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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.

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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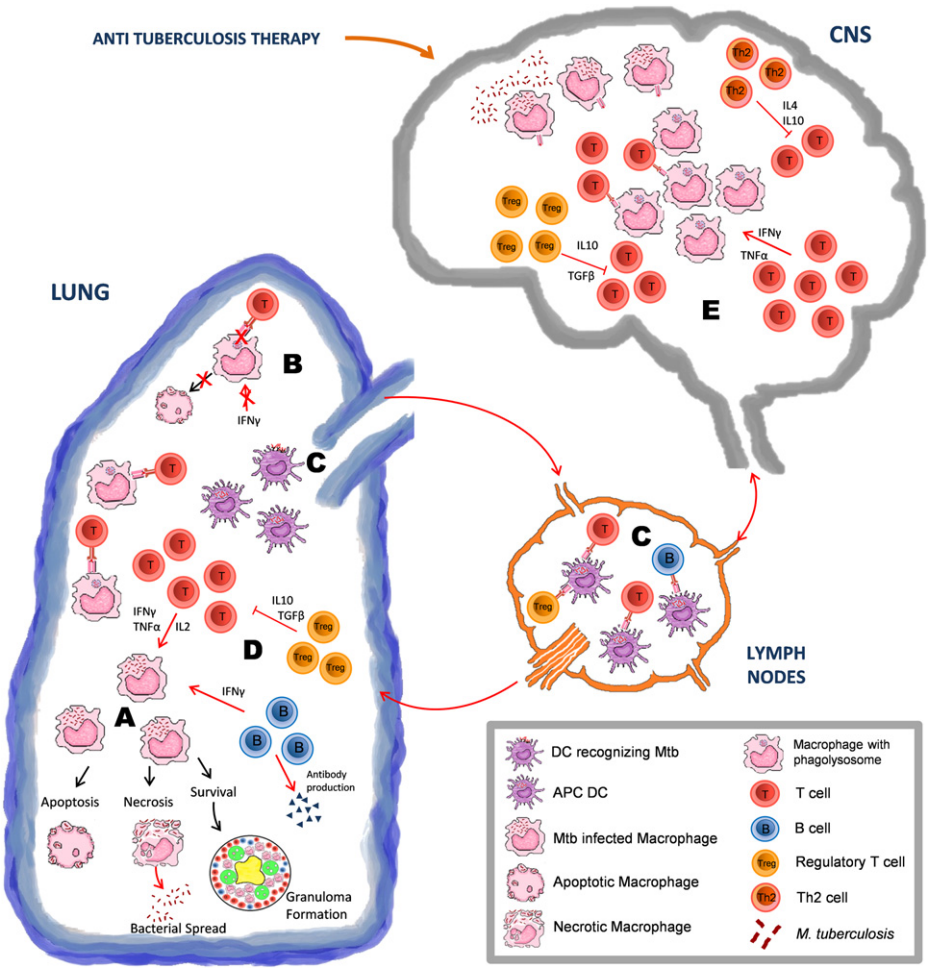

Figure 1. The antimycobacterial immunological mechanisms in lungs, lymph nodes and in the brain. The innate immune response occurs in the lungs when macrophages and dendritic cells recognize bacteria and respond to the infection. (A) Macrophages can undergo necrosis or apoptosis, or they can survive, 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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PAMPs mainly via DC-SIGN, TLR9 and dectin-1[3] and can efficiently present antigens to naïve T cells, leading to their activation. Recently, it has been described that DCs die after infection, probably arresting bacterial replication in a similar way to macrophages.[9]

Adaptive immune response begins in the local lymph nodes with myeloid DC transporting live Mtb present in the lungs, where bacilli may also infect antigen-presenting cells. The transport of DC from the lungs to the lymph nodes appears to be controlled by CCR5 and CCR7. After antigen presentation in lymph nodes, initial activation and proliferation of CD4+ T cells takes place and effector CD4+ T cells rapidly traffic to the lungs to arrest the bacteria progressive growth. Activated T lymphocytes produce IL-2, TNFα, and IFNγ. The latter has been implied as a regulator of T cell response[6]; in fact, CD8+ activated, IFNγ-producing lymphocytes are able to control bacterial growth inside infected cells. Due to the bacterial load and the anti-inflammatory mechanisms inhibiting the immune responses in the lungs, the cellular immune response only restricts the progressive bacterial growth, but rarely eradicates bacteria.

