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Mini Review

Endoplasmic reticulum stress and the on site function of resident PTP1B

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ABSTRACT

Growing evidence links the stress at the endoplasmic reticulum (ER) to pathologies such as diabetes mellitus, obesity, liver, heart, renal and neurodegenerative diseases, endothelial dysfunction, atherosclerosis, and cancer. Therefore, identification of molecular pathways beyond ER stress and their appropriate modulation might alleviate the stress, and direct toward novel tools to fight this disturbance. An interesting resident of the ER membrane is protein tyrosine phosphatase 1B (PTP1B), an enzyme that negatively regulates insulin and leptin signaling, contributing to insulin and leptin resistance. Recently, new functions of PTP1B have been established linked to ER stress response. This review evaluates the novel data on ER stressors, discusses the mechanisms beyond PTP1B function in the ER stress response, and emphasizes the potential therapeutic exploitation of PTP1B to relieve ER stress.

1. Introduction

Endoplasmic reticulum (ER) is a highly dynamic multifunctional organelle responsible for protein biosynthesis and folding, for lipid biosynthesis, xenobiotic detoxification, and cellular calcium storage. In physiological conditions, ER homeostasis allows the synthesis of secreted, plasma membrane, and organelle proteins with an appropriate tertiary conformation ensured by molecular chaperones and a variety of enzymes. In pathological conditions, ER protein folding capacity becomes overwhelmed, the unfolded or improperly folded proteins cannot be delivered to the Golgi apparatus, and accumulate within the ER lumen [1]. This perturbation in ER homeostasis is known as "ER stress".

The ER membranes anchor the ubiquitously expressed enzyme Protein–tyrosine phosphatase 1B (PTP1B). This enzyme is attached to the ER via a hydrophobic region made of 35 amino acids (residues 400–435) at the C-terminal tail, while the catalytic domain is exposed to the cytosolic side of the ER. Earlier studies showed that PTP1B is not a passive resident of the ER, but an active player that potentiates the inositol-requiring kinase-1α (IRE1α)-mediated ER stress signaling pathway [2]. In the last years, several articles documented a complex relationship between PTP1B and ER stress. The survey of the novel literature prompted us to assemble in this review the current knowledge on ER stressors and their pathological consequences, and to outline the mechanisms beyond PTP1B function in ER stress. Such topic is important for the potential delay or alleviation of ER stress via modulation of PTP1B expression/activity.

2. ER stress: from causes to responses and to the associated diseases

Several molecules and conditions have been recently identified to induce ER stress (Table 1). Stressors like high glucose concentration (in diabetes mellitus) and saturated fatty acids (as at high fat feeding and obesity) are in common to pancreatic β cells, adipocytes, hepatocytes, skeletal muscle, cardiomyocytes, kidney tubular cells, vascular endothelium, and macrophages of the atherosclerotic lesions. Other stressors are the presence of inflammatory signals (IL-1β, interferon-γ, TNF-α) and of reactive oxygen species, as ER stress is connected to inflammation and oxidative stress, respectively. To adapt to the stressors presence, the cells ER would be required to counteract the abnormal accumulation of improperly folded proteins into ER lumen. This task is accomplished by activation of Unfolded Protein Response (UPR) pathway, an evolutionarily conserved cytoprotective pathway that transmits information on protein folding status to the nucleus and cytosol to restore ER homeostasis. The three arms of the mammalian UPR are: (i) the protein kinase RNA (PKR)-like endoplasmic reticulum kinase (PERK), that phosphorylates the α-subunit of eukaryotic translation initiation factor 2(eIF2α), (ii) the IRE-1α, that processes the mRNA of the transcription factor X-box binding protein-1 (XBP-1), and (iii) the activating transcription factor-6 (ATF-6), that activates the transcription of ER chaperones [3,4]. Under basal conditions, PERK and IRE-1α are held in an inactive and inhibited state by their association with the molecular chaperone BiP/glucose regulated protein 78 (GRP78) through their luminal domain; under severe ER stress these effectors are activated in concert, but may not be activated equally in response to a lesser or gradual stress [5].

