Basic science

New ß-cells or more of the same?

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Transplantation of isolated pancreatic islets has always been recognised as a potentially safer and less invasive procedure for ß-cell replacement than solid-organ pancreas transplantation. It is only fairly recently, however, that islet transplants have been shown to be effective in achieving long-term insulin independence in the majority of type 1 diabetes recipients. The more widespread application of islet transplantation is severely hampered by the availability of primary donor islets, and this scarcity of tissue continues to drive research efforts aimed at finding new sources of ß–cells.

This excellent review by Hardikar considers the various mechanisms that play a role in maintaining a functional ß–cell mass within the pancreas. In particular, the possible adaptive growth response of the endocrine pancreas to tissue damage and injury is highlighted. A number of studies in animal models have confirmed that the adult mammalian pancreas does in fact possess the ability to repair and regenerate itself following partial resection and duct occlusion of the pancreas and after induction of diabetes by toxins and viruses. What is less clear, however, is the extent to which common adult pancreatic precursor cells participate in these processes. If adult stem cells play a major role in replacing lost ß-cells then they could become a major focus for researchers seeking alternative sources of tissue for replacement therapy. However, a recent paper in *Nature* (Dor et al, 2004; **429**: 41–46) has provided compelling evidence that it is the replication of pre-existing ß-cells that accounts for ß-cell renewal during adult life and following pancreatectomy in mice.

The debate over the relative contributions of replication and/or neogenesis to pancreatic regeneration is set to continue. What is clear is that an increased understanding of how the ß-cell mass is regulated will be essential in developing new approaches to replacement therapy in diabetes.

DIABETES CARE

Pancreas transplants improve macro-vascular disease

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

1 Although pancreas transplantation (PTX) normalises glucose and improves microvascular complications, its impact on macrovascular disease remains a point of debate.

2 Carotid intima-media thickness (IMT) correlates with risk and events of cardiovascular (CV) disease; it was determined prospectively using ultrasonography in people who had successful pancreas transplants, to evaluate the effect of PTX on CV disease risk.

3 Carotid IMT and CV disease risk factors of pancreas transplant recipients were compared in three groups: people with type 1 diabetes with no significant nephropathy (n=20); people without diabetes who had kidney transplants (n=16); and healthy controls (n=32).

4 After PTX, HbA_{1c} level decreased to normal. Creatinine level decreased but remained elevated compared with the control group.

5 Blood pressure, body mass index, fasting lipid levels, use of hypolipidaemic agents and smoking levels were unchanged.

6 Mean carotid IMT was increased in people who were candidates for pancreas transplants, but decreased 1.8 ± 0.1 following PTX. Levels were no longer different from that in the control group or in people with diabetes.

7 Carotid IMT therefore improves after successful PTX within two years of the procedure, with normalisation of HbA_{1c} and improved renal function, independent of changes in lipid levels, BMI, use of hypolipidaemic agents and smoking.

8 The researchers conclude that risk of CV disease, future events and mortality should improve after PTX in the absence of other untreated CV disease risk factors

Larsen JL, Colling CW, Ratanasuwan T et al (2004) Pancreas transplantation improves vascular disease in patients with type 1 diabetes. *Diabetes Care* **27**: 1706–11

TRENDS IN ENDOCRINOLOGY AND METABOLISM

Regeneration of the pancreas: advances

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

1 A key response to pancreatic injury is pancreas regeneration, which involves intra-islet precursor cells and pancreatic duct progenitor cells.

2 Inductive stimuli leading to pancreas regeneration include bone marrow-derived stem cell transplantation, surgical removal of the pancreas and obstruction by cellophane wrapping.

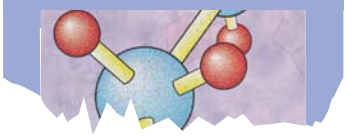
3 The precise role of growth and differentiation factors that regulate pancreatic ß-cell mass is not currently known.

4 The way that the pancreas responds to a deficit in cell mass and undergoes new islet formation, leading to a restoration of normal ß-cell mass, is studied through the integration of recent findings.

5 Further discussion revolves around recent advances in regenerating endocrine pancreatic cells, which may affect stem cell-based approaches to the treatment of diabetes.

