Received: 19 September 2020 | Revised: 16 January 2021 | Accepted: 26 February 2021

DOI: 10.1111/sji.13035

REVIEW

Scandinavian Journal of Immunology WILEY

Non-tuberculous mycobacteria immunopathogenesis: Closer than they appear. a prime of innate immunity trade-off and NTM ways into virulence

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Funding information
Rio Arronte. S590

Abstract

Introduction: The growing incidence of non-tuberculous mycobacteria (NTM) and changes in epidemiological factors have indicated that immune dysregulation may be associated with the emergence of NTM. Minireview entails to acknowledge complex interaction and new ways NTM are evolving around diverse immune status.

Methods: In order to perform this review, we selected peer reviewed, NLM database articles under the terms NTM, mycobacterium complex 'AND' -Host- immune response, immunity regulation, Disease, Single Nucleotide Polymorphism (SNP´s), and -pathogen- followed by a snow ball rolling basis search on immune components and NTM related with diseases distribution.

Results: The universal exposure and diversity of NTM are well-documented; however, hospitals seldom establish vigilant control of water quality or immunodeficiencies for patients with NTM infections. Depending on the chemical structures and immune mechanisms presented by various NTM varieties, they can trigger different effects in dendritic and natural killer cells, which release interleukin (IL)-17, tumour necrosis factor-α (TNF-α), interferon-γ (IFN-γ) and rIL-1B. The T helper (Th)2-acquired immune response is responsible for autoimmune responses in patients with NTM infections, and, quite disturbingly, immunocompetent patients have been reported to suffer from NTM infections.

Conclusion: New technologies and a comprehensive view has taught us; to acknowledge metabolic/immune determinants and trade-offs along transit through mutualism-parasite continuous.

1 | INTRODUCTION

Non-tuberculous mycobacteria (NTM), which is classified separately from *Mycobacterium tuberculosis*, includes a growing list of more than 200 mycobacteria species belonging to both commensal and pathogenic species. NTM are ubiquitous microorganisms,[1] often transmitted through water-based vectors.[2] Similar to *M tuberculosis*, the inhalation of

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aerosolized mycobacteria[3,4] is also favoured due to the lipid nature of the cell wall. The evolutionary pathways of individual species are often shaped by a combination of pertinent factors, such as changes in the immune responses to various microbiota, including avirulent species. No genes have been identified that are specific for *M tuberculosis*, which, instead, shares many genes that are also expressed by NTMs.[5] Because some of these genes expressed by NTMs may contribute to the development of an immune-friendly environment, the epitopes shared between NTM and *M tuberculosis* may also facilitate disease progression and result in NTMs gaining virulence.[6]

The expansion of susceptible hosts has been described as a distinctive trait of NTMs, as several shared epitopes have been found to induce inflammatory responses, such as interleukin-10 (IL-10) combined with interferon-γ (INF-γ), or tolerogenic responses (IL-10 alone),[7] depending on the context in which they appear. This pattern has been observed in developing countries, where diverse NTM populations are harboured by animals[8] and multiple human-made sources of exposure, which may have rendered the anti-tuberculosis Bacille Calmette-Guérin (BCG) vaccine less effective.[9]

In developed countries, where the incidence of mycobacterial infections caused by NTM surpasses the number of cases caused by *M tuberculosis*, the increased frequency of NTM infections has been reported under conditions characterized by IFN-γ signalling or transduction deficiencies,[10-12] which are frequently associated with low-penetrance variants[13] and environmental pressure. For example, the age-related attenuation of heme oxygenase-1 (HMOX1) results in the upregulation of suppressor of cytokine signalling 3 (SOCS3), which, in turn, may inhibit INF-γ, which can allow a cell-necrosis sustained infection to occur.[14] However, genetics is not destiny, and the microbiome has been shown to be a potent modulator of the IL-17 cascade[15] (Figure 1).

Although from 20% to 66% of NTM species isolated from lungs have been found to cause pulmonary infections, according to the American Thoracic Society (ATS) criteria,[16,17] *Mycobacterium abscessus* is always found among the top five species, regardless of geographic variations in the clinically significant varieties of NTM species.[18,19]

From a genomics perspective, the host-gene network participates in activating the immune response, and NTM appears among the most central and connected nodes in known immune networks, including nuclear factor-κB (NF-κB), extracellular signal-related kinase 2 (ERK2), and mitogen-activated protein kinase (MAPK)38; therefore, NTM appears to induce the activation of innate and adaptative immunity pathways, and autoimmune/inflammatory responses, which are shared among host targets, appear to be crucial to the development of infection.[20] The canonical gene pathway enrichment associated with NTM infection has revealed the importance of communications between innate and adaptative immunity, which is supported by the correlation between the progression of fibrocavitary radiographic lesions and PD-1$^+$ and CD4$^+$ markers on lymphocytes and regulatory CD4$^+$ lymphocytes (Tregs).[21]

