ADVANCES IN VETERINARY SCIENCE AND COMPARATIVE MEDICINE

Edited by

CHARLES E. CORNELIUS CHARLES F. SIMPSON

Volume 27

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PREFACE

This volume of *Advances in Veterinary Science and Comparative Medicine* contains scholarly presentations on a variety of topics of interest to the scientific community. Subjects discussed in the several chapters include avian lymphoproliferative diseases and their virus associations, heartwater, sickle red cells in Cervidae, immune-mediated diseases of the blood, histocompatibility polymorphisms of domestic animals, control and therapy of fish diseases, corticosteroid teratogenicity, acaricide resistance in ticks, embryo transfer in domestic animals, bovine paratuberculosis, and bovine congenital defects.

Studies of avian lymphoproliferative diseases provide insights into molecular genetics and genetic engineering. Avian leukemia viruses are models to analyze the interaction of viruses with various types of differentiating cells.

Heartwater, or cowdriosis, is an infectious disease of African ruminants transmitted by ticks of the genus *Amblyoma*. It is caused by the rickettsia *Cowdria ruminatium*. Research on heartwater in the Caribbean is just beginning.

Hemoglobin polymerizes within the red cells from most species of deer when exposed to oxygen and an elevated pH. The typical sickle cell in deer is virtually identical in shape, mechanical fragility, and viscosity to the human sickle cell.

The immune-mediated diseases of man and animals constitute a group of poorly understood disorders in which antibodies are produced against tissues of the body. The opportunity for recovery is best if the causative agent can be identified and removed.

Research on histocompatibility systems has increased dramatically during the past decade. The pig and dog have served as models of organ grafting in transplantation studies. Therefore, the major histocompatibility systems of these two animals have received the most attention.

Disease control in fish follows the same health management practices followed with other types of animals. Antimicrobials, vaccines, and bacterins are commonly used.

Ticks are probably the most important problem affecting livestock in the subtropical and temperate regions of the world. Continued use of acaricides in an indiscriminate manner may lead to the build up of a stable resistance that could persist.

The highly technical methods of embryo transfer currently used in cattle will soon be extended to other species. In addition, the produc-

tion of clones in domestic animals may soon be a reality using techniques such as nuclear transplantation.

Corticosteroids have been extensively studied as teratogenic agents since 1950 when it was found that administration of cortisone to pregnant mice caused cleft palates in offspring. It is now known that corticosteroids in all mammalian species that have been studied produce a wide spectrum of abnormalities. This demonstrated teratogenicity raises the question of possible human teratogenicity.

An update of information concerning Rift Valley fever, bovine paratuberculosis (Johne's disease), and bovine congenital defects is also included in this volume.

C. E. CORNELIUS
C. F. SIMPSON

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ERRATUM

ADVANCES IN VETERINARY SCIENCE AND COMPARATIVE MEDICINE
VOLUME 26

The subtitle on the spine of this volume should read

THE RESPIRATORY SYSTEM

as on the halftitle and title pages.

Histocompatibility Polymorphisms of Domestic Animals

MARK J. NEWMAN AND DOUGLAS F. ANTCZAK

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I. Introduction

The genes that control the successful engraftment or rejection of transplanted tissues and organs in mammals are collectively known as histocompatibility genes. At least 45 histocompatibility genes have been identified in experimental studies in mice (Klein, 1975), and similar numbers are thought to exist in other species. The products of these genes are known as histocompatibility or transplantation antigens.

Histocompatibility genes can be divided into three categories. The strong or major histocompatibility genes occur in tight linkage in a genetic region called the major histocompatibility system (MHS). Collectively, histocompatibility differences at MHS genes constitute the most important barrier to allograft survival. The weak or minor histocompatibility genes are scattered throughout the genome. Individually, their contribution to graft rejection is small (Klein, 1975). A third category of histocompatibility genes has recently been described. These code for the medial histocompatibility antigens, so called because they share properties of both MHS and minor histocompatibility antigens (Fischer-Lindahl and Langhorne, 1981). This article will concentrate primarily on the genes of the MHS.

