Tubercle and Lung Disease (1997) **78**(3&4), 145–158

Review

Examining a paradox in the pathogenesis of human pulmonary tuberculosis: immune activation and suppression/anergy

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Summary Protective immunity against *Mycobacterium tuberculosis* (MTB) in animal models is based on cell-mediated immunity (CMI), involving bi-directional interactions between T cells and cells of the monocyte/macrophage (MO/MA) lineage. Key factors include MO-derived interleukin (IL)-12 and tumor necrosis factor (TNF)-α as well as T cell derived IL-2 and interferon (IFN)-γ. These cytokines appear particularly crucial in the induction of MA-mediated elimination of mycobacteria. Several lines of evidence indicate that similar mechanisms are operating in humans.

During active pulmonary tuberculosis (PTB), signs of both immune depression and immune activation are concomitantly present. Decreased tuberculin skin test reactivity in vivo and deficient IFN-γ production by MTB-stimulated mononuclear cells in vitro are observed. On the other hand, the serum levels of several cytokines, including TNF, and other inflammatory mediators are increased and circulating MO and T cell show phenotypic and functional evidence of in vivo activation.

In this review, we will discuss the evidence for three models, which could explain this apparent paradox: 1. Stimulation of the T cell-suppressive function from MO/MA; 2. Intrinsic T cell refractoriness, possibly associated with tendency to apoptosis (programmed cell death), and 3. Compartmentalization and redistribution of immune responses to the site of disease.

The opportunistic behavior of MTB during human immunodeficiency virus (HIV) infection can be explained by suppression of type-1 responses at the level of antigen-presenting cells, CD4 T cells and effector macrophages. The ominous prognostic significance of intercurrent PTB during HIV infection seems primarily due to prolonged activation of HIV replication in macrophages.

Supportive immune therapy during PTB could aim at correcting the type-1 deficiency either by IFN-γ inducers (e.g. IL-12, IL-18) or by neutralizing the suppressive cytokines transforming growth factor β (TGF-β) and IL-10. Alternatively, inflammatory over-activity could be reduced by neutralizing TNF. Finally, anti-apoptotic therapies (e.g. IL-15) might be considered.

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1. IMMUNE DEFENSE AND IMMUNOPATHOLOGY IN PULMONARY TUBERCULOSIS

Primary pulmonary infection with *Mycobacterium tuberculosis* (MTB) induces long-term protective immunity in the large majority of infected subjects. Life-time risk on reactivation of latent infection is less than 5% in immunocompetent individuals. According to the prevailing paradigm, protection relies on type 1 cell-mediated immunity (CMI), involving interactions between MTB-specific CD4 and CD8 T lymphocytes and cells of the monocyte-macrophage (MO/MA) lineage.[1–3]

MO/MA, particularly the alveolar macrophages (AM), are the natural hosts for MTB. They have a limited intrinsic capacity to reduce the growth of mycobacteria but additional 'acquired' immune activation by CD4 T cells is necessary to control the infection.[4] To this end, MTB antigens (Ag) have to be presented to specific CD4+ T cells by professional antigen-presenting cells (APC), including dendritic cells (DC) and other cells of the MO/MA lineage. The CD4 T cells are induced to secrete interleukin-2 (IL-2), the main T cell growth factor, and interferon-gamma (IFN-γ), an important activating signal for MO/MA. The production of IFN-γ is regulated by APC-derived factors, including stimulatory IL-12 and suppressive IL-10 and transforming growth factor beta (TGF-β).[5–7]

Acquired deficiency of type-1 responses, e.g. during human immunodeficiency virus (HIV) infection, dramatically increases the chances of clinical reactivation of MTB infection.[8–10] Genetic deficiencies in the IL-12, IFN-γ, IFN-γ receptor axis result in increased susceptibility to mycobacterial diseases, not only in knock-out mouse models, but also in rare cases of human gene defects.[11–14]

Mechanisms, distinct from, but related to classical MO-CD4 T interactions, contribute to MTB control as well. In murine models, cell-subset depletion experiments in vivo showed that CD4 and CD8 αβ receptor(+) as well as γδ receptor(+) T cells all have a role in protective immunity in the order CD4 >CD8 > γδ T cells. Interferon-γ is already secreted by MTB-activated γδ cells before αβ T cells come into play. Both activated CD4 and CD8 T cells and γδ T cells can eliminate infected MO/MA by their potent cytotoxic activity.[15–17] In addition, there is evidence that double (αβ) negative T cells, other than γδ cells, may recognize non-protein mycobacterial antigens through mechanisms involving presentation via CD1.[18]

