The role of antibodies in Tuberculosis

Mycobacterium tuberculosis (Mtb) is the causative agent of tuberculosis, which is one of the top 10 causes for death worldwide. In 2017, 10 million individuals became sick with Tuberculosis (Tb), and 1.6 million people died from the bacteria, many of which were immunocompromised[1]. Because Mtb is an opportunistic infection, disease is more prevalent and severe among immune compromised individuals with conditions such as untreated HIV or autoimmune diseases. Especially in areas of poverty, both the Tb and HIV global pandemics are still evolving and ongoing despite continuous improvement in treatment options[2]. Together, Tb and HIV cause accelerated destruction of immunologic functions, resulting in serious health issues and death if untreated. Depletion of CD4 T-cells is the hallmark of HIV infection, and these immune cells are the ones essential for control of Tb, contributing to the high rate of progression to active disease in HIV/Mtb co-infected individuals[3]. Thus, both HIV and Mtb are a major health risk and in need of further research for disease control and pandemic eradication.

Mtb is a primarily pulmonary pathogen, which is spread between people via aerosol droplets if an individual with active Tb coughs up bacteria from infectious herds in their lungs. The understanding of the early phase of Mtb infection in humans is limited: after inhalation of the bacteria, they are transported to the lower respiratory tract[4]. Alveolar macrophages, which recognize the pathogen by toll-like receptors (TLR) and phagocytose the bacteria, are the primary cell then infected by Mtb. The bacteria employ different mechanisms to prevent macrophage defenses and escape from killing while replicating within the cells[5]. The bacteria secrete factors such as lipoarabinomannan (LAM) to inhibit phagosome maturation and acidification, allowing bacterial contents to be released into the cytosol after initiation of phagosomal rupture[6]. Finally, cytosolic bacteria trigger the host cell death programs. This allows the bacteria to escape host defenses and supports dissemination[5]. Before undergoing apoptosis, the host cell releases a variety of cytokines to attract immune cells, such as other macrophages, dendritic cells, and lymphocytes. The accumulation of immune cells around the infected macrophages and released bacteria then forms a granuloma, which is the hallmark of Tb. Granuloma formation allows the bacteria to remain in a latent state within the lung, often for very long periods of time[7]. While one third of the population is infected with the bacterium, only 10% of those individuals progresses to active Tb. This is why in most individuals, the infection causes few health issues because the bacteria remain in their latent state. It is not fully understood what causes reactivation, but some known factors are co-infection with HIV, organ transplantation with immunosuppressants, and close contact with individuals with active Tb disease[7,8].

To date, there are only two methods to diagnose latent tuberculosis infection: tuberculin skin test (TST) and interferon gamma release assays (IGRA)[9]. TST is widely used due to its low cost but has a high false-positive rate because it also detects mycobacterial proteins found in the Bacillus Calmette-Guérin (BCG) vaccine[10]. IGRAs, such as the commercially available QuantiFERON-TB Gold In Tube (QFT), are thought to be more specific, as they measure the release of IFN-γ by T-cells after stimulation with Mtb-specific antigens[11]. IGRAs can also distinguish between BCG- and Mtb infection-induced responses. TST and IGRA are both imperfect measurements of latent Tb because they cannot differentiate between new and recurring infections. Additionally, none of

these tests can assess the risk for development of active disease[4,12]. X-rays, microscopy, culture of replicating bacteria, and molecular tests such as nucleic acid detection are used to diagnose active Tb. Chest X-rays to identify granulomas are well established as a screening test but lack specificity, so a positive sample has to be complemented by a bacterial culture assay[4].

The immunology of Mtb infection is complex and still under investigation. CD4+ T-cells are of major importance for restricting Tb progression, which is why IFN-γ responses are measured as diagnostic markers by IGRA tests. Therefore, the majority of the Tb research field has focused on T-cell immunity for diagnosis, treatment, and vaccination. Conversely, humoral immunity has long been perceived as insignificant for the control of Tb due to the dogma that antibodies do not play a role against intracellular pathogens[13]. Members of the field focused on the serology of Tb showed that Mtb induces humoral responses to a wide array of Tb-specific antigens, especially LAM. IgG antibodies against Tb antigens have been shown to be increased in patients with active disease, giving hope for antibodies as a biomarker or indicator of exposure and disease progression[14]. Some of these antibody profiles have been associated with a reduced risk of infection, such as IgG titers against Ag85 in an infant case-control study[15]. Antibodies have also been shown to modulate immunity via Fc-receptor mediated phagocytosis and potentially confer protection[16].

Predominantly, IgG1 and IgG3 antibody are produced against Tb infection in humans[17]. These antibody subclasses are known to be highly functional and can strongly induce a variety of Fc-mediated antibody responses, such as antibody mediated phagocytosis by monocytes (ADCP) and neutrophils (ADNP) as well as complement and NK cell activation, especially against surface antigens[16,18]. Monoclonal antibodies were used in mouse models, and IgM antibodies specific to LAM and heparin-binding hemagglutinin (HBHA) have been shown to be able to reduce bacterial load and prevent dissemination from infection[19]. These studies suggest that humoral immunity indeed plays a role in protection against Tb and can serve as a diagnostic marker of exposure, infection, and disease progression.

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