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IL-23 and IL-17 in tuberculosis

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Summary

Tuberculosis is a chronic disease requiring the constant expression of cellular immunity to limit bacterial growth. The constant expression of immunity also results in chronic inflammation, which requires regulation. While IFN-γ-producing CD4+ T helper cells (Th1) are required for control of bacterial growth they also initiate and maintain a mononuclear inflammatory response. Other T cell subsets are induced by *Mycobacterium tuberculosis* (Mtb) infection including those able to produce IL-17 (Th17). IL-17 is a potent inflammatory cytokine capable of inducing chemokine expression and recruitment of cells to parenchymal tissue. Both the IL-17 and the Th17 response to Mtb are largely dependent upon IL-23. Although both Th17 and Th1 cells are induced following primary infection with Mtb, the protective response is significantly altered in the absence of Th1 cells but not in the absence of Th17. In contrast, in vaccinated animals the absence of memory Th17 cells results in loss of both the accelerated memory Th1 response and protection.. Th1 and Th17 responses cross-regulate each other during mycobacterial infection and this may be important for immunopathologic consequences not only in tuberculosis but also other mycobacterial infections.

Keywords

Tuberculosis; cytokines; inflammation

1. Introduction

The recent explosion of data regarding the cytokines IL-17 and IL-23 has been informative for those studying protective and damaging immune responses. In tuberculosis, as in other persistent infections, these cytokines play an important role. In this review we will cover the role of IL-23 in the induction of IL-17-producing antigen-specific CD4+ T cells (Th17) and in the control of tuberculosis. We will also outline the role of both IL-23 and IL-17 in expression of vaccine-induce protection against tuberculosis. Finally, we will discuss the ability of mycobacteria to induce both Th1 and Th17 cells and how these cells contribute to inflammation.

Mtb is delivered to the lung via an aerosol cloud that deposits 3-5 micron particles containing bacteria into the lower lung resulting in a granulomatous response within the alveolar parenchyma. It takes time for bacteria to grow and to initiate acquired immunity and inflammation in the lung tissue. Indeed in the mouse model of low dose aerosol infection, it takes 9-10 days for T cells within the draining lymph node to become activated [1]. Thereupon it takes 20 days for sufficient antigen-specific IFN-γ-producing T cells to accumulate in the lung and stop bacterial growth [2]. Bacterial growth occurs in an unrestrained manner in the

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absence of either an acquired immune response [3], IFN-γ [4], TNF-α [5] or IL-12p40 [6] and is restrained for only a short period in the absence of IL-12p35 [6], inducible nitric oxide synthase [7] or the ability to make a diverse antigen-specific response [8]. While the bacterial burden remains constant for a prolonged period of time in immunocompetent mice immunopathologic consequences continue to progress with the mononuclear granuloma becoming lymphopenic and granulocytic just prior to bacterial recrudescence [9]. The acquired immune response remains active throughout this period [10] and bacteria will begin to grow and disease recrudesce if the acquired response is limited [11]. IL-23 and IL-17 have roles throughout mycobacterial infection (Figure 1).

2. Role of IL-23 and IL-17 in the primary protective response

Upon exposure of dendritic cells (DCs) to Mtb IL-12p70 and IL-23 are induced [12-14]. When CD4+ T cells are primed with Mtb-infected DCs and their cognate antigen and then restimulated, the efficient generation of Th17 cells is dependent upon the presence of IL-23 during the initial priming [12,13], this is also true when *M. bovis* BCG is used [15]. Furthermore upon aerosol infection, the absence of IL-23 leads to ablation of the Th17 response and significant loss of IL-17mRNA expression in the lung [12]. These data demonstrate that IL-23 is essential to the expression of both the Th17 population and the IL-17 response to mycobacterial infection. This fits with other observations wherein the continued function of Th17 cells is associated with IL-23 [16]. These data do not define IL-23 as the initiator of the Th17 response to mycobacteria, indeed it is likely that this response is in mice dependent upon TGF-β [17,18]. In contrast, a critical role for IL-23 in the initiation of Th17 cells in humans has recently been reported [19,20]. Regardless of the specific role of IL-23, it is likely that this cytokine will be required for optimal Th17 responses to mycobacterial infection in humans.

IL-23 is also able to induce IFN-γ-producing Th1 cells in the absence of IL-12p70 as the residual Th1 response to Mtb seen in IL-12p35 gene-deficient mice, is lost when IL-23 is absent [12]. Neither the Th1 response nor protection is however lost in the absence of IL-23 [12,21]. Conversely, when IL-23 is delivered as an adenoviral construct prior to infection, it increases the IFN-γ and IL-17 response in the lung and mediates improved protection compared to adenovirus alone [22]. In addition, when co-delivered with the Mtb antigen, Ag85, encoded as DNA in a plasmid vaccine, IL-23 was able to induce a strong Ag85-specific IFN-γ response in IL-12p40 gene-deficient mice [23]. These data suggest that while IL-23 plays a secondary role to IL-12 in the induction of IFN-γ-mediated protective response, it may be able to augment these responses.

