Lung Remodeling in Pulmonary Tuberculosis

Keertan Dheda, Helen Booth, Jim F. Huggett, Margaret A. Johnson, Alimuddin Zumla, and Graham A. W. Rook

Centre for Infectious Diseases and International Health, Department of Thoracic and HIV Medicine, Royal Free Hospital, and Department of Thoracic Medicine, Middlesex Hospital, Royal Free and University College Medical School, London, United Kingdom

Tuberculosis is a global public health catastrophe responsible for >8 million cases of illness and 2 million deaths annually. Pulmonary cavitation with cough-generated aerosol is the principle means of spread, and lung remodeling (healed cavitation, fibrosis, and bronchiectasis) is a major cause of lung disability, surpassing all other diffuse parenchymal lung diseases combined. Efficient granuloma turnover is mycobactericidal, and extracellular matrix is disbanded without scarring. In many with progressive disease, however, there is dysregulated granuloma turnover, liquefactive necrosis, and pathological scarring. The pathological mechanisms and the related immunological pathways underpinning these phenomena are reviewed in the present article. Further studies are needed to identify and develop specific immunotherapeutic interventions that target immunopathology, since they have the potential to substantially reduce spread.

The lung remodeling associated with pulmonary tuberculosis (TB) (healed cavitation, fibrosis, and distorted architecture) has never been satisfactorily explained. This is despite TB being an international public health priority and despite cavitation, with associated tissue and liquefactive necrosis, being the mechanism by which disease transmission occurs. In addition to addressing the significant morbidity associated with lung remodeling, investigations that can elucidate mechanisms and immunological pathways relevant to tissue necrosis might lead to strategies for interrupting aerosol-mediated transmission. Such knowledge can be incorporated into immunotherapeutic strategies aimed at halting person-to-person spread of Mycobacterium tuberculosis.

Why do caseous and liquefactive necrosis occur? Moreover, why is fibrosis present in a disease characterized by a potent interferon (IFN)–gamma response, when this cytokine generally opposes fibrosis [1]? In this review, we reevaluate current knowledge of the immunopathogenesis of tissue necrosis and fibrosis. Peer-reviewed data for the present article were identified by searches of the Medline and PubMed databases, up to and including October 2004, in all languages, by use of the search terms “tuberculosis” and “remodeling,” “cavitation,” “fibrosis,” “immunopathology,” “extracellular matrix,” “protease,” or “necrosis.” Other sources were the references cited in retrieved articles and referenced textbooks.

DEFINITIONS

In asthma and chronic obstructive pulmonary disease, “remodeling” refers to anatomical and structural changes that are not easily reversible (laying down of extracellular matrix [ECM]), in contrast to reversible changes, such as edema and cellular infiltration) [2, 3]. In this review, we have extended the term “remodeling” to include residual cavitation, lung fibrosis or scarring, distortion of lung architecture leading to volume loss, and tuberculous bronchiectasis, all of which represent an inappropriate response to lung injury. An appropriate response occurs, for example, when granuloma formation occurs in a coordinated fashion, followed by disbanding of the granuloma, dissolution of ECM, and return to normal tissue architecture. “Fibrosis” implies a structural alteration, with laying down of collagenous ECM by fibroblasts and other cell types. The fibrosis may be interstitial; occur as a capsule around cavities; be bandlike, with distortion of the lung architecture;
Figure 1. Principle cell types and cytokines involved in competent granuloma formation. NK T (NKT) cells, CD4+ T cells, CD8+ T cells, and γδ T cells produce type 1 cytokines that activate macrophages, which are mycobactericidal. Granulocytes (not shown) may be important in early granuloma formation. Mycobacteria (rods) may be present within cells or extracellularly. Mycobacterial killing can occur by macrophage apoptosis, cytotoxic T cell lysis (jagged arrow), or directly through granulysin (star)–mediated destruction. Tumor necrosis factor (TNF)–α is a likely requisite for macrophage mycobactericidal activity, necrosis, and formation of the fibrous capsule. Cellular recruitment into the granuloma is facilitated by a chemokine gradient. IFN-γ, interferon-γ; TGF-β, transforming growth factor–β.

or be a combination of these. The term “tissue necrosis” encompasses both caseous and liquefactive necrosis.

