expert reviews
in molecular medicine

Endoplasmic reticulum stress and lipid dysregulation

Stephen M. Colgan, Ali A. Al-Hashimi and Richard C. Austin*

Cellular cholesterol homeostasis is a fundamental and highly regulated process. Transcription factors known as sterol regulatory element binding proteins (SREBPs) coordinate the expression of many genes involved in the biosynthesis and uptake of cholesterol. Dysregulation of SREBP activation and cellular lipid accumulation has been associated with endoplasmic reticulum (ER) stress and activation of the unfolded protein response (UPR). This review will provide an overview of ER stress and the UPR as well as cholesterol homeostasis and SREBP regulation, with an emphasis on their interaction and biological relevance.

The endoplasmic reticulum (ER) is the principal site for folding and maturation of transmembrane, secretory and ER-resident proteins (Ref. 1). Several post-translational modifications take place in the ER, including disulfide-bond formation, cleavage of the ER signal-recognition peptide, N-linked glycosylation and addition of glycophosphatidylinositol anchors. These post-translational modifications are required for the correct folding of transmembrane and secretory proteins (Ref. 2). Importantly, ER-resident molecular chaperones are required for the successful completion of each folding step.

N-linked glycosylation of newly synthesised proteins entering the ER lumen is an essential part of protein maturation and folding in eukaryotic cells. During this process, the attached N-linked oligosaccharides become substrates for ER chaperones, including calnexin and calreticulin. These chaperones assist in protein folding by binding to the oligosaccharides, as well as unfolded regions in the glycoprotein (Refs 3, 4, 5). As maturation continues, glucosidase enzymes remove glucose residues from the N-linked oligosaccharides. If the protein is properly folded, it is translocated to the Golgi complex for further processing (Refs 3, 5). If, however, protein folding is impaired, additional cycles of glucose addition (catalysed by glucosyltransferase), removal and chaperone binding continue until proper folding is achieved.

In addition to calnexin and calreticulin, the glucose-regulated proteins (GRPs), including GRP78 and GRP94, assist in proper protein folding by recognising exposed hydrophobic domains (Refs 1, 6). GRP78 binding to ATP, and its subsequent conversion to ADP, causes a conformational change in GRP78 that enhances its affinity to unfolded proteins (Ref. 5). The release of ADP from GRP78 by BiP-associated protein promotes another conformational change in GRP78 that releases the unfolded protein (Refs 5, 7). It is this repeated binding and release of GRP78 that promotes correct protein folding (Refs 5, 8).

ER stress and the unfolded protein response

Conditions that impair or change the folding capacity of the ER might lead to ER stress and induce the unfolded protein response (UPR), an

Department of Medicine and Division of Nephrology, St Joseph's Healthcare Hamilton and McMaster University, Hamilton, Ontario, Canada.

*Corresponding author: Richard C. Austin, 50 Charlton Avenue East, Room T-3313, Hamilton, Ontario, Canada L8N 4A6. E-mail: austinr@taari.ca

Accession information: doi:10.1017/S1462399410001742; Vol. 13; e4; February 2011

integrated, intracellular signalling pathway that induces translational inhibition and ER chaperone upregulation (Refs 9, 10) (Fig. 1). Pharmacological disruption of ER homeostasis and protein folding can be achieved through the depletion of ER calcium (Ca^{2+}) stores with Ca^{2+} ionophores or sarcoplasmic/ER Ca^{2+}-ATPase pump inhibitors. Depletion of ER Ca^{2+} in vitro causes the accumulation of unfolded proteins by decreasing ER chaperone activity and their capacity to fold proteins. Physiologically, induction of ER stress can result from changes in the rate of protein synthesis and folding, ER Ca^{2+} homeostasis or glucose deprivation (Refs 9, 10).

Disruption in ER function (termed ER stress) that interferes with the folding and maturation of newly synthesised proteins induces the UPR. The UPR is mediated by three ER sensors: type-I ER transmembrane protein kinase (IRE1, encoded by *ERN1*), activating transcription factor 6 (ATF6) and the proline-rich, extensin-like receptor (PKR)-like ER kinase (PERK). Under normal homeostatic conditions, UPR activation is repressed by GRP78 binding to the ER lumenal domains of IRE1, ATF6 and PERK. However, following ER stress, dissociation of GRP78 causes activation of the IRE1, ATF6 and PERK pathways (Refs 1, 9, 10, 11, 12).

IRE1 is an ER transmembrane protein that binds to GRP78 under non-ER stress conditions and becomes active following dimerisation and autophosphorylation in the presence of unfolded proteins (Refs 9, 13, 14). Recent evidence suggests that activation of IRE1 occurs not only following GRP78 dissociation, but upon the subsequent binding of unfolded proteins to the IRE1 lumenal domain (Ref. 14). In this model, GRP78 reduces UPR sensitivity by inhibiting the binding of unfolded proteins to IRE1 under conditions of low stress and returning IRE1 to an inactive state when ER stress is alleviated (Ref. 14). Following autophosphorylation, the RNase property of IRE1 splices mRNA from the X-box-binding protein 1 gene (*XBP1*), removing an intron and enabling translation into an active transcription factor that induces ER chaperone gene expression and components of the ER-associated degradation (ERAD) pathway (Refs 15, 16, 17).

Similarly to IRE1, ATF6 is a transmembrane protein that binds GRP78 under non-ER stress conditions. Golgi localisation signals (GLSs) in the lumenal domain of ATF6 are exposed following GRP78 dissociation in the presence of unfolded proteins. The exposed GLSs promote the translocation of ATF6 from the ER to the Golgi (Refs 18, 19). Proteolytic cleavage of ATF6 occurs in the Golgi by the site-1 and site-2 proteases (S1P and S2P, encoded by *MBTPS1* and *MBTPS2*) (Refs 20, 21), which also cleave the sterol regulatory element binding proteins (SREBPs) (see below). Following protease cleavage, ATF6 translocates to the nucleus and induces *XBP1* gene expression, thereby providing more substrate for IRE1 (Refs 16, 22).

Corresponding to the upregulation of UPR response genes, the accumulation of misfolded proteins leads to a decrease in protein translation via the PERK pathway. PERK is an ER transmembrane sensor that binds GRP78, and upon its dissociation, causes activation of its cytosolic kinase domain (Ref. 10). ER-stress-induced activation of PERK leads to the phosphorylation of eukaryotic translation initiation factor 2α (eIF2α), causing a general inhibition of protein translation (Ref. 23). Although eIF2α phosphorylation inhibits general protein translation, certain UPR-associated mRNAs (including ATF4 and GRP78) overcome translation inhibition through an internal ribosome entry site (IRS) that allows their translation during eIF2α phosphorylation (Ref. 10). Recently, studies have also demonstrated that sterol regulatory element binding protein-1 (SREBP-1) (discussed in detail below) can be translated by an IRS (Ref. 24).