T cells associated with innate response can also make IL-17. In particular, the γδ T cell population is a primary source of Mtb-induced IL-17 in the mycobacterial infection model [13,24]. Following intratracheal delivery of BCG, IL-17 mRNA can be detected 1 day post-infection and in the absence of this cytokine the induction of chemokines and early neutrophil accumulation were reduced [24]. The IL-17 being produced in this model was from γδ T cells and in its absence there was also reduced mononuclear granulomatous inflammation later in infection [24] similar to the altered granulomatous response seen in the absence of γδ T cells [25]. Mtb-infected DCs can induce IL-17 in T cells from uninfected mice and this is largely a result of IL-23-dependent induction of IL-17 in the γδ T cell population [13]. Following a low dose aerosol infection with Mtb, γδ T cells are major producers of IL-17 [13] and it is likely that these cells are dependent upon IL-23 as well as there is no IL-17mRNA in IL-23p19 gene deficient mice [12]. There is also an invariant natural killer T (iNKT) cell population in the lung that recognizes lipopolysaccharide and pathogen glycolipids. These cells produce IL-17 upon stimulation and are required for the airway neutrophilia induced by these products [26]. It is not yet known if these cells are involved in the initial response to Mtb infection.

3. Role of IL-23 and IL-17 in vaccination

While the role of IL-23 or IL-17 in the protective response to primary tuberculosis is dispensable, the fact that treatment with IL-23 can increase primary immunity [22] and that the IL-17 impacts the inflammatory response to mycobacteria [12,24] suggests that the protective role of these cytokines may be improved by vaccination. In tuberculosis, the delivery of BCG as a live attenuated vaccine results in protection against disseminated disease but is less effective against pulmonary disease in adults [27]. The animal model of disease provides some explanation of this discrepancy as, mice with a population of Mtb-specific memory cells are better able to control bacteria following systemic rather than aerosol challenge [28]. The cessation of bacterial growth in the lung corresponds to the accumulation of IFN-γ-producing CD4 T cells and this accumulation, although accelerated in memory mice, takes 15 days to be effective [2,28,29]. This delay in expression of memory immunity needs to be addressed if improvements are to be made in the development of effective vaccines against this disease. In this regard we have demonstrated that the accelerated Th1 memory response seen in the lungs of vaccinated mice infected with Mtb is dependent upon IL-23 and IL-17 [2]. Specifically, upon vaccination a population of antigen-specific IL-17 producing memory T cells able to populate the lung is generated and these cells respond more quickly than memory Th1 cells to aerosol challenge; this population of cells is dependent upon IL-23. The IL-17 produced by these cells induces the chemokines CXCL9, CXCL10 and CXCL11 in the lung by day 12 post-challenge and in the absence of this response, the accelerated accumulation of Th1 memory cells is lost along with vaccine-induced protection [2]. These data demonstrate that vaccination results in the generation of a surveillance cell that can recognize an invading pathogen rapidly in the tissue and promote the recruitment of protective cells. It will be important to determine whether these surveillance cells can be established in high number in the lung without damaging consequences.

When used as an adjunct to DNA vaccination, IL-23 can augment the induction of protective Th1 and Th17 responses to a level similar to that seen for IL-12p70 [14,23]. This is in contrast to an IL-27 containing plasmid, which does not augment protection upon DNA vaccination [14]; this is possibly due to the ability of IL-27 to down regulate Th17 responses [30,31]. The BCG vaccine generates an early antigen-specific Th17 response following systemic infection but this is down regulated by IFN-γ [15]. When BCG is delivered intratracheally, a γδ T cell IL-17 response is induced [24] however upon subcutaneous delivery no IL-17 response is seen unless IL-12p40 is absent [23]. In this latter case, not only the potentially regulating IFN-γ is missing but also IL-23, suggesting that an IL-17-producing CD4+ T cell population can occur in response to mycobacteria in the absence of IL-23 [23].

