Modern immunosuppression

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Abstract

Organ transplantation provides both life-saving and life-enhancing function for patients suffering from end-stage organ failure. Transplantation has only been possible due to the advances in immunosuppression. The viability of a transplanted organ depends on modulation of the human immune system to avoid rejection in response to foreign antigens. Modern immunosuppression consists of multi-modal therapy (chemical drugs and biological agents) acting on different parts of the immune response. Three phases of immunosuppression can be recognized: induction, maintenance and withdrawal. All patients must continue to take at least some immunosuppression to prevent rejection. Developments in immunosuppressant regimens have dramatically improved transplant success rates and experience over the years has helped to understand the side-effects and long-term complications of immunosuppression. Research continues to identify both novel compounds and ways of optimizing the use of current drugs.

Keywords Antibodies; drugs; rejection; transplantation

Introduction

The advent of solid organ transplantation, almost 60 years ago, heralded a new era for patients suffering from end-stage organ failure. The first successful life-extending organ transplant was a kidney transplant performed in 1954 in Boston. Prior to this all vascularized organ transplants had been rejected by the recipient's immune system. The key success here was identifying identical twin brothers and hence that rejection would not be an issue.

Early years

By the end of the 1960s 6-mercaptopurine (6-MP) and corticosteroids had permitted organ transplantation between non-identical patients. Although 6-MP was initially developed for the treatment of leukaemia, its benefits were soon translated into solid organ transplantation. Sir Roy Calne pioneered the use of its derivative azathioprine in kidney and liver transplantation in Cambridge, UK. In an initial series of canine experiments he had found that graft survival was significantly prolonged when combined with corticosteroids. Implementation of a similar protocol in humans moved transplantation from an experimental science into widespread clinical use.

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The quantum leap forward was the development in the late 1970s of ciclosporin. Its introduction not only significantly improved the outcomes of kidney transplantation but also heart, lung and liver transplants; transforming them from high-risk, high-mortality surgical endeavours into accepted and even 'gold standard' treatments.

Immunology of transplant rejection

It was Peter Medawar in 1944 that first showed that graft rejection is a 'host versus graft' response: but it has only been in the last two or three decades that the 'nuts and bolts' of this response have become apparent. A basic understanding of transplant immunobiology is essential to understanding the rationale of modern immunosuppression.

The rejection reaction can be broadly divided into two phases: sensitization and the effector response. In both phases the T-cell plays the key role (Figure 1).

The recognition of foreign antigens by recipient T-cells leads to a cascade of intracellular signals (signal 1), resulting in the synthesis of proteins including cytokines such as interleukin-2 (IL-2). During the antigen presenting cell (APC)/T-cell interaction, other ligands bind, some facilitating adhesion between cells (ICAM-1 with LFA-1) and others providing a second proliferative signal (signal 2). IL-2 and other cytokines provide the final proliferative signal (signal 3) to T-cells. Modulatory ligands are also present on the surface of T-cells, which may inhibit the immune response. One such example is CTLA4, which binds to the CD80/CD86 ligands on APCs to block co-stimulation, thus regulating the immune response (*vide infra* Belatacept).

Classes of immunosuppressants

General considerations

Immunosuppression is generally classified as having a temporal relationship to graft implantation and broken down into three phases: induction, maintenance and withdrawal. During the induction phase a bolus of steroids (methylprednisolone) is given prior to releasing the vascular clamps and reperfusion of the allograft. Often this is combined with a biological antibody agent (ATG, Basiliximab, Campath) to condition the recipient T-cell population.

After graft implantation there is a maintenance phase and most organ transplant recipients will receive triple therapy combining a calcineurin inhibitor, antiproliferative (azathioprine or MMF) and corticosteroids. In the withdrawal phase, the dose of all agents is gradually reduced as the risk of acute rejection recedes; however, in only a small minority of cases can immunosuppression be withdrawn completely.

Induction antibody agents

Antibody immunosuppression

Antibodies can be classed as polyclonal or monoclonal. Polyclonal antibodies are directed against multiple epitopes of antigens on human lymphocytes (such as anti-thymocyte globulin — ATG), whereas monoclonal antibodies have monovalent affinity (i.e. they bind to the same epitope). Antibodies are mainly used as induction agents; however, they can be used in cases of severe rejection as 'rescue' therapy.

