Review Article

The Role of Strain Variability in Granuloma Induction and Cough Mechanisms in Tuberculosis Infection

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Background: Tuberculosis (TB) caused by *Mycobacterium tuberculosis* (Mtb) remains a major global health concern, especially in low and middle-income countries. Granuloma formation is the hallmark of TB and is defined as organized immune structures designed to limit infection.

Aim: This narrative review aims to explore the strain-specific differences in granuloma formation, immune responses, and the mechanism of the cough reflex in TB, with a focus on how these factors contribute to disease progression, transmission, and potential therapeutic strategies

Methodology: A comprehensive literature search was conducted using PubMed, Google Scholar, Cochrane, and ClinicalTrials.gov databases. Studies were selected based on relevance to Mtb strain variation, granuloma morphology, immune response, and cough reflex.

Results: Granuloma structure and immunological behaviour differ across several Mtb lineages. Modern TB strains demonstrate increased viral load, induce necrotizing granulomas, and promote persistent cough through mechanical airway irritation and neuroinflammatory pathways. These strains are linked with higher bacterial loads, increased treatment failure, and greater potential for transmission. On the contrary, less virulent strains like H37Ra produce poorly organized granulomas and a weakened immune response. Granulomas near airways exacerbate cough through both mechanical and neuroinflammatory pathways. This kind of immune modulation affects granuloma gene expression, macrophage behavior, and cytokine profiles, influencing the severity of clinical symptoms and potential for transmission.

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Conclusion: Strain-specific differences in Mtb significantly impact granuloma dynamics and cough induction, both of which are crucial to the pathology and transmission of TB. Integrating such diagnostics, host-directed therapies, and targeted vaccines may improve TB control. Further human-based studies are needed to close gaps in understanding how genetic diversity among Mtb strains translates into clinical and epidemiological outcomes.

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Introduction

Tuberculosis (TB) is a chronic infectious disease that is caused by a non-motile, aerobic bacillus known as *Mycobacterium tuberculosis* (Mtb), along with other strains (*M. bovis, M. africanum, M. microti, M. caprae, M. pinnipedii, M. canetti,* and *M. mungi*) that together form the *M. tuberculosis* complex [1]. The 2024 World Health Organization (WHO) Global TB Report illustrates that the resurgence of TB poses a significant public health challenge [2]. The disease primarily affects third-world countries with poor socioeconomic conditions. Several factors influence its varying prevalence, such as poor hygiene, overpopulation, close squatter settlements, co-infections, multidrug resistance, inadequate health facilities, and more. According to the WHO TB report 2024, TB cases are heavily concentrated in some countries. India accounts for 26% of global cases, followed by Indonesia at 10%. China and the Philippines represent 6.8%, while Pakistan records 6.3% of the total cases worldwide [3][4][5].TB is primarily transmitted through airborne particles. Infectious Mtb bacilli are aerosolized when a person coughs, sneezes, or talks, allowing them to enter the respiratory system through the nasopharynx. TB may remain asymptomatic or present with nonspecific clinical symptoms like cough, dyspnea, hemoptysis, weight loss, night sweats, and fever [6][7].

Once infected, TB is a continuum spectrum of different states depending on the patient's immune system. Around 20-25% of people develop active infection, 5-10% get it within 5 years, depending on various risk factors, and the remaining 10% may develop TB later in life [8]. Risk factors for TB include co-infection with HIV, diabetes, malnutrition, organ transplants, chemotherapeutic agents, and other immunosuppressive states, along with obesity and weight irregularities in Asian patients [9][10][11][12][13].

Upon entry of aerosolized particles into the respiratory tract, Mtb induces immune modulation of host defences, which leads to the proliferation of adaptive cell lineages, with subsequent differentiation of

macrophages into granulomatous structures [14]. Granuloma formation is the key pathophysiological feature of TB, which serves as a hallmark of the host immune response to Mtb. Granulomas can be classified as foreign body granulomas or immune granulomas. The latter involves the transformation of macrophages into epithelioid cells, forming a rim of adaptive immune cells mixed with inflammatory material, creating a cluster of epithelioid cells and giant cells [15].

Granulomas were traditionally regarded as static structures; however, recent studies have demonstrated that they are secretory and vital in mobilizing mutated, drug-resistant bacteria. Additionally, they facilitate the ingress and egress of substances, thereby encouraging their dissemination throughout the treatment process and contributing to variable disease progression [16]. They may be regarded as a nidus for dissemination or a barrier to harbour infectiously active bacteria until it is breached. Lipid metabolism within the mycobacterium affects infectivity and granuloma induction [17][18].

M. tb is a complex bacterium characterized by genetic deletions that affect its transmission. It is categorized into two lineages: a modern lineage that has evolved in humans, including East Asian, East African, Indian, and Euro-American strains, and an ancient clade that comprises Indo-Oceanic, West African, and Ethiopian lineages. These lineages show differences in lipid metabolism, leading to varying entry rates into macrophages. For example, East Asian and Euro-American strains have unique cell wall lipids that improve uptake, while the Ethiopian lineage shows reduced uptake efficiency and transmissibility [19][20][21][22][23].

This study aims to elucidate comprehensively the distinctions among mycobacterial strains and their impact on granuloma formation as a mechanism to maintain, enhance latency, and analyze the severity

Methods

Two authors independently performed the literature search. The last update to the search was conducted on 15 May 2025 and accessed PubMed, Google Scholar, Cochrane, and ClinicalTrials.gov. Its detailed breakdown is shown in the PRISMA flowchart given below (Figure 1).

A comprehensive literature search was conducted across various databases for relevant studies using the following keywords in combination with the Boolean operator AND/OR: "Mycobacterium tuberculosis", "strain-specific", "lineage", "granuloma", "granulomatous inflammation", "immune response", "cough" and "cough reflex". No additional filters or time constraints were used for the search. Two authors independently screened the resulting articles. If the title and abstract matched the topic, the full-text

article was accessed. A cross-reference of the bibliographies was also performed. Disagreements were debated and solved by a third author.

The following studies were included in the narrative review: (1) Studies demonstrating the granuloma formation or immune responses in TB; (2) Studies comparing granuloma formation among various M.tb strains; (3) Studies demonstrating the relationship between strain-specific virulence and cough; (4) Studies reported in English; and (5) Review articles, cross sectional studies and experimental studies.

The following studies were excluded: (1) Studies not meeting the above inclusion criteria; (2) Studies not reported in English; (3) Unpublished articles; (4) Non-peer-reviewed articles; and (5) Comments, editorials, and case reports.

