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Chapter 7

Pathophysiology of Tuberculosis

Ruiru Shi and Isamu Sugawara

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1. Introduction

1.1. Inflammatory process of tuberculosis

When many infectious units of 1-3 bacilli are inhaled, a phenotypically hardy bacillus is likely to be among them. In addition, the alveolar macrophages apparently vary in their capacity to destroy bacilli [1]. Staining for acid-fast bacilli is very useful for demonstrating *M. tuberculosis* (A). Fig. 1 reveals histologic manifestation of tuberculosis over the time course. Histologically, tuberculosis displays exudative inflammation (B), proliferative inflammation (D) and productive inflammation (C) depending on the time course. Using animal experiments and an inhalation exposure system, the pathologic condition of the infected animals was followed up for one year. Exudative inflammation was observed for the first 10 days. Thereafter, granulomas, which corresponded to foci of proliferative inflammation, were formed. Cavity formation was not recognized in animal tuberculosis, except for rabbits. Using rabbit models, Dr. Arthur Dannenberg described the pathology of tuberculosis in detail [2, 3]. There are five stages: onset, symbiosis, early stages of caseous necrosis, interplay of cell-mediated immunity and tissue damaging delayed-type hypersensitivity, and liquefaction and cavity formation. In stage 1, tubercle bacilli are usually destroyed or inhibited by the mature resident alveolar macrophages that ingest them. If bacilli are not destroyed, they grow and eventually destroy the alveolar macrophages. In stage 2, bacilli grow logarithmically within the immature nonactivated macrophages. These macrophages enter a tubercle from the bloodstream. This stage is termed symbiosis because bacilli multiply locally without apparent damage to the host, and macrophages accumulate and divide. In stage 3, the stage at which caseous necrosis first occurs, the number of viable bacilli becomes stationary because their growth is inhibited by the immune response to tuberculin-like antigens released from bacilli. Stage 4 is the stage that usually determines whether the disease becomes clinically apparent. Cell-mediated immunity plays a major role in this situation. The cytotoxic delayed- type hypersensitivity immune response

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kills these macrophages, causing enlargement of the caseous center and progression of the disease. If good cell-mediated immunity develops, a mantle of highly activated macrophages surrounds the caseous necrosis. In stage 5, bacilli evade host defenses. When liquefaction of the caseous center occurs, the bacilli multiply extracellularly, frequently attaining very large numbers. The high local concentration of tuberculin-like products derived from these bacilli causes a tissue-damaging delayed-type hypersensitivity response that erodes the bronchial wall, forming a cavity.

