CHAPTER 3

IMMUNOLOGY AND THE CHALLENGE OF TRANSPLANTATION

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Abstract: Transplantation of tissues or organs between individuals who are not genetically related often leads to rejection by the recipient. The human genes responsible for this process are located on the short arm of the chromosome 6 and are called Major Histocompatibility Complex (MHC). Six main loci have been identified in the human MHC: HLA-A, HLA-B and HLA-C belong to the HLA class I, while HLA-DP, HLA-DQ and HLA-DR belong to HLA class II. The physiological function of MHC molecules is to present peptides to the T cells. Indeed, they are integral components of the ligands that recognise most T cells, since the receptor of the T cell (TCR) has specificity for complexes of foreign antigenic peptides, and self-MHC molecules. Thus the proteins of the MHC are responsible for the body being able to distinguish between its own and foreign cells, known as self-tolerance and consequently are the proteins which determine the evolution of transplants. The special case of foreign MHC antigen recognition is known as allore cognition and consists of the capacity of T cells to recognise peptide/MHC complexes with which they have not been in contact during the process of maturation in the thymus. There are two mechanisms of allore cognition, direct and indirect; both can lead to rejection of the transplant. Direct recognition prevails during the first few weeks or months after transplantation, and is caused by the APCs of the donor. These cells start disappearing from the transplanted organ and indirect recognition becomes important. There is evidence that the indirect pathway is sufficient to mediate both acute and chronic rejection. In this chapter we will describe fundamental aspects of the MHC system, as well as, specifically, its involvement in the allogenic response of the immune system against organ transplants.
INTRODUCTION

Transplantation of tissues or organs between individuals who are not genetically related often leads to rejection by the recipient. However, when carried out between genetically identical individuals, this does not occur. These types of observations were noted at the beginning of the nineteen forties by Peter Medawar when he performed autologous and allogeneic transplants of human skin. Transplant antigens were described by Snell at the end of the same decade, when he observed rejection of skin grafts and tumours between nongenetically identical individuals. When characterising the genes responsible for this process, he identified just one locus, which he called H2. This locus is a complex of murine genes on chromosome 17, was characterised as Major Histocompatibility Complex (MHC).

The characterisation of MHC in humans occurred later than in mice. In 1953, Jean Dausset found that, after many blood transfusions, individuals presented serum antibodies capable of inducing leukocyte adhesion. Some years later, in 1957, Rose Payne described the presence of these leukoagglutinins in the serum of all patients who have received multiple blood transfusions and in multipara women. He deduced that, in a similar way to in multiple transfusions, multiple pregnancies result in immunisation, in this case, of the mother against the father’s leukocyte antigens. In the same year, in The Netherlands, Jon van Rood reached similar conclusions when he saw a patient who, after previous unproblematic pregnancies, developed a severe febrile reaction when pregnant for the seventh time. All these studies demonstrated the need for a better understanding of the biology of these highly immunogenic proteins and, to this end, a series of techniques such as leukoagglutination, cytotoxicity and complement fixation began to be developed. Using antisera reactivity patterns, Dausset grouped these antigens as “MAC” and Van Rood as “H4a/b”, while Payne called them “LA-1” and “LA-2”. The first International Histocompatibility meeting, organised by D. Bernard Amos in 1964, led to the acceptance that all genes coding these human antigens were located in the same locus (Fig. 1A) and in 1965 a unified nomenclature, of HLA (Human Leukocyte Antigens), was agreed. Although the role of MHC polymorphism in organ rejection was not defined until much later, an important contribution was made by the research of Patel and Terasaki, who suggested in 1969 that recipient antibodies against MHC antigens were associated with early or immediate rejection of grafts.

The main functions of the T-lymphocytes include defence against intracellular pathogens and activation of other cells within the immune system. These functions require interaction of the T-lymphocytes with other cells, since they are only capable of recognising antigens displayed on the cell surface.

The physiological function of MHC molecules is to present peptides to the T cells. Indeed, they are integral components of the ligands that recognise most T cells, since the receptor of the T cell (TCR) has specificity for complexes of foreign antigenic peptides and self-MHC molecules. There are two main types of MHC molecules, MHC class I and II. MHC class I molecules present cytoplasmic peptides to T CD8+ lymphocytes, while class II present extracellular peptides to T CD4+ lymphocytes. These proteins are also responsible for the body being able to distinguish between its own (“self”) and foreign cells, known as self-tolerance, and consequently are the proteins which determine the evolution of transplants.

In this chapter we will describe fundamental aspects of the MHC system, as well as, specifically, its involvement in the allogenic response of the immune system against organ transplants.