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## Cytokines and Chemokines in *Mycobacterium tuberculosis* infection

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### 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 tumour necrosis factor family, the interleukins, and the chemokines.

Virtually every nucleated cell can produce and respond to cytokines placing these molecules at the centre 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* (Mtb) 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 Mtb infection of various animal models, including non-human primates, mice and rabbits. Perhaps the most important message of this chapter is that in a complex disease such as tuberculosis (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 upon context.

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 co-evolution between modern humans and Mtb (5). Evolutionary patterns based on genetic analyses suggest that Mtb 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 co-evolution between humans and Mtb, Mtb 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 harbours some form of Mtb infection (8).

Two facts illustrate the focus of Mtb on manipulating the human immune response. Firstly, Mtb 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. Secondly, we have exploited the strong and sensitive T cell-based inflammatory response to Mtb antigens as a skin test to indicate infection with Mtb. Thus teleologically speaking we may

suggest that Mtb 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 Mtb interaction when immune surveillance cells of the lung recognize danger through binding of their pattern recognition receptors to exquisitely refined Mtb 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, co-locate with Mtb-infected phagocytic cells and release cytokines which activate the infected cells to kill the Mtb (7, 9). If this induction of immunity is not met by Mtb, then the host dies rapidly with no effective transmission if 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 Mtb, 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 Mtb antigen (i.e. the skin test response). However for Mtb 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. Mtb expresses molecules which 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 co-ordination 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 I) and chemokines (Table II) in the context of Mtb infection and how they function to stop the development of TB and also how they might contribute to the progression of disease.

## CYTOKINES

### Tumour Necrosis Factor alpha (TNF $\alpha$ )

TNF $\alpha$  is a cytokine that is released following activation of the immune system. Although it is primarily produced by macrophages, TNF $\alpha$  can also be secreted by lymphocytes, mast cells, endothelial cells, and fibroblasts (10). Because most cells exhibit responsiveness to TNF $\alpha$ , it is considered a major proinflammatory mediator. It is produced as a type II transmembrane homo-trimeric protein (mTNF) which can become released into the extracellular milieu through the proteolytic action of TNF $\alpha$  converting enzyme (TACE) (11). Soluble TNF (sTNF) exists as a 51 kDA trimeric protein that is unstable upon reaching nanomolar concentrations (12) but which upon binding to cognate TNF receptors (TNF-R) induces activation of proinflammatory responses mediated by NF $\kappa$ B, 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 TNFR-2, also known as CD120b and p75/80, can bind either the membrane or the soluble form of TNF $\alpha$  (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). Signalling 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 TNF $\alpha$  and this regulation of immunity provides tempting targets for manipulation by Mtb.

Originally described for its ability to promote necrosis of tumours (21), TNF $\alpha$  has since been implicated in proliferation and differentiation of immune cells as well as multiple inflammatory processes including migration (20) apoptosis of Mtb-infected cells in vitro (22, 23). Upon initial Mtb infection, the interaction between immune surveillance cells such as phagocytes in the lung and the invading Mtb, results in the production of multiple proinflammatory cytokines, including TNF $\alpha$  (4) (Figure 1). Although both virulent and avirulent Mtb are able to induce comparable levels of TNF $\alpha$  by human alveolar macrophages, TNF $\alpha$  produced in response to infection with virulent Mtb strains has less bioactivity (24). This is an example of the ability of the bacterium to manipulate the host response as the decreased TNF $\alpha$  bioactivity has been attributed to the induction of IL-10 by the virulent strain which then results in release of soluble TNFR2 which binds the induced TNF $\alpha$ , thereby inhibiting its function (24). As infection progresses TNF $\alpha$  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 Mtb infection models, the importance of TNF $\alpha$  is exemplified by mice deficient in the TNF receptor or following TNF neutralization (26). In these models, TNF $\alpha$  deficiency results in increased susceptibility with mice succumbing to infection within 2–3 weeks, while harbouring a high bacterial burden (26). Critically, although inflammatory cells accumulate at the site of Mtb infection in TNF $\alpha$ -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 giant cells, CD4<sup>+</sup> and CD8<sup>+</sup> T cells, B cells, and neutrophils (30). In one of the earliest studies of the role of TNF $\alpha$  in mycobacterial disease it was shown that TNF $\alpha$  neutralization following BCG infection lead to the loss of granulomas (31). Neutralization of TNF $\alpha$  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, TNF $\alpha$  sits at the cross roads where innate immunity and acquired immunity as well as cytokines and chemokines interact. In the absence of TNF $\alpha$ , 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 Mtb to more immunoprivileged sites has long been appreciated (35). Indeed, inhibition of TNF $\alpha$  promotes dissemination of Mtb to sites such as the CNS (36, 37) wherein adverse events are profound and often irreversible. It is thought that Mtb 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 TNF $\alpha$  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 TNF $\alpha$ -deficient mice, has shown that neuron-derived TNF $\alpha$  production is dispensable for protection against CNS-TB (41). These data support the notion that TNF $\alpha$  is critical for the initiation and co-ordination of cellular responses but that it has the potential to be pathogenic when expressed in the absence of immunity.

TNF $\alpha$  is required throughout the life of the infected host as reactivation of pulmonary TB occurs in latently-infected mice upon neutralization of TNF $\alpha$  (42). Upon neutralization, less defined granuloma formation is seen along with increased bacterial burden in the lung, and extra pulmonary sites such as the liver and spleen (42) (Figure 2). Enhanced histopathology is also observed in TNF $\alpha$ -neutralized mice supporting the importance of a regulated cellular interaction during Mtb infection. The protective role of TNF $\alpha$  is further highlighted in those patients with autoimmune and chronic diseases who are undergoing anti-TNF $\alpha$  neutralizing therapies including infliximab, adalimumab, and etanercept (43, 44). Though this therapy is successful at treating the autoimmune disease, a significant correlation between reactivation of latent TB in patients undergoing anti-TNF $\alpha$  therapy has been reported (45–52). Patients using infliximab and/or adalimumab have a higher incidence of TB reactivation in extra pulmonary sites compared to etanercept (50). While a mechanism for this has not been determined, mathematical modelling and bioinformatic analysis suggests that reactivation is related to drug tissue penetration, drug half-life, and relative specificity for membrane-bound TNF $\alpha$  or soluble TNF $\alpha$  (53). An intriguing mechanism for the effect of infliximab on immunity to Mtb 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 Mtb-specific CD8 T cells (54). In a cynomolgus macaque model of TB, latently infected primates were given either soluble TNF $\alpha$  or adalimumab and exhibited increased reactivation and harboured higher bacterial burdens compared to their latently infected untreated counterparts (55). As would be expected due to the higher bacterial burden and the role of TNF $\alpha$  in limiting bacterial spread, there were more granulomas in the lungs of the treated monkey (26, 55). In the zebrafish model of *M. marinum* infection, TNF $\alpha$  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. TNF $\alpha$  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 TNF $\alpha$ -producing Mtb-specific CD4<sup>+</sup> T cells compared to 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). TNF $\alpha$  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 TNF $\alpha$  can mediate tissue damage and promote transmission (Table I).

