Mashhad University of Medical Sciences (MUMS)

Reviews in Clinical Medicine

Clinical Research Development Center Ghaem Hospital

B cell-mediated Immunity against Tuberculosis Infection: A Mini Review Study

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ARTICLE INFO

Article type
Review article

Article history
Received: 17 Oct 2019
Revised: 21 Dec 2019
Accepted: 22 Jan 2020

Keywords
Antibodies
B Cells
Mycobacterium tuberculosis
Tuberculosis

ABSTRACT

Mycobacterium tuberculosis (Mtb) is considered to be a major public health concern and a successful intracellular pathogen associated with high mortality worldwide. The Bacillus Calmette-Guerin (BCG) vaccine is the only available vaccine for the prevention of tuberculosis (TB) and tubercular meningitis in children. However, BCG is not adequately effective in the treatment of the adults affected to TB. According to the literature, there are controversial data on the potential role of B cells. B cells and humoral immune response play a key role in the amplification of the host immune response against TB. This review study aimed to discuss B cells and humoral immune responses in TB infection and assess its application as a therapeutic option. The monitoring of various B cell phenotypes in TB could be a reliable marker for the prediction of TB in individuals, especially in the latent form. According to the findings, the CMI response (especially Th1 activities) is not sufficient for efficient protection against TB, and B cells and Abs influence the innate immunocytes and Th1, while playing a pivotal role in various outcomes of exposure with tubercle bacilli. Although B cells may contribute to Mtb in the development of active TB, further investigations are required regarding the effects of B cells and humoral immunity on TB pathogenesis and the targeted harmful humoral-mediated response. Moreover, B cells and antibodies could be proper biomarkers to promote the studies regarding the detection of reliable diagnostic tools for the reactivation of latent TB, as well as use as a new generation of therapeutic options.

Please cite this paper as:
Karbalaei M, Soleimanpour S, Eslami M, Yousefi B, Keikha M. B cell-mediated Immunity against Tuberculosis Infection: A Mini Review Study. Rev Clin Med. 2019;6(4):140-145.

Introduction

Mycobacterium tuberculosis (Mtb) is the causative agent of tuberculosis (TB), which is associated with high mortality worldwide. According to the literature, approximately two billion individuals are contaminated with tubercle bacilli with no clinical symptoms, and 5-10% of Mtb-infected individuals are exposed to active TB (1-3). The available Mycobacterium bovis Bacillus Calmette-Guerin (BCG) vaccine is the only efficient agent for the prevention of TB and tubercular meningitis in children. However, BCG is ineffective in the treatment of the adults affected by TB (4). Moreover, the emergence and extension of multidrug resistant TB (MDR-TB), extensively drug-resistant (XDR-TB) strains or pandemic HIV have led to severe issues in TB control strategies (5). According to the World Health Organization (WHO) report in 2017, 10 million new TB cases are present across the world, 5.8 million of which are men, 3.2 million are women, and one million are children. In addition, 10.6 million patients have died of TB, and there are 550,000 cases of rifampin-resistant TB, more than 80% of which are MDR-TB (6, 7).

TB is classified as an infectious disease, and Mtb is an intracellular bacterium that inducesphagocytosis following entry into the alveolar macrophages. However, this bacterium

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is able to live inside the immune cells through the formation of phagolysosomes within the macrophage, causing persistent intracellular infections (8). Naturally, T regulatory (Treg) response and production of immune-suppressive cytokines in the inflammation process occur following delayed immune responses in order to prevent the host damage reaction of Th1 activities (9). Mtb is a clever pathogen, which induces the Treg response and alters the immune response regarding the induction of the Th2 response, so that it could develop into active TB (9-11).

