ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Tuberculosis immunology: a narrative literature review

Imunologia da tuberculose: uma revisão narrativa da literatura

Ana Cristina Favre Paes Barreto Alves[1], Alex Isidoro Ferreira Prado[2], Iukary Takenami[3]

ABSTRACT

The immune response developed by the host against *Mycobacterium tuberculosis* is considered a complex and multifaceted nature. This host-bacillus interaction, which in most cases results in an asymptomatic latent infection that may or may not evolve to the development of active pulmonary tuberculosis (TB). The present study aimed to update and summarize the current scientific knowledge regarding the immunological mechanisms associated with infection and the development of active disease. This is a narrative review, based on scientific articles indexed in the PubMed/MEDLINE and SciELO databases over the last 20 years. In recent decades, the characterization of Tγδ lymphocytes, MAIT, iNKT and CD1-restricted T cells has provided a better understanding of the role of innate immunity in bacilli infection. The migration of T CD4+ lymphocytes that produce IFN-γ, TNF-α and other soluble molecules, promotes the recruitment and formation of the granuloma, a structure that benefits both the host and the bacillus. Eventually, an imbalance in this complex interaction network results in an exacerbated inflammatory response that contributes to the development of a necrotic granuloma. Finally, exhaustion of the local immune response due to continuous exposure to the bacillus, associated with the anti-inflammatory profile of Th2 lymphocytes and Treg lymphocytes, favor functional inactivation and, consequently, the development of active disease. The immune response is crucial for the development of *M. tuberculosis* infection. Therefore, studies that enable a greater understanding of the host-bacillus interaction may enable the development of new diagnostic methods, therapeutic strategies and, above all, advances in the development of immunobiologicals.

Keywords: Tuberculosis, *Mycobacterium tuberculosis*, immunity, granuloma.

RESUMO

A resposta imune desenvolvida pelo hospedeiro contra o *Mycobacterium tuberculosis* é considerada de natureza complexa e multifacetada. Esta interação bacilo-hospedeiro resulta, na maioria das vezes, em uma infecção latente assintomática, podendo ou não evoluir para a forma ativa da tuberculose (TB). O presente estudo objetivou atualizar e sumarizar o conhecimento científico acerca dos mecanismos imunológicos associados à infecção e sua progressão para a TB ativa. Trata-se de uma revisão narrativa, realizada a partir do levantamento bibliográfico de artigos científicos indexados nas bases de dados PubMed/MEDLINE e SciELO, nos últimos 20 anos. Nas últimas décadas, a caracterização de linfócitos Tγδ, MAIT, iNKT e outra células T CD1 restritas proporcionaram um maior entendimento do papel da imunidade inata na infecção pelo bacilo. A migração de linfócitos T CD4+ produtores de IFN-γ, TNF-α e de outras moléculas solúveis, promove o recrutamento e formação do granuloma, estrutura que beneficia tanto o hospedeiro quanto o bacilo. Eventualmente, um desequilíbrio nesta complexa rede de interação, resulta em uma resposta inflamatória exacerbada que contribui para o desenvolvimento de um granuloma necrótico. Por fim, a exaustão da resposta imune local frente à contínua exposição ao bacilo, associada ao perfil anti-inflamatório dos linfócitos Th2 e linfócitos Treg, favorecem a inativação funcional e, consequentemente, o desenvolvimento da doença ativa. A resposta imunológica é crucial para o desenvolvimento da infecção por *M. tuberculosis*. Portanto, estudos que possibilitem uma maior compreensão sobre a interação bacilo-hospedeiro podem viabilizar o desenvolvimento de novos métodos diagnósticos, estratégias terapêuticas e, sobretudo, avanços no desenvolvimento de imunobiológicos.

Descritores: Tuberculose, *Mycobacterium tuberculosis*, imunidade, granuloma.

1. Universidade Federal do Vale do São Francisco, Graduation in Medicine - Paulo Afonso, BA, Brazil.
2. Universidade de São Paulo, Hospital das Clínicas da Faculdade de Medicina (HCFMUSP). Centro de Doenças Raras e da Imunidade do Hospital 9 de Julho - São Paulo, SP, Brazil.
3. Universidade Federal do Vale do São Francisco, Laboratório de Estudos Aplicados à Saúde - Paulo Afonso, BA, Brazil.

Submitted: 01/14/2022, accepted: 04/24/2022.

Arq Asma Alerg Imunol. 2022;6(2):239-50.

http://dx.doi.org/10.5935/2526-5393.20220024

Introduction

Tuberculosis (TB) is a chronic infectious disease caused by the bacillus *Mycobacterium tuberculosis* that preferentially affects the lung. Known sequences of the mycobacterial genome have already been identified in Egyptian mummies, proving the existence of the disease in ancient civilizations.[1] Although TB represents an ancient disease, at the present time, it continues to be a serious public health problem in Brazil and in the world, especially after the reallocation of human and financial resources for TB control to face the health crisis caused by the coronavirus disease 2019 (COVID-19).[2]

In 2020, tuberculosis attacked around 9.9 million individuals worldwide and was responsible for just over 1.5 million deaths, What represents a variation of 7,5% more compared to deaths recorded in 2019, previous year to the pandemic from COVID-19.[2,3] Still in the year 2020, Brazil registered approximately 67.2 thousand TB cases and 4.5 thousand deaths,[4] being considered the country with the highest number of absolute cases in the Americas and one of the 30 countries with the highest disease burden.[3] Such data reinforce the necessity to restructure public policies in order to allow more effective strategic planning in the fight against TB in the midst of the COVID-19 pandemic.

The natural history of the disease is closely related to biopsychosocial determinants, host immunogenetics and bacillus virulence.[5,6] Factors that promote an intense and complex bacillus-host relationship and that can culminate in the development of three clinical outcomes: (1) clearance and control of infection at the point of entry through an effective innate immune response, even before the adaptive immune response is initiated; (2) establishment of a latent *M. tuberculosis* infection (LTBI), or (3) development of active disease. In LTBI, *M. tuberculosis* is in a latent state (dormancy), in the lung lobes, within a tissue structure called granuloma. In these cases, the host controls but does not eliminate the bacillus, remaining asymptomatic and representing potential reservoirs of *M. tuberculosis*.[1,3] According to estimates by the World Health Organization, a quarter of the world's population is infected and at risk of developing active disease through the reactivation of these dormant bacilli.[3]

Given this perspective, several questions emerge from this discussion in order to clarify the phenomena involved in TB immunology. What initial events allow infection control? Why are some people infected and others not, even when they are equally exposed to the bacillus? Is the bacillus capable of modulating the host response? What factors contribute to the establishment of LTBI and progression to active disease? Thus, considering the need to promote the continuing education of health professionals with strategies for early detection of the disease and, for the improvement of public policies related to prevention and treatment, the aim of the study was to summarize current scientific knowledge in light of the immunological mechanisms already described in relation to the infection and development of active TB, emphasizing the bacillus-host interaction.

