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Apoptotic signal transduction pathways in diabetes

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Abstract

Failure of insulin producing pancreatic β-cells is a common characteristic of type 1 (insulin-dependent) and type 2 (insulin non-dependent) diabetes mellitus. Accumulating evidence suggests that programmed cell death (apoptosis) is the main form of β-cell death in these disorders. The β-cell is particularly sensitive to apoptotic stimuli due to the inherent features of the specialized β-cell phenotype. In type 1 diabetes anti-β-cell autoimmune reactivity delivers the apoptotic signals in the form of inflammatory mediators or T-cell effectors. In type 2 diabetes, the metabolic derangement is associated with production of inflammatory mediators in insulin-sensitive tissues leading elevated levels of circulating inflammatory mediators such as IL-6 and TNF. Further glucose has been suggested to induce β-cell apoptosis via the induction of β-cell synthesis of IL-1 which via autocrine action may elicit signalling cascades analogous to those seen in β-cell destruction in type 1 diabetes. Considering the apparent importance of IL-1-β signalling in β-cell failure in both type 1 and type 2 diabetes, we here review the modulatory effect exerted on IL-1signalling by cellular characteristics related to the specialized β-cell phenotype. We conclude that β-cell differentiation signals (Pdx-1), glucose metabolism, calcium handling as well as regulation of naturally occurring inhibitors of cytokine signalling contribute to sensitize the β-cell to apoptotic stimuli. We hypothesize that immunological stimuli in type 1 diabetes and metabolic/inflammatory signals in type 2 diabetes converge on common signalling pathways leading to β-cell failure and destruction in these two diseases.

Keywords: Calcium; Islet brain-1; Interleukin-1; JNK; MAPK

1. Introduction

Diabetes is an increasing worldwide health problem. It is estimated that the prevalence of diabetes is doubling every 10–15 years and that by 2010 there will be 250 million people affected with diabetes in the world [1]. Although treatment has significantly improved, life-expectancy and quality of life are reduced due to late diabetic complications. There is currently no cure for diabetes, and insulin treatment for absolute or relative insulin deficiency is still not able to completely substitute for loss of physiological insulin secretion. Intrahepatic islet transplantation is therefore a logical approach to a curative strategy but this procedure is associated with a high frequency of primary non-functioning of the grafts and secondary graft failure so that graft survival in type 1 diabetic patients is only approximately 20% after 36 months [2] with a few recent exceptions [3]. Prevention of β-cell failure in type 1 and type 2 diabetes by pharmacological intervention is not yet possible. The negative results of two recent large-scale randomized controlled studies of pharmacological principles aimed at protecting pancreatic β-cells from immune destruction in individuals at risk for type 1 diabetes (ENDIT and DPT-1) [4] emphasize that more knowledge about the basic mechanisms of β-cell destruction is needed to design rational pharmacological intervention in the future.

Since there is increasing evidence that β-cell apoptosis both in type 1 and type 2 diabetes as well as in islet graft failure seems to be a consequence of the effect of

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Abbreviations: IL-1, interleukin-1; IL-1R1, IL-1 type 1 receptor; IL-1RAcP, IL-1R1 accessory protein; Tollip, Toll/IL-1 interacting protein; MyD88, myeloid differentiation factor 88; PLC, phospholipase C; DAG, diacyl glycerol; PKC, protein kinase C; IRAK1, IL-1R1 associated kinase 1; TRAF6, tumour necrosis factor receptor associated factor 6; TAK1, transforming growth factor β-activated kinase 1; TAB1, 2-TAK1 binding protein 1–2; IKK1/2, IκB kinase 1/2; NFκB, nuclear factor κB; ECSIT, evolutionarily conserved signalling intermediate of Toll; MEKK-1, mitogen activated protein/external signal regulated kinase kinase; MAP, mitogen activated protein; SAPK, stress activated protein kinase; JNK, c-*jun* N-terminal kinase; ERK, external signal regulated kinase.