In mice, a delayed response of effector T cells occurs 10–12 days after infection and is preceded by the appearance of live Mtb in the mediastinal lymph nodes. Apparently, the number of bacteria reaching the lymph nodes, rather than the lungs, defines the outcome of the immune response.[10] This delayed response is partly due to the fact that during the early infection stages, Mtb resides within cells, avoiding the priming of the innate response and restricting antigen presentation to naïve CD4+ T cells, which allow a dramatic expansion of bacterial population. Also, it has been observed that other adaptive mechanisms, such as the action of regulatory T cells (Tregs), limits the effector T cell responses and contributes to bacterial survival.

Beyond these facts, clinical–epidemiological and experimental studies have demonstrated a distinct bacterial genotype isolated from patients with CNS-TB, suggesting a strain-dependent neurotropism.[11] These bacilli seem to produce phenolic glycolipid, which inhibits the innate immune response and may be responsible for CNS dissemination. Other possible candidates are mycobacterial heparin binding hemagglutinin and histone-like protein involved in the laminin interaction.[11]

3. Regulatory T cells in lungs

Tregs have been described as a subset of cells with a critical function in maintaining peripheral immune tolerance, preventing autoimmunity and modulating chronic inflammation. The role of Tregs in limiting effector responses in Mtb infection has two important implications: (1) they regulate the inflammatory immune response to prevent tissue damage and, (2) they limit Th1 immunity, modulating the control of infection. In humans, Tregs frequency is increased among peripheral blood mononuclear cells from patients with active TB, as well at the infection site. These cells are able to suppress IFNγ production.[12–14] In subjects with latent TB, despite the fact that Tregs are not increased, they do suppress T effector cells upon *in vitro* antigenic stimulation. Recently, a similar phenomenon has been reported in BCG-vaccinated individuals previously exposed to environmental mycobacteria. In fact, antigen-specific Tregs impair immunity to Mtb infection by suppressing the recruitment of effector T cells in the lung, as well as their proliferation and IFNγ production.[15]

Tregs are preferentially recruited and expanded in the inflamed TB-infected tissues.[16] Furthermore, Tregs are able to modulate antigen-specific immunity as shown in a mouse model, where *in vivo* depletion of CD25+ T cells enhanced IFNγ production without affecting the bacterial burden or the pathology.[15] In humans, *in vitro* Tregs depletion increases Mtb-specific responses as well as other recall antigen responses.[12–14,17,18]

Several pieces of evidence point to Tregs activation occurring in an antigen-specific manner, suggesting that Tregs initially recognize Mtb antigens presented by infected DCs in the lymph nodes, where they proliferate, and suppress effector T cells. Then, Tregs can exert their suppressor effect at the infection site, in which they are primed, and proliferate in parallel to effector T cells.[19,20] Tregs may also be induced by mechanisms other than antigen-specific activation. In fact, Tregs development has been observed to be dependent upon IFNγ induction of the transcription factor T-bet.[21] Also, it has been suggested that mycobacteria, by binding to TLR2, might function as a co-stimulatory trigger for the expansion/function of Tregs delaying adaptive immune response. Conversely, other studies report that TLR2 abrogates the suppressive capacity of Tregs, as seen in *Leishmania* infection and experimental models of Tregs function.[19,20,22]

It has been observed that Tregs depletion in Mtb-infected mice at a later infection stage does not necessarily result in protection from infection,[15] likely due to other concurrent suppressive mechanisms, i.e. IL-10 production. This regulatory cytokine has been involved in controlling mycobacteria immunity, probably produced in the lung by macrophages and DCs. As such, Tregs suppression along with IL-10 production may down-regulate the inflammatory response during Mtb infection.[16]

