Basic science

The β-cell gene bank – ordered network or tangled web?

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Type 1 diabetes mellitus develops in susceptible individuals as a result of a progressive and selective destructive process targeted at the insulin-producing pancreatic β-cell. Destruction occurs either through direct cell/cell contact with activated immune cells (T-cells, macrophages) or indirectly via soluble mediators released by the activated cells or β-cells themselves.

The list of factors capable of inducing β-cell death is extensive, but the weight of evidence clearly indicates a central role for inflammatory agents such as cytokines and reactive oxygen species. The predominant pathogenic mechanism of β-cell death associated with onset of type 1 diabetes is apoptosis, which itself is subject to complex regulatory processes.

The very impressive study by Kutlu et al used microarray technology to investigate the extremely complex patterns of gene expression that occur in the β-cell following cytokine exposure and subsequent apoptosis. The authors have not only attempted to identify the genes expressed, but also carried out time-course experiments. This detailed experimental approach permitted a cluster analysis of the microarray data, which showed that 700 of the 3000 genes expressed in the β-cell were differentially modified by cytokines. A comprehensive listing (seven pages) of these regulatory genes is given in the paper, and the authors have further classified them into functional groups related to metabolism, signal transcription and transcription factors.

The amount of data presented by the Brussels group is both breathtaking and bewildering. It is clear, however, that the fate of the β cell following cytokine exposure/apoptosis is determined by a complicated network of hundreds of genes which may be upregulated or downregulated, either in parallel or in sequence.

What makes this study particularly important is the statement from the authors that their β-cell 'gene bank' is an available resource for researchers interested in studying the cell/molecular basis of the disease processes operating in type 1 diabetes. This sort of collaborative outlook will ensure that research into the causes of diabetes is able to move forward towards the ultimate goal of a 'cure'.

TRANSPLANTATION INTERNATIONAL

Islet isolation, preparation and transplantation

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

1 The loss of β-cell mass associated with type 1 diabetes condemns people with this disease to a lifelong dependence on insulin therapy.

2 The advent of islet transplantation has raised hopes of long-term normoglycaemia in patients with type 1 diabetes.

3 This article reviews the development of islet isolation, purification and transplantation.

4 Successful clinical outcomes of pancreas transplantation for patients with long-standing diabetes were, until recently, much superior to those of islet transplantation.

5 There have been significant advances in islet isolation and purification technology, and the development of more specific and less diabetogenic immunosuppressants.

6 New strategies include pretreating islets to reduce their immunogenicity, protecting islets within immuno-isolation devices, and transplanting islets into immuno-privileged sites.

Lakey JRT, Burridge PW, Shapiro AMJ (2003) Technical aspects of islet preparation and transplantation. *Transplantation International* **16**(9): 613–32

DIABETES

Gene network regulation of β-cell dysfunction

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

1 The β-cell dysfunction and apoptosis seen in type 1 diabetes and after islet transplantation results from the release of mediators, such as cytokines, from activated macrophages and T-cells.

2 This article describes a time-course microarray study of cytokine-induced genes in insulin-producing INS-1 cells.

3 INS-1 cells were exposed to the cytokines interleukin-1β and interferon-α (for six different time points ranging from 1 h to 24 h) with or without an inducible nitric oxide synthase blocker.

4 Microarray analysis identified 698 genes as cytokine modified in at least one time point.

5 The genes were classified according to their temporal pattern of variation, and then further classified according to putative function.

6 This study has increased by more than twofold the number of known cytokine-modified genes in insulin-producing cells. It also provides information on the role of nitric oxide for these modifications in gene expression.

7 This information will be a useful resource for researchers interested in understanding the functional inhibitory and proapoptotic effects of cytokines in β-cells.

Kutlu B, Cardozo AK, Darville M et al (2003) Discovery of gene networks regulating cytokine-induced dysfunction and apoptosis in insulin-producing INS-1 cells. *Diabetes* **52**(11): 2701–19

THE LANCET

Genetic cause of hyperglycaemia and drug response

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

1 Heterozygous mutations in the hepatocyte nuclear factor (HNF-1α) gene are the most common cause of maturity-onset diabetes of the young (MODY). It is unclear whether different causes for diabetes change the response to oral hypoglycaemic therapy.

