Immune System and Kidney Transplantation

Badri Man Shrestha[1]

[1]Division of Renal Transplantation, Sheffield Kidney Institute, Sheffield Teaching Hospitals NHS Trust, Sheffield, United Kingdom.

ABSTRACT

The immune system recognises a transplanted kidney as foreign body and mounts immune response through cellular and humoral mechanisms leading to acute or chronic rejection, which ultimately results in graft loss. Over the last five decades, there have been significant advances in the understanding of the immune responses to transplanted organs in both experimental and clinical transplant settings. Modulation of the immune response by using immunosuppressive agents has led to successful outcomes after kidney transplantation. The paper provides an overview of the general organisation and function of human immune system, immune response to kidney transplantation, and the current practice of immunosuppressive therapy in kidney transplantation in the United Kingdom.

Keywords: *immune; kidney; system; transplantation.*

INTRODUCTION

Since the first successful kidney transplantation (KT) performed on 24th December 1954, KT has become a routine for end-stage renal failure. According to the World Health Organisation, in 2014, a total of 84347 kidney transplants were performed in 104 countries worldwide.[1] The current success of KT has been possible as a result research and advancements in the understanding of the immune system and its response to transplanted organ. The immune system recognises transplanted kidney as a foreign tissue and mounts response by initiating a variety of attack strategies, which must be offset pharmacologically for the kidney to survive.[2] This short communication seeks to provide information on the general organisation and function of human immune system, immune response to kidney transplantation (KT), and the current practice of immunosuppressive therapy in KT in the United Kingdom.

ORGANISATION OF IMMUNE SYSTEM

The myeloid and lymphoid precursor cells of haemopoietic stem cells give rise to cells which form the functional cells of the immune system. The cells of myeloid origin include granulocytes (neutrophils, eosinophils and basophils), mononuclear cells (monocytes and macrophages), and dendritic cells. Cells that are derived from lymphoid precursors include T lymphocytes (T cells), B lymphocytes (B cells), and natural killer (NK) cells. Lymph nodes, spleen and thymus provide support for the function of the cellular component of the immune system.

Of the granulocytes, neutrophils are the first cells to arrive at the site of inflammation and the proteolytic enzymes released from the granules kill the target cells. Monocytes produced in the bone marrow released into the blood stream migrate to tissues and differentiate into macrophages. They are responsible for digestion and destruction of foreign proteins and present antigens

Correspondence: Dr. Badri Man Shrestha, Division of Renal Transplantation, Sheffield Kidney Institute, Sheffield Teaching Hospitals NHS Trust, Sheffield, S5 7AU, UK. Email: shresthabm@doctors.net.uk, Fax: +44-1142714604.

to other cells of immune system. Dendritic cells are so named because they possess filamentous processes resembling the dendrites of nerve cells. Dendritic cells play a crucial role in initiating the adaptive immune response by presenting antigens to T helper cells.

The T, B and NK cells can be differentiated from each other by their expression of cell surface molecules known as "cluster of differentiation (CD)". T cells originate in the bone marrow and pass through thymus for maturation, which differentiate into helper T cells ($CD4^+$) and cytotoxic T cells ($CD8^+$). T helper cells recognise foreign antigens and then secrete various cytokines to orchestrate the destruction of tissues. On the other hand, cytotoxic T cells respond to the cytokines secreted by the helper T cells by releasing proteolytic enzymes (granzyme and perforin) that results in destruction of tissues. NK cells are lymphocytes those do not express surface molecules, hence do not recognise a specific antigen. Instead, these cells possess activating receptors that are capable recognising complement fragments and antibodies coating the target cell surface. B cells develop and mature in the bone marrow are characterised by the expression of membrane bound immunoglobulin (CD19). Once activated, they mature into plasma cells and secrete antibody.[3]

Two human individuals are distinguished from each other by the antigens expressed as human leucocyte antigens (HLA) on their cell membranes which are encoded by major and minor histocompatibility complex (MHC) in their genomes. Major MHC are located on the short arm of chromosome 6 and are divided into three classes: class I (HLA A, B, and C) and class II (HLA DR, DP and DQ) and class III (complements). Class I and class II molecules facilitate recognition and presentation of processed antigens to distinct lymphocyte populations, such as, the class I molecules interact with T cell receptor (TCR) hat are associated with CD8 molecule (cytotoxic T cell) and class II molecules interact with TCR associated with CD4 molecule (helper T cell).[4,5]

