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ER Stress Response Failure and Steatohepatitis Comorbid with Diabetes

Takayoshi Sasako and Kohjiro Ueki

Abstract

Dynamic metabolic changes occur in the liver during the transition between fasting and eating, which is mainly mediated by insulin, a hormone to promote anabolism and suppress catabolism. In obesity and diabetes, insulin resistance is induced via various mechanisms, and among them is endoplasmic reticulum (ER) stress. We recently reported that eating induces transient ER stress and consequent ER stress response in the liver. During eating, expression of Sdf2l1, an ER-resident molecule involved in ER stress-associated degradation, is induced as a part of ER stress response. XBP-1s regulates expression of Sdf2l1 at the transcription level, and Sdf2l1 terminates eating-induced ER stress in the liver, consequently regulating glucose and lipid metabolism. In obesity and diabetes, however, ER stress response is impaired, partly because insulin-mediated translocation of XBP-1s to the nucleus is suppressed, which results in further excessive ER stress. Induction of Sdf2l1 by XBP-1s is highly down-regulated, but restoration of Sdf2l1 ameliorates glucose intolerance and fatty liver. In diabetic patients, hepatic insulin resistance induces enhanced ER stress and ER stress response failure in the liver, which in turn promote hepatic fibrosis and contribute to the development of steatohepatitis comorbid with diabetes.

Keywords: liver, insulin signaling, insulin resistance, diabetes mellitus, feeding, endoplasmic reticulum stress, stromal cell-derived factor 2 like 1, X-box binding protein 1, fatty liver

1. Introduction

Organisms need to take in nutrients from outside for biological activities and survival, and deprivation of nutrients is a heavy burden for organisms. However, various responses are induced even during eating, in order to cope with the rapid influx of nutrients. The liver plays pivotal roles in the maintenance of systemic nutritional homeostasis depending on the feeding conditions, and dynamic changes are induced during the transition between fasting and feeding, or eating. During fasting, the liver releases glucose by glycogenolysis and gluconeogenesis, and ketone bodies by fatty acid oxidation, while during feeding, it stores excessive nutrition derived from food by synthesizing glycogen and fatty acids. Conversely, dysregulation of these processes may lead to metabolic disorders, such as insulin resistance and fatty liver disease [1].

In this chapter, we are going to discuss physiological and patho-physiological aspects of stress response during eating, by reviewing the insulin signaling cascade first, then endoplasmic reticulum (ER) stress, which is becoming an emerging player in the regulation of metabolism in the liver, and finally the roles of ER stress response failure in the development of steatohepatitis comorbid with diabetes.

2. Insulin action and downstream molecules

Insulin is the major regulator of metabolism which is secreted from pancreatic beta cells, and it promotes anabolism and suppresses catabolism in the targeted tissues including the liver [2–5].

In the early 1980s, tyrosine kinase activity of insulin receptor was first reported [6], and the whole cascade of the signaling has been uncovered in the past 40 years. In brief, in the presence of insulin, IR (insulin receptor) phosphorylates IRSs (insulin receptor substrates). Among the isoforms of IRSs, IRS-1 and IRS-2 are the major ones, and they activate two main signaling pathways: the PI3K (phosphatidylinositol 3-kinase)-Akt/PKB (protein kinase B) pathway and the Ras–MAPK (mitogen-activated protein kinase) pathway. The former is mainly responsible for metabolic actions of insulin, and the latter mainly regulates cell growth and differentiation [5] (Figure 1).

In obesity and diabetes, however, the insulin signaling cascade is impaired by various mechanisms despite normal or high concentrations of insulin, which is called insulin resistance. It is generally thought that serine/threonine kinases, such as PKC (protein kinase C), JNK (c-jun N-terminal kinases), IKK β (inhibitor of nuclear factor kappa-B kinase subunit β), and PP2A (protein phosphatase 2A), are activated in obesity via lipotoxicity, inflammation, hyperglycemia, mitochondrial dysfunction and subsequent oxidative stress, and ER stress, which is reviewed in the following subsection. Serine/threonine kinases thus activated in

