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The Role of Epidermal Growth Factor Receptor in Diabetes-Induced Cardiac Dysfunction

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ABSTRACT

The incidence of diabetes mellitus is increasing rapidly and set to reach near epidemic proportions with the latest estimates suggesting that by 2030 there will be over 550 million people with this debilitating disease. Cardiovascular complications and dysfunctions are three- to eight-folds more likely in diabetic patients and are major causes of increased mortality. The exact underlying mechanisms for the development of complications of the diabetic heart are poorly understood and may involve multiple signaling pathways that are affected by hyperglycemia. This focused article reviews the recent evidence for a possible dual role of epidermal growth factor receptor signaling in diabetes-induced cardiac dysfunction.

Introduction

The incidence of diabetes mellitus is increasing rapidly and set to reach near epidemic proportions worldwide.[1,2] From the current global count of about 375 million people with diabetes, the latest estimates suggest that this is expected to rise to over 550 million by 2030.[1] Diabetes and/or the associated hyperglycemia leads to the development of cardiovascular complications such as ischemic heart disease, myocardial infarction and cardiac myopathy that collectively are three to eight-folds more likely in diabetic patients and are major causes of mortality. Cardiac complications in diabetes may arise from the associated micro- and macro-vascular dysfunctions such as atherosclerosis and coronary artery disease or from a direct effect on the cardiac muscle as is indicated in cardiac myopathy.[3] Diabetic cardiomyopathy patients generally undergo a hidden subclinical phase of cellular structural remodeling that leads to compromised diastolic function, then systolic dysfunction and eventually to heart failure.[3] The exact underlying mechanisms for the development of complications of the diabetic heart are poorly understood and may involve multiple signaling pathways that are affected by hyperglycemia.[4] This focused article, reviews the recent mechanistic studies on the role of epidermal growth factor receptor (EGFR) signaling in diabetes-induced cardiac dysfunction.

Overview of the EGFR family

The EGFR family of receptor tyrosine kinases comprises four members: EGFR (erbB1), EGFR2 (erbB2, Neu, HER2), EGFR3 (erbB3) and EGFR4 (erbB4). Of these, EGFR is a 175-kDa glycoprotein that can be activated by several different ligands including epidermal growth factor (EGF), heparin-binding EGF (HB-EGF), amphiregulin and betacellulin[5] to induce either homodimerization or heterodimerization with other EGFR family members, most notably erbB2 which is the preferred partner for dimerization. The erbB2 receptor does not have a known ligand and therefore relies on dimerization with other EGFR family members for signaling. Dimerization of erbBs results in subsequent activation of several downstream effector proteins including Ras, Raf, extracellular-signal-regulated kinase 1/2 (ERK1/2), p38 mitogen activated protein (MAP) kinase and phosphatidylinositol 3 (PI-3) kinase/AKT (protein kinase B) pathways.[5,6] Alternatively, EGFR transactivation can occur via G-protein coupled receptors (GPCR), such as angiotensin II (Ang II), aldosterone and endothelin.[7,8]

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The EGFR family of receptors represents important signaling cascades that regulate cell growth, differentiation, migration, survival and apoptosis.[6]

The EGFR family of receptor tyrosine kinases is almost unique amongst receptor systems in that it serves as a molecular integration site and thus appears to be a central transducer of signals emanating from multiple types of stimuli including peptide ligands, metal ions, ultraviolet and gamma radiation, osmotic shock, membrane depolarization, and oxidative radicals.[9] Acting as a signaling relay for such a wide range of stimuli gives rise to the concept that the EGFR acts as a functional keystone in "higher-order" complex systems that may underpin multifactorial global somatic actions. Indeed the EGFR tyrosine kinase signaling pathway is known to be an important signaling hub in regulating cell growth, proliferation, migration and differentiation in normal and pathological states such as cancer [6] and diabetes-induced cardiovascular dysfunction.[10-12]

EGFR acts as "good guy" and "bad guy" in diabetic heart

In diabetes, EGFR may have a beneficial (good guy) role for example in regulating pancreas beta-cell mass where even a partial tissue-specific attenuation of EGFR signaling in the islets leads to the markedly reduced beta-cell proliferation and subsequent development of diabetes during the first weeks after birth.[13] Alternatively even in the same organ, EGFR can have a detrimental (bad guy) role in mediating pathologies such as pancreatic fibrosis.[14] EGFR pathways are also detrimental in mediating diabetes-induced kidney damage[15-17] and vascular dysfunction.[10,18-21] In experimental diabetes, upregulation of EGFR signaling as a result of increased gene expression and elevated receptor tyrosine kinase (RTK) activity leads to vascular dysfunction in several tissues and is therefore, detrimental in the micro and microvasculature of both type 1 and type 2 diabetes.[10,18-22] Recent evidence suggests that a dual (good-guy/bad-guy) role of EGFR might also exist in the heart.