4. Neuro-immune-endocrine alterations in tuberculosis

The neuro-immune-endocrine systems play an essential role in homeostasis maintenance, regulating behavioral, cardiovascular and metabolic processes, as well as distinguishing between self and non-self agents to protect the individual from external and internal threats. During inflammation, the interaction between neuro-immune-endocrine systems is particularly evident in the relation between the hypothalamic–pituitary–adrenal–axis (HPA) and the inflammatory/immune reaction. TNFα, IL-1, and IL-6, secreted from local inflammatory sites, independently and synergistically activate the HPA axis by acting on its hypothalamic, pituitary, and adrenocortical components. The paraventricular nucleus of the hypothalamus receives signals from distant organs and secretes corticotropin-releasing hormone and arginine vasopressin into the hypophyseal portal system. The pituitary gland is synergistically activated by these neuropeptides and secretes adrenocorticotropic hormone into the systemic circulation, stimulating the adrenal cortex to produce glucocorticoids (GCs) and dehydroepiandrosterone (DHEA). GCs and DHEA influence innate and adaptive mechanisms of the immune response down-regulating inflammatory responses, but display differential stimulating effects on the development of Th2 and Th1 responses, respectively. In general, activation of the HPA axis alters the activity of certain important facets of the immune system, mainly through GCs activity, which exert diverse actions on nearly all aspects of the innate and adaptive immune responses and also inhibit the production of pro-inflammatory cytokines, as well as other inflammatory mediators.[23] The same hormones, however, stimulate the production of several anti-inflammatory cytokines and other mediators, providing anti-inflammatory control during an inflammatory reaction and shifting the Th1/Th2 balance toward the Th2 phenotype, which potentiates humoral immunity. There seems to be a close link between elevated GCs resulting from HPA axis activation and impaired defensive reactions, which may leave the individual vulnerable to an infectious process that otherwise, could be held in control by the immune system. During chronic infectious diseases, excessive and/or protracted cytokine production may affect such bidirectional communication, favoring the establishment of an adverse state characterized by important alterations in essential immunological and metabolic functions, along with perpetuated inflammatory responses.[23]

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Studies on newly diagnosed HIV-negative TB patients revealed an immune-endocrine imbalance characterized by increased IFNγ, IL-6, prolactin, thyroid hormones, and cortisol blood levels along with decreased testosterone and DHEA levels. In turn, culture supernatants from Mtb-stimulated PBMC from TB patients inhibited DHEA secretion by a human adrenal cell line, this effect being partly reversed by TGFβ neutralization. *In vitro* studies performed by exposing PBMC from TB patients to physiological concentrations of both adrenal steroids showed that cortisol inhibited mycobacterial antigen-driven lymphoproliferation and IFNγ production, whereas DHEA suppressed TGFβ production in patients with progressive disease. Also, when analyzing the expression of the GC receptor alpha- and beta-isoforms (hGRα and hGRβ) in PBMC from TB patients, a reduced mRNA hGRα/β ratio was found in severe cases, suggesting some degree of GC resistance.[24] Furthermore, it was found that a series of immunoendocrine compounds participating both in the regulation and/or redirecting of energy sources and in the immune activity (leptin and IL-6) were related to the cachexia state of TB patients, which in turn accounted for the impaired specific cellular immune responses found *in vitro* in these patients. It follows that bidirectional communication between neuro-endocrine and immune systems alters the defensive mechanisms against TB and the disease course.[25,26]

Data about the immune–endocrine disturbances during HIV-TB co-infection are scarce, but reduced levels of DHEA and cortisol have been described, along with an increased cortisol/DHEA ratio. These findings may be the result of a persistent immune-inflammatory concomitant with an inefficient control of this inflammatory reaction, since the slightly increased cortisol levels would not compensate the anti-inflammatory effect of DHEA because of its markedly reduced levels. Studies also documented a negative association between DHEA levels and frequency of Tregs, together with DHEA-mediated inhibition of FoxP3 expression in HIV-TB patients; which provides novel information about the mechanisms by which DHEA modulates the immune response.[27,28]

5. Central nervous system tuberculosis, the paradoxical response and Tregs

Extrapulmonary TB is often related to an immunodeficient state. Indeed, young children and HIV-infected individuals have an increased risk for such disease form,[1] presumably due to an immature immune system and to low CD4+ T lymphocyte numbers, respectively. CNS-TB, the most hazardous type of systemic TB, accounts for 2–5% of all cases. It is often associated with high mortality and severe neurological sequels. CNS-TB spectrum includes three clinical–pathological forms: meningoencephalitis, tuberculomas and abscesses that can be observed in both immunodeficient and immunocompetent individuals.[2]

In seronegative-HIV individuals, intracranial tuberculoma and brain abscess may develop and/or increase in size during antituberculous therapy (ATT) for meningitis or pulmonary TB.[29] This reaction is known as paradoxical reaction. The inflammatory response takes place in the context of increased antigen exposure and Th1 cell-mediated immune response against Mtb. This phenomenon occurs in patients who initially relieved their symptoms and after few weeks they either develop new lesions or the latent ones become active, and it occurs no matter the HIV-serological status.