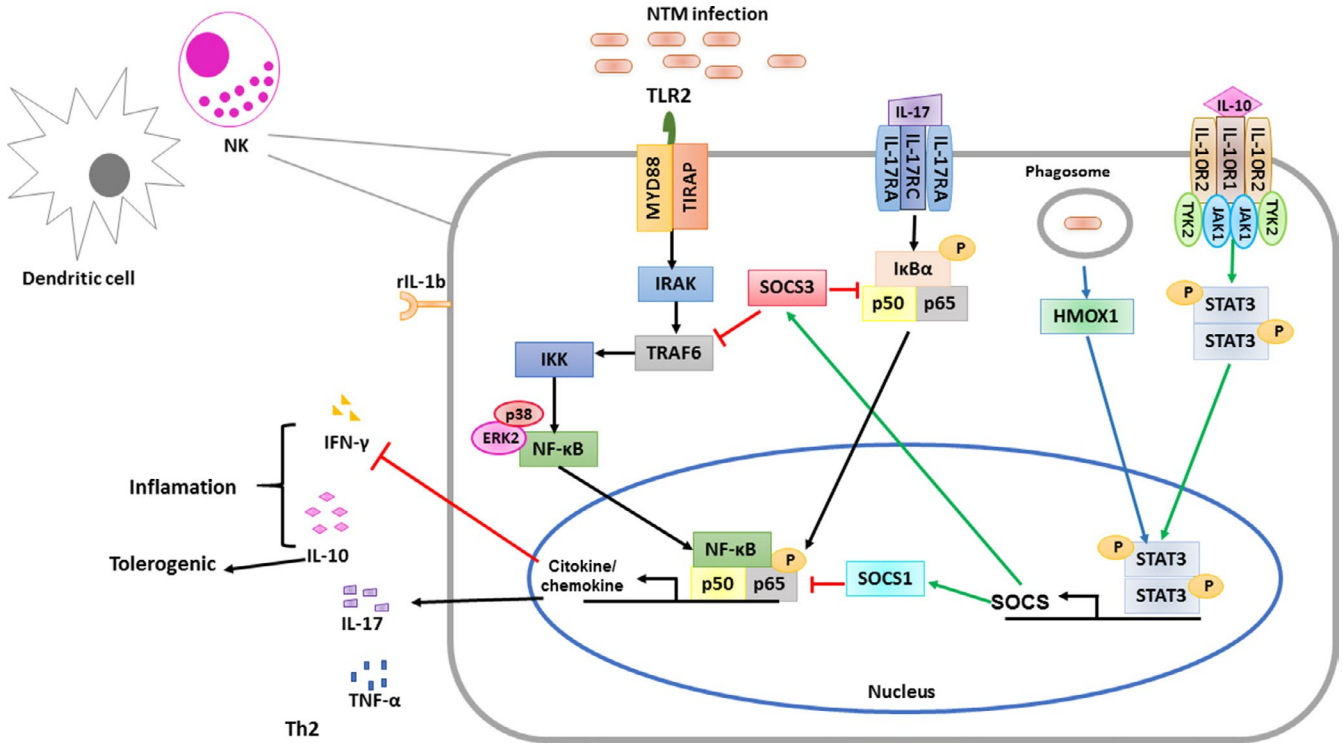

FIGURE 1 Schematic diagram showing the immune response against NTM infections, which involves HMOX-1 and SOCS3 signalling

2 | EPIDEMIOLOGY OF NTM

Reliable registers of NTM species that can be used to infer burden have not been developed, as only some strains of NTM clonal groups within the same clade evolve to virulence. Therefore, even known molecular markers, such as *16SRNAr*, *Rpob* or *65KDa*, may not provide sufficient granularity, being not specific enough to distinguish infectious species from other NTMs.[2,22] However, *M abscessus*. *Mycobacterium malmoense*, *Mycobacterium xenopi* and *Mycobacterium intracelulare* are among the most commonly identified species associated with significant clinical infections and are more common than *Mycobacterium avium* and *Mycobacterium kansasii*, which is a close relative of *M tuberculosis*.[16] Therefore, restriction fragment length polymorphisms (RFLPs), which can be used as genetic markers, or the serological typing of the insertion sequence IS1245, which has been genetically associated with clinically and environmentally transmitted species *M avium, Mycobacterium avium* ssp *paratuberculosis, M kansasii, Mycobacterium gordonae, M xenopi, M abscessus*, *Mycobacterium chelonae* and *Mycobacterium malmoense,* could be assessed to determine virulent strains.[23]

Among subjects with non-human immunodeficiency virus (non-HIV), socioeconomic conditions and the geographic variations in NTM species has been demonstrated. A higher risk of pulmonary NTM-related infections has been identified among subjects suffering from pre-existing respiratory distress associated with ciliary activity or other defence mechanisms. Direct associations between NTM-based pulmonary infections have been identified for cystic fibrosis, chronic pulmonary obstructive disease, diabetes, Lady Windermere syndrome, and others.[24-26]

The prevalence of extrapulmonary NTM disease is lower, caused by a wide array of epidemiologically univariant NTMs, and is associated with different risk factors, including primary immune deficiencies or human immunodeficiency virus (HIV) infection.

