The immunology of solid organ transplantation

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Abstract

Solid organ transplantation has progressed dramatically over the last 50 years. However, rejection still remains one of the barriers to successful transplantation. Immunological processes underlying the mechanisms of rejection are well described and numerous pharmacological agents exist to help suppress a recipient's immune system in order to prolong graft survival. Furthermore, clinician decisions and actions during both the work-up of a potential transplant recipient and in the perioperative phase can impact upon the immunological status of an individual and the likelihood of successful solid organ transplantation. In this article we aim to describe the key processes involved in solid organ immunology and their relevance in anaesthetic practice.

Keywords Human leucocyte antigen; immunology; immunosuppression; rejection; transplant

Royal College of Anaesthetists CPD Matrix: 1H02, 2A07, 2A12

Learning objectives

After reading this article, you should be able to:

- describe the important aspects of the immune system relevant to solid organ transplantation
- explain the actions of immunosuppressants currently used in clinical practice
- outline the different types of allograft rejection
- describe the factors which can lead to sensitization of potential recipients

Immunology in solid organ transplantation

Major histocompatibility complex/(HLA and tissue typing)

The major histocompatibility complex (MHC) are genes situated on chromosome 6 coding for cell surface antigens, termed human leucocyte antigens (HLA), responsible for the human body's ability to recognize genetically dissimilar tissue and inducing an appropriate immune response. HLAs consist of two main types: class I (A, B and C), which are expressed on all nucleated cells; and class II (DP, DQ, DR), which have a more limited expression and are found predominantly on B lymphocytes, antigen-presenting cells and endothelium.

HLA mismatch plays a key role in the likelihood of rejection and sub-optimal matches increase the risk of both acute rejection and long-term graft loss. Each individual expresses three HLA pairs, with donor–recipient HLA typing performed to determine compatibility. To optimize outcomes, HLA matching is a central component of UK organ allocation policy.

Historically, a pre-transplant 'crossmatch' test mixing donor and recipient cells had been performed to ensure compatibility. Now electronic comparison of tissue types and antibodies measured with high-affinity technologies such as Luminex® allows, a 'virtual crossmatch' for many patients. This avoids prolongation of organ cold ischaemic time which is beneficial to outcomes, particularly in kidneys donated after cardiac death.

ABO system

ABO blood group antigens can be responsible for hyper-acute (immediate) rejection due to the presence of preformed antibodies and occur more frequently in primarily vascularized grafts, particularly the heart and kidney. Recipient and donor ABO compatibility is essential to avoid this reaction, similar to packed red cell transfusion. However, in selected patients, desensitization using plasmapheresis to remove preformed haemagglutinin antibodies prior to solid organ transplantation is possible in ABO incompatible living donor renal transplantation. Rhesus antibodies are not expressed on endothelium and therefore are not of relevance in solid organ transplantation.

Sensitization

Prior exposure to HLA antigens can lead to the formation of specific HLA antibodies in the donor population, namely through blood transfusion, previous transplantation and pregnancy. This can reduce the potential donor pool for a recipient, as preformed HLA antibodies will cause acute antibody-mediated rejection. Furthermore, highly sensitized individuals have a lower chance of finding a compatible donor and can spend a significantly longer time on the transplant waiting list as a result. Therefore, it is necessary to avoid blood transfusions where possible in patients on the transplant waiting list or those who may require transplantation in the future. However, in newly transplanted patients, the presence of immunosuppression can allow for more liberal use of blood transfusions as the risk of forming HLA antibodies is reduced.

Immunosuppression in solid organ transplantation

Immunosuppressive drugs are the cornerstone of therapy in transplantation. Treatment protocols have steadily evolved from the poorly efficacious and toxic agents used in transplantation's

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early days. Commonly used regimens incorporate combinations of steroids, tacrolimus, ciclosporin, mycophenolate mofetil (MMF), azathiporine and occasionally mTOR inhibitors such as rapamycin. Most modern regimes incorporate a so called 'induction agent' to suppress or delete lymphocyte function around the time of transplantation.

All these agents modulate the recipient's immune response to prevent allograft rejection, but consequently increase the risk of infection and malignancy. Achieving the right balance between avoiding rejection and reducing infection risk is a delicate process that necessitates routine investigations and educating patients about the importance of drug compliance and identifying symptoms of infection and/or rejection. Clinical immunosuppression can be broadly split into induction, maintenance and management of acute rejection.

Induction therapy

These agents commonly include polyclonal anti-thymocyte globulins (Thymoglobulin®), basiliximab (Simulect®) and alemtuzemab (Campath®). Induction therapy involves the use of high potency biological agents to reduce risk of acute rejection and delay introduction of maintenance therapy. Therapy is commonly initiated intraoperatively or post-transplantation for up to 10 days.