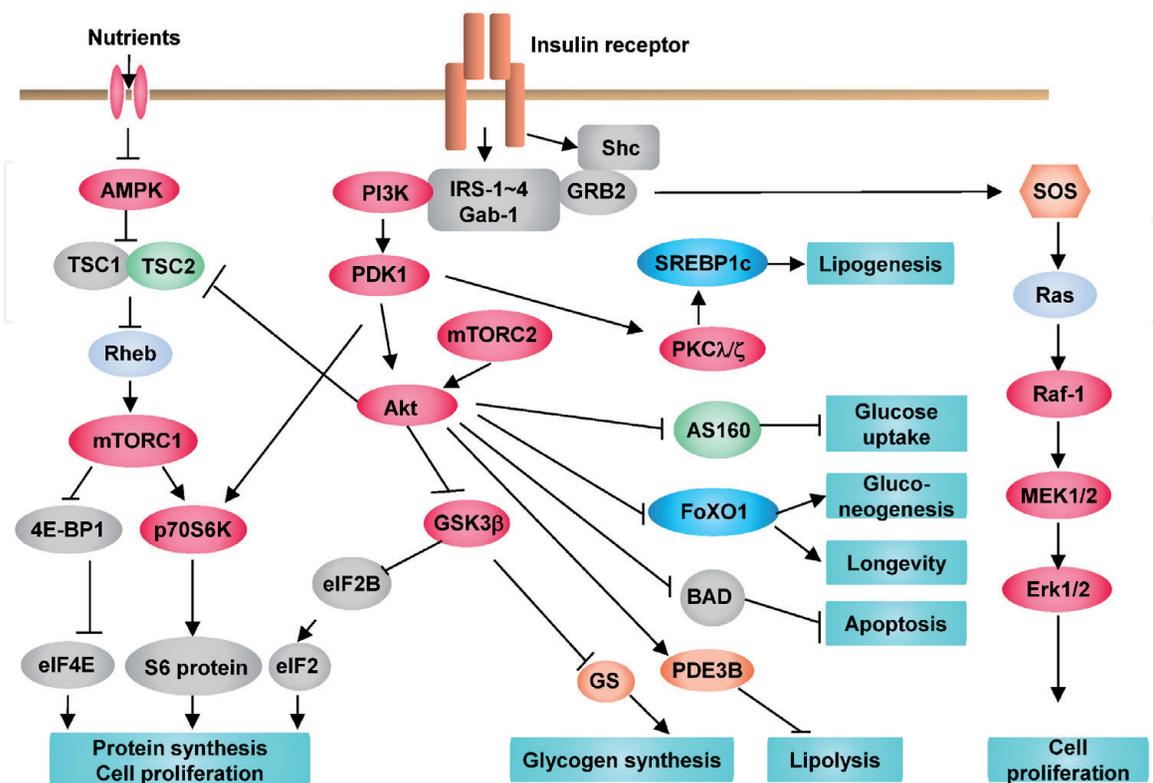


Figure 1. Insulin signaling pathways (adapted from [7]).

turn causes inhibitory phosphorylation of insulin receptor, IRSs, and Akt [8, 9]. Hyperinsulinemia also down-regulates expression of IRS-2 via suppression of a transcription factor, FoxO1 (forkhead box protein O1), in the liver, contributing to the induction of insulin resistance [10, 11].

3. ER stress and ER stress response

3.1 Overview of ER stress response cascade

The ER is an organelle involved in synthesis of secretory proteins and membrane proteins. In the ER, unfolded proteins, immediately after translation and entrance into the organelle, are matured through modification, such as folding, formation of disulfide bonds, and initiation of glycosylation. Under ER stress, in which unfolded or misfolded proteins accumulate in the ER due to increased protein synthesis or chaperone dysfunction, various kinds of ER stress response are induced, and some of them are cytoprotective and others are cytotoxic [12].

Among the numerous molecules involved in ER stress response, also called UPR (unfolded protein response), BiP (binding immunoglobulin protein), also known as GRP78 (glucose-regulated protein 78), is a chaperone with an ATPase domain, which plays pivotal roles in ER stress response mainly via interaction with ERdjs (ER-localized DnaJ family members) [13]. BiP binds to unfolded or misfolded proteins in the ER and promotes folding by consuming ATP. Moreover, BiP binds to ER stress sensor molecules, IRE1-alpha (inositol-requiring enzyme 1 alpha), ATF6 (activating transcription factor 6), and PERK (PKR-like endoplasmic reticulum kinase), and prevent them from activation. Under ER stress, however, BiP is mainly engaged in increased unfolded or misfolded proteins and dissociates from the ER stress sensors, resulting in phosphorylation of IRE1-alpha and PERK, as well as cleavage of ATF6 followed by nuclear translocation to the nucleus [12, 14].

It is well known that phosphorylated IRE1-alpha splices Xbp1 (X-box binding protein 1) mRNA [15]. XBP-1 s protein induces chaperones, including BiP and XBP-1 s itself, as a transcription factor by binding to motifs called ERSEs (ER stress response elements). XBP-1 s also promotes ERAD (ER-associated degradation) by binding to motifs called UPRs (UPR response elements), and attenuates translation via mRNA degradation. nATF6 (nuclear ATF6) also works as a transcription factor to induce chaperones by binding to ERSEs. Phosphorylated PERK phosphorylates eIF2 alpha (eukaryotic initiation factor-2 alpha), which suppresses translation and lowers protein loading. Overall, these responses are protective against ER stress, by suppressing protein synthesis, inducing chaperones, and promoting protein degradation.

Sustained ER stress is, however, known to induce rather cytotoxic responses. Phosphorylated IRE1-alpha activates JNK, resulting in inflammation, oxidative stress and apoptosis. Phosphorylated eIF-2 alpha also induces CHOP (CCAAT-enhancer-binding protein homologous protein), a transcription factor involved in apoptosis, as well as oxidative stress and inflammation, via another transcription factor, ATF4 [12, 14].

It is difficult to detect unfolded/misfolded proteins in the ER of mammals directly, but activation of the upstream ER stress sensors is considered to be a good marker to reflect ER stress. Activation or expression of the downstream molecules involved in ER stress response are also frequently used as ER stress markers, but we are going to discuss the discrepancy between the upstream sensors and the downstream effectors, which we call ER stress response failure, in subsections below (Figure 2).

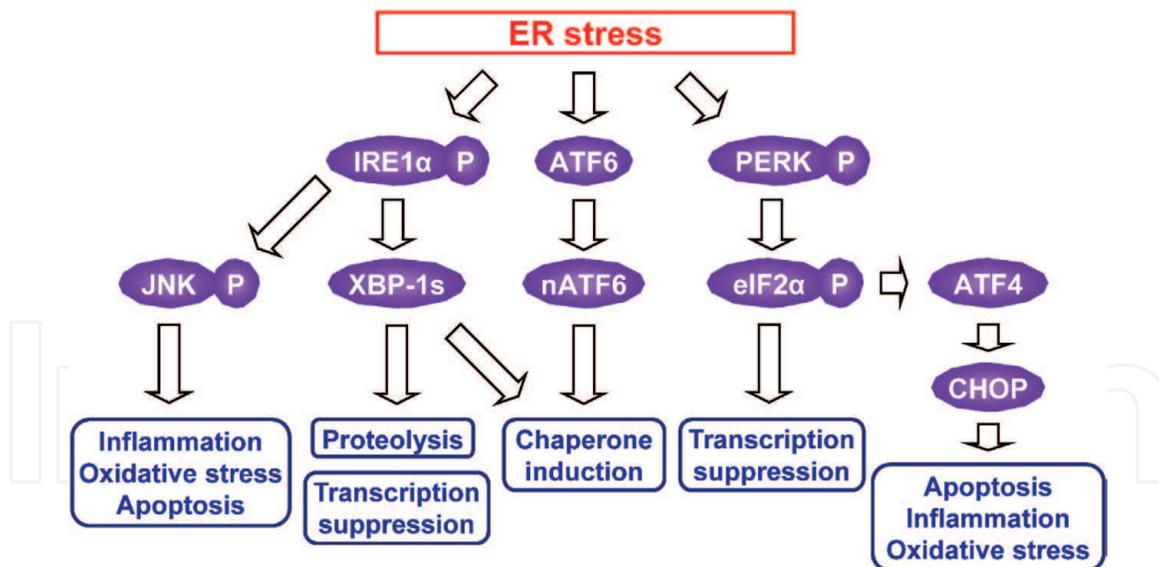


Figure 2.
Schematic description of the cascade of ER stress response.

3.2 ER stress and metabolic disorders

In the field of metabolism, ER stress causes metabolic disorders in various tissues and, in the liver, ER stress is considered to be involved in the development of insulin resistance and fatty liver disease [16]. It was first reported that ER stress markers were enhanced in the liver of mouse models of obesity and diabetes [17, 18]. Systemic Xbp1 knockout mice are a well-known model of impaired ER stress response, which shows elevated ER stress, impaired insulin signaling, and glucose intolerance [17]. Moreover, administration of chemical chaperones improves not only insulin resistance and hyperglycemia but also fatty liver [19]. Similarly, suppressed activation of the PERK branch of the ER stress response cascade, by dephosphorylation of eIF2 alpha, also improves hepatosteatosis as well as glucose tolerance [20]. Thus generally, impaired responses to chronic ER stress or excessive chronic ER stress in the liver are considered to result in hepatic insulin resistance and fatty liver disease, although these phenotypes were not necessarily replicated in other models [21, 22], and XBP-1 s protein was also reported to up-regulate lipogenic genes [23].

However, some years later, ER stress response was reported to be suppressed, contrary to the earlier reports, and a controversy was thus raised about whether ER stress and ER stress response are enhanced or suppressed in obesity and diabetes. Activity of nATF6 is suppressed in the liver of mouse models of obesity and diabetes [24]. Moreover, binding with p85, one of the key downstream molecules of insulin signaling, is required for XBP-1 s protein to be translocated to the nucleus and exert its activity as a transcription factor in the liver. In model mice of obesity and diabetes, however, insulin-mediated nuclear translocation of XBP-1 s protein is impaired due to insulin resistance [25, 26]. A similar insulin signaling-mediated nuclear translocation of XBP-1 s protein was recently reported in other tissues as well [27]. Interestingly, XBP-1 s protein regulates gluconeogenesis rather directly, via ubiquitination and consequent proteasome-mediated degradation of FoxO1, a transcription factor involved in the induction of gluconeogenic enzymes in the liver [28] (**Figure 3**).