3 | PATHOGENESIS OF NTM PULMONARY INFECTION

M tuberculosis can withstand intracellular infections. Pulmonary NTM, (PNTM) infections are likely the most-studied, due to knowledge regarding immunity against *M tuberculosis* infections, which precede PNTM infections in a number of cases.[27]

For *M tuberculosis*, T lymphocytes, including $CD4^+$, $CD8^+$ and CD1 + natural killer (NK) cells, accompanied by T lymphocyte γδ cells that produce IFN-γ, IL-2 and IL-12, induce a protective effect, whereas responses involving IL-4, IL-6, IL-10, tumour necrosis factor-α (TNF-α) and transforming growth factor-β (TGF-β) are not protective (Figure 2).

NTMs are increasingly important causes of pulmonary morbidity and mortality, worldwide, especially in industrialized countries, where NTMs can be prevalently found.[28,29] PNTM disease typically develops in individuals without recognized host immune defects, especially in slender, post-menopausal women, suggesting that gender-associated factors may play a role in host susceptibility to the establishment of PNTM disease, beyond environmental exposure. Several genetic diseases have been associated with PNTM infections, including cystic fibrosis and primary ciliary dyskinesia.[30] PNTM infections are most commonly observed in the setting of bronchiectasis, particularly among patients who suffer from cystic fibrosis, characterized by high rates of cystic fibrosis transmembrane conductance regulator (CFTR) heterozygosity and decreased ciliary beat frequency.[31,32] Other T cell deficiencies associated with *M abscessus* complex pulmonary infections[33,34] are highly lightly to be genetically codified, such as low TNF-α production during mitogen stimulation and polymorphisms in IL-10 (rs1800896), which have been associated with NTM disease[35] (Figure 3). In line with the hypothesis of multiple low penetrances and, as expected, the most frequently associated cause behind susceptibility to NTM infection is a polygenic background including ciliary defects. CFTR variants, connective tissue variants, and heterozygous macrophage-expressed gene 1 (MPEG1)/perforin mutations may combine to render subjects unable to efficiently neutralize *M avium*,[36,37] whereas several gene pathways may become upregulated, especially those associated with inflammation.[38]

In animal models, however, the deletion of Toll-like receptor 2 (TLR2), which is an upstream signalling molecule, results in macrophages that fail to produce the proinflammatory cytokine IL2 p70, in response to Myeloid differentiation primary response 88 (MYD88)[39] activation, which normally induces $CD4^+$, $CD8^+$ T cell migration and expands effector and memory T cells in response to *M abscessus*[40] (Figure 4A). Coincidentally, in humans, weaker innate immune responses associated with reduced levels of TNF-α, and IL 12 are suggested as being aggravated by low TLR2 expression[41] (Figure 4B).

In addition, NK cells may represent a major contributor of IFN-γ, which activates and enhances innate and adaptive immune responses,[42] particularly when the *M avium* complex (MAC) infects cells via TLR2, with CD14 downregulating IFN-γ signaling.[43]

Fibronectin motifs are highly conserved among mycobacteria and are definitively expressed by the MAC.[44] The multifunctional glycoproteins that are necessary for NTM colonization in mucous secretions facilitate attachment to the extracellular matrix, via fibronectin-binding protein (FBP); however, the proportions of infected cells associated