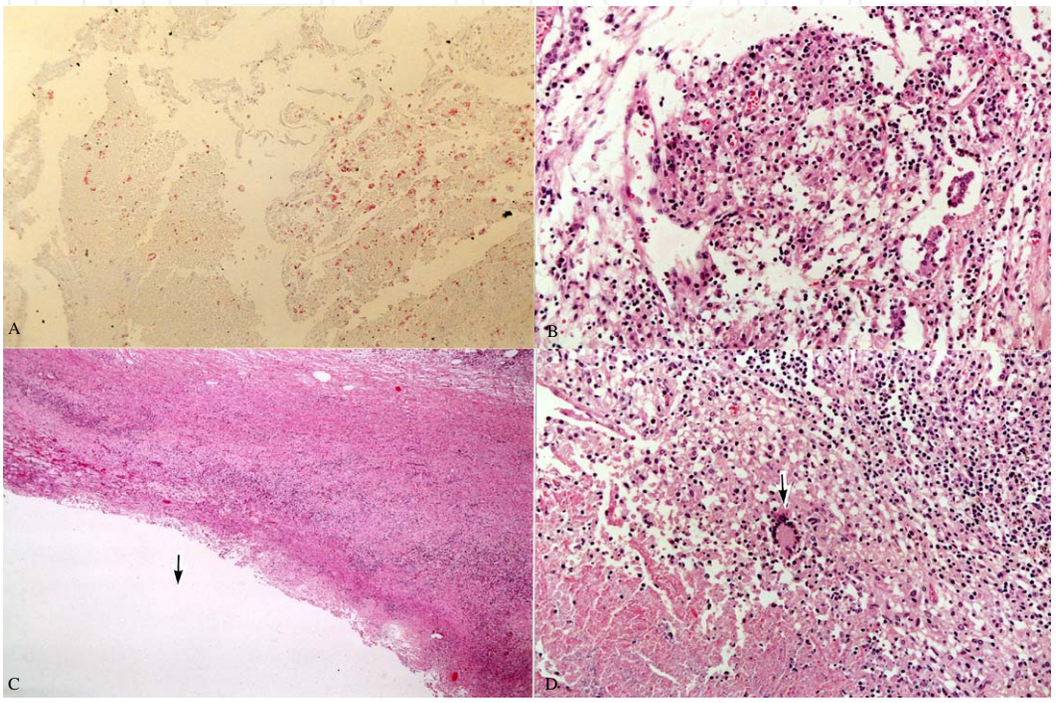

Figure 1. Histologic appearance of tuberculosis A. Staining for acid-fast bacilli, B. exudative stage, C. productive stage with cavity formation (→), D. proliferative stage with a multinucleated giant cell.

2. Clinical manifestations

As the cellular processes occur, tuberculosis may develop differently in each patient, according to the status of the patient's immune system. Stages include latency, primary disease, primary progressive disease, and extrapulmonary disease. Each stage has different clinical manifestations [4]. *M. tb* organisms can be enclosed but are difficult to completely eliminate [5]. Persons with latent tuberculosis have no signs or symptoms of the disease, do not feel sick, and are not infectious [5]. However, viable bacilli can persist in the necrotic material for years or even a lifetime [6], and if the immune system later becomes compromised, as it does in many critically ill patients, the disease can be reactivated. Primary pulmonary tuberculosis is often asymptomatic. Although it essentially exists subclinically, some self-limiting findings might be noticed. Associated paratracheal lymphadenopathy may occur because the bacilli spread from the lungs through the lymphatic system. Active tuberculosis develops in only 5% to 10% of persons

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exposed to *M. tb*. Fig. 2 shows typical chest X-ray before (A) and after (B) chemotherapy. Fatigue, malaise, weight loss, low-grade fever, night sweats, cough, sputum, are the main symptoms. The sputum may also be streaked with blood. Hemoptysis can be due to destruction of a patent vessel located in the wall of the cavity [7]. Extrapulmonary disease occurs in more than 20% of patients. The most serious location is the central nervous system, where infection may result in meningitis, which could be fatal in most cases. Another fatal form is infection of the blood stream by mycobacteria, this form is called disseminated or military tuberculosis. The most common extrapulmonary tuberculosis is lymphatic tuberculosis. Other possible locations include bones, joints, pleura, and genitourinary system [4].