Methodology

A descriptive narrative review was carried out with a qualitative approach, with the objective of knowing the "state of the art" of the immunological aspects of TB, but without the need to establish a replicable methodology at the level of data reproduction. Although this type of review does not use explicit and systematic methods, it plays a fundamental role in continuing education and updating knowledge on the proposed theme.[7]

Scientific articles indexed in the databases at the National Library of Medicine/ Medical Literature Analysis and Retrieval System Online (PubMed/ MEDLINE) and Scientific Electronic Library Online (SciELO) were retrieved during October and November 2021 using the following health science descriptors (DeCS): "tuberculosis", "*Mycobacterium tuberculosis* infection", "immunity", "immune response" and "granuloma" combined using the Boolean operator AND. Subsequently, upon need for theoretical complementation, gray literature sources and the manual search in reference lists of the selected articles were also consulted.

As an inclusion criterion, articles published in English or Portuguese were used, available in full, that addressed the proposed theme in the format of original articles and/or reviews, having the last 20 years as a reference period. The exclusion criteria adopted were: theses, monographs, dissertations and/or letters to the editor. Finally, the articles were critically reviewed and selected according to their degree of relevance in relation to the object of study of this review. Then the data were systematized into the following categories: "From exposure to infection", "Contributions of innate immunity: new and old paradigms", "Modulation of

acquired immunity and granuloma formation – a host defense?", "What to expect of humoral immunity?", and finally, "Development of active disease: regulatory mechanisms and tissue damage".

Results and discussion

From exposure to infection

The transmission of *M. tuberculosis* occurs from person to person mainly through contaminated droplets, known as "Flügge droplets", which are eliminated through the nose or mouth when a bacilliferous patient talks, sneezes or coughs. These droplets quickly dry up and turn into particles minors, what remain suspended in the environment for hours and can be easily inhaled by a host susceptible. In turn, these microparticles, also known as "core Wells", contain one to two bacilli that are able to reach distant segments of the bronchial tree, mainly the lower lobes of the lungs, where they multiply and cause the so-called primary TB or primary infection.[8-10]

Although transmission of the bacillus is classically associated with the production of infectious aerosols after coughing, a recent study showed that "tidal breathing" eliminates more bacilli per particle than coughing itself.[11] Similarly, it was possible to identify the presence of *M. tuberculosis* using the polymerase chain reaction technique in aerosols released by patients who did not report cough.[12] Taken together, the results suggest that transmission without coughing is possible in pulmonary TB and that, therefore, other signs and symptoms should be considered in the individualized diagnostic investigation.

Once exposed to the bacillus, the course of infection is variable and directly associated with environmental conditions (ventilation and lighting), host immunogenetics, coexisting illnesses, nutritional status, virulence of the infecting strain, among others.[5,13] In this context, it is plausible to consider that not all microparticles that reach the pulmonary alveoli result in a sustained infection. The multiple strategies of the innate immune response could act in the clearance of an incipient *M. tuberculosis* infection. Furthermore, there is evidence that such mechanisms can be enhanced through repeated exposure or an unrelated stimulus (cross-protection),[14-15] a phenomenon known as "trained immunity" that could explain the initial clearance and the absence of infection even after exposure to the bacillus.

The first line of defense of the host understands the lymphoid tissues associated with the mucosal surface of the respiratory tract. Mucosal epithelial cells play a crucial role in protecting against *M. tuberculosis*, as they produce many types of antimicrobial substances and act as physical barriers that limit the entry of the bacillus in the alveolar space. Eventually, in a second moment, alveolar macrophages play an important role in the recognition, phagocytosis and release of pro-inflammatory cytokines that result in the elimination of *M. tuberculosis*.[14,16,17]

Although there is not enough scientific evidence, the effectiveness of these mechanisms could be associated with the reason why some individuals are exposed to the bacillus, but do not show any evidence of immunological sensitization by the tuberculin skin test (TST) and/or by the interferon-gamma release assays (IGRAs)[15] (Figure 1A). Although further studies are needed to better characterize the host peculiarities associated with the resistance to *M. tuberculosis*, there are no study models capable of discerning initial clearance from non-exposure, since a negative TST or IGRA result may reflect either situation.

Contributions of innate immunity: new and old paradigms

In 10 to 30% of cases, immunity against *M. tuberculosis* is insufficient in completely sterilizing the bacillus and therefore requires the host to develop a chronic granulomatous inflammatory response (Figure 1B). Thus, in the early stage of infection, alveolar macrophages, of the M1 type, in reference to the classical activation pathway, phagocytize the bacillus by means of pattern recognition receptors (PRR) that bind to evolutionarily conserved structures called pathogen-associated molecular patterns (PAMP)[16,18].

The most studied PRRs in *M. tuberculosis* infection correspond to Toll-like receptors (TLR). The bacillusis initially recognized by TLR4, TLR9 and the heterodimers TLR2/1 and TLR2/6, which interact with the adapter protein myeloid differentiation factor 88 (MyD88) it's the domain of the toll-interleukin 1 receptor (TIR) containing the adapter protein (TIRAP), capable of activating macrophages and dendritic cells (DC). Furthermore, TLRs play an integral role in activating pro-inflammatory cytokine signaling pathways and other inflammatory mediators, leads gone by activation of transcription factors such as nuclear factor kappa B (NF-κB).[10,16,19,20] The observation of polymorphism of TLR genes has been associated with susceptibility to

TB,[21] demonstrating that these receptors play a role in regulating the expression of inflammatory cytokines produced by these phagocytic cells.

Although TLRs represent the main receptors in the initial recognition of *M. tuberculosis*, other type-domain of ligand oligomerization nucleotide (NLR), C-type lectins, receptors scavenger, among others, are involved in the recognition of different mycobacterial ligands. Furthermore, in addition to phagocytosis, the receptors are responsible for activating other cellular mechanisms, such as autophagy, apoptosis and pyroptosis/inflammasome assembly, contributing to the modulation of the innate immune response during *M. tuberculosis* infection.[14,20,22,23]

These early mechanisms of phagocytosis allow the elimination of the bacillus, through the action of lysosomal enzymes and formation of free radicals within the phagolysosomes. However, virulent strains of *M. tuberculosis* are sometimes able to evade host defense and remain viable within the lysosomes of macrophages and/or DCs. This is due to escape mechanisms that, although poorly understood, are related to: (1) inhibition of the production of cytokines such as IL-12 and IFN-γ by the 6kDa primarily secreted antigenic target, from the English *early secreted antigenic target-6kDa* (ESAT-6); (2) inhibition of phagosome fusion-lysosome and eventually escape of *M. tuberculosis* from the phagosomes of macrophages and/or DC into the cytoplasm; (3) inhibition of apoptosis of infected macrophages through increased production of IL-10 and reduced secretion of TNF-α.[16,24,25]

The study of the so-called inborn errors of immunity (IEI) reinforces what is known about the importance of the cytokines described above. Patients with the Mendelian susceptibility to mycobacterial disease (MSMD) have defects in the regulatory pathways of the IL-12/IFN-γ axis and their receptors, culminating in an infectious predisposition to intracellular pathogens. The most common defect is IL-12Rb1, which affects an average of 60% of patients diagnosed with MSMD.[26]

The bacilli that survive the host's primary phagocytic defenses are able to multiply exponentially within these macrophages and/or DC, inducing the production of a variety of chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL10) and cytokines (IL- 1β, IL-6, TNF-α, IL-12, IL-23, IL-17, IFN-γ) capable of recruiting and activating different populations of leukocytes to the infectious site.[27]

CXCL8 (IL-8) is anti-apoptotic and pro-angiogenic, and in tissues infected with *M. tuberculosis*, he can have additional immunological effects on chemotaxis. This is, is associated with the formation of tuberculous granuloma, since this chemokine acts through chemotaxis in the recruitment of neutrophils and death of the bacillus by macrophages.[28] Similarly, CCL2 or monocyte chemotactic protein-1 (MCP-1), CCL3 or macrophage inflammatory protein 1 alpha (MIP-1a), CCL5 or normally expressed and secreted T cells (RANTES), and CXCL10 or protein 10 induced by interferon-gamma (IP-10), are also chemokines that play an important role in chemotaxis, activation of monocytes and T lymphocytes and, consequently, granuloma formation.[10,14,16,29] Gene expression studies have shown that after infection by the bacillus, monocytes up regulate the transcription of these chemokines,[29] suggesting a potential role in prospecting biomarkers for infection.