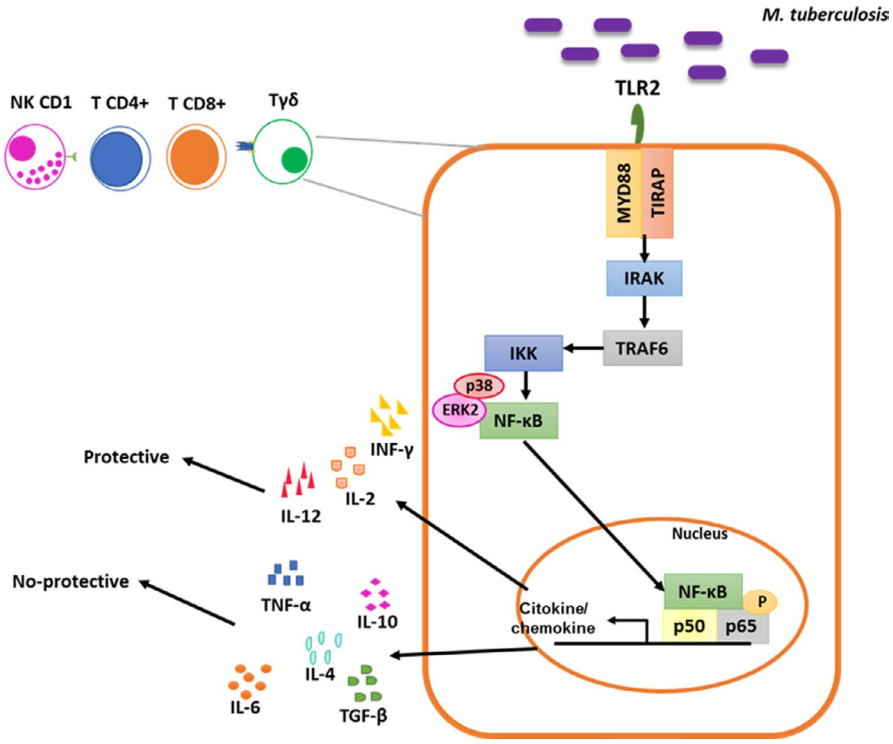

FIGURE 2 Diagram showing the adaptive immune response against *M tuberculosis* infection

with each cellular linage and the nuclear mechanism that is activated to initiate cell death appear to be mycobacterial species-dependent.

In support of the hypothesis that suggests that mycobacterial pathogenesis evolved independently, mycobacterial cell-wall constitutive lipids that exhibit subtle differences have been explored as a potential means through which mycobacteria species can manipulate host-macrophage apoptosis and the concomitant inflammatory response and granuloma formation activity. Because these processes are central to mycobacterial niche utilization during the course of the infection, efforts are currently being made to identify novel NTM-lipid-directed therapies to reduce the lung disease burden among infected individuals.[45]

During pathogenesis, an important role is played by the mycobacterial cell envelope, which is a complex structure comprised of the plasma membrane and a cell wall, comprised of lipids and containing fatty acids and lipoproteins. For example, mycolyl-arabinogalactan-peptidoglycan (mAGP) spans the cell wall to form an insoluble core skeleton, comprised of mycolic acids (MAs) linked to arabinogalactan (AG), which is anchored to a layer of peptidoglycans (PPGs) superficial to the plasma membrane. mAGP plays an important role in the overall architecture and impermeability of this specialized cell wall. MAs and their homologues, which are comprised of 2-alkyl, 3-hydroxy long-chain fatty acids, are essential mycobacterial structures that maintain cell structure and form serpentine-like cords; hence, mycobacteria are also known as 'cord-formers'. All mycobacteria, including NTMs, synthesize an array of lipids, including phosphatidyl inositol mannosides (PIMs), lipomannan (LM) and lipoarabinomannan (LAM). Although absent from *M tuberculosis*, glycopeptidolipids (GPL) are critical for the biology of NTMs. *M tuberculosis* and some NTMs also synthesize trehalose-containing glycolipids and phenolic glycolipids (PGL), which are key membrane constituents that play essential roles in metabolism. Although lipids facilitate immune evasion, they also induce host immunity against tuberculosis. However, much less is known regarding the significance of NTM-derived PIM, LM, LAM, GPL, trehalose-containing glycolipids and PGL as virulence factors, warranting further investigation.

GPLs are produced by most NTM species and share a common deglycosylated, N-linked, long fatty acyl chain, linked to a tetrapeptide-amino-alcohol core; however, these molecules utilize varying modifications, consisting of attached rhamnose and 6-deoxytalose.

The major difference between these types is the loss of surface-associated GPLs in the R type. Interestingly, the smooth-type of *M abscessus*, which features cell surface-associated GPLs and can be found in the mitochondrial compartment, inhibits macrophage apoptosis, contributing to disease spread.[46]

Divergent pathophysiological mechanisms have been identified both when comparing *M tuberculosis* and NTMs and among various species of NTMs. The ability to survive inside acidified macrophagic phagosomes has been demonstrated for *M avium* and *Mycobacterium fortuitum*, associated with the induction of caspase 8-mediated apoptosis, a mechanism that enhances the mycobacterial dissemination,

