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Genetic Variability and Its Vulnerability in Tuberculosis Infection

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Abstract

Tuberculosis (TB) is a world-wide infectious disease. It caused 10.4 million deaths in 2016. The study was aimed to describe some of the genes involved in the progression of the TB disease in the human population. This study is not only useful in understanding the pathogenesis of the disease and identifying the risk of population, but also paving way for the better treatment of the diseased individual.

Keywords: Tuberculosis; Genes; Pathogenesis; Human population

Introduction

Tuberculosis (TB) is a world-wide infectious disease mostly occurring in the lungs. It is caused by the pathogen *Mycobacterium tuberculosis* (M.tb). Though enormous efforts are being taken by World Health Organisation (WHO) yet TB still remains as one of the leading cause of disease.

In human beings reactivation of the passive infection causes active tuberculosis. Globally 1.8 million TB deaths occurred in 2016 and additionally 400,000 TB deaths from HIV co-infection. There were 6.3 million new TB cases of which 65% were men, 35% were women and 10% were HIV co-infected [1].

A person can get TB by inhaling Mycobacterium tuberculi that have been released into the air by a person with active TB. When a person with active TB disease of the lungs coughs, sneezes, or talks, droplets containing the M.tb are released into the air. The disease can be controlled by the activation of infected macrophages and antigen specific T-cell response and formation of granulomatous lesions which prevents the penetration of the bacilli to other parts of the body [2]. Macrophages are the important cells of the immune system which are formed in response to an infection. In immune system the main cells are macrophages which are a type of white blood cells resulted in response to infection. They recognise, engulf and destroy the mycobacteria infected cells. The function of macrophages is phagocytosis which is performed through mannose receptors (MR) and complement receptors. Toll-like receptors (TLR) activate the macrophage and dendritic cells (DC). The MR, TLR and complement receptors are cell surface binding proteins that provoke pro-inflammatory cytokine gene transcription and DC maturation on binding the pathogen-targeted molecules. Tumour necrosis factor (TNF) is a cytokine which help in the formation of granulomas. Other cytokines like IL-12, IL-8, IL-23 along with Major Histocompatable complex (MHC) Class II restricted Mycobacterial antigen helps in the differentiation of CD4+T cells into type1 T helper cells (Th1). *Mycobacterium tuberculosis* can be regulated immunologically by these Th1 cells [3]. The response of Th1 cells helps in the production of Interferon Gama (IFN-γ), which promotes phagosomal maturation and production of anti-mycobacterial molecules like reactive oxygen and nitrate intermediate [4].

Though the macrophages engulf the bacteria yet they fail to completely eliminate the M.tb [5]. So the remaining bacteria which survive after the attack by macrophages enter into a period of dormancy within the granulomatous lesion leading to a state of latent infection. The infection again gets activated by deterioration of the tissue and formation of cavities in the lung which endure the accumulation of M.tb by the influence of environmental factors like malnutrition, habitual smoking, aerosol transmission and HIV co-infection [6]. Not only the environmental factors but also the genetic factors are also associated with progression of the disease. Many studies revealed that the susceptibility of tuberculosis showed diversity in ethnic groups. Host predisposition to *mycobacterium tuberculosis* infection can be identified by different study designs [7] like case-control studies with candidate genes and family based genome wide linkage studies.

Previous studies revealed the evidence of linkage to tuberculosis with seven regions on chromosome 2, 3, 5, 6, 8, 9 and 'X'. Genetic association study can be conducted on candidate genes like various Cytokines, *NRAMP1*, Vitamin D Receptor *(VDR)*, Interferon-γ, Interleukin-1B, Interleukin-12, Human Leucocyte Antigen (HLA), Mannose Binding Lectin (MBL), Tumor Necrosis factor-α (TNF-α), Interleukin-4 and Interleukin-10 [8].

Vitamin D receptor

The *VDR* gene is located on the longer arm of chromosome 12. Before the emergence of TB drugs, Vitamin D was used to treat cutaneous TB [9]. It was found that the serum concentration of vitamin D3 is lower in untreated TB patients than in controls [10]. 1, 25 dihydroxy vitamin D3, the activated form of vitamin D3 is an immune-modulatory hormone that can activate human monocytes and inhibit the growth of mycobacteria [11,12].

Macrophages located on alveolar epithelium of lung produce large quantities of vitamin D3 [13] which help in the formation of granuloma. Several studies on different populations have been made on *Fok1* and *Taq1* gene loci [11-15]. *Fok1* and *Taq1* polymorphisms with low serum vitamin D3 levels reduce the VDR function which in turn is strongly associated with TB [11].

