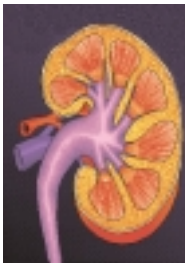
Delivering on immunosuppression

Helen Dell, BMN News



The potential of a novel immunosuppressing peptide could now be realized, thanks to a new cell-delivery system. The re-designed peptide supports successful transplantation of islets into mice and appears less toxic than standard immunosuppressors, report researchers.

Peptide delivery system

The new peptide delivery system opens possibilities for the development of new peptide drugs, says Masayuki Matsushita, a Physiologist at Okayama University in Japan (http://www.okayama-u.ac.jp/). Indeed, it could be useful to transport any chemical that can not enter the cell's cytosol.

Immunosupressants cyclosporin A and FK506, which are used to prevent transplant rejection in patients, inhibit the activity of an enzyme called calcineurin, explains Matsushita. In T cells, calcineurin activates the transcription factor NFAT (nuclear factor of activated T cells), which in turn, is responsible for switching on the genes involved in the T-cell immune response. Thus, blocking calcineurin dampens the immune response and prevents rejection.

But calcineurin has other functions outside the immune system, and interfering with its activity using cyclosporine A and FK506 causes loss of renal function, hypertension, increased malignancies, and other side effects. Matsushita's team has sought safer drugs.

Selective interference

Fortunately, Anjana Rao of Harvard's Center for Blood Research in Boston, Massachusetts (http://cbr.med.harvard.edu/indexb.html), and her team had already developed a possible solution – a peptide called VIVIT.

VIVIT interferes selectively with the calcineurin–NFAT interaction without affecting any of calneurin's other targets, notes Matsushita, so it might be useful as a therapeutic agent that is less toxic than current drugs. The problem was delivering VIVIT efficiently into cells *in vivo*, because peptides are often quickly degraded and have problems crossing the cell membrane.

To do this, Matsushita and his team fused VIVIT with a short stretch of arginine residues (11R–VIVIT). Polyarginine facilitates the uptake of peptides and protein into cultured cells, explains Matsushita, and he hoped that the 11R–VIVIT would not only be transported into the cells, but would remain effective at blocking the immune response.

NFAT function

As the investigators report in *Nature Medicine* [1], the 11R–VIVIT did indeed inhibit NFAT function in a T cell line, and appeared to be stable enough to survive in the circulation of a mouse model.

Using mice that had had their insulin-producing islet cells destroyed, the researchers next studied whether the 11R–VIVIT could prevent transplant rejection. Following transplantation of islet cells from other mice, treatment with the peptide prolonged survival of the grafts, and the transplanted islet cells were still producing insulin, 50 days later.

'I think this is a step forward in terms of demonstrating efficacy *in vivo*,' commented Kathryn Wood, Professor of Immunology at the Nuffield Department of Surgery at Oxford University, UK (http://www.jr2.ox.ac.uk/nds/). 'It's a very effective model for testing efficacy of an immunosuppressant because the islets are susceptible to rejection.'

Although the peptide is a long way from clinical trials, she says, the work is an interesting proof of concept as far as trying to reduce toxicity of calcineurin inhibitors. Safer immune suppressors will have benefits not only for transplant patients, she notes. If there are less side effects, the drugs could then be employed in treating autoimmune diseases, such as psoriasis, for which current drugs are considered too dangerous.

Reference

1 Noguchi, H. *et al.* (2004) A new cell-permeable peptide allows successful allogeneic islet transplantation in mice. *Nat Med.* 10, 305–309(Epub 2004 Feb 08; http://www.nature.com)