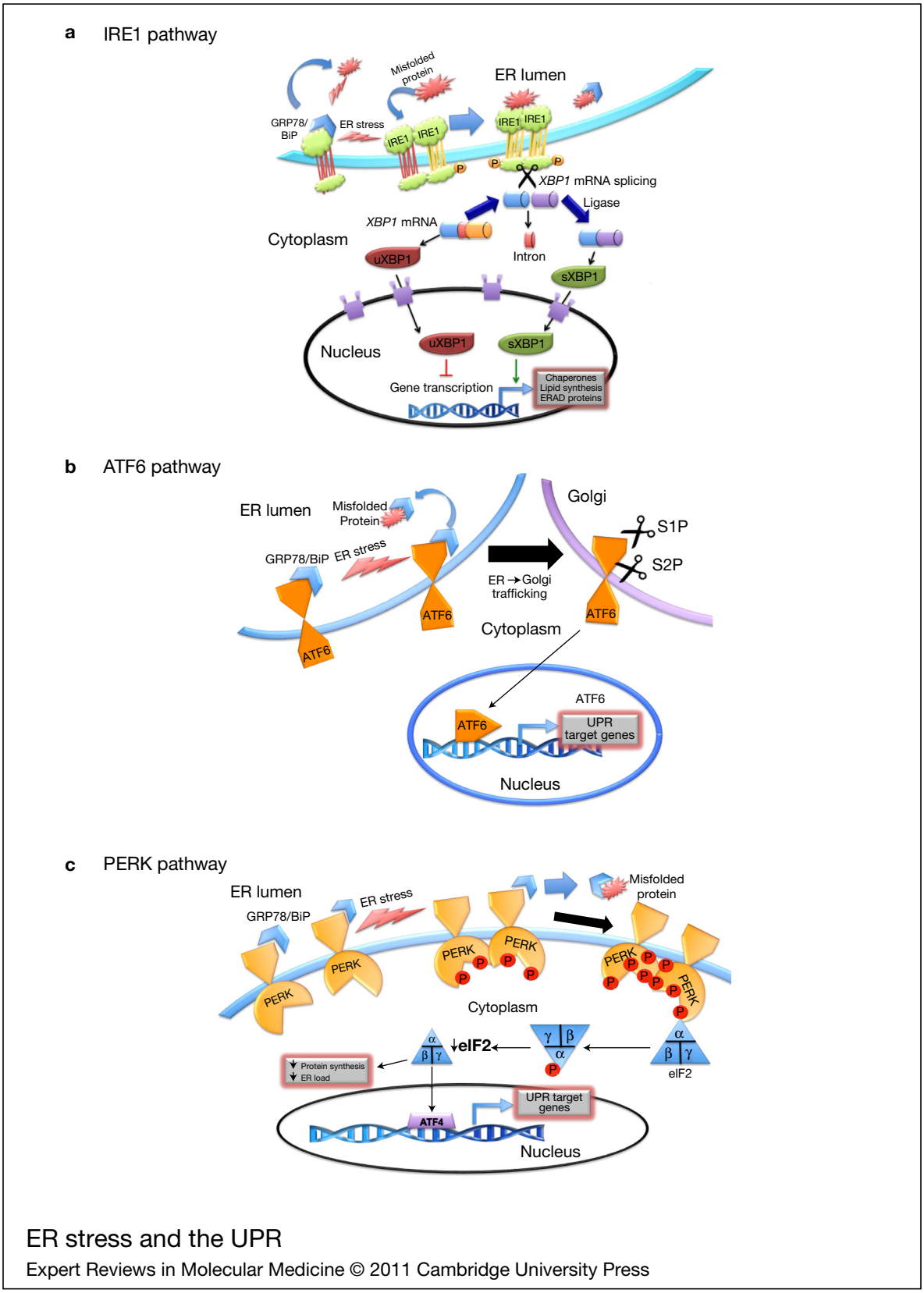
Together, IRE1, ATF6 and PERK respond to ER stress by inhibiting general protein translation while specifically upregulating the expression of ER chaperones as well as cellular factors that comprise the ERAD pathway. Initially, the UPR provides a protective advantage for the cell, but prolonged ER stress activates UPR-dependent pathways inducing apoptosis (Refs 25, 26, 27, 28).

Cellular cholesterol metabolism

In addition to being a precursor of steroid hormones, cholesterol is essential for the proper functioning of cellular membranes (Ref. 29). Although its distribution within membranes is essential for many biological functions, excess cholesterol can be toxic (Ref. 30). Therefore, levels of cholesterol are tightly regulated through cellular uptake, biosynthesis, trafficking, storage and excretion.

Exogenously derived cholesterol arrives at the cell membrane in low-density lipoprotein (LDL) particles that enter cells through an endocytic pathway regulated by the expression of the LDL

Accession information: doi:10.1017/S1462399410001742; Vol. 13; e4; February 2011



ER stress and the UPR

Figure 1. ER stress and the UPR. (*See next page for legend.*)

Accession information: doi:10.1017/S1462399410001742; Vol. 13; e4; February 2011

Figure 1. ER stress and the UPR. (*See previous page for figure.*) The UPR responds to ER stress through activation of the (a) IRE1, (b) ATF6 and (c) PERK pathways. Activation of these transmembrane proteins occurs following dissociation of GRP78 in response to ER stress. Once activated, the UPR functions as an intracellular signalling pathway to attenuate protein translation through eIF2α phosphorylation, increased ER chaperone expression and enhanced degradation of unfolded proteins by the proteasome. Abbreviations: ATF4, activating transcription factor 4; eIF2, eukaryotic translation initiation factor 2; ER, endoplasmic reticulum; ERAD, endoplasmic-reticulum-associated degradation; GRP78, glucose-related protein 78; IRE1, type-I ER transmembrane protein kinase; PERK, protein kinase receptor-like ER kinase; S1P and S2P, site-1 and site-2 proteases; sXBP1, spliced form of X-box-binding protein 1; UPR, unfolded protein response; uXBP1, unspliced form of X-box-binding protein 1.

receptor (LDLR). Through a series of steps, LDL-derived cholesterol exits the endocytic compartment and is transported to various cellular membranes, as required (Ref. 31). Intracellular cholesterol trafficking involves the movement of cholesterol to or from various intracellular compartments such as the late endocytic compartment, the ER and cytosolic lipid droplets (Ref. 32). Cholesterol is transported throughout the cell by incorporation into transport vesicles or by nonvesicular transport, including binding to cytosolic carrier proteins (Refs 29, 32). In addition to obtaining cholesterol from external sources, cells have the capacity to endogenously synthesise cholesterol. The cholesterol biosynthetic pathway is made up of many enzymes that are regulated by the SREBPs. HMG-CoA reductase (HMGCR), the rate-limiting enzyme in the cholesterol biosynthesis pathway, is localised to the ER membrane where it converts HMG-CoA to mevalonate. Mevalonate production is the first step in a series of enzymatic reactions leading to cholesterol synthesis (Ref. 33).

Levels of intracellular cholesterol are highly regulated because excess unesterified cholesterol disrupts membranes, leading to cell toxicity (Ref. 30). Increased membrane cholesterol negatively regulates expression of LDLR and the enzymes responsible for cholesterol biosynthesis (described in detail below). In addition, excess cholesterol is transported to the ER for esterification by acyl-coenzyme A cholesterol acyltransferase 1 (ACAT1) (Refs 31, 34). ACAT1 is an ER-membrane-bound protein that is responsible for the esterification of free cholesterol and its subsequent storage in cytoplasmic lipid droplets or use in lipoprotein assembly for transport and excretion (Ref. 35).

Role of SREBP in cholesterol homeostasis

Maintenance of intracellular cholesterol is achieved through the coordinated action of membrane receptors, transporters and enzymes responsible for cholesterol biosynthesis and uptake. Experiments conducted over the past three decades in the laboratory of Michael Brown and Joseph Goldstein have elegantly elucidated the molecular pathway that is responsible for maintaining intracellular cholesterol homeostasis (Ref. 36).