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inflammatory mediators (reviews [5,6]) and since pancreatic β-cells seem particularly sensitive to the apoptosis inducing effect of these mediators (reviews [7,8]) the purpose of this paper is to briefly review how inherent features associated with the specialized β-cell phenotype may modulate inflammatory mediator signalling in pancreatic β-cells. Hopefully deeper insight into these mechanisms may provide targets for the design of novel β-cell-specific pharmacological intervention.

2. β-Cell apoptosis in type 1 diabetes

It is generally accepted that β-cell destruction in type 1 diabetes is a consequence of an autoimmune reaction against the pancreatic β-cells triggered by environmental factors in genetically predisposed individuals [9]. Figure 1 shows the histopathological lesion in type 1 diabetes. The islets are infiltrated with mononuclear cells which are first cleared when the majority of the β-cells are destroyed. Since many patients with long-standing type 1 diabetes still have residual β-cell function there are clearly down-regulating mechanisms limiting the immune attack, but these mechanisms are not clearly understood in humans. It is believed that β-cell destruction occurs mainly by programmed cell-death, apoptosis [5,7,8,10]. The nature of the immunological effectors that induce apoptosis in β-cells leading to type 1 diabetes is still debated. According to one hypothesis interaction between antigen presenting cells and T-cells in the islet infiltrate leads to an inflammatory response in which the pro-inflammatory cytokines IL-1, tumour necrosis factor α (TNF-α) and interferon γ (INFγ) are released in high local concentrations in the islet micro-environment (Fig. 2). These cytokines in synergy then leads to induction of apoptotic signalling cascades. A second theory implies that β-cell apoptosis is induced by T-cell effector pathways such as Fas/Fas-ligand interaction and the perforin/granzyme system. Which of these T-cell effector pathways is the most important is much discussed. Pro-inflammatory cytokines, especially IL-1, may still be required in the latter model since β-cell expression of the Fas receptor is dependent upon induction by IL-1 [11]. Thus, understanding the IL-1 signalling pathway in β-cells will be central to understand β-cell destruction in both the inflammatory and the T-cell mediated scenario.

3. β-Cell apoptosis in type 2 diabetes

The β-cell mass displays a remarkable physiological plasticity. Thus, in obesity or during pregnancy β-cell mass is expanded to compensate for the increased need for insulin secretion caused by increased needs or insulin resistance (Fig. 3). Type 2 diabetes is believed to occur when insulin resistance cannot be compensated due to inadequate insulin secretion and there is extensive evidence that β-cell function is impaired in type 2 diabetes [12]. It has been much discussed whether β-cell mass is