## The Interferons

The interferon family demonstrates the potential for similar cytokines to play protective and pathological roles in TB disease. Based on receptor specificity and sequence homology, the interferons (IFNs) are classified into two types (58). IFN $\gamma$  is the only type II interferon and while structurally related to the type I interferons IFN $\alpha$  and IFN $\beta$ , these cytokines use different receptors and have distinct chromosomal locations (58). Unlike type I IFNs that bind to a common heterodimeric receptor comprised of IFNAR1 and IFNAR2 chains, IFN $\gamma$  binds to the IFN $\gamma$  receptor (IFNGR) which is comprised of two ligand binding IFNGR1 chains that associate with two signal transducing IFNGR2 chains (58). In addition while IFN $\gamma$  is essential for survival following Mtb infection the type I IFNs appear to be largely detrimental to the host during TB and may be co-opted by the bacterium for its own ends (Table I).

**Type II Interferon (IFN $\gamma$ )**—IFN $\gamma$ -IFNGR binding induces signalling 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, T cells (59–61). Innate production of IFN $\gamma$  by phagocytes stimulated through their pattern recognition receptors results in early pro-inflammatory responses to infection (58, 62) and unlike TNF $\alpha$ , which is regulated tightly by highly related molecules, production of IFN $\gamma$  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 IFN $\gamma$  pathway in humans is associated with increased risk for mycobacterial disease and Mendelian susceptibility to mycobacterial disease (MSMD) (65, 66). Autosomal complete recessive IFN $\gamma$ R1-deficient patients exhibit a predisposition for mycobacterial infections manifesting early in life and with poor prognosis (67). IFN $\gamma$ R2 deficiency (either total protein loss or loss of function) has also been observed and results in a similar outcome to IFN $\gamma$ R1-deficiency (68, 69). Similarly, mice that do not express IFN $\gamma$  due to 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 IFN $\gamma$  is as a phagocyte activating cytokine which instructs macrophages and other cells to change function. In particular, in the absence of IFN $\gamma$  Mtb 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 IFN $\gamma$  can activate macrophages there is very little control of Mtb growth in the absence of  $\alpha/\beta$  T cells or MHC class II following aerosol infection (74) suggesting that both IFN $\gamma$  and antigen-specific T cells are required for control of this

infection. However, whether it is T cells producing IFN $\gamma$  that is critical has not been definitively demonstrated but the strongest support of a critical need of CD4<sup>+</sup> T cells to make IFN $\gamma$  is from a transfer model in mice (75). In contrast memory T cells can mediate protection in the absence of either IFN $\gamma$  or TNF $\alpha$  suggesting other functions need to be identified (76). Both CD4<sup>+</sup> and CD8<sup>+</sup> T cells produce IFN $\gamma$  and accumulate with the infected lung and while absence of CD4<sup>+</sup> T cells results in rapid susceptibility to Mtb infection, the absence of CD8<sup>+</sup> T cells results in susceptibility later in the infection (77). The organization of the granuloma is also disrupted in the absence of CD4<sup>+</sup> T cells with predominantly perivascular cuffing of lymphocytes observed (78), suggesting that in the absence of CD4<sup>+</sup> T cells chemokine gradients are not established for T cell migration. It is also the case that while CD8<sup>+</sup> T cells can make IFN $\gamma$  during Mtb infection they require CD4<sup>+</sup> T cells to do so optimally (79).

The induction of IFN $\gamma$  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 (as those with HIV/AIDS develop TB readily) and that absence of IFN $\gamma$  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 co-locate with the phagocytes and/or the phagocytes are unable to respond to the signals delivered by the T cells then the number of IFN $\gamma$ -producing T cells circulating throughout the body is meaningless. It is therefore the case that IFN $\gamma$  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.

IFN $\gamma$  can act on cells other than macrophages; indeed it's most critical function in TB may not be to activate macrophages but rather to limit polymorphonuclear (PMN) inflammation (Figure 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 which lack IFN $\gamma$  exhibit high PMN infiltration as do mice lacking CD4<sup>+</sup> T cells (70, 78). Neutrophils which lack the IFN- $\gamma$ R fail to undergo apoptosis and accumulate in the lungs of Mtb-infected mice and their removal improves survival without altering bacterial burden (87). Similarly chimeric mice lacking IFN- $\gamma$ R on their radio-resistant cells over express IL-17 and have excessive neutrophil recruitment and reduced survival (88). It is possible that the high IFN $\gamma$ -producing CD4<sup>+</sup> T cells which populate the vasculature (80, 82) are located in such a position to reduce neutrophil accumulation.

Production of IFN $\gamma$  is a very useful diagnostic tool which has been developed to be more selective than the older skin test assay. In this prominent test for *Mtb* exposure, Mtb antigens (selected to be unique for Mtb versus other mycobacteria) are used to stimulate IFN $\gamma$  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, from those in the process of

developing active disease. Recently, studies have shown that patients that have more IFN $\gamma$ -producing T cells are actually more likely to progress to active disease, suggesting that this test may be optimised to identify those progressing toward disease (92).

**Type I Interferon (IFN)**—The Interferons (IFN) were first identified more than half a century ago for their antiviral activity (93). Type I IFNs represent the largest group, with at least thirteen gene products identified in humans and mice with IFN $\alpha$  and IFN $\beta$  being the best classified and the focus of this section. For clarity, IFN $\alpha$  and IFN $\beta$  will be collectively referred to as IFN $\alpha/\beta$  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 IFN $\alpha/\beta$  genes (94). Secreted IFN $\alpha/\beta$  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 IFN $\alpha/\beta$  regulated genes (94, 95).

The type I IFNs were not thought to play a major role in Mtb infection and indeed infection of IFNAR-deficient mice with a low dose aerosol of Mtb 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 Mtb strain HN878 is associated with IFN $\alpha/\beta$  dependent reduction in the activity of the pro-inflammatory cytokines IFN $\gamma$ , TNF $\alpha$ , IL-6 and IL-12, as well as in the anti-inflammatory IL-10 (97, 98) (Figure 1). Intranasal delivery of IFN $\alpha/\beta$  also results in increased bacterial burden and reduced survival in contrast to IFN $\gamma$  treated mice (97). Further, IFN $\alpha/\beta$  signalling interferes with IFN $\gamma$ -mediated killing of Mtb (99). One hypothesis regarding the role of type I IFNs during chronic Mtb 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<sup>+</sup> and CD8<sup>+</sup> T cells in the lung (98) (figure 1). Finally, transcriptional analysis of peripheral blood cells from those exposed to TB shows that both IFN $\gamma$  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 IFN $\alpha/\beta$  in TB, polyinosinic-polycytidylic acid and poly-L-lysine and carboxymethylcellulose (Poly-IC) was used to induce elevated levels of IFN $\alpha/\beta$  during Mtb infection (101). This poly-IC treatment results in elevated bacterial burden and increases the recruitment of an apparently permissive CD11b<sup>+</sup>GR1<sup>int</sup> cell phenotype recruited via chemokine (C-C motif) ligand 2 (CCL2) and C-C chemokine receptor type 2 (CCR2) (101) (Figure 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 signalling in that in its absence initial recruitment of target host cells for Mtb does not occur and immunity is compromised (102).

