Immunotherapy

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A forward looking conference took place at the Royal College of Physicians in June 1998. The audience, which included many scientific and clinical immunologists from both the university and pharmaceutical sector, participated knowledgeably and critically in the discussions on possible future treatments for immunologically caused diseases and on the scientific principles which may bring about further developments in immunotherapy.

Dr Thomas Waldmann (National Institutes of Health, Bethesda, Maryland, USA) presented an overview of the subject of immunotherapy, from its historical basis of immunological manipulation dating back to Jenner, to the current status of various immunotherapeutic strategies. He reviewed the processes of T lymphocyte activation, paying special attention to interactions between T cell receptor (TCR) and major histocompatibility antigens (MHC), costimulation by molecules such as B7/CD28, and the gene expression of interleukin-2 (IL-2) and its receptor.

Future therapeutic developments in this field are likely to include modulation of the normal inhibitors of immune responses, such as CTLA 4 (CD152), and apoptosis/activation-induced cell death (AICD). Recent data have suggested that AICD is involved in peripheral tolerance in the prevention of autoimmune disease, such that promotion of AICD may be therapeutically useful under certain circumstances.

Monoclonal antibodies can be used in the treatment of a variety of conditions such as neoplasia, autoimmune disease and allograft transplantation. Several methods have been employed to increase their efficiency such as humanisation, conjugation with toxins and combination with cytotoxic agents. Anti-IL-2 receptor monoclonals have been used in renal transplantation with significant success and have also shown promise in animal models of autoimmune disease. However, IL-15 has a specific receptor which is not bound by anti-IL-2R antibodies, and as this cytokine can, to a certain extent, substitute for IL-2, strategies to inhibit the common γ-chain of these receptors may prove even more successful.

Transplantation

Professor Herman Waldmann (Sir William Dunn School of Pathology, Oxford, UK) discussed the use of anti-CD4 monoclonal antibodies in transplantation. Based on a model of how antibodies induce tolerance to transplanted grafts, and on the concept of linked suppression, he explained how tolerance to specific antigens, induced by grafting under the cover of an anti-CD4 monoclonal, can lead to acceptance of tissues bearing other transplantation antigens, provided they are co-expressed with those to which tolerance was first induced. This tolerance is mediated by CD8+ T cells and is 'infectious', in that it can be transferred to a naive animal by a lymphocyte infusion. The most likely mechanism underlying these observations is that a subset of regulatory T cells is induced which suppresses the activity of effector T cells, either by direct inhibition or by competition for cytokines (the so-called 'civil servant hypothesis'). These models of graft tolerance, while successful in rodents, have been less so in human studies. There may be several reasons for this: first, there may be a greater contribution of other T cell subsets such as CD8+ T cells; secondly, the endothelium may be more immunogenic in humans; and thirdly, concomitant immunosuppression with drugs may interfere with the development of tolerance.

Multiple courses of antibody injection may help to maintain tolerance to organ grafts, but doing so causes an immune response to the antibody to develop, thus neutralising its effectiveness. High doses of monomeric immunoglobulin induce tolerance to that specific protein, and it is only when antibodies bind to cells that they become immunogenic. Therefore, by engineering antibodies with mutated Fc regions that do not bind to their target, it is possible to induce a state of tolerance to the actual antibody to be used. This has been effective in mice, where it is possible to give monoclonals indefinitely without an immune response to the antibody.

Professor Kathryn Wood (Nuffield Department of Surgery, University of Oxford, UK) pointed to several possible targets for gene therapy in transplantation, such as the induction of tolerance, the prevention of rejection and of reperfusion injury. The main questions to be answered are which genes to use and the mode of their delivery.

Tolerance can be induced by injecting recipient bone marrow cells transfected with donor MHC genes under the cover of anti-CD4 antibody. Transfection of the IL-10 gene into neonatal heart grafts can help to prevent graft rejection, as can expression of Fas ligand at the site of the engrafted tissue.

The future success of gene therapy in transplantation will rely on better strategies for gene transfer, a greater understanding of stem cell biology and the setting up of improved experimental models.

Professor Hans Reiser (Imperial College School of Medicine, Hammersmith Hospital, London, UK) outlined the role of costimulatory molecules as regulators of the immune response. The interactions of B7/CD28/CTLA-4 and CD40/CD40L in transplantation seem to be important, as blockade of these interactions can prolong the lifespan of
allografts and xenografts, particularly when both are blocked simultaneously. These findings may be of use in organ transplantation, as well as in the therapy of autoimmune disease.

