

MINI REVIEW

# Endoplasmic reticulum stress in the pathogenesis of diabetes

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## ABSTRACT

The accumulation of unfolded protein in the endoplasmic reticulum (ER) causes ER stress. Cells activate unfolded protein responses (UPR) to cope with such a stressful situation. Increasing evidence suggests that ER stress is involved in the pathogenesis of diabetes, especially insulin resistance and the impairment of insulin secretion. In addition, several UPR components have been suggested to play a key role in diabetes. In the present review, we summarize and discuss recent knowledge of ER stress regarding the pathogenesis of diabetes.

**Keywords:** *Endoplasmic reticulum stress, diabetes, PERK, ATF6, IRE1, eIF2 $\alpha$ , XBP1, beta cell, pancreas*

## Introduction

Secretory proteins are primarily processed through the ER-Golgi pathway. However, when cells are exposed to stress, immature unfolded protein accumulates in the ER. Such a situation is termed ER stress, and cells show several responses to cope with this. It has been reported that cells activate an unfolded protein response (UPR) to cope with such stress.<sup>1-3</sup> Several UPR components localized in the ER have been reported such as: inositol-requiring enzyme-1 (IRE1), activating transcription factor 6 (ATF6), and double stranded RNA-activated protein kinase (PKR)-like ER kinase (PERK). The activation of IRE1 causes X-box binding protein 1 (XBP1) splicing and produces spliced XBP1 (sXBP1).<sup>4,5</sup> The activation of ATF6 increases regulated intramembrane proteolysis (RIP)-mediated cleavage of ATF6, which produces an N-terminal cleaved product of ATF6 (p50ATF6).<sup>6,7</sup> sXBP1 and p50ATF6 function as transcription factors, which induce ER chaperones such as GRP78.<sup>4</sup> GRP78 reduces unfolded protein accumulation in the ER by assisting with protein folding. The PERK branch of UPR induces eIF2 $\alpha$  phosphorylation and reduces translation.<sup>8-10</sup> The inhibition of translation reduces unfolded protein accumulation in the ER. However, when stress exposure is marked and prolonged, cells will activate an apoptotic program.<sup>11</sup> ER stress was reported to be involved in liver insulin resistance and pancreatic  $\beta$ -cell failure in patients with diabetes. In the following section, we briefly summarize and discuss the involvement of ER stress in diabetes.

## ER stress and insulin resistance

Insulin resistance in the liver is one of the mechanisms of the pathogenesis of diabetes. It was reported that obesity-induced insulin resistance is mediated through ER stress in the liver.<sup>12</sup> ER stress in the liver activates the JNK pathway, which subsequently attenuates the insulin signal by phosphorylating the Ser residue of IRS1.<sup>12</sup> On the other hand, the expression of sXBP1 recovered the ER stress-induced impairment of insulin signaling.<sup>12</sup> Therefore, the UPR arm of sXBP1 induction may attenuate insulin resistance. Obesity is one of the major risk factors of diabetes. ER stress is involved in the pathogenesis of leptin resistance<sup>13, 14</sup> as well as insulin resistance. sXBP1 in the pro-opiomelanocortin (POMC) neuron was shown to improve leptin and insulin sensitivity in obesity.<sup>15</sup> Interestingly, sXBP1 expression in the POMC neuron improved hepatic insulin sensitivity.<sup>15</sup> These results suggest that a central sXBP1 may also control peripheral glucose homeostasis. Overall, these observations suggest that ER stress is involved in the pathogenesis of insulin resistance. Furthermore, several UPR components may regulate insulin sensitivity in the presence of diabetes.

## ER stress and pancreatic $\beta$ -cell failure

The failure of insulin-producing pancreatic  $\beta$  cells is the one of the mechanisms of the pathogenesis of diabetes. ER plays a key role in insulin maturation and production in pancreatic  $\beta$  cells. Insulin demand is increased in diabetes, which may result in  $\beta$ -cell overwork. It has been hypothesized that in diabetes, ER overwork in  $\beta$ -cells may cause ER stress due to the

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accumulation of immature pro-insulin in the ER.<sup>16, 17</sup> These conditions may lead to ER stress-dependent apoptosis, possibly resulting in the loss of  $\beta$  cells. Several reports support these possibilities. The targeted disruption of the ER stress-induced apoptotic transcription factor CHOP in the AKITA diabetic mouse model ameliorated diabetes.<sup>18</sup> A progressive loss of  $\beta$  cells is observed in PERK-deficient mice.<sup>19</sup> In humans, PERK mutation was found in patients with Wolcott-Rallison syndrome, which causes neonatal diabetes.<sup>20</sup> Furthermore, the pharmacological inhibition of PERK activation increases insoluble high-molecular-weight pro-insulin in adult pancreatic  $\beta$  cells.<sup>21</sup> Also, the attenuation of eIF2  $\alpha$ , a downstream regulator of PERK signaling, in mouse  $\beta$  cells caused a severe diabetic phenotype.<sup>22</sup> These results suggest that the UPR arm of translational attenuation may play a key role in inhibiting the over-production of immature insulin.

### Concluding remarks

The results indicate that one of the underlying mechanisms of diabetes may be mediated through ER stress. Therefore, ameliorating ER stress may be one of the useful strategies for treating the disease. Indeed, several compounds targeting ER stress were reported to be useful for treating diabetes<sup>23, 24</sup> or leptin resistance.<sup>13, 14, 25</sup> Pathogenesis of diabetes and obesity are also associated with inflammatory conditions. It has been reported that ER stress regulates the immune function.<sup>26-30</sup> Therefore, there are complex underlying mechanisms behind the pathogenesis of diabetes. Further analysis is required to elucidate the pathological mechanisms of diabetes, which may lead to the development of useful drugs against the disease.

### Conflict of interest

None Declared.

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