The purpose of this article is twofold: (1) to provide a short description of the structure and function of the MHS of mammals and (2) to summarize the extent of characterization of histocompatibility systems in seven species of veterinary importance. These are the dog, pig,

cow, horse, sheep, goat, and cat. The MHS of the chicken has been the subject of several recent reviews (Longenecker and Mosmann, 1981; Briles and Briles, 1982) and will not be covered.

The specialized vocabulary adopted by histocompatibility researchers has long been a barrier to the transplantation of ideas across disciplines. Hence, we have devoted considerable time to definition (and sometimes re-definition) of terms in this article.

Several unique characteristics of the MHS have served to make this system a focus for immunogenetic research. First, the MHS has a distinct chromosomal organization that is very similar in all mammalian species thus far examined (Götze, 1977; Gill *et al.*, 1978). This evolutionary conservation of genetic structure suggests that the MHS has functions that have proved worth preserving. Second, the genes of the MHS are extremely polymorphic: they occur in a very large number of allelic forms. This polymorphism has also apparently been maintained throughout species diversification (Bodmer, 1972). Third, in the artificial situation of tissue and organ transplantation, the gene products of the MHS have an overriding importance as antigens. It has been estimated that approximately 1 of every 10 T lymphocytes can respond to a full MHS-incompatible graft (Wilson *et al.*, 1968; Binz and Wigzell, 1975; Ford *et al.*, 1975), whereas the frequency of lymphocytes reactive to minor histocompatibility antigens (Ford and Simonsen, 1971) or nonhistocompatibility antigens (Lefkovitz, 1974) is several orders of magnitude lower. This bias of the T-cell repertoire toward the recognition of foreign MHS antigens has been termed "alloaggression," an expression that well describes the violence of immunological reactions toward MHS antigens. Finally, there is the question of the true biological function of the genes of the MHS. Although all of the functions of the MHS are not known, several important immunological traits have been demonstrated to be controlled or influenced by genes of the MHS, both experimentally and at the clinical level.

Any attempt to understand the MHS must address three important questions that are directed at the characteristics just outlined:

1. Why are the transplantation reactions that are directed against antigens of the MHS so violent?
2. How do the MHS genes and their products operate at the cellular level to regulate immune responses?
3. Why does the MHS exist in such a highly polymorphic state?

The answers to these questions are not yet fully understood, but it is possible to address them in general terms. This requires some knowledge of the genetic and molecular structure of the mammalian MHS.

The MHS of humans and of the laboratory animal species has been reviewed extensively (Klein, 1975, 1979; Snell *et al.*, 1976; Götze, 1977; Bodmer, 1978; Svejgaard *et al.*, 1979). We have attempted to summarize here only the most important aspects of the biology of major histocompatibility systems.

II. Structure and Function of the Major Histocompatibility System

A. Genetic Structure

The MHS is a chromosomal region that contains several genes with related functions (gene families). The exact number of genes within the MHS and its true boundaries are not precisely known and have been defined arbitrarily. In both human and mouse at least 10 genes that are considered to be part of the MHS proper have been identified.

Figure 1 shows a schematic diagram of the most important genes contained within the MHS. Some or all of the loci pictured have been described in all mammals that have been investigated (Götze, 1977), although the exact order of these loci varies between species. The MHS genes have been assigned to one of three categories, based on the structural and/or functional characteristics of their gene products. The categories are called simply Class I, Class II, or Class III (Klein, 1979). It is now believed that the genes within the different gene families have arisen by the process of gene duplication from a single primordial gene of each type. Three loci coding for Class I molecules have been

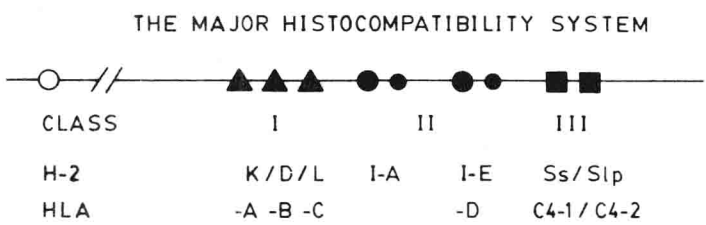

FIG. 1. Schematic view of the genetic structure of the MHS. The three major classes of MHS genes are depicted: Class I, Class II, and Class III. Below each type of gene are examples of the names given to them in the mouse (*H-2*) and human (HLA). Several other genes in the MHS have been identified, but they have been omitted for simplicity. The actual order of genes on the chromosome varies between species. The groupings shown here are for clarity.

described in the MHS of both human (Svejgaard *et al.*, 1979) and mouse (Klein *et al.*, 1978), and there is extensive evidence that other "Class I–like" genes exist in the MHS region (Margulies *et al.*, 1982; Soloski *et al.*, 1982). The number of Class II genes present in the MHS is not known. Three different Class II gene products have been characterized, but the exact numbers of genes that control the expression of these cellular products is still unclear (David, 1976, 1979; Klein and Figueroa, 1981).