Many review studies revealed the association between VDR polymorphisms and TB to be either protective or susceptible. Significant association was found in a South Indian population, Gambian population and Gujarati Asians living in West London [11,16,17]. No significant association was found between *VDR* gene polymorphism and PTB in Cambodian, Tanzanian, Tuvinian, Chinese Kazakh and Chinese Han population [13,18-21]. Significant association was found between *VDR* gene SNPs and PTB in another South Indian population showing protection against TB [22].

NRAMP1

Natural Resistance Associated Macrophage protein 1 *(NRAMP1)* is also called as solute carrier family 11 a member *(SLC11a1)*. It regulates cytoplasmic cation levels mainly iron, which is necessary for mycobacterial nutrient and thus it influences the killing of the mycobacterium [23,24]. It is also required by the cell to generate reactive oxygen and nitrogen intermediates. *NRAMP1* gene plays an important role in macrophage responses to intercellular infection. It is located on the long arm of chromosome 2. This gene encodes a multi-pass membrane protein. Its main function is to act as divalent transition metal iron and manganese transport. It also helps in iron metabolism and host resistance to certain pathogens [22,25]. The mutation in this gene is associated with predisposition to infectious diseases like TB, leprosy, Rheumatoid Arthritis and Crohn's disease. Several TB associated studies on different populations were made to find the association of the variants of *NRAMP1* like D543N, 3'UTR, 4INT, 274CT and 5' promoter.

It was observed that certain SNPs of *NRAMP1* gene were associated with TB in West Africans, Koreans, Chinese Han, Japanese, South African and South Indian populations [22,23,26-30].

MBL

Mannose Binding Lectin (MBL) is a complement activating protein and altering agent. It binds to the mannose residue in Lipoarabinomannan membrane of the Mycobacteria. Three codon regions in SNPs 52, 54 and 57 result in decreased serum levels of MBL [31]. G54D variant of MBL has been extensively studied in different ethnic populations. Decrease in MBL level leads to a reduced infection by Mycobacterium, due to reduced complement activation.

Studies on *MBL2* gene SNPs have suggested to be associated with vulnerability to TB. They co-exist as degraded oligomers, having low attachment capacity to mannose. MBL binds with Lipoarabinomannan a component of M.tb which promotes ingestion and elimination by phagocyte [32,33]. Predisposition of TB may be due to low serum levels of Mannose binding lectin.

Different population studies revealed the relation between *MBL* gene SNPs and predisposition to TB showing variation. Significant association was found between *MBL* gene polymorphisms and PTB susceptibility in Lur population of Iran and also in Italian population [34].

Some studies were observed to have protective function against TB with low MBL levels. While other studies revealed to have increased susceptibility to the disease with low MBL levels [35]. No significant association with *MBL* gene polymorphism and susceptibility to TB was found in Chinese population [36]. However in a South Indian population gene polymorphism in MBL was found to be associated with TB in HIV co-infected patients [37].

IFN-γ

IFN-γ is important for defending the host against TB pathogen. The SNPs in intron IL (+874A→T) present within a binding site for the nuclear factor Kappa B. In general population null mutation in IFN-γ R1 leads to susceptibility of mycobacterial infection [38].

Out of 874 IFN-γ gene polymorphism revealed to have protective effect for TB predisposition. Higher level expression of IFNG causes much resistance to M.tb. Genetic defects in IFN-γ gene and IFN-γ receptor leads to severe mycobacterial infections [39]. Some studies revealed reduced IFN-γ levels in cases with active TB [40,41].

MHC polymorphism

CD4+ and CD8+ T cells play an important role in host defence to TB [42]. Decrease in the number of CD4+ T cells in HIV infected person's results in progressive primary TB infection, reactivation of latent TB infection and also increases the susceptibility to TB reinfection [43-45]. HLA plays a major role in initiation and regulation of specific immune response to a foreign antigen [46]. The *HLA* genes encode for Class I, Class II and Class III histocompatibility proteins. They are important immune-modulatory molecules [47]. The *HLA* genes encode protein process and convey *M.tuberculosis* antigens to the T-lymphocytes for recognition. Polymorphism in DNA Sequence at different sites in HLA leads to allelic variation and antigen recognition due to differential binding proteins [48]. Heterozygosity of HLA alleles shows beneficial effect as they allow the immune system to present more peptide epitopes to the T-Lymphocytes [49] and may have arisen as a strategy by the host to counter antigenic peptides in infectious organisms. Most of the genes in the HLA are in linkage disequilibrium; therefore

susceptibility to infectious disease may be Polygenic. Since the pathogenesis of pulmonary tuberculosis is due to a harmful cell-mediated immune response, number of observations has illustrated the strong influence of HLA class II polymorphisms on tuberculosis predisposition [50].