Following Brown and Goldstein's description of the mechanism and regulation of LDLR-mediated lipoprotein uptake, they identified SREBPs as the transcription factors responsible for regulation of the LDLR (Refs 37, 38, 39, 40, 41, 42). Subsequent experimentation helped determine that the SREBPs also regulate LDLR degradation by influencing the expression of proprotein convertase subtilisin/kexin type 9 (PCSK9) (Refs 43, 44). In addition, the SREBPs have been identified as regulating genes that are required for lipid biosynthesis (through several enzymes involved in the conversion of acetyl-CoA to cholesterol) (Ref. 45), such as HMG-CoA reductase (Ref. 46). Further studies uncovered the complex regulation of SREBP activation, which leads to its transcriptional control of cholesterol and fatty acid homeostasis (Refs 47, 48).

Mammalian cells express three SREBP isoforms: SREBP-1a, SREBP-1c and SREBP-2 (Ref. 49). When overexpressed in cultured cells, both SREBP-1a and SREBP-1c activate transcription of cholesterol and fatty acid biosynthetic genes (Ref. 42). It was reported that SREBP-1c is predominantly expressed in the liver, adrenal gland and adipose tissue of adult mice, whereas SREBP-1a is more abundant than SREBP-1c in the spleen and numerous cultured cell lines (Ref. 50). The mRNA encoding SREBP-2 is expressed in a wide variety of human fetal and adult tissues. SREBP-2 was determined to be a more selective activator of cholesterol biosynthesis, and SREBP-1a and SREBP-2 are the predominant isoforms expressed in most

Accession information: doi:10.1017/S1462399410001742; Vol. 13; e4; February 2011

cultured cell lines, whereas SREBP-1c and SREBP-2 are found in most tissues (Refs 50, 51).

Regulation of SREBP activation

The SREBP regulatory pathway (Fig. 2) was determined by the characterisation of mutant Chinese hamster ovary cell lines with defects in sterol feedback regulation (Ref. 52). The study of sterol-resistant cells led to the identification of the SREBP-cleavage-activating protein (SCAP) (Ref. 52). The N-terminal domain of SCAP, with its membrane-spanning segments, provides an ER membrane anchor, whereas the C-terminal domain projects into the cytosol (Ref. 53). Co-immunoprecipitation experiments demonstrated that the C-terminal domains of SCAP and SREBP form a complex that is required for SREBP proteolytic cleavage (Refs 54, 55).

Cholesterol causes the SCAP–SREBP complex to bind to an ER-retention protein through an interaction involving the sterol-sensing domain of SCAP (Ref. 56). Mutations within the sterol-sensing domain disrupt SCAP's capacity to respond to sterols (Refs 57, 58). The identity of the ER-retention factor was determined to be insulin-induced gene-1 and -2 (INSIG), which binds to the sterol-sensing domain of SCAP and retains the SCAP–SREBP complex in the ER in the presence of sterols (Refs 59, 60). Following a decline in membrane cholesterol, the INSIGs dissociate from SCAP, allowing the SCAP–SREBP complex to become incorporated into COPII vesicles for transport to the Golgi (Refs 56, 57, 61, 62). Using recombinant COPII proteins, it was shown that in sterol-depleted cells, the COPII proteins bind to a specific six-amino-acid sequence (MELADL) on SCAP (Ref. 61). Together, these findings suggest that membrane cholesterol blocks the binding of COPII proteins to the MELADL sequence through the interaction of INSIG with SCAP. When membrane cholesterol levels decrease, dissociation of INSIG from SCAP allows COPII proteins to bind to MELADL and ultimately transport SCAP–SREBP to the Golgi for activation.

To upregulate the transcription of numerous genes responsible for lipid biosynthesis and uptake, the SREBPs must be proteolytically cleaved to their mature forms. A two-step proteolytic process has been described in which SREBPs are released from the ER membrane (Refs 63, 64). The first cleavage by S1P separates SREBP into two halves that remain bound to the membrane (Ref. 64). Following cleavage of SREBP within its luminal loop, a second protease S2P cleaves the N-terminal fragment within its membrane-spanning domain. It was determined that SREBP cleavage by S1P and S2P occurs in the Golgi and not as previously thought in the ER, and it was concluded that sterols regulate the cleavage of SREBPs by modifying the ability of SCAP to transport SREBPs to the Golgi, where they interact with S1P or S2P (Refs 58, 65).

In addition to the classic ER cholesterol-mediated regulation of SREBP-2, the predominant form of SREBP in the liver, SREBP-1c, is expressed and activated through nuclear liver X receptor and insulin signalling (Refs 66, 67, 68). Interestingly, inhibition of endogenous cholesterol synthesis results in an expected increase in SREBP-2 activation but a paradoxical decrease in liver SREBP-1c (Refs 47, 69). It was determined that levels of insulin reciprocally affect levels of INSIG-2, which induces SREBP-1c activation (Refs 67, 68). Together, regulation of the SREBPs differs between isoforms and tissues by changes in lipid and hormone signalling.

ER stress and SREBP activation

Although the accumulation of ER membrane cholesterol induces ER stress and apoptosis (Refs 25, 30), it has been reported that disruption in ER function, leading to the activation of the UPR, induces lipid dysregulation (Refs 70, 71, 72, 73, 74, 75). ER-stress-induced lipid dysregulation was observed in studies with homocysteine (Hcy), a thiol-containing amino acid reported to be an independent risk factor for cardiovascular disease (Refs 76, 77). In these studies, higher Hcy levels upregulate ER-stress-response genes and SREBP expression in human umbilical vein endothelial cells (Refs 77, 78). Subsequently, it was determined that Hcy-induced ER stress promotes hepatic steatosis through the activation of SREBPs and increased expression of genes essential for the biosynthesis and uptake of cholesterol and triglycerides (Ref. 73). Consistent with these findings (Refs 77, 78), cultured human hepatocytes responded to Hcy by increasing the expression of UPR-responsive genes GRP78 and GADD153/CHOP, and overexpression of GRP78 in vitro inhibited ER-stress-induced SREBP activation (Ref. 73). To verify the pathological mechanism in vivo, diet-induced hyperhomocysteinaemia caused