The immunological components involved in paradoxical reaction have not been fully described, but some studies suggest that dysregulation of the cellular immune response is involved in the establishment and the activation of the latent TB lesions. In a study of patients with culture-proved TB infection, subjects undergoing a paradoxical response showed lower absolute lymphocyte counts before ATT and exhibited higher lymphocyte counts during paradoxical response, compared to patients not experiencing this response to therapy.[30] In addition, a decreased production of TNFα in LPS-stimulated cells was reported in patients recovered from extrapulmonary TB and lower CD4+ T lymphocyte counts, when compared to controls with pulmonary or latent Mtb infection.[31–33] These findings suggest that the role of effector CD4+ T lymphocytes to control the progressive bacterial growth, together with production of the pro-inflammatory cytokines such as IFNγ and TNFα, are essential for macrophage activation for phagocytosis, autophagy and mycobacterial granuloma formation and maintenance that efficiently restrain Mtb establishment in the CNS, but this response can also induce severe immunopathology.

Another risk factor for paradoxical reaction is HIV co-infection with TB after highly active anti-retroviral treatment (HAART) leading to the immune reconstitution inflammatory syndrome (IRIS). This phenomenon is due to the marked improvement of the immune function; consequently many of these patients become strongly positive for tuberculin skin tests after HAART. The onset of the disease (IRIS TB in HIV patients) occurs early, and common manifestations include fever, lymph node enlargement, new pulmonary infiltrates and pleural effusions. A large South African study reported 23 patients with CNS-TB-IRIS, accounting for 12% of their total cases of TB-IRIS.[34]

In immunocompromised individuals, the pathogenesis of paradoxical and unmasking TB-IRIS differs significantly. Subjects with paradoxical TB-IRIS show a strong positive delayed-type-hypersensitivity for tuberculin purified protein derivate test and decreased MCP-1 and IL-10 levels, while *ex-vivo* stimulation, showed high levels of IL-18, and CXCL10, and low CCL2. On the other hand, unmasking TB-IRIS subjects show strong IFNγ response to ESAT-6 and CFP10 (RD1 antigens), high serum C-reactive protein, and TNFα levels, and markedly IL-18 levels on *ex-vivo* stimulation.[35,36] Experimental meningeal TB in mice showed a high expression of anti-inflammatory/cell-mediated immunity suppressor cytokines such as IL-10, IL-4 and TGFβ in infected brain, with no clinical correlate of nervous tissue damage.[11] Thus, it seems that the brain is an immune-privileged tissue with a natural bias to immunosuppression preventing the inflammation-associated tissue damage. Moreover, Th2 cytokines such as IL-4 also have beneficial activity for CNS healing after injury.

The role of Tregs in CNS-TB has been poorly explored. Recently, it has been reported increased Tregs and activated CD4+ T lymphocytes frequencies in patients recovered from extrapulmonary TB, suggesting an increased frequency of central Tregs before exposure to Mtb. This may predispose to acquire extrapulmonary TB, in a context of a dysregulated immune response.[35] Thus, Tregs in CNS-TB, may act by regulating the inflammatory immune response in CNS, but also may limit Th1 immunity, leading to the infection persistence and dissemination. This is the case for pulmonary active TB, in which Tregs act as suppressors of effector T cells and IFNγ production.[12–14]

Regarding the relation between Tregs and the paradoxical response, there are not reported studies about their role in the exacerbation of the immune response elicited after ATT, but probably Tregs take part modulating protective immune responses. Further studies to elucidate their role during the different stages of the disease evolution are needed.

A possible beneficial role of Tregs takes place during ATT with TNFα antagonists. In TB meningitis, a correlation between disease severity and TNFα levels in cerebrospinal fluid has been observed.[37] Recently, immunotherapy for TB with TNFα antagonists such as

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Table 1
Immunological events participating in the different outcomes after Mtb exposure.