Taken together, insulin signaling appears not only to promote protein synthesis, but also to be involved in quality control of synthesized proteins. Moreover, XBP-1 s is a multi-talented molecule which is closely associated with regulation of not only ER stress response but also glucose and lipid metabolism.

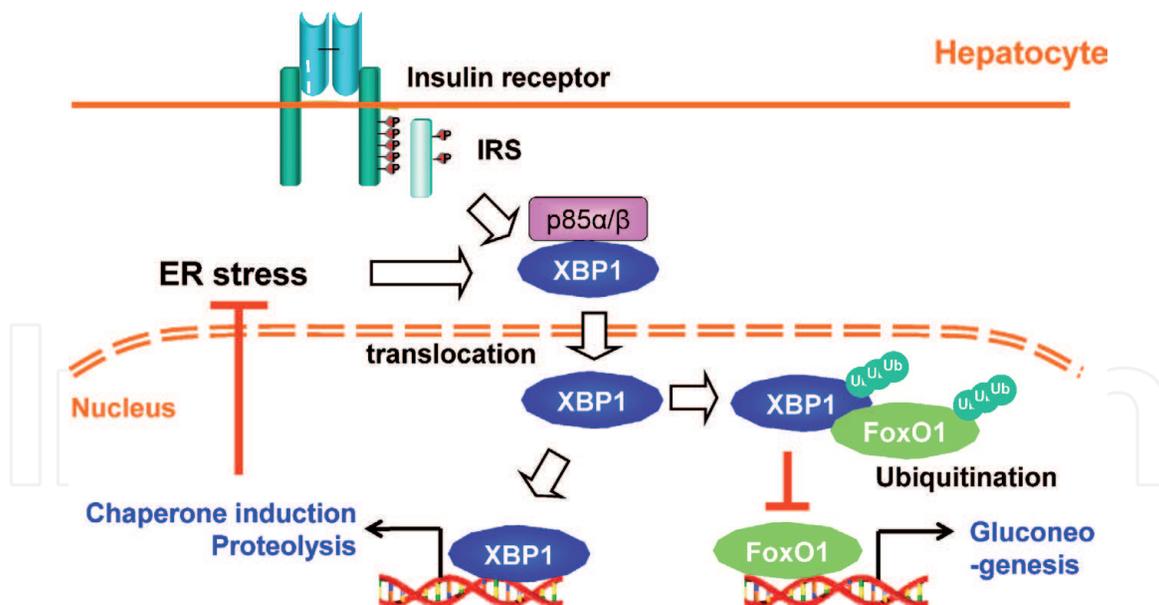


Figure 3.
XBP-1s protein in the regulation of glucose metabolism: insulin-mediated nuclear translocation and regulation of gluconeogenesis.

3.3 ER stress in the liver and diseases in humans

In humans, some ER stress markers are known to be affected by insulin resistance and nonalcoholic steatohepatitis (NASH). NASH is associated with phosphorylation of JNK and lower XBP-1 s protein levels [29]. Expression of sXBP1 and BiP mRNA is not correlated with insulin resistance [30], but is lowered by gastric bypass surgery [31]. We and colleagues previously reported that IRS-1 expression in the liver is negatively correlated with fibrosis [32], suggesting the protective role of insulin signaling against the development of NASH. These reports, however, did not distinguish ER stress and ER stress response or NASH in diabetic patients and NASH in non-diabetic patients.

4. Roles of Sdf2l1 in the regulation of ER stress and metabolism

4.1 Feeding induces ER stress response in the liver

Recently, we reported that a chaperone, Sdf2l1 (stromal cell-derived factor 2 like 1), plays crucial roles in the termination of feeding-induced ER stress in the liver and consequently in the maintenance of glucose and lipid metabolism. We propose that ER stress response failure, including suppressed induction of Sdf2l1 by XBP-1 s, is a key link between insulin resistance and steatohepatitis comorbid with diabetes [33].

Our first finding was that ER stress is induced transiently during feeding in the liver, based on the microarray data using murine liver samples comparing the fasting and refeeding conditions in the public domain [34]. We were particularly interested in Sdf2l1 among the genes highly up-regulated by refeeding, which showed a large increase in expression. Sdf2l1 had been reported to be induced by ER stress [35], and to function as a component of the ER chaperone complex including BiP [36–39]. Besides, the orthologs in yeast, Pmt1p and Pmt2p, are O-mannosyltransferases and known to enhance ubiquitination of unfolded proteins as an initiation of ERAD [40–42]. Little is known, however, of roles of Sdf2l1 in the regulation of glucose and lipid metabolism.

Indeed, the cascade of ER stress response is activated during feeding in the liver: phosphorylation, expression, and nuclear localization of the downstream ER stress marker proteins, as well as expression of ER stress marker genes, are elevated (**Figure 4**) [33].

Therefore, although major attention had been focused on the chronic and pathophysiological aspects of ER stress and ER stress response in the field of metabolism, transient ER stress and consequent ER stress response (just for a few hours) are induced in the liver by the physiological stimulation of feeding, or eating, even in lean nondiabetic mice. Such induction of ER stress during feeding is attributed to protein intake and insulin signaling [33], both of which reach the liver during feeding and promote protein synthesis [3, 5, 43].

