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Focus on: The Endocrine Pancreas

Forum

XBP1: A Pivotal Transcriptional Regulator of Glucose and Lipid Metabolism

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X-box binding protein 1 (XBP1) is a major, well-conserved component of the unfolded protein response (UPR) that is crucial for glucose homeostasis and lipid metabolism. Metabolic dysfunction has been associated with XBP1 transcriptional activity. Recently, compounds selectively targeting the IRE1α–XBP1 pathway have emerged as a potential approach for treatment of metabolic diseases.

Endoplasmic Reticulum (ER) Stress and Metabolic Disease

The growing incidence of metabolic diseases such as type 2 diabetes (T2D), obesity, and atherosclerosis, globally, has been attributed to a large extent to a dysfunctional ER response [1–4]. The ER constitutes the main organelle for calcium storage, protein folding and processing, as well as for lipid biosynthesis and metabolism [1–3]. The ER is equipped with a robust adaptive response system known as the UPR that functions to maintain homeostasis. Metabolic perturbations such as advanced glycation of proteins and lipids, *S*-nitrosylation, oxidative and carbonyl stress, that are often seen in obesity and related disorders, lead to ER stress and interfere with proper UPR function [1–3]. ER stress triggers the UPR via three stress sensors on the ER membrane (Box 1). A major advance in understanding the involvement of ER stress in the pathobiology of metabolic disorders has been the discovery of the transcription factor X-box binding protein 1 (XBP1), a downstream effector of the serine/threonine-protein kinase/endoribonuclease inositol-requiring kinase 1α (IRE1α), a modulator of glucose and lipid metabolism [1,5–7]. Spliced XBP1 (XBP1s) translocates to the nucleus and initiates transcription of UPR- and non-UPR-associated genes engaged in metabolic dysfunction.

XBP1 Regulation of Glucose Metabolism

Recent evidence indicates that XBP1 may regulate glucose homeostasis by modulating intracellular signaling in hepatocytes and pancreatic cells, as well as adipocyte function [5,6,8].

The IRE1α–XBP1 pathway has been involved in insulin resistance, T2D, and obesity through activation of c-Jun N-terminal kinase (JNK). In hepatocytes, ER stress activates IRE1α–JNK signaling which reduces insulin receptor substrate 1 (IRS1) tyrosine phosphorylation (pY896) and Akt phosphorylation, while enhancing IRS1 serine phosphorylation (pS307), hence blocking insulin signaling [1,8].

Furthermore, XBP1 interacts with the insulin signaling mediators p38 mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) to modulate UPR in the liver [6]. Specifically, p38 MAPK phosphorylates XBP1s and facilitates its translocation to the nucleus in mice [9,10]. Insulin promotes the association of PI3K regulatory subunits p85α and p85β with XBP1s, enhancing its nuclear translocation and inducing the

Box 1. The UPR/IRE1α–XBP1 Pathway

ER homeostasis is established through three adaptive signaling pathways known as the UPR. They are initiated by three transmembrane sensor proteins–transcription factor pairs, namely inositol-requiring kinase 1α (IRE1α)–X-box binding protein 1 (XBP1), eukaryotic translation initiation factor 2α kinase 3 (PERK)–activating transcription factor 4 (ATF4), and activating transcription factor 6 (ATF6) that has both sensor and transcription factor properties [1,2]. Target genes of the IRE1α–XBP1 axis are involved in lipid synthesis, protein folding and secretion, and ER-associated protein degradation. PERK–ATF4 target genes are implicated in redox and amino acid metabolism, proapoptotic *CHOP* gene expression, ER chaperones and foldases, while ATF6 target genes are involved in protein folding [5,8,9].

IRE1α is a ubiquitously expressed type I transmembrane protein consisting of an ER luminal N-terminal domain, a cytosolic C-terminal RNase domain, and a serine/threonine kinase domain. When misfolded proteins accumulate in the ER, dimerization and oligomerization of IRE1α takes place followed by *trans*-autophosphorylation and RNase domain activation. Although the exact mechanism of IRE1α potentiation is unknown, competitive binding to the ER chaperone-binding immunoglobulin (BiP) has been proposed to help IRE1α to associate with unfolded proteins, allowing it to dimerize.