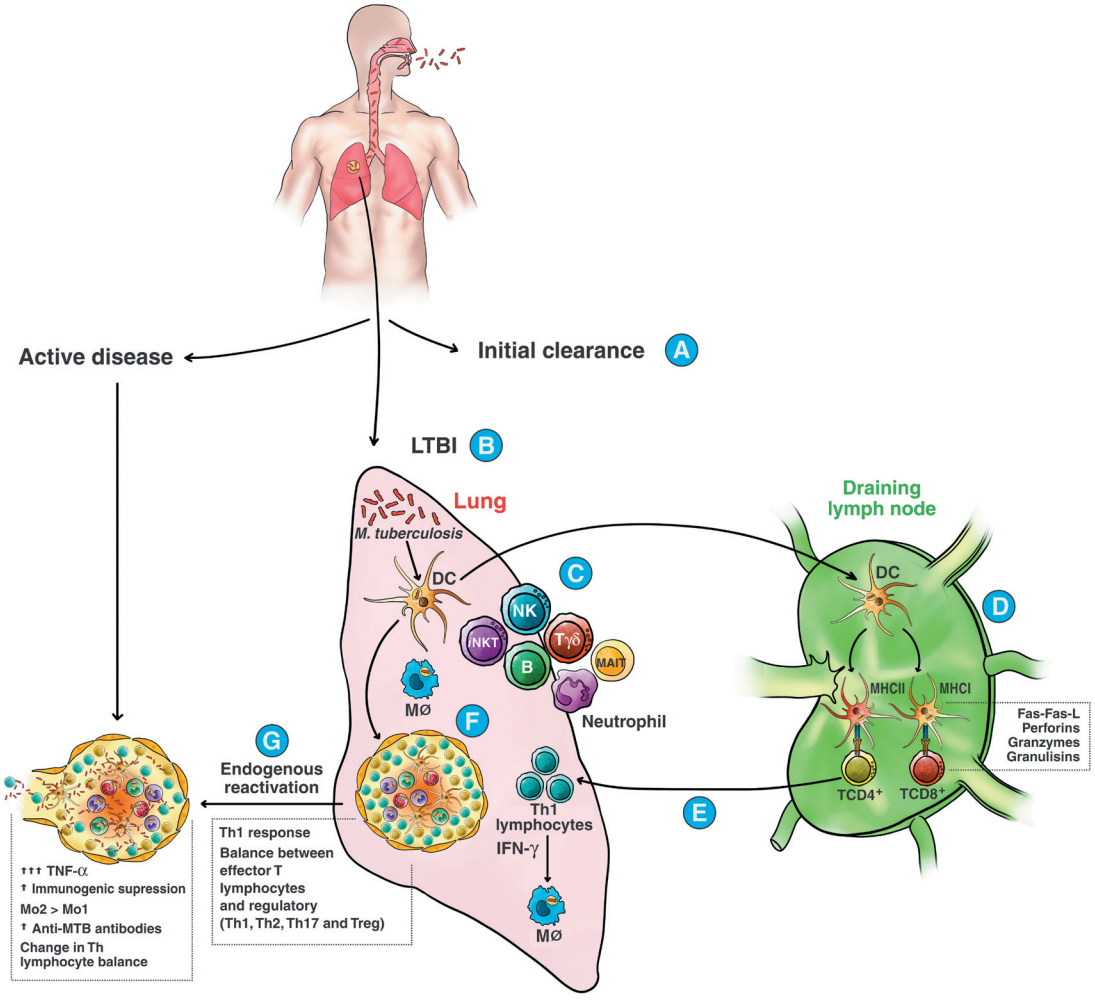
The IL-1β, together with TNF-α, are cytokines that during the inflammatory process increase the expression of endothelial adhesion molecules, promoting the aggregation of other inflammatory cells to the activated endothelium. Furthermore, they activate macrophages and/or DC, helping them to control mycobacterial replication and directly inhibit the intracellular growth of *M. tuberculosis*.[10,14,30] The IL-12p80 subunit increases the IFN-γ induction-in natural killer (NK) cells and the expansion of T lymphocytes $CD4^+$ helper 1 (Th1) antigen-specific, in addition to maintaining the activation and proliferation of lymphocytes, which induces a predominantly pro-inflammatory cellular response.[10,25] IL-6 is also a pro-inflammatory cytokine that acts by negatively regulating the p38 and JNK pathways involved in the autophagy process and contributes to the generation of T lymphocytes. $CD4^+$ helper 17 (Th17) in inflammatory conditions, regulating and promoting the balance between Th17 and $CD4^+CD25^+FoxP3^+$ regulatory T lymphocytes (Treg).[10,14,31]

There are interesting speculations about patients with autoinflammatory syndromes such as Familial Mediterranean Fever (FMF) that corroborate the importance of inflammatory cytokines in the pathogenesis of TB. Studies carried out by some groups in Turkey hypothesize that an evolutionary advantage in these patients would make them less susceptible to the development of infection by the bacillus. This would be explained, at least in part, by the exaggerated chronic inflammatory process with the release of pro-inflammatory cytokines such

as IL-1ß, which would probably be responsible for destroying intracellular pathogens by a process known as pyroptosis by activating inflammasome pathways.[32]

In addition to these cytokines and chemokines, NK cells also stand out through their cytolytic capacity. Although the NKs belong the innate immunity, its mechanisms are similar to those used by $CD8^+$ T lymphocytes, also called cytotoxic T lymphocytes (CTL). However, unlike $CD8^+$ T lymphocytes, they do not have the T lymphocyte receptor (TCRαβ) conventional method for recognizing major histocompatibility molecule (MHC) class I-associated antigens, therefore, they are not MHC-restricted.[16,20] Additionally, NK cells have been linked to an important source of IFN-γ and may also promote the proliferation of Tγδ lymphocytes, producing TNF-α, GM-CSF and IL-12.[20,33]

New lines of evidence suggest that unconventional T lymphocytes, such as those associated with mucosal invariant T cells (MAIT), Tγδ lymphocytes, invariant natural killer T cells (iNKT) and other CD1-restricted T cells are also involved in host defense against the bacillus[14,20,30] (Figure 1C). Unlike NK



B = B lymphocytes, DC = dendritic cells, LTBI = latent tuberculosis infection, iNKT = invariant natural killer T cells (iNKT), MAIT = mucosal invariant T cells (MAIT), MHCI = major histocompatibility complex class I, MHCII = major class II histocompatibility complex, MØ = macrophages, NK = natural killer, Tγδ = gamma delta T cells.