Mycobacterial products induce the production of tumor necrosis factor-α (TNF-α) by MO/MA. The latter cytokine has a complex role in the pathogenesis of tuberculosis (TB) as it can either increase phagocytic and killing capacities of MO/MA or promote the growth of MTB inside the cells, depending on the presence of other factors, including IFN-γ, 1,25 di-hydroxy vitamin D and iron.[2,19] TNF-α appears to be required, together with IFN-γ, for the formation of granulomas, which limit the spread of the infection. This has been clearly demonstrated in the murine model of bacille Calmette-Guérin (BCG) infection, in which animals pretreated with neutralizing antibody to TNF-α fail to contain the infection and develop progressive BCG disease.[20]

Whether TNF-α has a similar role in humans is less clear: TNF was shown to increase the killing capacity of the MO/MA, when they were infected with high doses of an avirulent MTB strain (H37Ra),[21] but this was not confirmed in the same in vitro model, with low doses of a more virulent strain (H37Rv) (Silver R: personal communication). In mice, TNF and IFN activation of MO/MA involves the generation of the bactericidal NO, whereas the role of this mediator in human immunocytes remains uncertain.

Excessive TNF-α production and/or increased sensitivity to TNF-α are involved in expression of many of the local and systemic toxicities evident in TB, including necrotizing (caseous) reactions, which promote the replication and dissemination of the bacteria. TNF is also an important mediator of systemic inflammation, clinically manifested by fever and wasting. Depending on the setting, TNF-α thus promotes containment or dissemination of MTB and can contribute to both immune protection and pathology.[2,6]

The role of type-2 responses and humoral immunity in MTB infections is generally considered to be marginal. Reports on in vivo or in vitro production of type-2 cytokines (IL-4, IL-5 and IL-13) during PTB are inconsistent. Although some of these cytokines theoretically could have a suppressive effect on type-1 immunity or increase the sensitivity to TNF-α, thus promoting immune pathology, there is no convincing evidence that these mechanisms are really operative during PTB.[22–24] Although MTB-reactive antibodies are abundantly produced during infection, they do not seem to contribute to protection.[25–27]

In a first approach, the immune reactions during PTB can be viewed as a balance between protective type-1 responses on one hand and inflammatory pathological reactions on the other. In the following paragraphs, we will highlight the importance of excessive immune activation, monocyte-mediated suppression and T cell apoptosis in the pathogenesis of PTB.

2. THE PARADOX OF ANERGY AND IMMUNE ACTIVATION IN PTB

Active PTB is characterized by signs of systemic immune activation, including polyclonal hyper-gammaglobulinemia, increased serum levels of TNF and elevated expression of HLA-DR on circulating T cells.[6,28,29] Although T

cells and monocytes show evidence of non-specific activation, there is simultaneous evidence of antigen-specific hyporesponsiveness. Up to 20–25% of patients with newly diagnosed HIV(–) PTB show a negative tuberculin skin test (anergy). More sensitive measurements of PPD-induced lymphocyte proliferative responses show reduction to values of 50% of healthy PPD reactors. Production of IL-2 and IFN-γ is even further reduced.[30–32] These anomalies are most pronounced in those subjects with radiologically far advanced disease.[33–36]

Theoretically, several models can be proposed to explain the apparent paradox of concomitant activation and immune depression.

1. the function of antigen-presenting cells (APC) may be dysregulated: reduced Ag-presentation and/or enhanced suppression of type 1 responses
2. immune (over)activation during active PTB could induce T cell refractoriness to stimulation and predispose to apoptosis (programmed cell death)
3. the most Ag-reactive T cells could be largely retained at the site of infection and consequently only less Ag-responsive T cells are recovered from the periphery (compartmentalization and redistribution).

The available data discussed in the following sections suggest evidence that all three of these mechanisms may be operating during PTB.

3. IMMUNE OVER-ACTIVATION OF MONOCYTES AND T CELLS DURING PTB (see table)

3.1. Various alterations in the monocytes from PTB patients

PTB is characterized by a relative increase in peripheral monocytes, which is particularly pronounced in subjects with decreased responses to PPD.[37] The circulating MO of PTB patients are functionally and phenotypically altered.[35,38] They show increased adherence to plastic, an enhanced hexose monophosphate shunt activity and increased killing capacity towards Schistosoma and Listeria infected cells.[39]

After stimulation in vitro, TB MO produce increased amounts of several inflammatory cytokines, including TNF-α, IL-1, IL-6 and IL-8.[6,7,41,42] Moreover, the membrane expression and the actual occupancy of TNF receptors is increased.[43,44] MO/MA from PTB patients presumably also constitute a major source of the elevated serum levels of neopterin and, together with other activated immunocytes, they contribute to high circulating β2-microglobulin concentrations, indicating increased cell turnover.[29,45] On the other hand, MO from PTB patients spontaneously secrete the immunosuppressive cytokine TGF-β. Production of both TGF-(β, and another anti-inflammatory cytokine, IL-10, are increased following in vitro stimulation with PPD.[41]

