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Reactivation of Latent Tuberculosis Infection in TNF-Deficient Mice

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TNF-deficient mice are highly susceptible to Mycobacterium tuberculosis H37Rv infection. Here we asked whether TNF is required for postinfectious immunity in aerosol-infected mice. Chemotherapy for 4 wk commencing 2 wk postinfection reduced CFU to undetectable levels. While wild-type mice had a slight rise in CFU, but controlled infection upon cessation of chemotherapy, TNF-deficient mice developed reactivation of infection with high bacterial loads in lungs, spleen, and liver, which was fatal within 13–18 wk. The increased susceptibility of TNF-deficient mice was accompanied by diminished recruitment and activation of T cells and macrophages into the lung, with defective granuloma formation and reduced inducible NO synthase expression. Reduced chemokine production in the lung might explain suboptimal recruitment and activation of T cells and uncontrolled infection. Therefore, despite a massive reduction of the mycobacterial load by chemotherapy, TNF-deficient mice were unable to compensate and mount a protective immune response. In conclusion, endogenous TNF is critical to maintain latent tuberculosis infection, and in its absence no specific immunity is generated. The Journal of Immunology, 2003, 171: 3110–3118.
Materials and Methods

Animals

C57BL/6 male mice (University of Cape Town breeding stock), 8–12 wk old, as well as homozygous TNF-deficient mice (39) were used in this study. The genotypes of the gene-deficient mice were confirmed by PCR analysis of DNA obtained from tail biopsies. Mice were kept under specific pathogen-free conditions at the University of Cape Town biosafety level 3 animal unit. All protocols employed in this study were approved by the University of Cape Town animal ethics committee.

Mycobacteria

M. tuberculosis H37Rv (40) was grown to mid-log phase in Middlebrook 7H9 medium (Difco, Detroit, MI) supplemented with 10% oleic acid albumin dextrose catalase (State Vaccine Institute, Pinelands, South Africa) and 1% glycerol (Merck, Munich, Germany) in 5% CO2 at 37°C and frozen in aliquots. Before use, an aliquot was thawed, briefly vortexed, and diluted in sterile saline containing 0.04% Tween 80 (Merck), and clumping was disrupted by aspirating through a 29-gauge needle (Omnican, Braun, Germany) 20 times.

Infection and antibiotic treatment of mice

Mice were infected with 30 viable CFU using an inhalation exposure system (Glas-Col, Terre Haute, IN). Mice were exposed to an aerosol produced by nebulizing 5 ml of a M. tuberculosis H37Rv bacterial suspension in saline containing 0.04% Tween 80 at a concentration of 10⁶ bacilli/ml. Two weeks postinfection, groups of mice were treated with 0.1 g/L RMP and 0.1 g/L INH (Sigma-Aldrich, St. Louis, MO) delivered ad libitum in the drinking water (changed weekly) for 4 wk. M. tuberculosis-infected control mice received plain drinking water ad libitum.

Quantitation of viable mycobacteria in organs

The initial infective dose was verified by sacrificing mice 24 h after aerosol exposure. Lungs were aseptically removed, weighed, and homogenized in saline containing 0.04% Tween 80, and 10-fold serial dilutions were plated in duplicate onto 7H10 agar (Difco) supplemented with 10% oleic acid albumin dextrose catalase and 0.5% glycerol. Plates were incubated at 37°C, and CFU were enumerated after 21 days. Thereafter, at specific time points, mice were sacrificed, and their lungs, livers, and spleens were aseptically removed and weighed. Two-thirds of each organ was homogenized in saline containing 0.04% Tween 80 for CFU enumeration as described above. Data are presented as the mean of log₁₀ CFU per organ, and SD is indicated by error bars (n = 3–5 mice/group).

Histopathology

One third of lungs, livers, and spleens of mice were prepared by fixing the tissue in 10% buffered formalin before paraffin embedding. Sections were stained with H&E and Ziehl-Neelsen acid-fast stain for evaluation of pathologic changes and mycobacterial load, respectively.

Immunohistochemistry

Formalin-fixed, paraffin-embedded sections were deparaffinized and rehydrated through graded alcohols. Sections were incubated with a rabbit antimouse Ab specific for NOS2 at 1/2000 dilution for 16 h at 4°C, followed by rinses in PBS as described previously (40). Sections were then incubated with a rat anti-rabbit secondary Ab for 30 min at room temperature, rinsed again in PBS, and incubated with ABC Vector (Vector Laboratories, Burlingom, CA) for 30 min at room temperature. Subsequently, sections were rinsed in PBS, incubated with 3,3-diaminobenzidine tetrahydrochloride substrate (Vector Laboratories) for 10 min at room temperature, washed in running water, counterstained in hematoxylin, and mounted in Entellan (Merck).

