The immunology of organ transplantation

Pankaj Chandak
Chris Callaghan

Abstract

Transplantation is the best treatment modality for most patients with end-stage organ failure. In addition to the medical and surgical challenges in organ transplantation, the major biological barrier is immunological. These barriers may lead to graft rejection and loss. An understanding of transplant immunology is essential in caring for patients with organ transplants who are on immunosuppression.

The aims of this article are to describe commonly used immunological terminology, the immunology of graft rejection (including the mechanisms by which grafts are recognized as foreign by the host immune system), the different types of rejection and how this process may be prevented with immunosuppressive therapy, the practical translation of transplant and, finally, antibody incompatible transplantation. This article aims to afford the reader an overall view of basic transplant immunology that will be of use in clinical setting or in preparation for examinations.

Keywords Antigens; graft; immunology; immunosuppression; rejection; transplant

Introduction

Organ transplantation is well-established as the best treatment modality for most patients with end-stage organ failure. There are surgical and medical barriers to successful organ transplantation, however the major biological hurdle is immunological. These immunological barriers are present when matching donors to recipients, and are also fundamental to subsequent graft survival as an immune response may lead to rejection and graft destruction. In addition, the immunosuppressive medications needed to prevent organ rejection have significant clinical implications to the recipient. Therefore, an understanding of transplant immunology is essential for all clinicians involved in organ transplantation.

The relative importance of the immune system with respect to transplantation varies between organs and recipients. There appears to be a hierarchy of immunogenicity between organs; small bowel, heart, lung, and kidney transplant recipients require more intense immunosuppression (in descending order), while liver transplant recipients generally require less immunosuppression and rejection episodes are relatively easy to treat.

These variations between organs mean that it is difficult to describe the relevant immunology for all organ transplants. In this article the kidney is used as a model for a discussion of transplant immunology for three main reasons: (1) the kidney is the most commonly transplanted solid organ; (2) kidney transplantation has well-established processes for immunologically matching donors and recipients; and (3) there is a good understanding of the impact of immunological factors on graft rejection and long-term organ survival.

The aims of this article are to describe the basic mechanisms by which organ transplants are recognized as foreign by the host immune system (and may subsequently be rejected), and how this process may be prevented. This article also discusses evolving therapies that enable kidney transplantation despite the presence of pre-existing anti-donor antibodies. In order for the reader to understand these concepts, an explanation of transplantation immunology terminology is first required.

Terminology

The strength of the recipient's immune response against a transplanted graft is largely dependent on the degree of genetic similarity between the donor and recipient. As a result, a shorthand system for describing the degree of genetic resemblance between individuals and species has developed (Box 1). The prefixes defined in Box 1 can be used in multiple ways, for example to describe a transplant, antigen, or the target of an antibody (e.g. xenograft, alloantigen, autoantibody). An example of an autograft would be a split-skin graft taken from the thigh and grafted to the abdomen of the same individual. Other terms relevant to transplant immunology and this article are also described in Box 1.

Immunology of graft rejection

The immune system is a highly complex biological system whose function is to differentiate self from non-self, and subsequently eliminate substances recognized as foreign. It is characterized by its complexity, multiplicity of effector mechanisms, and (in higher organisms) its immunological memory. Although these processes have evolved primarily to detect and destroy microorganisms, they are also effective at rejecting transplanted allogeneic organs.

Useful terminology in transplant immunology and surgery

Allo — prefix that refers to genetically non-identical individuals of the same species
Xeno — prefix that refers to individuals of different species
Iso — prefix that refers to genetically identical individuals from the same species (i.e. identical twins)
Auto — prefix that refers to the same individual
Graft — a broad term to describe any transplanted organ, tissue, or cell
Human leukocyte antigen (HLA) — a protein structure in humans that presents foreign proteins enabling the immune system to recognize self from non-self
Major histocompatibility complex (MHC) — area of the genome that encodes HLA antigens and other immune system proteins

Box 1

Pankaj Chandak *BSc (Hons) MRCS (Eng) is a Specialty Trainee in Transplant Surgery in the London Deanery, UK. Conflicts of interest: none declared.*