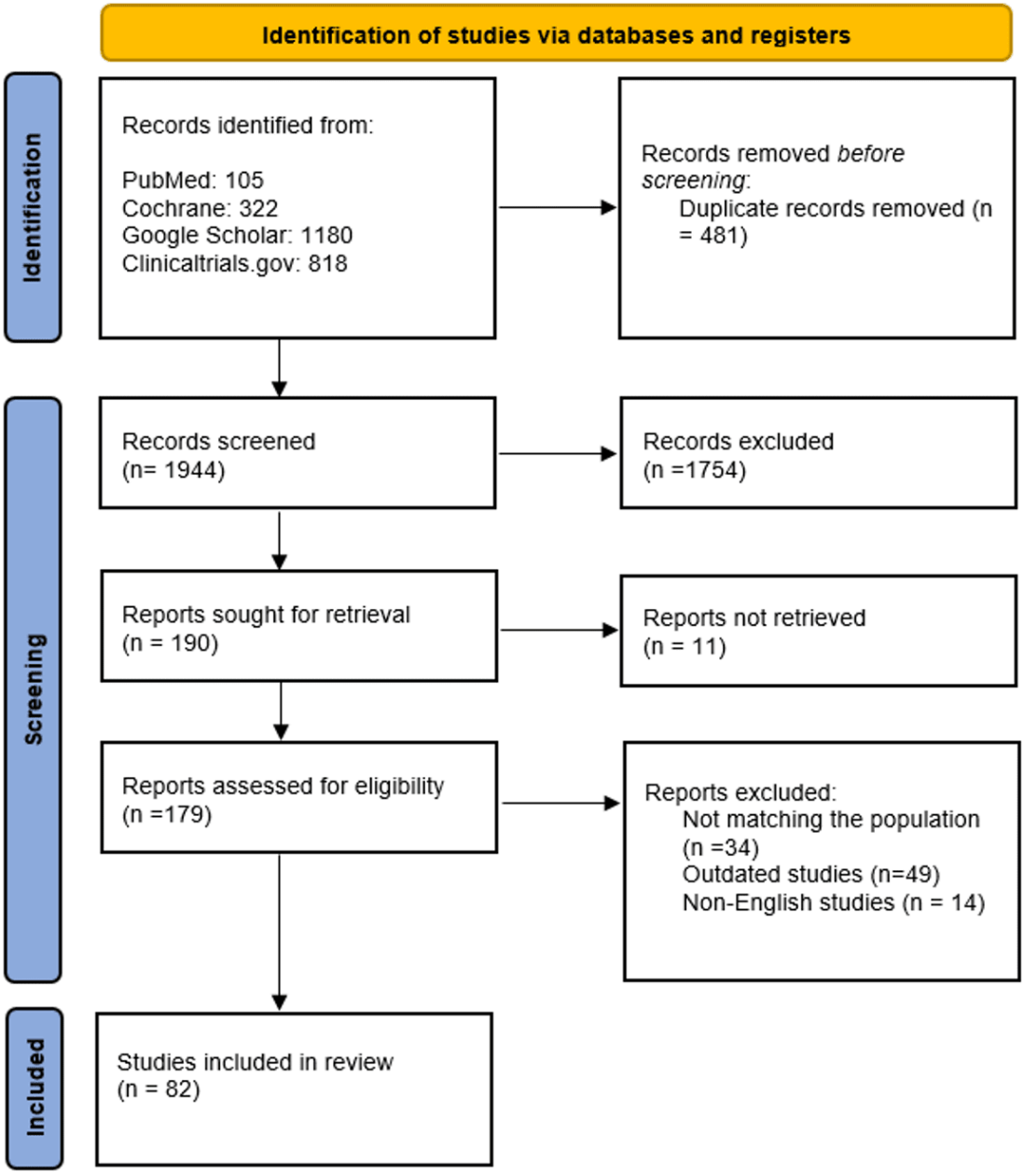

Figure 1. Flowchart illustrating the selection of studies

Granuloma Formation in Tuberculosis

Granuloma formation is the histopathological hallmark of Mtb infection and represents a highly organized host immune response aimed at containing the bacilli while minimizing tissue damage [23]. It

is a dynamic structure composed primarily of infected macrophages, foamy macrophages, epithelioid cells, multinucleated giant cells, dendritic cells, and lymphocytes, all surrounded by a fibrotic cuff [24].

The initial immune response begins when alveolar macrophages and recruited monocytes recognize Mtb through pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), C-type lectin receptors (CLRs), and NOD-like receptors (NLRs) [25]. Activation of TLR2 and TLR4, in particular, initiates intracellular signaling cascades via the MyD88-dependent pathway, resulting in the activation of NF-κB and subsequent transcription of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β) [26]. These early cytokines orchestrate the recruitment of additional immune cells to the site of infection through chemokine gradients involving CCL2, CXCL10, and other mediators [27].

The formation of the granuloma is further regulated by cytokines such as interferon-gamma (IFN-γ), which is secreted predominantly by Th1 CD4+ T cells in response to IL-12 produced by infected macrophages and dendritic cells [28]. IFN-γ plays a pivotal role in the classical (M1) activation of macrophages, enhancing their antimicrobial functions, including phagolysosomal fusion, nitric oxide production, and autophagy [29]. The importance of IFN-γ in granuloma integrity is underscored by the fact that its deficiency, whether due to genetic mutation or immunosuppression, results in uncontrolled Mtb replication and widespread dissemination [30].

Within the granuloma, macrophages differentiate into epithelioid cells characterized by enhanced phagocytic and antigen-presenting capacities. Some macrophages fuse to form Langhans-type multinucleated giant cells, while others develop into foamy macrophages laden with lipid droplets, which may serve as nutrient sources for dormant bacilli [31]. These cellular transformations are governed by signals such as granulocyte-macrophage colony-stimulating factor (GM-CSF), TNF-α, and transforming growth factor-beta (TGF-β) [32].

The granuloma's structure is further shaped by the induction of a fibrotic capsule, primarily mediated by fibroblasts and myofibroblasts activated by TGF-β and platelet-derived growth factor (PDGF) [33]. This fibrotic encapsulation serves as a double-edged sword: while it restricts the spread of bacteria, it also contributes to hypoxia and necrosis within the granuloma core, potentially favouring Mtb persistence in a non-replicative state [34].

The role of TNF-α is particularly complex. It is essential for maintaining granuloma integrity by promoting macrophage activation, apoptosis of infected cells, and chemokine-mediated recruitment of

immune cells [35]. However, excessive TNF-α can lead to tissue damage and necrosis, which may result in granuloma breakdown and dissemination of bacilli [36]. The importance of TNF-α is exemplified by clinical observations in patients receiving anti-TNF therapy for autoimmune diseases, who have a significantly increased risk of reactivating latent tuberculosis [37].

Another key cytokine is IL-10, which plays an immunoregulatory role by dampening proinflammatory responses. While IL-10 limits tissue damage, its overexpression can impair macrophage activation and antigen presentation, potentially allowing Mtb to evade immune clearance [38].

