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Acute cardiac effects of Neuregulin-1/ErbB signaling

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Neuregulin1 (Nrg1) is a member of the epidermal growth factor (EGF) family. Its biological effects are mediated by the ErbB family of receptor tyrosine kinases (ErbB2, ErbB3 and ErbB4). The Nrg1/ErbB signaling is an essential paracrine mediator of cell-cell interactions that is indispensable for cardiac development but also plays a crucial role in the adult heart.

In the fetal heart, Nrg1 is produced in the endocardial endothelium adjacent to the cardiomyocytes where the ErbB2 and ErbB4 receptors are expressed. In contrast to ErbB2 and ErbB4, the ErbB3 receptor is only expressed in the mesenchymal cells of the endocardial cushions, the structure that forms the valves.¹ The first evidence for a function of the Nrg1/ErbB pathway in cardiac morphogenesis was revealed by studies of mice lacking functional Nrg1, ErbB2, or ErbB4 signaling which display a similar impairment of cardiac development characterized by a failure to undergo expansion and trabeculation of the primitive ventricles, resulting in embryonic lethality at E10.5.²⁻⁴ The similar cardiac phenotypes observed between Nrg1, ErbB2 and ErbB4 deficient mice demonstrate the requirement of these three proteins in the Nrg1-dependent regulation of ventricular trabeculation. Impairment of the ErbB3 signaling displays less severe heart malformation. ErbB3-null mice exhibit hypoplastic endocardial cushions leading to blood reflux through defective valves and embryonic lethality at day E13.5.⁵ In the adult heart Nrg1, ErbB2 and ErbB4 but not ErbB3 continue to be expressed and are essential to maintain ventricular structure and function. Indeed, mice harboring a conditional deletion of the ErbB2 or ErbB4 receptors develop dilated cardiomyopathy with altered cardiac function.

In vivo and *in vitro* studies showed that numerous processes are regulated by the Nrg1 signaling. During heart development, the Nrg1 signaling is implicated in the regulation of cardiomyocyte differentiation,⁶ cardiac conduction system specification,⁷ proliferation⁸ and fetal cardiac function.^{9,10} In the adult heart, Nrg1 has been shown to modulate cell growth,

survival, sarcomere structure, myocardial performance¹¹ and cardiomyocyte reentry into the cell cycle.¹² Nrg1 downstream signaling pathways have been extensively characterized in other tissues and multiple signaling molecules, including Erk1/2, PI3K/Akt, FAK and eNOS appear to be involved.¹³ Nevertheless, how Nrg1 signaling impacts on adult cardiac physiology and on cardiac development still remains unknown.

In this issue, Brero *et al.*¹⁴ investigated the molecular mechanism involved in the regulation of cardiac function in the adult rat through Nrg1 pathway. They demonstrated that Nrg1 β 1 rapidly, within minutes, enhances NO production through a PI3K/Akt-dependent eNOS phosphorylation. Although not measured in this study, NO presumably increases intracellular cGMP via activation of the soluble guanylyl cyclase, which in turn activates PKG. PKG phosphorylation was shown earlier to regulate major components of the excitation-contraction coupling, such as the L-type Ca²⁺ channel (LTCC),^{15,16} phospholamban (PLN)¹⁷ and troponin I.¹⁸ Accordingly, Brero *et al.* found that Nrg1 β 1 induces PKG phosphorylation of PLN, causing an increased Ca²⁺ uptake into the sarcoplasmic reticulum and hence a larger Ca²⁺ transient amplitude. Surprisingly, Brero *et al.* found no effect of Nrg1 β 1 on the amplitude of the LTCC current (I_{Ca,L}). Although they did not examine whether Nrg1 β 1 modified the amplitude of I_{Ca,L} during a β -adrenergic stimulation, as generally observed with NO-donors in rat cardiomyocytes,^{19,20} their findings raise an interesting possibility that the pool of cGMP/PKG which is activated by Nrg1 β 1 controls exclusively the phosphorylation of PLN without affecting other PKG target proteins. Although this hypothesis needs to be directly tested in future experiments, it would support recent findings in the same preparation demonstrating a high degree of compartmentalization of intracellular cGMP²¹ that involves a feedback control by PKG.²²

While this study provides a complete picture of the molecular events involved in the Nrg1-signaling pathway (Nrg1/PI3K/eNOS/PKG/PLN), it also provides a temporal issue that

was not addressed in prior studies. While most other studies reported long term effect of Nrg1 on cardiomyocytes, Brero *et al.* investigated acute Nrg1-dependent regulation of cardiac function and suggested a potential role in the short term protection of cardiac function during ischemia.

