Asian Pacific Journal of Allergy and Immunology (1986) 4 : 149-156

SPECIAL ARTICLE

HLA and Tuberculosis—A Reappraisal

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Although a century has elapsed since the discovery of the causative organism of tuberculosis, the disease continues to be a great health hazard and one of the main public health problems in developing countries. The infection and the disease display certain interesting features. Although two-thirds of adults by the age of 25 years (in most developing countries) become infected with tubercle bacilli and harbour them in their body (as indicated by a Mantoux test and primary lesions on the chest radiograph), only about 2 per cent of these actually develop the disease.[1] It is apparent that in the causation of tuberculosis, interaction between the host, the environment and the causative organism appears to be important. On contact with *Mycobacterium tuberculosis,* the host most often is able to contain the bacillus, which, if and when the resistance of the host declines, multiply and cause the disease. It is conceivable that after the first attack, the bacilli may lie dormant for several years in various organs without causing any clinically apparent disease symptoms. In a small percentage of subjects, however, for some unknown reason, the pathogen starts to multiply, resulting in the typical lesions of the adult type. The post-primary activation of the dormant bacilli, which leads to disease, has been attributed largely to certain well recognised host factors, *viz.* state of nutrition, physical fitness, exposure to environmental pollution, immunosuppression (acquired or induced) *etc.* Nonetheless, these observations together with those suggesting familial aggregation of pulmonary tuberculosis (PTB) lead to some important questions : (1) Why is it that in 98 per cent of the individuals harbouring the bacilli, there is no disease ? and (2) Why is it that in families living under the same nutritional, environmental and socio-economic conditions, only some individuals develop the disease ?

Studies carried out in the past using non-HLA genetic markers have highlighted the importance of hereditary factors in governing susceptibility to pulmonary tuberculosis. The discovery of a highly polymorphic genetic system, such as the HLA which is the major histocompatibility complex (MHC) of man, has ushered in a new era in the immunogenetic approach to understanding disease. In particular, with the discovery in experimental animals of immune response genes (Ir genes) which also encode information for the genetic control of the immune response in man,[2] a large number of diseases have been studied for their association with the HLA antigens. Amongst these, infectious diseases are indeed important and studies carried out in the past have suggested that HLA plays an important role in determining the type of disease that develops following infection.

Biological significance of the HLA system

The HLA system is a part of the major histocompatibility complex (MHC) of man and is encoded by genes within a region located on the short arm of chromosome 6.

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This region, though only about one thousandth of the total human genome, continues to challenge biologists with its complexity and diversity. A unique feature of the HLA system closely related to its biological significance is its extraordinary polymorphism. The principal function of HLA gene products is in self/ non-self discrimination, which has relevance both in tissue or organ transplantation,[3] in cell-to-cell interaction in immunoregulation as well as in understanding the mechanisms underlying several disease associations. Indeed, HLA antigens or their gene products have been found to serve as recognition signals between cells of the immune system, promoting interactions that are essential for the efficient generation of an optimal immune response,[4] whether humoral, cell-mediated or both. A more detailed description of the HLA system has been provided in several review articles.[2,5,6]

HLA antigens fall into two principal structural classes : class I and class II molecules (Fig.1). The former comprise three series : HLA-A, -B and -C, each of which has a separate locus within the MHC. Biochemically, these consist of two chains- a transmembranous heavy chain of molecular weight 45 kd, non-covalently associated at the cell surface with a smaller (12 kd) peptide, *i.e.* β_2-microglobulin. The class II antigens have been shown to encompass a broad HLA-D region containing at least three sets of molecules officially designated now as DP, DQ and DR. In each case, the products include both α and β glycoprotein chains (approximate molecular weights 34 and 38 kd respectively) non-covalently associated on the cell surface. Recent studies involving molecular genetics and DNA recombinant procedures have helped in providing a more detailed understanding of the products of the HLA-D region. In particular, it has become evident that, although all β genes are polymorphic, there are clear differences in the extent of their variation. On the other hand, the α genes have only a limited polymorphism. Detailed knowledge of the class I gene products at the molecular level has progressed to a far lesser degree than that of the class II molecules. Using recombinant DNA techniques, it has been shown that the vast majority of the class I genes in the mouse H-2 complex map in the Qa and TL regions (the human equivalents of which have not yet been defined clearly) rather than in the conventional K, D and L regions (human equivalents of HLA-A, -B, -C loci).[6] However, it is not yet clear as to how many such genes are expressed and that why their gene products are not detected serologically.[6a] Also, not much data is available regarding their structural and functional characteristics.