Accession information: doi:10.1017/S1462399410001742; Vol. 13; e4; February 2011

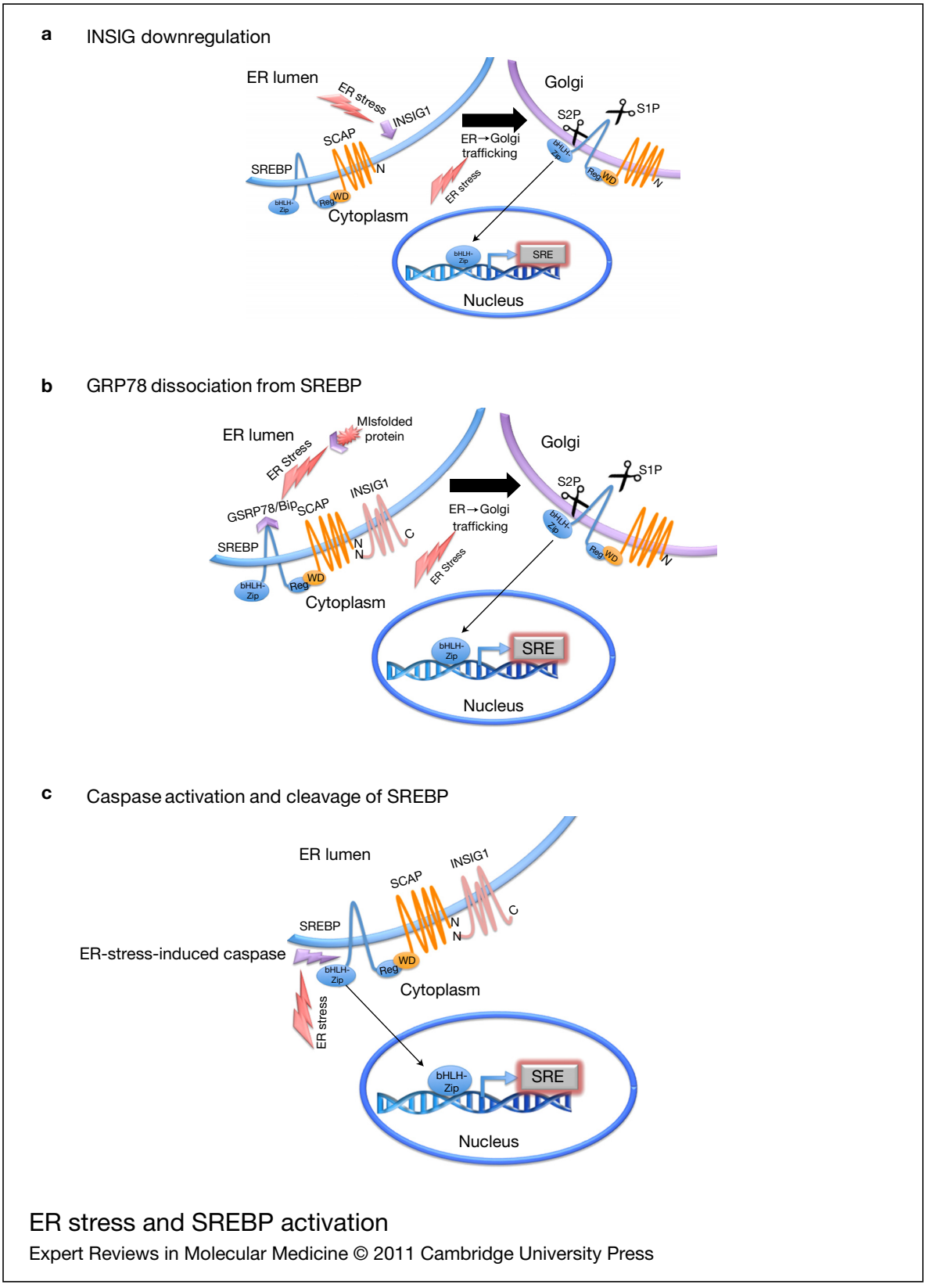


Figure 2. ER stress and SREBP activation. (*See next page for legend.*)

Accession information: doi:10.1017/S1462399410001742; Vol. 13; e4; February 2011

Figure 2. ER stress and SREBP activation. (*See previous page for figure.*) ER-stress-induced activation of SREBP can occur in cells by three potential mechanisms. (a) Phosphorylation of eIF2α can subsequently decrease INSIG1 protein levels. This allows the SCAP–SREBP complex to move to the Golgi where SREBP is activated by the S1P and S2P proteases. (b) Following ER stress, GRP78 dissociates from the SCAP–SREBP complex, which moves to the Golgi, where it is subsequently activated following its cleavage by S1P and S2P. (c) Activation of specific caspases can lead to direct cleavage of the SREBPs from the ER membrane. Abbreviations: bHLH-Zip, basic helix–loop–helix–zipper domain; eIF2, eukaryotic translation initiation factor 2; ER, endoplasmic reticulum; GRP78, glucose-related protein 78; INSIG, insulin-induced gene; IRE1, type-I ER transmembrane protein kinase; PERK, protein kinase receptor-like ER kinase; Reg, regulatory domain; S1P and S2P, site-1 and site-2 proteases; SCAP, SREBP-cleavage activating protein; SRE, sterol regulatory element; SREBP, sterol regulatory element binding protein; WD, WD-40 repeat domain.

hepatic accumulation of cholesterol and triglycerides in wild-type C57 mice. The observed hepatic steatosis was associated with ER stress as well as activation of the UPR and SREBP pathways (Ref. 73). Subsequent publications have confirmed that ER stress is associated with activated SREBP and lipid dysregulation (Refs 70, 71, 75, 79, 80).

Although the mechanism of ER-stress-induced SREBP activation is yet to be finalised, current literature suggests three potential mechanisms by which ER stress induces SREBP activation: caspase-induced SREBP cleavage, eIF2α-phosphorylation-dependent downregulation of INSIG and GRP78 dissociation from the SCAP–SREBP complex (Fig. 2).

Experiments conducted to identify the cellular proteases that activate SREBPs originally demonstrated that caspase-3 (Ref. 81) and caspase-7 (Ref. 82) can cleave both SREBP-1 and SREBP-2 at a site different from S1P and that proteolytic cleavage occurs in the presence of cholesterol (Refs 81, 82, 83). Using a reporter plasmid controlled by the sterol response element (SRE) of the human LDLR, it was determined that SRE-dependent gene expression is increased during the initial stages of apoptosis and can be blocked by caspase inhibitors (Ref. 84). These findings suggest that caspase-3 or other caspases might function independently of apoptotic cell death and have a role in cellular lipid metabolism. Although ER stress can lead to apoptosis and is associated with SREBP activation (Refs 70, 71, 72, 73, 74, 75, 78, 80, 81, 82, 83, 84, 85, 86, 87), the effect of ER stress on SREBP cleavage seems to occur through the conventional S1P–S2P proteolytic pathway (Refs 75, 80, 85).

Although ER-stress-induced SREBP-2 activation occurs in the presence of sterols, it might occur through the conventional pathway following intracellular cholesterol depletion. Translational inhibition following ER-stress-induced eIF2α phosphorylation causes SREBP-2 activation and is correlated with INSIG-1 degradation (Ref. 85). In vivo deletion of PERK in mouse mammary epithelium reduced the levels of *SREBP1* gene expression and showed a significant reduction in the free fatty acid content of secreted milk (Ref. 80). Further experimentation using mouse embryonic fibroblasts deficient in PERK provided evidence that SREBP activation and lipid accumulation are dependent on PERK and eIF2α phosphorylation and associated with reductions in INSIG-1 protein expression (Ref. 80). Because INSIG-1 binds and retains the SCAP–SREBP complex in the ER, it has been suggested that inhibition of protein synthesis during ER stress might decrease the levels of INSIG-1 protein, allowing SCAP–SREBP to exit the ER (Refs 80, 85). Alternatively, disruption of the INSIG–SCAP interaction under conditions that cause ER stress was also proposed as a mechanism to explain these findings.

Recently, an additional mechanism to eIF2α-phosphorylation-induced SREBP-2 activation under ER stress conditions has been described (Ref. 74). GRP78 was overexpressed in murine liver to determine its effect on ER stress and SREBP activation. Consistent with previous studies showing that in vitro overexpression of GRP78 could attenuate ER-stress-induced SREBP activation and lipid accumulation (Ref. 73), hepatic overexpression of GRP78 resulted in decreased markers of ER stress, SREBP-1 and SREBP-2 target gene expression, as well as hepatic lipid accumulation in ob/ob obese mutant mice (Ref. 74). In addition to the obvious role of GRP78 in reducing ER stress, evidence for a direct effect on SREBP was presented (Fig. 2). Experiments showed that GRP78 associates with the SREBP-1 precursor complex and suggested

Accession information: doi:10.1017/S1462399410001742; Vol. 13; e4; February 2011

that GRP78 might interact with SCAP and retain it in the ER under non-ER stress conditions (Ref. 74). This mechanism is comparable to the conventional role of INSIG binding to SCAP and anchoring SREBP in the ER. Thus, GRP78 might sequester the SREBPs in the ER through interaction with its regulatory complex in a manner similar to its regulation of other ER membrane proteins such as ATF6 (Ref. 74).