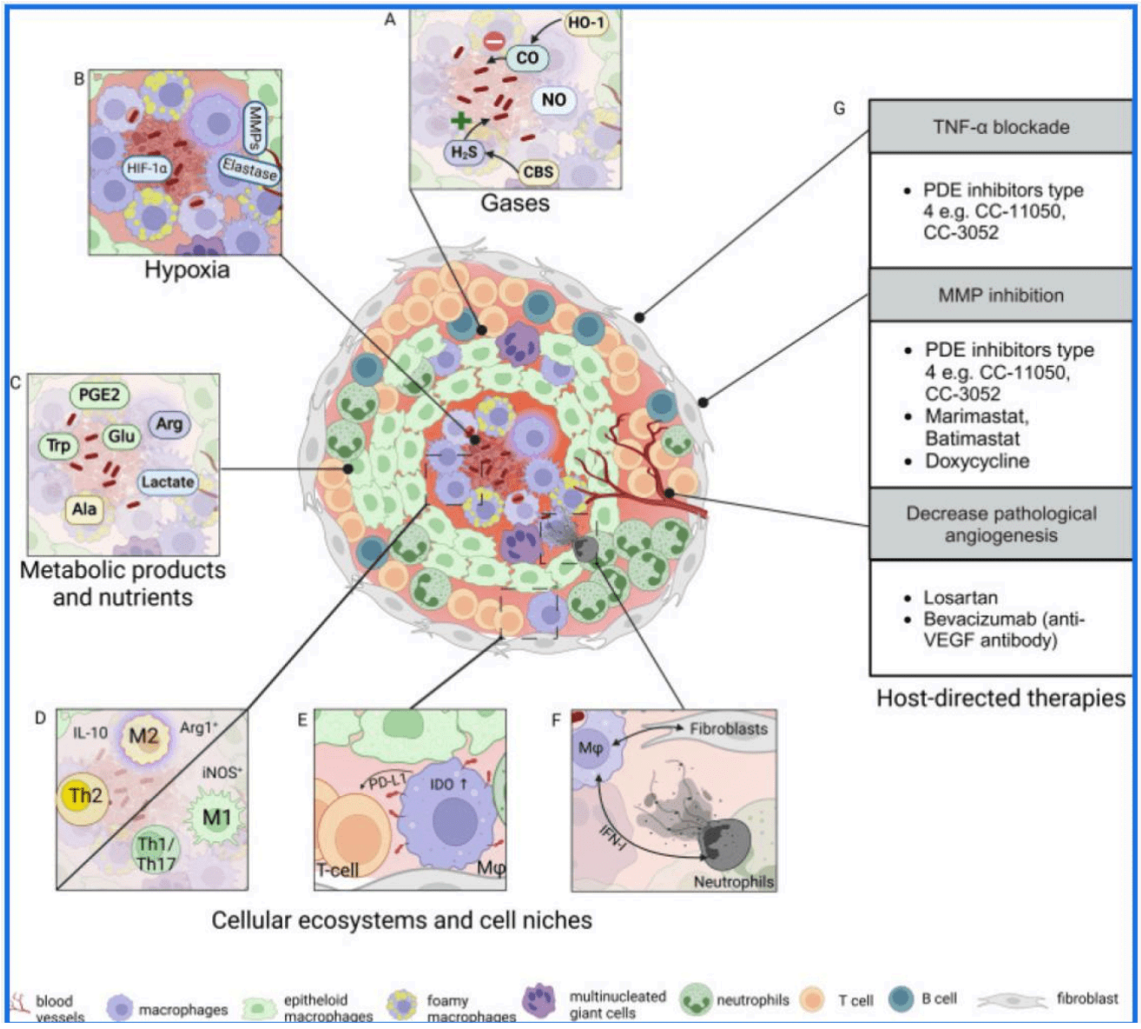

Figure 2. Tuberculous granuloma microenvironment and host-directed therapies[39]

Additionally, the hypoxic microenvironment within the granuloma induces the expression of hypoxia-inducible factor-1 alpha (HIF-1α), which influences macrophage metabolism and function [40]. HIF-1α

activation enhances glycolysis and the production of proinflammatory cytokines but also contributes to the formation of caseous necrosis due to the metabolic stress it imposes on cells [41].

Autophagy is another essential mechanism within granulomas. Induced by IFN-γ and nutrient deprivation, autophagy enhances the clearance of intracellular Mtb through lysosomal degradation pathways. Mtb, however, has evolved to inhibit autophagosome maturation via the ESX-1 secretion system and through the production of proteins such as Eis and PtpA, which interfere with host cell signalling and endosomal trafficking [42].

The central region of the mature granuloma often undergoes caseous necrosis, a hallmark of tuberculosis pathology. This caseation results from the cumulative effects of immune-mediated cell death, hypoxia, and lipid peroxidation. Mtb can survive in this acellular necrotic core in a non-replicating or slowly replicating state, protected from immune attack and antibiotics [43]. This latent bacillary population serves as a reservoir for reactivation, especially in immunocompromised hosts [44].

While granulomas are traditionally viewed as host-protective structures, emerging evidence suggests they may also be exploited by Mtb to facilitate persistence and dissemination. For instance, Mtb can manipulate host lipid metabolism to induce the formation of foamy macrophages, which serve as lipid-rich niches that support bacillary survival [45]. Additionally, the modulation of host cell death pathways—such as inhibiting apoptosis and promoting necrosis—enables Mtb to escape from dying cells and infect neighbouring cells [46].

Moreover, granulomas are not static entities; they evolve and exhibit spatial and temporal heterogeneity even within the same host. Studies using advanced imaging techniques and animal models have revealed the coexistence of sterilizing and non-sterilizing granulomas, reflecting the complexity of host-pathogen interactions and the challenges in achieving complete eradication of Mtb [47].

The intricate cellular and molecular architecture of the granuloma represents both a defensive barrier and a permissive niche, highlighting the dual nature of this structure in tuberculosis pathogenesis. Understanding the regulatory networks that govern granuloma formation, maintenance, and resolution is crucial for developing novel therapeutic and vaccine strategies aimed at modulating host immunity and eradicating latent infection [48].

Molecular Mechanisms Governing Granuloma Formation

Studies have reported that humoral immunity governs the displacement of cell lineages involved in granuloma formation. The primary function of the granuloma is to act as a barrier that contains the pathogen and prevents ongoing inflammation in the surrounding tissue. Granulomas contain various cells that interact with one another through cytokines and various proliferative molecules that aggregate. These include immature mononuclear phagocytes surrounded by lymphocytic effector cells, including CD4+ and CD8+ T cells. CD4+ Helper T cells are further divided into Th1 and Th2 cells, modulating this process [23][24].

This cascade of intermingling immune cell lineages establishes a mature barrier system, which can be divided into initiation, accumulation, effector, and resolution stages. In correlation with tuberculosis, it has been noted that a study conducted by researchers shows that two types of macrophages are impacted during infection after inhalation of the immunogen: M1 macrophage, a pro-inflammatory immune cell that promotes granuloma formation and controls infection, and M2, which is immunomodulatory and aids bacterial persistence. In the initial stages, both cell types show a mixed activation; however, with time, M2 predominates [24][25].

This is crucial because IFN-γ and LPS released by Th1 cells, a subtype of CD4+ T cells, stimulate M1 proliferation and enhance the secretion of IL-6, IL-12, and TNF-alpha, which are potent chemokines essential for granuloma formation. Additionally, IL-4 increases M2 markers [25]. As mentioned earlier, in the initiator phase, where aerosolized particles reach the respiratory parenchyma and lining, the *M. tb* bacilli induce the secretion of pro-inflammatory cytokines like IL-12, IL-1β, and TNF. IL-12 is critical in initiating the Th1 T-cell response. This begins a synergistic cascade where Th1 activates macrophages, prompting them to secrete TNF-α, eliminating and modulating infected macrophage apoptosis [26][27][28][29][30][31].

