Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 48, No. 7, 2006
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2006.07.005

EDITORIAL COMMENT

Novel—and "Neu"—Therapeutic Possibilities for Heart Failure*

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Adverse effects of pharmacotherapeutics in patients rarely lead to novel therapies in animal models of disease. In this issue of the *Journal*, however, Liu et al. (1) provide a remarkable case of such "bedside-to-bench" research: they demonstrate that neuregulin-1 therapy substantially mitigates heart failure in infarct-, viral-, anthracycline-, and pacing-induced models that employ rodents and dogs—experimental proofs of concept critical for launching human studies. The discovery by Liu et al. (1) derived, in part, from the observation that trastuzumab (Herceptin) therapy for breast cancer engenders cardiomyopathy (2). Why does

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myocardial function deteriorate consequent to treatment with this monoclonal antibody, which targets a receptor tyrosine kinase (RTK) called "neu"—an antibody that reduces expression of and therefore intracellular signaling by neu (also known as ErbB2 or HER2)? And why might we expect myocardial function to resist deterioration, or depressed myocardial function to improve, in response to an agent that activates neu (a "neuregulin")?

The ErbB family of RTKs. Receptor tyrosine kinases are cell surface proteins that regulate many essential cell type-specific functions, particularly cell growth, proliferation, and survival (Fig. 1). The ErbB family of RTKs includes 4 distinct receptors (ErbB1 to ErbB4), each of which shares sequence similarity with a protein encoded by the chicken retroviral oncogene v-erbB (for which this RTK family is named). ErbB2 was originally named "neu" because it was discovered in its oncogene form in rat neuroblastoma cells (3). In homage to history and the importance of ErbB2 in neural tissue, we refer to an important group of proteins that stimulate ErbB2 as the neuregulins. Neuregulins selectively promote heterodimerization between a monomer of ErbB2 and a monomer of either ErbB4 or ErbB3 (4), and appear to be critically important for normal cardiovascular function.

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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ErbBs and cardiac function. Although ErbB2 and ErbB4 are expressed on the surface of cardiomyocytes, neuregulin-1 is released from the surface of endocardial and microvascular endothelial cells (5). In this way, neuregulin-1 is believed to exert a paracrine influence on cardiomyocytes. Genetic deficiency of ErbB2, ErbB4, or neuregulin-1 in mice yields a remarkably congruent phenotype involving a failure of the cardiac ventricle to undergo trabeculation (4). Correlation between depressed myocardial function and depressed myocardial ErbB levels can be made in both adult rodents (6) and human subjects (7). Moreover, recovery of myocardial dysfunction with effective heart failure treatment has been correlated with recovery of myocardial ErbB levels (7). A causal relationship between ErbB2 deficiency and heart failure can be seen in mice with myocardium-specific gene targeting that reduces myocardial ErbB2 expression by ~70%: hearts that develop normally nonetheless develop a dilated cardiomyopathy that mimics human dilated cardiomyopathy in a number of ways (8). Lastly, when trastuzumab is used in breast cancer therapy to reduce ErbB2 signaling, left ventricular dysfunction develops in 13% to 28% of patients, depending on the relative timing of trastuzumab and anthracycline chemotherapy (2). Collectively, these previous data demonstrate that impairing ErbB2 signaling impairs myocardial function. Now we have evidence that the converse is also true: augmenting ErbB2 signaling can improve myocardial function (1).

ErbB signaling reduces cardiomyocyte apoptosis. There is evidence supporting a role for cardiomyocyte apoptosis, or "programmed cell death," in human heart failure and cardiomyopathy (9). By reducing the number of viable cardiomyocytes, apoptosis perpetuates a vicious cycle: ↓ myocardial function→ ↑myocyte mechanical stretch, ↑ neurohumoral activation→ ↑ cardiomyocyte dysfunction, ↑ apoptosis→ ↓ myocardial function. Neuregulin-1 therapy can interrupt this vicious circle (1), quite plausibly by reducing cardiomyocyte apoptosis. Neuregulin-1 promotes hypertrophy and proliferation of adult and embryonic cardiomyocytes, respectively, through activation of ErbB2 and ErbB4, and simultaneously protects cardiomyocytes from apoptosis (5). Conversely, reduction of ErbB2 signaling appears to *augment* cardiomyocyte apoptosis: in vivo, the 70% reduction in cardiomyocyte ErbB2 expression that engenders heart failure in mice also substantially increases apoptosis in cardiomyocytes (8). Moreover, gene therapy with an anti-apoptotic protein ameliorated the heart failure phenotype in these mice (8).

