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SIGNIFICANCE OF ANTIBODIES IN MYCOBACTERIUM TUBERCULOSIS AND THEIR ROLE IN DIAGNOSTICS

Microbiology

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ABSTRACT

Tuberculosis (TB) is considered as on the oldest infectious disease transmitted airborne by organisms of the Mycobacterium tuberculosis (MTB) complex. It remains as a huge challenge for the health of the human population and according to WHO, TB is a major killer after HIV/AIDS. It is highly prevalent among the population of lower socioeconomic conditions. In India, the implementation of the National strategic plan (2017-2025) for the national goal of eliminating TB by 2025 has led to several awareness and improvement in the livelihood of people with TB. The major drawback with the gold standard technique of TB is that it is highly time consuming. Diagnostic techniques that are both rapid to perform and are also highly sensitive than traditional methods are required at a less expensive rate than the molecular diagnostic tests relying on the amplification of nucleic acids. The serology of TB deals with several antibodies and antigens which can be employed for the diagnosis of TB. Serological diagnostic techniques are an ideal choice as they are usually based on the detection of the free soluble circulating antibodies against the mycobacterial antigens. The research in the identification of a suitable antigen for the serodiagnosis of TB has come a long way as the is a highly diverse reservoir for antigen and antibody in TB. This review describes on the role of antibodies in TB along with the most efficient antigen candidates that are capable of a rapid and sensitive diagnosis.

KEYWORDS

Tuberculosis, Antigen 60, Heat shock protein antigen, Trehalose 6, 6-dimycolate antigen, Lipoarabinomannan antigen.

INTRODUCTION

TB marked its existence as the most important infectious disease and is the primary burden in the low-income and middle-income countries where the diagnosis still relies on sputum smear microscopy and chest radiology. This promotes the great need for rapid point-of-care tests that can be used at all levels of healthcare [1]. Microscopic detection remains to be the primary diagnostic stool that is widely used because it is inexpensive and easily accessible along with the requirement for less man power and offers high specificity in settings prone to high TB prevalence. The alternative techniques developed in serology serve as a highly rapid and site independent technology in the field of TB diagnostics. Immunological methods use the mechanism of specific humoral or cellular responses to detect an infection or disease. The protective immune response associated with TB is cell mediated, but an antibody response is common and correlated with the lack of an effective cell-mediated response. The humoral immune response is characterized by the isotypic diversity of antibodies with different effector functions [2] and the IgG are the predominant antibodies. An efficient humoral response requires dynamic cooperation between the B cells and the T helper subsets.

Detection of antibodies is considerably simpler and less expensive and as a result serodiagnosis of TB is extensively investigated. However, the drawback is the poor sensitivity that is possibly due to the substantial and unexplained heterogeneity of antibody responses to different MTB antigens among patients Although the poor specificity is a limiting factor for serological tests, the occurrence of false positives access insight into the immunopathogenesis of TB. Antibodies produced by the Humoral response can act up as indicators for the development of a better diagnostic technique with rapidity and robustness in resource limited setups. This review discusses on the role of antibodies in Tuberculosis, the mechanism of employing them in diagnostics and on the prominent mycobacterial antigens with efficient candidature for diagnostic assays.

B Lymphocytes Generation, Activation and Induction of Humoral Response:

B lymphocytes develop from progenitor B cells (pro B cell) within the bone marrow due to the interaction of the B-Cell Receptors with stromal cells in the bone marrow compartment [3]. The BCRs are primary signaling molecule facilitating B cells in detection and response to an antigen and are generated by genetic rearrangement of germline DNA to generate receptors for recognizing a colossal range of antigenic targets produce multiple clonal B cell populations [4].

B cell activation is possible only with the onset of two signals which includes antigen crosslinking of the BCR constituting the primary signal [5] and T-cell interaction via CD40 and CD40L interactions which constitutes the Thymus-dependent (TD) antigen activation. B cell activation takes place within the lymph nodes employing the TD antigens [6]. The binding of the cognate antigen with the BCR leads to an assembly of large signaling complexes on the B cell surface such as the CD19, CD21 and CD81 thereby resulting in the increased expression of MHC class II and co stimulatory molecule B7 on the surface of B cell. After recognition and binding, receptor mediated endocytosis of antigen occurs and then they are processed and presented on the MHC class II molecules to recruit T-cell. Once a corresponding T-cell responds, a T and B cell signaling conjugate is formed for facilitating further interactions and enhancing cytokine release. After the antigen mediated B cell activation, the B cell undergoes intense proliferation, forming a clonal population [7].

The humoral response is mediated by B-cell and is induced when an antigen binds to the B-cell antigen receptor, internalized and then processed into peptides that activate the helper T cells. Signals from the bound antigen as well as helper T cell induce the B cell proliferation and differentiation into plasma cells for secreting specific antibody. These antibodies protect the host in three main ways which includes neutralization, opsonization and complement activation [8].