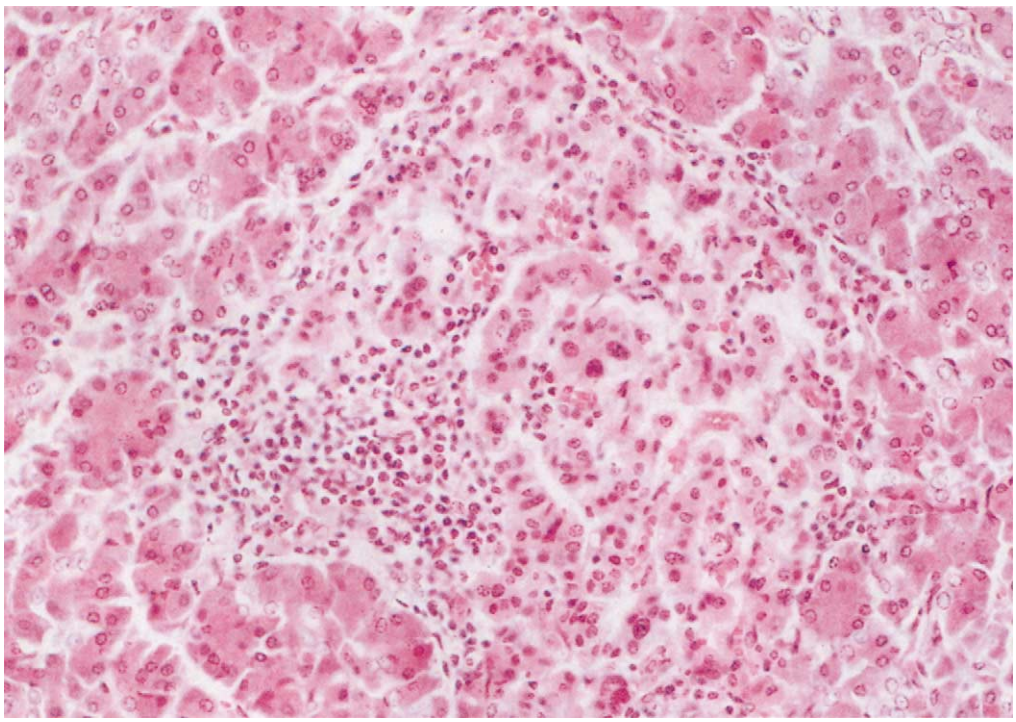

Fig. 1. Type 1 diabetes: an inflammatory disease of the pancreatic islet. The histopathology in type 1 diabetes is characterized by a chronic, atrophic, lymphocytic insulitis where mononuclear cells infiltrate the islets and selectively destroy pancreatic β-cells. Mononuclear cells can be seen in the lower left quadrant of the pancreatic islet.

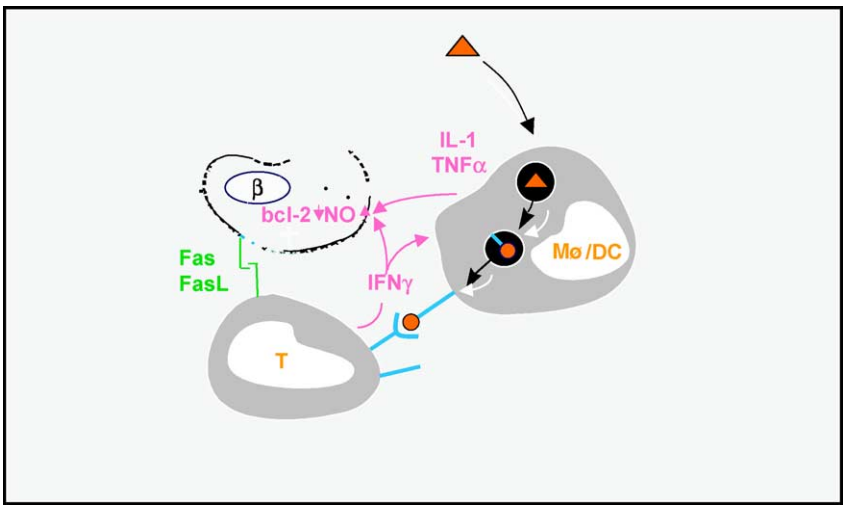

Fig. 2. A model for β-cell apoptosis in type 1 diabetes. β-Cell antigen (▲) is taken up by antigen presenting cells such as macrophages (M∅) or dendritic cells (DC) and processed by proteolytic cleavage into antigenic fragments (●). These peptides are bound to MHC-class II molecules in the endosomal compartment. By fusion with the plasma membrane, the antigen–MHC-class II complexes are externalized, enabling the recognition of the complex by T-helper cells (T). Activated by antigen recognition and other secondary signals the T-cell will produce interferon gamma (IFNγ), which can feedback-stimulate macrophages/dendritic cells to the production of interleukin-1 (IL-1) and tumour necrosis factor alpha (TNFα). In synergy, these cytokines are selectively β-cell cytotoxic by the specific up-regulation of nitric oxide synthesizing iNOS and by regulating the expression of genes involved in apoptosis. IL-1 also sensitizes the β-cell to T-cell-mediated killing via the Fas/Fas-ligand system by inducing the expression of the Fas-receptor on the β-cell (β) surface.

reduced in type 2 diabetes, to explain the progressive loss of β-cell in this disease [13]. Recently, however, in a unique autopsy material from the Mayo clinic it was clearly demonstrated that β-cell mass is reduced in obese humans with impaired fasting glucose and type 2 diabetes as well as in lean cases of type 2 diabetes when compared to non-diabetic obese and lean cases, respectively [14].

