A REVIEW OF MAJOR HISTOCOMPATIBILITY COMPLEX-DISEASE ASSOCIATIONS IN MAN AND DOG

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ABSTRACT

The organization and biology of the Major Histocompatibility Complexes (MHC) of man (HLA) and dog (DLA) are reviewed, and a summary is presented of laboratory techniques used to define allotypes.

The nomenclature of this field and the mechanisms of disease association with the MHC are discussed. Currently recognized HLA-disease associations are enumerated, with emphasis on the value of the complement C4 marker.

DLA-disease association studies into autoimmune disease, allergy and neoplasia are reviewed.

INTRODUCTION
The rejection of incompatible grafted tissue by lymphoid cells is initiated by recognition of foreign surface antigens (histocompatibility antigens) by the recipient. These products have also been identified as being important in many immune interactions which are either protective or pathogenic in nature (Bodmer and Bodmer, 1978; Antczak, 1982).

Histocompatibility antigens are encoded by genes of the Major Histocompatibility Complex (MHC). The basic genetic structure of the MHC is preserved between all mammalian species examined and has been localized to particular chromosomes in some cases. A feature of histocompatibility systems is the multiple allelism of their genes (polymorphism).

In recent years it has become clear that the susceptibility to certain disease states, primarily those with an immunological basis, is associated with particular products of the MHC. This article briefly reviews the biology of the MHC of man (Human Leukocyte Antigen; HLA system) and dog (Dog Leukocyte Antigen; DLA) and examines the current knowledge of disease associations with the MHC of these species.
Human Leukocyte Antigen System

Major histocompatibility antigens are divided into three main categories: Class I, II and III. Class I and II antigens are transmembrane glycoproteins with a characteristic two chain structure consisting of a large and small subunit. The heavy chain of Class I antigens (45,000 Daltons) is associated with the non polymorphic β2 microglobulin (12,000 Daltons). Class II antigens comprise an α chain (34,000 Daltons) and β chain (28,000 Daltons). These chains share areas of sequence homology with immunoglobulin molecules and other cell surface structures such as Thy 1.

Class I antigens coat the surface of all constituent cells of the body (except the red blood cells of man and domestic mammals) whereas surface coating with Class II histocompatibility antigens is mainly restricted to certain cells of the lymphoreticular system (Antczak, 1982; Newman and Antczak, 1983).

Class I histocompatibility antigens have an important role in tissue graft rejection and in recognition and subsequent cytolysis of virus infected cells. The function of Class II histocompatibility antigens is in cellular recognition between antigen presenting cells, and T and B lymphocytes.

Human Class I antigens are encoded by the HLA A, B and C loci and Class II products by the DP, DQ and DR loci (Bodmer and Bodmer, 1984). Genes encoding the α and β chains of these Class I products have been identified using recombinant DNA technology. There are 6 α chain genes (DRα, 2DQα, 2DPα, DZα) and 7 β chain genes (3DRβ, 2DQβ, 2DPβ) (Cohen et al., 1985).

Class III MHC products (which are not involved in T lymphocyte recognition phenomena) have been well characterized in man and include components of the complement system (C2, C4, Bf) and a single enzyme 21-hydroxylase which is involved in steroid metabolism (O'Neill and Nerl, 1982). There are 2 C4 loci (C4A, C4B) and 2 loci encoding 21-hydroxylase (21-OHA, 21-OHB). Amino acid sequencing has demonstrated that there is no homology between Class I/II and Class III antigens. The presence of Class III genes in the MHC cannot therefore be explained by evolution from common precursor genes (Carroll et al., 1985).

The currently delineated map of the human MHC is shown in Fig. 1. This system is located on chromosome 6. Each of the histocompatibility loci has multiple allelism, this polymorphism allowing many possible combinations or genotypes. A summary of the number of HLA allotypic variants currently recognized at each locus is presented in Table 1. Histocompatibility antigens show codominant inheritance, the products of loci on each haplotype