**CLINICAL ASPECTS**

Cavitation into airways, with cough-induced aerosol generation, is the principle method by which TB is spread. Untreated, there is a fatal outcome in 50% of individuals [4]. Despite chemotherapy, however, there may be widespread lung destruction with significant associated mortality [5]. Alternatively, subsequent healing can result in extensive fibrosis, traction bronchiectasis [6, 7], and bronchostenosis [8], all of which may result in volume loss, a restrictive defect during pulmonary function testing [9, 10], and increased morbidity. Cavitation may erode blood vessels, and bronchiectasis may cause significant hemoptysis [8, 11]. Poor drug penetration into cavities and fibrocaseous foci, which are immunologically “sealed off,” may facilitate latency and selection of drug resistance. Residual distortion of the lung architecture depends on the degree to which the connective-tissue matrix of a granuloma is degraded and removed. The key question is what determines whether a granuloma resolves completely without scarring or whether liquefactive necrosis and/or extensive scarring occurs.

**EFFICIENT GRANULOMA FORMATION AND DISSOLUTION**

The first cell types encountered by inhaled mycobacteria are the alveolar macrophages; phagocytosis is mediated by various host receptors [12, 13]. Lung γδ T cells, NK T cells, and granulocytes are important early arrivals that precede the second wave of expanded, IFN-γ– and tumor necrosis factor (TNF)–α–producing effector T cell populations [14–16]. Collectively, these cells initiate a chemokine and cytokine cascade that attracts other macrophages and, later, T cells to the site of infection [17] (figure 1). There is plasma exudation, and a fibrin clot is formed [18, 19]. Macrophage aggregation to form an early granuloma core is mediated by hyaluronic acid [20], which binds to macrophages via CD44 [21]. Detailed histological analyses of developing granulomata in the rabbit model [22] led to the view that macrophage activation driven by cell-mediated immunity is followed by destruction of the same macrophages, which then accumulate as caseous necrosis, and is often associated with death of the contained bacilli. An alternative view is that granulocytes are early arrivals that mediate the cell lysis that forms the core of developing caseous necrosis [16, 23, 24]. Recent pathological studies of granulomas in tuberculous human lungs indicate that the peripheral lym-
phocyte zones of the granuloma have secondary lymphoid follicles analogous to those found in lymph nodes [16].

Macrophages and other cell types, such as fibroblasts, endothelial cells, and neutrophils, also produce proteases (metalloproteinases [collagenase, gelatinase, andstromelysin]; the lysosomal proteinases [cathepsins]; and the plasminogen/plasmin system and its activator, urokinase]). Such enzymes may facilitate granuloma formation by mediating antigen processing, removal of ECM and cellular debris, and processing of cytokines and hormones [25]. They are tightly regulated at multiple levels, including transcription, proenzyme formation, and signaling control, as well as by tissue inhibitors of metalloproteinases (TIMPs) [26, 27].

Within the granuloma, both T cells and macrophages secrete TNF-α and lymphotixin α3. Not only is TNF-α crucial for host defense [28–32], but it also facilitates the structural integrity of the granuloma by mediating the formation of the encapsulating fibrous wall [33], together with transforming growth factor (TGF)–β [34, 35]. Macrophages also secrete insulin-like growth factor (GF)–1, fibroblast GF, fibronectin, and platelet-derived GF [36, 37]. These GFs are chemotactic and support macrophage proliferation and, hence, the laying down of ECM comprising collagen, fibronectin, and glycosaminoglycans [38–40]. Caseous necrosis—which occurs at ~2–3 weeks in the rabbit model [22]—and its associated low oxygen content create unfavorable conditions for mycobacterial multiplication [41]. This, together with macrophage activation and CD3+ effector cell mechanisms, culminates in mycobacterial sterilization. It was shown in 1927 that healed primary lesions are usually sterile within 5 years, although latent bacilli may persist in other, superficially normal, parts of the lung [42, 43].