Figure 1
Schematic representation of immunological aspects associated with *Mycobacterium tuberculosis* infection and its outcomes

cells, the effector mechanism of iNKT and other CD1-restricted T cells is dependent on the lipid antigen recognition pathway, and glycolipids presented by the CD1d and CD1a/CD1b/ or CD1c molecule, respectively. Thus, *M. tuberculosis* can be recognized by both iNKT and CD1-restricted T cells.[34] Since the bacillus cell wall is rich and has a wide variety of lipids, it is possible to hypothesize that these cells are essential in the control of the bacillus, because they respond quickly to mycobacteria in the initial stage of infection.

MAIT cells predominantly express the CD8 coreceptor ($CD8^+$) and also respond quickly and effectively to *M. tuberculosis*, even before the classic T lymphocyte response is established.[14] Another subgroup of lymphocytes that also have a TCR distinct from the classic receptors present on T lymphocytes are Tγδ lymphocytes, able to recognize small organic phosphate antigens and alkylamides. Furthermore, they are the main source of IL-17 in the lung during *M. tuberculosis* infection.[30] Altogether, although studies indicate that these unconventional T cells (MAIT, Tγδ lymphocytes, iNKT and other restricted CD1 T cells), may have a promising role in the pathogenesis of TB, the exact function and/or mechanisms of activation of these by the host during the infectious process have not yet been fully clarified and require more detailed studies. On the other hand, these cells have a possible therapeutic potential to be explored, according to their role in the immunomodulation of TB.

Another strategy of innate immunity evidenced in TB refers to the ability of neutrophils activated by *M. tuberculosis* to form complex extracellular networks composed of DNA and several other biologically active cytosolic and granular proteins. This mechanism, which stands for neutrophil extracellular traps (NETs), assists the host in the innate defense against the bacillus and plays an important role in the interaction between neutrophils and macrophages in the initial phase of *M. tuberculosis* infection. However, its formation is dependent on factors such as phagocytosis, production of reactive oxygen species and significant secretion of cytokines such as TNF-α, IL-6, IL-1ß and IL-10.[35] Together, the identification and discoveries of these "new" subsets of cells and/or of the host's effector mechanisms have raised interest and new perspectives in the study of innate immunity in the last 10 years, until then less explored than acquired immunity.

Modulation of acquired immunity and granuloma formation – a host defense?

Since the innate immune response is not capable enough to destroy *M. tuberculosis*, other cells such as monocytes and lymphocytes, are targeted to the site of infection for the development of a more effective response and granuloma formation. Peptides from the proteolysis of *M. tuberculosis*, present in the apoptotic vesicles of M1 and DC macrophages, called professional antigen-presenting cells (APC), bind to the class II MHC molecule, forming the peptide-MHC II complex on the surface of the APC and migrate towards the draining regional lymph node where they present to naïve T lymphocytes, also known as T helper type 0 (Th0) lymphocytes (Figure 1D).[19]

Recognition of the peptide-MHC II complex associated with costimulatory signals given by APC induces the expression of transcription factors, such as T-bet and RORgt, which promote clonal expansion and differentiation into Th1 and Th17 effector lymphocytes, respectively. Thus, $CD4^+$ T lymphocytes, especially the Th1 and Th17 subpopulations, represent the main effector populations that migrate to the primary site of infection, amplifying the immune response and mediating protection during *M. tuberculosis* infection.[14,16,31]

The immune response mediated by *M. tuberculosis*-specific Th1 lymphocytes is associated with the production of pro-inflammatory cytokines, such as IL-1ß, IL-2, IL-12, TNF-α and especially IFN-γ (Figure 1E). In turn, Th17 lymphocytes produce IL-17 which has an initial role in the secretion of IFN-γ, which stimulates the recruitment of Th1 lymphocytes.[14,16,31] Furthermore, in an animal model, Th17 lymphocyte responses precede a strong Th1 response in the lungs, suggesting that these cells are important in the recruitment of Th1 lymphocytes to the infectious site and subsequent granuloma formation.[27]

The IFN-γ is classically described in the literature as the key cytokine in infection control. However, studies in animal and human models indicate that the production of this cytokine alone is not sufficient to provide protection to the host.[10,19,30,36] Cytokine is well known for its ability to activate macrophages, stimulate phagocytosis, phagosome maturation, production of reactive oxygen and nitrogen intermediates, and antigen presentation, seeking to eliminate or restrict intracellular mycobacterial multiplication.[31] Not only $CD4^+$ T lymphocytes of the Th1 profile, but also $CD8^+$ T

lymphocytes and NK cells produce IFN-γ in response to IL-12 produced by APC.[14]

The $CD8^+$ T lymphocyte-mediated response is normally of lower magnitude than those of $CD4^+$ T lymphocytes. Activation of CTL occurs via peptide-MHC I through the mechanism of cross-presentation by DC after absorption of apoptotic vesicles, originating from infected macrophages and neutrophils and containing bacillus antigens. The action of these cells can occur in three different ways: (1) exocytosis of cytotoxic granules containing perforins, granulysin and granzymes that cause the lysis and apoptosis of macrophages and infected DCs; (2) interaction of surface proteins FasL and Fas that result in the death of the target cell infected with *M. tuberculosis*, and (3) production of IFN-γ and TNF-α by these cells, amplifying the microbicidal effects.[8,16,30,36]

In tissue, cell-cell interaction helps contain/isolate the infection through the formation of barrier physical and immune system known as granuloma, resulting from chronic stimulation of cells/cytokines (delayed hypersensitivity) and the inability of the immune system to destroy the bacillus. The architecture of the granuloma is characterized by masses of tissue of the chronically inflamed, formed by bacilli alive or dead, surrounded by macrophages and epithelioid cells that become giant and multinucleated, surrounded by a halo of $CD4^+$ and $CD8^+$ T lymphocytes, plasma cells and fibroblasts (Figure 1F).[37] Furthermore, the role of pro-inflammatory cytokines and chemokines in granuloma formation and stability is highlighted, especially TNF-α.