IFN $\alpha/\beta$  is another perfect example of a ‘goldilocks’ cytokine in TB (Table I). Just enough is required to initiate recruitment of phagocytes which provide activatable host cells for Mtb to invade: however, production of too much IFN $\alpha/\beta$  results in large numbers of permissive

cells which 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 (IL-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 non-lymphoid origin (103) and expression can be induced by other cytokines including IL-1, TNF $\alpha$  and IFN $\gamma$  (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 signalling 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 signalling (SOCS), which inhibits STAT signalling (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 as 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 Mtb 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 IFN $\gamma$  expression is observed suggesting that IL-6 can act to potentiate IFN $\gamma$  expression at the site of infection (108, 110). It appears also that IL-6 is required for optimal induction of protective responses during vaccination as, 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-signalling and is implicated in inflammatory diseases such as IBD (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 Mtb infection however 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 Mtb infection.

In vivo data support a protective role for IL-6 in the induction of early protective responses mediated through IFN $\gamma$  (108, 110). Human studies also give us considerable insights into the role of IL-6 during TB. Cavitory TB is the most destructive form of caseous TB whereby necrosis liquefies cellular material and results in compromised lung function. Humans with cavitory TB express lower levels of IL-6 and the chemokine IP-10 in their bronchial alveolar lavage (BAL) fluid when compared to TB patients without cavitory disease, thereby



indicating IL-6 and IP-10 as potential markers of controlled (non-cavitary) TB (114). As would be expected, elevated neutrophils were observed in BAL from cavitary TB patients while non-cavitary 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 maybe critical following high dose exposure or during immunodeficiency.

### IL-1 cytokines

The pro-inflammatory cytokines IL-1 $\alpha$ , IL-1 $\beta$  (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. Toll-like receptor, TLR), an adaptor molecule such as Myeloid differentiation primary response gene 88 (MyD88), and caspase-1 (120–122). Alternatively, IL-1 $\beta$  and IL-18 can also be induced by the non-canonical inflammasome pathway which 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 signalling to the transcription of inflammasome components (122).

IL-1 $\alpha$  is mostly associated with sterile cell injury (e.g. cigarette smoke), but is also induced during non-sterile cell injury (e.g. bacterial) where it functions locally as an alarmin (125–130). IL-1 $\beta$  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 IFN $\gamma$  (137–139). IL-18 activity results from co-localization of IL-18 receptor alpha (IL-18R $\alpha$ ) and IL-18 receptor beta (IL-18R $\beta$ ) on host cells including monocytes and epithelial cells (140).

**IL-1R/IL18R/MyD88**—Signalling through MyD88 is shared between TLR, IL-1R and IL-18R (141–143). MyD88 is an essential component in innate signalling in response to TB, as MyD88 gene deficient mice exhibit profound susceptibility to Mtb 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 Mtb 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 Mtb infection in the MyD88 gene deficient mice the accumulation of IFN $\gamma$ -producing T

cells was not affected. It is likely that these antigen-specific cytokine producing T cells were unable to mediate protection due to 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 Mtb infection in MyD88-deficient suggests that it is a failure of T cells to accumulate rapidly enough in naïve mice that contributes to their susceptibility (143).

What then is MyD88 signalling doing? Comparison of the phenotype of IL-1 deficient mice and MyD88 deficient mice is suggestive in this regard as 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-1 $\alpha$  and IL-1 $\beta$  are interdependent proinflammatory cytokines critical to defence against TB (145–149). Mice lacking either IL-1 $\alpha$  or IL-1 $\beta$  or both are susceptible to acute and chronic infection respectively following challenge with Mtb (145–148). IL-1  $\alpha/\beta$  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  $\alpha/\beta$  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-IL1 $\alpha$  and anti-IL-1 $\alpha/\beta$  antibodies delivered subcutaneously to Mtb-infected mice have also been shown to result in loss of body weight and lethality (148). Further, lung sections from anti-IL-1 $\alpha$ -treated mice exhibit lung parenchyma consumed by cellular infiltrates (148). During sterile mediated inflammation, IL-1 $\alpha$  appears to be involved in the expression of pro-inflammatory 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-1 $\beta$  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 Mtb strains, such as HN878 and for recall responses to H37Rv (149, 156, 157). Consistent with this, IL-1R1 gene deficient mice infected with the Mtb 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<sup>+</sup>Ly6G<sup>-</sup> cells following Mtb infection (145) and rescue of the lethal phenotype in IL-1 $\alpha$  mice can be accomplished by directed viral expression of IL-1 $\alpha$  in CD11c<sup>+</sup> cells transplanted in IL-1 $\alpha$  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 co-ordination of cellular responses by the induction of pro-inflammatory cytokines from the stroma (145, 147). One critical aspect of IL-1 function is in promotion of prostaglandin E2 (PGE2), which in turn mediates inhibition of type I IFN-induced accumulation of permissive macrophages at the site of infection (158) (Figure 1). Prostaglandins, such as PGE2 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 Mtb infection and delivery of PGE2 during Mtb infection results in a partial rescue of the lethal phenotype in IL-1 $\alpha/\beta$  infected mice (158). Taken together, the underlying function of IL-1 in Mtb 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 over recruitment of permissive macrophages mediated by type I IFN (102).