Monoclonal or polyclonal antibodies are the current immunosuppressive agents of choice for induction. Monoclonal antibodies can be further divided into cell-depleting muromonab-CD3 (anti-CD3 antibody) and alemtuzumab (humanized anti-CD52 antibody) or non-depleting agents, such as basilixmab and interleukin-2 (IL-2) receptor antagonists. This drug class specifically binds to the α-chain of the IL-2 receptor (also known as CD25 antigen) inhibiting the binding of IL-2 to its receptor (Figure 1). This prevents activation of T-lymphocytes, which is essential for a cell-mediated immune response in rejection.

The main polyclonal antibody used for induction is anti-thymocyte globulin (Thymoglobulin/ATG), a highly selective depleting agent that works by binding to various cell-surface antigens on T-lymphocytes causing cell death by complement-mediated cell lysis or apoptosis. Thymoglobulin can also be used to halt cell-mediated acute rejection.

Maintenance immunosuppression

Currently the most common maintenance therapy consists of a combination of tacrolimus, mycophenolic acid and prednisolone. This 'triple therapy' regimen has been shown to have better graft survival and function as well as less rejection than other common combinations involving ciclosporin or rapamycin. This combination has also shown the same benefits in unselected patient populations outwith clinical trials.

Tacrolimus works by binding an intracellular protein, FKBP, forming a complex that inhibits calcineurin activity. Calcineurin is a phosphatase enzyme involved in activation and differentiation of T-lymphocytes through upregulation of IL-2 gene expression (Figure 1). By inhibiting its phosphatase activity, calcineurin is unable to activate the transcription factor, NFAT, hence leading to inhibition of IL-2 gene expression, which hinders T-cell activation. Tacrolimus also enhances the effects of glucocorticoids and prevents their degradation. Consequently, hyperglycaemia is a well-recognized side effect of tacrolimus.

MMF is an inhibitor of nucleotide synthesis. It reversibly binds to and inhibits inosine monophosphate dehydrogenase (IMDH), the principle enzyme involved in synthesis of guanosine nucleotides. This leads to proliferation arrest in the T- and B-cell lineage, thereby dampening both cell- and humoral-mediated immunity.

The use of glucocorticoids (mainly prednisolone) has been a mainstay of organ transplantation. Glucocorticoids potentiate their immunosuppressive effects through binding to intracellular receptors. The hormone-receptor complex then translocates to the nucleus where it binds to hormone-response elements on the DNA leading to changes in gene expression. The ultimate effect is inhibition of T-cell proliferation and cytokine release.

Less commonly, maintenance solid organ transplant patients may be treated with Azathioprine or Rapamycin, either instigated some years ago or changed by indication. In the case of Azathioprine this is usually because of gastroenterological side effects of mycophenolic acid preparations. Sirolimus is less effective than calcineurin inhibitors as a primary immunosuppressive but has a role in the context of post-transplant skin malignancy.

Graft rejection

Despite very efficacious and tolerable maintenance immunosuppression, acute rejection — usually manifesting as acute graft dysfunction (rising creatinine in the case of kidney transplantation) — still occurs in over 15% of patients. The management and identification of organ rejection has been crucial to the success of solid organ transplantation. As we have already described, pharmacological agents can be used to modulate the immune system. However, these agents can lead to toxicity, sepsis or fail to sufficiently suppress the immune system — leading to graft rejection. If not recognized early, the rejection process ultimately destroys the allograft.

Hyper-acute rejection occurs within the first 48 hours of implantation, secondary to pre-formed cytotoxic antibodies caused by prior sensitization (predominantly from blood transfusion) against HLAs. These bind to the vascular endothelium, eventually leading to thrombosis from the activation of complement. This is an irreversible process and results in graft loss, hence the use of pre-transplantation work-up as described above to avoid this catastrophic complication.

Acute rejection is a relatively common complication within 3 months of renal transplantation and still remains a significant barrier to successful transplantation. Allograft rejection predominantly occurs secondary to the activation of T-cells, with two signals required for full T-cell activation — namely CD3 complexes to activate intracellular pathways and stimulatory signals originating from antigen-presenting cells. Multiple downstream signal transduction pathways, including the calcium —calcineurin pathway, promote T-cell clonal expansion, the production of cytokines and T-cell-mediated toxicity through CD8 cells. This condition is termed cell-mediated rejection. Treatment of cell-mediated rejection includes short-course high-dose intravenous steroids combined with the continuation of oral immunosuppression therapy.

Less commonly, rejection may be antibody mediated with a variable simultaneous cellular component. Graft injury occurs due to activation of the complement cascade or destruction from

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