The Epidermal Growth Factor Receptor
A Missing Link Between Endoplasmic Reticulum Stress and Diabetic Complications?

Tonomori Kobayashi, Satoru Eguchi

The endoplasmic reticulum (ER) is recognized as an organelle in which protein folding, calcium homeostasis, and lipid biosynthesis occur. The ER responds to stresses such as oxidative stress, ischemic insult, and disturbances in calcium homeostasis by upregulating ER chaperones, inhibiting protein translation, and accelerating degradation of unfolded proteins via signaling pathways collectively termed the “unfolded protein responses” (UPRs). Thus, UPRs are considered a form of cellular protection. On ER stress, the ER chaperone immunoglobulin heavy chain–binding protein (also known as HSPA5 or GRP78) binds to unfolded or misfolded proteins and dissociates from 3 well-characterized ER stress sensors, inositol-requiring 1, double-stranded RNA-dependent protein kinase–like ER kinase, and activating transcription factor 6 to initiate the UPR pathways. However, prolonged and excessive ER stress leads to inflammation and cell apoptosis via the UPR pathways.

In addition to the protective roles of the UPR, the literature increasingly suggests that prolonged ER stress and subsequent UPR activation likely contribute to the development and progression of various disease processes, including cardiovascular diseases such as heart failure, ischemic heart diseases, and atherosclerosis. Moreover, recent studies reveal that prolonged ER stress associated with metabolic syndrome leads to persistent UPRs and reduced insulin secretion, invokes oxidative stress and insulin resistance, and activates an apoptotic pathway. Therefore, there is strong scientific, as well as clinical, interest regarding the regulatory mechanisms and therapeutic applications of the UPR pathways associated with cardiovascular diseases.

The "trans"-activation of epidermal growth factor receptor (EGFR) has been proposed recently to act as a central transducer of heterologous signaling systems, such as those activated by angiotensin II, endothelin 1, and oxidative stress, all of which can lead to cardiovascular diseases and chronic kidney diseases. The exact molecular mechanism of EGFR transactivation remains unclear but appears to involve processing of transmembrane EGFR ligand precursors to produce mature growth factors mediated by metalloproteases such as A disintegrin and metalloprotease 17. On transactivation, the EGFR serves as a scaffold for various signaling molecules that promote cell proliferation, migration, and induction of a select set of downstream genes. Pharmacological and genetic approaches that interfere with EGFR transactivation in animal models have demonstrated the critical requirement of EGFR transactivation in cardiac hypertrophy/ fibrosis, vascular neointimal hyperplasia, and renal fibrosis. Interestingly, similar experiments that interfere with EGFR or A disintegrin and metalloprotease 17 also clarified the detrimental roles of the EGFR and A disintegrin and metalloprotease 17 activation in the development of insulin resistance and potentially in diabetic complications.

In this issue of Hypertension, Galán et al9 provide novel insights into the causal relationship between the EGFR activation and ER stress in cardiac fibrosis and microvascular endothelial dysfunction in a mouse model of type 1 diabetes mellitus. They used C57BL/6J mice injected with streptozotocin only or in combination with EGFR kinase inhibitor (AG1478), ER stress inhibitor (Tudca), or insulin to evaluate cardiac fibrosis and vascular function of the mesentery, as well as ER stress of the tissues and systemic metabolic/diabetic parameters. Their results indicate that inhibition of EGFR kinase activity decreases ER stress markers in both tissues, suggesting that EGFR activation contributes to the enhanced tissue ER stress associated with a diabetic condition. Importantly, either inhibition of the EGFR activity or ER stress appears to reduce cardiac fibrosis and microvascular dysfunction. These tissue-protective effects are associated with enhanced endothelial NO synthase activation and reduced expression of NADPH oxidase subunits NOX2 and NOX4 in the mesentery and reduced fibrotic markers (collagen type I and plasminogen activator inhibitor 1) in the heart. The study is scientifically novel, because this is the first study to connect EGFR and ER stress as important signal transduction events in diabetic tissues. The study may also be clinically relevant because it suggests the EGFR as one of the critical therapeutic targets for preventing cardiac remodeling and microvascular complications associated with diabetes mellitus.

Although the data of Galán et al9 support the upstream role of EGFR activation in ER stress and subsequent induction of oxidative stress in this model of type 1 diabetes mellitus, one should be cautious about applying this interpretation to a diabetic condition. According to a majority of publications, the oxidative stress seems to be a critical upstream "contributor" to the ER stress observed in diabetes mellitus/metabolic
EGFR, in that suppression of EGFR activity improves hyper-adipose tissue phenotype changes. The type 1 diabetes mechanism involves suppression of macrophage activation and responses resulting in systemic insulin resistance. This mechanism is illustrated with solid lines, and other potential interplays are included with dashed lines. A potential detrimental feed-forward loop is highlighted with a circle.

In conclusion, this study is the first to report the contribution of the EGFR to ER stress under diabetic conditions and to suggest the receptor as one of the critical therapeutic targets for preventing cardiac remodeling and microvascular complications associated with diabetes mellitus. However, information is still limited regarding the roles and their potential interactions of the EGFR cascade and ER stress in cardiovascular diseases, including hypertension. Further elucidation of the interactions between EGFR and ER stress by using tissue-specific gene manipulation in mice, large animal models, and human samples is desired and will provide us with a better understanding of the mechanism responsible for the progression of cardiovascular diseases.

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**Disclosures**
None.

**References**

**Figure.** The hypothetical mechanism by which endoplasmic reticulum (ER) stress is upregulated and participates in cardiac fibrosis and endothelial dysfunction under a diabetic condition. The cascade supported by the findings of Galán et al is illustrated with solid lines, and other potential interplays are included with dashed lines. A potential detrimental feed-forward loop is highlighted with a circle.

**Diabetes Hyperglycemia**

**Ang II**

**EGFR**

**ER stress**

**UPR**

**ROS** (NOX2/NOX4)

**Fibrotic gene (col 1/PAI-1)**

**eNOS inhibition**

**Cardiac Fibrosis**

**Endothelial Dysfunction**

**Disclosures**
None.

**References**
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