Peripheral MO from PTB patients show enhanced membrane expression of FcγR I and FcγR III receptors for IgG.[29] The α chain of the IL-2 receptor (IL-2Rα) is also upregulated at the cell surface, as well as cytoplasmic IL2-Rβ m-RNA levels.[46] Expression of HLA-DR, essential in antigen-presentation to CD4 T cells, is, however, decreased on freshly isolated MO, especially from those subjects who show reduced PPD responses in vitro.[47] In addition, in a mouse model of MTB-induced hyporesponsiveness, the important co-stimulatory B7 molecule was found to be downregulated.[48]

The overall immune profile of peripheral MO from PTB patients thus includes activation of both inflammatory and anti-inflammatory systems. Some effector functions (phagocytosis and bactericidal activity) are enhanced, whereas lowered HLA-DR and B7 as well as increased IL-10 and TGF-β might point to reduced APC function or enhanced suppression (see section 4).

Table Characteristics of peripheral monocytes and CD4 T cells in PTB

	Monocytes	CD4T cells
Numbers (in vivo)	= or ↑	= or ↓
Membrane marker expression		
HLA-DR	↑	↓
IL-2 R	↑ = (resting)	↓ (stimulated)
TNF-R	↑	
B_7	↓	
FcγRI and RIII	↑	
Cytokine profile		
Non stimulated (in vivo)	TGF-β ↑	IFN-γ ↑ and IL-4 ↑
MTB-Ag stimulated (in vitro)	IL-1, IL-6 and TNF-α ↑	IL-2 ↓
	IL-10 ↑	IFN-γ ↓↓
	Neopterin ↑	

3.2. T cell characteristics in PTB

A relative lymphopenia is seen in a proportion of HIV-uninfected PTB patients. The distribution of the major subsets is not significantly altered, although the γδ T cells were reported to be relatively expanded in some studies.[16,49,50] PTB patients, without HIV but with low absolute CD4 T cell counts (and normal CD4/CD8 ratio) tend to present with a low hematocrit, low body mass index and more extensive disease.[51]

More refined phenotypic analysis of peripheral T cells from a non-selected group of HIV(–) PTB patients showed enhanced expression of HLA-DR on both CD4 and CD8 T cells, but normal expression of IL-2Rα and CD45RO, the latter being associated with memory cells.[29] Increased levels of soluble IL-2Rα, observed in the serum of PTB

patients, presumably reflect release of the receptor from MO and/or T cells and correlate with the extent of disease.[33,52] Upregulation of IL2-Rα on T cells after in vitro activation, however, was reported as suboptimal, resulting in impaired responsiveness to IL-2 stimulation, either alone or in combination with MTB-Ag.[30] The latter alterations seemed to be restricted to patients with advanced disease.[34]

Whereas cytokines are usually not found in peripheral T cells from controls, IFN-γ m-RNA was present in one third and IL-4 m-RNA in two thirds of TB patients.[53] The message for IL-2 was found to be increased by some,[54] but not by other authors.[53] Recent studies by Kaplan et al further indicate increased serum/plasma levels of IFN-γ, IL-1, IL-4 and TNF in newly diagnosed patients. Interestingly, all cytokines fall with treatment, except TNF, which increases to a maximum at 7–14 days. This temporary rise in TNF is associated with a transitory clinical deterioration (personal communication).

Phenotype and function of peripheral T cells from PTB patients are not typical for a regular antigen stimulation, which induces increased production of IL-2 and upregulation of membrane-bound IL-2Rα and CD45RO, together with HLA-DR. The aberrant T cell activation pattern, associated with PTB, might predispose to activation-induced refractoriness (anergy) and/or activation-induced programmed cell death (PCD) by apoptosis (see section 5).

3.3. Mechanisms involved in the aberrant immune pattern during PTB

In vitro, live or killed mycobacteria, their secreted proteins (PPD or 30 kD protein) and/or lipo-arabinomannan cell wall components can induce the degradation of IkB and the consequent upregulation of NFkB. Increased constitutive expression of NFkB was recently found in MO from PTB patients in vivo.[6,55] The enhanced activity of nuclear transcription factors, including NFkB, results in cytokine overproduction by MO, including the inflammatory TNF-α but also the suppressive IL-10 and TGF-β.[6,54,56–58] Cytokine activity may have secondary phenotypical and functional effects on MO/MA: TGF-β can up-regulate the expression of FcγR III[59] and IFN-γ can increase the expression of FcγR I and the secretion of neopterin.[60,61] FcγR-expressing MO appear to be critical in MO-mediated suppression of T cells during PTB (see section 4).

