AJKD

Core Curriculum

Transplant Immunology and Immunosuppression: Core Curriculum 2015

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Kidney transplantation is the kidney replacement therapy of choice for patients with kidney failure as long as there are no comorbid conditions that preclude the surgery or interfere with the ability to adhere to long-term immunosuppression. In acceptable candidates, kidney transplantation is more cost-effective than dialysis and is associated with lower mortality rates than those observed in waitlisted individuals. During the past 3 decades, kidney transplant recipients have benefitted from remarkable improvements in short-term outcomes compared with recipients in earlier eras. Specifically, 1-year kidney transplant survival rates are now ~95%, and the incidence of acute rejection during the first year after transplantation is now ~15%. Long-term outcomes have improved much less impressively. Alloimmune reactions resulting in acute and/or chronic rejection remain the primary barrier to long-term survival of the kidney transplant. Immunologic tolerance can be achieved with relative ease in small animals. However, the human immune system is complex, containing redundant pathways that make tolerance difficult to achieve. Thus, in the current era, transplant rejection still constitutes the major threat to long-term survival of transplanted kidneys, and nearly all transplant recipients require life-long treatment with immunosuppression to mollify alloimmune responses and allow for long-term transplant survival. This review focuses on immune mechanisms of kidney transplant injury and treatments currently used to prevent or treat transplant rejection (see Box 1 for outline of topics).

Box 1. Overview of Transplant Immunology and Immunosuppression

- Mechanisms of transplant rejection
  - Allorecognition
  - T-cell activation and differentiation
  - Effector mechanisms
  - Role of B cells
- Types of rejection
  - Hyperacute rejection
  - Acute cellular rejection
  - Acute humoral rejection
  - Chronic rejection
- Prevention of rejection
  - Desensitization protocols
  - Induction therapy
  - Maintenance immunosuppression
- Treatment of rejection
  - Acute cellular rejection
  - Acute humoral rejection
  - Chronic rejection
- Strategies for achieving tolerance

MECHANISMS OF TRANSPLANT REJECTION

The main responsibility of the immune response is to defend against infectious pathogens, a role that requires both recognition of pathogens and subsequent activation of immune cells and soluble mediators of immunity. Similarly, the immune responses that lead to recognition and destruction of a transplant require mononuclear cells with migration capacity, antigen-presenting cells (APCs), soluble mediators such as cytokines, and effector cells that target and injure the transplant. It is useful to consider the cellular and noncellular components of alloimmunity (Box 2) when attempting to understand the effects and limitations of current therapeutics in transplantation.

Allorecognition

The major histocompatibility complex (MHC) comprises cell-surface proteins encoded by a gene family located on chromosome 6. The primary immunologic role of MHC gene products is to present antigens—in the form of fragments of foreign proteins—so that they can be recognized by T lymphocytes through their antigen-specific receptors. MHC molecules are required for presentation of foreign antigens because T cells are not capable of responding to soluble proteins.

Antigen presentation begins with binding of a peptide antigen by MHC (Fig 1). MHC molecules are composed of one highly polymorphic polypeptide α chain and a monomorphic β chain, consisting of β_2-microglobulin in the case of class I MHC. Allospecificity of class I MHC molecules, constitutively expressed on all nucleated cells, resides in the α chain, a polypeptide with a prominent groove or pocket in which foreign peptides bind for presentation to T cells. Class II MHC molecules are constitutively expressed only on APCs, including dendritic cells, macrophages, and B cells. For these molecules, adjacent portions of the highly variable α chain and a

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Box 2. Components of the Alloimmune Response

- Antigen (peptide)
- Major histocompatibility complex (MHC)
- Antigen-presenting cells (APCs)
- T and B cells
- Costimulatory factors and cytokines
- Effector cells, inflammation, and injury

nonvariable β chain create the peptide groove. For either class, the size of the grooves is too small to bind large intact proteins. Thus, native proteins must be processed into smaller fragments that can bind to MHC molecules. The highly variable amino acid residues located in the groove determine the specificity of peptide binding and T-cell antigen recognition. Functionally, the same T-cell receptor (TCR) can recognize either class I or class II MHC molecules, but restrictions are imposed by the engagement of the T-cell surface molecules CD4 and CD8 to class II and class I molecules, respectively (Fig 2A). Thus, CD4-positive T cells primarily engage peptides presented by class II MHC, whereas CD8-positive T cells engage peptides presented by class I MHC.

