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REVIEW

# B cells as multi-functional players during *Mycobacterium tuberculosis* infection and disease

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SUMMARY

Immunity to tuberculosis is still understood to be driven and maintained by T-cell derived immune responses. With a steady influx of data, it is becoming clear that B cells, the mediators of humoral immunity, have the capacity to function in roles not previously appreciated within the traditional B cell dogma. In this review we aim to discuss B cells, from its generation through to its functioning as effectors in both the innate and adaptive immune response, within the tuberculosis domain.



## 1. Introduction

*Mycobacterium tuberculosis* (*M.tb*) is the causative agent of tuberculosis (TB) and was responsible for 9 million newly reported TB cases during 2013 [1]. Although the World Health Organisation (WHO) reported that TB mortality has fallen by 41% since 1990 [2], the organism was still responsible for claiming 1.5 million lives during 2013 [1]. More than a century [3] of dedicated research into abolishing this threat has passed and the disease is still regarded as the most successful known infectious pathogen to man. During the 1990's, TB was declared a global emergency by the WHO [4], launching the “Framework for effective TB control” initiative that defined five required elements in controlling TB [5]. These globally accepted five elements are: (i) a government that is committed to the maintainable control of tuberculosis; (ii) using sputum-smear for diagnosis, mainly among patients who self-refer to health services with symptoms; (iii) utilising standardized short-course chemotherapy coupled with appropriate management conditions, including direct observation treatment (DOT); (iv) a functioning drug supply system; and lastly, (v) a recording and reporting system that allows the assessment of treatment outcome [4]. In 1995 this package was branded under the name Directly Observed Therapy, Short-course (DOTS) and subsequently became one of the most well-known brands in health. It is estimated that 4.6–6.3 million lives were saved between the programme's inception in 1995 and 2009 from the 49 million tuberculosis patients treated under the DOTS/Stop TB Strategy during this time frame [6]. Despite the fact that current TB management strategies is proving to be successful with increased patient cure and ultimately saving lives, the resulting impact on the epidemiology has shown to be less than expected [7]. Risk factors associated with an individual's susceptibility to TB, on a population level, include poor working and living conditions that facilitate TB transmission, and include factors like HIV infection, malnutrition, diabetes, alcohol abuse and indoor air pollution [7]. It is furthermore estimated that two billion people live with latent *M.tb* infection, where these people may serve as a reservoir for future active disease cases [8]. Latent tuberculosis infection (LTBI) is defined as being infected with the causative agent, but lacking clinical symptoms, without being exempt of future development into clinical disease. *M.tb* interacts with the host immune system in a very complex fashion. Not all people who are infected progress to active disease; latently infected individuals have a 10% lifetime risk of developing active disease with clinical symptoms. Immunosuppressive triggers such as anti-tumour necrosis factor (TNF) therapy for unrelated diseases, HIV infection and diabetes greatly enhances this risk, but it can also be reduced with prolonged isoniazid prophylaxis [9]. Conclusions made from studies specifically focussed on latent infection postulates that LTBI

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(latent tuberculosis infection) and active tuberculosis disease aren't mutually exclusive but rather represent a spectrum of disease states that is dynamically influenced by the host- and pathogen's interactions [10]. Being able to accurately distinguish between latent and active phases of the tuberculosis disease would be of supreme benefit to the proper management and eradication of the epidemic. The term "biomarker" is a portmanteau of "biological marker" and by definition refers to a broad sub-classification of medical signs (outside observations from the patient that objectively quantifies its medical state) which can be measured in an accurate and reproducible fashion [11]. An encompassing review on immunological biomarkers in tuberculosis by Walzl et al. defined the ideal TB biomarker as being capable of: (i) distinguishing between active and latent tuberculosis disease in patients, (ii) returning to basal levels during treatment, (iii) reproducibly predicting clinical outcomes (cure, relapse or sterilizing cure of *M. tuberculosis* infection) in diverse population settings and finally, (iv) predicting the efficacy of vaccines and serve as end points in clinical trials [12]. With MDR-TB (multi-drug resistant tuberculosis) and XDR-TB (extensive-drug resistant tuberculosis) becoming more prevalent, the need for effective biomarkers is paramount. Recent studies have broadened the views of biomarker research to not only focus on host cytokine responses [13–16], but also micro-RNA (miRNA) [17–19] and to even diagnose tuberculosis on a serological basis by combining different immunoglobulin (Ig) classes against selected *M.tb* targets [20]. This raises the possibility of the validity of utilising B cells as biomarkers in tuberculosis disease, not only by measuring their capacity as effectors/regulators in expressing cytokines, but also on a phenotypic level and observing dynamic changes in population groups.