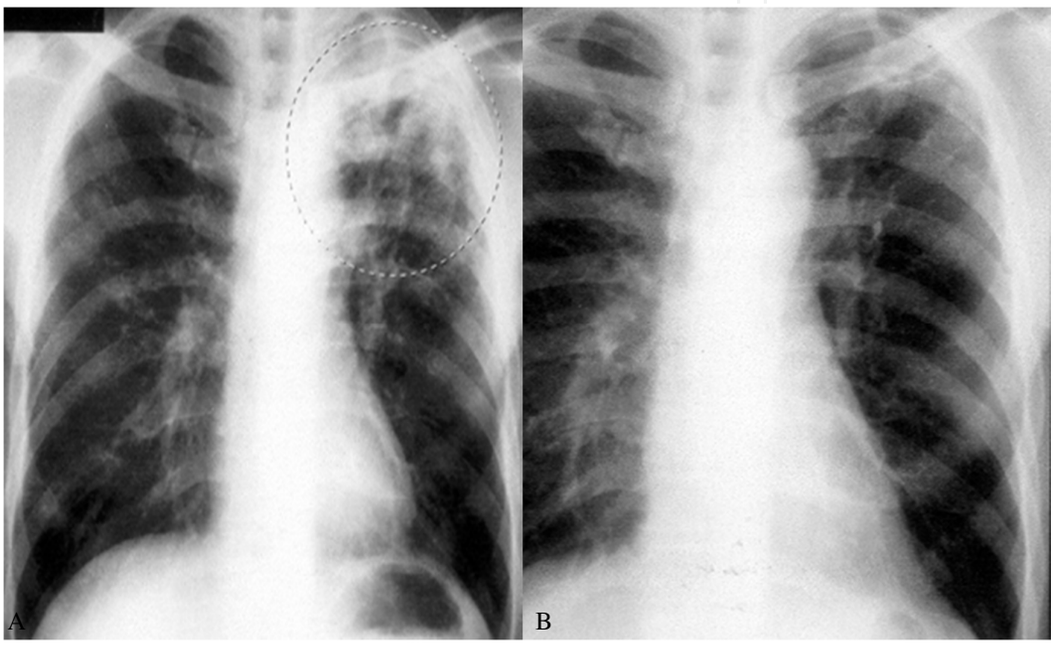

Figure 2. Chest X-ray of pulmonary tuberculosis and cured Tuberculosis A. before chemotherapy with rifampicin, isoniazide, ethambutol and pyrazinamide, B. after chemotherapy. Apical shadow (dotted circle) disappears.

3. T cell activation against *Mycobacterium tuberculosis*

In human, a TB index case may infect a contact person through cough and expectoration, so the lung is the primary route of infection and often the main tissue exhibiting TB. Infectious droplet nuclei are deposited in the alveolar spaces of the contact person where *Mycobacterium tuberculosis (M. tb)* can be phagocytosed by alveolar macrophages, epithelial cells, dendritic cells (DC) and neutrophils [8, 9]. Alveolar macrophages and DC are then believed to transport *M. tb* to local lymph nodes where T cell activation occurs and expand. Activation of the phagocytic host cell is much required to limit growth of *M. tb*; as in the absence of activation, disease outcome is extremely poor. Effective phagocyte activation requires a specific cellular response, as infected hosts lacking specific components of the acquired response have a poor outcome [10]. While acquired cellular protection is expressed rapidly

following systemic challenge with *M. tb*, it is less rapid in the lung. Slow expression of protection in the lung allows mycobacteria to grow and modulate the infection site. Until recently it has not been clear whether the slow response to aerosol delivery of bacteria resulted from limited availability of antigen or inhibition of antigen-presentation by *M. tb*. Several studies show that the first T cell activation occurs in the draining lymph node (DLN) of the lung 8–10 days following initial challenge. The activation of T cells correlated temporally with the arrival of bacteria and availability of antigen in the DLN, however conditions for T cell activation were unique to the draining lymph nodes as the presence of antigen-producing bacteria in the lung and spleen did not result in initial activation of T cells [11, 12]. While delivery of lipopolysaccharide (LPS) to the MTB-infected lung failed to accelerate T cell priming [11], increasing the bacterial dose did accelerate the response modestly suggesting that both antigen burden and refractory cells serve to slow the response. So, protective memory cells will not become activated until they see antigen, i.e. more than 8 days post infection. Once T cells become activated they differentiate into effector T cells that migrate to the lung. By day 14 of infection, when activated T cells first arrive in the lung, bacteria are within alveolar macrophages, myeloid DC and neutrophils [11]. T cells can recognize antigen within the mycobacterially-infected lung but the antigen presentation is not optimal. It takes time for the protective T cells to reach sufficient numbers to stop bacterial growth. T cells can be divided into two subsets, Th1 and Th2, on the basis of the cytokines they produce. In tuberculosis, Th1 plays a major role in defense against tuberculosis. Th1 cells suppress Th2 cells. CD4 + T cells have unambiguously been identified as the most important lymphocyte subset for mediating protection.CD4 T lymphocytes differentiate in the peripheral tissues to adopt a variety of fates such as the Th-1 cells, which produce interferon (IFN)-γ to down-regulate Th2 responses and Th-2 cells, which produce interleukin (IL)-4. CD8 T lymphocytes produce predominantly IFN-γ. Though CD4 response is greater than the CD8 response, the latter can provide protection in the absence of CD4 help [13]. During active TB there is a local pulmonary immune response characterized by α/β T cells and strongly enhanced *M. tuberculosis* antigen-specific Th1 responses, with large amounts of locally secreted IFN-γ [14].