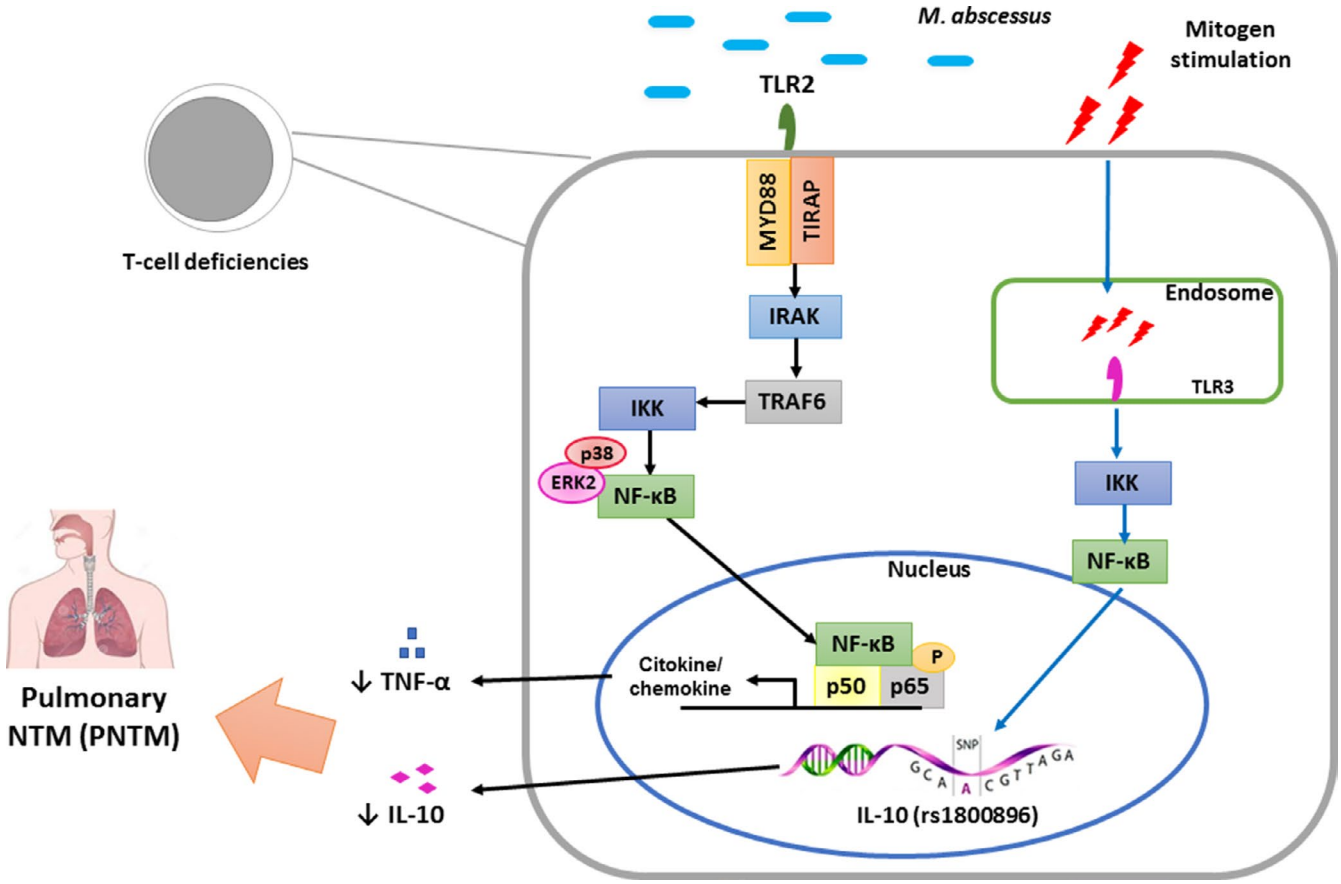

FIGURE 3 Schematic showing the pathogenesis of NTM-based pulmonary infections

unlike *M tuberculosis*.[47] However, although *M abscessus,* similar to *M tuberculosis*, can escape from the phagosome, it utilizes a different escape mechanism; the *M abscessus* quantity overloads phagosome capacity, disrupting the membrane and causing cell necrosis, followed by INF-I production and cell-to-cell spread.[48] According to Ruangkiattikul et al, the increased IFN-β induction observed in response to infection with the *M abscessus* rough colony strain (MAB-R) was associated with a corresponding increase in TNF-α expression and intracellular death induced by enhanced macrophage nitric oxide synthase 2 (NOS2) expression, resulting in increased nitric oxide production.[49] In contrast, deficiencies in TNF-γ release and the lack of IL-8 neutrophil chemoattraction results in anomalous granuloma formation[50] (Figure 5).

Although T cells are usually viewed as one of the most important elements for the regulation of the cytokine profile, the link between innate and acquired immunity is also a determinant; a prime-contact, low-virulence, distantly related NMT, such as *M scrofulaceum*,[51] were to be encountered, it would set T cell responsiveness to a low level[52] by increasing the expression of programmed cell death 1 (PD-1) and increasing the rate of programmed cell death ligand (PDL)-apoptosis in lymphocytes, as demonstrated in a set of patients with MAC-associated pulmonary infections.[53] A more complex scenario may also be involved because IL-12 and IL-23 are both critical for the homeostasis of the INF-γ-IL-17-axis.[54,55] Experimentally, innate immune-cell migration and INF-γ production have been closely associated with intestinal microbiome diversity, and clearance-specific clusters of intestinal microbiota have been shown to augment the severity of infections associated with respiratory viruses or *M tuberculosis* by interfering with Tregs.[56] Antimicrobial treatment has been shown to lower the number and activity of mucosal-associated invariant T (MAIT) cells, which are a type of innate regulatory lymphocyte that produce IL-17A and are putatively responsible for the early control of *M tuberculosis* infections. MAIT is only one of several innate immune cells that produce INF-γ in response to IL-23.