4.2 Regulation and function of Sdf2l1 as an ER stress response

We explored the regulatory mechanism underlying the induction of Sdf2l1, and found that Sdf2l1, as well as BiP, is regulated by transcription factors, XBP-1 s and nATF6 by not only chemically induced ER stress but also refeeding in the liver. XBP-1 s and nATF6 binds to an 11-bp motif responsible for the induction of Sdf2l1 upstream in the promotor region [33], which is similar to ERSEs targeted by XBP-1 s and nATF6 with nuclear factor Y as a co-factor [12].

We further explored the function of Sdf2l1 in ER stress response, and found that knocking down of Sdf2l1 leads to accumulation of exogenously expressed Ins2^{C96Y}, a mutant insulin found in Akita mice as a model of misfolded protein degraded by ERAD [44], showing that Sdf2l1 modulates ER stress via regulating ERAD. Although Sdf2l1 had been known to interact with BiP [36–38], knocking down of BiP did not affect such accumulation, suggesting the existence of some other counterparts of Sdf2l1. Then, based on the results of mass spectrometric analysis of microsomal fractions, we focused on TMED10 (transmembrane emp24-like trafficking protein 10), a membrane protein known to regulate protein transportation from the ER to the Golgi apparatus [45]. Indeed, knocking down of either Sdf2l1 or TMED10 results in increased accumulation of misfolded protein and enhanced ER stress, showing that TMED10 is the major counterpart of Sdf2l1 to regulate ERAD and consequently ER stress. Interestingly, in yeast, p24, the ortholog of TMED10, interacts with Pmt1/2p and promotes ER export of unfolded proteins for ERAD

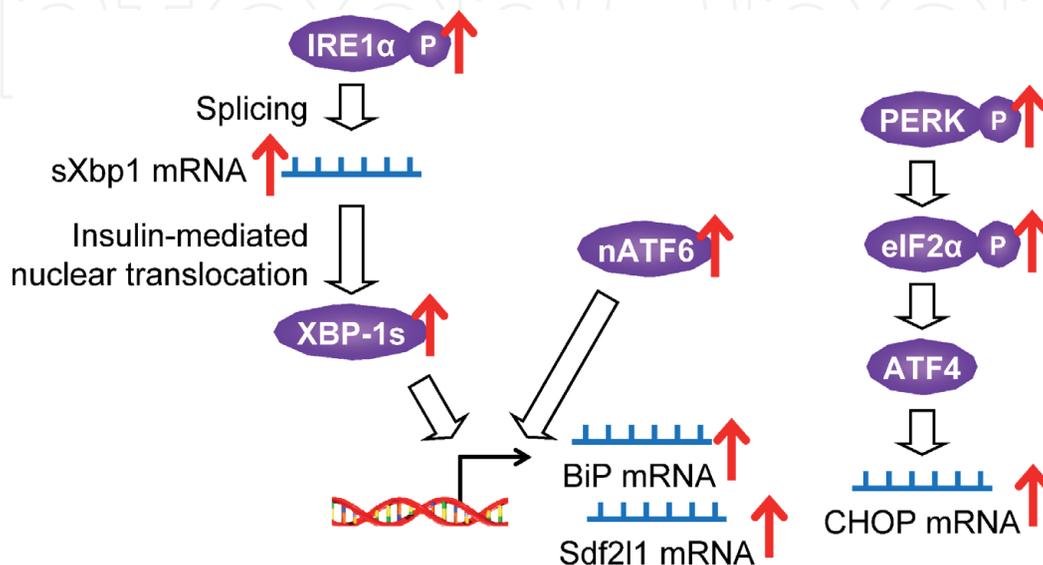


Figure 4. Schematic description of the ER stress response cascade in the liver during feeding (adapted from [33]).

[41], and now the orthologs in mice turns out to interact with each other to regulate ERAD to cope with ER stress [33].

4.3 Sdf2l1 modulates ER stress response and metabolism

We then assessed the physiological and pathophysiological roles of Sdf2l1 *in vivo*. Adenovirus-mediated knocking down and knocking out of Sdf2l1 specifically in the liver of adult mice both result in enhanced ER stress during refeeding, impaired insulin signaling in the liver, systemic insulin resistance, glucose intolerance, and markedly increased triglyceride contents in the liver.

Thus, impaired induction of Sdf2l1 results in sustained ER stress, leading to insulin resistance and increased triglyceride contents, even with a normal-chow diet, indicating that dysregulation of ER stress by suppression of Sdf2l1 is a causal factor of metabolic disorders. Together with the previous reports showing that ablation of key molecules in ER stress response links impaired glucose and lipid metabolism in mice fed on a high-fat diet or a high-fructose diet [17, 21, 22], our data strongly suggest that an appropriate transient response to ER stress is induced physiologically during feeding, or eating, and terminated by Sdf2l1, and that this process may be important for the maintenance of nutrient homeostasis [33].