M. tb-infected macrophages downregulate the proinflammatory cytokines and secrete anti-inflammatory chemokines such as IL-10 and TGF-β. This causes a balance between bacterial eradication and host survival. Combining these two immunomodulatory reactions results in the amalgamation phase, where infected macrophages recruit uninfected macrophages, primed T and B cells, and neutrophils, forming a granuloma [31][32].

Furthermore, researchers have examined two distinct types of macrophage classes, leading to the identification of two subtypes: one that proliferates in response to cytokines, referred to as classically

activated macrophages (CAMs), which increase due to the influence of Th1 T cell secretion of TNF-alpha and interferon-gamma. These cells also secrete pro-inflammatory cytokines such as TNF and IL-12. The other subtype is alternatively activated macrophages (AAMs), which secrete anti-inflammatory cytokines such as IL-10, TGF-beta, and IL-6 in response to Th2-mediated IL-4 and IL-13 [33][34][35][36][37][38].

Studies show that it is essential to acknowledge that *M.tb* exhibits multiple strains, which can be categorized into distinct clades. Clade 1 includes the modern strains Beijing, Haarlem, and H37Rv, while Clade 2 consists of EAI and WA2. The Beijing strain has demonstrated a weak cytokine response but a strong replicative potential. Haarlem strains have triggered a robust pro-inflammatory cytokine response and excessive growth potential in macrophages. In contrast, EAI has exhibited weak cytokine induction and limited growth potential replicability [25][39][40][41].

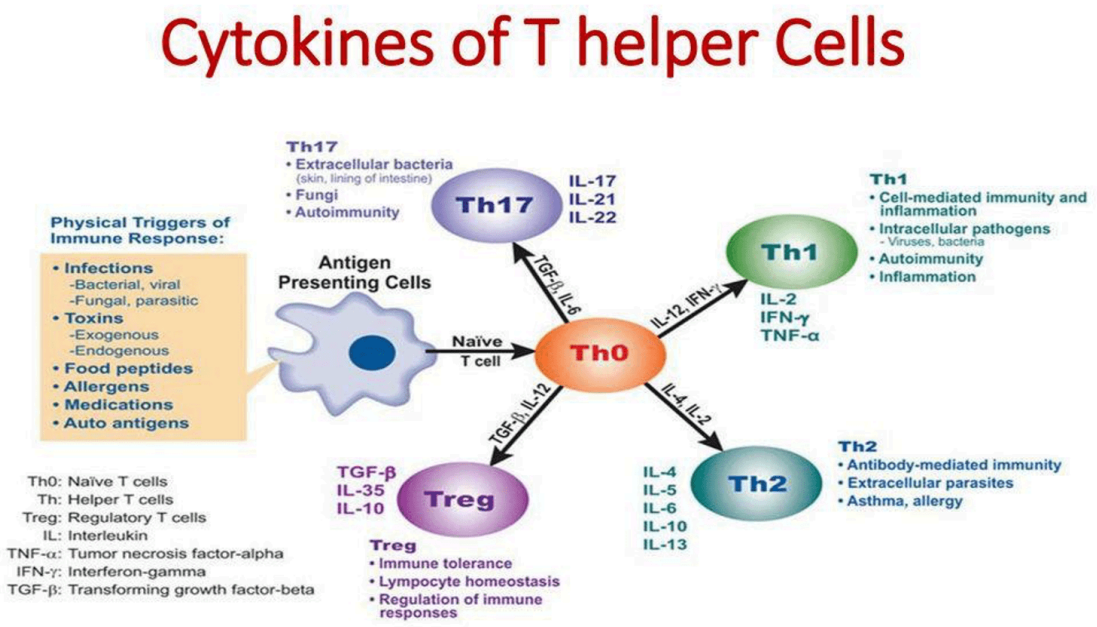

Figure 3. Molecular Mechanisms of Immune System Activation[40]

Strain Variability and Granuloma Characteristics

Recent studies have highlighted significant differences in the structure of granulomas among various *M. tb* lineages, highlighting the complex interplay between bacterial genetics and the immune response of the host [42][43]. Modern *M.tb*lineages such as lineages 2 and 3, have demonstrated distinct granulomatous responses compared to the ancient strain. Lineage 2 has been associated with increased

triglyceride lipid droplet accumulation, exhibiting a phenotype suggestive of dormancy, whereas Lineage 3 shows comparatively reduced lipid storage [42]. The variations observed show a considerably broad virulence strategy, with modern lineages being more aggressive with a faster growth rate. Robust CD4 and CD8 T cell activation coupled with elevated levels of immune mediators like CXCL9, granzyme B, and TNF are related to protective granuloma responses, which correlate negatively with bacterial proliferation among strains [42]. Additionally, virulent *M. tb* induces the formation of multinucleated giant cells within granulomas, which is a feature absent in infections caused by less virulent strains [44].

The high virulence strains, such as the Beijing lineage, demonstrate unique granuloma-modulating capabilities. These strains are often related to treatment failures and worldwide spread. A study conducted in Indonesia indicated that patients infected with the Beijing strain have higher post-treatment sputum culture positivity compared to those who were not infected with the Beijing strains [45]. The hypervirulence of Beijing strains has been attributed to the mutation of the *ppe38*gene which disrupts the ESX 5 substrate secretion and enhances pathogenicity [46]. In contrast, strains like H37Ra with a low virulence show reduced granuloma responses as a result of genetic alterations such as the PhoP regulator S219L substitution that affects the T cell activation and ESAT-6 secretion [47].

Strain variability highly affects granuloma outcomes like necrosis, fibrosis, and immune evasion. Many *M. tb* strains manipulate host immune response that in turn accelerate granuloma formation, which leads to variable tissue destruction [48]. Heightened inflammation and bacterial dissemination are associated with necrotic granulomas that are enriched with triglyceride-laden foamy macrophages [49]. Strain-dependent immune regulation is further reflected in the variability in granuloma gene expression profiles within the same host [50]. This can also be observed in latent TB infection granulomas that exhibit distinct cytokine production and bacterial survival patterns compared to active TB granulomas [31]. Non-tuberculous bacteria like *Chromobacterium violaceum* can elicit innate granuloma formation independent of adaptive immunity, highlighting the variability of granuloma-inducing mechanisms [51]. Figure 4: Understanding the development of tuberculous granulomas: Insights into host protection and pathogenesis, a review in humans and animals.

