MHC proteins and human diseases: A tale of recognition in two immune systems

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MHC proteins (in humans also called HLA proteins) are polymorphic, heterodimeric proteins encoded in the major histocompatibility complex (MHC) of all vertebrate species examined. They were originally called transplantation antigens by Peter Gorer who named them during his studies of graft rejection in the 1930s. The isolation and separation of the two classes of human MHC proteins, description of their primary and secondary structures and their domain organization, and separation of three isotypes in each class led, in collaboration with Don Wiley, to their crystallization and, finally, to elucidation of their three dimensional structures, including that of bound peptides in the "MHC grooves." Thus a detailed description of the molecular interactions involved in immune recognition, i.e., in the initiation of an immune response became available (along with the knowledge that their role in graft rejection was a by-product of their normal role in the immune response). Soon an understanding of the different roles that these MHC proteins play in their interactions with two distinct effector systems, that mediated by the effector T lymphocytes and that mediated by Natural Killer lymphocytes became evident. Not surprisingly for such highly precise systems, each of them is also involved in important human diseases.

The class I HLA-A and -B proteins and class II HLA-DR and -DQ proteins, at least, present foreign peptides for recognition by receptors on the T lymphocytes leading to effector functions such as cytolysis of infected cells or T cell help for antibody formation. Exquisite mechanisms have evolved that result in tolerance to self peptides that are also presented by the MHC proteins while permitting recognition of foreign peptides. Breakdown in the mechanisms of self tolerance leads to autoimmune diseases, i.e., the aberrant recognition of self peptides. The molecular understanding gained from our studies has allowed the precise definition of the self peptides recognized in these aberrant interactions in several autoimmune diseases (as well as of the foreign peptides involved in a normal immune response) and has also permitted rational therapeutic approaches. Examples of the application of these advances to develop approaches to therapy of autoimmune diseases will be described.

Natural Killer cells are the reciprocal of T cells. Peripheral T cells are normally inactive and are *activated* (for proliferation, cytokine release and cytolytic activity) by the recognition of specific MHC/peptide complexes. By contrast, Natural Killer cells are normally active and are *inhibited* (inactivated) by the recognition of class I MHC proteins, particularly HLA-C and HLA-E. One role of Natural Killer cells is to eliminate cells that have lost expression of class I MHC proteins. Class I MHC proteins are absent from cells in at least three circumstances:

1. The fetal extravillous cytotrophoblast forms the fetal- maternal interface. This cell layer of the placenta does not express the normal class I MHC proteins, a physiological regulation which must have evolved to prevent recognition by maternal effector T cells of paternal MHC proteins expressed on nearly all other fetal tissues. A special mechanism that utilizes a novel class I MHC protein (HLA-G) expressed only on the cytotrophoblast evolved to protect the fetus from attack by maternal Natural Killer cells.
2. Some tumor cells, for example, some colon carcinoma and melanoma cells, have also lost expression of class I MHC proteins, and should, therefore, be targets for lysis by Natural Killer cells. However, means of avoidance of this

recognition event have also evolved.
3. Viruses have evolved a variety of mechanisms to down-regulate expression of class I MHC proteins as a means of escape from immunosurveillance. A complex interplay between the virus and the host immune defenses involving both T cells and Natural Killer cells has resulted.
Examples of each of these three phenomena will be described.

The description of MHC molecules and their complexes with self and foreign peptide and their interaction with the two types of effector cells of the immune system has thus revealed many aspects of their normal and abnormal functioning. The molecular knowledge gained may in the future permit many advances in understanding aberrant conditions that result from abnormalities in this exquisitely tuned system.

But the problems before us now and in the future are not so much scientific or medical as they are social and economic. In order to reap the benefits of these advances we must learn to live together and to appreciate and treasure the differences among us and to also treasure and preserve the resources of this beautiful planet for ourselves in the present as well as for future generations. Perhaps we have something to learn from the Japanese people who now live in relative peace and prosperity on these crowded islands, so that in the spirit of the Prize established by the Science and Technology Foundation of Japan with the endorsement of the Japanese government, we may "further world peace and prosperity and thereby make a vital contribution to the positive development of mankind".