Together, these experiments provide evidence that ER-stress-induced SREBP activation probably constitutes several mechanisms. ER stress causes eIF2α-phosphorylation-induced translation inhibition, INSIG-1 degradation and release of the SCAP–SREBP complex from the ER (Ref. 85). Experiments that overexpressed the ER chaperone GRP78 observed a decrease in ER-stress-induced SREBP activation, suggesting a possible link between GRP78 and the SCAP–SREBP complex (Refs 73, 74). Future experiments will be necessary to directly examine the link between GRP78 and ER-stress-induced SREBP activation.

SREBP dysregulation and disease

Various pathologies have been associated with differential regulation of the SREBP pathway. Although transgenic mice expressing a constitutive active form of SREBP-1 and SREBP-2 developed hepatic steatosis with hepatocyte cholesterol and triglyceride accumulation, peripheral white adipose tissue decreased with symptoms associated with lipodystrophy (Refs 51, 88). In contrast to the in vivo overexpression of SREBP-1a in mouse adipose tissue associated with adipocyte hypertrophy, increased fatty acid secretion and hepatic steatosis (Ref. 89), the overexpression of the SREBP-1c isoform in mouse adipose tissue inhibits adipocyte differentiation with a resulting phenotype that includes lipodystrophy, diabetes and hepatic steatosis (Ref. 90). As described above, diet-induced hyperhomocysteinaemia caused ER-stress-induced SREBP activation and hepatic steatosis (Ref. 73). Attenuation of ER stress by overexpression of GRP78 blocked SREBP activation and decreased the expression of genes responsible for cholesterol and fatty acid biosynthesis (Refs 73, 74). Acute pharmacological renal toxicity is associated with proximal tubule lipid accumulation and has been extensively studied in response to ischaemia and cytotoxicity (Refs 91, 92, 93, 94, 95). Interestingly, common to these studies is the increase in the expression of enzymes and receptors responsible for the biosynthesis and uptake of cholesterol and triglycerides (Refs 91, 92, 93, 94, 95). Because the accumulation of lipids following cytotoxic stress has been suggested to provide an advantage to cells by protecting them from further injury (Refs 96, 97, 98), it will be important in future experiments to determine whether the activation of SREBP protects renal tubule cells from subsequent cytotoxic injury. The importance of the UPR in protecting cells from toxicity-induced renal cell damage has been reported (Ref. 99). Mutant GRP78 lacking an ER retention signal was used to inhibit the usual increase in GRP78 expression following ER stress. Following chronic protein overload-induced nephrotoxicity, mice expressing the mutant GRP78 suffered tubular lesions and cell apoptosis (Ref. 99). This study demonstrates the importance of the UPR in the normal physiological maintenance of renal cells challenged with toxic injury. Pharmacologically induced ER stress causes injury to renal proximal tubules resembling acute tubular necrosis induced in humans by ischaemia, infection or toxins. The expression of ER chaperones in proximal tubules was found to be dramatically increased following treatment (Ref. 100). This model is useful to study acute renal toxicity and future experiments should determine whether upregulation of ER chaperones is linked to SREBP activation and lipid accumulation. Atherosclerosis is a classic pathology that is characterised by higher intracellular lipid accumulation in arterial walls. Although it is well accepted that macrophages resident in atherosclerotic lesions express scavenger receptors that promote the internalisation of modified lipoproteins (Ref. 101), it has also been found that scavenger receptor knockout mouse models continue to develop atherosclerosis with pronounced foam cell formation (Ref. 102). It is unknown whether macrophages undergoing ER stress activate SREBP and promote lipid accumulation, which could offer an additional mechanism to explain macrophage foam cell formation and plaque progression. The relevant steps in the maturation of macrophages from circulating monocytes to lesion-resident foam cells include binding and migration, differentiation and lipid accumulation. It has recently been shown that SREBP activation is important during differentiation of monocytes to macrophages (Ref. 103). During cell

Accession information: doi:10.1017/S1462399410001742; Vol. 13; e4; February 2011

differentiation, lipid regulation is required for the development of cellular membranes and organelles (Ref. 103) and SREBP has been implicated in vascular endothelial growth factor-induced angiogenesis (Ref. 104) and required for efficient cellular proliferation and migration (Ref. 104). In addition, increased SREBP expression has been reported in atherosclerotic lesions and associated with increased expression and secretion of the pro-inflammatory cytokine IL-8 (Ref. 105). Although it is not known whether these findings are related to ER stress, together they represent mechanisms of SREBP activation that could potentially contribute to atherosclerotic lesion development.

Future directions

Important questions remain to be answered pertaining to the mechanism of ER-stress-induced SREBP activation and its role in clinical pathologies characterised by lipid accumulation. These questions include: (1) How does ER chaperone expression influence SREBP activation? (2) How does general protein translation inhibition affect the SREBP–SCAP–INSIG complex? (3) Is ER-stress-induced SREBP activation a normal physiological prosurvival cellular pathway or activator of cell death? (4) Does ER-stress-induced SREBP activation contribute to human disease?

In vivo overexpression of GRP78 has been shown to decrease markers of ER stress, SREBP activation and lipid accumulation (Refs 73, 74). In addition, coimmunoprecipitation experiments found that GRP78 binds to the SREBP–SCAP–INSIG complex but could not identify a specific binding partner (Ref. 74). A hypothesis has been presented in which GRP78 regulates SREBP in a similar manner to ATF6. It was suggested that under ER stress conditions, GRP78 dissociates from SREBP or its regulatory molecules SCAP and INSIG and allows the SCAP–SREBP complex to transport to the Golgi for S1P and S2P activation (Ref. 74).

The evidence that ER stress is an activator of the SREBPs is overwhelming. Future studies will allow for a better understanding of the underlying mechanisms by which ER stress and SREBP activation could contribute to the development and progression of cardiovascular disease, obesity, chronic kidney disease and diabetes. Based on these important findings, novel therapeutic strategies that attenuate ER-stress-induced SREBP activation could prevent or reduce the risk of these human diseases and their complications.

Acknowledgements

This work was supported in part by research grants to Richard C. Austin from the Heart and Stroke Foundation of Ontario and the Canadian Institutes of Health Research. Financial support from St Joseph's Healthcare Hamilton is also acknowledged. Richard C. Austin is a Career Investigator of the Heart and Stroke Foundation of Ontario and holds the Amgen Canada Research Chair in the Division of Nephrology at St Joseph's Healthcare and McMaster University. We thank the reviewers for their insightful comments and suggestions.

