ROLE OF HUMAN LEUCOCYTE ANTIGEN (HLA) AND NON-HLA GENES IN SUSCEPTIBILITY OR RESISTANCE TO PULMONARY TUBERCULOSIS

Human beings live in an environment endemic to various diseases. Under such conditions, some individuals are susceptible to certain diseases while most are resistant to those diseases. This raises many questions. One such question is whether the person who is susceptible is genetically different from the person who is resistant to the disease? Similarly, in a family, one of the parents may be affected with a particular disease *(e.g.* diabetes); among the children born to the parents, if one child (younger one) develops the disease and the other child (elder one) does not, the question arises why did the younger one develop the disease and the elder did not, when both of them were living together with the affected parent. This raises the possibility of the disease being inherited from parents. If genetic factors play a major role in disease susceptibility or resistance, in what way are they associated with the disease development? Do they control the immune response to an antigen and/or pathogen? Do they play a role in the immune mechanism of susceptibility or resistance to disease? This article gives an account of disease susceptibility or resistance in pulmonary tuberculosis in the context of the host genetic factors, *i.e.* HLA (Human Leucocyte Antigens) and non-HLA genes and their gene products.

HLA and disease association - a hypothesis

For considering genetic susceptibility to various diseases and disease association in the context of HLA, several hypotheses exist for explaining MHC (Major Histocompatibility Complex) associated diseases. The main hypotheses are:-

(1) That HLA A, B, C (Class-I) and DR, DQ and DP (Class-II) antigens could act directly as disease susceptibility agents. For this, three possible mechanisms have been suggested: (a) There could be antigenic cross reactivity or mimicry between infectious organisms and a given HLA antigen. This phenomenon is termed as "molecular mimicry". Serological cross-reaction between HLA 827 antigen and the bacterial strains *Klebsiella* and *Shigella* has been identified[1,2]. This means that common antigenic determinants are shared by HLA B27 and the bacteria; (b) HLA antigens could act as receptors for microorganism; and (c) HLA antigens could influence particular immune responses, acting as immune response (lr) genes. It has been shown that lr genes regulate the immune response to any antigen or pathogen).

(2) The MHC genes may be physically close to the chromosome region that carries a gene conferring susceptibility or resistance to a particular disease. This hypothesis may explain the lack of complete association, and geographical variation in the association, due to linkage disequilibrium.

(3) Genetic susceptibility due to non-HLA genes: Though classical genetic studies in humans and experimental models have clearly documented the primary contribution of the MHC genes, these genes themselves appear to be insufficient in conferring susceptibility or resistance to disease.

Susceptibility or resistance to tuberculosis

Pulmonary tuberculosis is a granulomatous lung disease caused by *Mycobacterium tuberculosis.* Susceptibility to tuberculosis has been suggested to be multifactorial. Though environmental and socio-economic factors are primarily related, numerous studies have emphasised the importance of host resistance and hereditary susceptibility[4,5]. Susceptibility or resistance to tuberculosis may be under the control of the genetic make up of an individual. The host genetic factors such as HLA (Human Leucocyte Antigen) and non-HLA genes may be associated with susceptibility or resistance to tuberculosis.

HLA gene polymorphism

Finding out of HLA and non-HLA genes/gene products (antigens) which are associated with susceptibility or resistance to tuberculosis will serve

to provide HLA genetic markers to development of the disease. Moreover, studying the role of these markers in the immune mechanism underlying susceptibility or resistance to tuberculosis will be useful for understanding the immunopathogenesis of the disease. Studies of HLA and tuberculosis susceptibility have been carried out, in populations as well as in families by several groups in differents part of the world. The association of various HLAs with disease susceptibility in different ethnic population groups has been shown in these studies[6-12].

The HLA association shows some geographic variation. It seems likely that evolutionary selection pressures have given rise to frequent polymorphisms in genes involved in resisting infectious pathogens and contributed to marked allele frequency differences at the same loci. When geographic variation in pathogen polymorphism is superimposed on host genetic heterogeneity, considerable variation may occur in detectable allelic association. Gene-environmental interactions are likely to introduce another layer of complexity[13]. The genes involved in defense against infectious pathogens evolve more rapidly than others.[14] and excessive polymorphism in the human genome may result from selection pressures exerted by infectious diseases. Similarly, the causative organism *M. tuberculosis* also has genetic variation. During evolution, all these polymorphic forms might have evolved due to the host-parasite interaction.

