Pancreatic islets are neuroendocrine organs that control blood glucose homeostasis. The precise interplay of a heterogeneous group of cell populations (β, α, δ and PP cells) results in the fine-tuned release of counterbalanced hormones (insulin, glucagon, somatostatin and pancreatic polypeptide respectively). Under the premises of detailed knowledge of the physiological basis underlying this behaviour, two lines of investigation might be inferred: generating computational and operational models to explain and predict this behaviour and engineering islet cells to reconstruct pancreatic endocrine function. Whilst the former is being fuelled by new computational strategies, giving biophysicists the possibility of modelling a system in which new “emergent” properties appear, the latter is benefiting from the useful tools and strategic knowledge achieved by molecular, cell and developmental biologists. This includes using tumour cell lines, engineering islet cell precursors, knowledge of the mechanisms of differentiation, regeneration and growth and, finally, therapeutic cloning of human tissues. Gaining deep physiological understanding of the basis governing these processes is instrumental for engineering new pancreatic islets.

Key words Islets of Langerhans · Bioengineering · Diabetes · Pancreatic β-cell · Insulin

Introduction

Restoration of physiological function by engineered human tissues such as artificial skin, bioartificial livers or endothelialized vascular grafts has prompted the introduction of new therapeutic approaches to a variety of diseases that have been difficult to manage in the past. The ability to manipulate and reconstitute physiological processes has tremendous clinical applications and is likely to play a relevant role in cell therapy in the next few years [118, 138]. The maintenance of glucose concentration in blood within the appropriate range is controlled mainly by the secretion of pancreatic islet hormones, principally insulin from the islet of Langerhans. Absence or diminution of insulin release results in types I and II diabetes, respectively. Diabetes mellitus (DM) is a heterogeneous metabolic disorder affecting 2–5% of the adult population in developed countries. DM can be classified broadly into two groups: the insulin-dependent type (IDDM or type I) and the non-insulin-dependent type (NIDDM or type II). Treatment of type-I DM is still based on self-injection of insulin 3–4 times daily. However, this does not prevent the long-term appearance of microvascular complications including diabetic retinopathy, nephropathy or neuropathy. A more recent clinical trial [34] has shown that tight control of blood glucose can delay and diminish the progression of long-term complications in type-I diabetes, a treatment that needs motivated patients and does not liberate them from insulin dependence. By restoring β-cell function with new therapeutic strategies, such as islet transplantation, patients can be freed from insulin therapy. Nevertheless, allo- and xenotransplantation still imposes problems: the scarcity of material, technical difficulty, high costs, risk of infection by endogenous animal viruses, immune rejection, etc. Either gene or cell therapy will overcome these problems. The possibility of repairing defective genes or introducing new genes (gene therapy) has a high therapeutic potential when mutations are restricted to single, identified genes. Repair of defective genes is under clinical trial in the case of human cystic fibrosis, adenosine deaminase deficiency, types A and B haemophilia, etc. However, poligenic diseases, such as diabetes, are less suitable for gene-repair therapy. Strategies have thus been developed both to increase the resistance of the β-cell to immune attack and to restore physiological function by creating bioartificial pancreatic islets.
The former is beyond the scope of this review. The latter, included in what is termed tissue engineering, needs a full understanding of the physiology of the cell or tissue to be restored. Different techniques are required to achieve this goal, such as cell culture and gene transfer to manipulate the tissue appropriately, thus avoiding rejection and ensuring physiological function. New insights into the biophysical, molecular and biochemical basis of nutrient-induced insulin release, together with identification of genes governing endocrine pancreas development and gene-transfer technology have fuelled new initiatives for engineering pancreatic islets [152]. The aim of this review is to discuss how pancreatic islets of Langerhans should be engineered to restore endocrine pancreatic function in type-I diabetic patients.

The integrated behaviour of the islet poses several questions to bioengineers, consideration of which may be of help when designing a new islet. For example, should we transplant isolated β-cells or β-cell aggregates? What is the role of non-β-cells in the islet and should we transplant them as well? Do all cell populations in the islet (α, β, δ and PP) function as a synchronous syncytium? How can we engineer β-cell surrogates, etc? Let us first analyse how pancreatic islets generate a co-ordinated response from a heterogeneous cell population in order to explore further how new β-cells may be engineered to build a pancreatic islet.

**The pancreatic islet as a functional unit**

**Stimulus-secretion coupling**

Pancreatic islets are formed by a heterogeneous population of cells: insulin-releasing β-cells (65–90%), glucagon-releasing α-cells (15–20%), somatostatin-producing δ-cells (3–10%) and pancreatic polypeptide-producing PP-cells (1%). Amongst this population β-cells have been the most frequently studied in terms of stimulus-secretion coupling. Pancreatic β-cells are a unique class of cells that couple nutrient metabolism with electrical activity and the synthesis and release of insulin [121, 130]. Insulin secretion is initiated by an increase in the cytoplasmic calcium concentration ([Ca²⁺]i) [177]. Glucose metabolism stimulates the rise in [Ca²⁺]i by closing adenosine 5′-triphosphate (ATP)-sensitive K-channels (K_ATP) in the plasma membrane [11, 87, 126, 166], thereby depolarising the membrane, activating voltage-gated Ca²⁺ channels and allowing influx of extracellular Ca²⁺ [10, 166, 177]. Electrical activity, and thus Ca²⁺ influx, occurs in bursts and gives rises to synchronous oscillations in Ca²⁺ and insulin release [82, 134, 166].

Figure 1 summarizes the chain of events that links the presence of nutrients, especially glucose, in the extracellular medium to the release of insulin. Although new players are continuously entering the stage [14], it can be accepted that the whole machinery includes not less that 100 distinct molecules, most of them proteins. These components can be classified into three groups: