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Review

Latent Tuberculosis: Interaction of *Mycobacterium tuberculosis* with Macrophages

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Abstract. Latent TB infection (LTBI) is a state of persistent immune response to *Mycobacterium tuberculosis* antigen stimulation but does not yet show clinically active TB. Macrophages can eliminate Mycobacterium tuberculosis through various mechanisms. The aim of this research is to determine the interaction of macrophages against *Mycobacterium tuberculosis*. Of the 116 articles screened, there were 42 articles that were in accordance with this literature study. Results from the studies reviewed It is possible that some individuals diagnosed with LTBI have recovered from the bacteria, while others have a very small chance of being reinfected. Granulomas are a pathological sign of Mtb infection. The location of bacteria in the granuloma may influence the immune response necessary to control the infection. Mtb produces lipid and protein effectors that control inflammation and macrophage activity. By preventing Mtb-macrophage interactions and entry into human cells, tuberculosis can be avoided. In addition, many mycobacterial factors play important roles in immune evasion or aid reactivation. The class of proteins encoded by the rpf gene are known as resuscitation promoting factors, which appear to play an important role in reactivation. The Rpf gene is thought to be important in driving mycobacteria out of a dormant (and possibly latent) state.

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1. Introduction

Humans have been infected with TB for many years. The main way that *Mycobacterium tuberculosis* (Mtb) bacilli spread is through the aerosols that individuals with active TB disease discharge into the air. Despite being mainly thought of as a lung illness, bacilli that can infect practically any organ in the body can cause tuberculosis. Despite the fact that there are 10 million new cases of tuberculosis and 1.3 million deaths from the disease each year, most of these instances are prevented by the Mtb infection. Latent tuberculosis (LTBI) is an infection that is not clinically evident. A tiny portion of LTBI patients will experience active tuberculosis years or decades after the first infection. As things stand, Mtb infections can cause a variety of infections, from subclinical infections to subclinical infections that manifest as mild, moderate, or severe acute disease [1-2].

Despite being debatable, it's likely that some people who were diagnosed with LTBI have recovered from the bacteria, while others have a very slim possibility of getting it back. Clinically categorizing Mtb infections in people is challenging. The diagnostic techniques employed to determine the presence of Mtb infection or illness are partially to blame for this. convenience based on sputum or other patient samples, host T cells responding to mycobacterial antigens, chest x-ray or CT scan, and/or culture or microscopy of these samples. Kindly. As a result, there are numerous and varied effects of Mtb infection that can be brought on by a multitude of circumstances, including exposure level, bacterial strain, and host immunological response. Consequently, infection can affect both the subject and the infected person; the illness can spread to one lung region and then clear up in another [3-4].

We still don't fully understand the combination of immune responses required to stop infection or the disease's progression, despite decades of research into the immunological responses that govern protection against tuberculosis. A multitude of cell types and functions are involved in the intricate immune response to a Mtb infection. Without much luck, researchers have searched for the "magic bullet" that will lead to a successful vaccination. Research on tuberculosis frequently concentrates on the function of a single cell type, cytokine, or pathway in the regulation or aggravation of infection.

Rather, we propose that distinct immune response components interact and impact one another across multiple distinct anatomical compartments to ultimately result in either infection clearance, containment, or progressive illness. Having said that, just as there are probably various "combinations" of elements that lead to the advancement of disease, there are probably a number other "combinations" of factors that can provide a favorable outcome. To find protective mechanisms, an integrated approach to the immunology of Mtb infection and illness is required. This is difficult since it calls for the integration of many data kinds in individuals as well as various model systems.

Since the principal site of infection between the bacillus and the host is in the tissues (granulomas, lymph nodes, lung, and airways), extrapolating from human samples—such as blood or occasionally bronchoalveolar lavage (BAL) fluid—can be challenging. However, this presents a challenge for current tuberculosis research: creating strategies to investigate what infection control entails without concentrating on a single cell type or function, but rather identifying the set of reactions that can result in the successful removal of the bacillus either during the initial stages of infection or in individuals who have already contracted the disease [5-6].

The epithelium lining, secreted soluble chemicals, inflammatory responses, and macrophages combine to produce the host mucosal barrier. Macrophages possess the ability to identify incoming infections, trigger microbicidal processes, and synchronize the ensuing immunological reactions. Every region of the body has macrophages, and in the lungs, two major populations have been found: interstitial macrophages and alveolar macrophages (which include tissue-resident and monocyte-derived alveolar macrophages). The first category, which makes about 55% of lung immune cells on the inside of the lungs, inhibits intracellular infections like Mtb [7-8].

MTB is an obligatory intracellular pathogen that affects around 10 million people annually, 1.5 million of whom die from it. These statistics have gotten worse as a result of the recent coronavirus disease pandemic (COVID-19), which has reversed gains and regressed the fight against tuberculosis by several years. This airborne infection targets aveolar macrophages when it reaches the lungs through the respiratory tract.

For Mtb to properly establish the infection, this contact between the virus and the host macrophage is essential. 1) Mtb attachment by *pathogen associated molecular patterns* (PAMPs); 2) Mtb identification by host macrophage *pattern recognition receptors* (PRRs); and 3) macrophage stimulation and activation of intracellular cascades and signaling pathways are the three random ways that the Mtb infection process can recommence. The hostile intracellular macrophage milieu (production of ROS and RNS, low pH, depletion of food, etc.) makes Mtb's intracellular interaction with macrophages complex and difficult. Even though macrophages have an impenetrable barrier, Mtb can successfully spread infection by eluding host defenses through evolved evasion tactics. Low vaccination efficacy, multi- and extensively-drug resistance (MDR-XDR), prolonged therapy, and high TB incidence are all impacted by this escape potential when it comes to tuberculosis control [9-11].

Resolving the coevolution of Mtb and host macrophage will help with TB management and treatment. Mtb-macrophage crosstalk is a topic that has been extensively studied, yet it is still not fully understood. Is it because Mtb's genetic armory enables it to endure and adapt in the noxious macrophage environment, The interaction of macrophages against Mycobacterium TB in latent tuberculosis is covered in this literature review.

2. Experimental Section

The authors of this literature review searched PubMed, Science Direct, Google Scholar, and any other database that had scientific articles or study findings between August 2022 and November 2022. Inclusion in the systematic review was restricted to studies that fulfilled the aforementioned search criteria. Latent tuberculosis, inflammation, mycobacterium tuberculosis, macrophages, immunological response, and (4) or (5) inflammation were among the search phrases utilized in this instance.

The only exclusion criterion was duplicate publications; there were no limitations on the study or publication year. In an effort to understand more about latent TB, we examined recent research. After these keywords were searched through several databases, 116 articles were found. There are twenty duplicate articles out of the 116 that need to be deleted at this time. Certain publications, ranging from abstracts to full-text papers, may be subject to screening. 51 of the 93 items that were supposed to be used were excluded since they didn't fit the criteria. 42 articles were therefore qualified for inclusion and awaiting evaluation. Figure 1 illustrates the article selection process.

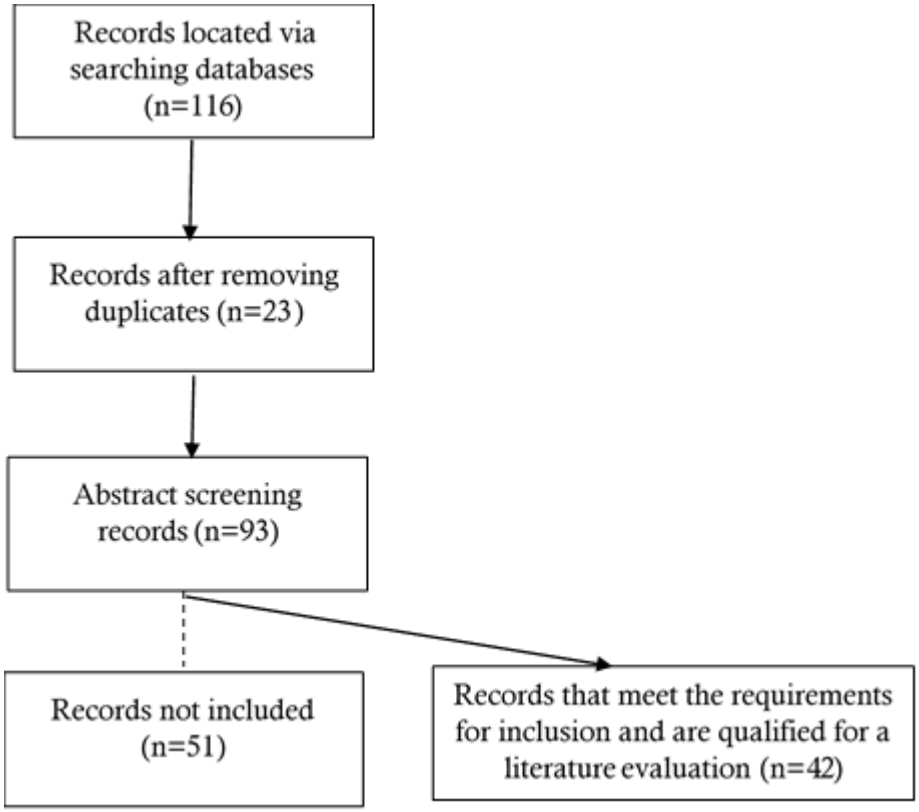

Figure 1. Illustrates the article selection process

3. Results and Discussion

3.1 The Granuloma

The pathologic hallmark of a Mtb infection is a granuloma. Aerosols from a person with active tuberculosis can spread MTB. The most common method that an infection happens is when a single bacillus is inhaled into the airways and comes into contact with alveolar macrophages. The bacilli can be swallowed by these macrophages, which may occasionally stop a productive infection. The host, however, produces an immunological response when the bacilli (probably in alveolar macrophages or maybe other phagocytes) transit to the lung parenchyma. Granuloma formation is triggered when monocytes, macrophages, neutrophils, and dendritic cells are drawn to the infection site, most likely as a result of chemokine and cytokine signals from the infected cells.

The bacilli are transported to the lymph nodes that drain the lungs, where they prime the adaptive immune response. Studies on mice show that this happens 7–14 days after infection, while in humans and non-human primates, peripheral adaptive T cell responses typically don't show up until 4-6 weeks after infection. After that, primed T cells (and probably B cells) move to the infection site, where they create an ordered granuloma. Lymphocytes encircle a layer of macrophages, and neutrophils frequently surround the necrotic center (Figure 1). Three to four weeks after infection, the completely developed granuloma in non-human primates can be seen. Mtb might be extracellular, mainly in the caseous necrotic center, or intracellular, mostly in macrophages, within granulomas. The position of the bacteria within granulomas can affect the immune responses required to control infection [12-13].

We showed that each granuloma is generated by a single bacillus using DNA barcoded strains of Mtb in macaques. Over the course of the following 4-6 weeks, the bacillus multiplies to reach 10^5 CFU/granuloma, which appears to be the "carrying capacity" of any single granuloma. At that

moment, the granuloma may limit replication or the Mtb may spread, or break free, to form additional granulomas in the lung. Most of the time, bacterial killing is not effective until 10 weeks after infection; this is probably because granulomas need longer to activate their adaptive immune response [14-15].

Granulomas can develop in other tissues as well, the thoracic lymph nodes being the most common site. When Mtb infection occurs, it frequently spreads the original infection to the thoracic lymph nodes. The migration of Mtb to the thoracic lymph nodes is probably essential for the start of adaptive immunity since thoracic lymph nodes are significant lymphoid structures. On the other hand, lymph nodes may be a major location for bacterial persistence and a possible trigger for reactivation. Imaging studies of humans with Mtb infection frequently reveal involvement of the thoracic lymph nodes; in children in particular, an infected lymph node can be highly big and result in lung lobe collapse.

The observations indicate that lymph nodes may be a source of bacterial dissemination, as we previously demonstrated that macaque thoracic lymph nodes are relatively inefficient at killing Mtb [16-17]. Although granuloma structure and function are essential for containing the infection, many of the mechanisms underlying this and the factors that cause failure are yet unknown. It takes comprehensive research on granulomas and other tuberculosis-related disorders to fully understand the intricate interactions between immunological factors that cause granulomas.

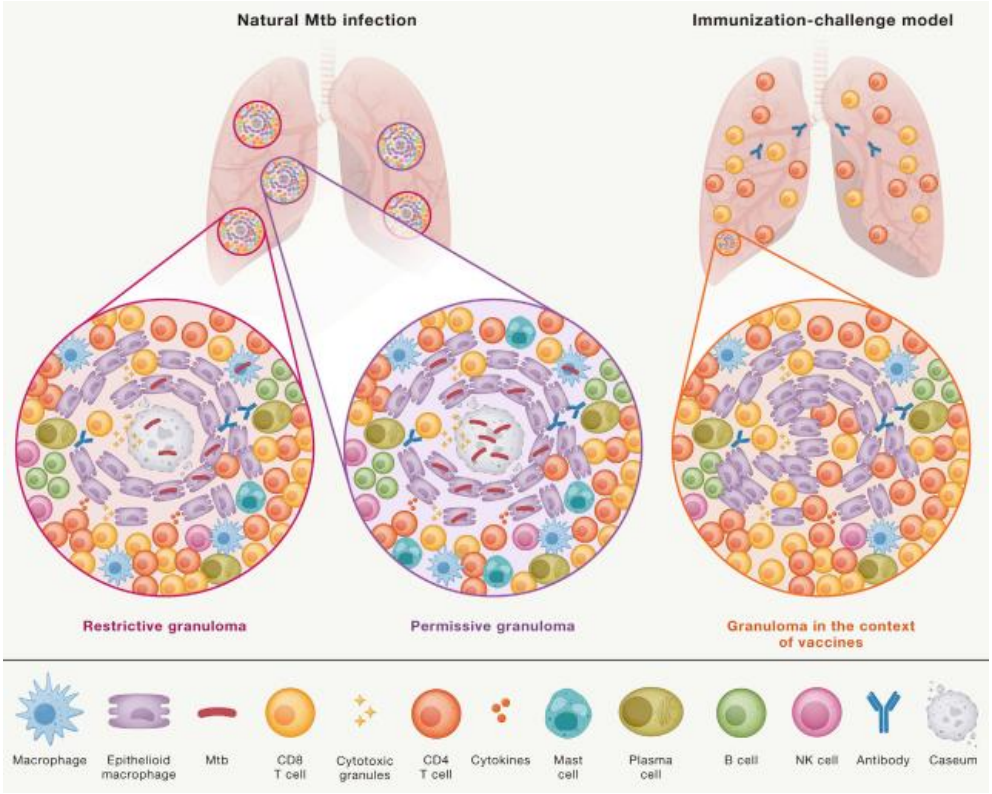

Figure 1. The diverse *M. tuberculosis*-host relationship in granulomas controls infection and illness consequences [17]

3.2 Macrophage

Despite being identified over 150 years ago, little is known about the biology of this extremely sophisticated phagocyte that is crucial for tissue homeostasis and defense against microorganisms. The idea of the mononuclear phagocyte system and the M/M2 paradigm of functional polarization have been revised, however, as we now know that there are distinct subsets of tissue-resident macrophages that differ in their ontogeny (bone marrow versus embryonic in origin), homeostasis maintenance, and functions. This knowledge is made possible by new technologies. Significantly, the tissue-specific niche that macrophage subsets occupy and their cellular source have functional implications. It is clear that an organ-specific niche can influence how tissue-resident macrophages form and persist, giving them unique characteristics and roles, such as metabolic processes. Clarifying the regulatory mechanisms underlying these activities is expected to yield valuable insights that could inform the development of therapeutic interventions targeting macrophages [18-19].

Since macrophages are the main host cell for Mtb, a lot of research has been done on the relationship between Mtb and host. The variety of outcomes produced by in vitro research, which employ cell lines and primary macrophages originating from various tissue compartments, is not surprising given our present understanding of tissue-resident macrophage function. According to Figure 2, lung-resident macrophages are composed of two different subsets that are relevant to Mtb, a pulmonary pathogen: *alveolar macrophages* (AM) and *interstitium macrophages* (IM), which are found in the lungs' interstitium and alveolus, respectively. Since AM in mice are self-replenishing and have an embryonic origin, they are not dependent on the bone marrow (Figure 2). However, monocytes can contribute to the replenishment of this population under specific experimental settings, such as irradiation and infections that cause AM depletion. The idea that there are subsets of AM is supported by newly available data. Comparably, IM are diverse, originating from both embryonic and monocytic sources, and include fractions that differ functionally from AM and from one another [20-22].

Huang et al. (2020) reported that interaction of Mtb with AM and IM in mice results in remarkably divergent infection outcomes [23]. This was achieved by using Mtb fluorescent reporter strains, which enable the assessment of mycobacterial fitness via determination of the replication status of intracellular bacilli and of the levels of stress they are subjected to, in conjunction with in vivo modeling and transcriptome analysis. When it comes to intracellular Mtb, AM are less stressful than IM and are more conducive to bacterial reproduction.

According to this finding, ablation of blood monocytes and IM results in the opposite effect from AM depletion, which reduces the lung bacterial burden. According to transcriptional data, the comparatively restrictive IM, which carry a reduced bacterial load, indicate a preference for the glycolytic pathway, whereas the permissive AM, which host a relatively higher number of Mtb, exhibit a preference for fatty acid oxidation. This observation on metabolism/Mtb control is consistent with the known lipid diet preference of intracellular bacilli and with experiments where certain metabolic pathways in macrophages and mice were inhibited.

The findings of a dual RNA sequencing (RNA-seq) investigation, which used sorted AM and IM from infected mice to enable simultaneous analysis of the intracellular bacterial and host cell transcriptomes, support the relevance of these observations. The latter study adds a variety of unique transcriptome characteristics to the previously identified divergent metabolisms exhibited by AM and IM. These signatures include varying degrees of stress signals imposed by reactive nitrogen intermediates and limitations on iron availability.

A flexible method that should enable in-depth examination of the host and bacillary in vivo responses to Mtb infection is the dual RNAseq platform. In fact, a recent study investigated in vivohost-cell-bacterial interaction at the single-cell level using the dual RNA-seq platform, fitness reporter Mtb strains, and the detection of specific cell surface marker expression. The study found that infected AM and IM in the lungs of mice three weeks after an intranasal infection with a relatively high inoculum are composed of heterogeneous subpopulations (four for each AM and IM), with both

AM and IM containing mycobacterial growth-restrictive and -permissive subsets; this functional diversity is further supported by their transcriptome profiles.

The fact that diverse subsets of pulmonary macrophages house bacilli with varying fitness profiles implies that interactions between Mtb and different subpopulations may affect infection and disease outcome differently, even though the specifics of these subsets are still unknown. BAL fluid from healthy, uninfected humans contains the alveolar macrophage subgroups found in this mice study, indicating their potential relevance to human tuberculosis. Notably, transposase-accessible chromatin sequencing (ATAC-seq) studies indicate that the response of each lung macrophage subgroup to Mtb infection may be influenced by preexisting epigenetic imprinting. Significantly, a recent study using single-cell RNA-seq (scRNA-seq) analysis has shown that the lungs of macaques infected with Mtb include a variety of macrophage subsets.

The findings of these incredibly insightful studies highlight the complexity of the lung macrophage landscape, which is characterized by distinct subsets that exhibit differential interaction with Mtb. This suggests that: (1) the heterogeneity in tuberculosis disease outcome and the variability of granulomas observed in the lungs of a single infected individual may be partially explained by the resulting differential interactions between subsets of these phagocytes with Mtb; and (2) targeting specific macrophage subsets and their local niche may allow for the manipulation of infection and disease outcomes. These findings should pave the way for future research aimed at elucidate the relative roles of the various lung-resident macrophage subpopulations in controlling the host response to the pathogen [24-27].

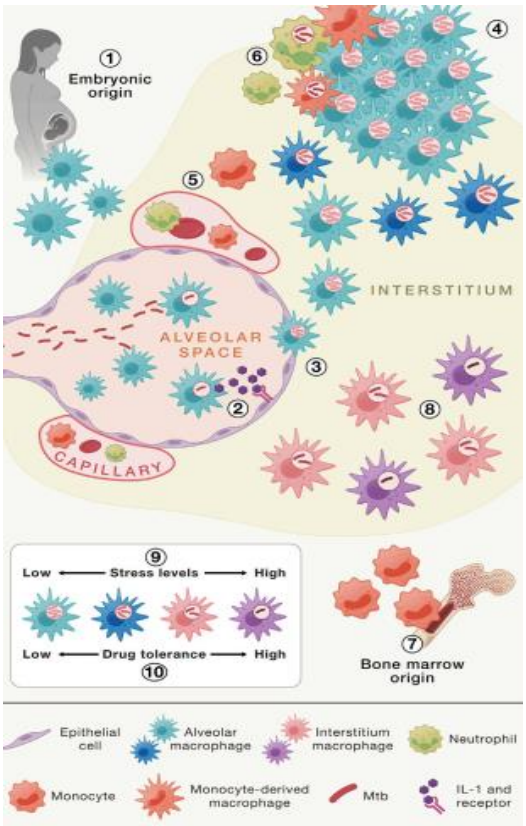

Figure 2. The way *that M. tuberculosis* interacts with lung macrophages influences how the host reacts to the tubercle bacillus [27]

3.3 Mtb Effectors Interacting with Macrophages

Mtb produces lipid and protein effectors that control the inflammatory process and macrophage activity. These effectors' coding code is integrated into the Mtb genome (4000 genes). A typical plasma membrane, a layer of peptidoglycans covalently connected to polysaccharides (arabinogalactans) with their penta-arabinosyl ends esterified by mycolic acids, and other components make up the intricate architectural framework known as the mycobacterial cell envelope. The Mtb cell wall's external surroundings are exposed to lipoproteins, peptidoglycans, trehalose mono- and di-mycolates, phosphatidylinositol mannosides, lipomannan, and lipoarabinomannan. Adenylyl cyclase protein kinases (pknG), enzymes (Mce family proteins, for example), and regulatory genes (DosR, WhiB, PhoP) are examples of other factors that do not belong in the surface-exposed group (miscellaneous factors).

According to reports, the virulence factors discussed above are involved in host-cell identification and phagosome maturation arrest, which are crucial aspects of host-pathogen interactions. Recently, new details on the complicated mycobacterial lipids and secretion mechanisms of the cell membrane have been discovered by researchers. The SecA2 secretion system exports SapM and PknG, which impede the acidity and development of the phagosome-containing Mtb. The ESX/type VII, the *twin-arginine translocation* (TAT) pathway, and the sec secretory pathway are other export pathways. Mycolyl transferases carried by the TAT secretion system catalyze the production of TDM by adding mycolate residues to arabinogalactan. The ESX-5 secretion system releases proteins in the PE/PPE family, which are named for the N-terminal Pro-Glu and Pro-Pro-Glu motifs they share. These proteins may be involved in the pathogenicity of Mtb. Mtb mutants missing ESX-5 exhibited significant attenuation, poor cell-wall integrity, and reduced PPE protein secretion. Nevertheless, more investigation is required to identify the fundamental virulence factors of the Mtb cell wall [28-30].

3.4 Early Mtb-Macrophage Interaction

TB can be avoided by preventing Mtb-macrophage interaction and entry into human cells. Mtb is a virus that travels through the air from sick to healthy individuals. The latter breathe in Mtb-containing droplet nuclei, which enter the alveoli of their lungs. There have been reports of both direct and indirect (opsonization) Mtb identification by macrophages. Soluble factors (collectins, complement systems, etc.) that chemically alter Mtb and promote its internalization within the macrophage are used in indirect Mtb detection. It has also been shown that host cell molecules are recruited to the surface of Mtb cells. On the other hand, nonsoluble components known as PAMPs are used in direct Mtb detection to identify Mtb ligands [31-32].

Mtb PAMPs on the cell surface or in the intracellular macrophage milieu (phagolysosome and cytosol) are recognized by certain macrophage PRRs. On the Mtb surface, Mincle and Macro receptors engage in interactions with TDM, whereas PRRs such MR, DC-SIGN, and Dectin-2 identify Mtb glycolipids (ManLAM). Furthermore, MDP produced by Mtb peptidoglycans is detected by NOD2 in the cytosol. While the ESX-1 secretion system disrupts the phagosomal membrane to enable the cytosolic identification of Mtb DNA and consequent cGAS/STING induction, the TLR9 recognizes phagolysosomal Mtb DNA. The pathogen or the macrophage may benefit or suffer from other cascade processes that are triggered downstream, such as phagosome biogenesis, endosomal trafficking, autophagy, or the release of soluble factors. For example, TLR9-based identification of the pathogenic Mtb DNA enhanced human monocyte antimicrobial mechanisms derived from M1 macrophages via phenotypic changes, higher production of TNF-a, and activation of autophagy. Autophagy can also be induced following Mtb by PRRs-activated immunological signals, such as PI3K, IRGM, and mTOR inhibition [33-35].

3.5 Reactivation Disease

Clinically, it might be challenging to discern reactivation illness from re-infection. It happens when dormant bacteria from long-since-scarred granulomatous lesions become active and pathogenic again. The most common cause of reactivation disease is a weakening or suppression of the host immune response. HIV+ people, who have low CD4+ T cells and a 10% annual risk of reactivation disease, are likely the most striking example of this. HIV and tuberculosis co-incidence is now widely known. According to studies conducted on mice, the immune response linked to the latent phase of infection may be different from that linked to the primary infection, with CD8+ T cells likely to play a larger role and CD4+ T cells a smaller one. Nevertheless, this does not entirely align with research conducted on humans and primates. Furthermore, a great deal of mycobacterial factors are important in immune evasion or in facilitating reactivation [36-38].

Resuscitation promoting factors (rpf), which are encoded by rpf genes, are a class of proteins that seem to play a significant role in re-activation. Research has demonstrated that when rpf genes are deleted, the bacteria are unable to reactivate, even when the host's immune system is suppressed. *M. tuberculosis* can withstand several mutations throughout the underlying genes and possesses five Rpf factors (Rpf A to E). Rpf genes appear to be essential for general viability, but they are thought to be critical for causing mycobacteria to emerge from a dormant (and hence potentially latent) state. It is thought that the Rpf proteins work by hydrolyzing peptidoglycan; they may even work in tandem with an additional, unidentified protein.

The fundamental theory is that when bacteria are under stress from the environment, they "shut down and close tight," thickening and decreasing the permeability of their cell wall due to strong cross-linking between peptidoglycan strands. Rpf genes are triggered with the removal of the stress factor, resulting in the production of Rpf proteins that cut the tight peptidoglycan strands and allow the bacteria to return to a growth phase. Finding creative ways to disrupt the persistence factor(s) would drive the bacteria out of their dormant stage and help prevent latent infection. Each of these might possibly be a target for medication [39-40].

The dormancy (DosR) regulon of the three-gene operon, which includes dosR (Rv3133c), has been found to be essential for M. tuberculosis to transition between respiring and non-respiring conditions without losing viability, and for the rapid resumption of growth once the organism leaves an anaerobic or NO-induced non-respiring state. In TNF-deficient mice, reactivation of a latent tuberculosis infection was seen, accompanied by necrosis and mouse mortality. In order to investigate the parameters linked to the reactivation of latent tuberculosis infection in immunocompromised individuals, a monkey model co-infected with mucosal simian immunodeficiency virus and latent tuberculosis was recently created. TB reactivation is more common in immunosuppressed animals with low peripheral CD4T cell counts. The study's findings imply that early T cell depletion has a significant impact on the course of HIV-M. tuberculosis co-infection and disease development [41-42].

4. Conclusion

Infections that are not clinically apparent are called latent tuberculosis (LTBI). Years or decades after the first infection, a small proportion of LTBI patients will develop active tuberculosis. Mtb infections can currently cause various types of infections, ranging from subclinical infections to subclinical infections that appear as mild, moderate, or severe acute disease. It is possible that some individuals diagnosed with LTBI have recovered from the virus, while others have a very small chance of being reinfected. This fact is still debated. Categorizing Mtb infections in humans is clinically difficult. Granulomas are a pathological sign of Mtb infection. The location of bacteria in the granuloma may influence the immune response necessary to control the infection.

Mtb produces lipid and protein effectors that control inflammation and macrophage activity. By preventing Mtb-macrophage interactions and entry into human cells, tuberculosis can be avoided. However, the immune response in the latent phase of infection is different from the immune response

in the primary phase of infection, with more CD8+ T cells and fewer CD4+ T cells. In addition, many mycobacterial factors play important roles in immune evasion or aid reactivation. The class of proteins encoded by the rpf gene are known as resuscitation promoting factors, which appear to play an important role in reactivation. In addition, the Rpf gene is thought to be important in driving mycobacteria out of a dormant (and possibly latent) state.

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