4. Animal models of tuberculosis

A wide variety of animal models have been used to test new vaccines and drugs [15]. Mice can harbor high numbers of *M. tb* within lung tissue without showing clinical signs [16]. Mice do not cough nor form cavitary lesions, making them a poor model for transmission studies [17]. Fibrous capsules are not observed histologically, which can affect the validity of antibiotic studies, as *M. tb* would be more easily accessed by drugs in the mouse lung. In addition, because of their short life span, mice are poor models for the study of latent infection. Rat TB also showed similar pathophysiology to murine TB [31]. Guinea pigs develop robust DTH response to mycobacterial antigens and, after infection with *M. tb*, reproduce many of the aspects of human infection, such as caseous and mineralized granulomas, primary and hemato-genous pulmonary lesions, fibrous capsule formation, and dissemination [19],

however, pulmonary lesions in guinea pig contain a high proportion of granulocytes, particularly eosmophils, which are not common features of human disease [20]. The rabbit is the only common laboratory animal in which the disease closely resembles the typical chronic cavitary type found in the majority of human beings [21, 22]. Rabbits infected with *M. tb* mount a moderate DTH response and form caseous granulomas and cavitary lesions [23-25]. Rabbits, including currently available inbred strains, are relatively resistant to *M. tb*, however, requiring the inhalation of 500 to 3000 bacilli to form one grossly visible tubercle at 5 weeks postinfection [23]. Most rabbits will also overcome disease completely, with few culturable bacilli [24]. This model is useful in the study of latent or paucibacillary TB states, however, without the use of antibiotics as in the Cornell model. Rabbits do need to be experimentally immunosuppressed as they will not spontaneously reativate disease [26]. There are minimal immune reagents, however, for this model, and the larger size of rabbits makes them more costly to use. There are inbred strains of rabbits, such as the Lurie and Thorbecke rabbits, which are more susceptible to *M. tb* infection. This susceptibility has been linked to suppressed macrophage antimycobacterial activity, decreased MHC Class 2 expression, and impaired development of type 4 hypersensitivity [27]. Other animal models, such as nonhuman primates, which are susceptible to *M. tb* and full spectrum of granuloma types can be observed [28], have not been widely used. Using mycobacterial inoculation into trachea, at necropsy, all unvaccinated monkeys (*Macaca fascicularis* and *Macaca mulatta*) exhibited extensive bilateral lung pathology characterized by the presence of multiple granulomas. These granulomas exhibited conglomeration to larger caseous areas, especially in the hilar region [55].

5. Alveolar macrophages in tuberculosis

When tubercle bacilli reach alveoli, they are phagocytosed by resident alveolar macrophages. Though tubercle bacilli are killed byalveolar macrophages, tubercle bacilli can also kill macrophages through apoptosis. What is the fate of tubercle bacilli once they enter the phagosomes of macrophages? Alveolar macrophages of aerially infected guinea pigs were collected by bronchoalveolar lavage. At 12 days after infection, one out of 10,000 alveolar macrophages of various sizes contained many tubercle bacilli [31]. This indicates that certain alveolar macrophages permit M. tuberculosis to replicate in the phagosomes, although most of tubercle bacilli are killed by activated alveolar macrophages. It will be of great interest to examine the survival mechanism of *M. tuberculosis* at the single-cell level, but we still do not know why macrophages targeted by tubercle bacilli cannot kill the bacilli.