3. The role of IL-23 and IL-17 in immunopathology of tuberculosis

IL-17 is recognized as an inflammatory cytokine capable of inducing chemokine gradients and initiating inflammation, particularly in the lung [32-34]. As IL-23 is responsible for the persistence and function of Th17 cells [16] it is also likely a key player in inflammation. It is surprising therefore that in the absence of IL-23 the inflammatory consequences of Mtb infection are modest. Specifically, while the extent of lung consolidation is similar between wild type and IL-23p19 gene-deficient mice, as disease progresses, the severity of the inflammation is increased and the extent of fibrin deposition decreased in the absence of IL-23 [12]. As discussed above, the absence of IL-17 also results in reduced mononuclear and polymorphonuclear infiltration early in the BCG model [24]. Further, despite the acknowledged role of IL-23 and IL-17 in neutrophil recruitment [34] and homeostasis [35] there are no differences in neutrophil numbers in the lungs of Mtb infected mice lacking IL-23 [12]. It is clear therefore that IL-23 and IL-17 are acting in a complex manner in the control of mycobacteria-induced inflammation. This is not so surprising as IL-17 can act as a mediator

of macrophage accumulation [32] and we have shown that IL-17 can mediate induction of CXCL chemokines containing IL-17 associated promoter elements [2,36]. These data suggest that during mycobacterial infection IL-17 can act to mediate accumulation of both polymorphic and mononuclear cells.

That the absence of IL-23 and IL-17 in the lung leads to increased severity of inflammation with increased tissue damage and reduced fibrin deposition may be related to the recent demonstration that IL-17 alters the survival [37] and IL-17 and IL-23 alter the functional profile of neutrophils [38]. These data suggest that one possible function of these cytokines in the late stages of Mtb-induced inflammation may be to maintain the integrity of the granuloma by limiting neutrophil death, this should be investigated. It will be intriguing to determine the extent to which the Th1 and Th17 responses balance each other as disease progresses and whether loss of the IL-17 response results in early breakdown of the granuloma and earlier recrudescence. In this respect it is of interest that the absence of IL-27 leads to increased Th17 cells [39] and increased protection and mononuclear inflammation upon Mtb infection [40, 41], unfortunately it also leads to earlier death of animals [40] suggesting that while Th17 cells can balance Th1 mediated inflammation, Th1 cells are also required to balance Th17 mediated inflammation.

The relative levels of IL-12 and IL-23 induced by mycobacterially-infected cells will be crucial for the balance between Th1 and Th17 cells. In primary Mtb infection, Th17 and Th1 cells are induced with the same kinetics but there are 5-10 fold more Th1 than Th17 cells [2,12]. In BCG infection the Th17 is rapidly suppressed by the Th1 response [15] and this may be related to differential induction of IL-12 and IL-23 by BCG compared to Mtb [14]. We have also shown that while IFN-γ dramatically increases IL-12p70 production by BCG-infected DCs, it also reduces IL-23; conversely IL-17 limits IL-12 production while augmenting IL-23 [15]. These data suggest that the cross-regulation of IL-12 and IL-23 by each other and by IFN-γ and IL-17 will be critical to the inflammatory outcome of any mycobacterial infection.

4. IL-23 and human tuberculosis

Genetic mutations resulting in altered IL-12-induced and IFN-γ-mediated responses have been reported since 1996, these mutations lead to increased susceptibility to mycobacterial disease [42-47]. However, while defects in the genes encoding IL-12Rβ1 and IL-12p40 have been associated with mycobacterial disease, there are no reported mutations in the genes for IL-12Rβ2 or IL-12p35 [48]. Importantly, the absence of IL-12p40 and IL-12Rβ1 will impair not only the IL-12p70 pathway but also the IL-23 pathway. Indeed in humans with IL-12Rβ1 deficiency, the ability of IL-23 to promote IFN-γ production is decreased [49]. As expected IL-23 also promotes IL-17 production however IL-12 reduces expression of this cytokine [50], suggesting a cross-regulatory role for these two cytokines in the human as well as the mouse model. This cross-regulation is intriguing in light of the demonstrated role for mutations in the gene for IL-23R in susceptibility to inappropriate inflammatory conditions, particularly of the gut [51]. Specifically, if there is an imbalance between IL-23 and IL-12 resulting in either excessive IFN-γ or IL-17-mediated inflammation in response to *M. avium* subsp. paratuberculosis this may explain the apparent association between this pathogen and Crohn's disease [52]. Many questions remain to be addressed regarding the relative roles of IL-12 and IL-23 in mycobacterial disease in humans.

5. Conclusion

Tuberculosis is a disease that persists in the host. This persistence leads to a complex interaction between host and pathogen that must develop over time to balance protective and inflammatory roles. The role of IL-23 and IL-17 in this balance does not appear to be protective but rather

as a regulator of inflammation. An important role for IL-23 and IL-17 has also been demonstrated for the expression of vaccine-induce protection with IL-23-dependent IL-17-producing memory T cells being required for chemokine expression and accelerated accumulation of protective IFN-γ-producing memory T cells. Finally, the balance between IL-12/IFN-γ and IL-23/IL-17 may be crucial to the regulation of inflammatory consequences not only of Mtb but also other mycobacterial infections. Understanding the relative roles of these cytokines in mediating protection and immunopathology will be important in light of the thrust towards inhibiting IL-23 as a treatment for autoimmune disease.