Several mechanisms may contribute to β-cell apoptosis in type 2 diabetes. It is clear that hyperglycaemia can induce apoptosis in several types of cells including mouse myocardial cells [15], human retinal pericytes [16] and even pituitary cells co-expressing the glucose transporter GLUT2 and glucokinase [17]. Hyperglycaemia induced apoptosis in these cells involve high glucose-activated NFκB, mitochondrial cytochrome C-mediated caspase 3 activation and formation of reactive oxygen species (ROS). Similar pathways have been suggested to be activated by glucose in pancreatic β-cells [18,19]. Further glucose-induced toxicity may in part indirectly be caused by "lipo-toxicity" implicating alterations in β-cell malonyl-CoA, peroxisome proliferator activated receptors α and γ and steroid regulatory element binding protein expression [20]. Free fatty acid-induced β-cell apoptosis was suggested to involve formation of ceramide, nitric oxide (NO) increased production and mitochondrial pathways (Fig. 4) [21,22], although the involvement of NO may be controversial [23]. In addition high glucose up-regulates the Fas-receptor in human islets [21] which might cause induction of apoptosis in neighbouring β-cells constitutively expressing Fas-ligand. Recently, the mechanism

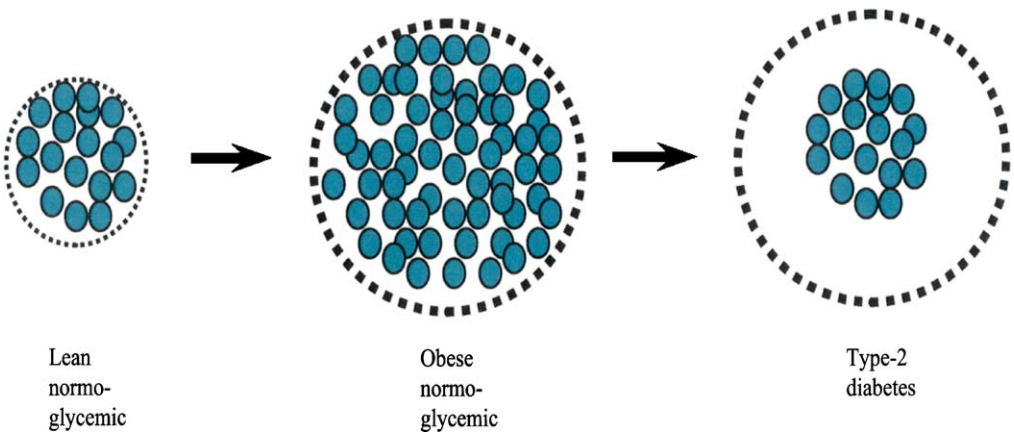

Fig. 3. Relative reduction in pancreatic β-cell mass in type 2 diabetes. Although not reduced compared to lean normoglycemic individuals the β-cell mass in type 2 diabetic patients is reduced when compared to obese normoglycemic individuals.

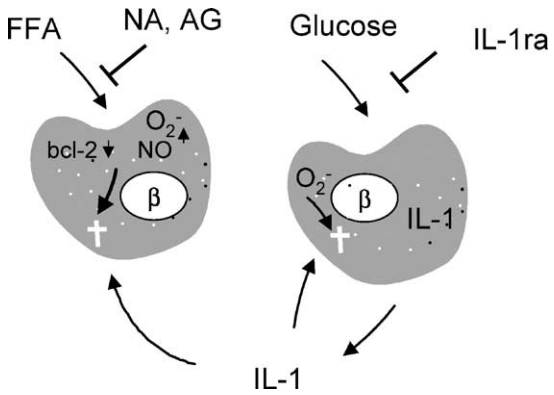

Fig. 4. A model for β-cell apoptosis in type 2 diabetes. Free fatty acids (FFA) cause β-cell apoptosis by induction of free oxygen radicals (O_2^-), nitric oxide (NO) synthesis and ceramide as well as down-regulation of anti-apoptotic proteins such as bcl-2. The toxic effect of free fatty acids can be blocked by nicotinamide (NA) or aminoguanidine (AG) both blockers of nitric oxide synthase. Glucose-induced β-cell apoptosis involves the induction of free oxygen radicals and β-cell synthesis of IL-1 which in autocrine/paracrine fashion activates IL-1 signalling leading to β-cell apoptosis. The pro-apoptotic effect of glucose on human islets can be blocked by interleukin-1 receptor antagonist (IL-1Ra).