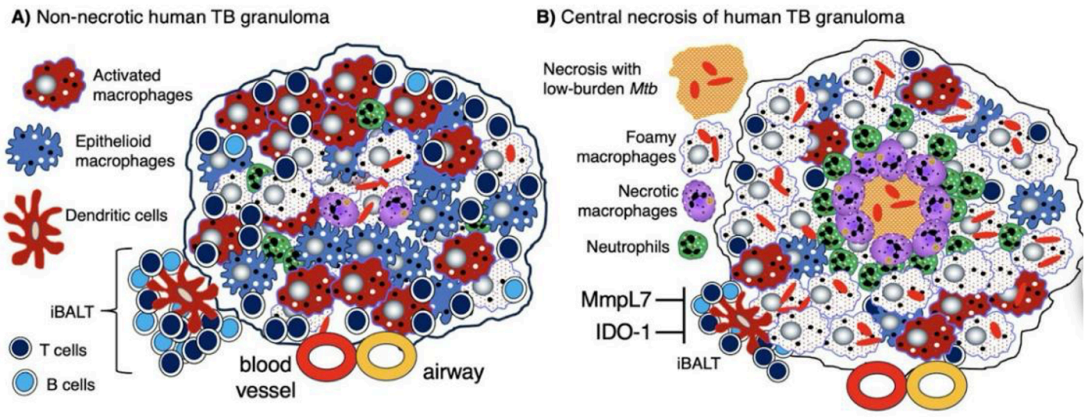

Figure 4. Understanding the development of tuberculous granulomas: Insights into host protection and pathogenesis, a review in humans and animals[52]

Link Between Granuloma Dynamics and Cough

Cough is an important protective reflex mechanism that facilitates mucociliary clearance, bronchoconstriction, phagocytosis, and effectively protects the respiratory tract from foreign bodies, irritants, and secretions, but in pathological conditions, it can become persistent and distressing [49][50]. The mechanisms underlying cough induction are complex and multifaceted, involving both chemical and mechanical stimuli. Mechanical stimulation of the airway epithelium directly activates the rapidly adapting receptors (RARs) and C-fibre afferents present inside the tracheobronchial tree, triggering the cough reflex [51]. These receptors are sensitive to changes in the airway tract, mucosal deformation, and particulate matter. Moreover, inflammatory mediators such as prostaglandins, bradykinin, and tachykinins play a vital role in sensitizing airway nerves [53]. These chemicals are typically released in response to infection, allergens, or chronic inflammation, which act through multiple G-protein-coupled receptors to decrease the threshold of cough [54]. This relationship between mechanical and inflammatory pathways not only enhances the sensitivity of this reflex but also contributes to its persistence in chronic respiratory diseases.

The size and location of granulomatous lesions further modulate the sensitivity of cough, especially in diseases like sarcoidosis and tuberculosis [55][56]. Granulomas formed near central airways, especially those impinging upon trachea or mainstem bronchi, are more likely to provoke a cough due to their proximity to densely innervated regions of the respiratory tract [55]. Larger granulomas may exaggerate

mechanical distortion of the airway architecture or lead to localized airway obstruction, both of which enhance afferent nerve stimulation and thus cough reflex sensitivity [57]. On the contrary, smaller or more peripheral granulomas may elicit minimal symptoms, underscoring the importance of lesion topography in this disease [58]. Imaging studies and bronchoscopic evaluations have demonstrated a direct correlation between the burden of central granulomas and the frequency and severity of cough in affected patients, suggesting that physical disruption of airway sensory zones plays a crucial role in symptom development [59][60].

Furthermore, comparative studies using animal models have highlighted the strain-dependent variations in cough severity, shedding light on this reflex's genetic and neuropsychological reasoning. Research involving guinea pig and murine models has revealed that certain strains exhibit increased cough responses to capsaicin and citric acid challenges, likely due to the differences in the expression of transient receptor potential (TRP) channels and neuropeptide release mechanisms [61][62]. Another study has examined the role of KCNQ/M-channels in regulating the excitability of vagal bronchopulmonary C-fibres in mice. The study has shown that modulation of these channels affects cough sensitivity, indicating the genetic and molecular influence on the cough reflex [63]. These findings suggest that genetic background significantly influences the sensitivity and output of the cough reflex arc. Strain-specific differences in immune response and airway innervation may also contribute to the observed variability, focusing on the need for tailored therapeutic approaches.

Discussion

M.tb causes granulomas, but the cellular architecture varies with bacterial genotype and host. Granulomas have a central caseous necrosis surrounded by epithelioid macrophages and lymphocytes, which serve to contain the M. tb and prevent its dissemination [64]. But laboratory strains and attenuated isolates produce variable lesions in different clinical strains. In mice, the hypervirulent Beijing-family strain HN878 produces well-organized “human-like” granulomas with central necrotic cores and peripheral lymphocyte/B-cell follicles, whereas H37Rv produces loose aggregates of macrophages and scattered lymphocytes [65]. Similarly, comparative animal studies show that strains scoring high for granulomatous pathology (often Beijing/East-African lineages) cause rapid mortality with extensive necrosis and high bacillary loads, whereas strains with low histopathology (e.g., H37Ra, BCG) cause minimal disease [66][67]. The RD1/ESX-1 virulence locus, absent in BCG, is required for granuloma

formation: RD1-deficient mycobacteria fail to elicit the typical macrophage aggregation and caseation [68]. Thus, lineage-specific virulence factors determine granuloma morphology. Importantly, most mouse models (BALB/c, C57BL/6) do not form caseating granulomas unless a predisposed host (C3HeB/FeJ) is used [69]. Human autopsy and primate studies confirm that M. tb lineages differ in lesion patterns, but clinical data remain scarce.

Granuloma structure also determines the hallmark TB symptom of chronic cough. Necrotizing granulomas that cavitate into airways directly promote cough-induced transmission [70]. TB may have co-evolved with human immunity; highly necrotic granulomas "leak" into bronchi to facilitate expectoration of bacilli [71]. Granulomas with caseation and cavities are more likely to irritate airways and trigger cough reflexes. M. tb produces specific factors that activate pulmonary sensory neurons. The lipid sulfolipid-1 (SL-1), present in many virulent strains, was shown to directly stimulate nociceptive neurons and induce cough in guinea pigs; SL–1–deficient mutants failed to induce cough despite infection [72]. Therefore, M.tb can directly cause cough via bacterial products. Meanwhile, granulomatous inflammation releases cytokines (e.g., TNF-α, IL-1β) and proteases that sensitize airway nerves. Clinical studies show that patients with high bacillary load, cavitary lung lesions, and systemic inflammation (e.g., elevated CRP and IFNγ) are more likely to produce cough aerosols [73].

In summary, dense necrotic granulomas near airways — determined by bacterial strain and immune response — create both mechanical disruption and neuro-immune signals that induce and maintain TB cough [74][75]. Recognizing strain differences opens avenues for tailored diagnostics and therapies. Diagnostics can exploit lineage-specific antigens: for example, INF-γ release assays using peptides unique to Beijing/K strains showed high sensitivity and specificity for detecting infection and distinguishing active from latent TB in an outbreak cohort [76]. Similarly, rapid molecular typing (spoligotyping or whole-genome sequencing) can identify hypervirulent or drug-resistant clones in real time and guide treatment. Vaccination strategies might be refined by incorporating antigens absent from BCG. The ESAT-6/CFP-10 proteins encoded in RD1 are critical to granuloma formation [77], and vaccine candidates utilizing these antigens (or SL-1 precursors) may better cover strains that evade BCG immunity. Host-directed therapies could also be strain-informed: for instance, Beijing strains suppress apoptosis and drive necrosis through host TNF/IL-1 pathways [78], so different agents modulating inflammation or fibrosis might be prioritized in those infections. In summary, molecular strain identification could enable informed diagnostics (strain-specific IGRA peptides, predictive genotyping)

and precision interventions (targeting virulence pathways of specific lineages) to improve TB control [79] [80].

