Pancreatic β-cells originate from gut endoderm during development. Pancreatic endocrine cells represent about 10% of the mature pancreatic cells, and β-cells represent the majority of endocrine cells. β-cells secrete insulin in response to elevation of nutrient concentrations. Insulin maintains glucose homeostasis by stimulating glucose uptake into muscle and adipose tissue. Aquaglyceroporin 7, permeable to water, glycerol and urea, is expressed in pancreatic β-cells and was recently described as being involved in the control of insulin secretion.

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Langerhans are made of a majority of insulin-producing β-cells surrounded by glucagon-producing α-cells, somatostatin-producing δ-cells and pancreatic polypeptide-producing PP cells.

After birth, the rate of β-cell mass expansion, governed by the rates of new β-cells formation and β-cells loss, slows down. A better understanding of the mechanisms involved in β-cell expansion has contributed to the identification of a whole set of distinct signaling pathways and molecules that can be used as potential target to allow in vitro and in vivo proliferation of β-cells (Puri and Hebrok, 2010; Dhawan et al., 2007). Generation of β-cells can be achieved by exocrine-to-endocrine transdifferentiation (Baeyens and Bouwens, 2008), differentiation of stem and progenitors cells (Dhawan et al., 2007; Puri and Hebrok, 2010).

Both insulin and insulin like growth factor (IGF) signalling pathways through insulin receptor substrate proteins (IRS) play important roles for proper maintenance and functioning of beta cells (Kubota et al., 2000). The latter is essential for the transmission of intracellular signalling from the insulin receptor to downstream pathways and transcriptional regulation.

Recently, it has been demonstrated that glucose effect on beta-cells growth and survival requires activation of insulin receptors (Assmann et al., 2009). Likewise, IRS1 and IRS2 seem to play critical roles in beta cells mass, as supported by IRS1 or IRS2 knockout mice (Burks and White, 2001).

3. Functions

During postprandial periods, β-cell insulin secretion is stimulated by elevated plasma glucose, free fatty acids (Nolan et al., 2006) and amino acids concentrations (Sener and Malaisse, 2002). Insulin secretion is required to maintain glucose homeostasis by promoting glucose uptake principally by muscle and adipose tissue.

In current models of stimulus-secretion (i.e. insulin) coupling, β-cells are featured as electrically excitable fuel sensors under hormonal and neural control. Stimulus-secretion coupling models emphasize the role of mitochondrial metabolism, ATP-sensitive potassium channels (K_ATP channels), calcium influx and increase in cytosolic calcium concentration (Henquin and Meissner, 1984). In addition to this triggering pathway, an amplifying pathway, increasing triggering calcium stimulated exocytosis, is also involved in insulin secretion (Henquin, 2009).

Unlike epithelial cells, β-cells are not likely to be exposed to important changes in extracellular osmolarity. However, alterations in extracellular osmolarity and cell volume are likely to occur in response to transport and intracellular metabolism of substrate and metabolites. It has been shown that β-cell volume increases in response to an increase in glucose concentration (Miley et al., 1997).

Importantly, cell volume was shown to profoundly influence the activity of β-cells. Indeed, exposure of β-cells to hypotonic extracellular solutions induce cell swelling, activating volume-regulated anion channel (VRAC) and cell membrane depolarization, leading to activation of voltage-sensitive calcium channels, allowing calcium entry, and thereby insulin exocytosis (Best et al., 1996; Drews et al., 2010).