**IL-18**—IL-18 is essential for the production of IFN $\gamma$  from T cells under some conditions (159–163) and in some instances its absence can result in increased susceptibility to Mtb (150) although in other conditions, increased susceptibility to Mtb 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 Mtb-infected IL-18 deficient mice, an increased frequency of IFN $\gamma$ -producing CD4<sup>+</sup> and CD8<sup>+</sup> T cells in the lungs is seen but total IFN $\gamma$  production by these T cell populations is decreased, suggesting that IL-18 could contribute to optimal IFN $\gamma$  induction during TB (150, 162, 163). It would appear therefore that IL-18 plays a role in inducing high IFN $\gamma$  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 Mtb 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, IFN's and IL-1 family members. The correct ratio of these cytokines is essential for the balance of permissive and non-permissive phagocytes and for the development of a granuloma such that infected phagocytes and antigen-specific T cells can communicate effectively to stop Mtb 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 super family and is the only family composed of heterodimeric cytokines (164, 165) and this unique feature bestows diverse and pleiotropic functions due to 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)<sub>2</sub>) 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 Mtb infection (173–178). Further, patients with Mendelian susceptibility to mycobacterial disease (MSMD) harbour deficiencies in IL-12R $\beta$ 1, IFN $\gamma$ R1, and IL-12p40 and exhibit susceptibility to Mtb and develop BCGosis following delivery of the BCG vaccine (66, 178–181). Genetic aetiology for MSMD is associated with mutations in the autosomal genes *IFNGR1*, *IFNGR2*, *STAT1*, *IL12B*, *IL12BR1*, and X-linked gene *IKKBG*, encoding NF- $\kappa$ B essential modulator (NEMO) (66). All these autosomal genes are associated with IL-12/IFN $\gamma$ -dependent signalling and the IFN $\gamma$ -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 Mtb-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 Mtb infection (185, 186) whereas those lacking IL-12p35 exhibit prolonged survival relative to the IL-12p40 deficient mice (186). This, in turn, is dependent upon the availability of the IL-23p19 subunit (187). The absence of IL-12p40 results in the substantial loss of antigen-specific IFN $\gamma$  production (185, 186) (Figure 2) while the presence of IL-23p19 in the IL-12p35 deficient mice appears to promote sufficient antigen-specific IFN $\gamma$  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 IFN $\gamma$  production and to limit bacterial growth long-term (188). This requirement for long term function may also apply in humans as absence of the IL-12R1 results in poor accumulation of IFN $\gamma$  producing memory T cells (189). The innate pattern recognition receptors, TLR2 and TLR9, are necessary for optimal production of IL-12p40 in response to Mtb exposure (190) while the Mtb lipoarabinomannans have been shown to negatively regulate TLR-mediated IL-12 production by inducing an inhibitor of TLR signalling, IRAK-M (191). In contrast, mycobacterial LprA is a TLR2 agonist and promotes IL-12p40 production (192) reflecting the need for Mtb 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-12R $\beta$ 1 and IL-12R $\beta$ 2, respectively (193–195) with the IL-12p40 interacting with IL-12R $\beta$ 1 on the target cell surface thereby allowing the IL-12R $\beta$ 2 to induce JAK and STAT signalling and activate STAT4 homodimers (166). The homodimers IL-12p40, IL-12(p40)<sub>2</sub>, antagonizes IL-12-mediated immune responses though competitive binding of IL-12R $\beta$ 1 (196–198). However, in TB, it appears that IL-12(p40)<sub>2</sub> 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 Mtb 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-12R $\beta$ 1-dependent manner (200, 203). Bone marrow derived dendritic cells from mice deficient in IL-12p40 are unable to activate naïve 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)<sub>2</sub>, is sufficient to restore migration of the dendritic cells to the draining lymph node and for activation of naïve 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<sup>+</sup> cells in the Mtb-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 Mtb-specific T cells (203)(Figure 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 DCs, 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). Prior to 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 determining the role of IL-23 in TB a critical undertaking. IL-23 stabilizes the induction of T<sub>H</sub>17 cell subset that produces IL-17A, IL-17F and IL-22 production 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<sub>H</sub>17 cells, which require 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 signalling 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 Mtb, lung DCs produce IL-23, likely mediating the induction of IL-17 production (187, 217, 218).

Although IL-23 is important for generation of Mtb-specific IL-17-producing T cells (Figure 2), mice deficient in IL-23p19 control Mtb effectively for up to 90 days whereupon bacterial growth increases relative to intact mice (187, 219). In addition, treatment of Mtb-infected mice with adenovirus-expressing IL-23 reduces Mtb burden and increases cellular responses (220). In the absence of IL-23p19 Mtb-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)(Figure 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<sup>b</sup>-restricted ESAT6<sub>(1-20)</sub> peptide, which induces both IFN $\gamma$ - and IL-17-producing antigen-specific CD4<sup>+</sup> T cell responses (157). Critically, the improved kinetics of the vaccine-induced IFN $\gamma$ -producing T cells is lost in the absence of IL-23 as this cytokine is required for the generation of lung resident IL-17 producing CD4<sup>+</sup> memory T cells which generate a chemokine gradient facilitating the accelerated IFN $\gamma$  response. In the absence of IL-23 vaccine-induced protection to Mtb challenge is lost (157). Co-immunization of mice with a DNA vaccine composed of Mtb antigen 85B (Ag85B) and an IL-23-expressing plasmid also confers enhanced protection through the induction of augmented T cell proliferation and IFN $\gamma$  production when compared to Ag85B alone (217). Other studies also support an important role for IL-17 producing CD4<sup>+</sup> T cell subsets in mediating mucosal vaccine-driven protection (156, 221–223). Specifically, adoptive transfer of Mtb-specific IL-17-producing T cells into unchallenged mice confers protection following exposure to Mtb (156). Further, use of adjuvants capable of driving lung-resident IL-17 producing cells are able to initiate early CXCL13 expression thereby promoting appropriate accumulation of CXCR5<sup>+</sup> T cells within the Mtb-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 pro-inflammatory 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-27R $\alpha$  (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 signalling to promote IL-10-producing Tr1 cell-like regulatory populations (232). It also promotes proliferation (229) and polarization via T-bet (233) in naïve T cells (Figure 2).

In the context of Mtb infection, IL-27R-deficient mice challenged with Mtb 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 pathological damage. Due to 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 Mtb 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<sup>+</sup> T cells within the infected lung parenchyma. Mtb-specific CD4<sup>+</sup> T cells lacking IL-27R are also intrinsically fitter than IL-27R-sufficient CD4<sup>+</sup> T cells mice within the same environment (82)(Figure 2). The importance of IL-27 is further confirmed in human patients, wherein IL-27 is significantly increased in active TB patients compared to 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 which limits their ability to locate to, and persist within, the inflamed granuloma.

**IL-35**—IL-35, a dimeric protein encoded by IL-12 $\alpha$  and IL-27 $\beta$  chains and has been shown to suppress CD4<sup>+</sup> T cell responses (237). It is thought to be primarily expressed by regulatory T (T<sub>REG</sub>) 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<sub>REG</sub> cells, termed iT<sub>R</sub>35 cells (239), which function independently of IL-10 and transforming growth factor  $\beta$  (TGF $\beta$ ). While a specific function for IL-35 in Mtb 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-F, with IL-17A and IL-17F being the most studied. Production of IL-17 is conventionally attributed T cells, however, 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  $\gamma\delta$  T cells are a primary source of early IL-17 (218), and likely support early neutrophil accumulation (243) (Figure 1). Following BCG infection, IL-17 expression can be detected as early as day 1 post-infection 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<sub>2</sub> 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 down regulate IL-10 production thereby allowing increased IL-12 which subsequently promotes IFN $\gamma$  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 IFN $\gamma$  producing T cells (244). This study was the first to show that PGE<sub>2</sub> 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 Mtb (i.e. H37Rv and CDC1551) in the absence of IL-17 results no obvious phenotype (149, 187, 245) until late in disease (219). In contrast, following infection with the W-Beijing strain HN878 of Mtb, IL-17R

expression on radio-resistant cells (likely fibroblasts) of the lung is required to co-ordinate the rapid accumulation of cells within the lung via the induction of CXCL13 and recruitment of CXCR5<sup>+</sup> T cells to lymphoid follicles within the tissue (149)(figure 2). Importantly, the W-Beijing HN878 Mtb strain induces high levels of IL-1 $\beta$  and IL-17 relative to other Mtb strains (149) and also induces excess type I IFN (97) which is capable of bringing in permissive macrophages in a CCR2 dependent manner (101)(Figure 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 which limit bacterial growth (149).