In the non-diabetic heart, a large body of evidence suggests that EGFR family of receptors is good guy. At least 3 out of the 4 erbB receptors, EGFR, erbB2, and erbB4, are detected in the adult human and rodent hearts[12,23-25] where they play an essential role in cardiac development during embryogenesis and might also be survival factors in the adult myocardium.[26,27] In the failing heart, the expression and activity of erbB2 and erbB4 receptors are depressed[28,29] and signaling via erbB2/erbB4 heterodimers appears critical for adult cardiomyocyte survival.[13,24,30,31] The importance of erbB receptor signaling in normal cardiac physiology was highlighted further with the unexpected and fatal cardiomyopathy reported in breast cancer patients treated with monoclonal antibody targeting erbB2.[32,33] Subsequent experiments in mouse models with ventricular-specific deletions of erbBs also resulted in cardiac-mediated toxicity and death.[34-36] In addition, evidence for the essential role of EGFR in maintenance of cardiac function was provided in C57BL/6J mice where chronic treatment with receptor antagonists leads to cardiac dysfunction.[37] Signaling through EGFR was also shown to provide cardioprotection against ischemic injury[38] and appears important in cardiac preconditioning (PC).[39,40] Inhibition of EGFR with AG1478, a selective antagonist, attenuated the beneficial effects of cardiac preconditioning (PC) to ischemia-reperfusion injury implying that activation of EGFR signaling during PC is important for improving recovery following ischemia-reperfusion (I/R) injury.[40]

A recent study shows that EGFR signaling is also beneficial for the recovery of diabetic heart from ischemia-reperfusion injury.[10] EGFR and erbB2 levels were reduced in diabetic rat hearts that led to worsening cardiac recovery from ischemia-reperfusion injury. Chronic *in vivo* treatment with receptor antagonists led to worsening recovery whereas acute activation of EGFR/erbB2 signaling with a receptor ligand improved recovery of diabetic hearts (significantly more than normal hearts) from ischemic injury implying that EGFR/erbB2 survival pathway may be more important in diabetes than that even in normal hearts.[10] The authors also noted that activation of the EGFR/erbB2 pathway by giving EGF after ischemia, rather than before ischemia, was equally or more effective in improving cardiac recovery following I/R[10] implying that EGF administration even after an ischemic event may represent a novel therapeutic strategy for improving cardiac recovery in patients with diabetes.

This report also suggested that attenuation of EGFR signaling by existing therapies may restrict their efficacy in diabetes-induced cardiac dysfunction.[10] Angiotensin II receptor blockers (ARBs) such as Losartan are clinically established cardioprotective agents in the treatment of diabetes-induced end-organ damage. However, since Losartan can also inhibit EGFR transactivation,[7] the authors hypothesized that the existing cardioprotective effects of ARBs might not be optimal and could be improved by preventing their inhibition of the pro-survival EGFR pathway. In diabetic hearts, Akhtar *et al.* showed that Losartan-induced reduction in EGFR phosphorylation was prevented by co-administration of EGF implying that rescuing the EGFR inhibitory effect of AT_1 receptor antagonists by co-treatment with EGF may also represent a novel clinical approach in improving cardiac function in diabetic patients.[10] This approach might also enhance the cardio-protective effects of other members of the renin-angiotensin-aldosterone-system (RAAS) including angiotensin (1-7),

a known counter-regulator of Ang II that not only is beneficial in diabetes-induced cardiac dysfunction[41] but has also been reported to inhibit EGFR transactivation.[11] However, further studies are required to explore this potential therapeutic strategy further.

In contrast to the above studies, EGFR may also be a "bad guy" when it comes to mediating diabetic cardiac hypertrophy, fibrosis and cardiac remodeling.[42-44] EGFR appears to be a central transducer of signals from oxidative-stress stimuli and G-protein coupled receptors agonists from the RAAS system such as Ang II and aldosterone that are known inducers of cardiac myopathy and dysfunction via EGFR transactivation in the diabetic heart. Early studies indicated that Ang II-mediated cardiac hypertrophy and fibrosis occurs via ADAM-mediated shedding of EGFR ligands and transactivation of EGFR in the heart; for reviews see.[7,8,43,44] However, more recent studies suggest that Aldosterone, which can also transactivate EGFR,[45] plays at least a synergistic role in mediating diabetic cardiac myopathy [43]. Both raised Ang II and Aldosterone plasma levels are associated with diabetic patients with cardiac dysfunction.[43,46] These RAAS members can also lead to generation of reactive oxygen species (ROS) and oxidative stress[43,47] via activation of NADPH that is thought to be an important mechanism in the development of cardiac myopathy.[48,49] ROS generation can then lead to endoplasmic reticulum (ER)-stress which involves upregulation of ER chaperone proteins, and accelerated degradation of unfolded proteins via "unfolded protein responses" termed UPRs.[50] Chronic oxidative- and ER- stress leads to diabetic cardiac complications.[50-52] ROS is also known to transactivate EGFR[53] and a recent study in C57bL/6J mice made diabetic with streptozotocin has shown that EGFR plays an important upstream role in inducing ER-stress that leads to cardiac fibrosis since inhibition of either EGFR or ER-stress attenuates the condition.[42]

In summary, there is emerging evidence for the dual role of EGFR signaling in mediating diabetic complication in the heart. EGFR family plays an essential role in cardiac development during embryogenesis and seems to represent a critical survival pathway in cardiac preconditioning and in mediating recovery of cardiac function following ischemic injury in normal and diabetic hearts. On the other hand, EGFR seems to mediate detrimental pathways leading to diabetic cardiac myopathy including those involving ROS, ER-stress and members of RAAS system. Thus any therapeutic strategies involving targeting of this important signaling receptor will require a careful assessment of its full effects in the diabetic heart as well as other organs and tissues, where its differential effects are also observed.

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Competing interests

Authors declare no competing interests.

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