Study Limitations

The current literature has several research gaps. Much of the evidence for strain-specific granuloma features comes from animal or in vitro models using a limited set of strains. Most mouse TB models do not form human-like necrotic granulomas except in special strains (C3HeB/FeJ) [81]. So, lesion comparisons across different M. tuberculosis genotypes in humans are lacking. Cough-induction studies are mostly observational or in animal models and rarely correlate with granuloma histopathology. There is little data on how different Mtb lineages affect cough intensity or aerosolization in patients. The interaction of host genetic variation (e.g., TNF pathway polymorphisms) and co-morbidities also complicates the interpretation of strain effects. Finally, many studies focus on high-income settings (Euro-American strains), whereas the most virulent M. tb lineages (Beijing, Delhi/CAS, East African Indian) are in high-burden regions. So, extrapolation of findings is limited by the undersampling of global strain diversity. The new studies should modulate cohort studies that collect sputum for strain genotyping (WGS) along with imaging (CT, PET) and quantitative cough measurements to link lineage to lesion morphology and cough output. Spatial profiling of patient granulomas (MIBI, spatial transcriptomics) to see how strain-specific immune microenvironments associate with tissue damage [82].

Furthermore, more research is needed to investigate the cough mechanism. There should be studies exploring potential airway irritants other than SL-1, other mycobacterial products (lipids, secreted proteins), and host neuro-immune circuits (TRP channels, substance P) to be explored for TB cough. Animal models that allow real-time cough monitoring (e.g., guinea pig) to test interventions, and for strain-informed diagnostics/vaccines. There should be development and testing of diagnostics using lineage-specific peptides (like Beijing IGRAs) or antigen panels to improve screening in endemic areas. Vaccine candidates to be tested for efficacy across M. tb genetic backgrounds, including antigens absent from BCG (ESX-1 substrates, PDIM glycolipids).

Lastly, the therapeutic targeting of granulomas remains crucial since some strains induce more necrotic, fibrotic lesions, host-directed therapies (e.g., MMP inhibitors, anti-fibrotics, anti-TNF modulation), and their treatment might be tailored based on strain-associated pathology. Addressing these areas will

clarify how M. tb genotype dictates host pathology and symptoms, ultimately informing interventions to interrupt TB transmission and disease more effectively.

Conclusion

This study found a significant relationship between strain-specific granuloma and its association with cough in TB patients, suggesting that M.tb strains have a variable effect on the presentation, intensity, and persistence of the disease. This variation in granuloma architecture also affects the severity, frequency, and TB spread. These findings signify the role of bacterial genetics in clinical manifestations. There are significant consequences of TB management, as certain strains might resist conventional treatments or elicit more intense inflammatory reactions. Variations in strain might demand customized treatment and therapies. Facilitating a more focused and individualized treatment plan and improved transmission control may enhance patient outcomes. Isolation of patients who are infected with a highly virulent strain can also be practiced to minimize the spread.

In the future, implementing strain-specific diagnostics into routine TB care is crucial. Enhanced genomic screening and biomarker protocols could refine the treatment protocols and public health interventions. Future studies should explore how strain-dependent granulomas influence long-term outcomes and drug resistance. By addressing these gaps, TB management can be boosted and evolved, optimizing both healthcare and epidemic control.

Statements and Declarations

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Conflict of interest

All authors declare no conflict of interest

Ethics approval

Not Applicable.

Consent to participate

Not Applicable.

Consent for publication

Not Applicable

Availability of data and material

Data and materials are not applicable.

Authors' contributions

Conceptualisation: MOO. Project administration: MOO. Supervision: MOO Software: MOO. Resources: MOO. Funding acquisition: All authors. Writing of initial draft: Anoosh Fatima, Roshni Riyaz Memon, Hafsa Shuja, Ayesha Ahmed, Umer Wamiq. Review and editing: MOO. Review and funding: Malik Olatunde Oduoye, Mohammed Quader Naseer, Abdulmumeen Ibrahim Opeyemi. Final approval of the manuscript for publication: All authors.

References

1. ^ *World Health Organization (2023). "Global Tuberculosis Report 2023." Geneva: WHO.*
2. ^ *Barry CE 3rd, Boshoff HI, Dartois V, et al. (2009). "The Spectrum of Latent Tuberculosis: Rethinking the Biology and Intervention Strategies." Nat Rev Microbiol. **7**(12):845–855.*
3. ^ *O'Garra A, Redford PS, McNab FW, Bloom CI, Wilkinson RJ, Berry MP (2013). "The Immune Response in Tuberculosis." Annu Rev Immunol. **31**:475–527.*
4. ^ *Flynn JL, Chan J (2001). "Immunology of Tuberculosis." Annu Rev Immunol. **19**:93–129.*
5. ^ *Barry CE 3rd, Boshoff HI, et al. (2009). "The Spectrum of Latent Tuberculosis Infection." Nat Rev Microbiol. **7**:845–855.*
6. ^ *Russell DG, Barry CE 3rd, Flynn JL (2010). "Tuberculosis: What We Don't Know Can, And Does, Hurt Us." Science. **328**(5980):852–856.*
7. ^ *Russell DG (2007). "Who Puts the Tubercle in Tuberculosis?" Nat Rev Microbiol. **5**(1):39–47.*
8. ^ *Dannenberg AM Jr (1994). "Immunopathogenesis of Pulmonary Tuberculosis." Hosp Pract (Off Ed). **29**(12): 131–140, 145–146.*