Dr Randall Morris (Stanford University School of Medicine, California, USA) spoke about the mechanism of action of the new immunosuppressive drugs currently in clinical practice. The rate of acute allograft rejection seems to be much lower with these new agents (including FK506, rapamycin and MMF) and their side effects are no worse than those of conventional drugs. However, as no data regarding long-term allograft survival are currently available, decisions about their efficacy have to be based on surrogate markers. Much of the development of immunosuppressive drugs is based on computer-aided design to reduce specific side effects, such as the gastrointestinal problems associated with MMF.

Dr Tony Dorling (Imperial College School of Medicine, Hammersmith Hospital, London, UK) elucidated recent insights into the mechanisms underlying vascular rejection, endothelial cell activation and cellular responses to xenogenic tissue, which have led to the development of novel methods designed to inhibit immune-mediated xenograft rejection. The first barrier to successful xenotransplantation is antibody-mediated hyperacute rejection. This has been approached by determining the expression of complement regulators, reducing the expression of the antibody epitopes and the intragraft expression of anticoagulant proteins. If both the hyperacute and the related delayed xenograft rejection can be prevented, it will still be necessary to induce tolerance to the graft since, contrary to earlier reports, T cell responses may well be strong and not well controlled by current immunosuppressive drugs.

**Autoimmunity**

Professor David Wraith (University of Bristol, UK) gave an account of the induction of tolerance by delivering antigen to mucosal surfaces. Mucosal targeting of a peptide antigen of myelin basic protein (MBP) can generate tissue-specific immune suppression and prevent the development of experimental autoimmune encephalomyelitis (EAE), a murine model of multiple sclerosis (MS). The T cells that cause this disease are generally of low avidity and as such are poor at inducing tolerance. This may help to explain why clinical trials of oral myelin in MS were unsuccessful. A way around this problem is to use mucosal adjuvants such as MBP conjugated to the β-subunit of cholera toxin. An alternative route of delivering the antigen is intranasal, which is remarkably effective at inducing antigen-specific T cell tolerance. The intranasal route of peptide administration can prevent the development of EAE, and displays epitope spreading via bystander suppression. Repeated intranasal peptide administration results in upregulation of IL-10, a cytokine with known immunosuppressive properties.

Professor Alastair Compston (University of Cambridge, UK) presented the results of a trial in 37 patients with MS of the humanised monoclonal antibody, CAMPATH-1H, which depletes T cells for several months after a single dose. All patients showed an acute deterioration, related to a cytokine release syndrome (tumour necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), IL-6), which was cured by intravenous methylprednisolone. The treatment reduced relapse rates (no new relapses up to 18 months after initiation of treatment) but in 50% of patients the disease progressed, with increasing cerebral atrophy due to continued axonal loss. Patients whose disease continued to progress after CAMPATH-1H had more inflammation prior to treatment, and axonal degeneration continued even after the inflammation has been suppressed. This suggests that immunological therapies will best prevent progression of disability if given early in the course of disease. Complications of this treatment are low, but 35% of patients in this trial have developed autoimmune thyroiditis, which has not been reported for other patients treated with this antibody (>3,000 patients).

Professor Marc Feldmann (Kennedy Institute of Rheumatology, London, UK) presented data from a trial using anti TNF-α monoclonal antibodies in the treatment of rheumatoid arthritis (RA). Cytokine expression in rheumatoid joints shows a common and persistent pattern. For anticytokine therapy to be effective, it is important to target rate-limiting cytokines. From a number of studies it would appear that TNF-α is such a molecule. Seventy per cent of patients treated with five doses of antibody showed marked clinical benefit which lasted for 12 weeks after the cessation of therapy. A few patients entered clinical remission and at low doses of antibody there was synergy with low doses of methotrexate.

The future of anti-cytokine therapies for autoimmune disease may include the use of anti IL-12 and anti VEGF (vascular endothelial growth factor) antibodies, perhaps in combination with anti TNF-α.