underlying glucose induced β-cell Fas-expression was explained by glucose-induced production of IL-1-β [24]. Thus, β-cells exposed to high glucose expressed IL-1-β, and the apoptotic effect of glucose could be blocked by the natural antagonist of IL-1 action interleukin-1 receptor antagonist (IL-1Ra). These events were associated with NFκB activation, DNA fragmentation and impaired β-cell function (Fig. 4). Thus, inflammatory mediators elaborated in type 1 diabetes as part of the autoimmune response or expressed in β-cells in response to high glucose in type 2 diabetes may be a common denominator for β-cell apoptosis in these two diseases.

4. Interleukin-1 (IL-1) signalling in β-cells

Since interleukin-1 is a central cytokine proposed to participate in β-cell destruction in both diabetic disorders we here review briefly IL-1 signalling (Fig. 5) [7]. IL-1 binds to IL-1R1 that are also expressed on pancreatic β-cells. Ligation of IL-1 to IL-1R1 recruits the IL-1RAcP and Tollip subsequently binds to the IL-1-RAcP and MyD88 to the IL-1R1. This complex can then dock IRAK-1. The activated kinase subsequently dissociates from the IL-1 receptor complex, phosphorylates TRAF6 which then either activates the IKK-NFκB pathway or the SAPK/MAPK. Further, independently of IRAK IL-1R1 activation can activate phospholipase C and thereby PKC, in particular, PKCδ which has been shown to be involved in β-cell apoptosis [25,26].

The molecular links between the three described pathways and the effector program of apoptosis are not fully understood. Microarray and proteomic studies have shown that IL-1 causes alteration of more than 100 genes in pancreatic β-cells, many of which are NFκB-dependent [27,28]. Ongoing efforts are aimed at understanding the transcription factors and key genes in IL-1 signalling in β-cells in these three main pathways. Not surprisingly similar signalling pathways are elicited in many other cells by IL-1. IL-1 clearly leads to a variety of cellular responses

