Review Article

Pathogenesis and Immune Response in Tuberculous Meningitis

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Submitted: 11 Dec 2013
Accepted: 16 Dec 2013

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Abstract

Cerebral tuberculosis is the most severe type of extrapulmonary disease that is in developing countries highly predominant in children. Meningeal tuberculosis is the most common form and usually begins with respiratory infection followed by early haematogenous dissemination to extrapulmonary sites involving the brain. In comparison with the lung, *Mycobacterium tuberculosis* induces a very different immune response when infect the central nervous system. Herein, we review several aspects of the pathogenesis and immune response in pulmonary and cerebral tuberculosis in humans and experimental models and discuss the implications of this response in the cerebral infection outcome.

Keywords: *tuberculosis, tuberculous meningitis, cerebrospinal fluid*

Introduction

Tuberculosis (TB) is a significant bacterial disease which principally affects the lungs; its causal agent is *Mycobacterium tuberculosis* (Mtb) an intracellular facultative organism which can produce progressive disease or latent asymptomatic infection (1). In the developing world Mtb primary infection is usually produced during childhood and in the majority of the cases is efficiently controlled by the immune system. In the world, TB causes 1.2 million of deaths and 9 million new active cases per year, it is estimated that one third of the world population is latent infected. Thus, TB is one of the most important infectious diseases in the world, particularly in developing nations where occurred the 95% of active TB cases and 98% of deaths (2).

Although TB is essentially a pulmonary disease, other organs and tissues can be infected, being cerebral TB the most severe form. Indeed, TB involvement of the central nervous system (CNS) is a significant and serious type of extra pulmonary disease, it constitutes approximately 5–15% of the extra pulmonary cases and in developing countries it has high predominance in children (3). There are different clinical/pathological manifestations of cerebral TB; the most common is tuberculous meningitis, followed by tuberculoma, tuberculous abscess, cerebral miliary tuberculosis, tuberculous encephalopathy, tuberculous encephalitis, and tuberculous arteritis (4). Cerebral TB is often fatal (30%) and many of survival patients have sequels (50%). Cerebral TB is usually caused by *Mycobacterium tuberculosis,* other non-tuberculous mycobacteria such as *Mycobacterium avium-intracellulare* can also produce CNS tuberculosis mainly in human-immunodeficiency virus-infected persons (4). It is estimated that cerebral TB is developed in approximately one patient from 300 non-treated cases of pulmonary TB, and in 50% of patients that suffer miliary TB. Some studies mentioned that at least the 75% of cerebral TB patients had pulmonary TB 6 or 12 months before the neurological symptoms started (5–8). It is interesting that approximately 25% to 30% of cerebral TB patients do not have active pulmonary TB. These different outcomes and clinical pathological forms of cerebral TB should induce diverse local immune responses which have not been totally studied. Here, we reviewed the clinical and experimental studies about the immune response induced by *M. tuberculosis* in the brain. It seems that significant brain tissue damage is produced by excessive cellular mediated immune response and related excessive inflammation, their proper characterisation and therapeutically control are important to preserve the structure and function

of the nervous tissue affected by this significant infectious agent.

Pathogenesis of Cerebral Tuberculosis

It is believed that cerebral TB, like any other forms of TB, begins with respiratory infection followed by early hematogenous dissemination to extra pulmonary sites, including the CNS. On the basis of their clinical and experimental observations, Rich and Mc Cordock suggested that cerebral TB develops in two stages (9). Initially small tuberculous lesions (Rich`s foci) develop in the brain during the stage of bacteremia of primary TB or shortly afterwards. These early tuberculous lesions can be located in the meninges, the subpial or subependymal surface of the brain, and may remain dormant for long time. Later, rupture or growth of one or more of the small lesions produces development of various types of CNS tuberculosis (9). Rupture into the subarachnoideal space or into the ventricular system produce meningitis, the most common form of cerebral TB (Figure 1).