Other effectors and memory T cells normally found in the lungs[57] are also lost after dysbiosis, and antimicrobial treatment has been shown to reduce mince expression on lung myeloid $CD11c^{+}CD11b^{+}$ dendritic cells (DCs) and impair the functional responsiveness of DCs, leading disruptions in the response of memory $CD4^{+}$ T cells in the lung.[57] Although microbiota compositions associated with NTM infections have not been characterized, to date, Actinobacteria enrichment at the expense of Bacteroidetes during *M tuberculosis* infections may indicate the important contribution of acetate fermenters relative to butyrate fermenters (*Prevottella* and *Veillonella*).[58] In addition, *Rothia*[59] and *Leuconostoc*

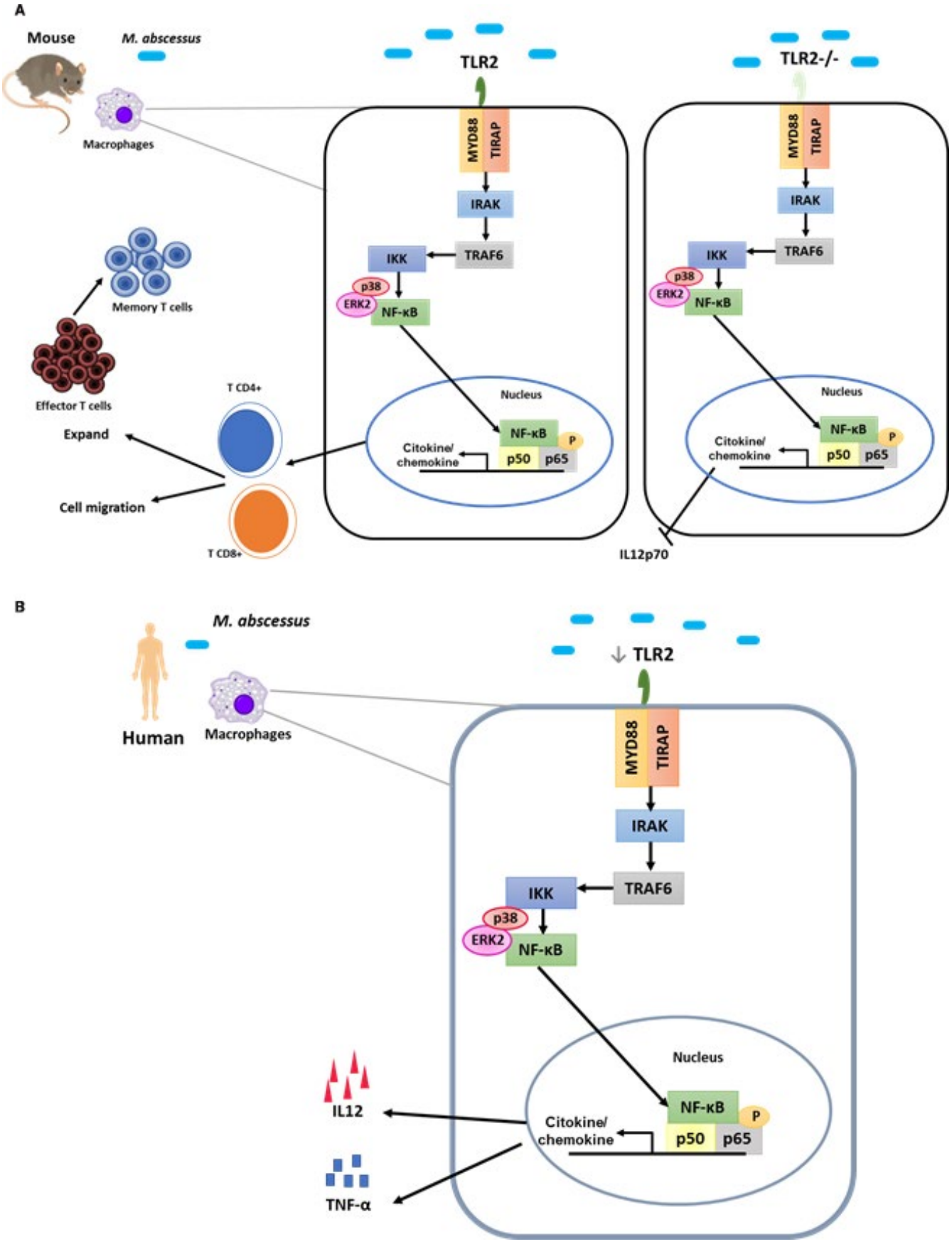

FIGURE 4 A. The innate immune response of an animal model against infection by *M abscessus*. B. Diagram of the innate immune response in humans against *M abscessus* infection

