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Drug-free tolerance of transplanted tissue

Jo Whelan, Freelance writer

Successful organ transplantation could be possible without the need for long-term use of immunosuppressant drugs. Work recently published demonstrates that diabetic monkeys given transplanted pancreatic tissue have remained in good health for more than one year after just two weeks of immune-modifying therapy[1].

Patients receiving transplants currently need to take expensive immunosuppressant drugs for the rest of their lives to prevent rejection of the donated organ. These inhibit the division of T and/or B lymphocytes. Although effective in the short-to-medium term, this regimen has not significantly improved long-term organ survival. For example, only 50% of all kidney transplants are still functional after ten years, the remainder failing as a result of acute or chronic rejection. In addition, the long-term use of immunosuppressants causes a range of side-effects including kidney toxicity, hypertension, diabetes, increased risk of cancer, susceptibility to infection, excessive hair growth and gastrointestinal disturbances.

Inducing tolerance

Because of these side effects, there is considerable interest in modulating the immune system so that transplanted tissue is tolerated without general immunosuppression. Some of this work has focused on isolated pancreas islet allotransplantation (IPIT), a promising treatment for type 1 (insulin-dependent) diabetes. The islet cells of the pancreas are the site of insulin production, and in type 1 diabetes these cells are destroyed by autoimmune attack. Transplanting clusters of islet cells into the liver can reinstate normal blood-glucose regulation[1], but immunosuppressive therapy is required. Even with this therapy, immune-induced deterioration of the cells often gradually reduces insulin output.

The ultimate goal of IPIT would be to treat type 1 diabetes in children before they develop the long-term complications associated with hyperglycaemia, but this is not currently an option because immunosuppressants produce side effects similar to, or worse than, diabetic complications.

A team from the University of Alabama at Birmingham (UAB; Birmingham, AL, USA) has induced 'operational tolerance' of IPIT in monkeys with streptozotocin (STZ)-induced diabetes, a well known animal model of the disease[2]. Operational tolerance is defined as the durable survival of islet allografts without maintenance by immunosuppressive therapy and without rejection or loss of functional islet mass or insulin secretory reserve.

Eleven rhesus monkeys underwent IPIT with donor cells that were deliberately mismatched for major histocompatibility complex (MHC) antigens. Immediately before and after transplantation, nine of the monkeys were given a 100 mg kg^{-1} bolus infusion of $F(Ab_2)$-IT (an anti-CD3 immunotoxin made by conjugating the $F(Ab_2)$ fraction of FN18 anti-rhesus CD3 monoclonal antibody with CRM9 mutant diphtheria toxin), which depletes the lymphoid system of all T cells[3]. Seven of the monkeys were then continuously infused with 2.5 mg kg^{-1} day^{-1} of 15-deoxyspergualin (DSG) for 14 days, which inhibits the nuclear translocation of nuclear factor kappa-B (NF-κB), and thereby blocks both proinflammatory cytokine production and the maturation of dendritic cells[4]. DSG is known to have a strong synergistic effect with anti-CD3 immunotoxin, which is thought to result from a coincidental reduction in lymph-node T-cell mass and mature dendritic cells. This situation, although transient, is thought to favour the development of a stable tolerance to transplanted material.

In all monkeys, non-fasting blood-glucose levels returned to normal within 72 h of IPIT. Rejection of the transplant occurred at 15 and 16 days in control monkeys given only DSG, and at 23 and 70 days in monkeys given only $F(Ab_2)$-IT. However, six of the seven monkeys treated with both agents still had stable blood-glucose levels after more than a year, without any further use of immunosuppressants or insulin.

1359-6446/01/$ – see front matter PII: S1359-6446(01)01899-2

Immune changes

The transplant-tolerant monkeys demonstrated a normal response to an environmental bacterial antigen (streptolysin O), suggesting they were immunocompetent rather than immunosuppressed and, therefore, that genuine tolerance had developed. However, the treated monkeys also showed significant immune-system changes compared with controls. Despite a phenotypically normal T-cell population, their long-term antibody response to a previously unmet antigen was much weaker, suggesting limited T-cell amplification. A mean 22-fold increase in plasma levels of interleukin-10 (IL-10) and a sixfold increase in IL-4 was also observed, and was sustained for at least 12 months. 'The cytokine changes indicate that tolerance induction by this novel strategy results in immune deviation from Type I to Type II immunity,' says lead author, Judith Thomas. 'Sustained IL-10 and IL-4 production in the presence of the graft suggests an active process, possibly due to a regulatory T-cell population that contributes to the stability of this tolerance.'

Type 1 diabetes in humans is an autoimmune disease, a condition that is not present in the STZ model. There is a risk, therefore, that transplanted islet cells might also be killed by autoimmunity. However, co-administration of IT and DSG has been shown to reduce the population of memory T-cells[3], suggesting that this might also control recurring autoimmunity. This would be highly significant because it could lead to new treatments for multiple sclerosis, rheumatoid arthritis and other autoimmune diseases.

Human trials are currently being planned: 'We need to complete the testing of anti-human CD3 immunotoxin, which is similar, but not identical to anti-monkey CD3 immunotoxin,' says Thomas. Future research will be focused on further understanding the mechanism of transplant tolerance to facilitate its safe and effective translation to clinical therapy.

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Electrifying new treatment for epilepsy

Janet Fricker, Freelance writer

Researchers believe that mild electric fields could control epilepsy, after results showing that seizure-like activity can be inhibited by applying these fields to brain cells *in vitro*[1].

Researchers at the Krasnow Institute for Advanced Study at George Mason University (Fairfax, VA, USA) say that using such electric fields to modulate neuronal activity offers the opportunity to minimize the use of invasive techniques such as medical and surgical treatments currently used in epilepsy.

Epileptic seizures can be defined as the paroxysmal discharge of cerebral neurones resulting in disorderly muscular activity and mental changes. 'It is thought that in epilepsy, small groups of neurons fire in a co-ordinated fashion, as opposed to the normal state of individual neurones firing infrequently,' explains Bruce Gluckman, Assistant Professor of Physics and Astronomy at the Krasnow Institute. 'But there is still a great deal to discover about the epileptic process. '

Current treatments

As many as one or two in 100 people have epilepsy, defined by the occurrence of more than one seizure. In one-third of these people with epilepsy, the symptoms can be well controlled using pharmacologically active agents; in another one-third the epilepsy can be reasonably controlled; and the final one-third of epileptic patients have pharmacologically intractable epilepsy. For the last group the principal treatment offered is surgical resection of the epileptic foci.

'With resection, there is always the potential hazard that the part of the brain you're cutting into is not going to function. There is almost no part of the brain that is not serving some useful function,' says Steven Schiff, the Krasnow Professor of Neurobiology. 'For example, when the temporal lobes are resected, there is some decrement in verbal memory if the left side is operated on, and spatial memory if the right side is operated on.'

1359-6446/01/$ – see front matter PII: S1359-6446(01)01900-6