References

1 Lee, A.S. (2001) The glucose-regulated proteins: stress induction and clinical applications. Trends in Biochemical Sciences 26, 504-510
2 Ellgaard, L. and Helenius, A. (2003) Quality control in the endoplasmic reticulum. Nature Reviews. Molecular Cell Biology 4, 181-191
3 Hebert, D.N., Foellmer, B. and Helenius, A. (1995) Glucose trimming and reglucosylation determine glycoprotein association with calnexin in the endoplasmic reticulum. Cell 81, 425-433
4 Sitia, R. and Braakman, I. (2003) Quality control in the endoplasmic reticulum protein factory. Nature 426, 891-894
5 Ma, Y. and Hendershot, L.M. (2004) ER chaperone functions during normal and stress conditions. Journal of Chemical Neuroanatomy 28, 51-65
6 Flynn, G.C. et al. (1991) Peptide-binding specificity of the molecular chaperone BiP. Nature 353, 726-730
7 Chung, K.T., Shen, Y. and Hendershot, L.M. (2002) BAP, a mammalian BiP-associated protein, is a nucleotide exchange factor that regulates the ATPase activity of BiP. Journal of Biological Chemistry 277, 47557-47563
8 Hendershot, L. et al. (1996) Inhibition of immunoglobulin folding and secretion by dominant negative BiP ATPase mutants. Proceedings of the National Academy of Sciences of the United States of America 93, 5269-5274
9 Kaufman, R.J. (2002) Orchestrating the unfolded protein response in health and disease. Journal of Clinical Investigation 110, 1389-1398
10 Ron, D. (2002) Translational control in the endoplasmic reticulum stress response. Journal of Clinical Investigation 110, 1383-1388

Accession information: doi:10.1017/S1462399410001742; Vol. 13; e4; February 2011

11 Lawrence de Koning, A.B. et al. (2003) Hyperhomocysteinemia and its role in the development of atherosclerosis. Clinical Biochemistry 36, 431-441
12 Rutkowski, D.T. and Kaufman, R.J. (2004) A trip to the ER: coping with stress. Trends in Cell Biology 14, 20-28
13 Ron, D. and Hubbard, S.R. (2008) How IRE1 reacts to ER stress. Cell 132, 24-26
14 Pincus, D. et al. (2010) BiP binding to the ER-stress sensor Ire1 tunes the homeostatic behavior of the unfolded protein response. PLoS Biology 8, e1000415
15 Yoshida, H. et al. (1998) Identification of the cis-acting endoplasmic reticulum stress response element responsible for transcriptional induction of mammalian glucose-regulated proteins. Involvement of basic leucine zipper transcription factors. Journal of Biological Chemistry 273, 33741-33749
16 Yoshida, H. et al. (2001) XBP1 mRNA is induced by ATF6 and spliced by IRE1 in response to ER stress to produce a highly active transcription factor. Cell 107, 881-891
17 Tirasophon, W. et al. (2000) The endoribonuclease activity of mammalian IRE1 autoregulates its mRNA and is required for the unfolded protein response. Genes and Development 14, 2725-2736
18 Chen, X., Shen, J. and Prywes, R. (2002) The luminal domain of ATF6 senses endoplasmic reticulum (ER) stress and causes translocation of ATF6 from the ER to the Golgi. Journal of Biological Chemistry 277, 13045-13052
19 Shen, J. et al. (2002) ER stress regulation of ATF6 localization by dissociation of BiP/GRP78 binding and unmasking of Golgi localization signals. Developmental Cell 3, 99-111
20 Haze, K. et al. (1999) Mammalian transcription factor ATF6 is synthesized as a transmembrane protein and activated by proteolysis in response to endoplasmic reticulum stress. Molecular Biology of the Cell 10, 3787-3799
21 Ye, J. et al. (2000) ER stress induces cleavage of membrane-bound ATF6 by the same proteases that process SREBPs. Molecular Cell 6, 1355-1364
22 Lee, K. et al. (2002) IRE1-mediated unconventional mRNA splicing and S2P-mediated ATF6 cleavage merge to regulate XBP1 in signaling the unfolded protein response. Genes and Development 16, 452-466
23 Harding, H.P., Zhang, Y. and Ron, D. (1999) Protein translation and folding are coupled by an endoplasmic-reticulum-resident kinase. Nature 397, 271-274
24 Damiano, F. et al. (2010) Translational control of the sterol-regulatory transcription factor SREBP-1 mRNA in response to serum starvation or ER stress is mediated by an internal ribosome entry site. Biochemical Journal 429, 603-612
25 Feng, B. et al. (2003) The endoplasmic reticulum is the site of cholesterol-induced cytotoxicity in macrophages. Nature Cell Biology 5, 781-792
26 Hossain, G.S. et al. (2003) TDAG51 is induced by homocysteine, promotes detachment-mediated programmed cell death, and contributes to the cevelopment of atherosclerosis in hyperhomocysteinemia. Journal of Biological Chemistry 278, 30317-30327
27 Morishima, N. et al. (2002) An endoplasmic reticulum stress-specific caspase cascade in apoptosis. Cytochrome c-independent activation of caspase-9 by caspase-12. Journal of Biological Chemistry 277, 34287-34294
28 Nakagawa, T. et al. (2000) Caspase-12 mediates endoplasmic-reticulum-specific apoptosis and cytotoxicity by amyloid-beta. Nature 403, 98-103
29 Maxfield, F.R. and Wustner, D. (2002) Intracellular cholesterol transport. Journal of Clinical Investigation 110, 891-898
30 Maxfield, F.R. and Tabas, I. (2005) Role of cholesterol and lipid organization in disease. Nature 438, 612-621
31 Chang, T.Y. et al. (2005) Niemann–Pick type C disease and intracellular cholesterol trafficking. Journal of Biological Chemistry 280, 20917-20920
32 Soccio, R.E. and Breslow, J.L. (2004) Intracellular cholesterol transport. Arteriosclerosis, Thrombosis, and Vascular Biology 24, 1150-1160
33 Espenshade, P.J. and Hughes, A.L. (2007) Regulation of sterol synthesis in eukaryotes. Annual Review of Genetics 41, 401-427
34 Sakashita, N. et al. (2000) Localization of human acyl-coenzyme A: cholesterol acyltransferase-1 (ACAT-1) in macrophages and in various tissues. American Journal of Pathology 156, 227-236
35 Chang, T.Y. et al. (2006) Cholesterol sensing, trafficking, and esterification. Annual Review of Cell and Developmental Biology 22, 129-157
36 Goldstein, J.L. and Brown, M.S. (2008) From fatty streak to fatty liver: 33 years of joint publications in the JCI. Journal of Clinical Investigation 118, 1220-1222
37 Briggs, M.R. et al. (1993) Nuclear protein that binds sterol regulatory element of low density lipoprotein receptor promoter. I. Identification of the protein and delineation of its target nucleotide sequence. Journal of Biological Chemistry 268, 14490-14496