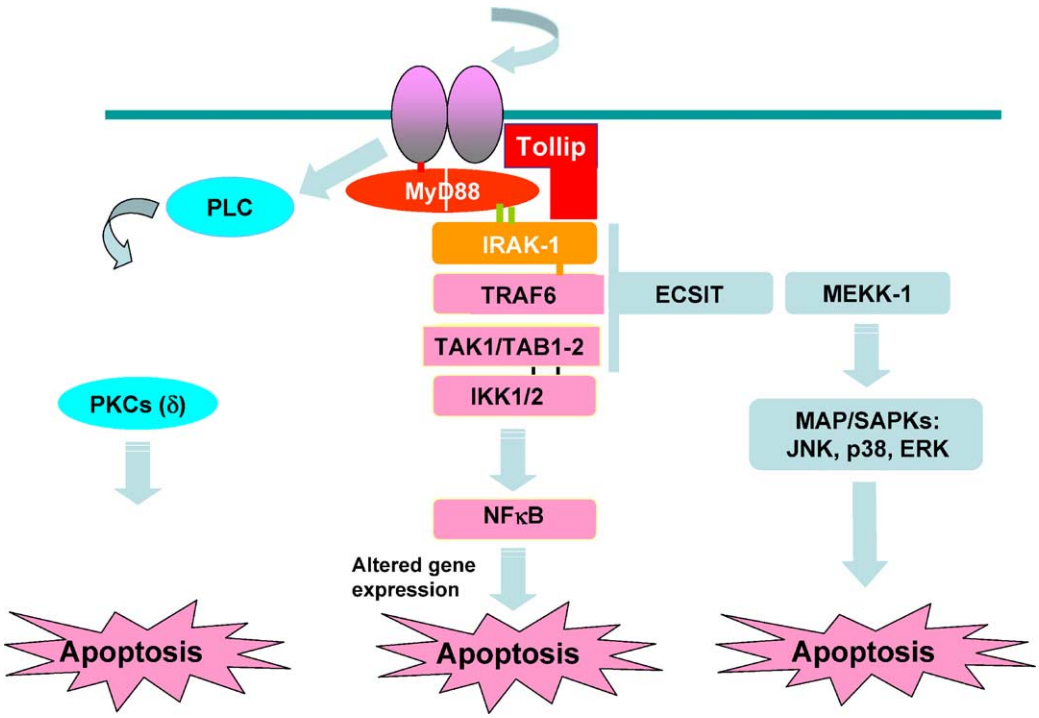

Fig. 5. IL-1 signaling in β-cells (for details see text).