4.4 Impaired ER stress response in obesity and diabetes

Then we explored the roles of ER stress response in the development of insulin resistance and fatty liver in obesity and diabetes. **Figure 5** summarizes the changes in the ER stress response cascade observed in a mouse model, *db/db* mice. The ER stress sensors are activated, suggesting excessive ER stress in the liver possibly due to hyperinsulinemia and over-nutrition. However, downstream molecules of the cascade that are expected to cope with ER stress are suppressed in expression or insufficiently activated. Among those, Sdf2l1 is highly down-regulated, and chromatin immunoprecipitation (ChIP) assay revealed that the down-regulation of Sdf2l1 is attributed to suppressed activity of XBP-1 s, not of ATF6 [33], presumably due to the decreased insulin action to promote the translocation of XBP-1 s to the nucleus by binding to p85 [25, 26].

We call it ER stress ‘response failure’, which results in further excessive ER stress, forming a vicious cycle. It is known that activation of the ER stress sensors

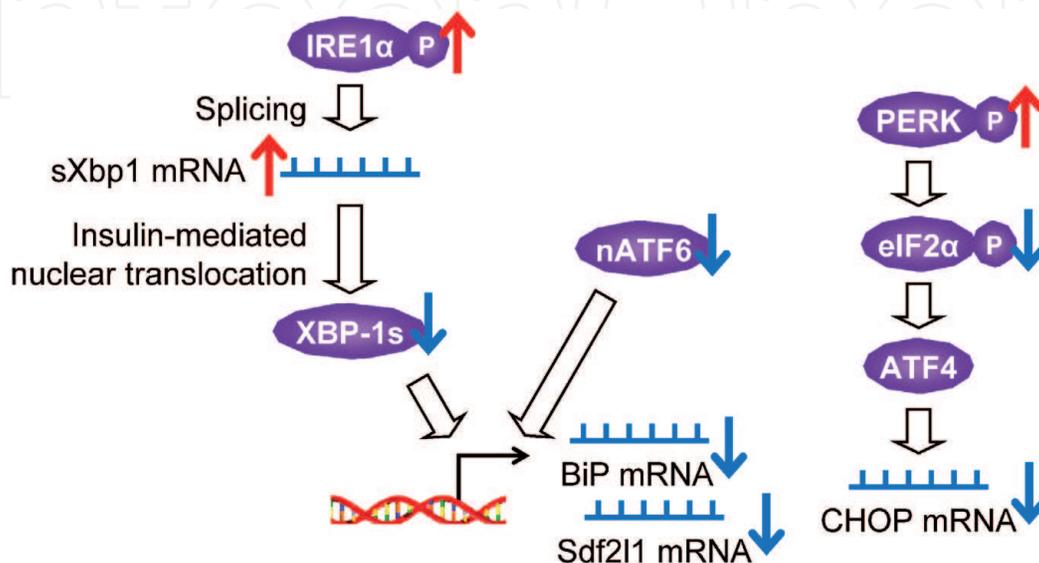


Figure 5. Schematic description of the ER stress response cascade in the liver in obesity and diabetes (adapted from [33]).

is attenuated during prolonged ER stress, resulting in only insufficient activation or induction of downstream molecules involved in ER stress response [46]. Suppression of the whole cascade of ER stress response might be called ER stress ‘sensing failure’, which draws clear contrast with ER stress ‘response failure’ [33], and this novel concept is now gaining publicity [47].

In order to rescue ER stress response failure, over-expression of the upstream XBP-1 s protein does not show full recovery of expression of downstream chaperones and consequently insulin resistance. On the other hand, restoration of suppressed expression of a downstream chaperone, Sdf2l1, does improve insulin signaling in the liver, systemic insulin resistance, glucose intolerance, and fatty liver. Moreover, larger beneficial effects come from co-restoration of Sdf2l1 and BiP, and in accordance with the findings *in vitro*, we conclude that Sdf2l1 improves insulin sensitivity independently of BiP, at least in part [33].

4.5 ER stress and ER stress response in humans

Lastly, we assessed whether impaired ER stress response could be associated with progression of human diseases by examining data from male subjects with suspected NAFLD (nonalcoholic fatty liver disease) who underwent liver biopsy after oral glucose tolerance test early in the morning, partially mimicking the fed state. In diabetic subjects, expression of the upstream sXBP1 mRNA is elevated in subjects with insulin resistance, but the downstream-to-upstream ratio, the SDF2L1/sXBP1 ratio, is lower in subjects with insulin resistance. Similarly, in those with diabetes, sXBP1 is positively, but the SDF2L1/sXBP1 ratio is negatively, correlated with stage or fibrosis of NASH. These changes and correlations are not observed in nondiabetic subjects, showing that impaired response to ER stress, as well as enhanced ER stress, are associated with the progression of insulin resistance and steatohepatitis, which is unique to patients with diabetes (**Table 1**) [33].

