The HLA System: Biological Function and Association with Disease.

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The HLA system is the major histocompatibility complex (MHC) of man and controls transplantation antigens, various immune responses, certain complement components, and the susceptibility to a variety of diseases. More specifically, the system codes for three sets of characters: the class I-III molecules. The Class I molecules are cell surface molecules carrying the HLA-A, B, and C antigens and present on all nucleated cells and on platelets. The Class II molecules are also cell surface molecules; they carry the HLA-DR, DQ, and DP antigens but are only present on some cell types, macrophages and B-lymphocytes in particular. The Class II molecules are properdin factor Bf of the alternative and factor 2 (C2) and 4 (C4) of the classical complement activation pathway. All Class I, II and III molecules are genetically highly polymorphic: there is a large number of different HLA types in the population, but all HLA factors show pronounced linkage disequilibrium with at least one other factor controlled by genes at a nearby HLA locus.

The Class I and II molecules are intimately involved in the specific thymus-dependent immune response. Thus, Class II molecules are required when macrophages present antigen to T-helper lymphocyted and when B-lymphocytes receive help from these. In analogy, Class I molecules are involved when virus-infected target cells present viral antigens to cytotoxic T-killer lymphocytes. Different Class I and Class II molecules present antigen with different efficiency and thus, they serve as immune response (Ir) determinants.

This biological function of the Class I and II determinants is probably the reason behind the associations between certain HLA factors and various "autoimmune" diseases. For example, insulin-dependent diseases occurs almost exclusively in DR3- and/or 4 positive individuals, rheumatoid arthritis mainly in DR4--positives, and multiple sclerosis in DR2-positives. Most recently, an absolute association between narcolepsy and DR2 have been found and suggest that this disorder may be due to autoimmunity against an as yet unknown receptor in the brain. However, not all HLA associated diseases are characterized by autoimmunity (e.g. idiopathic haemachromatosis and congenital adrenal hyperplasia) demonstrating that the HLA complex also control certain non-immunological functions.

Advances in Forensic Haemogenetics 1
Edited by B. Brinkmann and K. Henningsen