The biological function of MHC gene products is currently the subject of intensive investigation. However, it is clear that class I antigens act as restriction elements for antigen recognition by cytotoxic T lymphocytes (CTL)[7] whereas class II molecules control the differentiation of helper T cells (T_h).[8] This phenomenon is known as the MHC restriction. In order that a particular CTL be able to kill a virus-infected cell efficiently and also prevent further production of

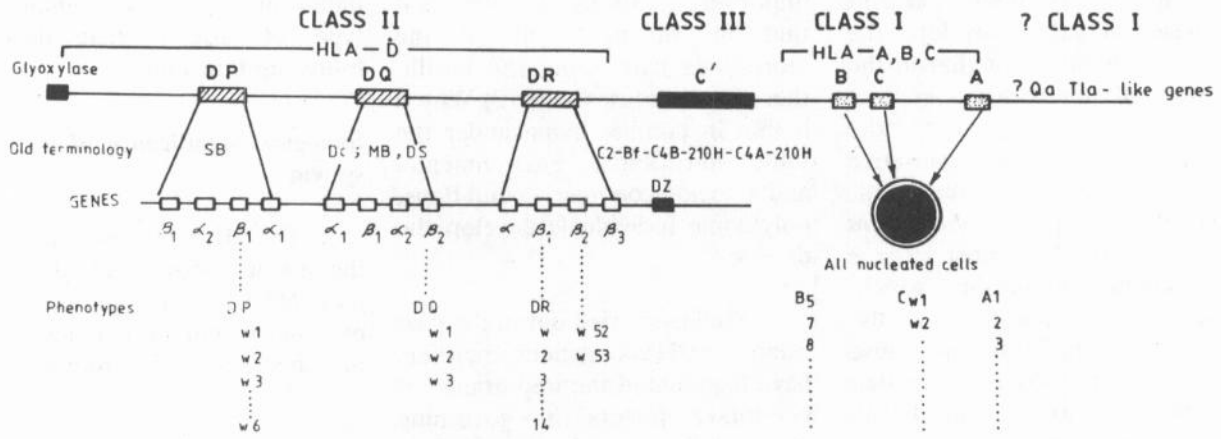

Fig. 1 Diagrammatic representation of the class molecules and gene products of the HLA complex on chromosome 6 of man. (Details in text.)

virus particles, it is imperative that the class I antigens be expressed on virtually all nucleated cells. On the other hand. T_h cells respond to antigen present on the cell membrane of only a limited number of cells, *i.e.* those expressing class II MHC genes, *viz.* B lymphocytes and antigen presenting cells (macrophages, epithelial cells, liver Küpfer cells, spleen dendritic cells, skin Langerhans cells). Much is known about the recognition of antigen by T cells and their receptor molecules. The T_h cells (principally helper/inducer cells) can only recognise " processed antigen " after it has been modified from its native state by the antigen presenting cell (APC) and that too together with the self HLA class II molecules. Moreover, in guinea-pigs the specific selection of the appropriate epitope on the original antigen molecule is under Ir-gene control[9] and is expressed at the level of the antigen presenting macrophage.[10]

The antigen presenting cell expressing an appropriate antigenic determinant on its cell surface in conjunction with the HLA class II determinants secretes a lymphocyte-activating factor (LAF) commonly known as interleukin-1 (IL-1). The latter activates the T-helper/inducer cells T_h cells carrying the CD4 phenotype as demonstrated by monoclonal antibody OKT4). The activation process involves the transcription and translation of interleukin-2 (IL-2) receptor genes followed by IL-2 secretion by the activated T cells.[11] This peptide growth hormone initiates cell cycling by a series of progressive signals[12] which leads to the stimulation of T-suppressor/effector cells and the generation of antigen specific clones of CTL expressing class I MHC products. In another pathway, the inducer process results in efficient helper signals resulting in B-cell IgG secretion. This step involves the production and activity of the B-cell growth and differentiation factors (BCGF, BCDF).