Accession information: doi:10.1017/S1462399410001742; Vol. 13; e4; February 2011

38 Horton, J.D., Goldstein, J.L. and Brown, M.S. (2002) SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver. Journal of Clinical Investigation 109, 1125-1131
39 Hua, X. et al. (1993) SREBP-2, a second basic-helix-loop-helix-leucine zipper protein that stimulates transcription by binding to a sterol regulatory element. Proceedings of the National Academy of Sciences of the United States of America 90, 11603-11607
40 Rawson, R.B. (2003) The SREBP pathway – insights from Insigs and insects. Nature Reviews. Molecular Cell Biology 4, 631-640
41 Wang, X. et al. (1993) Nuclear protein that binds sterol regulatory element of low density lipoprotein receptor promoter. II. Purification and characterization. Journal of Biological Chemistry 268, 14497-14504
42 Yokoyama, C. et al. (1993) SREBP-1, a basic-helix-loop-helix-leucine zipper protein that controls transcription of the low density lipoprotein receptor gene. Cell 75, 187-197
43 Jeong, H.J. et al. (2008) Sterol-dependent regulation of proprotein convertase subtilisin/kexin type 9 expression by sterol-regulatory element binding protein-2. Journal of Lipid Research 49, 399-409
44 Seidah, N.G., Khatib, A.M. and Prat, A. (2006) The proprotein convertases and their implication in sterol and/or lipid metabolism. Biological Chemistry 387, 871-877
45 Goldstein, J.L. and Brown, M.S. (1990) Regulation of the mevalonate pathway. Nature 343, 425-430
46 Vallett, S.M. et al. (1996) A direct role for sterol regulatory element binding protein in activation of 3-hydroxy-3-methylglutaryl coenzyme A reductase gene. Journal of Biological Chemistry 271, 12247-12253
47 Sheng, Z. et al. (1995) Independent regulation of sterol regulatory element-binding proteins 1 and 2 in hamster liver. Proceedings of the National Academy of Sciences of the United States of America 92, 935-938
48 Wang, X. et al. (1994) SREBP-1, a membrane-bound transcription factor released by sterol-regulated proteolysis. Cell 77, 53-62
49 Hua, X. et al. (1995) Structure of the human gene encoding sterol regulatory element binding protein-1 (SREBF1) and localization of SREBF1 and SREBF2 to chromosomes 17p11.2 and 22q13. Genomics 25, 667-673
50 Shimomura, I. et al. (1997) Differential expression of exons 1a and 1c in mRNAs for sterol regulatory element binding protein-1 in human and mouse organs and cultured cells. Journal of Clinical Investigation 99, 838-845
51 Horton, J.D. et al. (1998) Activation of cholesterol synthesis in preference to fatty acid synthesis in liver and adipose tissue of transgenic mice overproducing sterol regulatory element-binding protein-2. Journal of Clinical Investigation 101, 2331-2339
52 Hua, X. et al. (1996) Sterol resistance in CHO cells traced to point mutation in SREBP cleavage-activating protein. Cell 87, 415-426
53 Nohturfft, A., Brown, M.S. and Goldstein, J.L. (1998) Topology of SREBP cleavage-activating protein, a polytopic membrane protein with a sterol-sensing domain. Journal of Biological Chemistry 273, 17243-17250
54 Sakai, J. et al. (1998) Cleavage of sterol regulatory element-binding proteins (SREBPs) at site-1 requires interaction with SREBP cleavage-activating protein. Evidence from in vivo competition studies. Journal of Biological Chemistry 273, 5785-5793
55 Sakai, J. et al. (1997) Identification of complexes between the COOH-terminal domains of sterol regulatory element-binding proteins (SREBPs) and SREBP cleavage-activating protein. Journal of Biological Chemistry 272, 20213-20221
56 Yang, T., Goldstein, J.L. and Brown, M.S. (2000) Overexpression of membrane domain of SCAP prevents sterols from inhibiting SCAP.SREBP exit from endoplasmic reticulum. Journal of Biological Chemistry 275, 29881-29886
57 Nohturfft, A. et al. (2000) Regulated step in cholesterol feedback localized to budding of SCAP from ER membranes. Cell 102, 315-323
58 Nohturfft, A., Brown, M.S. and Goldstein, J.L. (1998) Sterols regulate processing of carbohydrate chains of wild-type SREBP cleavage-activating protein (SCAP), but not sterol-resistant mutants Y298C or D443N. Proceedings of the National Academy of Sciences of the United States of America 95, 12848-12853
59 Yang, T. et al. (2002) Crucial step in cholesterol homeostasis: sterols promote binding of SCAP to INSIG-1, a membrane protein that facilitates retention of SREBPs in ER. Cell 110, 489-500
60 Yabe, D., Brown, M.S. and Goldstein, J.L. (2002) Insig-2, a second endoplasmic reticulum protein that binds SCAP and blocks export of sterol regulatory element-binding proteins. Proceedings of the National Academy of Sciences of the United States of America 99, 12753-12758
61 Sun, L.P. et al. (2005) Insig required for sterol-mediated inhibition of Scap/SREBP binding to

Accession information: doi:10.1017/S1462399410001742; Vol. 13; e4; February 2011

COPII proteins in vitro. Journal of Biological Chemistry 280, 26483-26490
62 Sun, L.P. et al. (2007) Sterol-regulated transport of SREBPs from endoplasmic reticulum to Golgi: Insig renders sorting signal in Scap inaccessible to COPII proteins. Proceedings of the National Academy of Sciences of the United States of America 104, 6519-6526
63 Hua, X. et al. (1996) Regulated cleavage of sterol regulatory element binding proteins requires sequences on both sides of the endoplasmic reticulum membrane. Journal of Biological Chemistry 271, 10379-10384
64 Sakai, J. et al. (1996) Sterol-regulated release of SREBP-2 from cell membranes requires two sequential cleavages, one within a transmembrane segment. Cell 85, 1037-1046
65 Nohturfft, A. et al. (1999) Sterols regulate cycling of SREBP cleavage-activating protein (SCAP) between endoplasmic reticulum and Golgi. Proceedings of the National Academy of Sciences of the United States of America 96, 11235-11240
66 Hegarty, B.D. et al. (2005) Distinct roles of insulin and liver X receptor in the induction and cleavage of sterol regulatory element-binding protein-1c. Proceedings of the National Academy of Sciences of the United States of America 102, 791-796
67 Yellaturu, C.R. et al. (2009) Insulin enhances the biogenesis of nuclear sterol regulatory element-binding protein (SREBP)-1c by posttranscriptional down-regulation of Insig-2A and its dissociation from SREBP cleavage-activating protein (SCAP).SREBP-1c complex. Journal of Biological Chemistry 284, 31726-31734
68 Yabe, D. et al. (2003) Liver-specific mRNA for Insig-2 down-regulated by insulin: implications for fatty acid synthesis. Proceedings of the National Academy of Sciences of the United States of America 100, 3155-3160
69 Shimomura, I. et al. (1997) Cholesterol feeding reduces nuclear forms of sterol regulatory element binding proteins in hamster liver. Proceedings of the National Academy of Sciences of the United States of America 94, 12354-12359
70 Esfandiari, F. et al. (2005) Chronic ethanol feeding and folate deficiency activate hepatic endoplasmic reticulum stress pathway in micropigs. American Journal of Physiology. Gastrointestinal Liver Physiology 289, G54-G63
71 Ji, C. and Kaplowitz, N. (2003) Betaine decreases hyperhomocysteinemia, endoplasmic reticulum stress, and liver injury in alcohol-fed mice. Gastroenterology 124, 1488-1499
72 Kim, A.J. et al. (2005) Valproate protects cells from ER stress-induced lipid accumulation and apoptosis by inhibiting glycogen synthase kinase-3. Journal of Cell Science 118, 89-99
73 Werstuck, G.H. et al. (2001) Homocysteine-induced endoplasmic reticulum stress causes dysregulation of the cholesterol and triglyceride biosynthetic pathways. Journal of Clinical Investigation 107, 1263-1273
74 Kammoun, H.L. et al. (2009) GRP78 expression inhibits insulin and ER stress-induced SREBP-1c activation and reduces hepatic steatosis in mice. Journal of Clinical Investigation 119, 1201-1215
75 Colgan, S.M. et al. (2007) Endoplasmic reticulum stress causes the activation of sterol regulatory element binding protein-2. International Journal of Biochemistry and Cell Biology 39, 1843-1851
76 Zhou, J. and Austin, R.C. (2009) Contributions of hyperhomocysteinemia to atherosclerosis: causal relationship and potential mechanisms. Biofactors 35, 120-129
77 Outinen, P.A. et al. (1999) Homocysteine-induced endoplasmic reticulum stress and growth arrest leads to specific changes in gene expression in human vascular endothelial cells. Blood 94, 959-967
78 Outinen, P.A. et al. (1998) Characterization of the stress-inducing effects of homocysteine. Biochemical Journal 332 (Pt 1), 213-221
79 Woo, C.W. et al. (2005) Hyperhomocysteinemia induces hepatic cholesterol biosynthesis and lipid accumulation via activation of transcription factors. American Journal of Physiology. Endocrinology and Metabolism 288, E1002-E1010
80 Bobrovnikova-Marjon, E. et al. (2008) PERK-dependent regulation of lipogenesis during mouse mammary gland development and adipocyte differentiation. Proceedings of the National Academy of Sciences of the United States of America 105, 16314-16319
81 Wang, X. et al. (1995) Purification of an interleukin-1 beta converting enzyme-related cysteine protease that cleaves sterol regulatory element-binding proteins between the leucine zipper and transmembrane domains. Journal of Biological Chemistry 270, 18044-18050
82 Pai, J.T., Brown, M.S. and Goldstein, J.L. (1996) Purification and cDNA cloning of a second apoptosis-related cysteine protease that cleaves and activates sterol regulatory element binding proteins. Proceedings of the National Academy of Sciences of the United States of America 93, 5437-5442