Human Humoral Immune Response to TB:

TB serology furnishes abundant data indicating MTB as an inducer of humoral immune response in humans despite being existing as an intracellular pathogen [9]. Several studies have reported that intradermal BCG vaccination can elicit IgG and IgM responses to several mycobacterial antigens, and especially to the glycolipid lipoarabinomannan. Some of these antibody responses enhanced both innate as well as cell-mediated immune responses against mycobacteria [10]. The humoral immune response to mycobacterial antigens varies depending on the state of infection for example, LTBI patients have Abs to a much smaller and partially different repertoire of TB antigens than those with the TB. Furthermore, the data obtained from both animals and humans indicate that the antibody titres correlate with the degree of mycobacterial load [11]. Although we concur that many antibodies elicited by TB might not be highly functional or enhance an inflammatory response, various studies suggest that certain antibodies have protective function against TB [12].

Antibody Responses In TB As A Result Of Progressive Disease:

Although the MTB -specific antibodies involve in bacterial clearance

and subsequent immune control there is also a possibility that they enhance activation of antibody responses in human. TB is a result of impaired cellular immunity. Thus, the elevated antibody responses in the chronic phase of could exacerbate the disease. Elevated levels of the MTB -specific IgG-secretory cells in the peripheral circulation of patients with active TB are associated with reduced MTB-specific IFN-γ production and more severe disease. High levels MTB -specific serum antibodies were observed in patients with advanced TB disease, including the cavitary forms of pulmonary TB. Various studies indicate that B cells modulate cytokine production, macrophage activation, and immunopathology in TB macrophages. TB disease can be exaggerated by cross-reactive antibodies to nontuberculous mycobacteria, which are a common confounder to the anti- MTB humoral immune responses in humans. Thus, the MTB -specific antibody responses in the sera of TB patients serve diagnostic purposes as biomarkers of active and/or progressive disease [13].

Association of Antibodies with the T Helper Cells:

Two distinctive cytokine secretion patterns are defined among the CD4+ T cells that possess different functions. They include the Type 1 helper (Th1) cells producing interleukin (IL)-2, gamma-interferon (IFN-gamma) and tumour necrosis factor-beta and TH2 cells expressing IL-4, IL-5, IL-6 and IL-10. In general context, the Th2 cells are excellent helpers of B-cell antibody secretion and Th1 cells delayed-type hypersensitivity inducers. The respective role of the cytokine microenvironment in determining the isotype profile of humoral response in vivo are yet to be studied. The Ig subclasses in humoral immune responses are described with unique properties with regards to the antigen binding, immune complex formation, complement activation, triggering cell-mediated immunity, half-life, and their abundance in the plasma. Thus, important for evaluation of the host antibody subclasses profile during the different stages of infection and in response to the MTB antigens [14].

Antibody-Based Affinity Diagnostic Tests:

The interaction between an antibody and an antigen is highly specific and this has led to the development of a variety of immunologic assays, including enzyme-linked immunosorbent assays (ELISA) and Western blots. These assays detect the presence of either the antibody or antigen which is crucial in disease diagnosis. These tests usually employ samples like sputum, urine, or blood. Lateral flow assay (LFA) diagnostic tests are another very common tests apart from ELISA [15] and are similar to the sandwich ELISAs in that pair of antibodies with minimum binding competition to a same biomarker is needed [16] in a sample of some bodily fluid which is applied at one end of a paper strip. Unlike the sandwich ELISA, LFAs only make qualitative diagnoses. The current generation of LFA tests possesses high sensitivity and specificity due to integration with the thin-layer chromatography [17]. Dipstick assays are based on the immunoblotting principle [18]. In the case of dipstick assay, a paper or a membrane is usually used as an immobilization platform and it is different from LFA as it does not rely on the lateral fluid flow through a membrane and consists of a paper strip coated with a capture antibody that is serial dipped into a multiple solution. A blot produced will show the presence of biomarkers and this assay is simple and easy for point-of-care diagnosis in resource poor countries. In addition to the above mentioned three antibody-based tests, many other combinations of antibodies and physical and chemical mechanisms of signal generation are applied as high sensitivity and specificity diagnostics but still majority of those designs require laboratory facilities that are inaccessible in resource-limited areas [19].

Problems And Challenges For The Antibody-based Diagnostic Tests Applying For Resource Limited Areas:

The problems and challenges for the antibody-based test is that it should be sensitive, specific, affordable and suitable for point of care application. It should also be ideally laboratory free and should not require need technical manpower. Furthermore, the physical components should be conveniently delivered and stored in areas without refrigeration or places without reliable power. The ELISA, LFA and dipstick are excellent candidate diagnostic test designs for resource-limited areas [20].