During heart development, the Nrg1-ErbB2/4-Erk1/2 signaling is required for the maintenance of the cardiac transcription program in both trabecular and non-trabecular myocardium, which is essential for cardiac chamber specification.¹⁰ In addition, Nrg1 appears to be essential for the establishment of embryonic cardiac contractility, since Nrg1 treatment of E8.5-cultured embryos results in changes in the pattern of electrical activity.⁹ Moreover disruption of Nrg1 leads to altered cardiac function with abnormal base-to-apex muscular contraction pattern.¹⁰ The PI3K/Akt pathway has been described to be implicated in the regulation of cardiac progenitor and fetal cardiomyocyte proliferation and thus plays an important role in regulating heart morphogenesis and function.^{23,24} However, its connection with the Nrg1-signaling in cardiac development has not been established yet. In that respect, the study of Brero *et al.* provides a novel hypothesis regarding the role of the PI3K/eNOS pathway in the Nrg1-dependent regulation of heart morphogenesis and fetal cardiac function. Indeed, hemodynamic forces are critical for cardiac chamber growth and trabeculation.^{25,26} Therefore, alteration of the fetal cardiac function, as in the Nrg1-deficient animals, may act as an epigenetic input causing the observed cardiac malformations.

Disclosures

None.

References

1. Wagner M, Siddiqui MA. Signal transduction in early heart development (II): ventricular chamber specification, trabeculation, and heart valve formation. *Exp Biol Med* (Maywood) 2007;**232**:866-80
2. Gassmann M, Casagrande F, Orioli D, Simon H, Lai C, Klein R, Lemke G. Aberrant neural and cardiac development in mice lacking the ErbB4 neuregulin receptor. *Nature* 1995;**378**:390-4
3. Lee KF, Simon H, Chen H, Bates B, Hung MC, Hauser C. Requirement for neuregulin receptor erbB2 in neural and cardiac development. *Nature* 1995;**378**:394-8
4. Meyer D, Birchmeier C. Multiple essential functions of neuregulin in development. *Nature* 1995;**378**:386-90
5. Erickson SL, O'Shea KS, Ghaboosi N, Loverro L, Frantz G, Bauer M, Lu LH, Moore MW. ErbB3 is required for normal cerebellar and cardiac development: a comparison with ErbB2-and heregulin-deficient mice. *Development* 1997;**124**:4999-5011
6. Suk Kim H, Hidaka K, Morisaki T. Expression of ErbB receptors in ES cell-derived cardiomyocytes. *Biochem Biophys Res Commun* 2003;**309**:241-6
7. Patel R, Kos L. Endothelin-1 and Neuregulin-1 convert embryonic cardiomyocytes into cells of the conduction system in the mouse. *Dev Dyn* 2005;**233**:20-8
8. Hertig CM, Kubalak SW, Wang Y, Chien KR. Synergistic roles of neuregulin-1 and insulin-like growth factor-I in activation of the phosphatidylinositol 3-kinase pathway and cardiac chamber morphogenesis. *J Biol Chem* 1999;**274**:37362-9
9. Rentschler S, Zander J, Meyers K, France D, Levine R, Porter G, Rivkees SA, Morley GE, Fishman GI . Neuregulin-1 promotes formation of the murine cardiac conduction