Accession information: doi:10.1017/S1462399410001742; Vol. 13; e4; February 2011

83 Wang, X. et al. (1996) Cleavage of sterol regulatory element binding proteins (SREBPs) by CPP32 during apoptosis. EMBO Journal 15, 1012-1020
84 Higgins, M.E. and Ioannou, Y.A. (2001) Apoptosis-induced release of mature sterol regulatory element-binding proteins activates sterol-responsive genes. Journal of Lipid Research 42, 1939-1946
85 Lee, J.N. and Ye, J. (2004) Proteolytic activation of sterol regulatory element-binding protein induced by cellular stress through depletion of Insig-1. Journal of Biological Chemistry 279, 45257-45265
86 Rao, R.V. et al. (2002) Coupling endoplasmic reticulum stress to the cell death program. An Apaf-1-independent intrinsic pathway. Journal of Biological Chemistry 277, 21836-21842
87 Shiraishi, H. et al. (2006) ER stress-induced apoptosis and caspase-12 activation occurs downstream of mitochondrial apoptosis involving Apaf-1. Journal of Cell Science 119, 3958-3966
88 Shimano, H. et al. (1996) Overproduction of cholesterol and fatty acids causes massive liver enlargement in transgenic mice expressing truncated SREBP-1a. Journal of Clinical Investigation 98, 1575-1584
89 Horton, J.D. et al. (2003) Overexpression of sterol regulatory element-binding protein-1a in mouse adipose tissue produces adipocyte hypertrophy, increased fatty acid secretion, and fatty liver. Journal of Biological Chemistry 278, 36652-36660
90 Shimomura, I. et al. (1998) Insulin resistance and diabetes mellitus in transgenic mice expressing nuclear SREBP-1c in adipose tissue: model for congenital generalized lipodystrophy. Genes and Development 12, 3182-3194
91 Zager, R.A. and Johnson, A. (2001) Renal cortical cholesterol accumulation is an integral component of the systemic stress response. Kidney International 60, 2299-2310
92 Zager, R.A. et al. (2001) Cholesterol ester accumulation: an immediate consequence of acute in vivo ischemic renal injury. Kidney International 59, 1750-1761
93 Zager, R.A. et al. (2003) Acute tubular injury causes dysregulation of cellular cholesterol transport proteins. American Journal of Pathology 163, 313-320
94 Zager, R.A. et al. (2002) The mevalonate pathway during acute tubular injury: selected determinants and consequences. American Journal of Pathology 161, 681-692
95 Zager, R.A., Johnson, A.C. and Hanson, S.Y. (2005) Renal tubular triglyercide accumulation following endotoxic, toxic, and ischemic injury. Kidney International 67, 111-121
96 Zager, R.A. (2000) Plasma membrane cholesterol: a critical determinant of cellular energetics and tubular resistance to attack. Kidney International 58, 193-205
97 Zager, R.A. et al. (1999) Increased proximal tubular cholesterol content: implications for cell injury and "acquired cytoresistance". Kidney International 56, 1788-1797
98 Zager, R.A. and Kalhorn, T.F. (2000) Changes in free and esterified cholesterol: hallmarks of acute renal tubular injury and acquired cytoresistance. American Journal of Pathology 157, 1007-1016
99 Kimura, K. et al. (2008) Dysfunction of the ER chaperone BiP accelerates the renal tubular injury. Biochemical and Biophysical Research Communications 366, 1048-1053
100 Zinszner, H. et al. (1998) CHOP is implicated in programmed cell death in response to impaired function of the endoplasmic reticulum. Genes and Development 12, 982-995
101 Moore, K.J. and Freeman, M.W. (2006) Scavenger receptors in atherosclerosis: beyond lipid uptake. Arteriosclerosis, Thrombosis, and Vascular Biology 26, 1702-1711
102 Manning-Tobin, J.J. et al. (2009) Loss of SR-A and CD36 activity reduces atherosclerotic lesion complexity without abrogating foam cell formation in hyperlipidemic mice. Arteriosclerosis, Thrombosis, and Vascular Biology 29, 19-26
103 Ecker, J. et al. (2010) Induction of fatty acid synthesis is a key requirement for phagocytic differentiation of human monocytes. Proceedings of the National Academy of Sciences of the United States of America 107, 7817-7822
104 Zhou, R.H. et al. (2004) Vascular endothelial growth factor activation of sterol regulatory element binding protein: a potential role in angiogenesis. Circulation Research 95, 471-478
105 Yeh, M. et al. (2004) Role for sterol regulatory element-binding protein in activation of endothelial cells by phospholipid oxidation products. Circulation Research 95, 780-788

Accession information: doi:10.1017/S1462399410001742; Vol. 13; e4; February 2011

Further reading, resources and contacts

Reviews

There are currently several excellent reviews that address different aspects of ER stress, UPR and lipid dysregulation:

Lee, A.H. and Glimcher, L.H. (2009) Intersection of the unfolded protein response and hepatic lipid metabolism. Cellular and Molecular Life Sciences 66, 2835-2850

Ferré, P. and Foufelle, F. (2010) Hepatic steatosis: a role for de novo lipogenesis and the transcription factor SREBP-1c. Diabetes, Obesity and Metabolism 12(Suppl 2), 83-92

Marciniak, S.J. and Ron, D. (2006) Endoplasmic reticulum stress signaling in disease. Physiological Reviews 86, 1133-1149

Brown, M.S. and Goldstein, J.L. (2009) Cholesterol feedback: from Schoenheimer's bottle to Scap's MELADL. Journal of Lipid Research S15-S27

Books

Michael Conn P. (ed.) (in press) The unfolded protein response and cellular stress. Methods in Enzymology. Academic Press.

Websites

National Institutes of Health: Office of Rare Diseases Research is a highly informative site providing information about basic information, research and clinical trials and research resources with a focus on rare human diseases: http://rarediseases.info.nih.gov/

Features associated with this article

Figures

Figure 1. ER stress and the UPR.
Figure 2. ER stress and SREBP activation.

Citation details for this article

Stephen M. Colgan, Ali A. Al-Hashimi and Richard C. Austin (2011) Endoplasmic reticulum stress and lipid dysregulation. Expert Rev. Mol. Med. Vol. 13, e4, February 2011, doi:10.1017/S1462399410001742

Accession information: doi:10.1017/S1462399410001742; Vol. 13; e4; February 2011