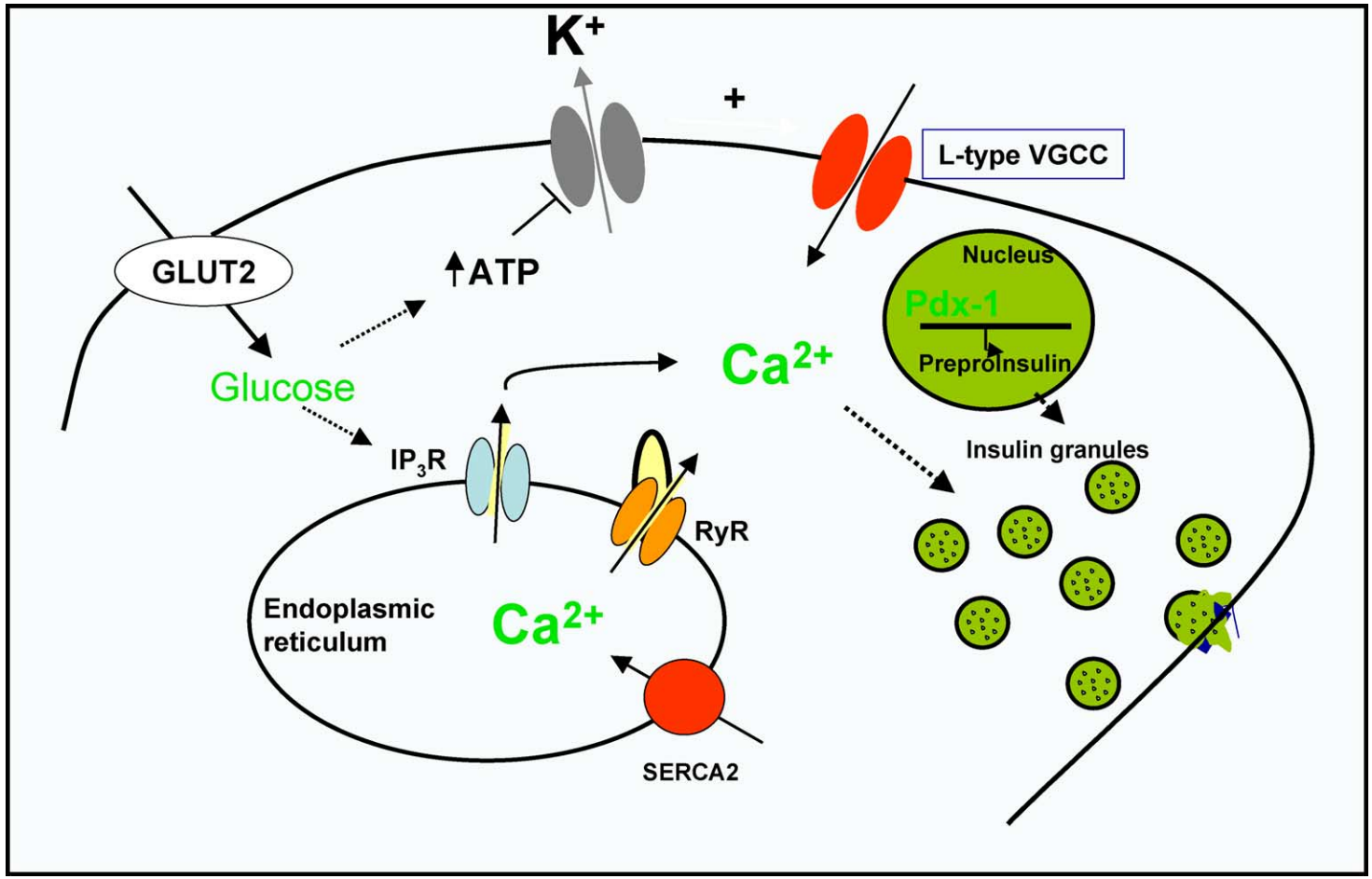

Fig. 6. Basic physiology of the β-cell. The Pdx-1 (pancreatic duodenum homeobox factor 1) defines the differentiated β-cell phenotype, e.g. by being an important transcription factor for pre-proinsulin transcription, transcription of the glucose transporter 2 (GLUT2) and synthesis of the ameloid protein. Glucose is transported into the β-cell via the GLUT2 transporter and is oxidised. The ensuing alteration in ATP/ADP ratio leads to closure of the potassium channels and depolarization of the plasma membrane. The change in plasma membrane potential leads to opening of L-type voltage-gated Ca^{2+} channels (VGCC) leading to influx of calcium. Glucose also mobilizes calcium from the endoplasmic reticulum via activating inositol trisphosphate (IP3) receptors and ryanodine receptors (RyR) which will mobilize calcium from the endoplasmic reticulum store. The increase in cytosolic calcium will lead to insulin granule exocytosis.

other than apoptosis. It will therefore be important to understand, how these inflammatory mediators induce cell-specific responses. IL-1 receptor activation in different cells operates on the background of the constitutive expression of genes related to that particular cellular phenotype. Therefore, the phenotypic characteristics of the specialized β-cell may modulate IL-1 signalling to promote a pro-apoptotic outcome.

5. β-Cell phenotypic modulators of apoptosis

The pancreatic β-cell is a highly specialized cell utilizing 70% of its protein synthesis for insulin production (Fig. 6). Due to the hazards of uncontrolled insulin secretion both β-cell-function and -mass must be tightly regulated. This fact may explain why β-cells are prone to apoptotic stimuli such as Fas, cytokines, nitric oxide, glucose, free fatty acids, ameloid, reactive oxygen species, etc. Below we briefly review hypotheses to suggest why β-cells are particular apoptosis prone.

(a) We hypothesize that the β-cell pays a price for its exquisite specialization in that the β-cell during differentiation acquires its particular apoptosis proneness. In support of this hypothesis is the observation that differentiated β-cells are more sensitive to toxins and cytokines [29] and that overexpression of the β-cell differentiation transcription factor Pdx-1 not only increases MAP and SAP kinase signalling in these cells but also leads to higher sensitivity to the pro-apoptotic effect of IL-1 [30]. The molecular mechanisms underlying Pdx-1 sensitization to cytokine-induced apoptosis have not been clarified but may involve Pdx-1-dependent expression of GLUT2 glucose transporter, insulin secretion and autocrine signalling or expression of other Pdx-1-dependent genes.

(b) The glucose stimulus/insulin secretion coupling is dependent on glucose oxidation leading to the synthesis of reactive oxygen species. Interestingly pancreatic β-cells have extraordinary low oxidative stress coping capabilities due to low concentrations of many antioxidant enzymes [31,32]. Increasing ambient glucose concentrations in islet cultures causes potentiation of IL-1-induced β-cell toxicity, and this is associated with the potentiation of IL-1-induced nitric oxide synthesis [33]. The potentiating effect of glucose on IL-1-induced NO-synthesis is blocked with a p38 MAP kinase inhibitor [34]. Since nitric oxide has been implicated in both β-cell necrosis and apoptosis, glucose may potentiate IL-1 toxicity by this mechanism.