Chris Callaghan *PhD FRCS is a Consultant Transplant Surgeon at Guy's Hospital, London, UK. Conflicts of interest: none declared.*

The ABO blood group system

Blood group	Antigen present on RBCs and tissues	ABO antibodies present in plasma	Compatible donor blood group(s)	UK population distribution
Group A	A	Anti-B	Groups A and O	45%
Group B	B	Anti-A	Groups B and O	9%
Group AB	A and B	None	Groups A, B, AB, and O	3%
Group O	Neither A nor B	Anti-A and anti-B	Group O	43%

Group AB is the universal recipient, while group O is the universal donor.

Table 1

In order for a transplanted graft to be rejected, the immune system of the recipient must be able to recognize the transplanted tissue as foreign, and then have effector mechanisms by which the graft can be destroyed. In clinical transplantation the recognition process is known as allorecognition, and the entire immune response is known as the alloresponse. There are essentially three types of tissue antigens that can be recognized by the immune system and subsequently provoke an alloimmune response: ABO blood group antigens, human leukocyte antigen (HLA) antigens, and non-HLA antigens (minor histocompatibility antigens).

ABO blood group antigens

ABO blood group antigens are glycoproteins present on red blood cells in large amounts, but also on other tissues such as vascular endothelium and urothelium. The distribution of blood groups in a population varies geographically worldwide. Blood groups B and AB are more common in South and Southeast Asians than the general UK population. Antibodies against non-self ABO antigens start to develop in childhood, and are thought to occur due to environmental exposure to viruses, bacteria, and some foods. These substances express antigens that lead to antibodies that are thought to cross-react with human ABO antigens. Anti-ABO antibodies are naturally occurring, complement fixing (i.e. activate the complement cascade), and are pre-existing at the time of transplantation (unless the transplant is done in a neonate). Transplantation of an ABO-incompatible organ will lead to rapid activation of the complement system, causing hyperacute rejection (see below) and graft loss in almost all organ types. Table 1 describes the ABO system and ABO-compatibility in more detail.

As there are only four different ABO blood groups, and identifying blood groups is a simple and reliable assay, ABO blood group compatibility is not usually a significant barrier to transplantation. Of note, the Rhesus system is not important in organ transplantation as Rhesus antigens are expressed only on red blood cells (not on tissues) and donor blood is flushed from the organ before implantation.

HLA antigens

In contrast, HLA antigens are a significant hurdle to organ transplantation as they are the major target for the immune response. HLA antigens are cell surface proteins whose biological function is to present small portions of proteins (peptides) for recognition by receptors of cells of the immune system. Genes that encode for HLA antigens are found in the major histocompatibility complex (MHC), a genetic region located on the short arm of chromosome 6 in humans. MHC and HLA are terms that are often used interchangeably, though strictly MHC refers to the area of the genome, and HLA refers to the human protein structure. There are two main classes of HLA antigens encoded by the MHC: class I and class II. The two classes of molecules have different structures and functions, though both are involved in the presentation of fragments of peptides derived from antigens (Table 2). These peptides are bound in the peptide binding groove (cleft) of HLA class I and II molecules where they can interact with T cell receptors on appropriate cells.

HLA class I molecules present peptides derived from intracellular proteins (either self-proteins, or from pathogens such as viruses). In contrast, APCs internalize extracellular proteins and

HLA antigens and their characteristics

HLA antigen	Structure	Function	Distribution	Major subtypes
HLA class I	Single heavy chain (α chain) associated with a smaller molecule (β2 microglobulin)	Presentation of intracellular peptide to CD8 T cells	Almost all cell types	HLA-A, HLA-B, HLA-C
HLA class II	Pair of non-identical protein chains (α chain and β chain)	Presentation of extracellular peptides to CD4 (helper) T cells	Antigen presenting cells (APCs), e.g. dendritic cells, B cells, and macrophages[a]	HLA-DP, HLA-DQ, HLA-DR

[a] HLA class II molecules can also be expressed on other cell types (e.g. endothelium and some epithelial cells) under the influence of pro-inflammatory signals, e.g. interferon-γ.

Table 2