IFN-γ knockout mice were infected with avirulent H37Ra or BCG Pasteur, multinucleated giant cells were recognized in the granulomatous lesions. The lesions also contained tubercle bacilli and consisted of multinucleated cell clusters, being immunopositive with anti-Mac-3 antibody. The alveolar macrophages were transformed into multinucleated ginat cells. We subsequently infected various cytokine-konockout mice with *M. tb*, but no Langerhans' multinucleated giant cells were recognized in the granulomas. Therefore, it seems that formation of multinucleated giant cells requires optimal combinations and concentrations of various cytokines, and the level of IFN-γ, at least, has to be significantly low.

6. Roles of cytokines, neutrophils, NK cells, NKT cells and γδT cells

IFN-γ and TNF have long been implicated as regulators of T cell responses in mycobacterial disease [29]. The technique of gene targeting (knockout) has swept through biomedical research. IFN-γ, TNF-α, IRF-1, NF-IL6, NF-κB p50, STAT 1 and STAT 4 knockout mice succumbed to *M. tuberculosis* infection over time. There appears to be a cytokine and transcription factor hierarchy in experimental tuberculosis. The results indicate that these molecules play major roles in defense against the disease, IFN-γ and TNF-α being the leading players in this respect [30].

The role of neutrophils in the development of tuberculosis remained unknown for a long time. We utilized LPS-induced transient neutrophilia in the lungs [31]. LPS (50μg/ml) was administered intratracheally to male Fischer rats, which were then infected with *M. tuberculosis* via an airborne route. Intratracheal injection of LPS significantly blocked the development of pulmonary granulomas and significantly reduced the number of pulmonary colony-forming units (CFU). Treatment with amphotericin B (an LPS inhibitor) or neutralizing anti-rat neutrophil antibody reversed the development of pulmonary lesions. LPS-induced transient neutrophilia prevented early mycobacterial infection. The timing of LPS administration was important. When given intratracheally at least 10 days after aerial infection, LPS did not prevent the development of tuberculosis. Neutrophils obtained by bronchoalveolar lavage killed M. tuberculosis bacilli. These results indicate clearly that neutrophils participate actively in defense against early-phase tuberculosis.

Natural killer (NK) cells are innate lymphocytes which are a first line of defense against infection. NK cells can kill autologous infected cells without prior sensitization, and are believed to play a pivotal role in innate immunity to microbial pathogens. In mouse model, NK cells are activated and produce IFN-γ during the early response to pulmonary tuberculosis [31] and NK cell-produced IFN-γ regulates the anti-mycobacterial resistance mediated by neutrophils [32]. However animal models do not give a clear answer to whether NK cells is important in *M. tb* infection in vivo. Depletion of NK cells had no effect on bacterial replication in the lung of immunocompetent mice [33], suggesting that NK cells may be redundant in the presence of intact adaptive immunity. Surprisingly, IFN-γ knockout mice, which are impaired in their ability to clear mycobacteria, cleared them as effectively as wild-type mice when NK cells were depleted, suggesting that NK cells can inhibit protective immunity [34].

Human NK cells use the NKp46, the natural cytotoxicity receptors (NCRs) and NKG2D receptors to lyse *M. tuberculosis*-infected monocytes and alveolar macrophages [35], through damage of infected cells and secretion of cytokines, such as IFN-γ [36]. Inhibitory receptors of NK cells include killer immunoglobulin-like receptors (KIRs) and the NKG2A:CD94 dimer and NK cell activation can also be triggered by loss of inhibitory ligands from the cell surface. In addition, NK cells can also be activated by cytokines, including type I interferons, IL-12 and IL-18. NK cells are a potent and early source of cytokines, particularly IFN- γ, but they can also produce Th2-associated cytokines, such as IL-5 and IL-13, and the regulatory cytokine IL-10 [37]. NK cell NKp46 expression and cytotoxicity are reduced in freshly isolated peripheral blood mononuclear cells (PBMCs) from tuberculosis patients, which may be attributable to

suppression by monocytes and IL-10. Recent studies have found that NK cells produce IL-22 [38], which was induced by IL-15 and DAP-10, an adaptor protein that is known to be involved in NK cell activation, in response to *M. tuberculosis.* Rohan Dhiman *et al*. also found that IL-22 can restrict growth of *M. tuberculosis* in macrophages by enhancing phagolysosomal fusion [39]. Nonetheless to fully understand the importance of NK cells in *M. tb* infection it may be necessary to differentiate their contributions at different stages of disease.