The mechanisms underlying the particular changes of T cell phenotype and function during PTB are incompletely understood, but most probably local or systemic overproduction of cytokines by regulatory cells, including MO/MA and possibly γδ T cells, are also involved. In fact infection of MO/MA by other 'intracellular parasites' (e.g. HIV, Trypanosoma cruzi) is associated with similar changes in T cells, including enhanced expression of selected cytokines, upregulation of particular membrane activation markers and T cell hyporesponsiveness.[62–66]

4. AN UNFAVORABLE BALANCE BETWEEN THE STIMULATORY AND SUPPRESSIVE FUNCTION OF ANTIGEN-PRESENTING CELLS IN PTB (see Figure)

Although a reduced type 1 response to MTB-Ag is a consistent finding in the peripheral blood mononuclear cells from patients with active PTB, the frequency of PPD-responsive T cells has been reported to be similar in PTB patients and in healthy tuberculin-reactive controls.[67] Moreover, PBMC responses to non-TB antigens are variably lowered in the patients, whereas mitogen-induced proliferation is better preserved.[7,31,34,41,52,68] Thus, both Ag-specific and more generalized T cell dysfunctions are evident. They could be due to either an intrinsic T cell defect and/or deficient antigen-presenting function and/or suppressive mechanisms.

With regard to APC function, quite different effects have been observed after in vitro infection of dendritic cells (DC) or MO/MA with mycobacteria. Infection of DC with BCG or MTB stimulates their maturation, cytokine production and capacity to efficiently stimulate MTB-specific CD4 T cells.[69–71] In contrast, infection of MO or MA reduces their APC function.[73,74] Depending on the strain of mycobacterium (BCG or MTB), the infectious dose and the maturation stage of the MO/MA, the reduced APC function may be restricted to the infectious agent itself, extend to PPD or even to non related recall Ag. In vitro MTB infection of MO, however, did not induce suppressive activity towards the Ag-specific responses in co-cultured uninfected PBMC. Although the latter experimental models provide interesting insights, they do not fully mirror the actual situation during clinical PTB, where several studies have documented the existence of active suppression.[38]

Earlier studies indicated that non-specific suppression could be induced by circulating immune complexes, containing mycobacterial polysaccharides, including D-arabino-D-galactan.[75] Lymphocyte-mediated suppression was also investigated: a significant contribution of classical CD8+ T suppressor cells could never be demonstrated, but CD16 (FcγR III)-positive large granular lymphocytes were shown to selectively suppress PPD-induced IL-2 production by T cells from PTB patients.[76–78]

The most striking and repeatedly confirmed observation is the partial correction of Ag responses after reducing the proportion of MO within PBMC by their adherence to plastic, clearly implying that MO act as sup-