In the early 19th century, the Rook and Hernandez-Pando experiments, as well as the Glatmann-Freedman and Casadevall studies on the role of cell-mediated immunity (CMI) in TB and serum therapy trials for TB, indicated that the humoral immune response is not involved in the incidence of TB (12-14). In the late 19th century, following the Elie Metchnik discovery (i.e., phagocytosis), intravenous immunoglobulin (IVIg) therapy and definition of B cell function in antibody production, cytokine induction (especially IFN-γ), innate response activator B cells or antigen presentation to naive CD4+ T cells were proposed to depict their effects on the CMI response and the obvious changes in TB outcomes (15, 16). Therefore, it seems that Th1 response is not efficient against TB without B cells and the humoral response (17). In contrast, ample evidence suggests that immunoglobulin (Igs) and B cell responses play a key role in the development of TB and improving the immune system response to specific Mtb antibodies during the chronic stage of TB and IFN-γ stimulation, while also increasing the host destructive response, production of IL-10, immunosuppressive cytokines mediated by Th2, and humoral activities or killer/regulatory B cells (FAS/FASL) as the limited immune-effective response against TB clearance throughout the human body (18, 19). Furthermore, it has been hypothesized that B cell phenotypes and humoral response could contribute to the development of treatment options or act as the biomarkers of TB diagnosis (20).

The Immune Response against TB

The key feature of the immune response to Mtb as a bacterium with intracellular life is mostly focused on the CMI, including the dendritic cells (DCs), lymphocytes, and monocytes/macrophages (21). Based on this approach, following the inhalation of Mtb via the contaminated droplets and entry into the lungs, the bacteria interact with the CMI as instantly engulfed by the DC cells and macrophages. As antigen-presenting cells (APCs), these cells present Mtb antigens to Th1 in the infection area through the major histocompatibility complex II (MHC II) (22). As the producing factor of interferon γ (IFN-γ) and interleukin 2 (IL-2), Th1 (TCD4+) cells play a pivotal role in TB infection. IFN-γ is expressed in terms of the response to mycobacterial antigens, activating the infected macrophages and leading to the intracellular killing of pathogens (23).

Neutrophils are among the first cells that contribute to the dueling against Mtb infections. Human studies have indicated that cationic proteins (e.g., defensins), which are produced by neutrophils, play a key role in the macrophage-mediated killing process (24). On the other hand, non-MHC restricted lymphocytes (i.e., natural killer [NK] cells [CD56+]) are able to respond potently during early pulmonary infection by Mtb (25). The IL-2 produced by Th1 interacts with the NK cells, increasing their cytotoxic activity. Activated NK cells are known as lymphocyte activated killer cells (26). The antimicrobial activity of NK cells may be direct or indirect. In the direct manner, the NK cells are able to kill extracellular bacteria or cause the apoptosis of the infected cells with the intracellular bacteria via perforin, granulysin, and granzyme production (27). In the indirect manner, the IFN-γ and tumor necrosis factor-alpha (TNF-α) that have been produced by the NK cells activate the infected macrophages, thereby leading to the intracellular killing of Mtb.

Based on experimental studies, the hyper-secretion of IFN-γ leads to excessive cellular response and destruction of the lung tissues. Another T cell subset is T cytotoxic (TCD8+) lymphocytes, the defense mechanisms of which resemble the NK cells. Unlike the NK cells, these cells identify the immunogenic antigens via MHC I (28). As a new subset of lymphocytes, Treg cells are able to secrete some regulatory cytokines (e.g., factor Foxp3 and IL-10) as inhibitory cytokines. As a result, the development of Treg cells leads to the reduction of Th1 cell immunity and IFN-γ production (29).

The Role of Humoral Immunity against Mtb

The CMI system plays a pivotal role in the immune responses against TB infection. On the other hand, the role of B cells has mostly been discovered in the TB infection. Despite its accumulation in the mycobacterial tissues, Mtb is basically an intracellular bacterium, which allows the avoidance of antibodies. Therefore, there must be extensive research regarding their anti-TB roles. With a more comprehensive approach, the antibody-mediated immunity could affect responsiveness in terms of Mtb (30).

Interaction of B Cells with Innate Immunity

Regarding the first strategy adopted for the containment of the progression of Mtb infection in infected lungs, the immune system forms an immunological structure known as granuloma. Granuloma forms a microscopic aggregation of macrophages with variable number of DCs, lymphocytes, and plasma cells (31). Granulomas play a pivotal role in inhibiting the progression of mycobacterial infections and assist in the clearing of pathogens from the lungs in the early stages of the disease. The subsequent hypoxic conditions of macrophage enzymes, nitric oxide synthase-2, and arginase-1 lead to the killing of intracellular pathogens (32, 33).