The mechanisms of UPR adaptive response consist in attenuation of protein translation (via PERK), diminishing protein

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Table 1
The convergence between ER stress and pathology.

Cells/tissues/organs	Inductors of ER stress	ER protective response	Consequences of ER stress	Pathology	References
Pancreatic β-cells	Free fatty acids, Glucose Glucolipotoxicity IL-1β Interferon γ	PERK and CHOP deletion, UPR PDX1 and nNOS	Proapoptotic pathways β-cell failure Reduced β-cells mass	Diabetes mellitus	[1,46–48]
Adipocytes	Free fatty acids High fat feeding	4-PBA, TUDCA Increase in DsbA-L GRP 78 heterozygosity	Insulin resistance Decreased secretion of adiponectin and leptin Alteration of ER phospholipid composition	Obesity	[19,49,50]
Hepatocytes	High fat feeding Obesity Alteration of lipid homeostasis	IRE1α, ATF6 α, 4-PBA, TUDCA AMPK activation Short-term insulin therapy, Cr(D-phe)(3) Trichostatin A Black soybean peptides	Suppressed insulin signaling Hepatic insulin resistance Impaired hepatic glucose metabolism Apoptosis	Hepatic steatosis Dyslipidemia	[1,17,18,40,41,51–55]
Cardiomyocytes	Diabetes Ang II	Metallothionein PARM-1 PUMA	Cell death PERK regulation ATF-6 and CHOP expression	Heart failure Ischemic heart disease	[7,20,21,42]
Kidney	Hyperglycemia Palmitic acid Ageing Cadmium	UPR	Upregulation of GRP-78 and GADD-153 Down-regulation of BCL-2 Renal fibrosis Apoptosis of tubular cells	Renal fibrosis Renal failure Glomerulonephritis Diabetic nephropathy	[22,56–60]
Hypothalamus	Tunicamycin Diet	4-PBA TUDCA	Leptin resistance	Weight gain and increased food intake	[50,61]
Vascular endothelium	Hyperglycemia Homocysteine Increased intracellular glucose level Dextrose Atherosclerotic risk factors: oxidized phospholipids, oxidized and glycated LDL Cyclosporine A	UPR and T-cad upregulation Chemical chaperones AMPK activation Antioxidants Salubrinal	Phenotypic changes, Inflammation Apoptosis Endothelial injury or death	Endothelial dysfunction	[6,12,62–65]
Macrophages of the atherosclerotic lesions	Oxidative stress, Oxysterols, Intracellular cholesterol, Saturated fatty acids		Apoptosis	Plaque necrosis	[65]

synthesis and ER overloading with new misfolded proteins, in activation of transcriptional programs with increase in the amount of ER-resident chaperones, expanding ER protein-folding capacity, and in acceleration of the clearance of misfolded proteins from the ER, followed by their subsequent degradation in the proteasome [1,6,7]. Specific molecules and procedures help cells to cope with ER stress. Thus, protective effects against ER stress are exerted by pancreatic and duodenal homeobox 1 (PDX1) transcription factor and nNOS (in pancreatic β cells), GRP78 heterozygosty and the increased levels of disulfide-bond-A oxidoreductase-like protein (DsbA-L) (in adipocytes), activation of AMPK (in hepatocytes and vascular endothelium), the chemical chaperones 4-phenyl butyric acid (4-PBA) and tauroursodeoxycholic acid (TUDCA) (in adipocytes, hepatocytes, skeletal muscle, and hypothalamus), the short term insulin therapy and administration of the chromium complex of D-phenylalanine (Cr(D-phe)(3), in liver), and deletion of pro-apoptotic transcriptional factor C/EBP homologous protein (CHOP)(in pancreatic β cells) (Table 1). Reportedly, UPR response is modulated by PI3K subunits p85α and p85β, facilitating nuclear entry of XBP-1 following induction of ER stress [8,9].