Studies in non-Asian countries

A large number of HLA association studies have been carried out in non-Asian countries[6-11]. One of the first reports of an association between HLA and tuberculosis showed an increased frequency of HLA B8 in Canada[6]. Other studies showed an increased frequency of HLA B5, B15 and DR5 in the North American blacks[7,8], HLA A2 and B5 in the Egyptian population and B27 in the Greek population[11]. A negative association has been reported for DR6 in American blacks[9]. Since more interesting findings have been reported from the Asian region, the discussion is being restricted to the Asian populations.

Studies in Asian populations

Several studies of HLA association with pulmonary tuberculosis have been carried out in Chinese[12,15], Korean[16], Indonesian[17], Indian[18-24] and Russian patients[25]. A significantly increased frequency of HLA-DR2 was seen in the major studies[20,21,23,24,17,25] which have revealed HLA DR2 association with higher susceptibility to tuberculosis.

Of the numerous Indian studies on HLA association with pulmonary tuberculosis[18-24], the earlier ones focussed on association of HLA Class-I antigens[18,19] in tuberculosis patients and later, in family studies in north India[21,23] and south India[20,24]. An increased frequency of HLA DR2 in pulmonary tuberculosis patients compared with the control subjects was found. Molecular study has revealed that the allele DRB1 * 1501 of HLA-DR2 was higher compared with DRB1 *1502 in north Indian patients[23]. While both DRB1 * 1501 and * 1502 were increased in south Indian patients[27], no deviation was seen between * 1501 and *1502 alleles. Association of HLA DP B102 and DQ1 with susceptibility to pulmonary tuberculosis has also been shown in patients in south India[27]. On the other hand, a decreased frequency of HLA-DR6 in pulmonary tuberculosis patients suggests that DR6 may be associated with resistance to tuberculosis[21,24].

Previous investigations showed a varied picture of the association in different populations mainly because of geographical distribution of antigens and the ethnic background of the populations. However, studies carried out in India, Indonesia and Russia have shown a definite association of HLA DR2 and DQ1 with pulmonary tuberculosis. It is well established that DR2 is in linkage disequilibrium with DQ1.

In a recent study[27], HLA DRB1 * 1501, DRB1 *08 HLA DQB1 *0601 (a subtype of HLA-DQ1) and DPB1 *02 were found to be positively associated with susceptibility to pulmonary tuberculosis while a negative association (preventive fractions associated with resistance) has also been identified (DRB1 *11(5), DRB1 *10, DQB1 *0501 and DPB1 *08). Haplotype analysis also supports the DRB1 * 1501 -DQB1 *0601 association with susceptibility to pulmonary tuberculosis.

HLA DR2 and immunity to tuberculosis

The association of HLA DR2 with severity of pulmonary tuberculosis has also been emphasised in Indian population. In south Indian patients, DR2 has been shown to be more strongly associated with

far-advanced, smear positive tuberculosis than with minimal and moderately advanced disease[20].

In Russian patients, DR2 was associated with chronic fibrocavitary cases who failed to react to PPD[25]. Our study has revealed that HLA DR2 is associated with both low and high tuberculin test response[28], Further, among north Indian patients a high frequency of DR2 was seen in treatment failures compared with healthy controls and treatment responders[23]. Though severity of the disease is associated with HLA DR2, follow up of patients treated with short course chemotherapy did not reveal any difference in DR2 frequency between relapse and quiescent patients[29].

Patients bearing DR2 antigen have higher level of antibodies to *M. tuberculosis* compared with other patients. Further, there is evidence favouring a spectrum wherein cell-mediated and humoral immunity are at the opposing ends of the spectrum. Our recent study suggests that in active tuberculosis, patients having DR2 and a trend towards higher antibody response to *M.tuberculosis* antigens possibly show that higher antibody titre may have suppressed the cell mediated immune response[26]. It has been suggested that patients and controls having DR2 give a high reaction to PPD[20]. Further study has revealed that DRB1 * 1501 (a subtype of DR2) is responsible for greater tuberculin induration compared with DRB1 * 1502[30]. Similarly, HLA DR2 is found associated with lymphocyte response to *M. tuberculosis* culture filtrate antigen both in active and cured (quiescent) tuberculosis patients[31]. A decreased level of plasma lysozyme, a phagocytic enzyme (lysosomal enzyme) involved in microbicidal activity has been found in DR2 positives as compared with non-DR2 active pulmonary tuberculosis patients[32]. This suggests that susceptibility to pulmonary tuberculosis is not only influenced by HLA DR2 genes/gene products but by non-HLA gene factors as well.