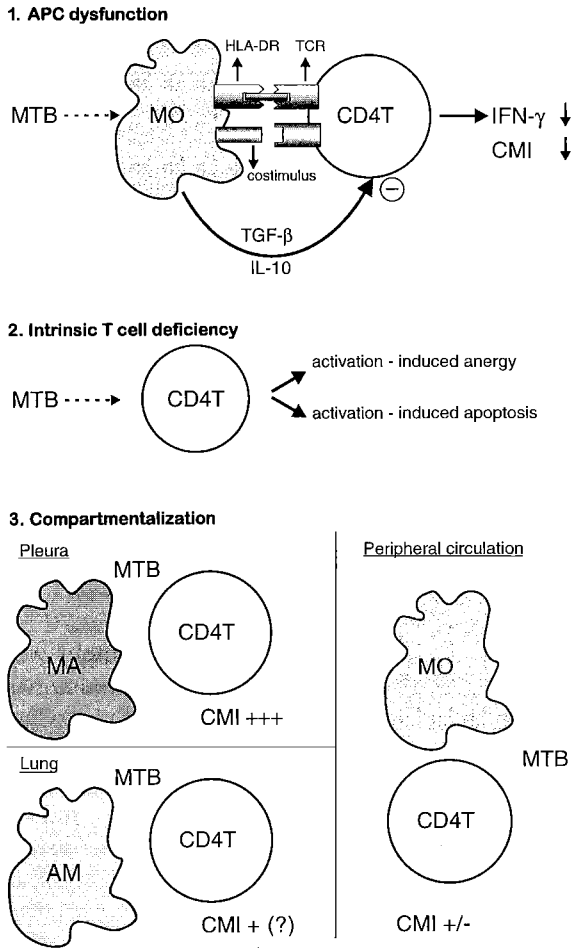

Figure Three models are proposed to explain immune dysfynction during pulmonary tuberculosis: 1. The function of antigen-presenting cells (APC), exemplified by monocytes (MO) in the peripheral blood, is dysregulated by MTB: (a) Their capacity to stimulate CD4 T cells might be lowered by decreased expression of HLA-DR, which is responsible for presentation of the antigenic peptides to the T cell receptor (TCR), and/or by downregulation of costimulatory mechanisms (e.g. B7 expression); (b) MO from PTB patients act as suppressor cells by producing high levels of TGF-β and IL-10. As a consequence of either mechanism, the cell-mediated (CMI) or type 1 immune response, including IFN-γ production, are lower in patients with active PTB as compared to PPD-reactive healthy controls. 2. The peripheral T cells from PTB patients are intrinsically deficient. In vivo over-activation of T cells by MTB results in refractoriness to additional stimulation and a tendency to apoptosis or programmed cell death. Both mechanisms might contribute to lowered CMI upon stimulation with MTB antigens. 3. The level of potentially protective CMI is different in the various compartments. The parameters of CMI are consistently higher in the mononuclear cells from the pleura as compared to those from the peripheral blood, while those from the lung (broncho-alveolar lavage cells) might take an intermediate position (but the latter is controversial). Different levels of CMI can result from redistribution of the most active T cells to the site of the disease, from differential function of the local accessory cells (e.g. peripheral, pleural or alveolar MO/MA and dendritic cells) or from other mechanisms.

pressor cells.[37,79,80] A first indirect suppressive mechanism is the relative over-expression of IL-2Rα on MO from PTB, which could reduce the availability of IL-2 to T cells.[41] Two other possible and extensively studied mechanisms include the reduced production/ activity of the prominent type-1 stimulatory cytokine IL-12[81] and the enhanced production of the suppressive cytokines TGF-β and IL-10.[85–88]

MTB readily induces bio-active IL-12 in human MO in vitro[55,82] and there is no evidence that IL-12 production is deficient in PTB patients: PBMC from TB patients actually expressed high levels of IL-12 m-RNA in vivo. Upon mycobacterial stimulation in vitro, MO from patients produced more biologically active IL-12 than PBMC from healthy donors.[83] Addition of IL-12 strongly increased the IFN-γ production in PPD-stimulated PBMC cultures from both patients and controls, indicating normal IL-12 receptor function.[41,84] Thus, no gross deficiency in overall IL-12 production or sensitivity is evident in PTB. The possibility of more subtle alterations, such as an imbalance between immunostimulatory and pro-inflammatory effects of IL-12 during PTB are not excluded (see also section 8).

As already mentioned in section 3.1, TGF-β was found to be significantly more expressed and spontaneously secreted by MO from TB patients as compared to healthy contacts.[40] Moreover, MTB-derived Ag (including PPD and the 30 Kd Ag) induced much more TGF-β in PBMC from TB patients than in healthy contacts. Blocking TGF-β activity in PPD-stimulated PBMC cultures from PTB patients, either by neutralizing antibodies or by the natural inhibitors decorin and latency-associated peptide, normalized their blastogenic response and also significantly enhanced, but did not normalize, their IFN-γ production. Data on PPD-induced production of IL-10 were less consistent, but anti-IL-10 also increased the T cell responses from the patients and acted synergistically with anti-TGF-β. Remarkably, neither anti-TGF-β nor anti-IL-10 enhanced the PPD response in the healthy controls, but both antibodies slightly increased the depressed T cell responses of the patients PBMC to a non-MTB Ag (Candida).[41,89]

Besides the systemic immunosuppressive effects of TGF-β and IL-10, the local production of these cytokines in the pleura or the lung might also have beneficial anti-inflammatory effects and limit excessive tissue destruction. Moreover, TGF-β displays a fibrogenic activity, which helps to isolate the infectious focus, but might also reduce the lung function by scarring and destruction of the parenchyma.[85]

Suppression by MO (and/or CD16+ lymphocytes) cannot be the full explanation for PPD-hyporesponsiveness, since depletion of both subsets does not completely restore the in vitro responses in most active PTB patients and even does not enhance them at all in some cases.[35,90] The latter observations suggest that intrinsic T cell defects also operate during PTB.

5. INTRINSIC T CELL ANERGY AND TENDENCY TO APOPTOSIS DURING PTB

In newly diagnosed PTB patients with advanced disease, neither depletion of suppressive cells, nor neutralization of TGF-β and/or IL-10, nor addition of IL-2 can increase the PPD-induced IFN-γ production to levels seen in healthy PPD(+) controls.[3,35] When a successful anti-mycobacterial treatment is given, the PPD-stimulated blastogenesis and the production of TGF-β in PBMC cultures normalize within a few months, but the PPD-induced IFN-γ production remains depressed for over one year after the end of the treatment (Hirsch & Ellner; unpublished). The long-lasting deficiency in IFN-γ production, despite the termination of MO-TGF-mediated suppression, points to an intrinsic T cell dysfunction, which is not rapidly corrected by treatment.