When ER stress is persistent, the UPR adaptive response fail to preserve homeostasis, and ER initiates apoptotic signaling by induction of the pro-apoptotic CHOP, and activation of c Jun NH_2-terminal kinase (JNK) and of caspase-12. These events eventually lead to cell death saving the tissue from necrotic injury [3,7,10]. Thus, ER emerges as a vitally important organelle that can decide cell survival or death [7]. When ER stress-induced apoptosis causes the loss of a large number of cells, the functions of tissues or organs are impaired. Thus, in insulin-producing pancreatic β-cells, the ER stress-induced apoptosis is associated with activation of the β-isoform of group VIA Ca^{2+}-independent phospholipase A2 (iPLA2 β) [11]. It is obvious that apoptosis will conduct to the reduction of β-cell mass and insulin resistance, leading to the onset and development of hyperglycemia/diabetes mellitus. The first indications that ER stress might contribute to diabetes were published 6–7 years ago, and were followed by an avalanche of studies in this area [1,10,12–16].

Besides pancreatic β-cells, several other cells initiate apoptosis in response to chronic ER stress (Table 1). In response to high fat feeding and obesity, hepatocytes UPR activates JNK that phosphorylates the serine residues of insulin receptor substrate (IRS) proteins, thereby inhibiting insulin signal transduction and contributing to the development of insulin resistance [1]. ApoB100 appears to function as a molecular link between lipid-induced ER stress and hepatic insulin resistance [17]. Moreover, when the lipid homeostasis is altered, and the triglyceride storage capacity of hepatocytes is exceeded, ER-stressed steatotic hepatocytes are formed [18]. Overfeeding causes also an increase in adipose tissue depots associated with adipocytes hypertrophy; the latter is a possible stress condition for the ER that activates inflammatory and apoptotic pathways and causes insulin-resistance in adipocytes [19]. Other reports indicate that the adaptive and pro-apoptotic pathways of UPR are involved in heart failure and ischemic heart disease [7]. As inductors of ER stress in cardiac myocytes, diabetes and angiotensin II (Ang II) have been recognized so far, causing finally cardiac cell death [20]. However, these cells possess a mechanism that may counteract ER stress, via induction of prostatic androgen repressed message-1 (PARM-1) expression, a molecule

that regulates PERK, ATF-6 and CHOP expression, and exerts a protective role [21]. Renal failure attributable to proteinuria and uremia also induces ER stress within the kidney, diminishing renal function [22]. ER stress is now recognized as contributor to endothelial dysfunction in type 2 diabetes [12]; hyperglycemia increases ER stress in endothelium, as demonstrated by the augmented levels of UPR signaling molecules GRP78, phospho-eIF2α, and CHOP [6]. Moreover, hyperglycemia-associated ER stress intervenes in the development and progression of diabetic atherosclerosis [23]. ER stress also seems to play a role in obesity and high fat feeding-induced leptin resistance, a condition prevalent in the majority of obese population [24].

Insulin- and leptin resistance are the common ground of PTP 1B intervention as negative regulator. This enzyme dephosphorylates the tyrosine residues in insulin receptor (IR) and in IRS proteins, and in this way attenuates insulin signaling. In addition, recent data show that PTP1B controls the activity of IR precursor during its biosynthesis [25]. The signaling by leptin receptor LEPRb is negatively regulated by both ER stress and PTP1B [26]. The mechanism of the latter effect consists in PTP1B binding to and dephosphorylation of the leptin receptor-associated Janus kinase 2 (Jak2), thereby inhibiting intracellular leptin receptor signaling and contributing to leptin resistance.

3. The on site function of ER-resident PTP1B

In physiological conditions, PTP1B plays a "quality control role" at the ER, by the ability to dephosphorylate tyrosine kinase receptors (RTKs) and to modulate the intensity of their signaling cascades. There are several circumstances in which ER-anchored PTP1B dephosphorylates the RTKs, as follows: (i) when both are present at the ER, such as during RTKs biosynthesis, (ii) when ER comes into contact with plasma membrane, allowing enzyme interaction with the cell surface ligand-activated RTKs, and (iii) when ER comes into contact with specific endosomal compartments containing the internalized RTKs; the latter mechanism emphasizes the control exerted by PTP1B on endocytic down-regulation of RTKs [27]. Moreover, PTP1B prevents ligand-independent activation of newly synthesized RTKs during their processing in the ER [28].