Certain T subsets, such as NKT cells and $\gamma\delta$ T cells, have features of innate immune cells including a partially activated phenotype, a rapid response following detection of infected cells, and the modulation of other cell types. Together with NK cells, these cell subsets are functionally defined as innate lymphocytes.CD1d-restricted invariant NKT (iNKT) cells are a conserved subset of T cells that express an invariant T cell receptor (TCR) α chain (Vα24-Jα18 in humans, and Vα14-Jα18 in mice) paired with TCR β chains encoded by one or a few Vβ gene segments (Vβ11 in humans, and predominantly Vβ2, 7 and 8 in mice). These cells show different phenotypes and functions [40].Many iNKT cells are CD4+, and they have been mainly associated with the induction of Th2 cytokines such as IL-4, IL-5, IL-13. This subset is believed to play a prominent role in suppression of autoimmune or chronic inflammatory diseases, and in promoting allergic conditions such as asthma. Few iNKT cells are CD8+, and most of those express only the CD8α subunit, which means that they likely express only CD8$\alpha\alpha$ homodimers. An additional fraction of iNKT cells are negative for both CD4 and CD8 (DN T cells). They have been found to produce predominantly IFN-γ and other Th1-associated cytokines. Studies of human iNKT cells have shown that they have the ability to kill *M. tuberculosis* organisms within infected macrophages, possibly through their production of the peptide granulysin [41]. Jin S. Im *et al*. [42] found that the percentages of iNKT cells among total circulating T cells in TB patients were not significantly different compared to those in healthy controls. However, TB patients showed a selective reduction of the proinflammatory CD4−CD8− (DN) iNKT cells with a proportionate increase in the CD4+ iNKT cells. The mouse model of tuberculosis has been used by Sada-Ovalle et al to find that iNKT cells have a direct bactericidal effect on *M. tuberculosis*, and protect mice against aerosol *M.TB* infection [43]. Their activation requires CD1d expression by infected macrophages as well as IL-12 and IL-18. In addition, pharmacological activation of iNKT cells with the synthetic ligand aGalCer often enhances host resistance to infection. iNKT cell use several mechanisms to modify host immunity. These include induction of DC maturation, secondary activation of effector cells (NK cells) or recruitment of inflammatory cells to the site of infection [44, 45]. Thus, by being an early producer of IFN-γ and suppressing intracellular bacterial growth, iNKT cells function as an important part of the early immune response against *M. tb* that affect both the innate and the adaptive arms of the immune response.

Antigen-specific γ/δ T cells represent an early innate defense that may play a role in antimycobacterial immunity. Studies done in humans and animal models have demonstrated complex patterns of γ/δ T cell immune responses during early mycobacterial infections and chronic TB. Like α/β T lymphocytes, γ/δ T cells carry antigen TCR that vary in the physical properties of their ligand-binding sites. γ/δ T cells are frequently activated by a variety of pathogens including *M. tb* [46]. Mice lacking γ/δ T cells succumb more rapidly than control