The interaction of B cells with the innate immune system remains largely covert. However, switching the B cells into plasma cells in the granuloma area is essential to the immune response to Mtb. Following the binding of specific antibodies to bacterial antigens (opsonization), they interact with the surface FC receptors of macrophages and facilitate the phagocytosis of the bacteria. Eventually, the phagocytosis bacteria or their components undergo the required process and are presented to Th1 through the MHC II molecules (34).

Interaction of B Cells with T Cells during the Immune Response

Evidently, B lymphocytes act as APC cells (e.g., DCs and monocyte/macrophages), providing antigens from their MHC II to Th1 cells. Moreover, they produce antibodies and cytokines. It seems that these properties may contribute to T cells against intracellular pathogens such as as Mtb (35). Through the interactions between B cells and T cells, B cells are developed into four subsets, including the B effector 1 (Be1), B effector 2 (Be2), B regulatory (Breg), and plasma cells. Be1 cells produce cytokines such as IFN-γ, IL-12, TNF-α, IL-10, and IL-6, while Be2 cells produce IL-2, lymphotoxin, IL-4, IL-13, and IL-10. Breg (B10) cells, which are known as anti-inflammatory B cells, produce IL-10 in the form of a combination through the stimulation of antigens, including CD154 (CD40L) and toll-like receptors 10 (TLR10), while also transforming the growth factor-β (TGF-β). Upon exposure to the secreted cytokines and cross-regulatory interaction phenomenon, B cells could be effective in the differentiation of T cells (Figure 1) (36-39).

Effect of B Cell Cytokines on the Immune Response

As mentioned earlier, B effector cells are produced through the interactions between B cells and T cells. Be1 cells are primed by Th1, while Be2 cells are primed by Th2. After the differentiation, each cell produces its own cytokines (40). Recently, it has been confirmed that upon stimulation by Mtb, the innate B cells resident in the infection area produces small amounts of type I IFN, which modulates macrophage polarization and acts as the stimulant of macrophages toward the anti-inflammatory/regulatory macrophages. However, the excessive production of type I IFN leads to the increases mycobacterial burden in the lungs, which in turn leads to tissue damage (41).

IL-6 and IL-10 are the prodigious cytokines secreted by the B cells in the granuloma. As anti-inflammatory cytokines, these cytokines play a key role in reducing inflammation in the derived-granulomas of the Mtb areas. Another prominent feature of IL-6 is the expansion of B cells (particularly the T cell residents in the granulomas)(42).

The Role of Antibodies against TB

Routinely, Mtb afflicts the lungs, causing pulmonary TB, and when mycobacteria spread from the lungs via blood and lymph to the other sites of the body, disseminated TB occurs.

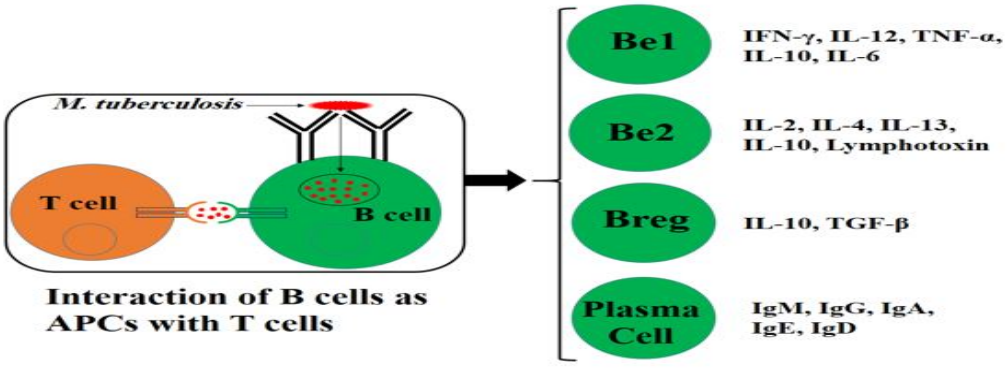

Figure 1: B cells can act as APCs against M. tuberculosis. B cells carry processed antigens of Mtb and interact with Th1 or Th2 cells via MHC II. Following interaction, B cells in return to change to four subsets, Be1 (IFN-γ, IL-12, TNF-a, IL-10, IL-6), Be2 (IL-2, IL-4, IL-13, IL-10, Lymphotoxin), Breg (IL-10, TGD-ß) and plasma cells (IgM, IgG, IgA, IgE, IgD). These subsets of B cells each, in turn, can be effective on Mtb infections.