Antibodies To Mycobacterial Antigens For Diagnosis Of TB:

Diagnosis of TB especially the extra-pulmonary TB in its early stages is complex due to the nonspecific clinical features. Rapid, sensitive and specific methods of diagnosing TB are the need of hour. Most of the antibody detection ELISA are designed to make use of defined antigens carrying multiple epitopes of which are specific to MTB. However, due to the presence of pre-existing antibodies to nonspecific epitopes, such methods produce false positivity. With the advent of highly purified and recombinant antigens specific for the TB complex, the specificity of the ELISA test has been improvised. Non recombinant and recombinant antigens of MTB such as the purified protein derivative (PPD), 38kDa antigen and HSP60 have been employed for the serodiagnosis of TB. Some of the mycobacterial antigens used commonly are reviewed further in this chapter [21].

Antigen 60 (A60):

A60 is a semi-purified thermo-stable macromolecular antigen complex derived from Mycobacterium bovis strain BCG (Bacilli Calmette Guerin) and is composed of proteins, carbohydrate, and lipid in roughly equal amounts. It contains 30 components of which majority are present in mycobacterial homogenates. The A60 ELISA is of major interest due to the fact that it represents an important fraction of total mycobacteria antigens. The majority of antimycobacterial antibodies in the blood and cerebrospinal fluid of TB patients are against A60 antigen. The A60 antigen-based kit (Anda Biologicals, Strausbourg, France) are widely used for estimation of IgA, IgG and IgM antibodies in serum, cerebrospinal fluid and pleural fluid (Zou et al., 1994). It can be employed for simple screening test for patients with results suggestive of TB in those who had no sputum or were sputum negative for acid-fast bacilli (AFB). The major application of this antigen is the determination of response to antitubercular chemotherapy, as the serum IgG levels increases with the infection and decrease after the therapy starts [22].

38kDa antigen:

It is also called antigen 5 or antigen 78 and is a lipo-glycoprotein antigen of MTB that can induce B- and T-cell responses with high specificity and these are prime candidates for development of new diagnostics. They were reported to be specific for the M. TB complex and is the serological antigen forming a core component in various commercial serological tests Anti-38kDa antigen ELISA are useful tool for monitoring the efficacy of chemotherapy and for differentiating between the active and treated cases. These techniques are highly specific, easy to handle and requires no equipment. Therefore, such ELISA is particularly useful for field studies [23].

Heat Shock Protein Antigen:

Heat shock protein antigens stimulate both T- and B-cell responses. The humoral response to these proteins such as the 60, 65, 70/71kDa M-hsp are exaggerated in the patients with active TB. Detection of anti M-hsp antibodies do not have a diagnostic purpose antigenic cross-reactivity between M-hsp and their human homologues were reported in previous studies [24].

Lipoarabinomannan Antigen:

Lipoarabinomannan (LAM) is the polysaccharide antigen present in mycobacterial cell wall. Purified LAM from M. TB in its native acylated state was first employed for serodiagnosis of leprosy [25].

Antigen Of Acylated Trehalose Family:

Antigens of the acylated trehalose family are frequently investigated group of glycolipids. They include the (1) 2, 3-diacyl trehalose (DAT, previously referred to as SL-IV antigen), (2) 2, 3, 6-triacyl trehalose (TAT), (3) 2,3,6,6 tetraacyl trehalose 20-sulphate (Sulfolipid, SL-1) and (4) trehalose 6,6-dimycolate (cord factor). ELISA technique was employed in several studies using these antigens and an extensive variation in the IgG or IgM titers was obtained. Till date no analysis has been undertaken to determine the presence of specific IgA against the glycolipids mentioned above. In the case of IgM detection in groups of children, no difference between the infected and sick children was reported [26].

Sulfolipid Antigen:

SL-1 is an exclusive antigen of the virulent strains of MTB (Daff˙e & Draper, 1998). Serological evaluations of the IgG, IgM and IgA antibodies revealed IgG and IgA reactivity against SL-1 antigen as reliable but IgM reactivity as negligible [27].

Trehalose 6, 6-Dimycolate (Cord-Factor) Antigen:

Mycobacterial cell wall contains the cord factor which is a key molecule for the pathogenesis and immunity in TB [28] and is one of the most characteristic and ubiquitous cell wall glycolipids. The glycolipids are extremely stable physico-chemically on microplate ELISA [29]. A TB glycolipid (TBGL) antibody detection system performed using the cord-factor antigen with minor glycolipid

antigens derived from MTB H37Rv has been developed [30] and evaluated for the clinical utility at early stages of the disease by a multi-centre study. The cord factor antigen shows better stability, reproducibility and low cross-reactivity when compared to other antigens only if one chooses an appropriate antibody detection system [31].

