Review

Research progress on immune response of B lymphocytes and anti-*Mycobacterium tuberculosis* infection

Jiacong You

Tianjin Lung Cancer Institute, Tianjin Medical University General Hospital, Tianjin China

Keywords
Mycobacterium tuberculosis bacteria; antibody; B cell; summary

Correspondence
Jiacong You,
E-mail: jcyoutjmu@126.com

DOI: 10.1515/ii-2017-0120

Abstract

Multiple studies elucidated the importance of cellular immune mechanisms for protection against *Mycobacterium tuberculosis*. However, recent studies showed that B lymphocytes play a role that is underestimated through various interactions with cellular immune response, forming an important aspect of host defense against *M. tuberculosis* bacteria. Therefore, the author hereby proposes a progressive perspective for immunology of tuberculosis, i.e., cellular immunity and humoral immunity are not necessarily mutually exclusive. The present study summarizes recent studies that support the important role of B lymphocytes in terms of *M. tuberculosis* infection.

Mycobacterium tuberculosis (Mtb) belong to *Mycobacterium* genus. This pathogenic species causes tuberculosis (TB). TB remains an important infectious disease nowadays. This disease can invade body organs, with pulmonary TB being the most commonly observed. Humoral immunity plays a negligible role in the defense against Mtb. However, antibodies were reported to pose effects on Mtb since the late 19th century. Humoral immunity indicates that under stimulations from antigens, as represented by B lymphocytes, immunocytes in the immune system of organisms differentiate and proliferate into plasma cells and synthesize various types of antibodies to generate specific immune responses with biological effects. Adoptively transferred B lymphocytes can limit deterioration of inflammations induced by TB [1]. This condition demonstrates the important role of immunoglobulin-mediated immune regulation. The present study summarizes recent studies on humoral immunity against Mtb.

Relevant antigens of humoral immunity against Mtb

Antigen 85 complex

Antigen 85 complex (Ag85) comprises at least three components, namely, 85A, 85B, and 85C. Up to 70%–80% of sequences of these components are the same. As a fibronectin-binding protein, Ag85 exists in higher amounts of serum of patients with active TB in comparison with patients with non-active TB or other lung diseases or healthy controls [2]. In the study among indigenous people of Mexico, Abebe *et al*. [3] proved that IgG exhibits good effect on Mtb complex Ag85. Another study showed that compared with patients cured by anti-TB treatment, effective antibody titer was more remarkable for Ag85 in non-cavernous TB. Antigen 85B (Ag85B) is one of the important immunoprotective antigens against Mtb infection, and it is widely used in studies on new vaccines for TB. Studies showed that when immunizing mice/guinea pig, effective immune response is induced by both plasmids encoding Mtb single Ag85B and plasmid expressed by multigene fusion of Ag85B and other protective antigens against Mtb. Thus, the number of bacteria in visceral organs, such as the lungs and spleen, significantly reduces, and survival time of experimental animals extends. Studies also showed that DNA vaccine encoding Ag85B exhibits good immunotherapy effects. Both Ag85B and early secretory antigenic target-6 (ESAT-6) in Mtb culture filtrate protein can stimulate organisms to generate protective immune responses. These antigens are also effective target for anti-TB infection of organisms. Ag85B and ESAT-6 can induce certain levels of cellular immune response, humoral

immune response, and certain degree of immune protection force, thus providing defense against Mtb infection.

Protein with a relative molecular mass of 38×10³

The protein is a membrane lipoid protein of *M. tuberculosis* and a specific protein of *M. tuberculosis* complex group. This molecule also exists in bacillus Calmette–Guerin (BCG) vaccine, with expression quantity 10 times higher than that of BCG [3]. The antigen contains seven antigenic epitopes and can induce humoral and cellular immune responses and be used for serological diagnosis of TB.

Lipoarabinomanna (LAM)

LAM is a Mtb-glycosylated lipoid protein and a membrane protein of Mtb. LAM contains seven monoclonal antibody-binding epitopes, features immune advantages for B lymphocytes, and can induce early immune response. Related experiments showed that specificity and sensitivity of LAM in immunologic diagnosis of patients with pulmonary TB reached 78.3% and 50.5%, respectively [4].