Controlled dissolution of the granuloma follows mycobacterial containment, although this may be incomplete if there has been massive production of caseum. Proteases cleave components of the ECM [26]. Macrophages phagocytose the partly degraded ECM components, which are terminally degraded within the lysosome or transported out of the lung [44–46]. Minor residual scarring may remain.

DYSREGULATED GRANULOMA TURNOVER AND LIQUEFACTIVE NECROSIS

In a significant minority of infected individuals—those with progressive primary and reactivation disease—there is progressive disease and liquefactive necrosis. This forms an ideal culture medium for mycobacteria; they multiply extracellularly to large numbers [47], since macrophages are unable to survive in necrotic tissue, partly because of its toxic fatty acid content [41]. The proteolytic enzymes [48] compromise the integrity of the fibrous granuloma capsule. Caseous material may discharge into surrounding blood vessels and airways, thereby facilitating systemic dissemination, and to the outside environment via cough-induced respiratory droplets. The cavity often has an external zone of collagen, internal to which is a zone of granulation tissue rich in fibroblasts, inflammatory cells, and capillaries [47]. The role of vasculopathy as a primary event in the facilitation of cavitation is unclear. With antimicrobial therapy, the cavities may persist as fibrotic walled structures lined by metaplastic squamous epithelium or as emphysematous bullae, or they may become distorted from without by traction fibrosis [47].

Although the exact mechanisms of liquefaction are unknown, the available data suggest that dysregulated proteolysis, direct mycobacterial toxicity, the Koch phenomenon [49] and Shwartzman reaction [50], and host effector cells and cytokines are key players (figure 2). These concepts are further discussed below.

Dysregulated Proteolysis and Direct Mycobacterial Toxicity

A variety of host proteases are up-regulated in mycobacterial infection [48, 51–53], and dysregulation of protease control mechanisms is likely to mediate proteolysis of structural components of the lung [54]. Cytokines such as TNF-α and interleukin (IL)–1β can up-regulate proteases [55–57] in mouse and human monocytes in response to mycobacterial proteins [58], and lipoarabinomannan induces collagenases in myeloid cells [54]. Macrophage destruction by cytotoxic T cells and the release of lysosomal contents are likely to play a significant role in tissue destruction and may explain some of the necrosis in the central part of the granuloma where macrophages predominate. Granulocytes may be important facilitators of early necrosis [16, 23]. As discussed below, local tissue damage will be more likely if the macrophages undergo necrosis rather than apoptosis. Although thought to be less important, mycobacteria themselves may produce endopeptidases [25] or other pro-necrotic virulence factors. Recently, however, a polyketide toxic factor, isolated from M. ulcerans, has been shown to have cytopathic properties and produced necrotic cutaneous lesions in guinea pigs [59]. Since the M. tuberculosis genome contains many polyketide synthesis genes [60], it is reasonable to speculate that this toxin may represent one of a family of virulence factors associated with immunopathology in mycobacterial diseases. Similarly, the secreted protein early secreted antigenic target 6 kDa (ESAT-6) is a virulence factor for M. tuberculosis and appears to cause lysis of lung epithelial cells and to facilitate local spread [61]. Its contribution to caseation is not known. Certain deletional mutants of M. tuberculosis have an unchanged ability to proliferate within the host but induce much less immunopathology, suggesting that mycobacterial virulence factors actively induce tissue-damaging cell-mediated immune responses [62, 63].
Factors that might contribute to dysregulated granuloma formation. Mycobacterial antigens mediate uncoupled protease metabolism activity, apoptosis, the Koch phenomenon, and, perhaps, cell lysis mediated by early secreted antigenic target 6 kDa (ESAT-6) and induce the release of cytokines (tumor necrosis factor [TNF]-α, mixed Th1/Th2, and transforming growth factor [TGF]-β), which collectively facilitate liquefactive necrosis and deranged extracellular matrix (ECM) turnover. Mycobacteria (solid capsules) multiply extracellularly, compromise the fibrous granuloma capsule, and may discharge into a bronchial lumen or blood vessel.

