

HLA System and applications

Pages with reference to book, From 230 To 232

Mirza Naqi Zafar (Zafar Research & Diagnostic Centre, 7/14 Rimpa Plaza, Clinic Side, M.A. Jinnah Road, Karachi.)

The human leucocyte antigen system, HLA, is a series of tissue groups which are mostly exhibited on all body tissue and not confined to leucocytes. It is analogous to the H2 histocompatibility system in the mouse and is used in the selection of donor recipient pairs for transplantation. In man, the direct serological techniques available use leucocytes and platelets whereas in the mouse and in the rat haemagglutination techniques are possible.

The antigens are controlled by four or five genetic loci, each showing extreme polymorphism. Two allelic series were originally described LA and FOUR. It is now known that the loci which make up the major histocompatibility complex (MHC) in man are situated in the middle of the short arm of autosome number 6. LA and FOUR are now called HLA-A and B respectively and the other loci are C, D and DR. The DR series of antigens which were described at the Seventh International Histocompatibility Workshop in 1977, are restricted in their distribution and occur mainly on B ' and monocytes. They appear to be homologous to the mouse Ia (immune associated) antigens, but because their relationship to the HLA-D series is close, it is not yet known whether D and DR are separate loci or whether the antigens are different expressions of the same genes. In man they have been designated DR meaning 'D related'. Direct serological techniques are used to demonstrate antigens of the A,B,C, and DR series, also referred to as serologically determined (SD) antigens.

The inheritance of the HLA antigens obeys Mendelian laws and each individual inherits one antigen at each locus from each parent. The MHC contribution from a parent is called a haplotype, so the genotype consists of two haplotypes. If an individual's parents have been HLA typed it is usually possible to establish the haplotypes within the phenotypes and therefore the genotypes. Although the antigenic series are determined at separate loci and in theory all combinations of alleles exist in a population there is a tendency for some haplotypes to be more common than others. This allelic association is called linkage disequilibrium and it is sometimes possible to identify the most likely genotype given the phenotype without a full family typing.

The laboratory test most widely used for serological typing for HLA antigens is the micro-lymphocytotoxicity test originally described by Terasaki and McClelland¹ and modified over the years. Through UK Transplant and the National Institutes of Health in America, tissue typing laboratories have been receiving antisera for HLA typing recipients and donors for kidney transplantation. These derive from bulk contributions by the laboratories involved and subsequent re-distribution. Similar arrangements exist in Eurotransplant, Scandiatransplant and France Transplant. This ensures that antisera with a wide range of specificities are available to all workers so that meaningful comparisons can be made between them. Because of the complexity of the system and the low frequency of even the most common genotypes in the population good HLA matches between unrelated individuals can only rarely be made without cooperation between transplant centres and an agreement to exchange organs. In Britain, UK Transplant undertakes computer matching of cadaveric kidneys to the waiting recipients and also arranges the necessary transport of cadaveric organs to the hospitals carrying out the transplant operations.

Most analyses indicate that good HLA matching favours graft survival, although many other factors also influence the outcome of transplantation, particularly prior blood transfusion which is now considered to be beneficial. Serological tests only allow matching for antigens at the A,B, C and DR loci and it is not possible to carry out prospective mixed lymphocyte reactions with cadaveric donors, so some apparently well matched pairs for SD antigens may be discrepant for their D locus antigens. It is hoped that HLADR matching, because of the close relationship of D and DR antigens, will give a

better assessment of histocompatibility. The situation is different in bone marrow transplantation. Likely identical pairs as judged by their SD antigens can be examined for a lack of reaction in MLC. Within a family a match for loci A,B, C, and DR will also be a match at the D locus, unless recombination between the loci has occurred. This is not true for unrelated individuals and very large pools of potential donors would have to be built up if unrelated bone marrow transplantation graft versus host (GVH) as well as host versus graft (HVG) reactions occur, because, immunologically competent cells are transferred in the donor marrow. Thus only identical grafts should be considered.

Occasionally antibodies to HLA antigens cause severe febrile reactions during transfusion of whole blood which make's it necessary to use only leucocyte-poor blood. The development of white cell antibodies after multiple transfusions is very common, but as these tend to be multispecific matching for transfusion is impractical. If patients with antibodies react to leucocyte-poor blood, then frozen red cells, which are completely free of white cells are indicated.

Although there is some evidence that patients requiring multiple platelet transfusions over long periods respond better when HLA compatible platelets are given, there would be almost unsurmountable problems in supplying these from a routine blood bank. As previously mentioned even the commonest HLA genotypes are rare and as with bone marrow transplantation, the only practical solution is to use related donors.

The HLA system provides precise genetic markers and some interesting work has been carried out both in linkage and association studies. Lamm et al.², were able to show that the MHC is on autosome 6 in a family with a pericentric inversion. Lamm et al.³, showed earlier that HLA is linked to the enzyme phosphoglucomutase-3 (PGM). Other markers, the red cell enzyme glyoxylase, GLO⁴, and genes for complement components C2⁵C4⁶, and Bf of the alternative pathway⁷, have all been assigned to chromosome 6, some by both classical and hybridisation methods of the demonstration of genetic linkage. O'Neill et al.⁸, reported that the red cell antigens Chido and Rodgers, which had already been linked to HLA, are in fact markers for genes controlling C4 protein.

Many disease associations have also been described e.g. HLA-B27 and ankylosing spondylitis⁹, HLA-B8 and coeliac disease^{10,11} and multiple sclerosis and DW-2¹². Most of those reported have been collected together to form the HLA and Disease Registry¹³. Some HLA-B associations have been extended to include DR antigens in linkage disequilibrium with them and in addition some new associations with this locus have been found e.g. from the data in the Seventy International Histocompatibility Workshop in 1977, an association between HLA- DR4 and rheumatoid arthritis was shown.

It is interesting to speculate upon the significance of these associations. The surface antigens are a fundamental part of immune recognition processes and it seems likely that disease association with these could have influenced natural selection, particularly as it is now being observed that in these studies a resistant genotype i.e. a negative association, is often recognised. There are already indications that in man, as in the mouse, immune response (Ir) genes will be found either within or close to the MHC region and this may lead to a better understanding of the modes of inheritance and the immunological mechanisms involved in some of the diseases.

Further interesting developments have included a clear demonstration in congenital adrenal hyperplasia that 21 -hydroxylase deficiency is determined by a gene linked to the MHC¹⁴. Doubtless, many more studies of this sort will become an increasing part of the role of HLA typing laboratories.

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