In order to study its pathogenesis, diverse experimental animal models of brain TB have been established in rabbits (4,5), mouse (6,7), and pigs (8). Although they reproduce in some extend the human lesions, these models are artificial because they use the direct intracerebral or intravenous route of infection, instead of the natural respiratory route. We informed the results from an experimental study using a model of pulmonary TB in BALB/c mouse; animals were infected by the intratracheal route with *M. tuberculosis* clinical isolates with distinctive genotype, these strains were obtained from the cerebrospinal fluid (CSF) of meningeal TB patients from an epidemiological study in Colombia. These bacilli were able to rapidly disseminate and infect the mouse brain (10). This experimental model closely reproduces the human disease and suggests the existence of bacilli strain with distinctive genotype that probably expresses specific molecules that permit CNS infection (neurotropism). The expression of these bacterial molecules is important considering that the CNS is protected by an especial barrier which maintains the nervous tissue isolated from circulating infectious organisms. This structure is called blood brain barrier (BBB) and the organisms able to infect the brain have evolved specific virulence factors that aloud endothelial adherence and infection followed by nervous tissue invasion (11). In vitro studies have shown that *M. tuberculosis* can adhere, invade, and traverse endothelial cells (12), and clinical-epidemiological studies have identified diverse risk factors related to meningeal TB development, such as some ethnic groups that suggest some genetic contribution from patients to develop cerebral TB (13), as well as some specific polimorphisms of cellular receptors from innate immunity and mycobacterial antigens such the invasin hemoaglutinin associated to heparin, which is an antigen expressed on the bacterial surface that is recognized by specific receptors located in the membrane of endothelial cells, permitting bacterial invasion, and dissemination

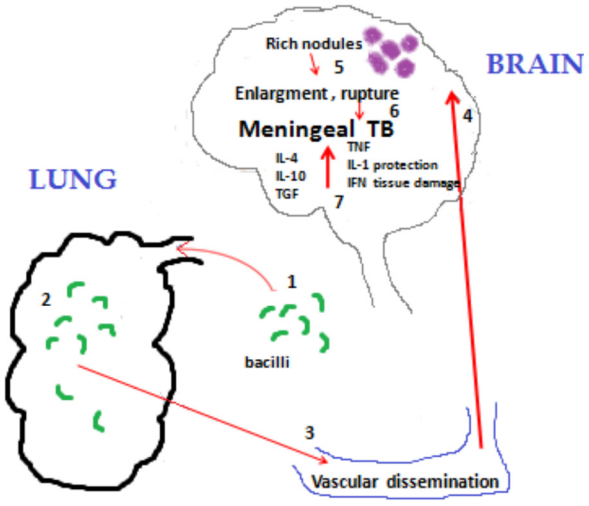

Figure 1: Pathogenesis and immune response of cerebral tuberculosis: The lung is initially infected by the aereal route (1); bacilli grow in the lungs and disseminate after blood vessels invasion (2) producing systemic infection (3) affecting the brain (4). Small groups of inflammatory cells are located in the subpial or subependymal areas (Rich nodules) after early bacteremia (5), where bacilli are content and may remain dormant for long time. Later, growth and rupture of these lesions produces meningeal tuberculosis (6). Mycobacterial infection induces the production of proinflammatory cytokines that are important for bacilli killing but they can also produce immunopathology (7). Antinflammatory cytokines are also highly produced; they protect tissue damage by excessive inflammation and induce nervous tissue regeneration (7).

(14). Other potential antigen is the histone like protein (HLP) which interacts and contributes to the invasion of *M. leprae* to Schwann cells using laminin as receptor (15), this molecule is also expressed by *M. tuberculosis* and we have found over-expression of both antigens in the above mentioned strains from Colombia.

At the early stage of brain infection, cytokines such as TNFα, IL-1, and IL-6 are released by migrated activated macrophages, microglial cells, astrocytes, and endothelial cells. These cytokines can contribute to the entry of diverse compounds into the brain by breaching the BBB (16). It has been demonstrated an increase in the permeability of endothelial cells in vitro after the administration of these proinflammatory cytokines (17). Moreover, IL-1 is produced by damaged BBB and its permeability is increased by this cytokine (18). Astrocytes and microglial cells can also produce IL-1 affecting the BBB permeability (19). Thus, it seems that the function and integrity of BBB is affected by the production of proinflammatory cytokines produced by astrocytes, microglial, and endothelial cells (16), which perhaps are not specific for mycobacterial infection and other organisms may trigger this inflammatory process in the nervous system with similar consequences.