Conceivably, the intrinsic T cell hyporesponsiveness might be genetically defined or acquired. A particular HLA type or a specific T cell receptor repertoire defect could preclude the generation of protective responses. Reports on associations of HLA types with susceptibility to mycobacterial diseases have been widely divergent.[91–93] Acquired T cell deficiency, resulting in increased susceptibility to PTB, is observed during HIV infection (see section 7), but, to a lesser extent, also in other conditions of relative immunodeficiency, including diabetes, malnutrition and ageing.[68,94]

Apoptosis or programmed cell death (abbreviated PCD) is in the first place a physiological process to terminate normal immune responses.[95] Chagas' disease, malaria and HIV, infections characterized by immune responses that are not fully protective, are associated with excessive immune activation, secondary T cell refractoriness and/or programmed cell death.[96–98] Especially in the case of HIV, there is compelling evidence that the inappropriate induction of apoptosis is one of the mechanisms of immunodeficiency.[99–101] The question whether apoptosis could have a role in T cell hyporesponsiveness during PTB, therefore, seems relevant.

In a recent study, we demonstrated that fresh ex vivo T cells from untreated PTB patients displayed a significant level of deoxyribonucleic acid (DNA) fragmentation (a key event in apoptosis), which was absent in fresh T cells from controls. In the patients, PCD was further enhanced by in vitro stimulation with MTB and correlated with T cell hyporesponsiveness (reduced proliferation and IFN-γ production). This activation-induced PCD was disease- and antigen-specific, as it was not observed after MTB-stimulation of control PBMC, nor after stimulation of the patients' PBMC with a non-MTB-related Ag (Candida) ([102] and Hirsch, submitted).

The death pathway of MTB-related PCD remains to be established, but several theoretical possibilities are open. Apoptosis could be linked to the Fas system e.g. increased expression or activity of the Fas/APO1 receptor on T cells and increased expression or secretion of Fas-ligand by monocytes or other cells.[103–105] Other members of the TNF and TNF-R families could also be involved.[106–109] Alternatively, refractoriness to additional stimulation and/or induction of apoptosis might be the consequence of defects in costimulatory interactions between the B7 molecules on APC and the B7-receptors on the Ag-specific T cells (including the agonistic CD28 and the antagonistic CTLA4).[99,103,110,111] Similarly, deficient upregulation of IL-2 receptor α chain and/or lowered production of 'survival' cytokines IL-2, IL-7 or IL-15 (which all trigger a common receptor γ-chain) could render the T cells hypo-responsive and/or more vulnerable to cell death.[112,113]

6. COMPARTMENTALIZATION OF MTB SPECIFIC T CELLS TO THE SITE OF DISEASE

All of the observations in the previous paragraphs were made on peripheral blood cells from active pulmonary TB patients. Although peripheral T cells and monocytes obviously can be influenced by pulmonary pathology, as they travel through the lung many times each day, the evaluation of their function still provides rather indirect information on what happens at the site of the disease. Mononuclear cells, recovered from the pleural space (in the case of TB pleuritis) or from broncho-alveolar lavage (BAL) in pulmonary affected patients, offer a more direct view on in situ immune responses. Tuberculous pleurisy is frequently self-limiting and therefore is considered as an example of protective immunity. Active PTB, on the other hand, is less likely to heal spontaneously and therefore is associated with non-protective immune reactions and immunopathology.[68,114]

Pleural T cells from TB pleuritis patients show phenotypic signs of activation in vivo and produce a variety of cytokines in situ.[115–122] Moreover, pleural T cells are intrinsically more responsive to ex vivo PPD stimulation than the corresponding PBMC.[68,115,123,124] Alveolar T cells from patients with PTB, on the other hand, also have a high cytokine content[125] and their alveolar MO/MA show evidence of immaturity.[126,127] The in vitro responsiveness of the BAL-T cells from PTB patients remains a controversial topic, since both decreased and increased responses to mycobacterial stimulation have been reported.[128,129]

Overall, most data point to a different degree of activation and responsiveness in mononuclear cells from PTB patients, depending on their source: the pleural cells seem most active in cell-mediated immune functions while peripheral cells are rather hyporesponsive and BAL-T cells probably occupy an intermediate position. It is not established whether this apparent functional compart-

mentalization is due to redistribution of the most MTB-reactive T cells to the site of disease, to a local selective expansion and/or to a different balance between T cell stimulatory and suppressive functions of pleural and lung MO/MA as compared to the peripheral blood MO. Similarly, how this compartmentalization relates to protective immune responses or immunopathology, remains to be clarified.