How can signaling initiated by ErbB2 and ErbB4 protect cardiomyocytes from apoptosis? Cardiomyocyte anti-apoptotic ErbB signaling involves activation of at least one other (serine/threonine) kinase, Akt (10,11). Gene deletion studies in mice have demonstrated that a specific Akt isoform is critical for cardiac development, and that Akt prevents apoptosis in vivo (12). Moreover, when ErbB-

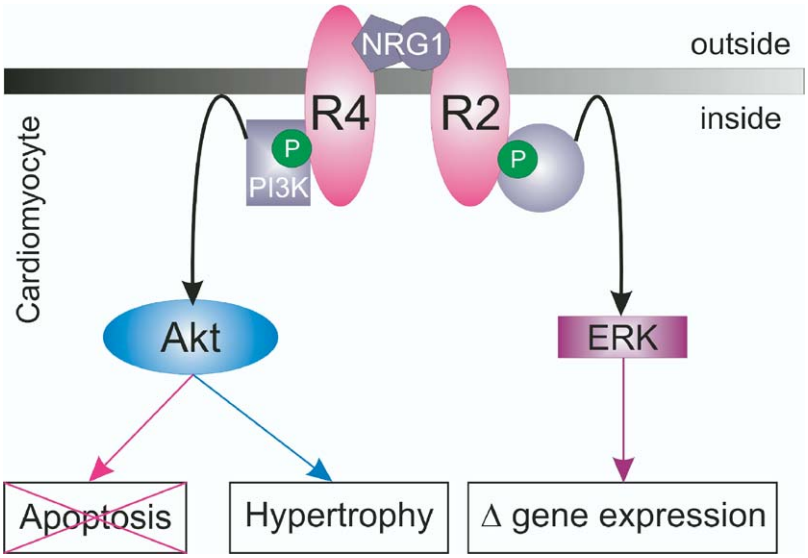

Figure 1. Schematic for ErbB action in cardiomyocytes. Neuregulin-1 (NRG1) activates ErbBs by promoting dimerization between the neuregulin receptor ErbB4 (R4) and its co-receptor ErbB2 (R2). ErbB2 and ErbB4 phosphorylate each other on tyrosyl residues (designated "P"), which then serve as "docking" sites for multiple signal transduction proteins (**shaded gray/blue**). Subsequent activation of "docked" proteins (such as the phosphoinositide 3-kinase [PI3K], at **left**) initiates multiple signaling cascades, including those involving Akt and extracellular signal-regulated kinase (ERK). While Akt interdicts apoptotic signaling and promotes cellular hypertrophy, ERK phosphorylates transcription factors that promote gene transcription.

mediated cardiomyocyte Akt activation is inhibited, the anti-apoptotic activity of neuregulin-1 is abrogated (11). It is believed that Akt attenuates apoptosis by phosphorylating (and thereby inactivating) a variety of proteins that mediate important steps in the choreography of programmed cell death (9).

Although activation of cardiomyocyte Akt by cell surface receptors may be necessary to protect cardiomyocytes from apoptosis, it is clearly not sufficient. Angiotensin II, for example, activates cardiomyocyte Akt and engenders cardiomyocyte hypertrophy but also promotes cardiomyocyte apoptosis (13). Thus, it seems likely that the net effect of myriad variables—including the degree of Akt activation and concurrent activation of other cardiomyocyte signaling pathways—determine whether a stimulus will result in cardiomyocyte survival or apoptosis. Other agonists that appear to promote a favorable anti-apoptotic balance between Akt and other cardiomyocyte signaling include insulin-like growth factor-1 (which stimulates its own RTK) (14) and cardiotrophin-1 (which stimulates cytokine receptors that signal through non-RTKs) (15). In neither of these cases, however, do we have therapeutic data comparable to those provided by Liu et al. (1) for neuregulin-1.

From bench to bedside—again. Like many seminal studies, the work of Liu et al. (1) raises a plethora of questions. What will be the therapeutic index for neuregulin-1 in human subjects, given its potential for pleiotropic effects involving the other cell types that express ErbB2, ErbB3, and ErbB4 (skeletal muscle, neuronal, glial, and epithelial)? Unlike receptor antagonists, whose effects are fairly stable over time, receptor agonists engender desensitization of signaling pathways with prolonged use (16). Will tachyphylaxis complicate, or even vitiate, long-term therapy with neuregulins in human subjects? Liu et al. (1) have carefully noted that dosing of neuregulin-1 therapy is critical for its safety and efficacy in heart failure, even in mice. What timing and frequency of administration will be optimal for neuregulin-1 efficacy in patients? We have witnessed spectacular success in breast cancer (17) and chronic myeloid leukemia (18) patients treated with *antagonist* or inhibitor therapies, respectively, targeting the ErbB2 tyrosine kinase or the BCR-ABL tyrosine kinase. Will the pro-neoplastic potential of prolonged *agonist* therapies involving RTKs be an insuperable barrier to therapeutic use of neuregulin-1? By analogy to the use of anti-ErbB2 therapy for only breast adenocarcinomas with ErbB2 overexpression, will neuregulin-1 therapy for heart failure be a targeted therapy for patients with the lowest levels of myocardial ErbB expression? In addressing these and other questions, the bench-to-bedside odyssey of neuregulin-1 heart failure therapy should productively occupy us for many years to come.

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