The Koch Phenomenon and Shwartzman Reaction

Koch [49] showed that tuberculous guinea pigs developed necrosis locally and at distant sites of infection after rechallenge with tuberculin. High tuberculin reactivity occurs in experimental animals with liquefaction [64]. Similarly, the tuberculin test is frequently necrotic in humans with TB but not in healthy bacille Calmette-Guérin (BCG)—vaccinated individuals [47]. More recently, an elegant study showed that *M. tuberculosis*—infected mice developed increased lung inflammation and elevated TNF-α levels when rechallenged with mycobacterial antigens [65]. Moreover, when prophylactic-vaccine candidates are tested for therapeutic effects in mice with TB, they develop increased immunopathology [66] and classical Koch reactions characterized by cellular necrosis within granulomas [67]. One explanation may be the systemic Shwartzman reaction [50], which referred originally to cutaneous necrosis at a site of a previous endotoxin injection after intravenous injection of lipopolysaccharide (LPS). The concept is that the initial skin inflammation causes endothelial activation and accumulation of inflammatory cells. Then, a subsequent systemic cytokine-inducing signal administered ∼24 h later preferentially triggers necrosis in the “prepared” skin site. Indeed, *M. tuberculosis*—infected mice developed caseous necrosis after inoculation with LPS [68]. Moreover, LPS shares many physical properties and biological functions with a major mycobacterial antigen, lipoarabinomannan [69].

Host Cytokines and Effector Mechanisms

Necrosis and cavitiation can occur in response to nonviable, nontoxic components of mycobacteria [48, 64, 70]. This suggests that host cytokines and enzymes are responsible for the necrosis. Although the precise mechanisms inducing progression from controlled protease release and granuloma formation to dysregulated protease production with liquefactive necrosis are unknown, a likely facilitator is TNF-α.

TNF-α. Although TNF-α is essential for immunity to TB, in progressive disease TNF-α is associated with fever and wasting [71–73] and correlates with disease activity and immunopathology [29, 74–77]. Cells containing *M. tuberculosis* are rendered exquisitely sensitive to killing by TNF-α [75, 78]. As outlined above, TNF-α can up-regulate metalloproteinases and urokinase and thereby facilitate proteolysis of structural lung elements. However, under what conditions is the protective TNF-α molecule toxic? Data, as outlined below, support a possible role for Th2 cytokines in such toxicity.

**Th1 and Th2 cytokines.** Recent data have convincingly demonstrated the presence of Th2 cytokines in human TB [79]. Th2 cells may mediate local tissue damage that is IL-4 dependent [80]. In *M. tuberculosis*—infected mice, susceptibility to the toxic effects of TNF-α injected into the footpads coincided temporally with the emergence of Th2 cytokines in the lungs [81]. IL-4 may also regulate TNF-α—mediated enteropathy in *Trichinella spiralis* infection [82], and necrosis in a schistosomiasis model coincides precisely with the superimposition of Th2 response on an existing Th1 pattern [83]. Mouse (BALB/c) models of TB showed high IFN-γ levels early during infection, with increased levels of IL-4 during the chronic phase of infection, which was characterized by progressive fibrosis and necrosis [84, 85]. The Th2 response may exacerbate tissue damage by enhancing the pathological effect of TNF-α [81]. More
recent evidence, from IL-4 gene knockout experiments in BALB/c mice, showed an absence of TNF-α–mediated toxicity after TNF-α challenge in the absence of IL-4 [86]. Collectively, these murine data suggest that, under the influence of superimposed Th2 cytokines, TNF-α is toxic in dominantly Th1-mediated lesions. It is not unreasonable to suggest that a similar mechanism operates in humans. Studies of lavage fluid from patients with TB show the presence of IL-4–producing Th2 lymphocyte subsets in those with cavitary TB [87] and the presence of a Th1 cytokine profile in those with noncavitary disease [74]. Similarly, expression of IL-4 in peripheral blood lymphocytes correlates with cavitary disease [88].

