Editorial Commentary

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

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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.1

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.2 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.3 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 17.4 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 neo-intimal hyperplasia, and renal fibrosis.5,6 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.7,8

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.9 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...
syndrome, atherosclerosis, and other cardiovascular dysfunctions, as opposed to the authors’ conclusion. However, because a feed-forward loop of multicomponent mechanisms likely enhances ER stress under these disease conditions (Figure), the authors’ findings are very attractive and point out that EGFR activation is one of the critical steps to accelerate ER stress.

The downstream consequences of the enhanced ER stress generally involve UPRs, including the UPR-specific gene programs, as well as enhancements of the nuclear factor-κB and c-Jun N-terminal kinase cascades. Although it remains undetermined whether any of these downstream signaling events of UPR regulate profibrotic conditions and endothelial NO synthase inactivation, it is reasonable to speculate the involvements of nuclear factor-κB and c-Jun N-terminal kinase. In addition, the molecular mechanism of EGFR activation in heart and microvessel under type 1 diabetes mellitus remains unclear but may involve high-glucose states, reactive oxygen species, and angiotensin II. Enhanced renin-angiotensin system and overproduction of reactive oxygen species are well recognized in diabetic conditions, and both angiotensin II and reactive oxygen species are capable of activating EGFR, as referenced above. Moreover, high-glucose condition has been shown recently to activate EGFR via a disintegrin and metalloprotease 17–dependent heparin-binding endothelial growth factor–like growth factor generation in cultured mesangial cells.

In a type 2 diabetes mellitus model, it has been reported that the EGFR contributes to adipose tissue inflammatory responses resulting in systemic insulin resistance. This mechanism involves suppression of macrophage activation and adipose tissue phenotype changes. The type 1 diabetes mellitus model of Galán et al in part confirms this role of the EGFR, in that suppression of EGFR activity improves hyperglycemic conditions. Therefore, in metabolic syndrome/obesity/type 2 diabetes mellitus, EGFR inhibition may improve systemic insulin resistance and provide tissue protection from diabetic complications. The EGFR inhibition may also protect islet from ER stress-induced β-cell dysfunction.

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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