A more extensive discussion on pleural and pulmonary immune responses during PTB is beyond the scope of this review and was recently covered by others.[4]

7. ROLE OF IMMUNE DEFICIENCY AND ACTIVATION IN THE INTERACTION BETWEEN MTB AND HIV

7.1. Mechanisms involved in the opportunistic behavior of MTB during HIV infection

It is well known that active PTB is a very important and relatively early complication of HIV infection. HIV increases the risk of overt PTB more than 10-fold.[10] The reasons for this association have been elucidated to a large extent:

- HIV and MTB share the MO/MA, including AM, as important host cells[131–133]
- dysfunction and later depletion of the CD4 T cells by HIV profoundly reduces the 'adaptive or acquired' defense against MTB. HIV particularly affects type 1 cell-mediated responses[134,135]
- the predominant weakness of type 1 responses partly relies on dysfunction of the APC, which, during HIV infection, produce less stimulatory IL-12 and relatively more suppressive IL-10.[136–139] Whether HIV also adversely influences antigen processing per se remains controversial.[140–142]

7.2. Aberrant activation of MO might explain the adverse effect of PTB on HIV prognosis

An intercurrent episode of PTB, even when adequately treated, results in a worsening of the course of HIV infection in dually infected subjects.[143] This might be related to the 5 – 160-fold increase of HIV viral load, which has been noted during active PTB.[144] A high plasma viremia is associated with increased CD4 T cell depletion, with a rapid switch to a more virulent (i.e. syncytium-inducing and coreceptor CXCR4-using) phenotype and high chances of immune escape mutants.[145–150] There is evidence that any in vivo immune activation, including vaccination or blood transfusion, can temporarily increase the viral load.[151–153] As compared to these stimuli, the immune activation induced by an episode of PTB is much more intense and prolonged.

Several lines of evidence indicate that interactions at the level of the MO/MA are very important in this process.[154] Blood MO from PTB patients are more susceptible to productive infection with HIV than those from healthy controls.[155] MTB or PPD can activate latent HIV-1 in alveolar macrophages from acquired immune deficiency syndrome (AIDS) patients in vitro.[156] Alveolar macrophages from MTB-HIV dually infected subjects produce significantly higher levels of HIV-1 particles if they are taken from the MTB-infected as compared to unaffected lung segments or than AM from MTB-uninfected subjects.[157] Finally, MTB-HIV co-infected MA show an increased capacity to transmit HIV-1 to activated T cells, as compared to HIV only infected MA.[133] The stimulatory effect of MTB is partly due to upregulation of TNF-α and IL-1, associated with activation of NFkB, which triggers the promoter of HIV proviral DNA and thus potently induces viral transcription.[158–160]

8. THERAPEUTIC POSSIBILITIES OF IMMUNOMODULATION IN PTB

Excessive activation, MO-mediated suppression, T cell anergy and apoptosis all might contribute to the pathogenesis of PTB. Some of these pathological mechanisms could be corrected in vivo by selective interventions, aiming at the stimulation of MTB-specific T cell proliferation and IFN-γ production as well as at the neutralization of inflammatory and suppressive MO functions.

Interleukin-2 production is deficient during active PTB and addition of IL-2 could enhance, although perhaps not fully correct, T cell proliferation in vitro.[30,33] An open label trial with low dose daily IL-2, subcutaneously injected, was set up during the first month of a conventional multidrug anti-TB therapy and in patients with drug-resistant PTB. Under these conditions, IL-2 was safe and had moderate, but significant additive effects on chemotherapy.[161] Placebo-controlled trials are underway to further substantiate these findings.

Since type-1 responses are crucial to protection, IFN-γ or its inducers provide another logical option. Treatment with IFN-γ has been proposed, but when administered systemically, could induce pathological levels of TNF-α.[162–164] In lepromatous leprosy, the intradermal injection of IFN-γ was shown to have favorable effects on the bacillary load, but also induced erythrema nodosum leprosum. This complication was most probably mediated by the secondary release of TNF and could be treated with Thalidomide (THAL).[165] In seven patients with refractory and disseminated non-tuberculous mycobacterial infections, clinical improvement was observed during subcutaneous treatment with IFN-γ.[166] Recently, bacteriological and clinical improvement was reported in five multidrug-resistant pulmonary TB patients, during treatment with

IFN-γ via aerosol.[167] Clearly, these positive results in a limited number of various patients, treated in an open-label setting, need to be confirmed in placebo-controlled trials.

Mycobacterium vaccae is a naturally occurring inducer of type-1 responses, which can be safely injected in a three dose schedule. [168] The first non-controlled trials in TB patients seemed promising, but analysis of a recent South-African trial showed no effectiveness ([169,170] and personal communication). A placebo-controlled trial in Uganda with immunological as well as bacteriological endpoints is still in progress.