Independently of the origin of β-cell swelling, e.g. exposure to hypertonic extracellular medium or hypotonic intracellular medium, aquaporins are likely to play a role in cell swelling. Aquaporins are membrane water channels of about 28 kDa possessing sequences motifs, present in the first intracellular and third extracellular loop, involved in the formation of the water pore (Agre, 2004). The thirteen mammalian aquaporins cloned so far can be classified into three subfamilies according to their permeability: (1) aquaporins: exclusively permeable to water (AQP1, AQP2, AQP4, AQP5, AQP6, AQP8); (2) aquaglyceroporins: permeable to water as well as small solutes such as glycerol and urea (AQP3, AQP7, AQP9, AQP10); and (3) aquaporins with unusual NPA motifs and permeability remaining controversial (AQP11, AQP12) (Agre, 2004). Aquaglyceroporin AQP7 is expressed in mouse (Matsumura et al., 2007) and rat (Best et al., 2009) β-cells and pancreatic β-cell line BRIN-BD11 (Delporte et al., 2009) (Fig. 1). Pancreatic β-cells from AQP7 knockout mice display reduced size, mass, insulin content, and increased rates of basal and glucose-stimulated insulin secretion (Matsumura et al., 2007). Furthermore, β-cells from AQP7 knockout mice also showed increased glycerol and triglyceride contents, increased glycerol kinase activity and decreased forskolin-induced glycerol release through CAMP lipolysis stimulation (Matsumura et al., 2007). Based on the analysis of AQP7 knockout mice, the role of AQP7 in pancreatic β-cells insulin secretion is summarized in Fig. 2. Isoosmotic addition of glycerol to the extracellular medium of normal rat β-cells induced in β-cell the sequential swelling, VRAC activation, membrane depolarization, electrical activity and concomitant insulin release (Best et al., 2009) (Fig. 3). The effects of glycerol, in contrast to urea, persist throughout exposure to osmoles. Moreover, glycerol activates β-cells even when added hyperosmotically in the extracellular medium. These data suggest that β-cell activation by glycerol is the results of its transport into the cells as well as an additional action concomitant to glycerol metabolism (Best et al., 2009). In BRIN-BD11 cells, glycerol uptake occurs rapidly and is higher when cells are submitted to hypotonic extracellular medium or to medium deprived of 50 mM NaCl but enriched with 100 mM urea, compared to isoosmotic medium. Insulin output was concomitantly higher in BRIN-BD11 cells exposed to hypotonic extracellular medium or to medium deprived of 50 mM NaCl but enriched with 100 mM urea or 100 mM glycerol, compared to isoosmotic medium. Furthermore, an inhibitor of VRAC, 5-nitro-2-(3-phenylpropylammo)benzoate, suppress insulin output induced by medium deprived of 50 mM NaCl but enriched with 100 mM urea or 100 mM glycerol. These data confirm that under extracel-
Fig. 2. Role of AQP7 in pancreatic β-cells based on the analysis of AQP7 knockout mice. AQP7 knockout mice display increased glucose entry, increased intracellular glycerol and triglycerides (TG) concentrations, decreased intracellular insulin concentrations, increased insulin secretion. Increased intracellular glycerol concentrations induce increased glycerol kinase (GK) activity. Glycerol kinase promotes re-esterification of glycerol and accelerates TG accumulation. Increased glucose capitation contributes to increased glucose metabolization by glycolysis.

Fig. 3. Sequential events leading to insulin exocytosis in response to glycerol entry via AQP7. (A) Glycerol enters β-cells via AQP7 (1). (B) Glycerol entry causes cell swelling (2). (C) Cell swelling activates VRAC channels with concomitant Cl⁻ exit (3). (D) Cl⁻ exit induces membrane depolarization (4). (E) Membrane depolarization stimulates voltage-sensitive calcium channel and calcium entry into the cell (5). (F) Increased intracellular calcium concentration induces insulin exocytosis (6).
Pancreatic beta cells are sensitive to attack by reactive oxygen or nitrogen species (ROS or RNS) and contribute to gluco- and lipo-toxicity in the development of diabetes. Furthermore, islets for transplantation undergo detrimental oxidative stress. Consequently, the addition of a redox modulation strategies could be a beneficial clinical approach for islets preservation for islets transplantation (Sklavos et al., 2010).

AQPF, controlling glycerol transport, plays a key role in insulin secretion. Two AQPF knockout mice display hyperinsulinemia (Matsumura et al., 2007; Hibuse et al., 2005, accompanied (Hibuse et al., 2005) or not accompanied (Matsumura et al., 2007) by hyperglycemia. In a third AQPF knockout mice model displays normal glycaemia, while insulinemia has not been determined (Skowronska et al., 2006). The existence of different AQPF knockout mice phenotypes may be attributed to the different genetic backgrounds of the mice. In Japanese subjects, the frequency of missense mutations (R12C, V59L, G264V) and silent mutations (A103A, G250G) of AQPF were not associated with the phenotype for diabetes or obesity, despite the absence of glycerol transport in a subject with the G264V mutation (Kondo et al., 2002). More recently, it was shown that a single-nucleotide polymorphism in the human AQPF promoter region (A-953G) resulted in a decreased C/EBP-β DNA binding and AQPF expression in adipose tissue from obese individuals (Prudente et al., 2007). Furthermore, this polymorphism is associated with increased risk of type 2 diabetes in women (Prudente et al., 2007). Concerning the possible existence of a relationship between the level of AQPF expression and obesity and type 2 diabetes, data remain controversial. Indeed, decreased AQPF expression in adipose tissue was observed in severe obesity (Ceperuelo-Mallafre et al., 2007), while no relationship was found between AQPF expression in adipose tissue and the presence of glucose abnormalities in morbid obesity (Miranda et al., 2009; Catalan et al., 2008). No modification (Ceperuelo-Mallafre et al., 2009) or an increase in AQPF expression was observed in adipose tissue from patients with type 2 diabetes (Miranda et al., 2010). Different pathological conditions involve different sets of perturbed metabolic pathways and therefore the implication of a single gene product cannot necessarily have the same impact in all settings. Therefore, it remains difficult to assess if the AQPF polymorphism (A-953G), AQPF mutations, or/or AQPF expression level contribute to obesity and type 2 diabetes. Further studies will help validate or invalidate the hypothesis. Moreover, AQPF regulation could become an attractive drug-target pathway for therapeutic obesity and type 2 diabetes strategies.

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