The role of IL-17 in initiating early co-ordination of cellular responses in naïve mice is apparent when the challenge is significant as in the case of HN878; however the concept of IL-17 as a co-ordinator 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 IFN $\gamma$ -producing memory T cells (157). Further studies have shown that adoptive transfer of Mtb-specific IL-17-producing T cells into naïve mice are 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 Mtb antigens induces potent IL-17 responses which improve upon BCG vaccine-induced protection in mice (221). Interestingly, in mucosal vaccine models, IL-17 rather than IFN $\gamma$  appears to most important for vaccine-induced protection against Mtb providing support for the model that it is the co-ordination 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 post vaccination (222). These memory T cells appear to be metastable and become IFN $\gamma$ -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 rBCG ureC:Hly (223). Thus, IL-17 drives the induction of CXCL9–11 to recruit protective antigen-specific T cells, as well CXCL-13 to localize CXCR5<sup>+</sup> 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 I).

**IL-22**—IL-22 is primarily produced by CD4<sup>+</sup> T cells as well as  $\gamma\delta$  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 co-expression 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  $\beta$ -defensins (245, 250, 252). In the context of Mtb, IL-22 is expressed at higher levels than IL-17 at the site of infection and within granulomas from TB patients and non-human primate models (253, 254). Furthermore, in non-human primate infected with Mtb, CD4<sup>+</sup> T cells expressing membrane-bound IL-22 limit Mtb intracellular growth in macrophages (255). IL-22 can also inhibit intracellular growth of Mtb 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 Mtb-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<sup>+</sup>CD1d<sup>+</sup>CD5<sup>+</sup> 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 IFN $\gamma$  (259). In the absence of this cytokine however there appears to be no significant consequences (260). However, in a BCG vaccine model, NK1.1<sup>+</sup> cells appear to make IL-22 which contributes to protection by regulating T<sub>REG</sub> 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<sup>+</sup> T lymphocytes which are now known as T<sub>H</sub>2 T cells (262, 263). T<sub>H</sub>2 responses inhibit T<sub>H</sub>1 responses (264–266). IL-4, IL-5, and IL-13 are the signature cytokines associated with T<sub>H</sub>2 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 hetero-dimerization of IL-4R $\alpha$  (shared with IL-13) and the common gamma chain (shared with IL-2) (271). The IL-4 receptor (IL-4R) is the primary mediator 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<sub>H</sub>2 cells from other T<sub>H</sub> cells, including T<sub>H</sub>1 and T<sub>H</sub>17 (270). IL-4 expression is in part, regulated by IL-2 and is associated with the differentiation of T<sub>H</sub>2 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) 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 PBMCs (285) and IL-4-producing T cells isolatable from TB patients (286); however, PBMCs from active, Mtb-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 to 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<sup>+</sup> patients with pleural TB (292) and is consistent with increased CD4<sup>+</sup> cells expressing IL-4 in TB patients exhibiting cavitory disease (293). In a non-human primate model, IL-4-expressing T cells are increased transiently at week 6 post-Mtb 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 Mtb is associated with expression of the IL-4 antagonist IL-482 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 Mtb infection of mice deficient in IL-4, IL-4/IL-13, IL-4R $\alpha$  or STAT-6 fails to result in early differences in bacterial burden (298, 299) despite increased levels of IFN $\gamma$  (110); however, during chronic infection, bacterial burden increases in IL-4R $\alpha$  and STAT-6 gene deficient mice (298). IL-4 can influence Mtb-induced granulomas as over-expression 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 Mtb-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 cytokines may play a role however is in HIV co-infection as IL-5 is not observed in NHP monocytes infected with Mtb but during co-infection with SIV, IL-5 and IL-13 are increased (303). Non-human primate models co-infected with SIV and Mtb show disrupted CD4<sup>+</sup> 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 pro-inflammatory cytokine production (304, 305); IL-13 function has since been extended to include regulating airway restriction and anti-helminth responses (306–308). Furthermore, IL-13 is not only produced by T<sub>H</sub>2 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<sub>H</sub>2 lymphocytes’ (CRTH2)-type 2 ILCs (309–313). It is structurally similar to IL-4 and signals through cell surface receptor heterodimers composed of IL-4R $\alpha$  and IL-13R $\alpha$ 1 subunits to activate STAT6 (313). Though not much is known regarding IL-13 in Mtb infection, whole blood mRNA from latently infected children shows increased IL-13 compared to 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 IFN $\gamma$ -induced autophagy-mediated killing of Mtb (317). Transgenic mice overexpressing IL-13 succumb to infection with Mtb sooner than control mice and have more necrotic granulomas within the lung (318) and this is associated with delayed

expression of IFN $\gamma$  and IL-17-producing CD4<sup>+</sup> T cells and increased arginase production by macrophages within the necrotic granulomas (318). While this over-expression 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  $\beta$  (TGF $\beta$ )**—TGF $\beta$  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). TGF $\beta$  can be made by various cell types, including all leukocytes (e.g. lymphocytes, macrophages, monocytes, dendritic cells) (325, 326). Not surprisingly, the impact of TGF $\beta$ -on disease outcomes is dependent on cell type and stage of cellular differentiation, as well as the cytokine milieu (327).