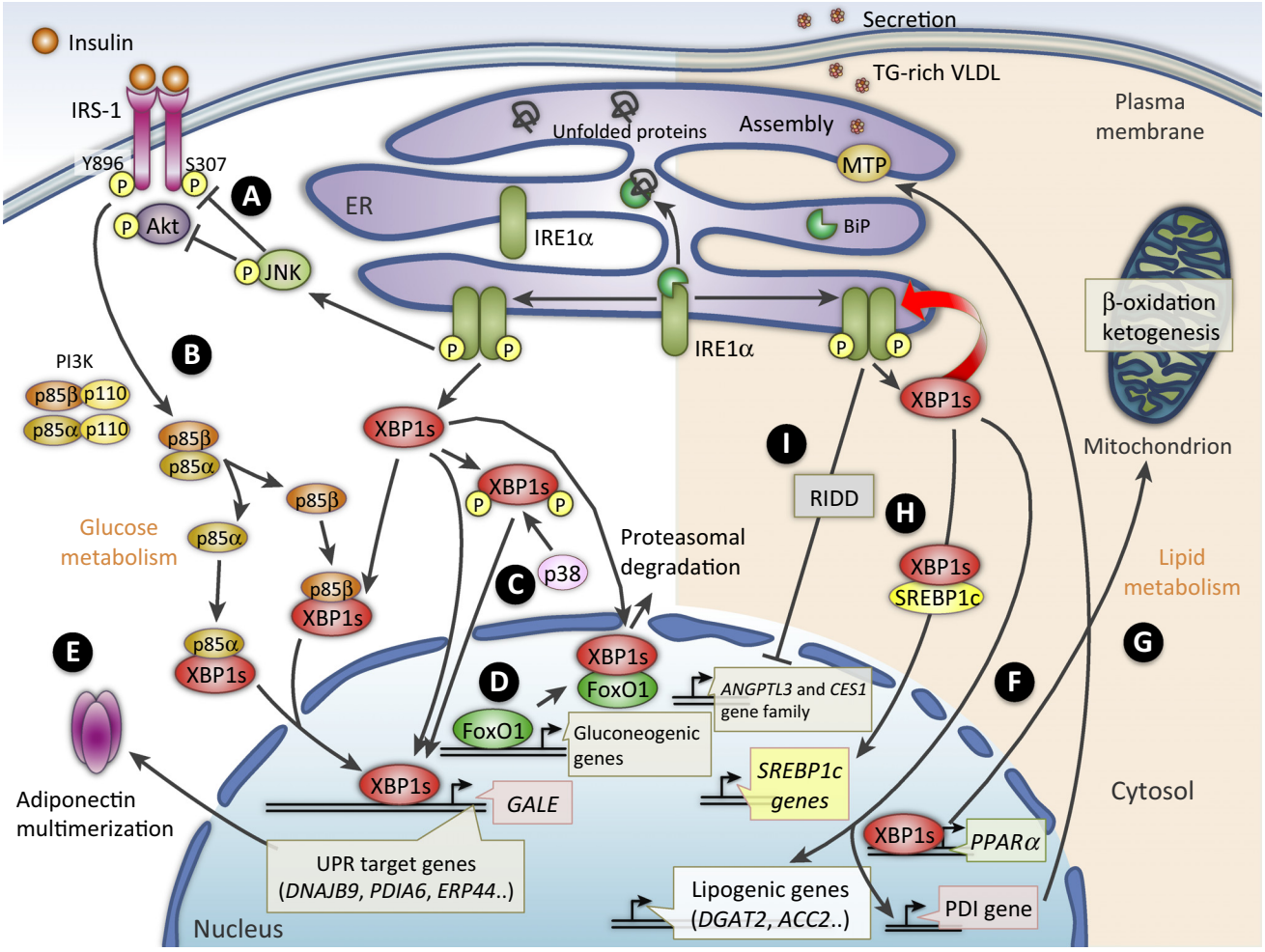
Activation of IRE1α triggers unconventional splicing of 26 nucleotides from the unspliced XBP1 mRNA (XBP1u), generating the spliced variant XBP1s [1]. Moreover, IRE1α activation allows degradation of ER-bound mRNAs through cleavage by IRE1-dependent decay (RIDD) that reduces folding overload and resolves ER stress.

