Basic science

DIABETES

Islet transplantation

Readability	✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓✓

1 Islet transplantation was followed up in 17 subjects who attained insulin independence.

2 Subjects were assessed for immediate and long-term complications related to the procedure or to immunosuppressive therapy.

3 In 14 subjects who maintained demonstrable C-peptide secretion, glucose control was stable, and glycaemic lability and problems with hypoglycaemic reactions were corrected.

4 There were some acute risks associated with the procedure, and hypercholesterolaemia and hypertension were seen with longer-term follow-up.

5 Apart from a rise in serum creatinine in two subjects, there were no serious consequences of immunosuppressive therapy.

6 Results indicated that prolonged insulin independence can be achieved after islet transplantation.

Ryan EA, Lakey JRT, Paty BW, Imes S et al (2002) Successful islet transplantation: continued insulin reserve provides long-term glycemic control. Diabetes 51: 2148–57

Islet transplantation – a formula for success

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Although whole or segmental pancreas transplantation has been successfully performed for several years, it is a complex surgical procedure carrying a significant risk of peri- and postoperative morbidity and mortality. The notion of transplanting islets is attractive because it is a minimally invasive procedure that can be carried out on a 'day-case' basis. Until recently, however, the International Islet Cell Transplantation Registry had recorded very few transplanted patients as continuing 'off' insulin for any protracted period of time. All this changed in 2000 when James Shapiro and his team in Edmonton, Canada, reported their pioneering work demonstrating successful clinical islet transplantation in a series of patients with unstable diabetes.

The paper from Ryan et al provides follow-up data on 17 Edmonton protocol-treated subjects, all of whom regained insulin independence after transplantation. It is the combined improvements in procedures for organ retrieval, islet isolation/transplantation and steroid-free graft protection that have led to the remarkable improvement in clinical outcome, with more than 80% of patients remaining off insulin for over a year.

Clearly, several challenges remain before islet cell transplantation can be widely available for the treatment of type 1 diabetes.

- First is the source of cells, as demand will always far exceed organ donor supply. Research is focused on identifying alternative tissue sources including islets from 'humanised' transgenic pigs, differentiated human pancreatic duct cells and fetal pancreatic stem cells.
- Second is the need to promote and improve long-term graft survival by protecting against immune-mediated attack. Possible approaches under investigation include induction of immune tolerance and immunoisolation by microencapsulation of islets.
- Third is to prevent the impaired reaction to hypoglycaemia seen in some transplant recipients. It might be necessary to explore alternative sites for islet implantation so as to restore blunted glucagon and epinephrine responses.

Islet cell transplantation obviously still has some way to go, but the latest report from the Edmonton group tells us that it is a safe and extremely effective treatment for patients suffering from debilitating brittle diabetes and severe episodes of hypoglycaemia. Indeed, such is the success of this approach that parallel programmes have been initiated at several transplant centres within the UK in an attempt to reproduce the winning Edmonton formula.

Y2 knockouts

Readability	✓✓✓
Applicability to practice	✓✓
WOW! factor	✓✓✓

1 Hypothalamic neuropeptide Y (NPY) stimulates food intake, and induces many neuroendocrine and metabolic changes that favour energy storage. Chronically elevated hypothalamic levels of NPY contribute to obesity.

2 Mice in which the NPY receptor Y2 had been specifically deleted in the hypothalamus showed a significant decrease in body weight and an increase in food intake.

3 This phenotype was associated with changes in hypothalamic mRNA levels.

4 Although the mRNA changes persisted until at least 34 days after Y2 deletion, the effect on body weight and food intake subsided within this time, consistent with an adaptation to maintain homeostasis in these vital processes.

5 In contrast to the hypothalamic knockouts, germ-line Y2 receptor knockout mice showed a sustained reduction in body weight and adiposity. Therefore, hypothalamus-specific Y2 receptor knockouts provide more direct insight into the role of these receptors in energy homeostasis than do germ-line knockouts.

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6 This study provides in vivo evidence for the involvement of hypothalamic Y2 receptors in energy homeostasis.

Sainsbury A, Schwarzer C, Couzens M, Fetissov S et al (2002) Important role of hypothalamic Y2 receptors in body weight regulation revealed in conditional knockout mice. Proceedings of the National Academy of Sciences 99(13): 8938–43

'IP-10 was found more frequently in newly diagnosed type 1 diabetics and in control subjects with a high risk of the disease.'

DIABETOLOGIA

IP-10/CXCL10 link with type 1 diabetes

Readability	✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

1 The IP-10 chemokine is pathogenetically involved in several immunoinflammatory and autoimmune diseases. Because cell-mediated immunity is primarily responsible for the development of type 1 diabetes, the role of this chemokine was investigated.