TGF $\beta$  levels are increased in blood monocytes isolated from TB patients compared to uninfected individuals (328) and TGF $\beta$  localizes primarily to multinucleated Langhans giant cells within the granulomas of TB patients (328). TGF $\beta$  is induced in human blood monocytes by Mtb lipoarabinomannans (LAMs) (329) and human monocytes treated with TGF $\beta$  allow for increased intracellular Mtb survival, suggesting that TGF $\beta$  can play a regulatory role and potentially negative role in the context of Mtb infection (330). T cells and monocytes from TB patients co-cultured with natural inhibitors of TGF $\beta$ , such as decorin and latency associated peptide (LAP), exhibit restored T cell proliferation and monocytic control of Mtb again suggesting that TGF $\beta$  is a regulatory inhibitor of both T cell responses and anti-bacterial activity (331). TGF $\beta$  is also able to induce IL-10 and to synergize with this cytokine to suppress IFN $\gamma$  production (332). The contribution of TGF $\beta$  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 Mtb in patients harboring this polymorphism. Our knowledge of the importance of context in the function of TGF $\beta$  suggests that other genetic or indeed cultural differences may mask the contribution of this polymorphism. Taken together, the data suggest that TGF $\beta$  plays an inhibitory role in host responses to Mtb 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<sub>H</sub>1 and T<sub>H</sub>17 cells, macrophages, some dendritic cell subsets, myeloid derived suppressor cells, B cells and neutrophils (336). In addition, T<sub>REG</sub> 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 is comprised of 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). Further, antigen-specific IL-10 production is found in pulmonary TB patients (341, 342) and along with TNF- $\alpha$  production can be used to

reliably distinguish between latent TB and pulmonary TB (342). In addition, increased accumulation of T<sub>REGS</sub> 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 IFN $\gamma$  and IL-17 responses, which is dependent on IL-10, as IL-10 blockade significantly increases frequencies of IFN $\gamma$  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 Mtb to replicate and survive within the phagosome (349). In addition, IL-10 can inhibit aspects of IFN $\gamma$ -mediated macrophage activation (350). In dendritic cells, mycobacterially-induced IL-10 production can inhibit antigen presentation through the down regulation 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 Mtb exhibit increased T<sub>H1</sub> and T<sub>H17</sub> responses, and this coincides with improved Mtb control during chronic infection (336) (Figure 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 Mtb infection (355). This increased susceptibility also coincides with reduced expression of TNF- $\alpha$  and IFN- $\gamma$  in T cells and can be reversed by blocking IL-10R signaling very early in infection (355). In CBA IL-10 gene deficient mice, Mtb 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 Mtb challenge experiments (244), demonstrates that IL-10 limits IFN $\gamma$  and IL-17 responses during priming and decreases protective vaccine-induced protection against Mtb 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 Mtb 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 Mtb 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 dovetails 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, and lymphocytes, 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 non-conserved 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, signalling via pattern recognition receptors drive 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 the respective chemokine ligands (363). CXC chemokine ligands, denoted as CXCL, contain a non-conserved 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<sub>H</sub>1 and T<sub>H</sub>2 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). As 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 II).

### 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<sup>+</sup> T lymphocytes expressing CCR1 are elevated in the pleural fluid (371), and in the blood, increased levels of CCR1<sup>+</sup> T lymphocytes, natural killer (NK) cells and neutrophils are seen (372). In vitro, human neutrophils express both CCR1 and produce CCL3 upon infection with Mtb (373). Infection with Mtb 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 Mtb 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 has been reported (379) and is associated with the damaging influx of inflammatory cells during TB pleurisy (371, 372). At a minimum, in TB patients the presence of CCR2 and its ligands are potential indicators of disease severity.

Low dose aerosol Mtb infection of mice elicits increased expression of CCL2, CCL7 and CCL12 in the lung during the acute stages of Mtb infection (380). Accordingly, mice deficient in CCR2 or CCL2 are defective in macrophage and T lymphocyte recruitment following Mtb infection (380–383) (Figure 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, Mtb-infected CCL2 gene deficient mice also exhibit decreased granulomatous inflammation in Mtb-infected lungs (382, 383), despite these innate and adaptive immune defects, CCR2 gene deficient mice are not more susceptible to low dose Mtb 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 (Figure 1).

**CCR4**—CCR4 is expressed on T cell subsets including T<sub>H</sub>17, T<sub>H</sub>2, and T<sub>REG</sub> 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 Mtb infection, T<sub>REG</sub> are increased in the peripheral blood of TB patients and inhibit production of IFN $\gamma$  by Mtb-specific CD4<sup>+</sup> 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 Mtb 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 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 Mtb-infected alveolar macrophages from HIV

patients results in enhanced Mtb growth (374), suggesting that CCL5 can directly promote bacterial killing by Mtb-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 Mtb infection, all three CCR5 ligands are upregulated in the lungs, with CCL5 being induced to the highest level (375, 401). Upon Mtb 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) (Figure 1). The observed delayed T cell recruitment into the lungs of CCL5 deficient mice (401) is not entirely surprising as 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<sup>+</sup> and CD8<sup>+</sup> 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 Mtb infections, emerging data supports a protective role for CCR6 (407). Specifically, memory CD4<sup>+</sup> T cells specific for Mtb antigens co-express CXCR3 and CCR6 and these CXCR3<sup>+</sup>CCR6<sup>+</sup> CD4<sup>+</sup> T cells are associated with an IFN $\gamma$  response (386). Following ex vivo expansion, those CD4<sup>+</sup> T cells that produced IL-17A in response to Mtb co-expressed CXCR3 and CCR6 (408). In a detailed analysis of reactivity to mycobacterial antigens it was found that CXCR3<sup>+</sup>CCR6<sup>+</sup> IFN $\gamma$ -producing CD4<sup>+</sup> T cells from latently Mtb-infected individuals responded to three immunodominant antigenic islands within the Mtb genome that were all associated with bacterial secretion systems (409) (Figure 2). The CCR6 ligand, CCL20 appears to 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 non-human primate lung (412, 413). It is likely therefore that CCR6 mediates the localization of memory cells to sites of Mtb-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 Mtb 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 requires further study.

**CCR7**—Correct localization of dendritic cells, 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) (Figure 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 *Mtb* infections, it is thought to be necessary for dendritic cells from the lungs to relocate in the SLOs, activate naïve 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)(Figure 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 *Mtb*-specific CD4<sup>+</sup> 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 cells 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 is sufficient to control *Mtb* 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 IFN $\gamma$ -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<sup>+</sup> T cells into lymphoid follicles following *Mtb* 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 of these CXCLs contain the E-L-R 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 MAP-kinase (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 *M.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 Mtb infection in vitro (431–434) (Figure 1). Following in vivo Mtb 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 decreases 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 (Figure 1).

CXCL5 which is also a CXCR2 ligand plays an important role in host responses against Mtb (440) as both CXCR2 and CXCL5 gene deficient mice display lower bacterial burden following Mtb 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 Mtb and blocking of neutrophil recruitment improves outcome lung (440) (Figure 1). It appears that CXCR2 plays an important role in the pathological 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<sup>+</sup> and CD8<sup>+</sup> 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) (Figure 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 Mtb 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) however CXCR3 deficient mice do not exhibit differences in bacterial burden following low dose aerosol infection with Mtb (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 co-expression 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 (Figure 2). Human data support a protective role for CXCR3-binding chemokines as CXCL9 levels correlate with disease severity (379, 450) although the role of CXCL10 is unclear. CXCL10 has been proposed as a biomarker for improvement, as reduction of this chemokine in the serum relative to levels at recruitment is observed following TB treatment and non-responders 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 non-cavitary 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 are induced and whether their induction is a direct result of Mtb 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) (Figure 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 *Candida albicans* infection model as well as in synovial fluid from patients with rheumatoid arthritis (461). CXCL13 expression recruits CXCR5-expressing B cells and co-ordinates the correct position of these cells within SLO (462). A similar role has also been highlighted during Mtb infections. Mtb 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 Mtb-infected mice and is

important for the localization of CXCR5<sup>+</sup> T cells to the lung parenchyma as well as the activation of phagocytes and control of bacterial growth (422, 459) (Figure 2). Using NHP and mouse models of Mtb, CXCR5<sup>+</sup> T cells have been shown to traffic towards 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 Mtb (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. Further, CXCR5 is required for the maintenance Mtb-specific CD4<sup>+</sup> T cells during chronic infection (81). B cells from Mtb 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 Mtb-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 Mtb infection, suggesting that this cytokine/chemokine axis is non-redundant in Mtb infection (Figure 2).