system. Proc Natl Acad Sci U S A 2002;**99**:10464-9

10. Lai D, Forrai A, Liu X, Wolstein O, Michalicek J, Ahmed I, Garratt AN, Birchmeier C, Zhou M, Hartley L, Robb L, Feneley MP, Fatkin D, Harvey RP. Neuregulin 1 sustains the gene regulatory network in both trabecular and nontrabecular myocardium. Circ Res 2010;(in press)
11. Lemmens K, Doggen K, De Keulenaer GW. Role of neuregulin-1/ErbB signaling in cardiovascular physiology and disease: implications for therapy of heart failure. Circulation 2007;**116**:954-60
12. Bersell K, Arab S, Haring B, Kuhn B. Neuregulin1/ErbB4 signaling induces cardiomyocyte proliferation and repair of heart injury. Cell 2009;**138**:257-70
13. Pentassuglia L, Sawyer DB. The role of Neuregulin-1beta/ErbB signaling in the heart. Exp Cell Res 2009;**315**:627-37
14. Brero A, Ramella R, Fitou A, Dati C, Alloatti G, Gallo MP, Levi R. Neuregulin-1β1 rapidly modulates nitric oxide synthesis and calcium handling in rat cardiomyocytes. Cardiovasc Res 2010;(in press)
15. Méry P-F, Lohmann SM, Walter U, Fischmeister R. Ca²⁺ current is regulated by cyclic GMP-dependent protein kinase in mammalian cardiac myocytes. Proc Natl Acad Sci USA 1991;**88**:1197-1201
16. Schroder F, Klein G, Fiedler B, Bastein M, Schnasse N, Hillmer A, Ames S, Gambaryan S, Drexler H, Walter U, Lohmann SM, Wollert KC. Single L-type Ca²⁺ channel regulation by cGMP-dependent protein kinase type I in adult cardiomyocytes from PKG I transgenic mice. Cardiovasc Res 2003;**60**:268-277

17. Raeymaekers L, Hofmann F, Casteels R. Cyclic GMP-dependent protein kinase phosphorylates phospholamban in isolated sarcoplasmic reticulum from cardiac and smooth muscle. *Biochem J* 1988;**252**:269-273
18. Blimenthal DK, Stull JT, Gill GN. Phosphorylation of cardiac troponin by guanosine 3':5'-monophosphate-dependent protein kinase. *J Biol Chem* 1978;**253**:334-336
19. Abi-Gerges N, Fischmeister R, Méry P-F. G protein-mediated inhibitory effect of a nitric oxide donor on the L-type Ca^{2+} current in rat ventricular myocytes. *J Physiol* 2001;**531**:117-130
20. Abi-Gerges N, Szabo G, Otero AS, Fischmeister R, Méry P-F. NO donors potentiate the β -adrenergic stimulation of $\text{I}_{\text{Ca,L}}$ and the muscarinic activation of $\text{I}_{\text{K,ACh}}$ in rat cardiac myocytes. *J Physiol* 2002;**540**:411-424
21. Castro LRV, Verde I, Cooper DMF, Fischmeister R. Cyclic guanosine monophosphate compartmentation in rat cardiac myocytes. *Circulation* 2006;**113**:2221-2228
22. Castro LRV, Schittl J, Fischmeister R. Feedback control through cGMP-dependent protein kinase contributes to differential regulation and compartmentation of cGMP in rat cardiac myocytes. *Circ Res* 2010;(in press)
23. Chang Z, Zhang Q, Feng Q, Xu J, Teng T, Luan Q, Shan C, Hu Y, Hemmings BA, Gao X, Yang Z. Deletion of Akt1 causes heart defects and abnormal cardiomyocyte proliferation. *Dev Biol* 2010;(in press)
24. Hutson MR, Zeng XL, Kim AJ, Antoon E, Harward S, Kirby ML. Arterial pole progenitors interpret opposing FGF/BMP signals to proliferate or differentiate . *Development* 2010;**137**:3001-11

25. Hove JR, Koster RW, Forouhar AS, Acevedo-Bolton G, Fraser SE, Gharib M.
Intracardiac fluid forces are an essential epigenetic factor for embryonic cardiogenesis.
Nature 2003;**421**:172-7
26. Reckova M, Rosengarten C, deAlmeida A, Stanley CP, Wessels A, Gourdie RG,
Thompson RP, Sedmera D. Hemodynamics is a key epigenetic factor in development of
the cardiac conduction system. Circ Res 2003;**93**:77-85