(c) Insulin exocytosis in response to glucose stimulation is dependent on active calcium handling (Fig. 6). Interestingly cytokine-induced β-cell apoptosis can be prevented using both L- and T-type calcium channel blockers [35,36]. Curiously changes in calcium currents have not been demonstrated following cytokine treatment, but alterations of the activity of calcium-dependent proteins such as the calcium-dependent phosphatase calcineurin indicated that IL-1 exposure of β-cells is associated with fluctuations in intra-cellular calcium concentrations. The signalling pathways and molecular links to the apoptotic machinery have not been elucidated.

(d) A number of natural inhibitors of cytokine signalling have been discovered in recent years. The suppressors of cytokine signalling (SOCS) constitutes a family of proteins that have traditionally been considered to be negative feed-back regulators of IFNγ signalling. Surprisingly, however, SOCS3 also down-regulates

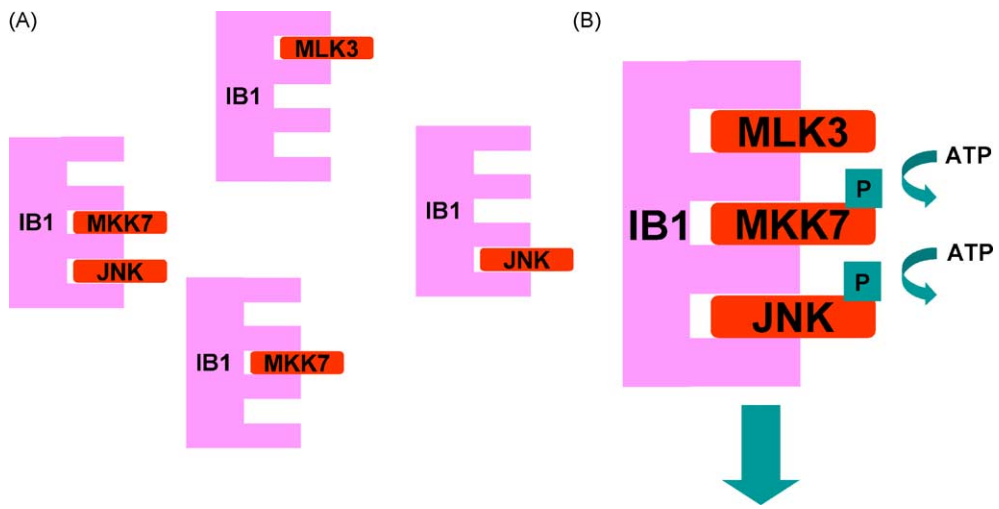

Fig. 7. The scaffold protein islet brain-1 (IB-1) regulates JNK activity. (A) Normally IB-1 concentration is high in pancreatic β-cells leading to inhibition of the JNK signalling pathway because of formation of incomplete MLK3, MKK7, JNK signalosomes. (B) At a reduction of the IB-1 content as is the case following cellular stress by IL-1, UV-irradiation or specific JNK-activation, efficient signalosomes are formed leading to pro-apoptotic JNK-signalling.

IL-1 signalling [37]. Interestingly, SOCS3 up-regulation in response to IL-1 is delayed and may therefore be insufficient to down-regulate IL-1-mediated signalling in β-cells thereby contributing to the sensitivity of β-cells to cytokines. Similarly, the scaffold protein of the SAPK cascade islet brain-1 (IB-1), which is prominently expressed in the central nervous system and in the islets, is down-regulated in response to a number of stressors including IL-1 [38,39]. Down-regulation of the IB-1 content will lead to more effective assembly of the JNK signalosome (Fig. 7) and thereby apoptotic signalling.

6. Summary and conclusion

Although type 1 and type 2 diabetes are etiologically and genetically different diseases we suggest that type 1 and type 2 diabetes may share common molecular mechanisms underlying β-cell failure. We propose that immunological mediators in type 1 diabetes and metabolic factors in type 2 diabetes converge on common signalling pathways in the β-cells that may be unopposed due to deficient down-regulating mechanisms or potentiated due to other inherent features of the β-cell. We suggest that these inherent properties may explain the particular sensitivity of β-cells to cytokine-induced apoptosis. These mechanisms may provide novel β-cell-specific targets for pharmacological interventions.

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