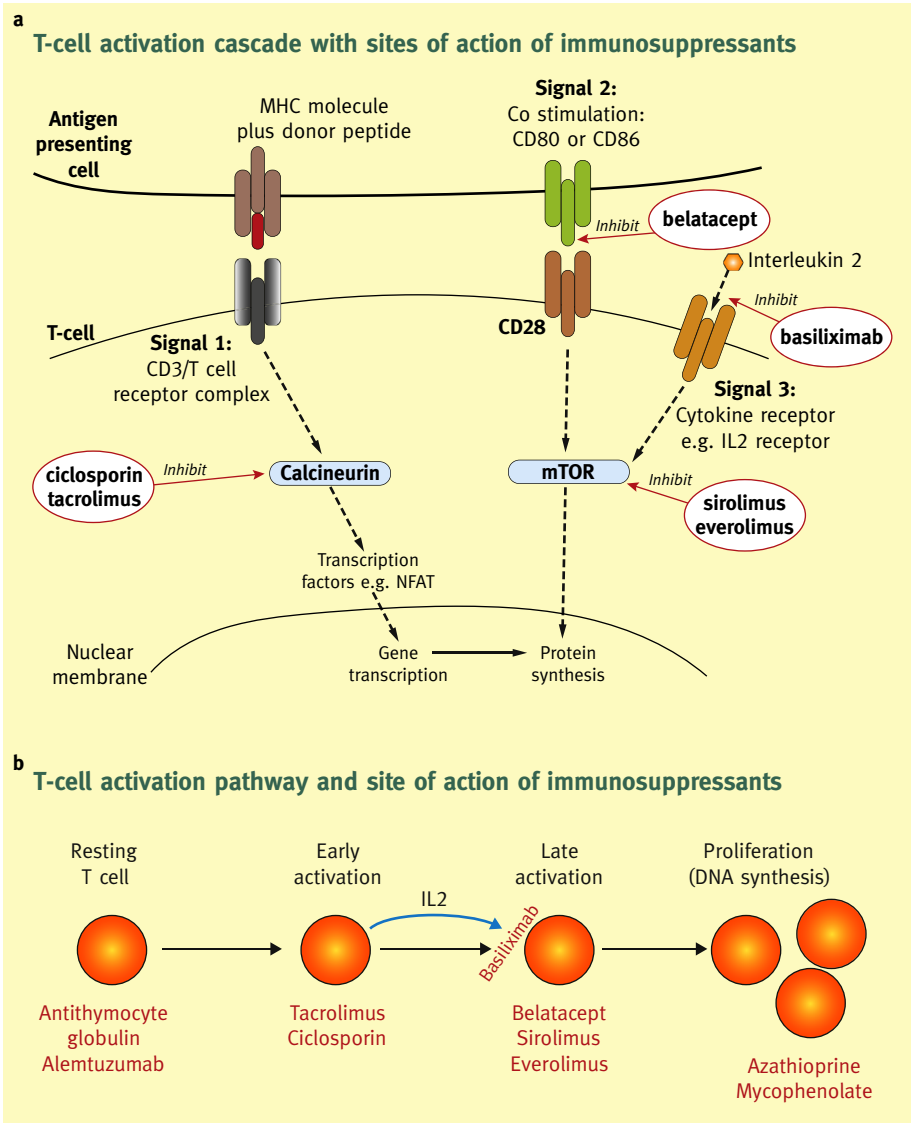

Figure 1 T-cell activation cascade with sites of action of immunosuppressants. IL2, interleukin-2; MHC, major histocompatibility complex; mTOR, mammalian target of rapamycin; NFAT, nuclear factor of activated T-cells. (Courtesy of Jolly EC and Watson CJE[1])

Anti-thymocyte globulin

There are many different varieties of ATG, but they all follow the same principles. Human lymphocytes are injected into a mammalian host (rabbit, horse) and the resulting antibodies generated are then purified from the animal's serum. This means that no two batches are the same and the patient experience in consequence is very variable. However, a profound reduction in circulating T-cells is apparent — through a combination of complement-dependent and antibody-dependent cytotoxicity. This massive cell lysis can lead to a cytokine release syndrome or 'storm' with systemic effects such as fever, pruritus, hypotension, flushing and occasionally severe bronchospasm. The severity of the reaction is dependent not only on the number of circulating lymphocytes prior to administration, but also the 'batch efficacy'.

OKT3 is a murine monoclonal antibody directed against the CD3 cluster present on all lymphocytes and which has a similar side effect profile. Case reports of severe anaphylaxis have reduced its popularity.

Both ATG and OKT3, which cause profound and long-lasting changes in lymphocyte populations, have been associated with the development of opportunistic infections and post-transplant lymphoproliferative disorder (PTLD, see below; Figure 2).

Interleukin 2 receptor blockers

Basiliximab and daclizumab (now withdrawn from the market due to economic reasons) are humanized monoclonal antibodies directed against the alpha subunit of the CD25 antigen present on activated T-cells. These antibodies bind and competitively inhibit the proliferative response of T-cells to Il-2, rather than causing cell lysis (c.f. ATG) and studies in kidney transplantation suggest a reduction in acute rejection (relative risk 0.66) when added to conventional therapy, with no discernable side-effects or increase in infection.[2]

Alemtuzumab (Campath 1H)

Alemtuzumab targets the CD52 antigen, present on most mature nucleated bone marrow-derived cells. Like ATG, the