Below each of the gene regions shown in Fig. 1 are the names that have been assigned to the principal MHS genes of human and mouse. The name *H-2* has been given to the MHS of the mouse, whereas the MHS of the human is called HLA. The abbreviation *H-2* stands for "histocompatibility locus-2," and HLA stands for "human lymphocyte antigen." The differences between species in the terminology for MHS loci and alleles are of historical origin. In general, the MHS genes of domestic animals have been named following the model used for the HLA system.

The principal Class I loci of mouse and human are called *H-2K*, *H-2D*, and *H-2L*, and HLA-A, HLA-B, and HLA-C, respectively. The Class II loci of the mouse code for at least three different products that are labeled A, E, and J. Analysis of the A and E gene products has shown that each consists of an α and a β polypeptide chain, which are expressed on the cell surface as a dimer. The Class II region of the mouse MHS should therefore contain an α and a β gene for both the A and E molecules. This appears to be true. However, the genes controlling the A and E molecules are not distributed as was originally expected. The genes that code for the A-α, A-β, and E-β proteins all map in the A region, whereas the E-α protein chain is controlled by an E-region gene (Uhr *et al.*, 1979). The significance of this type of gene distribution is not known, but it may be of importance when an interaction between these different genes and/or their products is required. The J region of the *H-2* system is poorly understood, and homologous genes have not yet been identified in other species. Only one Class II region, called D or DR, has been well characterized in humans. However, there is mounting evidence that the region contains several genes coding for different products (Markert and Cresswell, 1980; Dick, 1982). The particular constellation of alleles on a single chromosome is called an MHS haplotype.

The Class III MHS genes code for components of the complement system. The relationship between the Class III molecules and the Class I and II molecules is not clear, and the Class III loci are not considered to be part of the MHS proper by some (Klein and Figueroa, 1981).

B. Molecular Structure and Tissue Distribution

The Class I and Class II MHS molecules have several points in common. They are both transmembrane glycoproteins that are expressed codominantly as cell surface antigens. Both classes of molecules exhibit considerable antigenic polymorphism, and both are involved in immune regulation. However, considerable information about the molecular biology of the Class I and II MHS molecules is available, and on this basis they can be distinguished (Table I).

The Class I MHS antigens are the classical transplantation antigens. They consist of two polypeptide chains: a large subunit of approximately 44,000 daltons and a small subunit of approximately 11,500 daltons, called β2 microglobulin. The two chains are noncovalently bound and expressed on the cell surface as a dimer. The larger subunit is coded for by an MHS gene and contains the polymorphic antigenic determinants. The gene for β2 microglobulin is not part of the MHS and is located on a separate chromosome (Strominger, 1981).

The large subunit can be divided into five regions or domains based on the overall three-dimensional structure that is generated by intrachain disulfide bonding. These domains include short intracellular and transmembrane portions, and three longer extracellular domains, each of approximately 10,000 daltons. These domains are called α-1, α-2, and α-3, of which α-3 is closest to the cell membrane (Strominger, 1981). It has structural homology with β2 microglobulin, an immunoglobulin domain, and the THY-1 molecule (Williams and Gagnon, 1982). The variable portions of the Class I molecule that characterize

TABLE I

Distinguishing Characteristics of Class I and Class II MHS Molecules

Characteristic	Class I	Class II
Approximate molecular weight	44,000	32,000 (α chain); 28,000 (β chain)
Membrane association with β2 microglobulin[a]	+	−
Tissue distribution	Wide: all nucleated cells	Narrow: restricted primarily to certain cell types of the lymphoreticular system
MHS Restriction	Cytotoxic lymphocytes	T-helper cell function; delayed-type hypersensitivity

[a] +, Association present; −, no association evident.