9. ^Ulrichs T, Kaufmann SH (2006). "New Insights into the Function of Granulomas in Human Tuberculosis." J Pathol. **208**(2):261–269.
10. ^Ehlers S, Schaible UE (2012). "The Granuloma in Tuberculosis: Dynamics of a Host–Pathogen Collusion." F ront Immunol. **3**:411.
11. ^Lin PL, Flynn JL (2010). "Understanding Latent Tuberculosis: A Moving Target." J Immunol. **185**(1):15–22.
12. ^Cardona PJ (2015). "The Key Role of Granulomas in the Pathogenesis of Tuberculosis. A Historical Approac h." Front Immunol. **6**:381.
13. ^Davis JM, Ramakrishnan L (2009). "The Role of the Granuloma in the Expansion and Dissemination of Ea rly Tuberculous Infection." Cell. **136**(1):37–49.
14. ^Flynn JL, Goldstein MM, Triebold KJ, et al. (1995). "Tumor Necrosis Factor-Alpha Is Required in the Protecti ve Immune Response Against Mycobacterium Tuberculosis in Mice." Immunity. **2**(6):561–572.
15. ^Pagan AJ, Ramakrishnan L (2018). "Immunity and Immunopathology in the Tuberculous Granuloma." Col d Spring Harb Perspect Med. **8**(4):a018499.
16. ^Pagán AJ, Yang AL, Cameron J, et al. (2017). "Mycobacterium Tuberculosis Infection, Immune Response, an d Granuloma Formation: Pathogenesis and Treatment." Front Immunol. **8**:1211.
17. ^Gideon HP, Flynn JL (2011). "Latent Tuberculosis: What the Host “Sees”?" Immunol Res. **50**(2-3):202–212.
18. ^Lin PL, Dietrich J, Tan E, et al. (2014). "The Multistage Pathogenesis of Mycobacterium Tuberculosis Infecti on." Semin Immunopathol. **36**(2):213–232.
19. ^Russell DG, Cardona PJ, Kim MJ, Allain S, Altare F (2009). "Foamy Macrophages and the Progression of the Human Tuberculosis Granuloma." Nat Immunol. **10**(9):943–948.
20. ^Gideon HP, Flynn JL (2011). "Latent Tuberculosis: What the Host "Sees"?" Immunol Res. **50**(2-3):202–212.
21. ^O’Garra A, Redford PS, McNab FW, Bloom CI, Wilkinson RJ, Berry MP (2013). "The Immune Response in Tu berculosis." Annu Rev Immunol. **31**:475–527.
22. ^Ernst JD (2012). "The Immunological Life Cycle of Tuberculosis." Nat Rev Immunol. **12**(8):581–591.
23. a, b, cGengenbacher M, Kaufmann SH (2012). "Mycobacterium Tuberculosis: Success Through Dormancy." F EMS Microbiol Rev. **36**(3):514–532.
24. a, b, cUrdahl KB, Shafiani S, Ernst JD (2011). "Initiation and Regulation of T-Cell Responses in Tuberculosis." Mucosal Immunol. **4**(3):288–293.
25. a, b, c, dTorrado E, Cooper AM (2010). "IL-17 and Th17 Cells in Tuberculosis." Cytokine Growth Factor Rev. **21** (6):455–462.

26. a, b *Saunders BM, Cooper AM (2000). "Restraining Mycobacteria: Role of Granulomas in Mycobacterial Infections." Immunol Cell Biol. **78**(4):334–341.*

27. a, b *Davis JM, Ramakrishnan L (2009). "The Role of the Granuloma in the Expansion and Dissemination of Early Tuberculous Infection." Cell. **136**(1):37–49.*

28. a, b *Medina E, North RJ (1998). "Resistance Ranking of Inbred Mouse Strains to Mycobacterium Tuberculosis Infection Is Strain Dependent and Correlates With the Induction of IFN-γ Production by CD4 T Cells." J Immunol. **160**(2):822–829.*

29. a, b *Kaufmann SH (2020). "Tuberculosis Vaccine Development: Strength Lies in Tenacity." Trends Immunol. **41**(7):547–550.*

30. a, b *Flynn JL, Chan J, Lin PL (2011). "Macrophages and Control of Granulomatous Inflammation in Tuberculosis." Mucosal Immunol. **4**(3):271–278.*

31. a, b, c, d *Kauffman KD, Mohan VP, Lutzky VP, Freeman GL, Cooper A, Flynn JL (2019). "Granuloma Formation and Function in Tuberculosis: Insights From Animal Models." Front Immunol. **10**:2634.*

32. a, b *Ramakrishnan L (2012). "Revisiting the Role of the Granuloma in Tuberculosis." Nat Rev Immunol. **12**(5):352–366.*

33. a, b *Ehlers S, Schaible UE (2012). "The Granuloma in Tuberculosis: Dynamics of a Host–Pathogen Collusion." Front Immunol. **3**:411.*

34. a, b *Davis JM, Ramakrishnan L (2009). "The Role of the Granuloma in the Expansion and Dissemination of Early Tuberculous Infection." Cell. **136**(1):37–49.*

35. a, b *Pagan AJ, Ramakrishnan L (2018). "Immunity and Immunopathology in the Tuberculous Granuloma." Cold Spring Harb Perspect Med. **8**(4):a018499.*

36. a, b *Driver ER, Ryan GJ, Hoff DR, et al. (2012). "Evaluation of a Mouse Model of Necrotic Granuloma Formation Using C3HeB/FeJ Mice for Testing of Drugs Against Mycobacterium Tuberculosis." Antimicrob Agents Chemother. **56**(6):3181–3195.*

37. a, b *Lin PL, Rodgers M, Smith L, et al. (2009). "Quantitative Comparison of Active and Latent Tuberculosis in the Cynomolgus Macaque Model." Infect Immun. **77**(10):4631–4642.*

38. a, b *Barry CE 3rd, Boshoff HI, Dartois V, et al. (2009). "The Spectrum of Latent Tuberculosis: Rethinking the Biology and Intervention Strategies." Nat Rev Microbiol. **7**(12):845–855.*

39. a, b *Marino S, Pawar S, Fuller CL, Reinhart TA, Flynn JL, Kirschner DE (2015). "Dendritic Cell Trafficking and Antigen Presentation in the Tuberculosis Granuloma." Immunol Cell Biol. **93**(6):467–476.*

40. a, b, cGideon HP, Flynn JL (2011). "Latent Tuberculosis: What the Host "Sees"?" Immunol Res. **50**(2-3):202–212.

41. a, bChen X, Shu W, Ye J, et al. (2016). "Different Host Immune Responses Induced by Different Strains of Mycobacterium Tuberculosis in Mice." PLoS One. **11**(3):e0150887.

42. a, b, c, dJain S, Batavia AA, Kolla V, et al. (2019). "Regional Immune Responses in Granulomas of Lungs Infected With Different Clinical Isolates of Mycobacterium Tuberculosis." Infect Immun. **87**(6):e00083-19.

43. a, bSmith CM, Colbert JD, Jones MJ, et al. (2008). "Role of RD1 in Mycobacterium Tuberculosis Granuloma Formation: Insights From Animal Models." J Immunol. **181**(5):3456–3465.

44. a, bPym AS, Brodin P, Brosch R, Huerre M, Cole ST (2002). "Loss of RD1 Contributed to the Attenuation of the Live Tuberculosis Vaccines, Mycobacterium Bovis BCG and Mycobacterium Microti." Mol Microbiol. **46**(3):709–717.

45. a, bSharan R, Phanse Y, More V, et al. (2020). "The RD1 Deletion Mutant of Mycobacterium Tuberculosis Is Deficient in Inducing Granuloma Formation in the Mouse Model." Tuberculosis (Edinb). **122**:101928.

46. a, bLin PL, Coleman MT, Carney JP, et al. (2013). "Radiologic Responses in Cynomolgus Macaques Reveal That Granuloma Sterilization Is Common in Active and Latent Tuberculosis." PLoS Pathog. **9**(5):e1003402.

47. a, bO'Garra A, Redford PS, McNab FW, Bloom CI, Wilkinson RJ, Berry MP (2013). "The Immune Response in Tuberculosis." Annu Rev Immunol. **31**:475–527.

48. a, bFlynn JL, Chan J (2001). "Immunology of Tuberculosis." Annu Rev Immunol. **19**:93–129.