It is already known that TNF-α plays a critical role in the host response to infection, as it influences the migration of leukocytes to until the infectious focus, promoting the formation of the granuloma capable of containing the multiplication and preventing the dissemination of the bacillus. Although other cytokines and chemokines influence leukocyte recruitment, TNF-α seems to have a major role in maintaining the structural integrity of the granuloma. These findings were later validated by the observation of endogenous reactivation in LTBI patients who used TNF-α inhibitors in the treatment of immune-mediated diseases such as rheumatoid arthritis, Crohn's disease, and immune dysregulated IEI such as adenosine deaminase deficiency type 2 (DADA2).[38-40]

Similarly, people living with HIV (PLHIV) with a $CD4^+$ T lymphocyte count of less than 350 cells/mm^3 are of equal importance, as the risk of TB reactivation among those with LTBI is considerably high. HIV has a tropism for $CD4^+$ T lymphocytes, therefore, the intense viral replication compromises cellular immunity and the organizational structure of the granuloma in the host. This scenario of TB/HIV co-infection not only impacts the reactivation and development of active disease among those with LTBI, but also increases the mortality and lethality rate of TB, characteristics that encourage timely HIV testing in TB patients and vice versa.[8,14,30] In addition, it is worth mentioning that polymorphisms in the CARD8 gene – responsible for controlling inflammation and apoptotic pathways – in PLHIV exponentially increase the chance of active infection due to uncontrolled inflammasome and exaggerated cell death.[41] Therefore, the ability of the host's immune system to contain the bacillus involves a complex network of genes and different subpopulations of lymphocytes, cytokines, among other inflammatory mediators, responsible for the formation and maintenance of the granuloma, especially $CD4^+$ T lymphocytes and TNF-α.

Although granuloma formation is traditionally considered necessary to limit infection, the mechanisms that regulate cell dynamics, behavior and maintenance have only been understood with the latest advances in the use of microscopy intravital, which has allowed a more accurate and detailed analysis of granuloma formation. New findings suggest that mycobacteria benefit from tissue structure formation. Using the experimental model zebrafish, Davis and Ramakrishnan[42] demonstrated that in infection with *M. marinum* (and presumably, *M. tuberculosis*), macrophages are highly mobile and that the initial granuloma benefits the bacillus as it allows the recruitment of uninfected macrophages to the site of infection, providing an environment constant of renewable cells susceptible to the entry of the bacillus. More recently, advances in the creation of in vitro granuloma models have also provided the use of this technique in the study of granuloma biology.[43] Although incipient, the experimental model for study is feasible and should be used from the perspective of a translational approach correlating in vivo experimentation with clinical studies.

Over the years, this complex becomes stable, with areas of fibrosis or even calcification (healing) and, although the infection is controlled, the bacilli can remain viable inside these lesions for many years (primary tuberculosis). In these cases, the production of transforming growth factor beta (TGF-β), which actively participates in the induction of fibrosis.[37] The formation of the granuloma is therefore known as a

primary nodule or Ghon's nodule, usually located in the middle and lower lobes of the lungs, occurring most often in children. In turn, its association with a lymph node is commonly visualized through chest radiography and is called Ghon's complex, these characteristics result in the LTBI condition that represents a "successful" balance in the bacillus-host interaction, with blockage bacillary multiplication and lesion expansion.[8,37,44]

That said, LTBI is defined solely through evidence of immunological sensitization. In TST, effector and memory cells, previously sensitized, migrate to the inoculation site of the purified protein derivative (PPD) and develop a strong late hypersensitivity response, with skin induration equal to or greater than 5 mm. However, the skin reaction is only visible after 48 to 72 hours of intradermal application of PPD. In turn, in the most recent versions of IGRA, the whole blood of the host and, consequently, the cells previously exposed to *M. tuberculosis*, are cultured with a pool of antigens (ESAT.6, CPF-10 and TB7.7) for a period of 24 hours. Consequently, they induce the production of IFN-γ, a cytokine that is measured by an enzyme-linked immunosorbent assay and that is present at levels equal to or greater than 0.35 IU/mL. In both cases, immunological sensitization is observed approximately two to three weeks after exposure to a bacilliferous source, at which point the test results will be positive.[45] Although the tests have high sensitivity and specificity for identifying exposure to *M. tuberculosis*, none of them distinguishes latent from active infection.

What to expect from humoral immunity?

Although immunity against TB is primarily mediated by a cellular response, the role of the humoral response through the participation of antibody-producing B lymphocytes anti-*M. tuberculosis* is still unclear.[16,19,36] Numerous studies have demonstrated high serum levels of antibodies in response to structures present in *M. tuberculosis* in individuals with the latent form and, more often, in patients with active disease, so that higher antibody titers correlate with active disease and/or severity of illness.[46,47] However, patients with active disease and with high levels of anti-*M. tuberculosis* show absence of specific cellular immune response (anergy) to PPD,[48,49] as well as in the more advanced clinical forms of leprosy.

It is known that antibodies, when coating the *M. tuberculosis*, can promote (1) the opsonization process through phagocytic cells that have receptors for the Fc portions of antibodies, (2) antibody-dependent cellular cytotoxicity (ADCC) through NK cells that also recognize the Fc portion of antibodies, (3) activation of the complement system, (4) immune regulation in inflammation, and (5) elimination and neutralization of bacilli in the extracellular environment.[50] However, as is the case with many intracellular bacteria, *M. tuberculosis* is able to evade antibody-mediated antimycobacterial effects as they are able to survive within alveolar macrophages and/or DC.

Although little is said about the role of B lymphocytes in TB, some studies have evaluated the subpopulations of these cells revealing interesting results. The presence of atypical B lymphocytes ($CD21^{-}CD27^{-}$ or $CD27^{-}IgD^{-}$), in addition to activated lymphocytes ($CD27^{+}IgD^{-}$) were increased compared to healthy controls. However, they showed reduced proliferation associated with deficient production of cytokines and antibodies. These functions normalized after adequate treatment with anti tuberculostatic drugs. Other studies corroborated the above finding showing that mycobacteria suppress or deplete the effector functions of B lymphocytes. In turn, memory lymphocytes ($CD19^{+}IgM^{+/-}CD27^{++}$), plasmablasts ($CD19^{+}IgM^{+/-}CD138^{+}CD27^{+}$), memory plasmablasts ($CD19^{+}IgM^{+/-}CD138^{+}CD27^{++}$), as well as circulating marginal zone lymphocytes ($CD19^{+}CD27^{-}CD23^{-}$) were significantly increased in patients diagnosed with TB compared to those already treated, presenting as a potential biomarker of response to treatment.[51]

Another important subtype, recently described in the literature of B lymphocytes, refers to regulatory B lymphocytes ($CD19^{+}CD1d^{+}CD5^{+}$), which would be increased in active TB with cavitation and in more severe forms of the disease. Interestingly, another cellular phenotype of regulatory B lymphocytes, also known as killer B lymphocytes ($CD19^{+}CD5^{+}IgM^{+}FasL^{+}$) is increased in patients with active disease, but with much higher levels in LTBI with normalization after treatment and re-elevation after stimulation in vitro with BCG,[51] results that suggest a potential protective role in infection against mycobacteria, requiring further confirmatory studies.

However, a study published by Lu et al.[50] showed that individuals with the latent and active form of the disease have different anti-*M. tuberculosis*. Thus, individuals with LTBI exhibit a unique functional profile, selective binding to the FcγRIII isoform, and a distinct glycosylation pattern, features that appear to contribute to infection control. In light of these findings, it is possible to consider (1) high amounts

of anti-*M. tuberculosis* are not necessarily able to provide a satisfactory response, and (2) immunity against the bacillus in individuals with LTBI appears to be associated with a profile of functional antibodies, regardless of their quantity, and with the generation of regulatory B lymphocytes in these individuals.