Chemokine assays in the lung

Mice infected with M. tuberculosis H37Rv and treated with RMP and INH from wk 2–6 were sacrificed at 10 wk postinfection. Whole lungs were removed from infected mice and were homogenized in 1 ml of saline containing 0.04% Tween 80. Supernatants were collected after low speed centrifugation, aliquoted, and frozen at −80°C. Supernatants were then assayed for chemokine content using commercially available ELISA reagents for macrophage inflammatory protein-1α (MIP-1α), monocyte chemotactic protein-1 (MCP-1), and RANTES (R&D Systems (Abingdon, U.K.) and BD PharMingen (San Diego, CA)).

Nitrile concentrations in lung homogenate supernatants were determined using the Griess reagent (41) (3% phosphoric acid, 1% p-aminobenzene sulfonamide, and 1% n-1-naphthylethenediamide) as described previously (42).

FACS analysis of cell surface markers

Lung cells were obtained from mice at 10 wk as described previously (43). In brief, lungs were perfused, chopped into small pieces, and incubated with RPMI 1640 (Sigma-Aldrich) containing optimal concentrations of collagenase (Sigma-Aldrich) and DNase (Sigma-Aldrich) for 60 min at 37°C. The cell suspension was then passed through a 100-μm pore size mesh, and cells were collected by centrifugation. The cells were stained with the following Abs (BD Pharmingen): CD3 (anti-CD3-PE, clone 145.2C11), CD4 (anti-CD4-FTTC, clone H129.19), CD8 (anti-CD8-FTTC, clone 53-6.7), CD11a (anti-CD11a-PE, clone M17/4), CD44 (anti-CD44-PE, clone IM7), I-A/I-E (anti-I-A/I-E PE, clone M5/114.15.2), and CD16/32 (clone 2.4G2). All staining procedures were performed in PBS containing 0.1% BSA and 0.1% sodium azide (FACS buffer) for 20 min at 4°C. Cells were fixed with 4% paraformaldehyde for at least 1 h and analyzed by flow cytometry using CellQuest software (BD Immunocytometry Systems, San Jose, CA). Cells were gated on the lymphocyte or monocyte population by forward and side scatter.

Statistical analysis

Data are presented as the mean, and SD is indicated by error bars. Statistical significance was determined using Student’s t test. A value of p ≤ 0.05 was considered significant.

Results

TNF gene-deficient mice rapidly succumb to infection following cessation of chemotherapy

C57BL/6 and TNF-deficient mice were infected with 30 CFU of M. tuberculosis H37Rv via the aerosol route and treated with RMP-INH for a period of 4 wk starting 2 wk postinfection. While C57BL/6 mice survived for the duration of the experiment (44 wk), all TNF-deficient mice succumbed to infection between 7 and 12 wk after cessation of chemotherapy (Fig. 1). While all TNF-deficient mice reactivated spontaneously with tuberculosis following cessation of RMP-INH treatment and succumbed to infection, reactivation in wild-type mice was subclinical and could only be...
assessed by the determination of bacterial counts. Untreated wild-type mice, also infected with 30 CFU of M. tuberculosis H37Rv, seemed to control the infection during the experimental period (100% survival), whereas untreated TNF-deficient mice succumbed to infection within 5–6 wk (Fig. 1).