## CONCLUSION

Chemokines and cytokines are critical for initiating and co-ordinating the organized and sequential recruitment and activation of cells into Mtb-infected lungs (Figures 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 I and II). Much of the data highlighted in this chapter appears at first glance to be contradictory but it is the balance between the cytokines and chemokines which 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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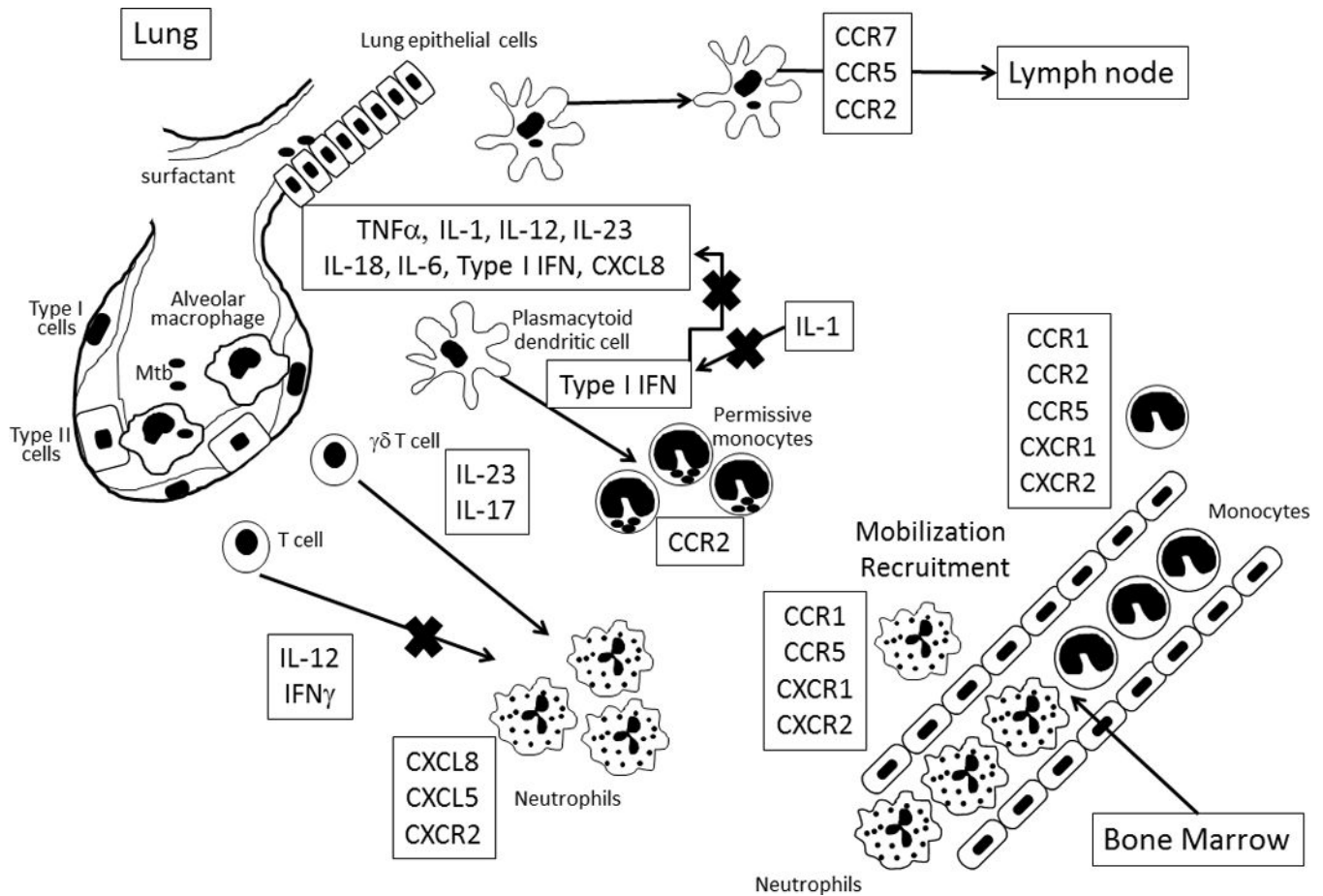
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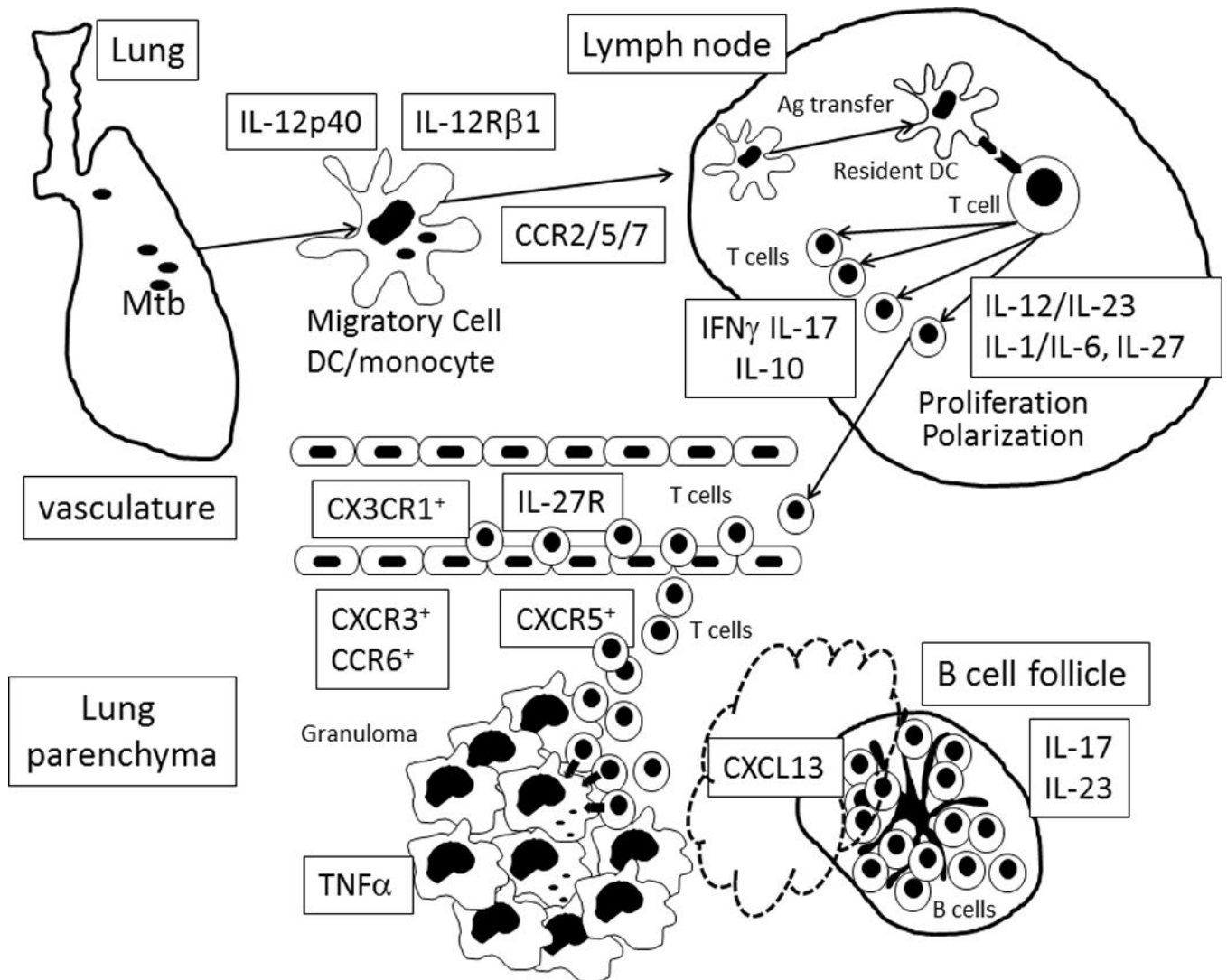
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### Figure 1. The role of chemokines and cytokines in the innate response to *Mtb* infection