Response To Mycobacterial Antigens In Children:

The difficulties of TB diagnosis in children and attempts for improvisations are not new. Although various scoring systems for the diagnosis of TB in children are often underutilized, misused or not used at all, the sensitivity and specificity are variable. Several diagnostic methods for children include the PCR, high resolution computerized tomography (CT) and improved serological tests [32]. Several combinations using different antigens or specific antibodies increase the sensitivity and specificity of serological testing of TB in adult patients [33]. ELISA for immunodiagnosis of TB has shown that he humoral response to mycobacterial antigens is low in the children, especially when combined responses against antigens or specific antibodies are not employed [34].

Other Newer Diagnostic Methods For Diagnosis Of Tb:

The nucleic acid amplification tests (NAAT) provide a reliable way for increasing the specificity of diagnosis (ruling in disease) but still sensitivity remains poor, especially in smear-negative (pauci-bacillary) disease where the clinical diagnosis is equivocal. For extra-pulmonary TB, the clinical judgment has both poor sensitivity as well as poor specificity. For pleural TB and TB meningitis, adenosine deaminase tests have higher sensitivity but limited specificity. NAATs have high specificity and could be used alongside the ADA (or interferon-g) for increasing the sensitivity of ruling out the disease and NAAT for higher specificity [35]. Various studies from low-prevalence countries suggest that the RD1 antigen-based assays are more accurate than TST- and PPD-based assays for the diagnosis of LTBI and if their superior diagnostic capability is found can be employed for routine clinical practice and can confer several advantages on TB control programs [36]. There are also several non-nucleic acid-based techniques on the commercial front and the most common ones have been tabulated in Table 1.

Table 1: Diagnostic Tests Not Based On The Nucleic Acid [37]

S.No	Diagnostic test	Technology
1	Signature Mapping Medical Sciences TbDX	Automated smear microscopy slide reader
2	Becton Dickinson MGIT Bedaquiline-Delamanid	Semiautomated liquid culture
3	Thermo Fisher Sensititre MYCOTB MIC plate	Culture system to determine MICs for rifampicin, isoniazid, ethambutol, ofloxacin, moxifloxacin, amikacin, streptomycin, rifabutin, para-aminosalicylic acid, cycloserine, kanamycin, and ethionamide
4	Salubris Mycolor Tk platform	Colorimetric culture media

A number of mycobacterial antigens can be applied for detection of specific antimycobacterial antibodies in terms of clinical use however one has to be very careful in using/choosing the test. The various factors that should be taken into serious consideration before these tests are used for clinical application are:

- The site involved (pulmonary/ extra-pulmonary),
- severity of disease (localized/generalized),
- AFB status (positive/negative), duration of illness (acute/ subacute/chronic),
- endemicity of disease (endemic/ nonendemic),
- genetic makeup of the individual,
- population-based response,
- cut off value for the local population (regular surveillance in endemic area), availability of sample (sera/body fluid from representative site),
- HIV status of patient (positive/negative),
- level of health care facility (primary/secondary level),
- purpose of test (diagnostic/prognostic/assessing progression of disease/assessing response to treatment),
- availability of laboratory support, etc.,

Detection of the antibody using specific antigens has been considered as a diagnostic marker for TB. However, the variability in the humoral responses in different population has been indicated by estimating the IgG antibodies. Selective increase in IgG1 and IgG3 antibodies in TB patients with advanced pulmonary disease were indicated. The factors that regulate these IgG subclasses are not well characterized [38]. A predominant IgG1 response to ESAT-6 and CFP-10 along with IFNγ, TNFα and IL-6 has been reported in the Brazilian TB patients [39]. The evolution of serological assays have come up a long way and with the selection of the appropriate antigen and application of it into diagnostics can serve as an efficient alternative for the gold standard techniques.

CONCLUSION

The World Health Organization (WHO) has so far estimated a worldwide total of about 10 million cases of TB (TB) and 1.5 million deaths in 2020. As smear microscopy has variable, sputum culture is much time-consuming with requirements for biosafety level three facilities and GeneXpert requires trained professionals with high equipment costs, an alternative rapid and cost-effective diagnostic technique is urgently required for TB. The potential advantages of tests based on the antibodies are cost-effective, easy to implement and are fast test performers thereby favoring their use in low-resource TB high-endemic settings. Serological tests are faster and do not require samples to possess tubercle bacilli. The Sensitivity and specificity depend on the antigen used and the type of tubercular infection. Though most of them have high specificity, their sensitivity is poor. There is, however, a promise in serodiagnostic tests such as the ELISA tests owing to their value in the early diagnosis of the disease with easy performance that are also rapid and reliable for the detection of TB.

Competing Of Interest:

There are no conflicts of interest.

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