Although the importance of antibodies is currently uncertain and may differ from host to host, the fact that antibodies have the ability to modulate and potentiate host immunity (opsonization, complement activation, inflammation, etc.) suggests that this arm of the adaptive immune system may contribute to the outcome of *M. tuberculosis* infection and therefore should not be ignored.

Development of active disease: regulatory mechanisms and tissue damage

Eventually, about 5-10% of infected individuals, that is, with LTBI, develop active disease within the first two years.[3,18] This endogenous reactivation occurs mainly in patients with some degree of immunosuppression – a condition that can lead to granuloma rupture and dissemination of viable bacilli (Figure 1G). The main risk factors and vulnerable populations established in the literature are smoking, alcoholism, illicit drug use, diabetes mellitus, malnourished children, the elderly, PLHIV, other chronic diseases and exposure to environmental mycobacteria.[3,52] In these cases, in addition to the development of active lung disease, patients are more likely to progress to severe and disseminated forms, the latter being a result of the dissemination of the bacillus, via the hematogenous, lymphohematogenous, contiguity or intracanalicular route, to other organs and tissues, such as the kidneys, skin, genitourinary system, central nervous system, bones, among others.[14,53]

Considering the multifactorial influence on the outcome of *M. tuberculosis* infection, the generalizations in the immunopathology of active TB presented here may be limited. In immunocompromised individuals and children, the absence of an effective cellular immune response facilitates the multiplication of the bacillus and promotes the development of the disease. In immunocompetent adults, the exacerbation of cellular immunity is responsible for tissue damage and dissemination of the bacillus, as can be seen in PLHIV when they present the so-called Immune Reconstitution Inflammatory Syndrome. Since the mechanisms of disease development are heterogeneous, this work aimed to focus on cases of development of active pulmonary TB in immunocompetent individuals.

That said, most of the time, reactivation occurs in the adult phase and results in an imbalance of the complex network of bacillus-host interaction, which causes a necrotic process in the central area of the granuloma, known as caseous necrosis. Necrotic lesions are similar to cheese, as they have a homogeneous, white appearance, rich in proteins and fats due to bacillary metabolism,[37] and, when they reach the blood vessels, they lead to the occurrence of sputum with hemoptoics, findings that characterize the bronchial cavitations (caves) of secondary (post-primary) TB and that symbolize the classic symptom of pulmonary TB: productive cough accompanied by hemoptoic sputum. In these cases, the formation of cavities can range from a few centimeters, especially in the posterior apical lung segments, to extensive areas. The so-called secondary TB is, therefore, a consequence of the reactivation of a primary focus or, in most cases, through a new contact with bacilliferous patients (exogenous reinfection).[44]

Although the inflammatory response mediated by Th1 lymphocytes is primarily responsible for protecting against infection with *M. tuberculosis*, it is also capable of provoking the exacerbation of a harmful inflammatory response to the host, which results in the development of active disease and the formation process of cavities. In this context, host-derived factors, such as excess TNF-α, the degranulation of phagocytic cells with the release of proteinases, nucleases and lipases, favor the liquefaction of the caseum with the formation of cavities in the centers of the granulomas and, therefore, the loss of the architecture of the lung tissue.[27] In addition, TB patients have an excessive production of cytokines such as IL-1, IL-2 and IFN-γ, associated with an increase in hepatic synthesis and in serum levels of acute phase proteins, such as C-reactive protein, erythrocyte sedimentation rate and serum amyloid A protein, characterizing a classic hyperinflammatory state.[54] Differing from these results, hospitalized TB patients show a decrease in the Th1 response, most likely due to the exhaustion of the local and/or systemic immune response. Thus, antigen-specific T lymphocytes reduce the ability to proliferate and produce inflammatory mediators. Some studies have even shown that IFN-γ levels are lower in TB patients when compared to individuals with LTBI.[55] In turn, Bertholet et al.[56] and Peresi et al.[54] also showed that throughout treatment there is an increase in IFN-γ levels, suggesting a possible restoration of

the specific immune response. These observations are supported by cases of pulmonary TB in which immunocompromised patients with advanced disease are shown to be TST-anergic.[48] Given the results, it is plausible to consider that these are not divergent data, but different stages of the disease in which the exacerbated inflammatory response, most likely, precedes the exhaustion of the immune system.

Interestingly, a study carried out by Berry et al.[57] showed that transcripts of genes induced by IFN type I, most frequently associated with viral infections, are able to discriminate active pulmonary TB from healthy individuals, patients with other chronic respiratory diseases and most individuals with LTBI. Since then, numerous studies have shown that high levels of IFN type I result in increased bacillary burden and disease exacerbation in experimental models of TB.[53,58-60]

On the other hand, cellular hypersensitivity stimulates important mechanisms in the host capable of regulating and preventing the harmful effects of inflammation, which can invariably reduce protective immunity and contribute to cellular suppression. $CD4^+$ helper 2 T lymphocytes (Th2) and/or Treg lymphocytes secrete anti-inflammatory cytokines such as IL-4, IL-10 and TGF-β, and interact directly with other cells through inhibitory molecules such as CTLA-4 and PD-1, which are present on the cell surface.[30]

More recently, studies have shown that, during the development of active disease, differentiation and polarization of M1 macrophages to the M2 profile is observed, which is directly related to the evasion of *M. tuberculosis*.[14] Normally, M1 macrophages are the main effectors of the host response against mycobacteria and produce immunostimulatory cytokines. In contrast, alternatively activated M2 phenotype macrophages have a low ability to promote antigen presentation and are induced by IL-4, IL-13, IL-10 and TGF-β, cytokines that suppress the Th1 lymphocyte response.[20] Therefore, it can be concluded that the M1 phenotype is pro-inflammatory and acts in the initial control of *M. tuberculosis* infection, while M2 can be induced through the anti-inflammatory microenvironment promoted by Th2 lymphocytes and by Treg in active disease. Finally, the quality of the immune response associated with early diagnosis and appropriate treatment can promote lesion regression with scarring and fibrosis. Otherwise, the greater the delay in therapeutic management, the greater the destructive process, making tissue repair in the affected parenchyma unfeasible.[44]

Conclusion

The immune response developed by the host directly affects the course of infection by *M. tuberculosis*. Despite considerable advances in the area, the understanding of natural resistance to the bacillus is still uncertain. Similarly, the contribution of different B-lymphocyte subpopulations and antibodies remains to be elucidated. On the other hand, latent asymptomatic infection is a model associated with the development of an innate and acquired immune response in which numerous soluble mediators (cytokines and chemokines), cells (macrophages, neutrophils, NK) and several subpopulations of conventional lymphocytes (T $CD4^+$ Th1 profile, Th17 lymphocytes, $CD8^+$ T lymphocytes) and unconventional (Tγδ lymphocytes, MAIT, iNKT and other restricted CD1 T cells) participate.

This complex bacillus-host interaction allows the formation of granuloma, a tissue structure capable of containing the multiplication and dissemination of the bacillus, often leading to scarring. Sometimes, unfavorable immunological conditions, which promote an environment of exacerbated inflammation and/or suppression of cells and soluble mediators that orchestrate the granuloma, contribute for the development of immunopathology. However, in an attempt to prevent tissue damage, $CD4^+$ T lymphocytes, Th2 profile, Treg lymphocytes and M2-type macrophages, also favor the progression of pulmonary TB, through the production of cytokines that suppress the inflammatory immune response necessary for the formation and maintenance of the granuloma.