Upon reactivation in both wild-type and TNF-deficient mice, only TNF-deficient mice lost body weight significantly (19.75 ± 4.37 g) compared with reactivated wild-type mice (27.71 ± 2.46 g; \( p < 0.001 \); Fig. 2A). Furthermore, lung weights, an indicator of an inflammatory process, dramatically increased at wk 14 postinfection in TNF-deficient, but not in wild-type, mice (Fig. 2B). Mean lung weights of reactivated TNF-deficient mice (5.40 ± 1.33%), expressed as a percentage of body weights, were significantly higher (\( p < 0.001 \)) than those of their reactivated wild-type counterparts (0.647 ± 0.10%) due to extensive inflammation, as confirmed by histopathology. There were no significant differences in lung weights between untreated wild-type infected controls (0.765 ± 0.01%) and reactivated wild-type mice at this time point (\( p < 0.01 \)). In contrast, infected, but untreated, TNF-deficient mice lost 24% of their body weight within 4 wk of infection, preceding death. At postmortem their lung weights were increased almost 2-fold, and microscopically the lungs displayed abundant recruitment of mononuclear cells in the absence of granuloma formation. The data are in accordance with previous reports (30, 44). Gross splenomegaly was observed in reactivated TNF-deficient mice (1.480 ± 0.43%) compared with reactivated wild-type mice (0.333 ± 0.08%; \( p = 0.001 \)), which indicates systemic inflammation. By contrast, no differences were observed in spleen weights between reactivated wild-type and chronically infected wild-type mice (0.415 ± 0.01%; \( p = 0.124 \)). Lastly, gross hepatomegaly was found in TNF-deficient mice following reactivation of infection (8.917 ± 1.31%) compared with wild-type reactivated mice (\( p = 0.016 \)).

**Course of infection in TNF gene-deficient mice following short-course antituberculous chemotherapy**

In view of the rapid deterioration of the health status and the weight changes observed in mice, we asked whether those were correlated with increased bacillary growth in the lungs, spleen, and liver following aerosol infection with 30 CFU of M. tuberculosis H37Rv. A rapid increase in bacilli in lungs, spleens, and livers was observed upon cessation of chemotherapy, with a plateau in bacterial load representing a stable and controlled infection in untreated wild-type mice (Fig. 3).

RMP-INH treatment for 4 wk controlled infection in both TNF-deficient and C57BL/6 mice with undetectable CFU in lungs, spleen, and liver in both groups of mice at the end of chemotherapy (wk 6). However, the 4-wk chemotherapy course did not prevent spontaneous reactivation in both groups of mice. In wild-type mice, the bacterial load increased from undetectable levels to \(~10^4\), \(10^5\), and \(10^6\) CFU in lungs, spleen, and liver, respectively. By contrast, in TNF-deficient mice the reappearance of bacilli following reactivation was much more rapid and uncontrolled. The bacillary burden in the lungs of TNF-deficient mice sharply rose to \(~10^9\) CFU within 8 wk after therapy, significantly higher than the \(10^5\) CFU in the lungs of reactivated wild-type mice at the same time point (\( p < 0.01 \)). A similar pattern was observed in reactivation in the spleen and liver, with an increase from undetectable levels to \(10^6\) and \(10^7\) CFU, respectively, in TNF-deficient mice, which is significantly higher than that in wild-type mice (liver, \( p = 0.05 \); spleen, \( p < 0.01 \)). By contrast, infected, but untreated, TNF-deficient mice are unable to control infection and show a dramatic increase in CFU in the lungs (\(1.2 \times 10^7\) CFU), spleen (\(9.0 \times 10^6\) CFU), and liver (\(1.4 \times 10^7\) CFU) at 4 wk postinfection, before death.

**Severe necrotic pneumonia in TNF gene-deficient mice following short-course chemotherapy and reactivation**

Two weeks after aerosol infection, a slightly increased cellularity was observed in the alveolar septae of both experimental groups (Fig. 4, A, D, and G). Untreated wild-type mice developed substantial peribronchial inflammation with granuloma formation at 6 wk postinfection (Fig. 4B), which gradually progressed to chronic pneumonia at 14 wk (Fig. 4C). By contrast, chemotherapy-treated wild-type and TNF-deficient mice presented largely normal lungs at 6 wk postinfection (Fig. 4, E and H). Upon cessation of therapy, reactivation of infection was visible at 14 wk with mild chronic pneumonia and granuloma formation with abundant macrophages.

![Graph](http://www.jimmunol.org/)