Lymphocytes subsets (T, B and natural killer (NK) cells) have similar appearances under the microscope, but can clearly be distinguished by their function. One of the characteristics which differentiates lymphocytes from other immune cells is the unique antigen receptors they contain following a recombination process of the V, D and J gene segments. For B cells this results in functional IgH and L-chain genes. The T cell counterpart results in the T cell receptor (TCR) gene repertoire, including TCR $\alpha$, $\beta$, $\delta$ and $\gamma$ [21]. This empowers the immune system to have very high specificity to a broad spectrum of antigenic challenges. Some of the functions associated with lymphocytes are the production of antibodies, the regulation and drive of the immune system and direct cell-mediated killing of tumour cells and cells intracellularly infected with pathogens [22]. Classically, B cells are known for producing antibodies which are the primary effectors of humoral immunity. These antibodies have the ability to nullify elements harmful to the body, including extracellular pathogens and toxins. Other functions of B cells include the activation of the compliment system and to facilitate opsonisation.

Characteristically, tuberculosis research was T-cell driven because of the pathogens intracellular nature. And although numerous advances in delineating tuberculosis disease have been made, it still remains an unsolved problem and accounts for great loss and morbidity globally. It is now clear that previously under-appreciated cell types are playing a prominent role in the immune response to tuberculosis. This review aims to give an overview of B cells during disease (HIV-TB coinfection), B cell development, its role during immune activation as well as the functional capacity of effector/memory B cells and their regulatory role.

## 2. The TB/HIV syndemic

Human immunodeficiency virus (HIV) primarily infects lung lymphocytes and, like tuberculosis, alveolar macrophages. This accounts for the poor prognosis concerning patients with HIV and TB co-infection. HIV actively reduces the host's specific immune defence by infecting all major lymphocyte populations (including B cells) while TB flourishes in compromised immune environments. It is now well established that HIV rigorously impairs lung immune responses [23].

Elementary work done by Young et al. in 1985 compared Broncho alveolar lavage (BAL) immunoglobulins from HIV infected patients displaying pulmonary symptoms with uninfected individuals and found increased levels of total IgG, IgM and IgA [24]. This supports the notion that HIV infection results in the systematic polyclonal activation of B cells.

Acute infection with HIV-1 results in a detrimental delay and decrease in the host's humoral immune response, rendering it ineffective. Integrin $\alpha_4\beta_7$ on T cells are the binding site for the envelope protein gp120 of HIV-1 virus. The virus also uses this protein to signal through to the cell. Jelicic et al. recently showed that gp120 also binds naïve B cells through $\alpha_4\beta_7$ and that this resulted in an abortive proliferative response. When applied to primary B cells, signalling through this complex resulted in increased expression of both TGF-$\beta$1 and FcRL4, whose functions are as an immunosuppressive cytokine and inhibitory B cell receptor respectively. The group further showed that co-culturing of autologous $CD4^+$ T cells (infected with HIV-1) with B cells resulted in an even higher increase of FcRL4 expression on B cells [25]. This work showed that viral proteins not only facilitate the chronic activation of the immune system, but that they play a central role in HIV-1 associated B cell dysfunction. The work identified a potential mechanism the virus employs to subvert early humoral responses during infection. The early role of B cells in the activation of T cells, can thus directly affect the host's immune response to T cell driven protection in diseases like tuberculosis.

A recent study showed that natural autoantibodies found in human serum have the capability to be functional in the protection against *in vitro* HIV-1 infection [26]. These autoantibodies were denoted as IgG-reactive antibodies, and an immunoglobulin subclass analysis showed that IgG2 was dominant in presence, both in Gamma Bind G Sepharose Flow through (GBF) and normal human serum (NHS). Isolated IgG-reactive antibodies from the GBF fraction neutralized an *in vitro* HIV-1BaL strain infection with almost 100% effectiveness when a 2 μg/ml concentration was used [26]. These findings support the notion that IgG reactive antibodies should be investigated as a possible use in the treatment of HIV-1.

Plasmablasts are the result of B cells that have undergone terminal differentiation following infection or vaccination. These cells then circulate transiently in the blood, with the ability to produce antibody. But, as a hallmark of HIV, B cells surmise to hyperactivity and undergo this terminal form of differentiation early, and abnormally high levels of these plasmablasts are observed in viremic individuals [27].

Buckner et al. reported that HIV viremic individuals display increased amounts of $IgG^+$ plasmablasts not only in the early phases of disease, but predominantly in individuals with chronic HIV viremia as opposed to the predominant $IgA^+$ plasmablast profile observed in both HIV-negative and aviral HIV-infected individuals who are on treatment [27]. This study also concluded that although plasmablasts may contribute specifically to the HIV immune response, that this B cell response is not HIV specific and arise prematurely on the suggested basis of indirect immune-activation effects of HIV replication [27]. This level of B cell dysregulation might explain why HIV infected individuals have insufficient antibody responses, even during early phases of the infection.

The immunological environment of HIV/TB co-infection is not only characterised by this incomplete humoral response, but also by cytokine and chemokine irregularities that results in immune activation, increased viral replication and T cell dysfunction

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