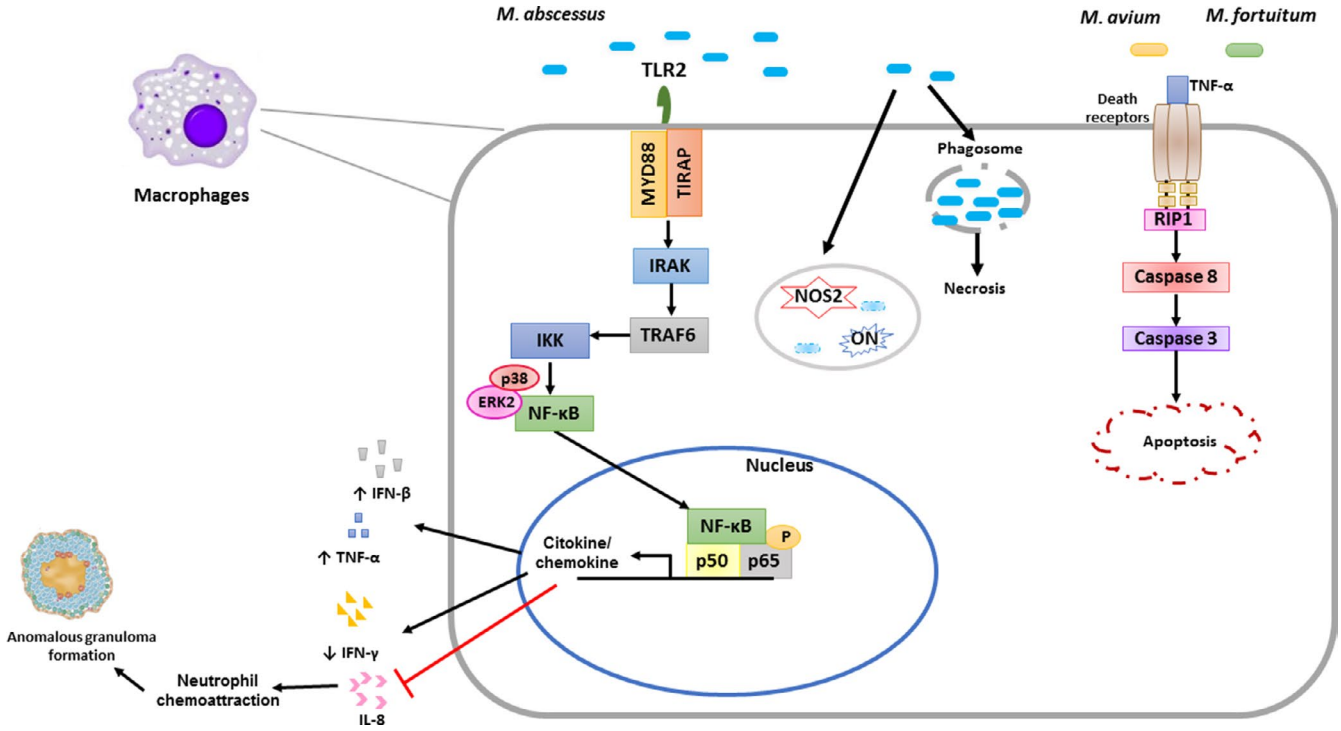

FIGURE 5 Pathophysiological mechanisms between *M tuberculosis* and NTM

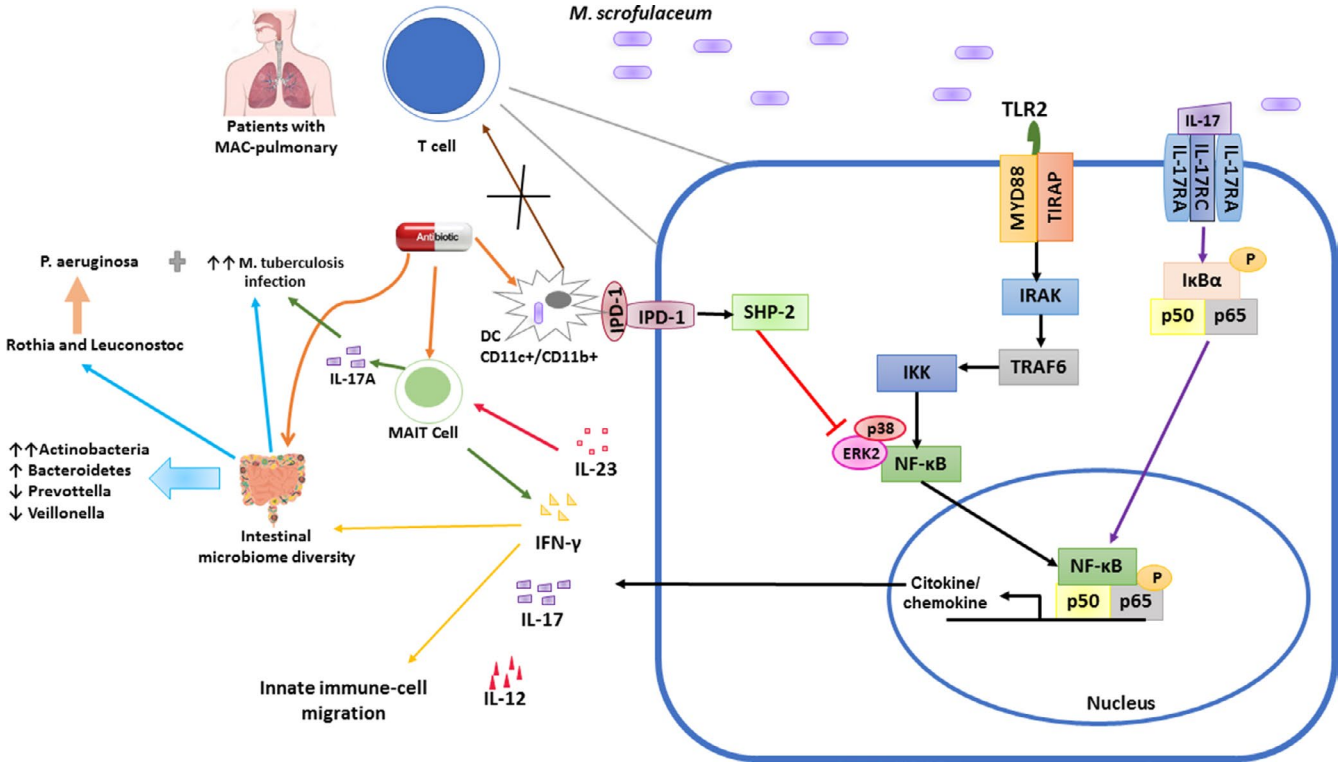

FIGURE 6 Role of intestinal microbiome diversity in the immune response to *Mycobacterium* infections

nutritionally supplement *Pseudomonas aeruginosa*, which is a frequently reported companion of *M tuberculosis*[60] (Figure 6).

In addition to ciliary variants, alterations in the expression of IL-12 receptor A (IL-2RA), IL-12RA-IFN-γ autoantibodies, have been associated with acquired susceptibility to NTM

infections. The increasing number of recent NTM infection reports and undiagnosed cases[61] have indicated that we could be looking at the tip of the iceberg. These is particularly true if we consider most of disseminated NTM occurring in subjects without obvious immunodeficiency show however, INF γ auto antibodies. Whenever Noc 2 protein of *Aspergillus* epitope (a.a 121-131) is recognized, IFN-γ receptor activation (IFN-γR)- is shut with direct consequences over innate immunity functioning activation.[62]

Disease is primarily reported in women. The current profile for high-risk, to date, includes several factors that increase the risk of more severe inflammatory status and associated autoimmunity among women, compared with men. The activation of dormant copies of forkhead box P3 (FOX P3) and other immune genes encoded on the X chromosome may hamper immunoregulatory responses.[63] In addition, increased levels of TLR7, INF-α and INF-β in females might be on the way to exhaustion. Furthermore, the microgenderome, reduced levels of short-chain fatty acids (SCFAs),[64] and low levels of acetate in a low IL-12 environment may cause autoreactive B cell and autoreactive T cell expansion.[65]