In the ‘two-hit hypothesis’ on the development of NASH, accumulation of lipids or steatosis is promoted by the first ‘hit’, whereas the further progression to steatohepatitis requires the presence of the second ‘hit(s)’ [48]. Given that ER stress is one of the major potential second hits (and others are inflammation, oxidative stress, autophagy failure, and mitochondria dysfunction), our data show that not only ER stress but also ER stress response failure serve as the second hits in the progression from NAFLD to NASH. Moreover, insulin resistance is one of the major potential first hits, but diabetes is a disease in which insulin resistance fails to be compensated and insulin action is impaired. Decompensated insulin resistance leads to insufficient induction of ER stress response via suppressed nuclear translocation of XBP-1 s protein to the nucleus [25, 26]. Thus, our data show that insulin-mediated nuclear translocation of XBP-1 s protein links the first and second hits, and the SDF2L1/sXBP1 ratio is a promising biomarker [33]. It is also implied that mechanisms underlying NASH in diabetic patients and those underlying NASH in non-diabetic patients could be different and should be elucidated separately (**Figure 6**).

| | Insulin resistance | Stage (fibrosis) |
|--|--------------------|-----------------------|
| sXBP1 mRNA (upstream) | Elevated | Positively correlated |
| SDF2L1/sXBP1 mRNA ratio (downstream-to-upstream ratio) | Lowered | Negatively correlated |

Table 1. Summary of ER stress and ER stress response in diabetic patients (adapted from [33]).

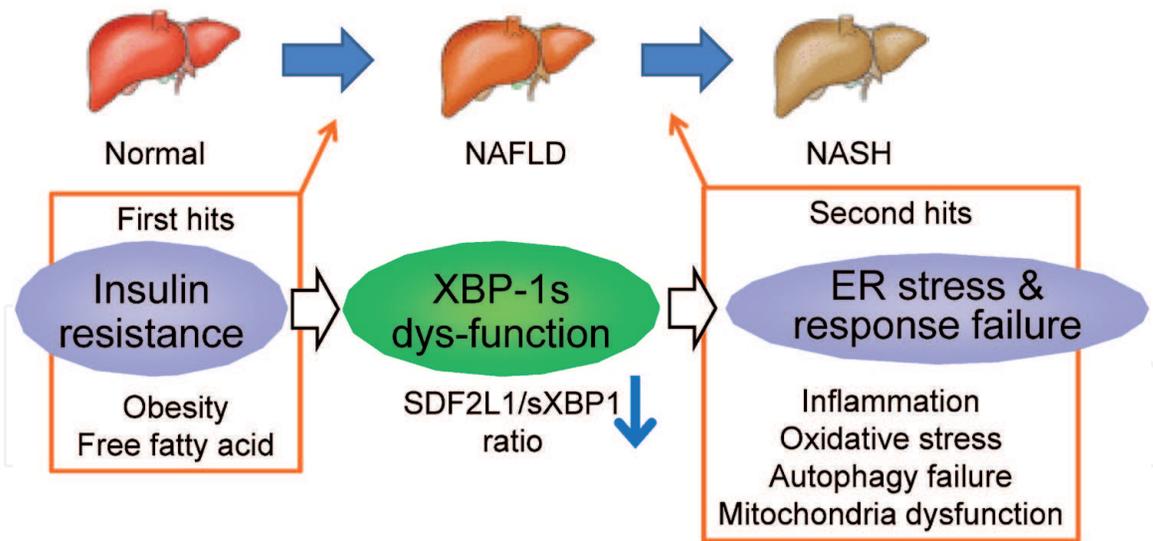


Figure 6. Schematic description of ER stress and ER stress response in the 'two-hit hypothesis' on the development of NASH comorbid with diabetes (adapted from [33]).

These findings could account for the therapeutic effects of insulin sensitizers against not only diabetes but also NASH [49], although insulin signaling itself promotes anabolism of lipids [1]. Moreover, it may be useful to identify the effectors downstream of Sdf2l1 to regulate ERAD more directly, when we consider development of more effective drugs for these diseases by shutting down the vicious cycle due to ER stress response failure [33].

