CHAPTER 13

MHC Molecules of the Preimplantation Embryo and Trophoblast

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Abstract
The mechanisms of protection of the allogeneic fetus from the maternal immune response during pregnancy remain mysterious more than fifty years after the paradox of maternal tolerance was first raised by Peter Medawar. Preimplantation embryos express paternal antigens early in development. After implantation, placental tissue is derived from both maternal tissue and paternal-antigen expressing fetal tissue that is in intimate association with and bathed in maternal blood. There appears to be a key role for an unusual subset of major histocompatibility complex (MHC) Class I proteins of both maternal and paternal origin in the mediation of tolerance at the maternal/fetal interface and in the control of preimplantation embryonic growth rate. This subset of MHC products is composed of two nonclassical MHC Class Ib proteins, HLA-E and HLA-G in combination with a classical MHC Class Ia protein, HLA-C. This chapter reviews the history of the discovery of the major histocompatibility complex Class I genes and the elucidation of the biological role of the proteins encoded by these genes in the immune response and in reproduction. MHC genes have also been implicated in reproductive choice and nurturing behaviors. We hypothesize that the vertebrate immune system derived from ancestral recognition systems driven by reproductive requirements, and was later coopted for immune recognition under additional evolutionary pressures. The complex interactions of MHC Class I proteins with components of both the innate and the adaptive immune systems in the context of the preimplantation embryo and the trophoblast of early pregnancy are described in detail, as are the difficulties inherent in studying these systems. Finally, potential future directions of research and the need for new model systems to study both preimplantation embryos and the maternal/fetal placental interface are discussed.

Introduction
The acquired immune system, also known as the adaptive immune system, exhibits signature attributes of pathogen specificity and memory response. It emerged abruptly and mysteriously in the vertebrate lineage some 500 million years ago. Antigen-recognizing T and B cell receptor genes, combinatorially rearranged by recombinae activating gene (RAG) enzymes, together with antigen-presenting genes of the major histocompatibility complex (MHC) apparently appeared simultaneously in jawed vertebrates. These characteristic components of the acquired immune system coexist in the earliest jawed fishes but are absent in jawless hagfish and lamprey. There is no conclusive evidence of the evolution of transitional molecules in the 50 million years between the divergence of the jawless and jawed fishes from their last common ancestor. Over time the functions of the acquired immune system in vertebrates have become

inextricably blended with those of the innate immune system. The first goal of this review is to discuss the evolution of the MHC with respect to its role in reproduction. We will propose the hypothesis that the vertebrate immune system derived from ancestral recognition systems driven by reproductive requirements, and was later coopted for immune recognition.

The function of the MHC in graft rejection was first defined by Gorer and Snell in studies of the role of the mouse histocompatibility (H-2) locus in rejection of transplanted 'nonself' tissue. The equivalent human leucocyte antigen (HLA) locus was first identified by Dausset in 1958. What was at first defined as a major histocompatibility genetic "locus" is now known to encompass many genes, resulting in the present day use of major histocompatibility "complex" to describe this genetic region. For many years the biological function of the MHC was unknown. The groundbreaking discovery, by Doherty and Zinkernagel, that T-cells recognize peptide only when presented in the context of an MHC molecule, defined an immunological function for MHC molecules. Crystallization and X-ray diffraction studies in the laboratories of Jack Strominger and Don Wiley provided a molecular understanding of peptide presentation first by Class I MHC molecules and later by Class II molecules.

The MHC is a four megabase continuous region of DNA located on chromosome 6 in humans and chromosome 17 in the mouse. The complex is composed of three subregions encoding MHC Class I, Class II and Class III genes which in turn encode Class I, Class II and Class III proteins. Class I MHC genes and proteins are the main subject of this review and are discussed in detail later. Class II MHC genes are very polymorphic in human populations, and their protein products are expressed primarily on "professional" antigen-presenting cells: macrophages, dendritic cells and B-cells. Class II proteins present 13-18 amino acid peptides derived from extracellular pathogens to CD4 T helper cells and are important in the priming and maintenance of the humoral immune response. Class III MHC genes are more conserved and encode a variety of secreted proteins, some of which play a role in antigen processing, in inflammatory responses and in the complement cascade. Class II and Class III MHC genes and proteins are not discussed in detail in this review.

Class I MHC proteins are used by cells to present 8-11 amino acid intracellularly-derived peptides to CD8 T cytotoxic cells and to natural killer (NK) cells. Class I MHC molecules consist of a trimeric complex of three noncovalently bound components: the MHC Class I heavy (alpha) chain encoded in the MHC, the small antigenic peptide which is being presented to immunocytes, and beta2 microglobulin (β2m), which is encoded in chromosome 15 in humans and chromosome 2 in the mouse. Displayed peptides may be endogenous cellular peptides (self peptides) or peptides derived from intracellular pathogens (nonself peptides). Peptide-MHC Class I-β2m complexes (pMHC) interact with the T cell receptor (TCR) on CD8 T cells of the acquired immune system, and with multiple receptors on natural killer (NK) cells of the innate immune system. MHC Class I genes are subdivided into "classical" Class la genes and "nonclassical" Class Ib genes. The human Class la genes, HLA-A, -B and -C, are highly polymorphic and are expressed on the surface of almost all nucleated cells. HLA-A and -B genetic loci were first identified by van Rood using human pregnancy serum containing alloantibodies against fetally expressed paternal histocompatibility antigens; his discovery led to significant advances in kidney transplantation because these reagents could be used to tissue-type donors and recipients. A decade later the third locus, HLA-C, was identified. These products are notable for lower levels of expression at the cell surface than other class la counterparts. Nonclassical Class Ib genes HLA-E, -F and -G were initially defined in comparison to Class la genes by reduced polymorphism, restricted tissue expression and unknown function. Class Ib genes and their products remain somewhat enigmatic, but recent studies have shown that they can exhibit polymorphism and either tissue restriction or more ubiquitous expression.

Polymorphism in MHC Class I genes is most evident in their peptide binding region. Such polymorphism is generated by amino acid-altering mutations in the MHC genes and is sustained by balancing selection during evolution. Heterozygosity of MHC alleles in an