Future research should examine whether IFN-γ autoantibodies are selected by the same or by different mechanisms involved in the development of diabetes mellitus 1 or rheumatoid arthritis. The involvement of microbiota remains unclear, especially *Prevottella copri*, which has been found to be significantly enriched in subjects with an increased risk of rheumatoid arthritis[66]; however, an association between microbiota populations and active disease remains inconsistent.[67]

From a clinical perspective, subjects that suffer from T cell deficiencies and cytokine dysregulation[68,69] may require additional anti-infective precautions, such as the monitoring of water quality in hospitals. Protocols designed to address at-risk populations should be addressed and established.[70]

Sensitive diagnostic methods that are capable of segregating virulent NTMs from non-virulent species, based on heterologous protein sequences, and the identification of NTMs responsible for the synthesis of lipids that regulate immune interactions are urgently necessary.[71,72] Overall, the microbiota metabolites appear to be the most influential and easily modifiable factor that may be used to alter susceptibility. An in-depth study examining these contributions is of the uppermost priority.

ACKNOWLEDGEMENTS

Marisa Cruz-Aguilar is the recipient of a DGAPA-UNAM post-doctoral fellowship. Grant funded by DGAPA-PAPIIT, UNAM IT202020.

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How to cite this article: Cruz-Aguilar M, Castillo-Rodal AI, Arredondo-Hernández R, López-Vidal Y. Non-tuberculous mycobacteria immunopathogenesis: Closer than they appear. a prime of innate immunity trade-off and NTM ways into virulence. *Scand J Immunol*. 2021;94:e13035. https://doi.org/10.1111/sji.13035