In other murine knockout models of immunopathology induced by mycobacteria, γ/δ T cells [89], αβ-positive T cells, IL-12, IFN-γ, and TNF-α [90, 91] also seem to be essential for necrosis of granulomata (figure 3). It has been suggested that caseous necrosis is a protective mechanism to reduce the logarithmic growth of the organisms [47]. However, it is apoptosis rather than necrosis that destroys M. tuberculosis (see below), so it is intriguing to speculate that M. tuberculosis has evolved components that exploit the host’s tissue-damaging protective responses by driving a Th2 response and necrosis. It is interesting that particularly virulent Beijing strains of M. tuberculosis cause human monocytes to express IL-4 and IL-13 [94].

**Apoptosis.** Caseation is a mixture of necrosis and apoptosis. Large numbers of apoptotic T cells and macrophages are seen in caseous foci [98]. Immunohistochemical analysis and in situ hybridization have shown that macrophages surrounding caseous foci are negative for the antiapoptotic protein bcl2 but positive for the proapoptotic protein bax, whereas the associated T cells express IFN-γ and FasL [98]. Apoptosis of macrophages may be beneficial to the host. Both in mice [99] and in humans [100], CD8+ cytotoxic T cells that use the granule-mediated pathway to induce apoptosis (as opposed to the Fas–Fas ligand pathway) lead to killing of the contained mycobacteria too. The role of the granule contents, particularly granulysin, has been reviewed [101]. Apoptosis induced by ATP [102, 103], TNF-α independent of IFN-γ [104], Fas ligand [105], and hydrogen peroxide [106] all promote killing of virulent M. tuberculosis within macrophages, whereas the necrotic mode of death does not [105, 107]. Moreover, M. tuberculosis has mechanisms that tend to inhibit apoptosis. Mannose-capped lipoarabinomannan (Man-LAM) stimulates phosphorylation of Bad, a proapoptotic protein, and so inhibits apoptosis [108]. Another group has shown that Man-LAM inhibits apoptosis by a mechanism involving calcium-dependent signaling [109]. Recently, cathepsins have been shown to modulate apoptosis in human pulmonary epithelial cells [110], although their role in TB has not been investigated. It is, therefore, possible that the material that accumulates as caseum is, in fact, a product of inappropriate necrosis. Apoptotic cells are usually removed by surrounding cells with minimal inflammatory consequences, whereas necrotic cells accumulate. However, it is also possible that, when a sufficient percentage of the cells are undergoing apoptosis, the normal clearance mechanism fails, and apoptotic cells can themselves contribute to caseum.

**FIBROSIS IN TB**

**TNF-α, TGF-β, and the pathogenesis of fibrosis.** Extensive deposition of ECM occurs in the guinea pig model of TB [111]. Available data suggest that TGF-β, together with TNF-α, plays a key role in the formation of the fibrous wall that encapsulates the tuberculous granuloma [33–35]. The importance of TGF-β with respect to pulmonary fibrosis has been established in human [38, 112] and animal [113, 114] models. Although

---

**Figure 3.** The roles of the “subversive” Th2-like component of the immune response in progressive human tuberculosis. This Th2-like interleukin (IL–4 response, modulated by IL-482, may be primed by environmental mycobacteria and helminths and is most striking in developing countries [92, 93]. After exposure to Mycobacterium tuberculosis, certain cell-wall components and protein antigens [94–97] are then able to drive and enhance this IL-4 response, which may contribute to deactivation of macrophages, as well as to necrosis and fibrosis. TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor α.
the exact signaling pathways that drive fibroblasts to lay down ECM and macrophages to dissolve ECM are poorly understood, it is reasonable to speculate that TGF-β may contribute to the dysregulation of ECM turnover in TB. Indeed, TGF-β may also perpetuate fibrogenesis by inhibiting apoptosis of fibroblasts [115] and mediating localized production of inhibitors of TIMP [116]. However, it seems that TGF-β, although necessary, is not sufficient for fibrosis. The importance of other molecules, such as TNF-α, in lung fibrosis is illustrated by models of bleomycin and hypersensitivity pneumonitis, in which anti-TNF-α antibodies ameliorate lung fibrosis [117, 118]. The role of other cell types—such as alveolar epithelial cells, which can harbor M. tuberculosis [42] and can be an important source of cytokines and GFs in idiopathic pulmonary fibrosis [119]—merits further investigation.