2 The aim of this study was to determine whether the glycaemic response to the sulphonylurea gliclazide and the biguanide metformin differed in HNF-1α diabetes and type 2 diabetes.

3 The primary outcome was fasting plasma glucose in this randomised trial of 36 patients with HNF-1α or type 2 diabetes who were matched for BMI and fasting plasma glucose at baseline.

4 Patients with HNF-1α diabetes had a 5.2-fold greater response to gliclazide than to metformin, and a 3.9-fold greater response to gliclazide than those with type 2 diabetes.

5 Patients with HNF-1α have marked sulphonylurea sensitivity.

6 The cause of hyperglycaemia changes the response to hypoglycaemic drugs. These results have implications for patient management.

Pearson ER, Starkey BJ, Powell RJ et al (2003) Genetic cause of hyperglycaemia and response to treatment in diabetes. *Lancet* **362** (9392): 1275–81

DIABETOLOGIA

Role of reduced β-cell sensitivity to glucose

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

1 The relative roles of insulin resistance and insulin deficiency in people with impaired glucose tolerance (IGT) have been disputed.

2 Indices of insulin sensitivity of fasting glucose production and glucose disposal, and of β-cell function, were measured in 40 patients with IGT and 63 sex-, age- and weight-matched controls with normal glucose tolerance.

3 Patients with IGT had a moderate degree of insulin resistance of glucose disposal compared with controls.

4 Despite higher baseline insulin secretion rates, IGT was characterised by a 50% reduction in glucose sensitivity and impaired potentiation of insulin release. This defect in glucose sensitivity dominates over insulin resistance in people with IGT.

5 The glucose sensitivity of the β-cell insulin response is the single strongest determinant of oral glucose tolerance.

Ferrannini E, Gastaldelli A, Miyazaki Y et al (2003) Predominant role of reduced beta-cell sensitivity to glucose over insulin resistance in impaired glucose tolerance. *Diabetologia* **46**(9): 1211–19

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Expression of transcription factors in α and β cells

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

1 Disturbances of α- and β-cell function are central to the failure to maintain physiological glucose levels.

2 Patterns of gene expression in αTC1.6 *vs* MIN6 cell lines were analysed using oligonucleotide microarrays.

3 Approximately 9–10% of more than 11 000 transcripts examined showed significant differences between α and β cells.

4 Analysis revealed fundamental differences in expression of transcription factor regulator subtypes within the two islet cell types.

5 New approaches to downregulation of α-cell activity in type 2 diabetes may help to reduce the excessive production of glucagon, thereby allowing a relative deficiency of β cells to provide more adequate control of the blood glucose level.

6 These findings, which need further exploration, have implications for the regulation of diabetes.

Wang J, Webb G, Cao Y, Steiner DF (2003) Contrasting patterns of expression of transcription factors in pancreatic α and β cells. *Proceedings of the National Academy of Sciences USA* **100** (22): 12660–665

'The cause of hyperglycaemia changes the response to hypoglycaemic drugs. These results have implications for patient management.'

TRENDS IN ENDOCRINOLOGY AND METABOLISM

Progress in β-cell replacement therapy

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

1 Current methods of insulin delivery often fail to match insulin with prevailing blood glucose concentration.

2 β-cell transplantation is a successful approach; however, the lack of cadaveric islets available for transplantation means that alternative methods must be sought.

3 This paper reviews recent progress in pancreas development, and discusses the role of newer approaches to the treatment of diabetes.

4 Cell engineering has the potential to produce cells with β-cell-like properties. There are problems, however, with finding acceptable mechanisms for genetic manipulation.

5 Embryonic stem cells can serve as a source of insulin-producing cells, and could go on to form the basis of alternative cell replacement strategies.

Ball SG, Barber TM (2003) Molecular development of the pancreatic β cell: implications for cell replacement therapy. *Trends in Endocrinology and Metabolism* **14** (8): 349–55

'Embryonic stem cells can serve as a source of insulin-producing cells, and could go on to form the basis of alternative cell replacement strategies.'