XBP1 was originally cloned as a protein that binds to the *cis*-acting X-box of human major histocompatibility complex class II genes promoters [1]. It has an extremely short half-life, and plays a crucial role in protein degradation processes, mainly through direct binding to FoxO1 and recruitment to the 20S proteasome [5]. Upon prolonged ER stress, XBP1u controls UPR responses by terminating them via XBP1s-mediated degradation in the cytosol.

The multiple functions of XBP1s are required for differentiation of immune cells including $CD8^+$ T cells and B cells, the proper function of α and β pancreatic cells, and of plasma cells; it is involved in synthesis and secretion of IgG and IgM, glucagon and insulin, as well as VLDL. XBP1s also regulates transcription of non-UPR genes, including estrogen receptor α (*ESR1*), a group of inflammatory cytokines (*IL8*, *ICAM1*, *VCAM1*), and a subset of lipogenic genes (*DGAT*, *ACC2*). Furthermore, XBP1s regulates the beclin 1 (*BECN1*) gene involved in endothelial cell autophagy and *RUNX2* involved in calcification of coronary artery smooth muscle cells [1,3,7].

expression of UPR target genes [9,11]. A recent study demonstrated that interaction of bromodomain-containing protein 7 (BRD7) with p85α/p85β/XBP1s is enhanced by insulin, leading to accelerated XBP1s translocation to the nucleus and activity [6]. Notably, interaction with BRD7 was reduced in obese mice, suggesting that obesity negatively impacts on the capacity of XBP1s to translocate to the nucleus and interact with p38 and p85. This is in accord with the downregulation of UPR targets and reduced levels of XBP1s observed in obesity that can further enhance insulin resistance (Figure 1).

In addition, in the nucleus XBP1 directly interacts with the transcription factor forkhead box O1 (FoxO1) that is involved in hepatic gluconeogenesis. The XBP1/FoxO1 interaction is cell type-specific (hepatocytes, pancreatic cells, adipocytes) and independent of the effects of XBP1s on ER folding capacity [5]. Hepatic



Trends in Endocrinology & Metabolism

Figure 1. XBP1 Regulation of Glucose Homeostasis and Lipid Metabolism. In hepatocytes, ER stress activates IRE1α–JNK signaling which reduces insulin receptor substrate 1 (IRS1) tyrosine phosphorylation (pY896) and Akt phosphorylation, while enhancing IRS1 serine phosphorylation (pS307), thus increasing insulin resistance (A). Insulin promotes the association of PI3K regulatory subunits p85α and p85β with XBP1s, enhancing its nuclear translocation, and inducing UPR target genes (B). p38 MAPK phosphorylates XBP1s and facilitates its translocation to the nucleus, inducing UPR target genes (C). In the nucleus, XBP1 directly interacts with the transcription factor FoxO1 that is involved in gluconeogenesis, leading to proteosomal degradation, thus enhancing glucose tolerance (D). During UPR activation in adipocytes, nuclear XBP1s can regulate UPR target genes engaged in adiponectin multimerization, thus improving insulin sensitivity (E). XBP1s can directly increase expression of several lipogenic genes (*DGAT2*, *ACC2*) (F). XBP1s binds to the *PPARA* promoter to upregulate its expression, thus modulating mitochondrial β-oxidation and ketogenesis. XBP1s is involved in VLDL synthesis and secretion, affecting MTP activity via transcriptional regulation of PDI (G). XBP1s can bind to the *SREBP1c* promoter after insulin treatment, thus inducing lipogenesis (H). IRE1α hyperactivation downregulates lipid metabolism genes (*ANGPTL3, CES1*) controlled by RIDD (I). Abbreviations: ER, endoplasmic reticulum; MAPK, mitogen-activated protein kinase; MTP, microsomal triglyceride transfer protein; PDI, protein disulfide isomerase; PI3K, phosphoinositide 3-kinase; PPARα/PPARA, peroxisome proliferator-activated receptor α; RIDD, IRE1-dependent decay; SREBP, sterol regulatory element-binding protein; TG, triglyceride; UPR, unfolded protein response; VLDL, very low density lipoprotein; XBP1, X-box binding protein 1.