Heat shock protein

Heat shock protein is a heat stress protein that exists extensively from bacteria to mammals. When exposed to high temperatures, thermal excitation induces synthesis of such protein to protect organisms and to stimulate responses from T and B lymphocytes. As a somatic protein, heat shock protein exhibits regulatory functions and protective effects on cells, and high homology is observed between the same kinds of protein in prokaryotic and eukaryotic cells. In heat shock protein family, one Mtb and BCG-specific epitope exists, exhibiting good immune protection and immunotherapy effects [5].

Surface molecules and subgroups related to B lymphocytes and TB humoral immune response

B lymphocyte surface displays surface molecules, such as B cell receptor, Igα, Igβ, CD40, and B7. These molecules induce humoral immune response when B lymphocytes are stimulated by antigens. FcγRII, also called CD32, can be divided into two subtypes, namely, FcγRIIa and FcγRIIb, which are IgG receptors with low-to-medium affinity and mainly combine with polymerized IgG. FcγRIIb is the only prohibitive Fcγ receptor. This antigen mainly transmits suppression signal through its own molecular cytoplasmic domain coupling with immunoreceptor tyrosine-based inhibitory motif (ITIM), playing an important negative regulatory role in inherent and adaptive immunities. FcγRI, IIa, and III are all activated Fcγ receptors, which mostly transmit activation signal by coupling with γ dimer containing ITIM. FcγRIIb defect can increase the number of Mtb in mice; thus, through Fcγ receptor in TB, B lymphocytes can significantly influence host immune and disease prognosis, activation of Th1, the number of mycobacteria and generation of interleukin (IL)-10 in lungs [6]. By influencing activation of immune complex with Fcγ receptor in cells, B lymphocytes may induce immature dendritic cells to secrete IL-10. This phenomenon indicates that B lymphocytes can provide defense against Mtb infection and also directly induce responses by regulating cellular immunity. Zhang *et al.* [7] reported that the most prominent change in peripheral blood of TB patients is the significantly increased ratio of CD19+ CD5+CD1d+ B lymphocyte subgroup. The B lymphocyte subgroup is considered a group of B lymphocytes with regulating function. This group can inhibit CD4+ T cells from secreting IL-17, indicating that these cells exhibit certain immunosuppressive function. CD19+CD5-CD1d+B, CD19+CD5-CD1d-B, and CD19+CD5+CD1d-B cells do not inhibit IL-17, and their specific functions remain unclear. Corominas *et al.* [8] discovered through their study that CD86 expressed by B cell surface can regulate immune response to Mtb infection. As antigen presenting cells, B lymphocytes can induce generation of certain cytokines that favor Th2 response. This phenomenon indicates that B7 (CD80/CD86) expression plays an important role in anti-TB function of T lymphocytes.

Antigen presentation of TB humoral immune response

Maglione *et al.* [1] observed that B lymphocytes display different functions at various stages of TB infection. In acute infectious stage, B lymphocytes participate in granuloma response and effectively inhibit pulmonary TB infections. Deletion of B lymphocytes leads to aggravated inflammations and granulomatous dysregulation. In chronic stage of Mtb infection, activated subgroups of B lymphocytes may exhibit immune effects on Mtb of primary lesions and thus prevent disease relapse. Such role is partially fulfilled

by B lymphocytes as antigen-presenting cells. Although antigen uptake is performed by BCR in a specific manner, B lymphocytes can absorb receptor-specific peptides that fail to conform to major histocompatibility complex. Zhang *et al.* [9] proposed that granulomas are highly germinal centers for B lymphocytes, and B lymphocytes effectively present antigens and simulate activation of immune cells in lesions.