Immunity	No infection	Latency	Progressive disease
Innate	**Macrophages** 1. Activation for phagocytosis, autophagy and production of ROI and RNI, production of IFNγ, TNFα and IL-6 2. IL-1β, IL-23, IL-17 through TLR signaling 3. TLR induction of cathelicidin in macrophage vacuoles 4. Macrophages and DC apoptosis induction 5. Defensins production **Natural Killer cells** 1. Activation induced by IL-12 and IL-18 2. IFNγ production **Neutrophils** 1. Activation of phagocytosis 2. Defensins production **Bronchial epithelial cells** 1. Defensins and protease inhibitors production	**Macrophages** 1. Production of IL-12 and activation of Th1 response 2. Granuloma formation induced by TNF α production 3. Production of IL-10 trough DC-SIGN and MMR signaling **Dendritic cells** 1. Antigen presentation in lymph nodes 2. Production of IL-10 trough DC-SIGN and MMR signaling ***Mycobacterium bacilli*** 1. 1. Macrophage inhibition of phagosome-lysosome fusion 2. Inhibition of production of IFN γ	**Neutrophils** 1. Recruitment by IL-17, IL-27 and IL-8 in lungs **Macrophages and Natural Killer cells** 1. Deficient production of TNFα ***Mycobacterium bacilli*** 1. Interference of TLR signaling by ESAT-6 protein 2. Necrosis of Macrophages and DC necrosis 3. Apoptosis inhibition
Adaptive	No participation	**Dendritic cells** 1. Delayed T Cell priming 2. Th2 inhibition of macrophage autophagy **T reg cells** 1. Suppression of Th1 response **CD4+ T cells** 1. Delayed response and production of IL-2, TNFα and IFNγ	**Dendritic cells** 1. Increased antigen exposure after anti-tuberculosis therapy **Macrophages and diverse immune cells** 1. High production of anti-inflammatory/ immunosuppressive cytokines such as IL-4, IL-10, IL-13, TGFβ **Macrophages and Natural Killer cells** 1. Impairment production of TNFα 2. Impairment of the effector role of CD4+T lymphocytes after anti-tuberculosis therapy

DC-SIGN: DC-specific intercellular-adhesion-molecule-3 grabbing non-integrin; MMR: macrophage mannose receptor; ROI: reactive oxide intermediates; RNI: reactive nitrogen intermediates.

anti-TNF antibody Infliximab, the inhibitor of monocyte TNFα production Thalidomide and the soluble TNF receptor Etanercept have been proposed to control steroid-resistant TB paradoxical reaction.[29,38] It is hypothesized that, when TNFα production is inhibited and macrophage activation is suboptimal, bacilli may be more likely to remain in an active growing state, rather than shifting into latency, and hence more responsive to the bactericidal action of antibiotics.[38,39] CNS inflammatory phenomenon may probably be mitigated in part by reactivation of Tregs. This event has been demonstrated in other diseases treated with TNF antagonists, for example, increased numbers of peripheral Tregs have been observed in patients with rheumatoid arthritis responding to Infliximab, and the suppressive phenotype of these cells is restored, as well.[40] Also, in inflammatory diseases, therapy with Infliximab or Etanercept induces the number and function of Tregs, leading to a diminution in the disease activity and the inflammatory response.[41–43] It would be important to study the role of Tregs after TNFα antagonist therapy, as well the function of these cells in the mitigation of the exacerbation of the immune response in the paradoxical reaction.

Affectation of the CNS may further compromise the neuro-endocrine regulation of the immune response adding an extra level of complexity, worth exploring.

6. Conclusions

The host response against TB encompasses a complex reaction involving the participation of neuro-endocrine and immune mechanisms. As regards the latter ones, the innate immune response plays a critical role in the mycobacteria establishment, whereas the adaptive immune response is involved either in protection or tissue pathology (Table 1).

The role of immune–endocrine components participating in paradoxical reaction at the CNS can be compared with Janus Bifrons. This mythological god was represented with two faces looking in opposite directions. In TB, either an ineffective or an exuberant inflammatory response could lead to disease; specially, Tregs can have a beneficial role in alleviating the inflammatory response and preventing tissue damage, but may also be detrimental in suppressing the effector T cell response, favoring the establishment of a chronic infection. In this sense, it is clear that the delicate balance between pro-inflammatory and anti-inflammatory responses in TB is of crucial importance. This condition is even more important in highly specialized, vital tissues such as the brain, since its damage by excessive inflammation could be irreversible and affect significantly its functions. Thus, efficient Mtb elimination by chemotherapy, which can lead to antigen liberation with an excessive inflammatory response, could worse the disease by immunopathology. This efficient therapy that worsens the clinical course is the referred Janus Bifrons, which needs an accurate evaluation of the patients' initial immunological status, as well as the study of the role of Tregs in modulating the immune response toward Mtb. The knowledge in these crucial aspects, defined for example by specific clinical markers, could be useful to predict a potential predisposition that may lead a life-threatening condition.

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