**Allergy**

Dr Anthony Frew (University of Southampton, UK) emphasised the importance of T cells in the pathogenesis of asthma, particularly by the production of IL-4, IL-5 and IL-13. In addition to the current therapeutic strategies of anti-inflammatory agents and bronchodilators, future treatments for asthma may well include cytokine or anticytokine therapy. Further targets for intervention may be the pathways responsible for cellular recruitment into the affected airways. Such pathways include adhesion molecules and the soluble chemoattractant proteins known as chemokines.

Professor Barry Kay (Imperial College School of Medicine at the National Heart and Lung Institute, London, UK) presented the results of administering anti-CD4 monoclonal antibodies in the treatment of severe steroid-dependent
asthma. At the highest dose of this depleting antibody, there was a significant improvement in peak flow recordings (n=22). This improvement lasted for 14 days and although the mechanism of action is not entirely clear, suggests that T cell directed therapies may be of use in severe asthma.

Cancer

Professor Cornelius Melief (Leiden University Medical Centre, The Netherlands) spoke about T cell immunity to tumours and how an understanding of the underlying mechanisms could lead to specific therapeutic manoeuvres to induce anti-tumour immunity. T cell immunity occurs naturally against tumours induced by viruses and other causes. In the case of non-virally induced tumours, self-antigens are often found to be targets of tumour-associated cytotoxic T lymphocytes (CTL). In all types of tumours, the T cell response is usually suboptimal and would benefit from vaccination. The outcome of immunisation with vaccines containing tumour virus CTL epitopes depends on the mode of epitope delivery. For example, specific CTL tolerance can be induced by a single injection of peptide in adjuvant, whereas in vivo presentation of the same peptide on dendritic cells or in an adeno viral vector leads to strong anti-tumour immunity.

Recent results from Leiden and two other groups indicate that priming of CTL requires CD4+ T cell help via the interaction of CD40 with CD40L (CD154), as anti CD40L antibodies can block cross-priming which is reconstituted by stimulatory CD40 monoclonal antibodies. These data support a new model of T cell help which places less emphasis on the production of IL-2 from the CD4+ T cell. Instead the CD4+ T cell recognises its cognate antigen on a dendritic cell and activates it via the CD40–CD40L interaction. This activated dendritic cell then primes effector CD8+ cytotoxic T lymphocytes. This new mechanism may have significant implications for the generation of anti-tumour immunity.

Infection

Professor Adrian Hill (Institute of Molecular Medicine, Oxford, UK) presented data regarding the design of antimalarial vaccines for eliciting CD8+ T cell responses. Due to the polymorphism in malarial antigens, vaccines are made up of ‘strings’ of epitopes. In general, it is better to choose conserved antigens or epitopes, as antagonism is often observed with polymorphic antigens owing to generation of altered peptide ligands. Priming with DNA and boosting with a replication-defective modified vaccinia virus gives 100% protection in a murine malaria model, at least in the short term. This method, known as the prime-boost regime, generates high levels of peptide-specific CTL. This type of regime is now undergoing clinical trials in order to ascertain its efficacy in humans.

Acknowledgment

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References

1 Cobbold SP, Adams E, Marshall SE, Davies JD, Waldmann H. Mechanisms of peripheral tolerance and suppression induced by monoclonal antibodies to CD4 and CD8. Immunol Rev 1996;149: 5–33.
Science-based complementary medicine
Edited by Tom Meade FRS

An increasing number of patients who feel that conventional medical treatment provided by their doctors has not met their expectations are seeking ways to complement, or to replace it with some alternative therapy.

Doctors trained in western medicine and its scientific basis have been suspicious of the claims of therapies based on different concepts, attributing any reported benefits at best to a placebo effect or dismissing them as fraudulent. An important step in bridging the gap between these therapeutic cultures was the setting up of the Research Council for Complementary Medicine which aims to introduce genuine, acceptable scientific methods of assessing these treatments. At about the same time, Professor Tom Meade's unit conducted a carefully controlled comparison of chiropractic with conventional physiotherapy for lower back pain which is reported here.

Based on papers given at a conference organised by the RCP, this book describes how to gather and examine the evidence of a scientific basis for complementary medicine, illustrates what can and cannot be achieved with homoeopathy, herbal remedies and manipulations of the spine, and what doctors and patients expect of such therapies.

This marks the start of a new epoch in the relationship between conventional and complementary medicine which can only be to the benefit of patients.

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