Introduction

Transplantation, which is the transfer of organs, cells, and tissues from one location to another, began many centuries ago as a primitive practice and has since evolved into a modern reality. Modern medicine has triumphed over many challenges and overcome many hurdles to achieve successful organ transplantation. The contemporary practice of medicine includes transplantation of tissues, partial organs, and whole organs. In addition, successful bone, heart valve, cartilage, vein, and cornea transplantations are being performed on a daily basis ***(Sharma et al., 2006)***.

Rejection of transplanted organs is the main barrier of transplantation today. It occurs as a result of humoral and cell-mediated responses by the recipient to specific antigens present in the donor tissue. These antigens are known as major histocompatibility complex (MHC) molecules. In humans, this group of molecules is referred to a human leukocyte antigen (HLA) complex molecule in humans. The recognition of these foreign MHC antigens initiates rejection, which occurs in two stages. During the first stage, known as sensitization, lymphocytes are alerted and respond to the foreign MHC molecules. Rapid proliferation occurs in this stage. In the second 'effector' stage, the graft is destroyed by several cellular and molecular mechanisms ***(Kuby, 2007)***.

The importance of the immune system in protecting the body against harmful foreign molecules is well recognized. However, in some instances, this protection can result in serious problems. For example, the introduction of an allograft can elicit a damaging immune response, causing rejection of the

transplanted tissue. Transplantation of organs and tissues (for example, kidney, heart, or bone marrow) has become routine due to improved surgical techniques and better tissue typing. Also, drugs are now available that more selectively inhibit rejection of transplanted tissues while preventing the patient from becoming immunologically compromised. Earlier drugs were nonselective, and patients frequently succumbed to infection due to suppression of both the antibody-mediated (humoral) and cell-mediated arms of the immune system. Today, the principal approach to immunosuppressive therapy is to alter lymphocyte function using drugs or antibodies against immune proteins. Because of their severe toxicities when used as monotherapy, a combination of immunosuppressive agents, usually at lower doses, is generally employed ***(Harvey and Champe, 2009)***.

Immunosuppressive drug regimens usually consist of anywhere from two to four agents with different mechanisms of action that disrupt various levels of T-cell activation. The immune activation cascade can be described as a three-signal model. Signal 1 constitutes T-cell triggering at the CD3 receptor complex by an antigen on the surface of an antigen-presenting cell (APC). Signal 2, also referred to as costimulation, occurs when CD80 and CD86 on the surface of APCs engage CD28 on T cells. Both Signals 1 and 2 activate several intracellular signal transduction pathways, one of which is the calcium-calcineurin pathway, which is targeted by cyclosporine and tacrolimus. These pathways trigger the production of cytokines such as interleukin (IL)-2, IL-15, CD154, and CD25. IL-2 then binds to CD25 (also known as the IL-2 receptor) on the surface of other T cells to activate mammalian target of rapamycin (mTOR), providing Signal 3, the stimulus for T-cell proliferation ***(Finkel et al., 2009)***.