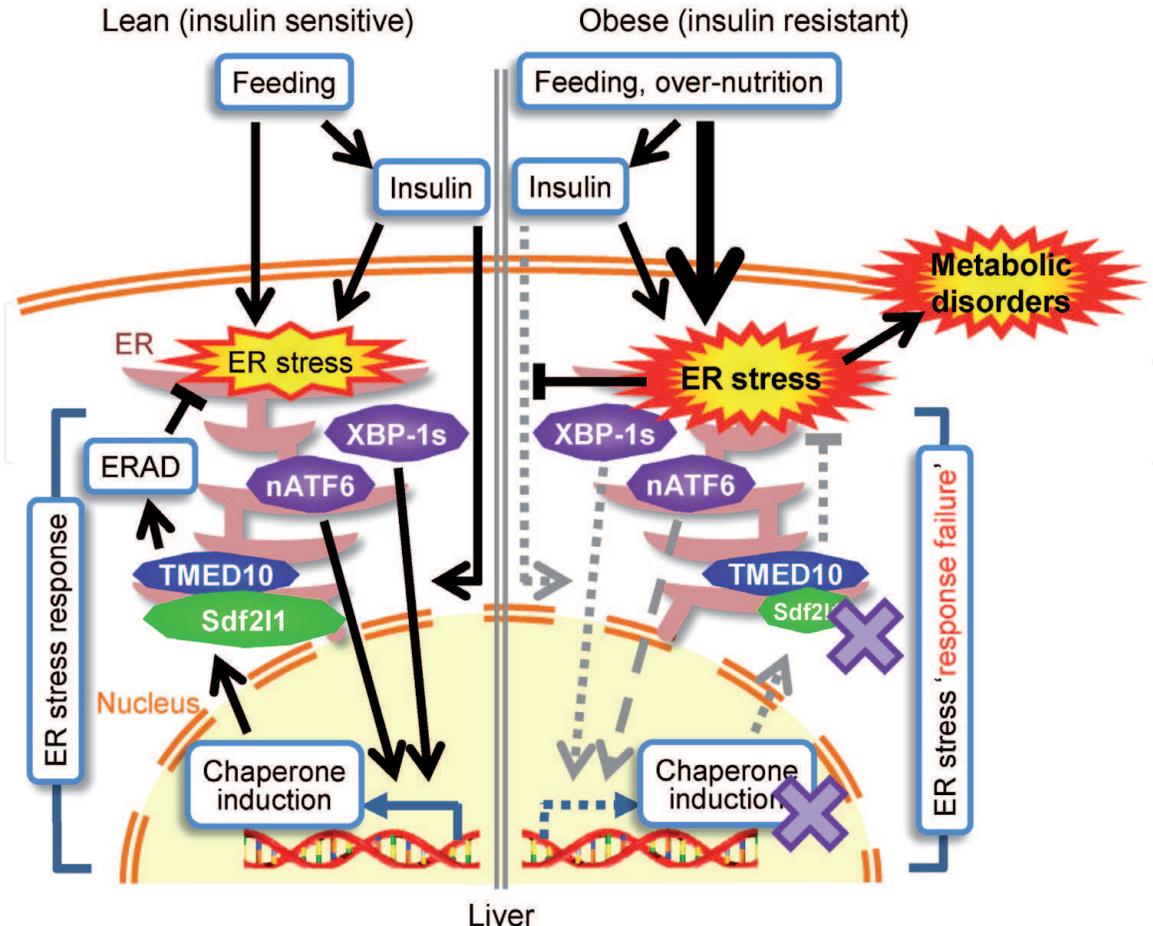


Figure 7. Schematic description of our hypothesis on physiological and pathophysiological roles of Sdf2l1-centered ER stress response in the liver [33].

Recently, a novel concept of metabolic dysfunction-associated fatty liver disease, or MAFLD, was proposed [50, 51], a broader concept than NAFLD, which was proposed in the 1980s [52]. The roles of insulin resistance are considered to be increasingly important [53], and ER stress response failure is expected to contribute also to the development of steatohepatitis in patients with diabetes and MAFLD.

Most recently, Fib-4 index, a marker of hepatic fibrosis, was reported to be a good prognostic factor for the development of hepatocellular carcinoma in diabetic patients, in a nationwide survey in Japan [54]. Given that our data show that ER stress and ER stress response failure are associated with hepatic fibrosis, improvement of ER stress and ER stress response failure might be protective against carcinogenesis as well.

Overall, feeding, or eating, induces physiological and transient ER stress in the liver, and induced Sdf2l1 appropriately terminates ER stress, in cooperation with TMED10, and contributes to normal glucose and lipid metabolism. In obesity and diabetes, impaired ER stress termination signals, including the down-regulation of Sdf2l1 that is caused by decreased insulin signaling, sustains ER stress and exacerbates insulin resistance, creating a vicious cycle. Thus, Sdf2l1 is expected to be a therapeutic target and a sensitive biomarker in obesity-associated diseases (**Figure 7**).

5. Conclusions

We reveal that eating induces physiological and transient ER stress and ER stress response, including up-regulation of Sdf2l1, in the liver. In obesity and diabetes, however, ER stress response failure, including down-regulation of Sdf2l1, results in sustained ER stress, which links insulin resistance and the development of steatohepatitis comorbid with diabetes.

Acknowledgements

We thank the co-workers, especially Dr. Naoto Kubota (The University of Tokyo), Prof. Kazuyuki Tobe (The University of Toyama), Prof. Kazuhiko Koike (The University of Tokyo), and Prof. Takashi Kadowaki (The University of Tokyo; Toranomon Hospital).

Conflict of interest

The authors declare no conflict of interest.

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