Although different soluble mediators and cells play a key role for the host in the defense and containment of *M. tuberculosis* infection, it is still unclear which ones are more effective in preventing TB, as there are different pathways involved in triggering an immune response successful protector. Thus, further studies are necessary, since knowledge about the immunology of TB is of great importance for the development of new correlates of infection and/or disease, which can be used to build new diagnostic methods and therapeutic strategies, especially in the current era of immunobiologicals.

References

1. Donoghue HD. Insights gained from ancient biomolecules into past and present tuberculosis – a personal perspective. Int J Infect Dis. 2017;56:176-80.

2. WHO. Global Tuberculosis Report 2020 [Internet]. [Cited 2022 Jan 12]. Available from: https://apps.who.int/iris/handle/10665/336069.
3. WHO. Global Tuberculosis Report 2021 [Internet]. [Cited 2022 Jan 12]. Available from: https://apps.who.int/iris/handle/10665/346387.
4. Brasil. Ministério da Saúde. Boletim Epidemiológico Especial Tuberculose [Internet]. [Cited 2022 Jan 12]. Available from: https://www.gov.br/saude/pt-br/media/pdf/2021/marco/24/boletim-tuberculose-2021_24.03#:~:text=Em%202020%2C%20o%20Brasil%20registrou,óbitos%20por%20100%20mil%20habitantes.
5. Coelho Filho JC, Takenami I, Arruda S. Revisiting the Rich's formula: an update about granulomas in human tuberculosis. Braz J Infect Dis. 2013;17:234-8.
6. Pedrazzoli D, Boccia D, Dodd PJ, Lönnroth K, Dowdy DW, Siroka A, et al. Modelling the social and structural determinants of tuberculosis: opportunities and challenges. Int J Tuberc Lung Dis. 2017;21(9):957-64.
7. Rother ET. Revisão sistemática X revisão narrativa. Acta paul enferm. 2007;20:v-vi.
8. Mack U, Migliori GB, Sester M, Rieder HL, Ehlers S, Goletti D, et al.; C. Lange; TBNET. LTBI: latent tuberculosis infection or lasting immune responses to M. tuberculosis? A TBNET consensus statement. Eur Respir J. 2009;33(5):956-73.
9. Nardell EA. Wells Revisited: Infectious Particles vs. Quanta of Mycobacterium tuberculosis Infection – Don't Get Them Confused. Mycobact Dis. 2016;06(05).
10. Zuñiga J, Torres-García D, Santos-Mendoza T, Rodriguez-Reyna TS, Granados J, Yunis EJ. Cellular and humoral mechanisms involved in the control of tuberculosis. Clin Dev Immunol. 2012;2012:193923.
11. Dinkele R, Gessner S, McKerry A, Leonard B, Seldon R, Koch AS, et al. Capture and visualization of live Mycobacterium tuberculosis bacilli from tuberculosis patient bioaerosols. PLoS Pathog. 2021;17(2):e1009262.
12. Patterson B, Wood R. Is cough really necessary for TB transmission? Tuberculosis (Edinb). 2019;117:31-5.
13. Dubé JY, Fava VM, Schurr E, Behr MA. Underwhelming or Misunderstood? Genetic Variability of Pattern Recognition Receptors in Immune Responses and Resistance to Mycobacterium tuberculosis. Front Immunol. 2021;12:714808.
14. Ferluga J, Yasmin H, Al-Ahdal MN, Bhakta S, Kishore U. Natural and trained innate immunity against Mycobacterium tuberculosis. Immunobiology. 2020;225(3):151951.
15. Verrall AJ, Netea MG, Alisjahbana B, Hill PC, van Crevel R. Early clearance of Mycobacterium tuberculosis: a new frontier in prevention. Immunology. 2014;141(4):506-13.
16. de Martino M, Lodi L, Galli L, Chiappini E. Immune Response to Mycobacterium tuberculosis: A Narrative Review. Front Pediatr. 2019;7:350.
17. Li W, Deng G, Li M, Liu X, Wang Y. Roles of Mucosal Immunity against Mycobacterium tuberculosis Infection. Tuberc Res Treat. 2012;2012:791728.
18. Brasil. Ministério da Saúde. Manual de Recomendações para o Controle da Tuberculose no Brasil [Internet]; 2018. [Cited 2022 Jan 12]. Available from: https://bvsms.saude.gov.br/bvs/publicacoes/manual_recomendacoes_controle_tuberculose_brasil_2_ed.pdf .
19. Cooper AM. Cell-mediated immune responses in tuberculosis. Annu Rev Immunol. 2009;27:393-422.
20. Liu CH, Liu H, Ge B. Innate immunity in tuberculosis: host defense vs pathogen evasion. Cell Mol Immunol. 2017;14(12):963-75.
21. Zhou Y, Zhang M. Associations between genetic polymorphisms of TLRs and susceptibility to tuberculosis: A meta-analysis. Innate Immun. 2020;26(2):75-83.
22. Killick KE, Ní Cheallaigh C, O'Farrelly C, Hokamp K, MacHugh DE, Harris J. Receptor-mediated recognition of mycobacterial pathogens. Cell Microbiol. 2013;15(9):1484-95.
23. Lerner TR, Borel S, Gutierrez MG. The innate immune response in human tuberculosis. Cell Microbiol. 2015;17(9):1277-85.
24. Jamwal SV, Mehrotra P, Singh A, Siddiqui Z, Basu A, Rao KVS. Mycobacterial escape from macrophage phagosomes to the cytoplasm represents an alternate adaptation mechanism. Sci Rep. 2016;6:23089.
25. Moutinho ILD. Tuberculose: aspectos imunológicos na infecção e na doença. Rev méd Minas Gerais. 2011;21(1):42-8.
26. Bustamante J. Mendelian susceptibility to mycobacterial disease: recent discoveries. Hum Genet. 2020;139(6-7):993-1000.
27. Flynn JL, Chan J, Lin PL. Macrophages and control of granulomatous inflammation in tuberculosis. Mucosal Immunol. 2011;4(3):271-8.
28. O'Kane CM, Boyle JJ, Horncastle DE, Elkington PT, Friedland JS. Monocyte-Dependent Fibroblast CXCL8 Secretion Occurs in Tuberculosis and Limits Survival of Mycobacteria within Macrophages. J Immunol. 2007;178(6):3767-76.
29. Méndez-Samperio P. Expression and regulation of chemokines in mycobacterial infection. J Infect. 2008;57(5):374-84.
30. Nunes-Alves C, Booty MG, Carpenter SM, Jayaraman P, Rothchild AC, Behar SM. In search of a new paradigm for protective immunity to TB. Nat Rev Microbiol. 2014;12(4):289-99.
31. Lyadova IV, Panteleev AV. Th1 and Th17 Cells in Tuberculosis: Protection, Pathology, and Biomarkers. Mediators Inflamm. 2015;2015:854507.
32. Ozen S, Balci B, Ozkara S, Ozcan A, Yilmaz E, Besbas N, et al. Is there a heterozygote advantage for familial Mediterranean fever carriers against tuberculosis infections: speculations remain? Clin Exp Rheumatol. 2002;20(4 Suppl 26):S57-8.
33. Allen M, Bailey C, Cahatol I, Dodge L, Yim J, Kassissa C, et al. Mechanisms of Control of Mycobacterium tuberculosis by NK Cells: Role of Glutathione. Front Immunol. 2015;6:508. doi: 10.3389/fimmu.2015.00508.
34. Paquin-Proulx D, Costa PR, Terrassani Silveira CG, Marmorato MP, Cerqueira NB, Sutton MS, et al. Latent Mycobacterium tuberculosis Infection Is Associated With a Higher Frequency of Mucosal-Associated Invariant T and Invariant Natural Killer T Cells. Front Immunol. 2018;9:1394.
35. Braian C, Hogea V, Stendahl O. Mycobacterium tuberculosis - induced neutrophil extracellular traps activate human macrophages. J Innate Immun. 2013;5(6):591-602.
36. Walzl G, Ronacher K, Hanekom W, Scriba TJ, Zumla A. Immunological biomarkers of tuberculosis. Nat Rev Immunol. 2011;11(5):343-54.
37. Santos AFS dos, Lima AF de. Tuberculose pulmonar e a formação do granuloma: uma revisão de literatura. Ciências Biológicas e da Saúde UNIT. 2017;4(2):111-24.
38. Anton C, Machado FD, Ramirez JM, Bernardi RM, Palominos PE, Brenol CV, et al. Infecção latente por tuberculose em pacientes com doenças reumatológicas. J Bras Pneumol. 2019;45(2):e20190023.
39. Harris J, Keane J. How tumour necrosis factor blockers interfere with tuberculosis immunity. Clin Exp Immunol. 2010;161(1):1-9.
40. Sharma A, Naidu G, Sharma V, Jha S, Dhooria A, Dhir V, et al. Deficiency of Adenosine Deaminase 2 in Adults and Children: Experience From India. Arthritis Rheumatol. 2021;73(2):276-85.
41. Pontillo A, Carvalho MS, Kamada AJ, Moura R, Schindler HC, Duarte AJ, et al. Susceptibility to Mycobacterium tuberculosis infection in HIV-positive patients is associated with CARD8 genetic variant. J Acquir Immune Defic Syndr. 2013;63(2):147-51.
42. Davis JM, Ramakrishnan L. The role of the granuloma in expansion and dissemination of early tuberculous infection. Cell. 2009;136(1):37-49.
43. Elkington P, Lerm M, Kapoor N, Mahon R, Pienaar E, Huh D, et al. In Vitro Granuloma Models of Tuberculosis: Potential and Challenges. J Infect Dis. 2019;219(12):1858-66.
44. Silva DR, Rabahi MF, Sant'Anna CC, Silva-Junior JLRD, Capone D, Bombarda S, et al. Diagnosis of tuberculosis: a consensus statement from the Brazilian Thoracic Association. J Bras Pneumol. 2021;47(2):e20210054.