Interleukin-12 is probably the single most potent IFN-γ-inducing cytokine[171,172] and was found to increase the defective IFN-γ response to PPD of PBMC from PTB patients to the level of healthy controls.[41] However, it is not clear whether only Ag-responsive CD4 T cells or also non-Ag-specific cells (either αβT, γδT or NK cells) produce the additional IFN-γ. In the latter case, an inappropriate inflammatory response could be triggered as well. Animal studies with IL-12 have met with some success, but a narrow therapeutic range was evident: IL-12 not only induces IFN-γ, but also inflammatory cytokines, including TNF-α.[173] Human trials have been set back by lethal complications in pilot studies, although recent data suggest that serious side-effect can be prevented by modifying the schedule.[174,175]

Other regulatory cytokines, including IL-15 and IL-18, also have IFN-γ-inducing capacities[176–178] and are of possible relevance for mycobacterial diseases.[179–181] IL-18 was recently shown to play an important role in both innate and acquired type-1 responses and to act synergistically with IL-12,[182] but more data are needed on the activity and toxicity profiles of IL-18 in vivo.

Counteracting the immune-suppressive TGF-β or IL-10 could significantly improve the IL-2 and IFN-γ production. In a first approach, naturally occurring inhibitors, including decorin and latency-associated peptide, seem a better alternative than injection of neutralizing antibodies, because the latter are more likely to induce adverse immune reactions (unless they could be fully humanized).[89]

Neutralization of inflammatory cytokines, especially TNF-α, is still another option. Dexamethasone (DEX), pentoxyfilline (PTX) and THAL all inhibit TNF-α production in vitro, but through different mechanisms.[183,184] DEX, as well as PTX, however, might suppress potentially beneficial cytokines, including IL-2 and IFN-γ,[187–189] whereas THAL, on the contrary, was reported to enhance their production.[190] Despite these theoretical differences, all three agents have proven to be of benefit, when properly used in adjunction to chemotherapy. DEX has been mainly applied in tuberculous meningitis and was shown to improve survival and to reduce neurological sequellae.[191,192] In a randomized controlled trial in Ugandan HIV(+) TB patients, all treated with standard chemotherapy, the addition of PTX significantly lowered HIV replication, raised blood hemoglobin levels in anemic patients and tended to improve performance scores.[186] In two recent trials, one in HIV(–) and HIV(+) PTB and the other in HIV(+) subjects with or without PTB, THAL was shown to reduce circulating TNF levels and to enhance the weight gain in HIV(–) and HIV(+) PTB. THAL also lowered HIV plasma load in dually infected HIV-patients, whereas the anti-viral effect in HIV only infected subjects was less convincing.[193,194] In patients with AIDS disease, THAL had, however, considerable side effects, resulting in premature cessation of the therapy.[195] The development of inhibitors of the MTB-related inflammation with a higher potency and low toxicity, is clearly desirable.

Anti-apoptotic therapies are an emerging possibility. IL-15 can already be cited as a potential candidate. Like other γ-chain activating cytokines, it has clear cut anti-apoptotic effect,[196] but it has several other theoretical advantages, especially in HIV(+) TB patients: it can trigger T cells, which only express low-affinity receptors for IL-2,[177] it is known to induce IFN-γ in vitro;[197] it has less HIV-stimulating activity than IL-2 and improves several T cell functions, critical for HIV control, including cytolytic T cell activity.[198–201]

9. SOME CONCLUSION AND PERSPECTIVES

Active PTB is characterized by failing immune control and pathological inflammation. A large body of evidence indicates that dysfunction of MO/MA has a central role in TB pathogenesis. MO/MA are both the source of pro-inflammatory cytokines, including TNF-α, and of the T cell-suppressive factors TGF-β and IL-10. MO-mediated suppression, as well as a prolonged intrinsic T cell dysfunction and a tendency to T cell apoptosis are associated with the characteristic anergy in vivo and the lowered MTB-specific IFN-γ production in vitro. Therefore, both IFN-γ-inducing and anti-apoptotic treatments as well as neutralization of TNF, TGF-β or IL-10, could have a beneficial effect on the course of the disease, especially in multidrug-resistant cases.

Two important sets of basic questions remain to be further investigated:

1. are the immune dysfunctions, described mainly in the peripheral blood of active PTB patients, in fact underlying (and preceding) the (re)activation of MTB or are they induced by the disease itself? Prospective cohort studies (e.g. within households) are underway to answer this question
2. which exactly are the local immune reactions, resulting in protection (e.g. during TB pleuritis) or in chronic disease (e.g. PTB)? And how does local

immunity relate to the immune dysfunction, measured in the peripheral blood?

The current intense efforts of several groups to unravel the immunology of TB will not only result in a better understanding of its pathogenesis, but also in the development of new immunotherapeutic strategies, which could significantly improve TB treatment.

ACKNOWLEDGEMENTS

This work is supported by the Tuberculosis Research Unit contract of the NIH to Case Western Reserve University. Dr. G. Vanham is supported by a grant from the Damien Foundation, Brussels, Belgium

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