The immunology of organ transplantation

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Abstract

Transplantation is the gold standard treatment for many patients with end-stage organ failure. In addition to the medical and surgical challenges in organ transplantation, the major biological barrier is immunological. This barrier may lead to graft rejection and loss. An understanding of transplant immunology is essential in order to care for transplant recipients. The aims of this article are to describe commonly used immunological terms, the immunology of graft rejection the different types of rejection, and how this process may be prevented with immunosuppressive therapy. Finally, the article will review the practical translations of transplant immunology. This article aims to afford the reader an overall view of basic transplant immunology that will be of use in the clinical setting or in preparation for examinations.

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

Introduction

Organ transplantation is the gold standard treatment for many patients with end-stage organ failure. There are surgical and medical barriers to successful organ transplantation; however, the major biological hurdle is immunological. This immunological barrier is present when matching donors to recipients, and is 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. 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 their 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; (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 allografts 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 donor and recipient has been developed (Box 1). The prefixes defined in Box 1 can be used in multiple ways to describe a transplant, antigen, or the target of an antibody (e.g. xenograft, alloantigen, autoantibody). In clinical practice, organs are donated from one person to another, and are therefore described as allografts. 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 (and cancer), the same mechanisms result in the rejection of foreign tissue or transplants.

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 leucocyte 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

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Please cite this article in press as: Phillips BL, Callaghan C, The immunology of organ transplantation, Surgery (2017), http://dx.doi.org/10.1016/j.mpsur.2017.04.004

In order for an allograft 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, HLA antigens, and non-HLA antigens (minor histocompatibility antigens).

ABO blood group antigens

ABO blood group antigens are glycoproteins present on the cell membranes of red blood cells, and a wide variety of tissues including endothelium. There are four major ABO phenotypes: A, B, O and AB. In addition to surface antigens, individuals develop antibodies against the A and/or B antigens that are not present on the individual's tissue (see Table 1). For example, blood group A individuals will have anti-B antibodies circulating in the blood. These antibodies appear in the blood soon after birth following exposure to antigens of similar structure to A and B antigens (molecular mimicry).

Transplantation of an ABO-incompatible organ will lead to rapid deposition of antibodies directed against non-self ABO antigens, followed by massive activation of the complement system, and other downstream effector mechanisms, leading to hyperacute rejection (see below) and graft loss in almost all organ types.

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 clinical 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 clinical organ transplantation as they are a 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 classes of HLA antigens, each with different structures and functions, though both are involved in the presentation of fragments of peptides derived from antigens (Table 2). HLA class I molecules present peptides derived from intracellular proteins (either self-proteins, or from pathogens such as viruses). In contrast, antigen-presenting cells (APCs) internalize extracellular proteins and then load the degraded peptide products onto HLA class II molecules.

There are six main subgroups of HLA antigens:

- HLA-A, HLA-B, HLA-C (class I)
- HLA-DP, HLA-DQ, and HLA DR (class II).

Within each subgroup are further variations in protein structure. For example, there are over 1000 different alleles encoding HLA-A proteins. This means that there is a high degree of polymorphism (diversity) between individuals. The diversity in HLA antigen structure is beneficial, as it prevents the entire population from being susceptible to a specific pathogen, as at least some members of the species should be able to present the peptide antigen and therefore develop an immune response against it. However, this means matching HLA antigens between potential organ donors and recipients is difficult. This situation contrasts with that of the ABO antigen system, where matching is relatively straightforward.

Minor histocompatibility antigens

Non-HLA antigens may also be able to act as transplant tissue antigens. These non-HLA proteins show some degree of polymorphism between individuals. As a consequence, peptides derived from these non-HLA antigens on allogeneic grafts can be presented on HLA class I or II molecules and recognized by the recipient's immune system. The clinical significance of these non-HLA antigens is thought to be minimal in solid organ transplantation, thus explaining why they're also known as minor histocompatibility antigens.

Antigen recognition

In order for the recipient's immune system to respond to foreign (non-self) antigens and reject the tissues on which they are expressed, the immune system must be able to recognize these antigens. Recipient CD4 T cells (T helper cells) play a central role in activating and maintaining the alloimmune

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

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