45. Machado A Jr, Emodi K, Takenami I, Finkmoore BC, Barbosa T, Carvalho J, et al. Analysis of discordance between the tuberculin skin test and the interferon-gamma release assay. Int J Tuberc Lung Dis. 2009;13(4):446-53.
46. Jacobs AJ, Mongkolsapaya J, Screaton GR, McShane H, Wilkinson RJ. Antibodies and tuberculosis. Tuberculosis (Edinb). 2016;101:102-13.
47. Takenami I, de Oliveira CC, Petrilli JD, Machado A, Riley LW, Arruda S. Serum antiphospholipid antibody levels as biomarkers for diagnosis of pulmonary tuberculosis patients. Int J Tuberc Lung Dis. 2018;22(9):1063-70.
48. Encinales L, Zuñiga J, Granados-Montiel J, Yunis M, Granados J, Almeciga I, et al. Humoral immunity in tuberculin skin test anergy and its role in high-risk persons exposed to active tuberculosis. Mol Immunol. 2010;47(5):1066-73.
49. Scriba TJ, Coussens AK, Fletcher HA. Human Immunology of Tuberculosis. Microbiol Spectr. 2017;5(1).
50. Lu LL, Chung AW, Rosebrock TR, Ghebremichael M, Yu WH, Grace PS, et al. A Functional Role for Antibodies in Tuberculosis. Cell. 2016;167(2):433-443.e14.
51. Rijnink WF, Ottenhoff THM, Joosten SA. B-Cells and Antibodies as Contributors to Effector Immune Responses in Tuberculosis. Front Immunol. 2021;12:640168.
52. Young DB, Perkins MD, Duncan K, Barry CE. Confronting the scientific obstacles to global control of tuberculosis. J Clin Invest. 2008;118(4):1255-65.
53. O'Garra A, Redford PS, McNab FW, Bloom CI, Wilkinson RJ, Berry MPR. The immune response in tuberculosis. Annu Rev Immunol. 2013;31:475-527.
54. Peresi E, Silva SMUR, Calvi SA, Marcondes-Machado J. Citocinas e proteínas de fase aguda do soro como marcadores de regressão da resposta inflamatória ao tratamento da tuberculose pulmonar. J Bras Pneumol. 2008;34:942-9.
55. Hozumi H, Tsujimura K, Yamamura Y, Seto S, Uchijima M, Nagata T, et al. Immunogenicity of dormancy-related antigens in individuals infected with Mycobacterium tuberculosis in Japan. Int J Tuberc Lung Dis. 2013;17(6):818-24.
56. Bertholet S, Horne DJ, Laughlin EM, Savlov M, Tucakovic I, Coler RN, et al. Effect of chemotherapy on whole-blood cytokine responses to Mycobacterium tuberculosis antigens in a small cohort of patients with pulmonary tuberculosis. Clin Vaccine Immunol. 2011;18(8):1378-86.
57. Berry MP, Graham CM, McNab FW, Xu Z, Bloch SA, Oni T, et al. An interferon-inducible neutrophil-driven blood transcriptional signature in human tuberculosis. Nature. 2010;466(7309):973-7.
58. Dorhoi A, Yeremeev V, Nouailles G, Weiner J 3rd, Jörg S, Heinemann E, et al. Type I IFN signaling triggers immunopathology in tuberculosis-susceptible mice by modulating lung phagocyte dynamics. Eur J Immunol. 2014;44(8):2380-93.
59. McNab FW, Ewbank J, Howes A, Moreira-Teixeira L, Martirosyan A, Ghilardi N, et al. Type I IFN induces IL-10 production in an IL-27-independent manner and blocks responsiveness to IFN-γ for production of IL-12 and bacterial killing in Mycobacterium tuberculosis-infected macrophages. J Immunol. 2014;193(7):3600-12.
60. Ottenhoff TH, Dass RH, Yang N, Zhang MM, Wong HE, Sahiratmadja E, et al. Genome-wide expression profiling identifies type 1 interferon response pathways in active tuberculosis. PLoS One. 2012;7(9):e45839.

No conflicts of interest declared concerning the publication of this article.

Corresponding author:
Iukary Takenami
E-mail: iukary.takenami@univasf.edu.br