Hardikar AA (2004) Generating new pancreas from old. *Trends in Endocrinology and Metabolism* **15**: 198–203

MECHANISMS OF AGEING AND DEVELOPMENT



Retinoic acid may help prevent progress of diabetes

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

1 The effects of retinoic acid (RA) on cytokine-induced ß-cell dysfunction were examined.

2 RA significantly protected interleukin-1ß (IL-1) and interferon-γ-mediated cytotoxicity of rat insulinoma, and also reduced in IL-1 and IFN-γ-induced nitric oxide production.

3 This correlated well with reduced levels of the inducible form of nitric oxide synthase, mRNA and protein.

4 The molecular way that RA inhibits nitric oxide synthase gene expression seems to involve the inhibition of NF-κB activation.

Kang M-K, Yoon Y-E, Yang J-Y, Kwon K-B, Park J-W, Jhee E-C (2004) Protective effect of retinoic acid on interleukin-1β-induced cytotoxicity of pancreatic β-cells. *Mechanisms of Ageing and Development* **14**: 197–98

JOURNAL OF BIOLOGICAL CHEMISTRY

Can antioxidant strategies protect ß-cells?

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

1 Multiple biochemical mechanisms and pathways for glucose toxicity have been suggested – these are discussed in a mini-review.

2 The different theories include protein kinase C activation, glucose autoxidation, methylgloxal formation and glycation, sorbitol formation, hexosamine metabolism and oxidative phosphorylation.

3 There are many potential mechanisms where excess glucose metabolites could damage ß–cells.

4 All of the pathways share the formation of reactive oxygen species that over time cause chronic oxidative stress, which in turn causes defective insulin gene expression, insulin secretion and increased apoptosis.

5 A final consideration is whether antioxidant strategies could be used to protect further deterioration of the ß-cell after the onset of diabetes.

Robertson RP (2004) Chronic oxidative stress as a central mechanism for glucose toxicity of pancreatic islet beta cells in diabetes. *Journal of Biological Chemistry* **16**: E-pub

NATURE GENETICS

A new pathway in the pathogenesis of type 1 diabetes

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

1 Research has suggested over 20 genetic intervals that are associated with susceptibility to type 1 diabetes.

2 The identification of specific genes has been challenging, and mostly limited to known candidate genes.

3 The researchers cloned a new gene (SUM04), encoding small ubiquitin-like modifier 4 protein, in the *IDDM5* interval.

4 They found that type 1 diabetes was strongly associated with a substitution (M55V) at an evolutionarily conserved residue of the crucial CUE domain of SUM04.

5 SUM04 conjugates to IκBα and negatively regulates NFκB transcriptional activity.

6 The M55V substitution resulted in 5.5 times greater NFκB transcriptional activity, and about twice as much expression of IL12B and NFκB-dependent gene.

7 A new pathway may be implicated in the pathogenesis of type 1 diabetes.

Guo D, Li M, Zhang Y et al (2004) A functional variant of SUM04, a new IκBα modifier, is associated with type 1 diabetes. *Nature Genetics* 36: 837–41

'A final consideration is whether antioxidant strategies could be used to protect further deterioration of the ß-cell after the onset of diabetes.'

DIABETOLOGIA

Pancreatic duct cells help threaten ß-cells in diabetes

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

1 This study investigated whether human duct cells are a source of tumour necrosis factor- (TNFα-) mediated interactions with ß-cells and immune cells.

2 Human duct cells were isolated from donor pancreases and were examined for their ability to produce TNFα after a stress-signalling pathway.

3 TNFα was tested for its in vitro effects on activation of human dentritic cells and on the survival of human ß-cells.

4 It was found that exposure of human pancreatic duct cells to interleukin-1ß (IL-1ß) induces TNFα gene expression, synthesis of the 26 000 M_r TNFα precursor and conversion to the 17 000 M_r mature form, which is quickly released.

5 The effect involves p38 MAPK and NF-κB signalling and is NO independent.

6 Duct-cell-released TNFα induced activation of human dendritic cells, and contributed to cytokine-induced apoptosis of isolated human ß-cells.

7 Human pancreatic duct cells are a potential source of TNFα that can cause apoptosis of neighbouring β cells and start an immune response by activating dendritic cells.

Movahedi B, Casteele V, Caluwé N et al (2004) Human pancreatic duct cells can produce tumour necrosis fact-α that damages neighbouring beta cells and activate dendritic cells. *Diabetologia* 47: 998–1008

'Human pancreatic duct cells are a potential source of TNFα that can cause apoptosis of neighbouring ß-cells and start an immune response by activating dendritic cells.'