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REVIEW

The dual face of central nervous system tuberculosis: A new Janus Bifrons?

Brenda Sáenz [a], Rogelio Hernandez-Pando [b], Gladis Fragoso [a], Oscar Bottasso [c], Graciela Cárdenas [d,*]

[a] Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, Laboratorio de Inmunología, Ciudad de México, Mexico
[b] Instituto Nacional de Ciencias Médicas y de la Nutrición, Laboratorio de Patología experimental, Ciudad de México, Mexico
[c] Instituto de Inmunología, Facultad de Ciencias Médicas, Rosario, Argentina
[d] Instituto Nacional de Neurología y Neurocirugía, Departamento de Neuroinfectología, Ciudad de México, Mexico

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SUMMARY

Tuberculosis (TB) is still a common infectious disease in developing countries, but it is also re-emerging in industrialized nations due to the HIV/AIDS pandemic. In addition to bacillary virulence, the host immune response plays a major role in the development of an active disease (either as a primary infection or reactivation) and in controlling the infection.

Even though several mechanisms are involved in regulating the human immune response, biological environment seems to be determinant. In this context, the integrated neuro-immune-endocrine system strongly influences TB clinical outcome. One of the most important clinical aspects of TB is shown when the infection locates in the central nervous system (CNS), in which a very different set of immune responses is induced. Herein we review several aspects of the paradoxical immune response triggered during CNS-TB infection, and discuss the implications of this response in the cerebral infection outcome.
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1. Introduction

Tuberculosis (TB), the world's second most common cause of death by infectious diseases after HIV/AIDS, remains a major health threat with high morbidity and mortality. According to estimates by the World Health Organization, one-third of the world's human population is latently infected with *Mycobacterium tuberculosis* (Mtb), and 1.7 million people die of TB each year.[1] Main traits of TB are the diverse clinical manifestations and severe sequels, which constitute a huge challenge for physicians, requiring accurate diagnosis and treatment. Mtb infection can produce a progressive disease or, more commonly, a latent state, and although the involved mechanisms are not well understood, an opportune and modulated effective immune response against Mtb may determine the infection outcome.

In the first encounter between the immune system and Mtb, the effectiveness of the innate immune response will dictate the clinical outcome. If this response is strong enough and the bacilli are not highly virulent, bacteria will be eradicated; otherwise, Mtb will be confined to the host cells, leading to a latent infection. At this point, the adaptive immune response is determinant for the progress of the disease, from an active to a progressive one. Central nervous system (CNS) involvement is the most devastating form of TB, associated with a high mortality and severe neurological sequels.[2]

In this review, we aim to discuss the immunological components involved in the dual face of the central nervous system tuberculosis (CNS-TB), capable of turning a latent infection into a progressive one. In this context, the local immune-endocrine response in the CNS involved in the development of a paradoxical reaction can be compared with Janus Bifrons, the Roman god who had two faces looking in opposite directions.

2. Immune response against tuberculosis

The immune response in TB is very complex, both in the periphery (lung, lymphatic nodes, etc.) and in the CNS (Figure 1). Innate mechanisms are crucial in limiting Mtb growth in the initial phase of the infection. The first cells encountering the bacilli are alveolar macrophages and tissue dendritic cells (DC), which recognize mycobacterial components (pathogen-associated molecular patterns, PAMP's) via pattern recognition receptors (PRRs), i.e. Complement (mainly CR3), Toll-like (TLR2, TLR4 andTLR9), C-lectin type, mannose, immunoglobulin Fc, scavenger, and nucleotide oligomerization receptors.[3]

Several mycobacterial wall glycolipids are recognized by TLRs. TLR2 recognizes a wide array of mycobacterial structures including

* Corresponding author.
E-mail address: grace_goker@yahoo.de (G. Cárdenas).