Immediately following vascularization of a transplanted organ, donor antigens enter the systemic circulation and travel to the lymph nodes and spleen, where naive T cells become activated. At the same time, recipient cells enter the transplant. Direct allorecognition (Fig 2A) occurs in either the secondary lymphoid system or the transplant. In the lymphoid system, this happens when the recipient's naive lymphocytes are engaged with donor APCs that have traveled to the lymph nodes or spleen. In the transplant, direct allorecognition occurs when donor APCs engage with recipient lymphocytes. Indirect allorecognition (Fig 2B) occurs in the secondary lymphatic system when donor proteins or peptides are processed by recipient APCs and presented to the TCR. In the transplant, indirect allorecognition occurs when recipient APCs process donor peptides and engage recipient lymphocytes by presenting those processed peptides. The direct pathway of allorecognition plays a dominant role in early T-cell–mediated acute rejection episodes, whereas the indirect pathway is believed to be more important in mediating chronic rejection.

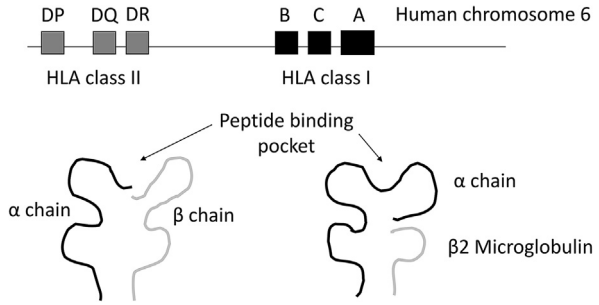

Figure 1. Schematic of the peptide-binding pockets for class II molecules derived from the DP, DQ, or DR loci of the major histocompatibility complex of chromosome 6 and for class I molecules derived from the B, C, or A loci. Figure courtesy of Dr P. Heeger; adapted from Schröppel and Heeger (*Transplantation Immunology*. In: Hricik DE, ed. *Kidney Transplantation*. 2nd ed. London: Remedica, 2007:9-38) with permission of Remedica Medical Education and Publishing.

T-Cell Activation and Differentiation

The TCR is a heterodimer that consists of 2 linked polypeptide chains, α and β. The TCR is then linked to another group of cell-surface molecules known as CD3, a complex that consists of at least 5 covalently bound peptide chains: γ, δ, ε, ζ, and η. When the TCR binds to an MHC-presented antigen, there is a conformational change in CD3 that activates intracellular signal pathways, including tyrosine kinases on the intracytoplasmic tails of the CD3 complex, as well as the CD4 and CD8 accessory molecules. This antigen-driven signal that is transduced by the TCR-CD3 complex to the T-cell cytoplasm has been called "signal 1." This signal is essential, but not sufficient, for full activation of T cells.

A second antigen-independent signal (signal 2) must be provided through additional accessory molecules that costimulate the T cell. Although the family of known costimulatory ligands continues to grow, the most important are ligands between 2 T-cell surface molecules, B28 and CD154 (CD40 ligand), and the APC surface molecules B7 and CD40, respectively (Fig 3). The provision of signals through the TCR alone (without costimulation) leads to clonal and antigen-specific anergy. The T cell does not produce cytokines or undergo cell division and it becomes unresponsive to appropriate stimulation or apoptosis (undergoes programmed cell death).

With adequate costimulation, T-cell activation continues and signals are transduced to the nucleus. A key step in activating T cells is phosphorylation of proteins that form the signaling chain for gene transcription. The immediate effect is phosphotyrosine kinase–mediated phosphorylation of tyrosine residues of several proteins. The phosphorylation modification activates an enzyme that catalyzes the breakdown of plasma membrane phospholipids and the generation of the second messengers inositol 1,4,5 triphosphate (IP3) and diacylglycerol (DAG). IP3 triggers the release of ionized calcium from intracellular stores while DAG activates protein kinase C, leading to the synthesis of nuclear regulatory elements such as the proto-oncogenes c-fos and c-jun. Released cytoplasmic calcium forms a complex with calmodulin, a calcium-dependent regulatory protein. These calcium-calmodulin complexes activate other kinases and