2 IP-10 levels were quantified in the sera of patients with either newly diagnosed or long-term type 1 diabetes, and in their first-degree relatives (subdivided into healthy, low-risk and high-risk categories).

3 IP-10 was found more frequently and at increased concentrations in newly diagnosed type 1 diabetics and in control subjects with a high risk of the disease, compared with healthy control subjects, those with a low risk of the disease and patients with long-term type 1 diabetes.

4 Circulating IP-10 concentrations are increased in patients with type 1 diabetes, but only during the early and subclinical stages of the disease.

5 If this upregulated synthesis of IP-10 mirrors chemokine production in the pancreas, IP-10 could be pathogenetically important by attracting and stimulating diabetogenic Th1 cells to the pancreas.

Nicoletti F, Conget I, Di Mauro M, Di Marco R et al (2002) Serum concentrations of the interferon-γ-inducible chemokine IP-10/CXCL10 are augmented in both newly diagnosed Type 1 diabetes mellitus patients and subjects at risk of developing the disease. Diabetologia 45: 1107–10

'Fat-specific insulin receptor knockout produced selective insulin resistance in the adipose tissue, but did not affect whole-body glucose metabolism.'

DIABETES

Central leptin gene therapy

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓✓

1 Rats consuming a high-fat diet (HFD) were injected intracerebroventricularly with a construct encoding leptin.

2 Caloric consumption and body weight were monitored weekly until the rats were killed at 9 weeks.

3 Leptin expression reduced food intake and blocked the HFD-induced increase in weight, adiposity and metabolic variables (e.g. serum leptin, free fatty acids and insulin).

4 Leptin expression significantly increased thermogenic energy expenditure in HFD rats.

5 These findings suggest that leptin gene therapy overcomes the leptin resistance that develops when eating a HFD.

6 Central leptin gene therapy was effective in preventing weight gain, and increased adiposity and hyperinsulinaemia in HFD-fed rats.

Dube MG, Beretta E, Dhillon H, Ueno N et al (2002) Central leptin gene therapy blocks high-fat diet-induced weight gain, hyperleptinemia, and hyperinsulinemia: increase in serum ghrelin levels. Diabetes 51: 1729–36

BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS

NOD response to hsp60

Readability	✓✓✓
Applicability to practice	✓✓
WOW! factor	✓✓

1 Injections of human heat shock protein 60 (hsp60) protect non-obese diabetic (NOD) mice from disease development.

2 Therefore, it was investigated whether innate immune cells of NOD mice exhibit an abnormal response to extracellular hsp60.

3 Hsp60-stimulated bone marrow-derived macrophages from NOD mice were compared with those from NOD variants.

4 Replacing the diabetes-associated MHC-encoding allele with the NON-specific allele caused a reduction in IL-12(p70) secretion, whereas introducing the MHC region of the NOD mouse into the NON background did not result in elevated hsp-60-induced IL-12(p70) secretion.

5 This finding points to a genetic association of hsp60 hyperresponsiveness of NOD mice with the MHC region, and to an interaction between MHC and non-MHC genes.

Adler T, Akiyama H, Herder C, Kolb H, Burkart V (2002) Heat shock protein 60 elicits abnormal response in macrophages of diabetes-prone non-obese diabetic mice. Biochemical and Biophysical Research Communications 294: 592–6

DEVELOPMENTAL CELL

Selective insulin receptor knockouts

Readability	✓✓
Applicability to practice	✓✓
WOW! factor	✓✓✓

1 FIRKO (fat-specific insulin receptor knockout) mice were created.

2 These mice have reduced fat mass, reduced whole-body triglyceride stores, and loss of the normal relationship between plasma leptin and body weight.

3 The knockout produced selective insulin resistance in the adipose tissue, but did not affect whole-body glucose metabolism.

4 The knockout also produced almost complete protection against age-and hyperphagia-associated obesity and the impairment of glucose tolerance associated with these conditions.

5 The mice exhibited a heterogeneity in fat cell size and protein expression pattern, and inappropriately elevated leptin serum levels, suggesting previously unrecognised roles of insulin in the regulation of adipose tissue biology.

6 FIRKO mice provide a novel model for investigating the role of insulin in the regulation of leptin secretion from adipose tissue in vivo.

Bluher M, Michael MD, Peroni OD, Ueki K et al (2002) Adipose tissue selective insulin receptor knockout protects against obesity and obesity-related glucose intolerance. Developmental Cell 3: 25–38