Immune Response in Pulmonary Tuberculosis

Immune response against *M. tuberculosis* in the lung is very complex but also quite efficient; in fact only 5% of people with primary infection develop progressive disease. Innate immunity is crucial in pulmonary response and is essentially carried out by alveolar macrophages and dendritic cells, which recognize diverse bacterial moieties or pathogen-associated molecular patterns (PAMPS) using specific receptors, such as Toll (TLR2, TLR4, TLR9), manose, C3, or IgG Fc receptors among others (20). Some of these receptors also participate in macrophage activation mediated by cytokines or chemokines. Airways epithelial cells are also significant participant of the innate immunity against mycobacteria, these cells are the principal source of antimicobacterial peptides such as beta-defensins and cathelicidin which are efficient factors in bacterial killing and also are chemotactic and activate lymphocytes (21).

Phagocytic activity conducted by alveolar macrophages is essential in mycobacterial elimination; it is mediated by the production of oxygen radicals, nitric oxide and the interaction of phagosomes with lysosomes. However, is in this process in which mycobacteria has developed diverse molecular strategies in order to avoid their elimination, for example lysosomes acidification (22). Mtb can also manipulate macrophages avoiding their death by apoptosis, this is an important mechanism due that during apoptosis not only infected macrophages died but also intracellular bacilli are eliminated (23). Dendritic cells are a bridge between innate and acquired immunity, these cells recognize diverse mycobacterial PAMP with their receptors DC-Sign, TLR9 and dectin 1, then these cells present selected antigens to T lymphocytes inducing their activation.

Adaptative immunity against mycobacteria starts in the lung and mediastinal lymph nodes. Dentritic cells transport the bacilli from the lung to the mediastinal lymph nodes; it seems that this process is controlled by chemokines and their receptors, such as CCR5 and CCR7. Dendritic cells present mycobacterial antigens inducing the activation and expansion of Th-1 cells, these are essential in the bacilli growth control with the participation of significant cytokines such as IFNγ or TNFα. In fact, T-lymphocytes and activated macrophages conglomerate producing nodular structures called granulomas, where bacilli are confined preventing their dissemination and favoring their elimination, in this later process the participation of cytotoxic CD8 T cells is also important and is mediated by especial molecules such as perforins and granzimes.

Activation and proliferation of T-lymphocytes and monocytes differentiation to macrophages in pulmonary lesions produce extensive inflammation, which can produce tissue damage (24), being necrosis a significant process in bacilli dissemination. Thus, it is important the participation of anti-inflammatory mechanisms, such as the emergence of Th-2 lymphocytes and T-regulatory cells that produce specific cytokines, such as interleukin IL-4, IL-10, IL-13, and transforming growth factor beta (TGFβ), which suppress the activation and proliferation of lymphocytes and macrophages, limiting inflammation and tissue damage as well as promote tissue regeneration, but at the same time this response can reduce immune protection facilitating bacilli proliferation (24). Thus, the balance between proinflammatory and antiinflammatory responses is critical in the immune protection and immunopathology of TB.

Immune Response in Cerebral Tuberculosis

There is limited information about the immune response in human meningeal TB. Some studies have determined cytokines concentration in the CSF of meningeal TB patients. High concentrations of interferon γ (IFNγ), and tumor necrosis factor α (TNFα) have been detected in the CSF of meningeal TB patients in correlation with the severity of the disease, and although these levels decreased after treatment, high levels were maintained at the end of six months of treatment (25). Other studies that reported high concentrations of cytokines such as IFNγ, TNFα, IL-1β, IL6, IL-8, and IL10 after long time of the treatment initiation did not found relation with disease severity, implying that cerebral inflammation persists for long time (26,27). It was also reported that IFNγ and TNFα were elevated prior to treatment but non-detectable after six months of therapy when antibiotics were administrated with corticosteroids during the first and two months of treatment (28), suggesting that this combined treatment has some benefit only in those patients who are genetically predisposed to overproduce TNFα, while in patients that produce low amounts of TNFα, corticosteroids may be detrimental (29,30). This is particularly important in children, since it seems that they usually produce low TNFα, corticosteroids may have no beneficial effect or even could be detrimental considering the significant protective effect that TNFα has in *M. tuberculosis* infection (30). Other pro-inflammatory mediators such as IL1β and its receptor, NO2/NO3, MCP-1 and IL-8 were also elevated and correlated positively with TNFα levels in adults with meningeal TB, and some of them remained detectable during and after treatment (31–33).