MHC and disease

Ever since the first demonstration by Amiel[13] suggesting an association between an HLA antigen-then called " 4c " (now know as B5+B35+B18+B15) - and Hodgkin's disease, a large number of diseases have been reported to be associated with antigens of the HLA complex. Many of these diseases have been studied as a part of the International Histocompatibility Workshops (Histocompatibility Testing 1984, 2nd AOHWC 1981) involving major population groups and have been reviewed elegantly several times.[5,6,14,15] With the advent of powerful tools of molecular biology, it has now been possible to reach the HLA genes directly at the DNA level. Using a class II cDNA probe and a battery of restriction endonucleases, progress has been made in identifying specific restriction fragment length polymorphism (RFLPS) in various diseases. In this regard, the best known example is that of insulin dependent diabetes mellitus (IDDM) in which the presence of TaqI 14.5 and 1.8-kb fragments and the absence of a TaqI 12.7 kb fragment in HLA-DR3/DR4 positive patients confers a level of relative risk approximately 10 times greater (about 400) than the risk calculated using only serologically defined markers.[16]

Essentially, there are two major approaches for studying the role of HLA antigens in disease susceptibility/resistance. One of these consists of population studies in which the gene frequency of HLA antigens in a group of unrelated sporadic patients is compared with the corresponding frequencies in a group of healthy controls of the same ethnic background. This approach gives information only on the " association " of a particular HLA specificity with the disease state. Also, it is best used with many technical artifacts, population heterogeneity, linkage disequilibrium between HLA gene products, *etc.* Moreover, the HLA characters under study may not include those which are truly responsible for disease susceptibility and if an association is found, it may well be due to linkage disequilibrium, thus making it even more difficult to determine the degree to which HLA is involved in disease susceptibility or resistance. The other approach involves HLA haplotype segregation analysis within multiple case families. Family studies enable us to detect " genetic linkage " between the HLA allele and a major disease predisposing gene. These, therefore, provide information on the inheritance and penetrance patterns of the disease susceptibility (DS) genes. In this approach, although the problems associated with population heterogeneity or linkage disequilibrium are overcome, in practical terms, it is more difficult to select or identify the appropriate families, fulfilling all the selection criteria for the study.

Immunological status in tuberculosis

Though much work has been done since the classic discovery by Robert Koch, a methodical description of its natural history correlating with the evolution of the immune response has been made only recently.[17] The nature of protective immunity has been found to be of the cell mediated type.[18] If a person suffers from post-primary tuberculosis, it in

itself is an indication of a breakdown in the host's resistance with reactivation of the dormant tuberculous focus. Evidence of a subtle degree of altered cell-mediated immune response (CMIR) in PTB has been detected by Holden and co-workers.[19] In progressive tuberculosis, an immunopathological spectrum comparable to that seen in leprosy could be observed, with dormant disease (Mantoux positive, normal CMI, low antibody levels and only a few bacilli in the tissues) at one extreme, and diffuse, disseminated lepromatoid or miliary non-reactive tuberculosis (abnormal CMI with lymphopenia of T4 helper/inducer cells, tendency towards an increase in antibody levels, the presence of a large number of bacilli in the tissue) at the other. In between these two forms, there is an intermediate form with two further subtypes[20] having a continuous range of clinical and histopathological manifestations.

Recently, a subset of patients with tuberculosis was described in which the ability of the peripheral blood mononuclear cells to produce gamma interferon in response to PPD was appreciably reduced.[21] Among the factors contributing to such an anergy, the role of host determined genetic factors leading to an abnormal production of lymphokines by the T cells may be crucial.

Genetic predisposition to tuberculosis

Epidemiological surveys carried out amongst different racial groups have emphasised marked differences in the degree of innate resistance to *M. tuberculosis* infection. American Negroes[22] and certain African tribes[23] were found to be particularly susceptible to the disease compared with Jewish whites, who remained relatively immune. Similarly, " coloured " youths in the age group 1 to 20 suffered many more deaths due to tuberculosis compared with white youths in the same age group.[24] In a study of tuberculosis amongst soldiers, it was found that the incidence of the disease amongst Gurkhas (nationals of Nepal) was higher compared with that of soldiers of other nationalities working in the same areas.[25]