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Abbreviations

Mtb, Mycobacterium tuberculosis; DCs, Dendritic cells; Ag 85, Antigen 85.

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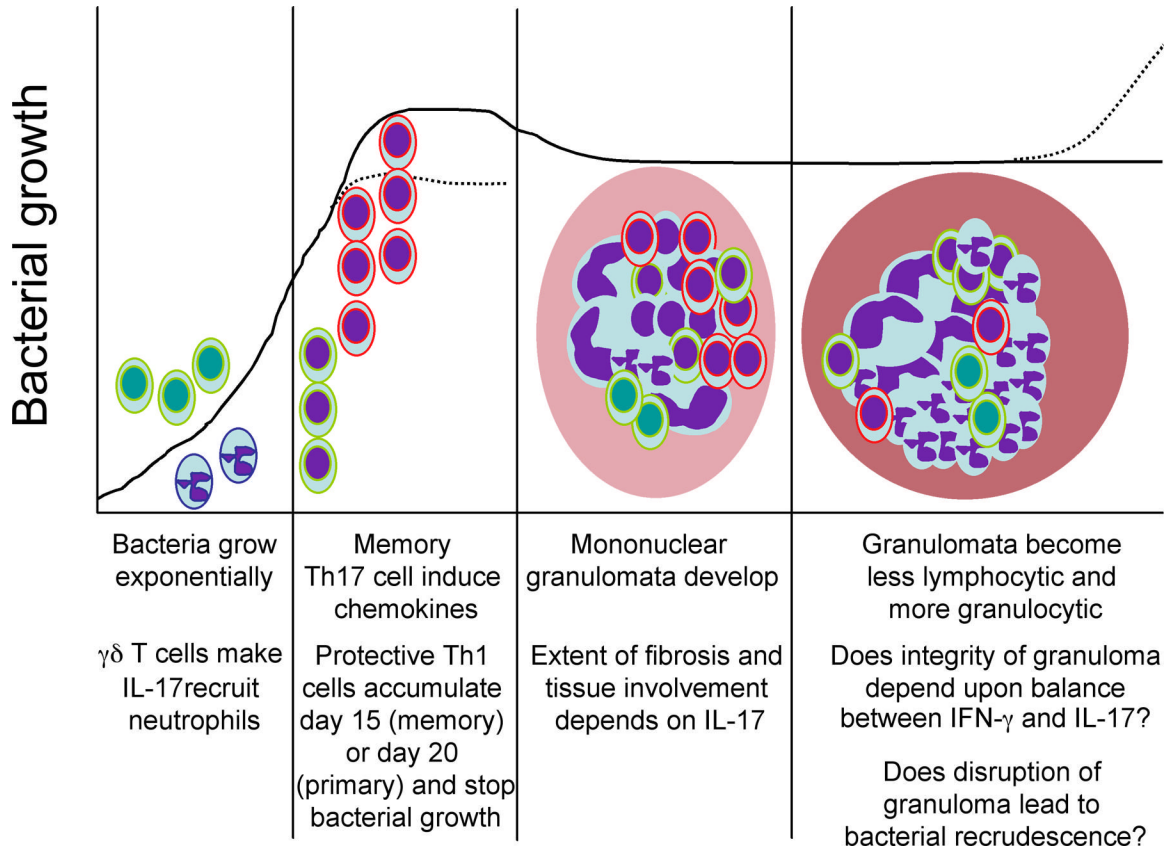

Figure 1. Tuberculosis represents a chronic interaction between host and pathogen with IL-23 and IL-17 playing roles throughout

Bacteria are deposited at low numbers within the lung and γδ T cells (green nuclei) make IL-17 (green lined cells) to recruit neutrophils (purple nuclei, purple lines). If mice have been vaccinated, memory Th17 cells (purple nuclei, green lines) make chemokines and accelerate the accumulation of memory Th1 cells (purple nuclei, red lines). In either the memory or the primary response it is the arrival of IFN-γ-producing cells (purple nuclei, red lines) at sufficient numbers that correlates with cessation of bacterial growth. Initially a mononuclear granuloma develops in the lung parenchyma (pink), the extent and content of which depends upon IL-17. As infection progresses, lymphocyte numbers decrease while polymorphonuclear cells increase. We propose here that the balance between the IL-12/IFN-γ and IL-23/IL-17 pathways define the late consequences of mycobacterial infection with disruption of the lung parenchyma (dark pink) and bacterial recrudescence being the consequences of imbalance.