The mortality rate of disseminated TB is remarkably higher than pulmonary TB, particularly in children. Patients with undetectable levels of antibodies against mycobacterial components (e.g., lipoarabinomannan [LAM]) in their serum samples are at a higher risk of disseminated TB (43).

According to the recent studies, investigation of the serum of vaccinated infants with TB vaccine MVA85A (Modified Vaccinia virus Ankara expressing Ag85A from Mtb) confirmed that increased Ag85A-specific IgG antibody is associated with the reduced risk of active TB (44, 45). Furthermore, some clinical findings have demonstrated that vaccination with immunodominant mycobacterial antigens (e.g., Acr, Ag85, CFP10, ESAT-6, and heparin-binding haemagglutinin antigen) leads to the induction of protective antibodies, IgA or IgG (IgG1 and IgG3), followed by the Mtb burden (46, 47).

Humoral Vaccine-based Design as the Future Perspective

Mtb-specific B Cells as the TB Diagnostic Marker

Several B cell phenotypes could act as a guide to predict the development of TB (46-47). In a study in this regard, Loxton et al. observed that CD138+ (plasma cell), CD27+ (memory cell), CD23+ (active B cell), and CD19+IgM+CD23−CD27+ (marginal zone B cell) were present in various stages of TB. Therefore, the monitoring of different B cell phenotypes in TB could be a reliable marker for the prediction of TB, especially latent TB (48, 49).

Antibody-based Vaccines

Today, the role of humoral immunity in the control of infectious diseases has been confirmed, especially the antibodies that influence the CMI response through Ag presentation, apoptosis of Mtb-infected cells (deletion of the Mtb reservoir), opsonization or Abs-mediated NK cell activation (50). According to the literature, several types of Mtb-specific antibodies have been detected in the animals and humans infected with tubercle bacilli as for IgG LAM in Mtb-infected children (51).

Based on experimental evidence, monoclonal Abs (e.g., arabinomannan, LAM, heparin-binding haemagglutinin or hspX) could cause animals to produce a protective response against TB. In addition, high-dose IVIg has been reported to lower the tubercle bacillary load in the C57BL/6 mice model (15). Vaccination with BCG in B cell-deficient mice has shown no efficient Th1 mediated results or uncontrolled destructive response of IL-17/neutrophil response to Mtb in the B cell knockout mice model (52-55). Therefore, the antibody could influence the immunoprotective response of TB and collaborate with the innate immunocytes and CMI in order to eradicate tubercle bacilli (52).

In recent decades, monoclonal antibodies have been suggested as potential candidates for replacement with the BCG vaccine for the induction of humoral and cellular protective immunity in adults with TB and HIV-infected individuals even as a therapeutic option for XDR-TB (53, 54).

Conclusion

Classically, it has been claimed that humoral immunity is only efficient in extracellular pathogens, while recent findings have demonstrated the potential role of B cells and antibodies in the CMI response. According to the results of this review, the CMI response (especially Th1 activities) is not sufficient for the efficient protection against TB. B cells and Abs also influence the innate immunocytes and Th1, playing a key role in various outcomes of exposure to tubercle bacilli. Although B cells contribute to Mtb in the development of active TB, our knowledge should be extended regarding the effects of B cells and humoral immunity on TB pathogenesis and targeted harmful humoral-mediated responses. Moreover, B cells and antibodies are considered proper for the promotion of the investigations on the discovery of reliable biomarkers to diagnose the development of TB in cases with latent TB infection as they might be a new generation of therapeutic options in this regard.

Acknowledgements

Hereby, we extend our gratitude to the Antimicrobial Resistance Research Center at Mashhad University of Medical Sciences and Department of Microbiology and Virology of the School of Medicine at Mashhad University of Medical Sciences for assisting us in this research project.

Conflict of Interest

The authors declare no conflict of interest.

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