas, and bronchoalveolar lavage in the NHP model, as well as in the lungs of infected mice (428). The presence of these cells correlates with elevated expression of CXCL9, CXCL10, and CXCL11 localized within granulomas (428), but CXCR3-deficient mice do not exhibit differences in bacterial burden following low-dose aerosol infection with *M. tuberculosis* (448, 449). Despite the absence of a bacterial phenotype, CXCR3-deficient mice do develop fewer granulomas of decreased size (448, 449), suggesting that CXCR3 is important for granuloma formation. The coexpression of CXCR3 with CCR6 on memory T cells in latently infected humans supports the importance of this receptor on the migration and function of human T cells during TB, but the precise role is not clear (Fig. 2). Human data support a protective role for CXCR3-binding chemokines because CXCL9 levels correlate with disease severity (379, 450), although the role of CXCL10 is unclear. CXCL10 has been proposed as a biomarker for improvement, because reduction of this chemokine in the serum relative to levels at recruitment is observed following TB treatment, and nonresponders do not show the same decrease (439, 451). Unfortunately, CXCL10 levels cannot distinguish between active and latent TB in children (452).

The mechanistic basis for CXCL10 activity in TB is not fully defined. In some cases, active TB can result in destruction of the lung parenchyma, leading to cavities. In AIDS-associated TB, increased CXCL10 is associated with noncavitary TB, whereas cavitary TB is associated with increased GM-CSF (114, 453). CXCL10 is important for modulating CXCL9 and CCL2, which promote disease, while CXCL10 is significantly increased

in patients with active pulmonary tuberculosis (100), and there may be a genetic association between a single-nucleotide polymorphism within the CXCL-10 promoter (135G/A) and TB susceptibility (454).

Additional studies are needed to confirm whether CXCR3 and its ligands are protective or harmful to disease outcome. It is also unclear how CXCL9-11 is induced and whether its induction is a direct result of *M. tuberculosis* infection or whether upregulated expression results from expression of cytokines capable of inducing CXCL9-11 expression (455–458). Still, animal models support CXCR3 and expression of its ligands as important regulators for granuloma formation (449, 459) (Fig. 2).

CXCR5

The B-cell chemoattractant, CXCL13, is the only known ligand for CXCR5. It is preferentially produced in B-cell follicles and, through its binding with CXCR5, is important for the development of lymphoid follicles. In lymphoid organs, the main source for CXCL13 is the follicular dendritic cell (460). However, IL-17-producing T cells have also been shown to express CXCL13 in a *Candida albicans* infection model as well as in synovial fluid from patients with rheumatoid arthritis (461). CXCL13 expression recruits CXCR5-expressing B cells and coordinates the correct position of these cells within SLO (462). A similar role has also been highlighted during *M. tuberculosis* infections. *M. tuberculosis* granulomas contain B cells, follicular dendritic cells, and high endothelial venules and thus provide important points of entry for trafficking lymphocytes (4, 428). CXCL13 is also elevated in *M. tuberculosis*-infected mice and is important for the localization of $CXCR5^+$ T cells to the lung parenchyma as well as the activation of phagocytes and control of bacterial growth (422, 459) (Fig. 2). With the use of NHP and mouse models of *M. tuberculosis*, $CXCR5^+$ T cells have been shown to traffic toward ectopic lymphoid follicles (bronchus-associated lymphoid tissues [iBALT]), adjacent to granulomas where CXCL13 is localized. In the absence of CXCR5, mice fail to develop iBALT and are more susceptible *M. tuberculosis* (459) with the impaired response being rescued through the adoptive transfer of CXCR5-sufficient T cells, suggesting that CXCR5 expression on T cells is important for both protection and the development of B-cell follicles. Furthermore, CXCR5 is required for the maintenance of *M. tuberculosis*-specific $CD4^+$ T cells during chronic infection (81). B cells from *M. tuberculosis*-infected murine lungs are also able to migrate along a CXCL13 chemotactic gradient *in vitro* via their expression of CXCR5 (463). IL-23- and IL-17R-dependent induction of CXCL13 within the *M. tuberculosis*-infected lungs appears to be important for control of this infection, and CXCL-13- and CXCR5-deficient mice are the only chemokine-deficient mice that show increased susceptibility upon *M. tuberculosis* infection, suggesting that this cytokine/chemokine axis is nonredundant in *M. tuberculosis* infection (Fig. 2).

CONCLUSION

Chemokines and cytokines are critical for initiating and coordinating the organized and sequential recruitment and activation of cells into *M. tuberculosis*-infected lungs (Figs. 1 and 2). Correct mononuclear cellular recruitment and localization are essential to ensure control of bacterial growth without the development of diffuse and damaging granulocytic inflammation. An important block to our understanding of TB pathogenesis lies in dissecting the critical aspects of the cytokine/chemokine interplay in light of the conditional role these molecules play throughout infection and disease development (Tables 1 and 2). Much of the data highlighted in this review appear at first glance to be contradictory, but it is the balance between the cytokines and chemokines that is critical, and the "goldilocks" (not too much and not too little) phenomenon is paramount in any discussion of the role of these molecules in TB. Determination of how the key chemokines/cytokines and their receptors are balanced and how the loss of that balance can promote disease is vital to understanding TB pathogenesis and to identifying novel therapies for effective eradication of this disease.

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