**FIGURE 2.** Reactivated tuberculosis results in significant changes in TNF-deficient mouse body weights (A) and lung weights (B). C57BL/6 and TNF gene-deficient mice were aerogenically infected with 30 CFU M. tuberculosis H37Rv and chemotherapeutically treated with RMP-INH for a period of 4 wk starting 2 wk postinfection (indicated by the arrows). Treated C57BL/6 mice (○) reactivated after cessation of treatment (100% reactivation), but controlled the infection (100% survival), whereas TNF gene-deficient mice (□) reactivated, but rapidly succumbed to infection (100% reactivation, 0% survival). ◆ Body and lung weights of C57BL/6 infected, but untreated, control mice. Following spontaneous reactivation in both C57BL/6 and TNF gene-deficient mice (100% reactivation for both groups), body weights (\( p = 0.0003 \)) and lung weights (\( p = 0.0004 \)) were significantly different between these two groups at 14 wk postinfection. Body and lung weights of uninfected C57BL/6 (▲) and TNF-deficient (●) mice are indicated. Body and lung weights are expressed as the mean ± SD. Data represent three independent experiments with three to five mice per group per time point.
We further tested the expression of NOS2 as a marker of macrophage activation in liver (data not shown) and lungs. While wild-type mice with distinct granulomas expressed abundant NOS2 immunoreactivity in the lungs, NOS2 expression in TNF-deficient mice was distinctly reduced (Fig. 7). Concomitant with reduced NOS2 expression, NO levels in the lung homogenate at 4 wk after cessation of drug treatment were significantly lower in TNF-deficient mice compared with wild-type controls ($p < 0.005$). Untreated wild-type mice had slightly lower levels than treated wild-type controls (Fig. 8). Therefore, the results demonstrate that TNF is required for NOS2 expression and NO production in addition to its pivotal role in granuloma formation.

Reduced lymphocyte recruitment and activation in TNF-deficient mice with reactivated M. tuberculosis infection

Recruitment of T cells to the site of infection has been shown to be critical to form granulomas and control M. tuberculosis infection. In accordance with the microscopic findings, the total mononuclear cell counts obtained from infected lungs 4 wk after cessation of RMP-INH chemotherapy was reduced in TNF-deficient mice. Flow cytometric analysis revealed $4.8 \times 10^7$ T cells from the lungs of TNF-deficient mice and $7.3 \times 10^7$ from those of wild-type mice. We further quantified T cell subpopulations and assessed activation status. Recruitment of CD4$^+$ T cells was significantly decreased in TNF-deficient mice at 10 wk postinfection, while CD8$^+$ T cell counts were similar in both groups (Fig. 9). Using CD11a and CD44 as activation markers of CD4$^+$ cells, TNF-deficient mice revealed significantly lower numbers of activated T cells at 10 wk postinfection ($p < 0.001$). Furthermore, CD11b$^+$ macrophages expressing MHC class II were also significantly reduced in TNF-deficient mice ($p < 0.001$). Thus, both lymphocyte and macrophage recruitment and activation were decreased in the absence of TNF. Since chemokines orchestrate the recruitment of mononuclear cells, we asked whether the production of chemokines was altered in TNF-deficient mice.

Reduced chemokine production in the absence of TNF

The TNF dependence of chemokine expression has been reported in vitro (45), and decreased CXC and CC chemokine expression upon tuberculosis infection has been shown in TNF-deficient mice (43). We therefore assessed the production of selected chemokines in the lungs upon reactivation of tuberculosis infection. We determined the pulmonary levels of MCP-1, MIP-1$\alpha$, and RANTES after reactivation of infection (Fig. 10). MCP-1 levels in the lung were significantly lower in TNF-deficient mice 10 wk following M. tuberculosis infection compared with those in wild-type controls ($p < 0.001$). Similarly, pulmonary production of MIP-1$\alpha$ and RANTES was significantly decreased in TNF-deficient mice ($p < 0.001$). These data suggest that reduced chemokine production might explain in part the reduced cell recruitment and granuloma formation.

Discussion

Here we show that TNF is required to control latent M. tuberculosis infection upon cessation of chemotherapy in aerosol-infected mice. Despite the elimination of bacilli to undetectable levels after short-course RMP-INH treatment, we observed massive reactivation, with necrosis and death of mice, in the absence of TNF. TNF gene-deficient mice usually succumb to a primary aerosol infection with 30 CFU within 5–6 wk, whereas these mice survived 7–12 wk postchemotherapy. The survival times of primary and reactivated infection are comparable, and the small difference in time could be ascribed to the lower number of persistent bacilli that survived chemotherapy compared with the infective dose. Whereas
both wild-type and TNF-deficient mice reactivated spontaneously following short-course RMP-INH chemotherapy, wild-type mice presented with subclinical tuberculosis, unlike mice deficient in TNF, which reactivated rapidly with fatal infection. Differences between wild-type and TNF-deficient mouse body weights as well as gross differences in lung, liver, and spleen weights were noted, exemplifying characteristics of clinical disease vs subclinical infection.