Two paradoxes immediately arise. The first is the presence of increased ECM at the periphery of the granuloma but dissolution of ECM in the central part of the granuloma. Possible explanations include a cytokine gradient within the granuloma [120], including low IFN-γ levels in the central macrophagedominant part of the granuloma or selective binding of cytokines to glycosaminoglycans in different parts of the granuloma [121]. Therefore, in the center of the granuloma, high TNF-α concentrations, protease activity, and lysis of infected macrophages predominate, whereas, in the periphery, TGF-β activity and fibroblast activation predominates.

The second paradox is the presence of fibrosis where there are potent IFN-γ responses, which down-regulate TGF-β and production of collagen by fibroblasts [122, 123]. The answer may lie in the significant Th2 response that develops parallel to and within the framework of a Th1 response.

**Role of Th2 cytokines in fibrosis.** IL-4 and IL-13 are profibrotic and enhance collagen production by fibroblasts [123]. Mice, when infected with saprophytic mycobacteria, only develop peribronchial and interstitial fibrosis when primed for IL-4 [84]. Even a single epitope (16 aa) inducing a Th2 response can drive fibrosis in a murine model of TB [124].

In all human diseases characterized by marked pulmonary fibrosis (systemic sclerosis, idiopathic pulmonary fibrosis, radiation-induced pulmonary fibrosis, and chronic lung allograft rejection; reviewed in [125]), there is expression of type 2 cytokines. The same is true in the bleomycin murine model [125] and in schistosomiasis, in which fibrosis and tissue remodeling do not occur if induction of type 2 cytokines by the ova is blocked by preimmunization with ova plus IL-12 [126]. Notably, there are no data on cytokine profiles in the late stages of fibrotic sarcoidosis [127]. These observations have led to the “type 2 cytokine hypothesis of fibrosis” [125]. This paradigm implies an initial Th1-type response to antigenic challenge, followed by a Th2 response that seeks to “wall off,” or isolate, a persistent antigen from the host [128–130]. M. tuberculosis may be exploiting this host response to remain immunologically “sealed off” in fibrocaseous foci.

The Th2 phenotype causes fibroblast activation and collagen deposition in human [131, 132] and animal [114, 133] models. Collagen synthesis in granulomata is stimulated by Th2 cytokines (IL-4, IL-13, and IL-42) and reciprocally inhibited by Th1 cytokines such as IFN-γ and IL-12 [1, 126]. Moreover, granulomatous inflammation and fibrosis are significantly reduced in Stat6−/− mice [124]; IL-4 and IL-13 are the major activators of Stat6. Fibrosis is particularly pronounced in mice overexpressing IL-13 [125]. This cytokine, like IL-4 and IL-42 [135], activates fibroblasts and promotes collagen formation. However, IL-13 also drives expression and activation of TGF-β [125]. Significantly, the increase in expression of type 2 cytokines in human TB extends to IL-13, which, like IL-4 and IL-42, is increased 80–100-fold [136, 137].

Smoking can reactivate TB, probably because nicotine switches off secretion of TNF-α by macrophages, leaving IL-10 secretion unchanged [138]. Similarly, TNF-α-mediated fibrotic lung diseases like sarcoidosis and extrinsic allergic alveolitis [139, 140] are less common in smokers, and smoking improves survival in a Th2-type fibrotic lung condition, idiopathic pulmonary fibrosis [141, 142]. The common denominator facilitating fibrosis in all of these disorders might be the presence of a Th2 cytokine component acting synergistically with TNF-α.

**IL-4 or IL-42 from CD8+ T cells and their role in fibrosis.** In systemic sclerosis, Th2 cytokine expression is associated with pulmonary fibrosis [135]. Interestingly, in several patients, the “IL-4,” made mostly by the CD8+ T cells, was in fact not IL-4 at all but rather IL-42, raising the likelihood that the CD8+ T cells making IL-4 in TB reported by van Crevel et al. might be really making IL-42 (van Crevel et al. used reagents that do not distinguish between the 2 cytokines [88]). IL-42 is antagonistic to IL-4 with regard to lymphocyte function [143, 144], but it is an agonist on fibroblasts [135].