Antibodies of TB humoral immune response and their functions

In vitro studies on mechanism of humoral immune protection of organisms [10] showed that specific antibodies can inhibit replication of pathogenic bacteria, neutralize toxins secreted by pathogens, enhance antibody-dependent cell-mediated cytotoxicity (ADCC), play the role of opsonin, and induce a series of complement reactions. Antibodies in the body can enhance endocytosis for Mtb and lethal effects of neutrophil granulocytes and macrophages. Mtb coated with specific antibodies can stimulate responses from CD4 and CD8, thereby enabling their effective processing and presentation. Serological test for diagnosis of TB became a research topic because of study results indicating enhanced humoral immunity of TB patients but weakened cellular immunity. Julian *et al.* [11] developed serological diagnosis methods, including detection of Ig60 antibody, Kp90ImCRAC (mycobacterial immuno-cross reactive), and LAM antibodies, showing sensibility of 20%–93% and specificity of 62%–100%. Recently, Reis *et al.* [12] proposed that antibodies may display the following functions in infection sites. As for Mtb coated with antibodies (extracellular) with FcγR in immune response, after Fc receptor combines with immune complex, it intracellularly transmits activation signals through γ-chain immunoreceptor tyrosine-based activation motif. Fc receptor also mediates multiple immune responses, such as cell activation, ADCC, generation of super-oxygen ion, antigen presentation, phagocytosis, and pinocytosis, playing an important role in elimination of immune complexes and regulation of immune functions of organisms. Reljic *et al.* [13] discovered from mouse model infected with TB that anti-Mtb monoclonal antibodies, including LAM, 16 ku crystalline, and heparin-binding hemagglutinin adhesion, all function effectively in TB treatment. These antibodies indirectly protect organisms in various ways: some reduce Mtb microbial load in tissues, and some delay progression of inflammations and prolong survival time of animals.

After diagnosis with TB, organisms first respond by increasing anti-TB IgM, followed by continuous increase of IgG. Periods of presentation of humoral immunity and anti-TB IgM and IgG also differ because of different courses of TB. Detection of TB antibody IgM is an important reference for early TB diagnosis. Saunders *et al.* [14] showed in a study on macaque that B lymphocytes mainly gather in granulomas and express CXCR5 and human leukocyte antigen-D related. Phuah *et al.* [15] observed that compared with non-infected tissues, tissues containing Mtb can generate higher levels of specific IgG, and Mtb granuloma-specific antibodies can be detected in plasma cells. All the above findings indicated that B lymphocytes exist in certain Mtb pathogen infection sites (pulmonary granuloma and chest lymph nodes) and can accordingly produce antibodies that control local infections. Jasmer *et al.* [16] reported that in patients infected with TB combined human immunodeficiency virus (HIV), IgG levels of anti-PPD antibodies vary because of different stages of HIV infection. This phenomenon may be caused by phosphorylation of defective T cell receptors, inducing deletion and activation of zeta-chain-associated protein kinase 70 and IL-2 gene transcription-related mitogen-activated protein kinase protein and protein mass deficiency after T lymphocyte stimulation by antigens. Decreases in γδT cells result in decreased generation of interferon (IFN)-γ and increased content of IL-10, which is responsive to PPD, whereas antituberculin isotype IgG3 antibody can prevent TB reactivation [17]. Recently, Balu *et al.* [18] revealed that after inoculating human anti-Mtb α-crystal protein IgA antibody into nasal cavity of CD89 transgenic mice, infection of H37Rv *M. tuberculosis* strain reduced.

Immune regulation of B lymphocytes in TB infection

In addition to serving as antigen-presenting cells and producing antibodies, B lymphocytes can stimulate proliferation, growth, and differentiation of T lymphocytes. Activated B lymphocytes can generate different cytokines. Secretion of cytokines (e.g., IFN-γ and IL-12) in certain effector B (B-1) cells is related to Th1. Activated B lymphocytes can secrete large amounts of IL-6 and IL-10, playing an auxiliary role in immunity of T lymphocytes. IL-6 is a vital factor that synergistically stimulates responses of T lymphocytes. By contrast, IL-10 inhibits immune response of

T lymphocytes. IL-10 can strongly inhibit dendritic cells and macrophages and also prevent generation of IL-6 and IL-12 through these cells [19].

Conclusion

TB is a serious and globally spreading infectious disease. However, to date, studies provide inadequate information regarding TB and TB pathogens and fail to elucidate mechanism of anti-TB infection of hosts. Sustained and long-term efforts should be applied to control and eradicate TB. Continuous development of molecular biology and immunology laid theoretical and practical foundations for studies on related substances and mechanisms of humoral immune in TB infection. We believe that breakthroughs can be achieved by future research in this field.

Declarations

Acknowledgements
No.

Competing interests
The author declares that she has no competing interest.