The kinetics of mycobacterial replication showed a rapidly progressing infection, with CFU reaching fatal numbers in the organs of TNF-deficient mice within 7–12 wk of reactivated infection. Despite initially undetectable CFU after chemotherapy, TNF-deficient mice were unable to control bacterial growth, while bacteria in wild-type mice reached a plateau following reactivation, during which the infection was controlled. Additionally, abundant acid-fast bacilli were detected both intracellularly and extracellularly in TNF-deficient mice shortly before they succumbed to the overwhelming infection.

The importance of TNF in the protection and pathogenesis of tuberculosis has been investigated by the use of neutralizing Abs and gene-deficient mice. Both TNF- and TNFR-deficient mice showed delayed granuloma formation and lack of control of mycobacterial infection (22, 30, 31). Furthermore, signaling through the TNF type 2 receptor is not critical to control mycobacterial infection (31).

Apart from the role of TNF in controlling multiplication of mycobacteria during infection, it also contributes to the destructive pathology typically seen in tuberculosis (35, 37, 46). We have observed progressive pathology, most notably in lung tissue, in the absence of TNF, which might be due to compensatory production of other proinflammatory cytokines (data not shown). The TNF-deficient mice developed severe pneumonia with focal necrosis, associated with an increase in bacterial burden, within a short time following reactivation of infection.

Granulomas, a hallmark of mycobacterial infection, are formed when Ag-specific T cells are recruited and activate macrophages at the localized site of infection (47–49). Containment of M. tuberculosis depends on this granulomatous response, and any defect that prevents efficient granuloma formation results in the failure to isolate mycobacteria from surrounding tissue (29, 50). Following RMP-INH chemotherapeutic treatment, TNF-deficient mice presented with minimal lung and liver pathology, but during reactivation of tuberculosis, necrotic lesions formed because of the lack of organized granuloma differentiation. Our results confirm the importance of rapid and efficient granuloma formation, as TNF-deficient mice, lacking these abilities, rapidly succumb to overwhelming infection as a result of uncontrolled replication and dissemination of mycobacteria. We found that T cells and macrophages were not efficiently recruited to the lung, and no

**FIGURE 4.** Mostly normal lung morphology of chemotherapeutically treated C57BL/6 and TNF-deficient mice, with severe focal necrosis in TNF-deficient mice during reactivation of tuberculosis infection. Mice were aerogenically infected with 30 CFU of M. tuberculosis H37Rv and treated with short-course RMP-INH for 4 wk, starting 2 wk postinfection. A, B, and C, Lung morphology of infected control wild-type mice during primary infection (A), 6 wk postinfection (B), corresponding to the period after chemotherapy of the other groups, and at 14 wk postinfection (C), corresponding to the time point of reactivated disease in the treated C57BL/6 (D–F) and TNF gene-deficient mice (G–I). Magnification, ×40.

**FIGURE 5.** Abundant acid-fast bacilli in the lung tissue of TNF gene-deficient mice (A) vs low numbers of bacilli in C57BL/6 mice (B) during reactivation of disease 14 wk postinfection. Mice were aerogenically infected with 30 CFU of M. tuberculosis H37Rv and treated with short-course RMP-INH for 4 wk, starting 2 wk postinfection. Tissue was fixed in buffered formalin, sectioned, and Ziehl-Neelsen stained to detect acid-fast mycobacteria. Magnification: A, ×40; B, ×100.
proper granulomas were formed. NOS2 expression and nitrite levels in the lungs of TNF-deficient mice were low compared with levels in reactivated wild-type mice. By contrast, NOS2 expression and serum nitrite levels in the acute infection model (28) and in the persistent model of tuberculosis infection are apparently TNF independent (8). IFN-γ and IL-12 were elevated in TNF-deficient mice (data not shown), suggesting that IFN-γ and IL-12 alone are not sufficient to activate macrophages to produce NO in the face of an acute primary or reactivated mycobacterial infection.

The exact mechanism by which TNF and IFN-γ activate macrophages to produce NO is likely to be more complex than our current understanding. It seems that early activation and production of NO are essential to control mycobacterial replication. A delay in RNI production in splenic macrophages and in lung granulomas was observed by Flynn et al. (22) in both TNF p55 receptor-deficient mice and mice in which TNF was neutralized with an anti-TNF mAb. The fine equilibrium between host immune control and mycobacterial burden seems to be a determining component in the outcome of primary infection as well as reactivated infection.