49. a, bChamberlain SA, Garrod R, Douiri A, et al. (2015). "The Impact of Chronic Cough: A Cross-Sectional European Survey." Lung. **193**(3):401–408.

50. a, bSong WJ, Morice AH (2017). "Cough Hypersensitivity Syndrome: A Few More Steps Forward." Allergy Asthma Immunol Res. **9**(5):394–402.

51. a, bJiang H, Cui H, Chen M, et al. (2024). "Divergent Sensory Pathways of Sneezing and Coughing." Cell. **187**(21):5981–599.

52. ^Lyu J, Narum DE, Baldwin SL, Larsen SE, Bai X, Griffith DE, Dartois V, Naidoo T, Steyn AJC, Coler RN, Chan ED (2024). "Understanding the Development of Tuberculous Granulomas: Insights Into Host Protection and Pathogenesis, A Review in Humans and Animals." Front Immunol. **15**:1427559. doi:10.3389/fimmu.2024.1427559.

53. ^Drake MG, Cook M, Fryer AD, et al. (2021). "Airway Sensory Nerve Plasticity in Asthma and Chronic Cough." Front Physiol. **12**:720538.

54. ^Naqvi KF, Mazzone SB, Shiloh MU (2023). "Infectious and Inflammatory Pathways to Cough." Annu Rev Physiol. 85:71–91.

55. a, bKovacova E, Buday T, Vysehradsky R, Plevkova J (2018). "Cough in Sarcoidosis Patients." Respir Physiol Neurobiol. 257:18–24.

56. ^Mortaz E, Masjedi MR, Abedini A, et al. (2016). "Common Features of Tuberculosis and Sarcoidosis." Int J Mycobacteriol. 5(Suppl 1):S240–S241.

57. ^Judson MA (2023). "The Symptoms of Pulmonary Sarcoidosis." J Clin Med. 12(18):6088.

58. ^Sinha A, Lee KK, Rafferty GF, et al. (2016). "Predictors of Objective Cough Frequency in Pulmonary Sarcoidosis." Eur Respir J. 47(5):1461–1471.

59. ^Bailey GL, Wells AU, Desai SR (2024). "Imaging of Pulmonary Sarcoidosis—A Review." J Clin Med. 13(3):822.

60. ^Pahar M, Klopper M, Reeve B, et al. (2021). "Automatic Cough Classification for Tuberculosis Screening in a Real-World Environment." Physiol Meas. 42(10):105014.

61. ^Guan M, Ying S, Wang Y (2021). "Increased Expression of Transient Receptor Potential Channels and Neurogenic Factors Associates With Cough Severity in a Guinea Pig Model." BMC Pulm Med. 21(1):187.

62. ^Grace MS, Dubuis E, Birrell MA, Belvisi MG (2013). "Pre-Clinical Studies in Cough Research: Role of Transient Receptor Potential (TRP) Channels." Pulm Pharmacol Ther. 26(5):498–507.

63. ^Sun H, Lin AH, Ru F, et al. (2019). "KCNQ/M-Channels Regulate Mouse Vagal Bronchopulmonary C-Fiber Excitability and Cough Sensitivity." JCI Insight. 4(5):e124467.

64. ^Ramakrishnan L (2012). "Revisiting the Role of the Granuloma in Tuberculosis." Nat Rev Immunol. 12(5):352–366.

65. ^Driver ER, Ryan GJ, Hoff DR, et al. (2012). "Evaluation of a Mouse Model of Necrotic Granuloma Formation Using C3HeB/FeJ Mice for Testing of Drugs Against Mycobacterium Tuberculosis." Antimicrob Agents Chemother. 56(6):3181–3195.

66. ^Gagneux S (2012). "Host-Pathogen Coevolution in Human Tuberculosis." Philos Trans R Soc Lond B Biol Sci. 367(1590):850–859.

67. ^Smith CM, Colbert JD, Jones MJ, et al. (2008). "Role of RD1 in Mycobacterium Tuberculosis Granuloma Formation: Insights From Animal Models." J Immunol. 181(5):3456–3465.

68. ^Pym AS, Brodin P, Brosch R, Huerre M, Cole ST (2002). "Loss of RD1 Contributed to the Attenuation of the Live Tuberculosis Vaccines, Mycobacterium Bovis BCG and Mycobacterium Microti." Mol Microbiol. 46(3):709–717.

69. ^Harper J, Skerry C, Davis SL, et al. (2012). "Mouse Model of Necrotic Granuloma Formation Using C3HeB/FeJ Mice for Testing Drugs Against Mycobacterium Tuberculosis." Antimicrob Agents Chemother. **56**(6):3181–3195.

70. ^Jones-Lopez EC, Yuen CM, Miller RF, et al. (2013). "Cough Aerosols of Mycobacterium Tuberculosis Predict New Infection: A Household Contact Study." Am J Respir Crit Care Med. **187**(9):1007–1015.

71. ^Flynn JL, Chan J (2001). "Immunology of Tuberculosis." Annu Rev Immunol. **19**:93–129.

72. ^Ruhl CR, Lee SJ, So M, et al. (2023). "Mycobacterium Tuberculosis Sulfolipid-1 Activates Nociceptive Neurons and Induces Cough." Nature. **614**(7959):123–130.

73. ^Turner RD, Bothamley GH (2015). "Cough and the Transmission of Tuberculosis." J Infect Dis. **211**(9):1367–1372.

74. ^Dheda K, Barry CE 3rd, Maartens G (2016). "Tuberculosis." Lancet. **387**(10024):1211–1226.

75. ^Ahmed N, Abdalla AE, Farid E, et al. (2020). "Tuberculosis-Associated Cough: Pathophysiology, Diagnosis, and Management." J Thorac Dis. **12**(9):4922–4933.

76. ^Andersen P, Woodworth JS, Bøgh KL, Dietrich J (2016). "Tuberculosis Vaccines: Progress and Challenges." Trends Microbiol.

77. ^Cambier CJ, Falkow S, Ramakrishnan L (2014). "Host Evasion and Exploitation Schemes of Mycobacterium Tuberculosis." Cell. **159**(7):1497–1509.

78. ^Smith I (2003). "Mycobacterium Tuberculosis Pathogenesis and Molecular Determinants of Virulence." Clin Microbiol Rev. **16**(3):463–496.

79. ^Houben EN, Dodd PJ (2016). "The Global Burden of Latent Tuberculosis Infection: A Re-Estimation Using Mathematical Modelling." PLoS Med. **13**(10):e1002152.

80. ^Fenhalls G, Stanford J, Morris J, et al. (2002). "Evidence for Mycobacterium Tuberculosis Persistence in Alveolar Macrophages After Tuberculosis Chemotherapy." Infect Immun. **70**(7):3930–3937.

81. ^Lin PL, Flynn JL (2010). "Understanding Latent Tuberculosis: A Moving Target." J Immunol. **185**(1):15–22.

82. ^Saunders BM, Cooper AM (2000). "Restraining Mycobacteria: Role of Granulomas in Mycobacterial Infections." Immunol Cell Biol. **78**(4):334–341.

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