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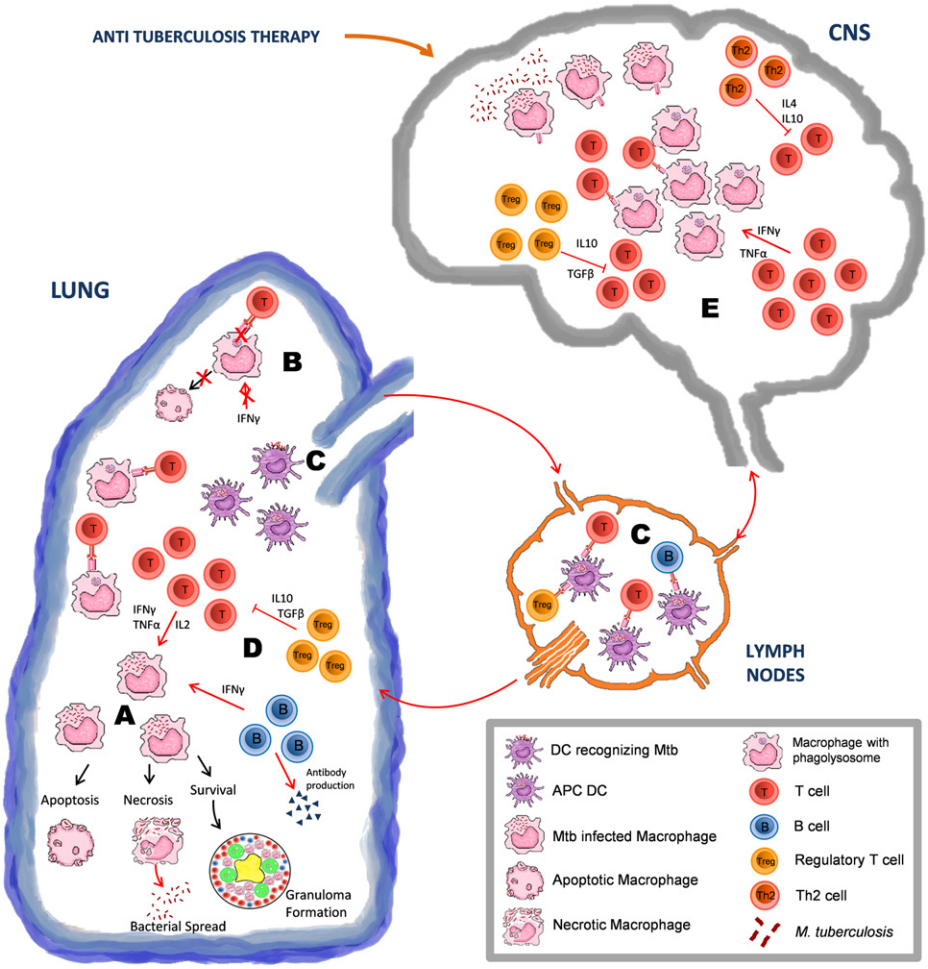

Figure 1. The antimycobacterial immunological mechanisms in lungs, lymph nodes and in the brain. The innate immune response occurs in the lungs when macrophages and dendritic cells recognize bacteria and respond to the infection. (A) Macrophages can undergo necrosis or apoptosis, or they can survive, leading to a bacterial spread and a latency state of the infection or, in the best scenario, help in bacterial elimination. (B) Mtb can evade the innate immune response leading to latency, by arresting the phagolysosome formation, inhibiting apoptosis as well as macrophage response to IFNγ stimuli. (C) Resident dendritic cells that capture Mtb antigens activate T and B cells as well as regulatory T cells. (D) In the lungs, all activated T and B cells attracted by chemokines released by lung resident cell control bacterial growth. This control is done through the production of cytokines and antibodies respectively, whereas regulatory T cells help to control the inflammatory response producing IL10 and TGFβ. (E) During anti-tuberculous therapy or when the host immune response is activated, lymphocytes and infected macrophages can also enter the CNS, leading to an exacerbation of the inflammatory response, the so-called paradoxical reaction. Activation of the latent TB lesions increases antigen exposure and exacerbates the inflammatory T cell response against Mtb through the production of pro-inflammatory cytokines, such as TNFα or IFNγ. In this immune-privileged organ, the role of Tregs and Th2 cells may be of relevance to relieve the inflammatory response through the production of the anti-inflammatory cytokines IL10 and TGFβ as well as IL4. Mtb: *Mycobacterium tuberculosis*; DC: Dendritic Cell; APC: Antigen-presenting cell.

lipoarabinomannan and phosphatidylinositol mannoside, as well as heat shock proteins: Hsp65 and Hsp70. TLRs are also involved in a vitamin D-dependent production of cathelicidin and defensins, which are highly effective antimicrobial peptides against Mtb.[4] Macrophages and bronchial epithelial cells are the most important source of antimicrobial peptides, playing a significant role in the innate immune response against Mtb. Mycobacterial nucleic acids, particularly the CpG motif, induce macrophage activation via TLR9. Some of these receptors can also prime macrophages for activation by cytokines or initiate the synthesis of antimicrobial molecules, chemokines and cytokines. However, TLRs (TLR2, TLR4, TLR9, and possibly TLR8) may also hamper cell activation by allowing a silent entry of Mtb into the macrophage.[5]

The manner by which macrophages respond in TB is crucial for the host immune response. Three major outcomes are observed: (1) necrosis, (2) apoptosis, or (3) survival of the infected macrophages. Necrosis may be detrimental since it causes tissue damage and bacterial spread, whereas apoptosis is beneficial for the host because both the infected cells and the microorganisms die. Finally, the survival of macrophages also leads to Mtb replication.

In general, macrophages are pivotal cells in the PRR-mediated phagocytosis process, resulting in phagosome acidification and fusion with lysosomes, the ensuing phagolysosome formation and potential bacterial destruction. However, once inside the macrophage, mycobacteria are capable of evading the innate microbicidal machinery by inhibiting phagosome acidification and preventing its further biogenesis and acquisition of lysosomal components.[6] Interestingly, Mtb infection can also lead to apoptosis inhibition. This may promote its intracellular maintenance and further affect the cell function via the ESAT-6 protein, which interferes with TLR signaling by preventing the assembly of myeloid differentiation factor 88 (MyD88).[7] Finally, another mechanism favoring latency is the blockade of IFNγ-inducible genes in macrophages.[8]

Dendritic cells (DCs) are regarded as the link between the innate and the adaptive immune response in Mtb infection. DCs recognize

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