Scanga and colleagues (51) investigated the relative importance of RNI in both aerosol and i.v. infection models in mice. They found that RNI indeed play an important role in vivo in both aero- and i.v. models regardless of whether laboratory strains or clinical isolates of M. tuberculosis were used (51). The role of RNI in host defense in human tuberculosis has been a controversial point for quite some time. However, localized expression of NOS2 in human lung lesions within granulomas, alveolar macrophages, and epithelial cells in pneumonitis areas has been demonstrated recently (52). This study provides specific evidence that NOS2 is expressed at the foci of M. tuberculosis infection in human lung.

NO is also produced by human macrophages in vitro (reviewed in Ref. 53), and it is able to kill M. tuberculosis (54). Moreover, the presence of active NOS2 expression and NO production has been demonstrated in alveolar macrophages from tuberculosis patients (55, 56). Therefore, the overall significance of RNI against M. tuberculosis in humans is likely to be an important antimycobacterial mechanism.

An intact T cell response is also essential for adequate host immune control and granuloma formation in tuberculosis infection, as demonstrated in T cell-deficient mice (57, 58). After their
Chemokines are critical for cell recruitment and cell activation (61, 62). Several chemokines, including RANTES, MIP-1α, MCP-1, and IFN-γ-inducible protein-10, were elevated in both in vitro and in vivo M. tuberculosis experimental infections (63, 64) as well as in pulmonary tuberculosis in man (65–67; reviewed in Ref. 68). A critical role for CCR2 has been shown for the recruitment of mononuclear cells into the infected lung and to control infection (68). CCR2-deficient mice rapidly succumb to aerosol M. tuberculosis infection, which is unlikely to be mediated by MCP-1, as MCP-1-deficient mice control M. tuberculosis infection (69); hence, other ligands of CCR2 may be required.

TNF appears to be required for the induction of several chemokines, such as MIP-1α, MIP-1β, and RANTES on human lymphocytes (45). Delayed chemokine transcription for MCP-1, MIP-1α, MIP-1β, MIP-2, eotaxin, and RANTES was reported in the liver of M. smegmatis- and M. tuberculosis-infected TNF-deficient mice (67). Chemokine transcripts in the liver in the i.v. infection model were normalized or even increased at 4 wk of infection, but no data on protein expression are available, and the results may be different upon aerosol infection, as in the present infection. Therefore, our data showing reduced MCP-1, MIP-1α, and RANTES production in the lung upon reactivation in TNF knockout mice might contribute to the reduced cell recruitment and activation and, hence, the control of infection.

We found a reduction of pulmonary RANTES, MIP-1α, and MCP-1 in TNF-deficient mice compared with wild-type mice. The delayed and defective granuloma formation in these mice might therefore be a direct result of reduced chemokine secretion. These data are in agreement with decreased CXC and CC chemokine expression shown in TNF-deficient mice (43). Reduced CXC and CC class chemokine expression was associated with reduced CD11b+ macrophage and CD4+ T cell recruitment to areas of granuloma formation. Furthermore, a critical role of CCR2 signaling had been demonstrated in the generation of mycobactericidal granulomas (70), but MCP-1, one of several CCR2 ligands, did not appear to be involved (69).

Several publications address the reactivation of tuberculosis in patients receiving anti-TNF therapy for a variety of inflammatory disorders, such as Crohn’s disease and rheumatoid arthritis (71–83), of which some develop severely disseminated forms. Considering the estimates that one-third of the world population is latently infected with tuberculosis, the use of these anti-TNF agents might have devastating long term effects. Additionally, testing of latent tuberculosis is not a practical option with the currently used Mantoux skin test in countries where people have been vaccinated with Calmette-Guérin bacillus. The implications of our findings together with those of others show that TNF is a critical cytokine that is essential for the early control of primary infection, the maintenance of latent infection, and as a safeguard against reactivated tuberculosis. Our experimental studies also demonstrate that it is indeed possible to control and eventually eradicate tuberculosis with efficient RMP-INH treatment, even in an immunocompromised state, such as seen with the high numbers of HIV- and tuberculosis-coinfected individuals in high burden countries.

In conclusion, we demonstrate that the immune system is unable to control latent tuberculosis infection in the absence of TNF. We demonstrate that TNF is required for the secretion of chemokines that enhance the recruitment and activation of T cells and macrophages to form mycobactericidal granulomas.

References