Recently, association of multi candidate genes has been suggested for various infectious diseases[13]. In north Indian pulmonary tuberculosis patients, compared with control subjects, the "Transporter" associated with antigen processing gene 2 (TAP2) has been found associated with active tuberculosis, along with HLA DR2[33]. Studies on non-HLA gene polymorphism have revealed that functional mutant homozygotes of mannose binding protein genes are associated with pulmonary tuberculosis independent of HLA DR2[34]. Moreover, study of Vitamin D receptor (VDR) gene polymorphism has revealed a significant increase of VDR mutant homozygotes (tt) in female patients compared with female contacts while a significant increase of wild type homozygotes (TT) was observed among female contacts compared with female cases[35], suggesting that HLA DR2 gene/gene products in combination with other HLA and/or non-HLA genes, play a major role in susceptibility to pulmonary tuberculosis.

Non-HLA gene polymorphism

Non-HLA gene polymorphism studies in tuberculosis have revealed definite association between tuberculosis and the haptoglobin 2-2 phenotype[36], except in Indonesia[37] and India[19].

Recently, human genome analysis has revealed several candidate non-HLA genes, including cytokine genes, but due to point mutations most of these non-HLA genes occur as diallelic polymorphic forms. Such polymorphic genes have been shown to be associated with susceptibility to a number of infectious and non-infectious diseases. Some of the important non-HLA genes are as follows:

Mannose-binding protein

Mannose-binding protein (MBP), also known as mannose-binding lectin (MBL) is an acute phase protein secreted by liver. It binds mannose and N-acetylglucosamine terminated glycoproteins and plays an important role in host defence against pathogens. Upon binding with certain carbohydrate moieties, such as terminal N-acetyl glucosamine or mannose, on various pathogens, MBP activates complement via specific protease and acts directly as an opsonin using the Clq receptor on macrophages. Mutations are found at the coding regions of the MBP genes *i.e.* at codons 52, 54 and 57 that lead to low or near absent serum MBP levels in heterozygotes and homozygotes, respectively. Low serum level of MBP is associated with a common opsonic defect and is frequent in recurrent infections of infancy and possibly infections in adult life.

Studies carried out in Gambia have revealed that MBP is not associated with pulmonary

tuberculosis[38]. But in an Indian population, an increased genotype frequency of MBP functional mutant homozygote (including 52, 54 and 57) was found in pulmonary tuberculosis (10.9%) compared with control subjects (1.8%). Analysis of association of MBP genes and HLA DR2 has revealed that these genes are associated with susceptibility to pulmonary tuberculosis, independent of each other)'.

Vitamin D receptor

Vitamin D regulates calcium metabolism. Vitamin D3 is an immunoregulatory hormone and activates monocytes and stimulates cell-mediated immunity. Further, Vitamin D3 is one of the few mediators which have been shown to impair the growth of *M. tuberculosis* in macrophages[39]. Vitamin D effects are exerted through interaction with Vitamin D receptor (VDR). It has been suggested that the mutant allele of the VDR gene may be associated with reduced VDR mRNA expression. Allelic variants of Vitamin D receptor appear to be associated with differential susceptibility to several infectious and non-infectious diseases[13]. Vitamin D receptor gene polymorphism studied in Gambian tuberculosis patients suggested that the tt genotype (mutant) is less frequent in cases of pulmonary tuberculosis[40] but in Indian leprosy patients the tt genotype has been shown to be associated with tuberculoid leprosy whereas the opposite TT genotype is associated with lepromatous leprosy[41]. Our study of VDR gene polymorphism in pulmonary tuberculosis patients revealed a significant increase in VDR mutant homozygotes (tt) in female patients as compared with female contacts (spouses of male patients). Similarly, a significant increase of wild type homozygotes (TT) was observed in female contacts compared with female patients. This suggests that the mutant genotype variant of VDR gene (tt) is associated with susceptibility to pulmonary tuberculosis in female patients and the wild type genotype (TT) with resistance in female contacts, in India[35].

