Paving new paths for neuregulin-1-assisted cardiac regenerative medicine.

Focus on “Improving murine embryonic stem cell differentiation into cardiomyocytes with neuregulin-1: differential expression of microRNA”

Katrien Lemmens and Gilles W. De Keulenaer
Laboratory of Physiology, University of Antwerp, Antwerp, Belgium

THE PLURICELLULARITY OF THE HEART, allowing an intense communication among cells and cell types in the myocardial tissue, has long been recognized (2). Adaptations within this communication network, mostly between endothelial cells, fibroblasts, and cardiomyocytes, are part of the autoregulatory properties of the heart during its role as the hemodynamic pump in the cardiovascular system, and participate during changes of ventricular contraction and relaxation, the development of ventricular hypertrophy, etc. Over the past 20 years, the neuregulin-1 (NRG1)/ErbB pathway has emerged as a prototypical example of cell communication in the heart (11, 17). NRG1, a member of the epidermal growth factor family, is synthesized by and released from endothelial cells in the myocardial microvasculature and in the endocardium. Its biological effects are mediated by tyrosine kinase receptors ErbB2, ErbB3, and ErbB4. NRG1 binds to ErbB4 (and ErbB3 in the fetal heart) on surrounding cardiomyocytes, leading to receptor (hetero-)dimerization, preferably with ErbB2, transphosphorylation of the dimer partners, and downstream signaling (12). The endothelial synthesis and release of NRG1 is controlled by hemodynamic and neurohormonal stimuli and is increased in (patho)physiological conditions such as pregnancy, heart failure, ischemia, etc. (7, 10, 13).

The function of the cardiac NRG1/ErbB system in the adult heart is to protect it from injury and to promote myocardial regeneration. Thereto, NRG1 desensitizes the myocardium from adrenergic (over)stimulation (12), increases the cardiomyocyte threshold for apoptosis and ischemic cell death (8, 13), induces mitosis of mononucleated cardiomyocytes (1), and regulates cardiomyocyte-cell and cell-matrix interactions (8). An important translational extension of these discoveries is recent experiments showing that treatment with recombinant NRG1 improves ventricular function and survival in various animal models of heart failure (1, 14). The underlying mechanisms leading to these improvements during heart failure have, however, not been verified. Nevertheless, physiological properties of the NRG1/ErbB system are in the process of being translated into therapeutic applications: phase II clinical trials with NRG1 improving ventricular function and survival in various animal models of heart failure (1, 14). The authors reasoned that by identifying microRNAs regulated by NRG1 in embryonic stem cells (ESCs), they might discover new microRNAs important for cardiac differentiation of ESCs, hence contributing to the development of strategies for ESC-based cell therapies of cardiac repair. Stem cell therapy is a promising treatment option after ventricular injury, but gaps in the understanding of stem cell biology limit its clinical use (18). An important challenge remains—the control of their differentiation into the cardiac lineage (20).

The authors succeeded in their goal by microRNA profiling of ESCs during hanging drop-induced differentiation. ESCs were treated with either NRG-1 or a (nonspecific) ErbB inhibitor, thereby linking the differential expression of three microRNAs to NRG1-induced ErbB signaling in ESCs. Inhibition of each of these microRNAs influenced the cardiac differentiation of ESCs, showing their functional importance. Interestingly, in absence of NRG1, these microRNAs had a pattern of expression as if NRG1/ErbB signaling occurred as a spontaneous phenomenon during hanging drop-induced differentiation of ESCs, a finding that was confirmed in separate experiments. In conclusion, this study confirms the importance of NRG1/ErbB signaling during ESC differentiation into the cardiac lineage, and it identifies novel NRG1-controlled microRNAs as intermediate mediators of the cardiac lineage differentiation process.

Inherent to any successful experimental study, apart from revealing new scientific information, are the new scientific questions that it raises. First, one may wonder whether the identified set of microRNAs is part of a larger set of microRNAs, which may be characteristic of ESC differentiation into a cardiac cell lineage. Is a specific set of microRNAs coupled to NRG1-induced cardiac differentiation of ESCs, or are these microRNAs common to other mediators and conditions that promote a cardiac lineage? Does an inhibition of this set of microRNAs simply block ESC cardiac cell differentiation, or does such inhibition push differentiation toward a specific cardiac (beating vs. nonbeating) cardiac cell type? One of the weaknesses of this study is that it only assessed the effect of targeted microRNA inhibition on two molecular markers of differentiation, not on the regulation of the cardiac cell subtype.

Accordingly, the study by Sun et al. paves the path of ESC-mediated cardiac regeneration by identifying intermediate microRNAs. The next step is to scrutinize how this new information contributes to the original goal of this study, i.e., the development of strategies for ESC-based cell therapies of cardiac repair. This study is another example of the central role that NRG1/ErbB signaling may play in future endeavors to reverse the pathophysiology of heart failure, either by stimulating ErbB signaling in vivo in the failing heart, or by cell therapy with NRG1-programmed ESCs (see Fig. 1). One may
Cell communication network in the pluricellular heart

Neuregulin-1 / ErbB signaling

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<th>PRE-NATAL</th>
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<td>Cardiac development</td>
<td>Cardiac regeneration/protection</td>
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<td>• cardiac cushion formation</td>
<td>• beta-1 receptor desensitization</td>
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<td>• ventricular trabeculation</td>
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<td>• cardiac cell transdifferentiation</td>
<td>• mitosis of cardiomyocytes</td>
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<td>• regulation of micro-RNA</td>
<td>• cell-matrix interactions</td>
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NRG-1-guided ESC cardiac differentiation for stem cell therapy

NRG-1 as a drug for chronic heart failure

New strategies for regenerative medicine for heart failure

wonder which of these two strategies will be the most successful. Time, and more importantly, future data should reveal the answer!

GRANTS

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REFERENCES