Both MHC Class I and Class II case-control association studies have found to be susceptible to TB. Positive genetic association was found in MHC class I with TB, but both negative and positive association was observed between TB and MHC class II polymorphism [51]. This suggests a strong influence of MHC Class II in the modulation of the immune response to Mtb infection through cell mediated immunity. Significant association was found in HLA DRB1* 04, DRB1* 07, DRB1* 11, DQA1* 0101, HLA DRB1* 1302 was found to be associated with TB in Syrians, Iranians, Indonesians and South Africans [52-55]. HLA-DR2 was observed as the main allele which is positively associated with PTB in an Indian population [56-58] and Polish population [59].

Transporter associated with Antigen Processing -2

TAP1 gene and *TAP2* genes are located in between HLA-DQ and HLA-DP regions. Antigenic peptides bind to HLA class II molecules and are transported to CD8 T cells through endoplasmic reticulum [60].

Case-control studies revealed significant association between *TAP* gene polymorphism and TB infection in Li population of China [61]. Statistical associations were reported between alleles of *TAP2* gene and PTB in North Indian population [62]. But no significant association was found between *TAP1* gene and TB in North Indian population and in a North Western Columbian population [63].

Interleukins

Several studies have been performed on the polymorphisms of *IL1, IL2, IL4, IL6, IL10* and *IL12* genes. Interleukin-2 is necessary to initiate and amplify immune response. IL-12 is a hetero dimeric pro-inflammatory cytokine consisting of P40 and P35. It is produced by activated macrophages. Both IL-12 β1 and IL-12 β2 receptors are expressed mainly on T cells and natural killer cells [64].

Association between interleukins and TB differs with different ethnic groups. *IL-10* plays a critical role during latent stage of TB infection. Studies reported significant association between *IL-10* gene polymorphism and TB in Asians, but reduced association in Europeans and Americans [65]. Significant or marginal association of PTB with IL12B polymorphisms was found in Gambia, Guinea-Bissau and African-Americans [66].

TNF-α

TNF- α plays a complex role in immune response against TB and influences the secretion of TNF by the macrophages, dendritic cells and T cells [67-69]. TNF-α in synergy with IFN-γ induces nitric oxide synthetase-2 (NOS2) expression [69]. TNF-α is essential for removal of infection and preventing dissemination. Convincing data on the importance of this cytokine in granuloma formation in TB and other mycobacterial diseases have been reported [70].

Cell transportation, within tissues is affected by TNF-α in *M.tuberculosis* infection. TNF-α influence expression of adhesion molecules as well as chemokines and chemokine receptors, and this is certain to affect the formation of functional granuloma in infected tissues. TNF-α has also been implicated in α-immune-pathologic response and is often a major factor in host-mediated destruction of lung tissue [71]. Many studies revealed, elevated levels of TNF-α at the site of lesion observed in pleural fluid, as compared to systemic response in blood showing that the compartmentalized immune response must be containing the infection [72]. Genetic heterogeneity studies revealed risk of PTB in association with TNF-α gene in Bashkorstan population [73]. Significant association between TNF-857 and TB was also identified in Iran population, but no significant association was found in Cambodian population [74,19]. Also no significant association was found with TNF-238, 308 in Iran population, Thai, Indian and Turkey population [53,75-77].

TLR- toll like receptors-2

Toll Like Receptor (TLR) are mammalian cell surface proteins that provoke pro-inflammatory cytokine gene transcription when they bind to pathogen associated molecular pattern. TLR-2 signalling is required for the activation of cytokine responses against mycobacteria [78]. The interactions between *M.tuberculosis* and toll-like receptors interact each other. TLR2, TLR4, are activated immunologically by *M.tuberculosis* in CD14 a independent ligand specific manner [79,80].

Many studies revealed that *TLR4* and *TLR9* play an essential role in the risk of MTB. No significant association was found between *TLR4, Asp299, Gly* and *TLR9. T-1486C* polymorphism with PTB in Iran and Gambian population [81,82]. But significant association between *TLR-4, ASP299, Gly* and *Thr* 399LLe polymorphism and PTB was found in Indian population [83].

Conclusion

Many polymorphisms contribute the predisposition to TB in several populations. The genetic vulnerability and the protective response of host to pathogen interaction involved in tuberculosis are multifactorial where the balance between genetic and environmental factors plays an important role. Hence it is difficult to detect the genetic mechanism involved in immunity. Recent studies using animal models and humans through genetic manipulation techniques like recombinant DNA technology will enhance the understanding of the pathogen and host genetic mechanism in the future generations. The varying results obtained from the studies in different ethnic groups reflect the differential contribution of the genetic predisposition of all polymorphic alleles. The effects of polymorphism which confers the susceptibility to one population and protection in another population may be due to linkage disequilibrium. The study of mycobacterial infection is not only useful for understanding the disease but also in identifying the population risk. This study is also useful to promote pharmaco-genomic strategy to prevent reactivation of the disease.

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