There are also high levels of anti inflammatory cytokines, such as IL-10 and TNFα soluble receptors (TNF-R55, TNF-R75), indicating active antiinflammatory response which probably explains the absence of significant proinflammatory cytokines such as IL-12. Interestingly, young human children could be particularly susceptible to suffer meningeal TB, considering that in healthy human neonates the production of IL-10 is highly increased, while the production of IL-1 and IL-12 are low during the first and second year of life respectively (30).

Regarding to experimental brain TB, the model of meningeal TB in rabbits clearly demonstrated the pathogenic importance of TNFα (34). High concentrations of TNFα are induced after the intracisternal Mtb infection which produce severe meningitis that was prevented by the administration of thalidomide, an efficient blocker of TNFα mRNA translation (35). Moreover, the brain infection of recombinant non-virulent mycobacteria that overexpress TNFα or the intracisternal administration of TNFα induces breach of the blood brain barrier, brain edema, and local trombi formation causing local ischemia and necrosis (34).

Murine models of brain mycobacterial infection, such as the produced by the intracerebellar administration of Bacillus Calmette-Guerin (BCG), induced higher expression of NFκB in inflammatory cells located in the subarachnoid space and in all cerebellar layers close to the site of infection, in coexistence with endothelial activation that over express iNOS. These increased NFkB and iNOS expression are in coincidence with microglial activation (36).

Other murine model of meningeal TB induced by intratracheal infection showed high expression of antiinflammatory cytokines in the brain, such as IL-10, IL-4, and TGFβ which apparently protect tissue destruction by excessive inflammation (10). It is also important that in the nervous tissue, Th-2 cytokines such as IL-4 contribute to neural regeneration and protection (37).

It is interesting that in some patients with cerebral tuberculomas or tuberculous abscesses, brain lesions increase their size with worsening of clinical evolution after efficient chemotherapy (38). This condition is called paradoxical response and it seems that is produced by excessive inflammation induced by massive release of mycobacterial antigens and pro-inflammatory cytokines. These patients usually exhibited a significant clinical improvement after chemotherapy, but some weeks after they showed new lesions or the previous lesions increase their size in coexistence with high increase of lymphocytes (39).

HIV/TB co-infection is a risk factor for the development of paradoxical response, usually after active antiviral treatment which induces the immune reconstitution inflammatory syndrome (IRIS). This condition is produced as consequence of efficient improvement of the immunological function, patients exhibited strong Purified Protein Derivative (PPD) response, fever, adenomegaly, and new pulmonary lesions; approximately 12% of IRIS patients suffer paradoxical reaction (40). These patients show lower production of MCP-1 and IL-10 with

high production of IL-18, TNFα, and CXCL10 (41–43), in other words, lower production of antiinflammatory factors and high secretion of proinflammatory cytokines. Paradoxical response is treated with potent antiinflammatory drugs such as glucocorticoids or TNF antagonists (44).

Conclusion

In conclusion, cerebral TB is the most severe type of extrapulmonary TB and its more frequent type is tuberculous meningitis. Brain TB is the consequence of hematogenous bacilli dissemination after pulmonary infection and limited knowledge exist about the host and bacterial factors that participate in its development, so proper animal models are required.

Acknowledgement

None.

Conflict of Interest

None.

Funds

We acknowledge the Research University Team grant from Universiti Sains Malaysia number 1001/PPSP/853001 which has brought Prof Pando as a Visiting Professor to the Department of Neurosciences, School of Medical Sciences, Universiti Sains Malaysia in 2013.

Authors' Contributions

Drafting of the article and provision of study materials or patient: BEI
Conception and design, critical revision of the article for the important intellectual content, final approval of the article: HPR

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