ALLORECOGNITION AND T CELL ACTIVATION

Both innate (dendritic cells, macrophages, neutrophils, mast cells and natural killer cells) and adaptive (T and B cells) immune systems are implicated in the allograft rejection process. The innate immune system is activated by damage-associated molecular patterns (heat-shock proteins, adenosine triphosphate, uric acid, ribonucleic acid (RNA), deoxyribonucleic acid (DNA)), proteins derived from extracellular matrix (hyaluronan fragments and heparin sulphate), and cytokines and chemokines released due to ischaemia-perfusion injury and microbial products.[6] The activated innate immune system triggers the adaptive immune system leading to cellular rejection. In addition, recognition and presentation of the alloantigen leads to activation of the adaptive immune system.[7]

Allorecognition can occur by direct or indirect pathways.[8,9] After establishment of the vascular connection between donor and recipient, the activated dendritic cells migrate out of the graft to the T-cell rich regions of the recipient lymph nodes where they encounter naive recipient T cells [10]. The donor dendritic cells and recipient T cells engage each other using cell surface receptors, the MHC molecules on the dendritic cell and the T cell receptor (TCR), the junction is called an "immunological synapse", thereby generating antigen-specific intracellular signal (signal 1).[11,12] Simultaneously, additional molecules coalesce in the synapse to generate second signal called co-stimulation signal (signal 2), which is essential for complete T cell activation. Lack of signal 2 leads to either anergy or apoptosis.[8,11]

The receptor-ligand interaction between T-cells and the antigen presenting cells (APCs), which are involved in generation of co-stimulatory signals are CD28-B7 and CD154-CD40. CD28 and CD154 are expressed on T cells and their ligands B7 and CD40 are expressed on APCs. CD28 consists of two ligands, B7-1 (CD80) and B7-2 (CD86). T cells also express cytotoxic T-lymphocyte associated antigen-4 (CTLA-4), which is homologous to CD28, but has a higher affinity than CD28 to bind B7. Binding of CTLA-4 to B7 (both CD80 CD86) leads to generation of inhibitory signal to terminate T cell response.[13,14]

Following assembly of immunological synapses, the combination of signal 1 and 2 activates three downstream signal transduction pathways within the cytoplasm of the T cell: the calcium-calcineurin pathway, the RAS-mitogen activated protein kinase pathway, and the IKK-nuclear factor $_{\kappa}$B (NF-$_{\kappa}$B) pathway.[15-17] The signals reach the nucleus and activates gene transcription factors including the nuclear factor of activated T cells (NFAT), activated protein-1, and NF-$_{\kappa}$B, respectively. As a result of gene transcription, several new molecules and cytokines including CD25, CD154, interleukin-2 (IL-2) and interferon-$\gamma_{(IFN-\gamma)}$ are secreted and their receptors expressed.

IL-2 binds to its own receptor on the surface of T cell in autocrine fashion (signal 3), which, activates the mammalian target of rapamycin (mTOR) pathway, phosphoinositide-3-kinase (PI3K) pathway and Janus kinase/signal transducers and activators of transcription protein pathway (JAK/STAT), which allow the activated T cells to progress through the cell division cycle and clonal expansion of donor HLA/ peptide -specific effector

(CD8$^+$ cytotoxic T cells) T cells.[18,19] These cells produce CD8$^+$ T-cell mediated cytotoxicity, help macrophage-induced delayed type hypersensitivity response (CD4$^+$Th1) and help B cells for antibody production (CD4$^+$Th2).[20,21] A subset of activated T cells (CD4$^+$ or CD8$^+$) survive in an inactive state for a long period, called the memory T cells, but will quickly expand and mount an aggressive immune when re-exposed to the same alloantigen.[22]

DONOR-SPECIFIC ANTIBODIES

Plasma cells can produce antibodies against both HLA and non-HLA antigens. Non-HLA antibodies directed against donor endothelial antigens such as MHC class I polypeptide-related sequence A or B (MICA and MICB), smooth muscle antigen (vimentin), collagen-V and cell surface receptor such a type I angiotensin II receptor are reliably detected by currently available techniques.[23] Several studies have suggested that donor-specific antibodies (DSA) to HLA antigens and endothelial antigens may be a driver for both acute and chronic antibody-mediated rejection (AMR).[24] Antibody mediated rejection occurs through activation of complement cascade and thereby complement-mediate cytotoxicity leading to graft destruction.