mice following intravenous challenge with virulent *M. tb*; however, such a difference has not been observed following infection by the aerosol route. γ/δ T cells constitute a whole system of functionally specialized subsets that have been implicated in the innate responses against tumors and pathogens, the regulation of immune responses, cell recruitment and activation, and tissue repair [47]. Human alveolar macrophages and monocytes can serve as antigen presentation cells (APCs) for γ/δ T cells. Furthermore, the predominance of Vγ9Vδ2 T cells in TB disease has been confirmed [48]. When MTB-activated CD4+ and γ/δ T cells from healthy tuberculin-positive donors were analyzed for cytokine production in response to MTB-infected monocytes, both groups secreted large amounts of IFN-γ [49]. Previous studies have also demonstrated an increased proliferative activity of Vγ9Vδ2 T cells from patients with TB [50], but reduced production of IFN-γ, compared with that of healthy tuberculin-positive donors [51]. Additionally, Dieli *et al.* reported that decrease of Vγ9Vδ2 T cell effector functions involves not only IFN-γ production but also expression of granulysin [52]. Fig. 3 shows interaction of cells and cytokines involved in tuberculosis.

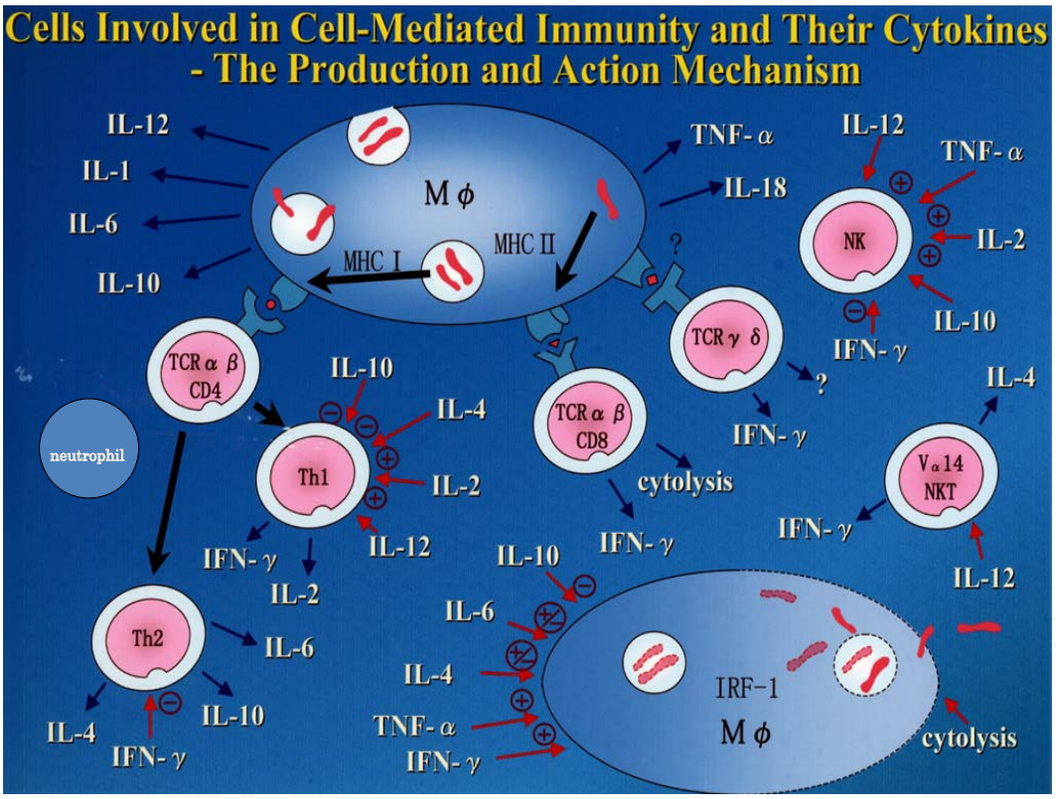

Figure 3. Cytokine and cellular network in tuberculosis +. Production of cytokine, -. No production of cytokine.

7. Conclusion

Tuberculosis is an international public health problem. It is becoming evident that *M. tb* infection is a dynamic state with a wide spectrum of pathology. An improved understanding

of the immunopathogenesis of TB can facilitate the design of effective vaccines, new drug candidates and evaluation of their efficacy [53]. Understanding latent tuberculosis can also be the key to improve diagnostic and novel treatment strategies [54].

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