Much of the knowledge on PTP1B function in ER stress condition comes from the studies on mice deficient in PTP1B and on cells lacking this enzyme [2,29]. Thus, in the liver of PTP1B(−/−) mice and in the hepatic cell lines in which this enzyme was silenced, PTP1B protein and mRNA expression were up-regulated in response to acute and chronic ER stress [30]. Furthermore, the recent studies in mice show that PTP1B deficiency in liver leads to improvements in metabolic parameters, including increased hepatic insulin signaling and sensitivity, reduced serum and hepatic triglycerides and cholesterol levels, and protection against high-fat diet-induced ER stress [29,31].

Multiple lines of experimental evidence indicate that PTP1B intervenes in the adaptive UPR signaling cascade by using PERK as substrate. Dephosphorylation of the latter is an important reaction, as PERK pathway rapidly attenuates protein translation [32]. Other substrates of PTP1B are the ER-resident antioxidant peroxiredoxin 4 (Prdx4) and emerin. PTP1B reduces the phosphorylation of Prdx4, and contributes to the redox-controlled processes occurring at the ER [33]. PTP1B regulates also tyrosine phosphorylation of emerin, a key inner nuclear membrane protein, conducting to accumulation of sumoylated and inactive enzyme in the inner nuclear membrane contiguous with ER [34]. As for control of PTP1B expression, reports indicate it is increased by high-fat feeding (in the liver and the pancreatic β-cells) [35], is regulated by ATF6 [36], and is inactivated via H_2S-mediated sulfhydration of the essential Cys 215 at the catalytic site [32,37]. The latter reaction can be reversed by reducing agents such as thioredoxin [32].

4. Potential therapeutic strategies to relive ER stress

The novel data emphasize that restoration of ER homeostasis prior to ER stress-induced cell death may provide a therapeutic rationale in steatosis associated diseases, such as obesity, viral hepatitis, and alcohol-induced liver injury [18]. The restoration may be attained by efficient manipulation of UPR component pathways, including promotion of ER folding capacity through chemical chaperones [7,38]. Several reports identified specific molecules that can be targeted to relive ER stress. Thus, depletion of Src homology domain-containing adaptor protein Nck1 attenuates hepatic ER stress signaling, and improves glucose tolerance and insulin signaling [39]. ER stress can be ameliorated by Trichostatin A, a histone deacetylase (HDAC) inhibitor [40], and is suppressed by black soybean peptides that act as antidiabetic agents [41]. In the heart, suppression of P53 upregulated modulator of apoptosis (PUMA) activity prevented both ER stress and ischemia/reperfusion-induced cardiomyocyte loss [42]. In the cardio-renal syndrome, stimulation of GRP78 upregulation and eIF 2α phosphorylation may hold promise to alleviate ER stress [22]. In ER stress-associated neurodegerenerative diseases, the inducer X (BIX) of ER-mediated chaperone BiP/GRP78 was identified to prevent neuronal death induced by ER stress [43].

As PTP1B deficiency protects against high-fat diet-induced ER stress in liver, the inhibitors of this enzyme may hold promise in treating the metabolic syndrome [29,31]. Among PTP1B inhibitors, Astragalus polysaccharide (APS) was reported to decrease PTP1B over-expression in Type 2 diabetes mellitus animal models, and to partly inhibit ATF activation; thus, APS enhanced the adaptive capacity of the ER, promoting insulin signaling [36,44]. Another inhibitor of PTP1B is H_2S that causes enzyme sulfhydration; as PERK is a substrate of PTP1B, inhibition of the latter would promote PERK activity during the response to ER stress [32]. Moreover, PTP1B inhibitors could protect β-cell secretory function in type 2 diabetes, and targeting UPR pathway may preserve β-cell function [14,45]. These exciting results indicate PTP1B inhibition as another strategy towards alleviation of ER stress response. A valuable resource to be exploited is the PTP1B inhibitors identified so far. These are to be examined for the potential delay or reversal of ER stress response execution, particularly in diabetes associated insulin and leptin resistance.

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