Strong support for the involvement of genetic factors in tuberculsis comes from animal experiments which suggest differential susceptibility to tuberculosis amongst various inbred strains.[26] Webster[27] experimented with 15 generations of mice and showed that only when resistant animals comprised the stock, no epidemic disease resulted in comparison with the development of an almost explosive epidemic in colonies where only susceptible animals were bred together. More conclusive evidence for the host-determined predisposition to tuberculosis came from studies carried out on twins[28] which revealed a marked difference in morbidity between monozygotic and dizygotic twin partners. Also, the actual " risk " of developing the disease increased in a strict proportion by the degree of blood relationship to the tuberculous index case. These studies concluded that hereditary factors do play a decisive role in both the origin as well as clinical course of the disease. Numerous workers have also attempted to correlate the prevalence of certain blood groups with the occurrence of tuberculosis.[29-31] These studies, however, presented conflicting data. Whereas Chinese with the blood group 'O' were more resistant to PTB,[30] bacillary-positive Danish patients were characterised by an excess of group 'O'and 'AB' and a lack of groups 'A' and 'B'.[31] The same investigators who made these studies also documented during a follow-up study of 2-5 years increased mortality in patients with blood group 'O' as compared with those with 'A' blood group.

In conclusion, the number of studies indicating genetic control in tuberculosis has been substantial, but the data generated has remained frequently multi-interpretable and often conflicting.

HLA and pulmonary tuberculosis : population studies

Although the HLA system has been found to play a critical role in controlling the immune response that develops following infection,[32-43] the number of studies on HLA and tuberculosis has remained small compared with those on other diseases. Until about a couple of years ago, there were just a few reports on HLA and PTB and even these included the study of only the class I antigens while ignoring the HLA-DR antigens, which are the equivalent of the mouse Ia molecules and contain information for the putative Ir genes. In most of these studies, the number of patients studied was small and the selection was made on the basis of past history and hospital admission.[44] Moreover, proper statistical procedures were not applied and the evidence of diagnosis was not well documented. The standard criterion of sputum positivity with acid-fast bacilli was not strictly adhered to. Sometimes there were clear technical problems with HLA typing; in general, the investigators did not use the same typing reagents. All these factors make comparisons and interpretation a difficult task. Perhaps the most important methodological criticism is that concerning the selection of a well matched control group for the

study. Table 1 shows the data on a population study carried out on various ethnic groups. As is evident, the associated antigen in almost all these studies is variable and does not reach statistical significance when P correction for the number of antigens studied is applied.

Association with HLA-DR antigens

The first large-scale study involving HLA-DR antigens in pulmonary tuberculosis was conducted by Singh and coworkers.[52] It showed a marginal increase in DR2 and a concurrent significant decrease of antigen DRw6 in the patient group as compared with controls (Table 2). This indeed was interesting since both these alleles have been implicated in tuberculoid leprosy.[37,38] These data raise a possibility that both diseases might be related through a common gene in the MHC having common inheritance and susceptibility patterns. Another significant point is that both DR2 and DRw6 occur with a rather high frequency in the healthy population and that this might be responsible for the observed weak association of these antigens with PTB. It implies, therefore, that MHC-related genes controlling the course of *M. tuberculosis* infection have a low penetrance.

Multiplex family studies

In order to test that the disease controlling factor in pulmonary tuberculosis was not the HLA allele itself, but a gene closely linked to the HLA locus, multiple case family studies were undertaken by Singh *et al.*[55] Such studies do not rely on linkage disequilibrium and provide important information on the " genetic linkage " of putative disease susceptibility (DS) genes within the MHC. In particular, these studies were aimed to see whether the affected siblings in these families shared most frequently the parental HLA haplotypes as compared with the healthy siblings, *i.e.* a non-

Table 1 HLA-A and -B antigen association in tuberculosis patients of different ethnic groups

Population (ethnic group)	Number tested		HLA association	%Phenotype frequency		Reference
	Patients	Controls		Patients	Controls	
New Foundlander	46	543	B8 ↑	56.5	20.2	(44)
European Caucasoid	-	-	No association	-	-	(45)
Japanese	70	-	No association	-	-	(46)
Chinese	101	310	B35 ↑	32.7	6.1	(47)
North American	45	100	B15 ↑	20.0	3.0	(48)
Mexican	100	100	No association	-	-	(49)
Russian	18	50	No association	-	-	(50)
North Indian	45	95	B15 ↑	35.7	16.9	(51)
	124	109	No association	-	-	(52)
	63	59	B18 ↑	29.0	8.0	(53)
Egyptian	42	156	A2 ↑	57.1	35.8	(54)
			B5 ↑	40.5	21.7	

P value insignificant in all of these studies when correction (Pc) for the number of antigens studied is applied.