**ARE THERE ANTIGENS THAT PREFERENTIALLY DRIVE NECROSIS AND FIBROSIS? IMPLICATIONS FOR IMMUNOTHERAPY**

It is not yet clear whether there are antigens that preferentially drive Th2, or whether M. tuberculosis merely contains Th2 adjuvant activity. The recent discovery that virulent Beijing strains contain lipids that cause human monocytes to make IL-4 and IL-13 suggests that adjuvanticity is part of the mechanism [94]. Similarly, dendritic cells derived from BCG-infected precursors can drive a Th2-like response [145]. Nevertheless, there does seem to be some antigenic specificity to the Th2 response. ESAT-6 fails to drive IL-4 production [146], but certain epitopes from within the 16-kDa heat-shock protein do so [95]. Identification of the antigens or epitopes that drive IL-4 production will allow design of vaccines that sup-
press the unwanted Th2 component [79]. Agents like *M. vac-
cae*, which attenuate Th2 responses [147, 148], have demon-
strated the ability to modulate lung remodeling and radiographic
absorbance in both drug-sensitive and resistant TB [149, 150];
clinical trials using multiple dose regimens are currently under
way [151].

In conclusion, further research into the genetic, molecular,
immunological, and cellular pathways that drive cavitation and
fibrosis are required. This could yield clinical benefit and has
the potential to interrupt transmission. For instance, vaccines
that target immunopathology (either host responses or bac-
terial virulence factors), even if they are not completely protec-
tive, may have the ability to reduce global disease burden by
minimizing cavitation and interrupting transmission. Like the
anti-TNF-α agents [152–154], other immunotherapeutic mod-
alties could target pathways relating to cytokine signaling, ap-
optosis, protease activity, and ECM turnover. However, such goals
are tenable only if adequate funding is committed by government
agencies, the pharmaceutical industry, and international charities.
Moreover, there will have to be a global organizational structure
committed to achieving such goals.

