Type 1 diabetes: TNF agonists selectively kill autoreactive T cells *in vitro*

Targeted destruction of autoreactive T cells is an optimum treatment goal for type 1 diabetes. In animal models of type 1 diabetes, administration of tumor necrosis factor (TNF) selectively kills autoreactive T cells and prevents or suppresses the disease. To assess the human therapeutic potential of this approach *in vitro*, Ban *et al.* tested whether TNF or TNF agonists selectively killed autoreactive T cells isolated from blood samples of patients with type 1 diabetes.

The researchers developed magnetic cell-separation methods to isolate high yields of purified, viable CD4 and CD8 T cells from blood samples of patients with type 1 diabetes and healthy controls. No CD4 T cells from patient or control samples were killed by TNF treatment; however, the treatment did kill a subset of CD8 T cells from the patient samples. Crucially, the subset killed was identified as the CD8 T cells responsible for the autoimmune destruction of pancreatic islets. In addition, a TNF agonist that acts through the restrictively expressed TNF receptor type 2 (which would probably have less toxicity than TNF), also specifically killed these autoimmune T cells. Importantly, CD8 T cells targeted against two common viruses in patient samples were not killed by TNF or TNF agonist treatment.

The findings raise the possibility of a highly targeted therapy for type 1 diabetes that has much higher specificity than current immunosuppressive approaches.

Original article Ban L *et al.* (2008) Selective death of autoreactive T cells in human diabetes by TNF or TNF receptor 2 agonism. *Proc Natl Acad Sci USA* **105:** 13644–13649

Tight glycemic control does not reduce mortality in critically ill adults

Tight glycemic control has been shown to reduce mortality in critically ill, surgical patients and is now widely recommended for all critically ill adults. However, a growing body of evidence suggests that in these patients such control might increase the risk of hypoglycemic events and even mortality, which prompted Wiener *et al.* to conduct a meta-analysis to assess the risks and benefits of tight glycemic control versus normal care in critically ill adults.

The authors searched MEDLINE (1950–2008), the Cochrane Library, multiple trial registries, reference lists and abstracts from selected medical conferences, and identified 29 relevant, randomized, controlled trials for inclusion. In analyses of pooled data, tight glycemic control was not associated with significant reductions in hospital mortality or need for dialysis, either overall or in subgroups stratified by intensive-care setting (i.e. surgical, medical, or all critically ill patients) or glycemia target—very tight (≤6.1 mmol/l) or moderately tight control (<8.3 mmol/l). The risk of hypoglycemic events (glucose ≤2.2 mmol/l) was increased in patients receiving tight glycemic control; this risk was particularly high for the subgroup receiving very tight control. By contrast, the tight-control group had a decreased risk of septicemia, although this decrease was limited to critically ill, surgical patients.

The findings refute a mortality benefit of tight glycemic control in critically ill adults and highlight the need to re-evaluate this recommendation.

Original article Wiener RS *et al.* (2008) Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. *JAMA* **300:** 933–944