Table 2 Percent phenotype frequency of important HLA-DR antigens in pulmonary tuberculosis*

HLA-DR	Patients (N=124)	Controls (N=109)	χ^2	P-value	Relative risk
DR2	50.8 (63)	38.5 (42)	3.05	NS	1.6
DR3	20.2 (25)	22.0 (24)	0.03	NS	0.9
DR4	24.2 (30)	29.4 (32)	0.55	NS	0.8
DRw6	12.1 (15)	23.9 (26)	4.75	< 0.05	0.4

* Data derived from Singh *et al.* A marginal increase of HLA-DR2 and a significant decrease of DRw6 is observed in the patient group as compared with the controls.

random segregation of the normal Mendelian segregation pattern.

An analysis of segregation of parental HLA haplotypes in siblings affected with pulmonary tuberculosis is shown in Table 3. In 18 families with either parent affected, a significant deviation from random segregation was observed ($\chi^2 = 4.94$, $p < 0.05$). No significant deviation from random segregation was observed in the remaining seven families in which both parents were healthy. Also, there was a skewed transmission of DR2 to the diseased offspring from both the diseased as well as the healthy parents in contrast with the transmission of this allele to healthy offspring in these families. These data provide strong evidence in favour of susceptibility to pulmonary tuberculosis being HLA-linked with the putative gene being in linkage disequilibrium with HLA-DR2. Also, the observation of non-random segregation of haplotypes in only those families having either parent affected suggests a dominant mode of inheritance in this disease. This is in contrast to the situation in tuberculoid leprosy where a recessive rather than dominant inheritance has been observed.[38,39] As in leprosy, it is possible that the HLA-linked factors in tuberculosis do not directly influence susceptibility to infection, but rather modulate the immune response to *M. tuberculosis*. This proposal is similar to observations in mice for other intracellular pathogens such as *Listeria*[57] and *Leishmania*[58] for which it has been demonstrated that the development of specific immunity rather than susceptibility to infection is linked to H-2.

Perspectives

The pathogenesis of tuberculosis is complicated and the factors that predispose to or determine the outcome of infection with *M. tuberculosis* are still poorly understood. From the foregoing, it appears that there is polygenic control of susceptibility to tuberculosis and that the genetic factors involved are not simple and may not be confined to HLA alone. It may be argued that the susceptibility genes in pulmonary tuberculosis may have a low penetrance and may be under the influence of " modifier genes " located on other chromosomes. Population and multiplex family studies conducted on other ethnic groups should help to improve the identification of MHC-linked disease predisposing factors in tuberculosis. Attempts should be made to identify products of the susceptibility genes as well as correlate Mantoux reactivity of the family members (both affected and unaffected) with the HLA haplotypes. The role of immune response (Ir) and immune suppression (Is) genes, which are believed to control interactions amongst immunocompetent cells, should be evaluated in tuberculosis. One approach would be that used for streptococcal infection.[58] The responder status (high or low) of the affected and unaffected members in tuberculous families as determined by antigen specific T-cell proliferation could be correlated with the HLA haplotypes. Using the same protocol, the cellular mechanisms of these genetic regulations, *i.e.* whether expressed at the T-cell or macrophage level, could be determined by preparing cultures from HLA-identical sibling pairs, with T cells from high responders and macrophages from low responder, and *vice versa*. These approaches would provide further insight into the mechanisms of genetic predisposition to tuberculosis.

Recently, with the advent of molecular genetic procedures and Southern blot assays, it is possible to digest the DNA molecules both in the coding and non-coding regions using a battery of type II restriction endonucleases. The specific restriction fragment length polymorphism (RFLPS) thus obtained has provided much higher " relative risks " to a disease process than that obtained using serological-DR markers.[16] Such studies of tuberculosis should also help to delineate any immunogenetic rela-

Table 3 HLA haplotype segregation in siblings affected with pulmonary tuberculosis in multiplex families*

Segregation of haplotype from	Number of families	Observed (F)	Expected (f)	χ^2	P
Affected parent/ parents	18	33.0	22.5	4.94	0.05
Healthy parents (both)	7	18.0	16.0	0.13	NS

tionship between this disease and tuberculoid leprosy, in both of which DR2 and Drw6 have been implicated. Indeed, a number of epidemiological similarities have been defined between these two infectious diseases.[59] However, a definite immunogenetic relationship between them remains to be demonstrated.

ACKNOWLEDGEMENTS

This review was supported by funds from the Indian Council of Medical Research (ICMR), the Medical Research Council (MRC), U.K., and Mahidol University, Thailand.

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