Natural resistance-associated-macrophage-protein-1 (NRAMP-1)

Studies in mice of acute susceptibility to infection with *Leishmania donovani* and *Salmonella typhimurium* led to the mapping of a major gene denoted as *Lsh* or *lty* on mouse chromosome-l. Subsequently, this was found to affect susceptibility to some strains of BCG *(Bacille Calmette Guerin).* This gene is expressed in macrophages and appears to influence macrophage activation. The equivalence for the BCG gene is the NRAMP-1 gene, which encodes for NRAMP-1 protein localised in the phagosome membrane. Several polymorphisms in the human homologue NRAMP-1 have been defined. Genetic linkage and association of tuberculosis and leprosy have been reported[42]. Recently, Bellamy *et al* [43] have identified variants in the NRAMP-1 gene that are associated with a significantly increased risk of pulmonary tuberculosis in Gambian population. Our study of one of the NRAMP-1 CA repeat microsatellite polymorphism at 199 and 201 region of the human NRAMP-1 gene revealed no such association in Indian patients (Selvaraj *et al.*, unpublished data) but other gene polymorphisms of the NRAMP-1 gene are under study.

Cytokine genes and receptors

An analysis of the course of infection in gene-knock-out mice has provided examples of the potential relevance ofpolymorphism in cytokine and cytokine receptor genes to infectious disease susceptibility in humans.

1) Tumor necrosis factor -a (TNF -a)

Increased production of inflammatory cytokines, such as tumour necrosis factor-µ (TNF-µ) has been found in tuberculosis and various other infectious diseases. The TNF $-\alpha$ is mainly produced by monocytes and macrophages and variant genes of TNF $-\alpha$ are associated with increased production of TNF $-\alpha$. Association studies have been carried out on polymorphisms in and near the tumor necrosis factor (TNF) gene located in class III region of MHC. Studies of gene polymorphism, at -308 promoter region in Cambodian patients have revealed no association with TNF $-\alpha$ in tuberculosis patients[44]. Our study of TNF-µ and -238 and -308 gene polymorphisms in Indian pulmonary tuberculosis patients also revealed no association either with susceptibility or resistance[35]. However, studies in Indian leprosy patients have revealed that the -308 variant is associated with lepromatous leprosy[45].

2) IL-1 receptor antagonist (IL-I RA)

Interleukin-1 receptor antagonist (IL-1 RA) is

another cytokine which competes for the IL-1 binding site. The production of IL-1 µ and IL-1 ß is controlled by IL-1 RA. The association of IL-1 RA gene polymorphism has been studied in various diseases[46]. Macrophages from carriers of IL-1 RA allele 2 have been shown to produce more IL-1 RA and less IL-1 µ than other genotypes[47]. Our study of IL-1 RA gene polymorphism in Indian pulmonary tuberculosis patients revealed no association with any of the genotypes[35] but spinal tuberculosis patients showed an increased frequency of genotype 22 compared with the control subjects (Selvaraj *et al.*, unpublished data).

Non-HLA gene polymorphisms such as Interferon g receptor/gene polymorphism have shown recessive susceptibility to atypical mycobacterial species such as *M. fortuitum, M. cheloni* and *M. avium.* A different mutation was identified in a child with fatal disseminated BCG infection.

Over the last few years, interest has increased in both MHC and non-MHC genes that are important to the immunogenetics of human infectious diseases. Susceptibility is mainly determined by a large or very large number of polymorphic host genes, each contributing a relatively small effect. Polygenic determination/ candidate gene studies in infectious disease have been more rewarding than other multifactorial diseases. With better knowledge of the mechanism of immunity, variants are being found that are likely to affect resistance to many infectious pathogens[13]. Finding out new MHC and non-MHC genes which are associated with susceptibility or resistance to disease will serve as genetic markers for predetermining development of disease. Moreover, the role of these multi-candidate genes on the immune mechanism of disease susceptibility or resistance will throw light on the mechanism of susceptibility or resistance to tuberculosis.

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