Upon early infection of the lower airways, *Mtb* encounters alveolar macrophages and lung epithelial cells. Alveolar macrophages are a major source of proinflammatory cytokines (TNF $\alpha$ ), although stromal cells can produce cytokines and chemokines which will also modulate immune responses. During early infection, dendritic cell trafficking from the lungs to the lymph node via CCR7 results in primed naïve T cells and initiation of adaptive immune responses. Replicating bacteria generate a fulminant reaction which 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, over-expression of this cytokine results in high levels of CCR2 expressing monocytes with limited ability to control bacterial growth. Type II IFN (IFN $\gamma$ ) regulates the recruitment of neutrophils which is promoted by IL-17. CXCL5 and CXCR2 mediate the recruitment of damaging neutrophils.



**Figure 2. The role of chemokines and cytokines in the adaptive response to *Mtb* infection**

Following *Mtb* 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 which 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<sup>+</sup>) while others migrate into the parenchyma (CXCR3<sup>+</sup>CCR6<sup>+</sup>). 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 *Mtb* infected macrophages. T cells express a variety of cytokines in the lung including IFN $\gamma$ , TNF $\alpha$ , IL-17, and IL-10 which have both protective and negative effects depending upon the context.



**Table I**

The positive and negative roles of cytokines in TB

Cytokine	Receptor/Signal	Role in TB
TNF $\alpha$	TNFR1, TNFR2 JNK, p38, NF $\kappa$ B	<b>Positive:</b> Essential for survival following Mtb infection. Initiation of innate cytokine and chemokine response and phagocyte activation <b>Negative:</b> Mediator of tissue damage
IFN $\gamma$	IFNGR1, IFNGR2 JAK/STAT	<b>Positive:</b> Essential for survival following Mtb infection. Coordinates and maintains mononuclear inflammation. Expressed by antigen specific T cells <b>Negative:</b> Potentially pathogenic
IFN $\alpha$ /IFN $\beta$	IFNAR1, IFNAR2 JAK, TYK, ISG, ISRE	<b>Positive:</b> Required for initial recruitment of phagocytes to the lung <b>Negative:</b> Over expression of IFN $\alpha$ /IFN $\beta$ results in recruitment of permissive phagocytes and regulation of T cell accumulation and function
IL-6	IL-6R, gp130 JAK, STAT3, MAPK	<b>Positive:</b> Potentiates early immunity – non essential unless a high dose infection.
IL-1 $\alpha$ /IL-1 $\beta$	IL-1R1, IL1RAcP MyD88, IRAK4, NF $\kappa$ B	<b>Positive:</b> Essential for survival following Mtb infection. Induction of IL-17. Promotes PGE2 to limit Type I IFN
IL-18	IL-18R $\alpha$ , IL-18R $\beta$ MyD88, IRAK, NF $\kappa$ B	<b>Positive:</b> May augment IFN $\gamma$ – non-essential. Regulator of neutrophil/monocyte accumulation. of neutrophil and monocyte accumulation, optimal induction of IFN $\gamma$ by T-cells
IL-12 p40, p35	IL-12R $\beta$ 1, IL-12R $\beta$ 2 JAK2, TYK2, STAT4	<b>Positive:</b> IL-12p40 and IL-12p35 essential for survival following Mtb infection. Mediate early T cell activation, polarization and survival. <b>Negative:</b> Over expression of IL-12p70 is toxic during Mtb infection.
IL-23 p40, p19	IL-23R, IL-12R $\beta$ 1 JAK2, TYK2, STAT3	<b>Positive:</b> Required for IL-17 and IL-22 expression during Mtb infection. Non-essential in low dose challenge required for long term control. <b>Negative:</b> Mediates increased pathology during chronic challenge
IL-27 EBI3, p28	IL-27R $\alpha$ , gp130 JAK1/2, TYK2, STAT1/3	<b>Positive:</b> May control inflammation and reduce pathology <b>Negative:</b> Regulates protective immunity to Mtb infection by limiting the migration and survival of T cells at the inflamed site.
IL-35 p35, EBI3	IL-12R $\beta$ 2, gp130 STAT1/4	<b>Positive?</b> Regulate the availability of subunits of IL-12, IL-27 <b>Negative?</b> Potential immunoregulatory role.
IL-17A/F	IL-17RC, IL-17RA	<b>Positive:</b> Essential for survival following infection with some strains of Mtb. Induction and maintenance of chemokine gradients for T cell migration. <b>Negative:</b> Drives pathology via S100A8/A9 and neutrophils
IL-22	IL-22R1, IL-10R2 TYK2, JAK1, STAT3	<b>Positive:</b> Induces antimicrobial peptides and promotes epithelial repair, inhibits intracellular growth of Mtb in macrophages.

**Table II**

The positive and negative roles of chemokines in TB

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