IMMUNOSUPPRESSIVE AGENTS

When a kidney is transplanted from a HLA non-identical donor, the recipient mounts an alloimmune response, that leads to T lymphocyte activation, antibody production, complement activation, allograft rejection and transplant failure.[25] Immunosuppressive agents are used to prevent acute cellular and AMR, both early and late, which lead to chronic allograft injury (CAI) in long-term. Significant advances have been made in the immunosuppressive strategies over the past three decades to reduce the incidence of allograft rejection and side-effects of the drugs, and to improve long-term graft and patient survivals

Immunosuppressive agents used in RT are classified into three groups: induction, maintenance and rescue agents (Table 1). Induction agents comprise of polyclonal antibodies (rabbit antithymocyte globulin (rATG)) and interleukin -2 receptor antagonist (IL-2RA) (basiliximab and daclizumab). The anti-CD3 monoclonal antibody (OKT3) is no longer used because of severe adverse side-effects. Newer induction agents include alemtuzumab and rituximab. The maintenance agents comprise of calcineurin inhibitors (CNIs) (cyclosporine and tacrolimus), antiproliferative agents (azathioprine and mycophenolate mofetil (MMF)), mammalian target of rapamycin inhibitors ((mTOR-I) (sirolimus and everolimus) and corticosteroids. Three newer maintenance agents include belatacept, a co-stimulation blocker; sotrastaurin, a protein kinase C inhibitor; and tofacitinib, a JAK 3 inhibitor, which are under investigation.

Transplant rejection can be acute cellular and acute AMR. Mild cellular rejection can be treated with corticosteroids, whereas steroid-resistant, moderate and severe acute cellular rejection are typically treated with ATG. Antibody-mediated rejection is treated with plasmapheresis, intravenous immunoglobulin and rituximab. Refractory AMR is treated with proteasome inhibitor bortezomib and C5 inhibitor, eculizumab.[26,27]

Table 1. Classification of immunosuppressive agents.

Induction agents	Maintenance agents	Rescue agents
Polyclonal and monoclonal antibodies: ATG OKT3 Alemtuzumab Rituximab	Calcineurin inhibitors: Cyclosporine Tacrolimus	Mild to moderate cellular rejection: Corticosteroids
Interleukin-2 receptor antagonists: Basiliximab Daclizumab	Anti-metabolites: Azathioprine Mycophenolate mofetil	Moderate to severe cellular rejection: Polyclonal and monoclonal antibodies: ATG OKT3
Methylp-rednisolone	m-TOR inhibitors: Sirolimus Everolimus	Acute antibody-mediated rejection: Immunoglobulins Rituximab Bortezomib Eculizumab
	Newer agents: Co-stimulation blocker: Belatacept Protein kinase C inhibitor: Sotrastaurin JAK 3 inhibitor: Tofacitinib	

CURRENT IMMUNOSUPPRESSIVE REGIMENS IN THE UK

Immunosuppressive agents are tailored to need of the KT recipients based upon their risk profile of immune response to the transplanted organ. There is a variation in the adoption of immunosuppressive regimens between transplant centres in the UK. However, the

commonly adopted immunosuppressive regimen is describe in this section. Patients receiving first KT with 0-HLA DR mismatch, and non-sensitised, are classed as standard risk transplants, who are given Basiliximab (20 mg intravenously on day 1 (before surgery) and day 4), tacrolimus (0.1 mg/kg body weight in two divided dosage to maintain a trough level 8-12 ng/ml for first 3 months and 6-8ng/ml and prednisolone (20-25 mg/day) as long-term maintenance. Patients receiving second KT, non-sensitised, or first transplant with HLA DR mismatches, receive mycophenolate mofetil (MMF) (500-750 mg twice daily) in addition to the drugs received by standard risk recipients. High risk transplant recipients are those who are sensitised from previous transplants with presence of DSA and those with failed previous transplants from rejection episodes receive rATG (1- 1.5 mg/kg day intravenously) for 5-7 days instead of basiliximab and continue with triple therapy (tacrolimus, MMF and prednisolone). Patients intolerant to CNIs are given sirolimus (2 mg daily), usually at least 3 months after KT to reduce the risk of wound dehiscence and lymphocele. Patients undergoing blood group incompatible KT receive rituximab (200 mg / day) and plasmapheresis preoperatively, followed by maintenance with triple drugs. Kidney transplants in patients with positive cross-match due the presence of DSA undergo desensitisation by repeated plasma exchanges and rATG therapy followed by long-term maintenance on triple therapy. In some centres, alemtuzumab is used instead of ATG for the ease of administration, as the former can be administered subcutaneously.[28-30]

The outcomes of KT has significantly improved due to availability of effective immunosuppressive agents. However, the side-effects of the drugs, particularly over-immunosuppression leading to increased risk of infection and malignancies and CNI nephrotoxicity leading to early transplant loss are the major issues after KT. Having appropriate understanding of the immunologic process implicated after KT and the role of immunosuppressive agents in regulating the allogenic response is paramount in the effective clinical management after KT.

Conflict of Interest: None.

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