References

1. Sempowski GD, Derdak S, Phipps RP. Interleukin-4 and interferon-
gamma discordantly regulate collagen biosynthesis by functionally
2. Caughy GH. Chairman’s summary: mechanisms of airway remod-
3. Jeffery PK. Remodeling in asthma and chronic obstructive lung dis-
4. Smith PG, Moss AR. Epidemiology of tuberculosis. In: Bloom BR,
ed. Tuberculosis: pathogenesis, protection, and control. 1st ed. Wash-
5. Bobrowitz ID. The destroyed tuberculous lung. Scand J Respir Dis
6. Curtis JK. The significance of bronchiectasis associated with pulmonary
7. Rosenzweig DY. The role of tuberculosis and other forms of bron-
chopulmonary necrosis in the pathogenesis of bronchiectasis. Am Rev
Respir Dis 1966;93:769–85.
8. Kim YH, Kim HT, Lee KS, Uh ST, Cung YT, Park CS. Serial fiberot-
ic bronchoscopic observations of endobronchial tuberculosis before and
9. Lopez-Majano V. Ventilation and transfer of gases in pulmonary tu-
10. Skoogh BE. Lung mechanics in pulmonary tuberculosis. I. Static lung
11. Thompson JR. Mechanisms of fatal pulmonary hemorrhage in tubercu-
12. Ernst JD. Macrophage receptors for *Mycobacterium tuberculosis*. Infect
13. Heldwein KA, Fenton MI. The role of Toll-like receptors in immunity
against mycobacterial infection. Microbes Infect 2002;4:937–44.
(NKT) cells [correction of natural killer cells] contribute to the gran-
ulomatous reaction caused by mycobacterial cell walls. Proc Natl Acad
15. Kaufmann SH. γδ and other unconventional T lymphocytes: what
do they see and what do they do? Proc Natl Acad Sci USA 1996;93:
2272–9.
16. Ulrichs T, Kosmiadi GA, Trusov V, et al. Human tuberculous gran-
ulomas induce peripheral lymphoid follicle-like structures to orches-
17. Ulrichs T, Kaufmann SHE. Cell-mediated immune response. In: Rom
WN, Garay SM, eds. Tuberculosis. 2nd ed. Philadelphia: Lippincott
Williams & Wilkins, 2004:251–62.
of pulmonary granulomas, macrophage procoagulant activity, and
tumor necrosis factor-alpha by trehalase glycolipids. Ann Clin Lab
19. Perez RL, Roman J, Staton GW Jr, Hunter RL. Extravascular coag-
ulation and fibrinolysis in murine lung inflammation induced by the
mycobacterial cord factor trehalase-6,6′-dimycolate. Am J Respir Crit
20. Love SH, Shannon BT, Myrvik QN, Lynn WS. Characterization of
macrophage agglutinating factor as a hyaluronic acid-protein com-
21. Green SJ, Tarone G, Underhill CB. Aggregation of macrophages and
fibroblasts is inhibited by a monoclonal antibody to the hyaluronate
to tuberculosis in the light of the host-parasite relationships in natively
after aerosol *Mycobacterium tuberculosis* infection is regulated by neu-
rophils via CXCR3-signaling chemokines. Eur J Immunol 2003;33:
2676–86.
24. Turner OC, Basaraba RJ, Orme IM. Immunopathogenesis of pulmonary
granulomas in the guinea pig after infection with *Mycobacterium tub-
WN, Garay SM, eds. Tuberculosis. 2nd ed. Philadelphia: Lippincott
26. Chapman HA Jr. Role of enzyme receptors and inhibitors in regulating
proteolytic activities of macrophages. Ann N Y Acad Sci 1991;624:
87–96.
27. Mauviel A. Cytokine regulation of metalloproteinase gene expression.
28. Appelberg R. Protective role of interferon gamma, tumor necrosis
factor alpha and interleukin-6 in *Mycobacterium tuberculosis* and *M.
fliximab, a tumor necrosis factor α-neutralizing agent. N Engl J Med
2001;345:1098–104.
alpha on host immune response in chronic persistent tuberculosis:
31. Ogawa T, Uchida H, Kasumoto Y, Mori Y, Yamamura Y, Hamada S.
Increase in tumor necrosis factor alpha- and interleukin-6-secreting
cells in peripheral blood mononuclear cells from subjects infected with
32. Roach DR, Briscoe H, Saunders B, France MP, Rimington S, Britton
WJ. Secreted lymphotxin-alpha is essential for the control of an
33. Lukacs NW, Chensue SW, Strieter RM, Warmington K, Kunkel SL.
Inflammatory granuloma formation is mediated by TNF-α-inducible
growth factor-β but not tumor necrosis factor-α, interferon-γ, and
interleukin-4 in granulomatous lung lesions in tuberculosis. Tuber
35. Marshall BG, Wangoo A, Cook HT, Shaw RJ. Increased inflammatory
cytokines and new collagen formation in cutaneous tuberculosis and
36. Wangoo A, Taylor IK, Haynes AR, Shaw RJ. Up-regulation of alveolar

Remodeling in TB • JID 2005:192 (1 October) • 1207


43. Opie EL, Aronson JD. Tubercle bacilli in latent tuberculosis lesions and in lung tissue without tuberculosis lesions. Arch Pathol 1927; 4:1–21.


85. Agrewala JN, Wilkinson RJ. Differential regulation of Th1 and Th2 cells in tuberculosis. JID 2005; 192 (1 October) • 1209
89. Agrewala JN, Wilkinson RJ. Differential regulation of Th1 and Th2 cells in tuberculosis. JID 2005; 192 (1 October) • 1209


137. Seh G, Rook GA. High levels of mRNA encoding IL-4 in unstimulated peripheral blood mononuclear cells from tuberculosis patients revealed by quantitative nested reverse transcriptase-polymerase chain reaction; correlations with serum IgE levels. Scand J Infect Dis 2001; 33:106–9.