Authors' contributions
YJ You made the literature analysis and wrote, discussed and revised the manuscript of this review.

References

1 Maglione P, Xu J, Chan J, *et al*. B cells moderate inflammatory progression and enhance bacterial containment upon pulmonary challenge with Mycobacterium tuberculosis. Immunol, 2007, 178(11):7222-34.

2 Abebe F, Holm-Hansen C, Wiker HG, *et al*. Progress in serodiagnosis of Mycobacterium tuberculosis infection. Immunol, 2007, 66(23):176-91.

3 Aiken AM, Hill PC, Fox A, *et al*. Reversion of the ELISPOT test after treatment in Gambian tuberculosis cases. BMC Infect Dis, 2006, 6:66-72.

4 Tessema TA, Bjune G, Hamasur B, *et al*. Circulating antibodies to lipoarabinomannan in relation to sputum microscopy,clinical features and urinary anti-lipoarabinomannan detection in pulmonary tuberculosis. Scand J Infect Dis, 2002, 34(2):97-103.

5 Dubaniewicz A, Trzonkowski P, Dubaniewicz-Wybieralska M, *et al*. Comparative analysis of mycobacterial heat shock proteins-induced apoptosis of peripheral blood mononuclear cells in sarcoidosis and tuberculosis. Clin Immunol, 2006, 26(3):243-50.

6 Maglione PJ, Xu J, Casadevall A, *et al*. Fc gamma receptors regulate immune activation and susceptibility during Mycobacterium tuberculosis infection. Immunol, 2008, 180(5):3329-38.

7 Zhang M, Zheng X, Zhang J, *et al*. CD19+CD1d+CD5+B cell frequencies are increased in patients with tuberculosis and suppress Th17 responses. Cell Immunol, 2012, 274(1-2):89-97.

8 Corominas M, Cardona L, Gonzalez L, *et al*. B-lymphocytes and co-stimulatory molecules in Mycobacterium tuberculosis infection. Int J Tuberc Lung Dis, 2004, 8(1):98-105.

9 Zhang M, Wang Z, Graner MW, *et al*. B cell infiltration is associated with the increased IL-17and IL-22expression in the lungs of patients with tuberculosis. Cell Immunol, 2011, 270(2): 217-23.

10 MxManus DP, LoukasA. Current status of vaccines for schistosomiasis. Clin Microbiol Rev, 2008, 21(1):225-42.

11 Julian E, Matas L, Hernandez A, *et al*. Evaluation of a new serodiagnostic tuberculosis test based on immunoglobulin A detection against Kp-90antigen. Int J Tuberc Lung Dis, 2000, 4(11):1082-5.

12 Reis MC, SILva BD, Sousa EM, *et al*. Role of antibodies reactive to HspX in discriminating pulmonary tuberculosis contacts with high risk of developing active disease. Braz J Infect Dis, 2011, 15(6):617-8.

13 Reljic R, Clark SO, Williams A, *et al*. Intranasal IFN-γextends passive IgA antibody protection of mice against Mycobacterium tuberculosis lung infection. Clin Exp Immunol, 2006, 143:467-73.

14 Saunders BM, Britton WJ. Life and death in the granuloma: immunopathology of tuberculosis. Immunol Cell Biol, 2007, 85(2):103-11.

15 Phuah JY, MattILa J. Activated B cells in the granulomas of nonhuman primates infected with Mycobacterium tuberculosis. Am J Pathol, 2012, 181(2):508-14.

16 Jasmer PM, Nahid P. Clinical practice. Latent tuberculosis infection. New Eng J Med, 2002, 347(23):1860-6.

17 Encinales L, Zuniga J, Granados-Montiel J, *et al*. Humoral immunity in tuberculin skin test anergy and its role in high-risk persons exposed to active tuberculosis. Mole Immunol, 2010, 47(5):1066-73.

18 Balu S, Reljic R, Lewis MJ, *et al*. A novel human IgA monoclonal antibody protects against tuberculosis. J Immunol, 2011, 186(5):3113-9.

19 Hoehlig K, Lampropoulou V, Roch T, *et al*. Immune regulation by B cells and antibodies a view towrds the clinic. Adv Immunol, 2008, 98:1-38.