Editorial

Cardiac development: from current understanding to new regenerative concepts

This special issue is devoted to the 3rd Munich Conference on Cardiac Development, "Cardiac Development—From Current Understanding to New Regenerative Concepts," that was held on June 1–3, 2016, at the German Heart Center Munich, Munich, Germany.

In recent years, innovative and significant progress has been made in cardiac developmental biology, cardiovascular genetics, and stem cell research. The 3rd Munich Conference on Cardiac Development focused on our current understanding of the mechanisms that underlie heart development, cardiac disease, and cardiac ageing and ways to develop new regenerative concepts to foster future therapeutic regenerative treatment strategies.

The paradigm of an entirely postmitotic mammalian heart was recently challenged, offering perspectives for the development of new regenerative strategies. Adult mammalian hearts are able to regenerate, even if at a markedly lower rate than the hearts of zebrafish and newts (1,2). However, there is ongoing debate about the source of this homeostatic cardiac turnover in mammals. One possible source is cardiomyocytes that pass through a phase of dedifferentiation, in which they reenter the cell cycle and start to divide again (3). Cardiomyocyte proliferation is well described in the zebrafish heart as being fundamental to their tremendous heart regeneration capacity (4). Another possibility that is still under debate is that resident cardiac progenitor/stem cells are reactivated from their niches and then contribute to cardiomyocyte proliferation or even differentiate directly into cardiomyocytes (5). Few scientists have discussed the contribution of circulating cells to cardiomyocyte regeneration after injury (6).

Current regenerative approaches include the transplantation of various cell types [ideally combined with tissue engineering; e.g., (7)], the stimulation of endogenous repair mechanisms [e.g., the induction of cardiomyocyte proliferation (8-11)], and the direct reprogramming of fibrotic parts of the failing heart back to a functional myocardium [e.g., (12,13)].

For the development and improvements of such innovative therapies, a detailed understanding of cardiac development and the processes by which cardiac progenitor cell populations mature into cardiomyocytes is essential (14,15). However, the highly complex temporal and spatial interactions between transcription factors, growth factors, and non-coding RNAs that act in various progenitor cell populations during cardiac development are not completely understood. Alexanian *et al.* (16) review the knowledge about how long-non-coding (lnc)-RNAs contribute to mesoderm specification. New omics techniques, combined with single-cell analysis tools, will help shed light on above mentioned mechanisms and offer the possibility to expand our knowledge of the cardiac developmental network [reviewed by (17)].

Furthermore, the processes and factors that are involved in cardiac aging have become increasingly important because the world's population is aging, and aging itself is a major cardiovascular risk factor (18). A thorough understanding of the underlying mechanisms may provide novel targets for regenerative strategies. In this issue, Cannatà *et al.* review the role of circulating humoral factors in cardiovascular aging (19).

A true understanding of the cell types that are involved in cardiac injury, disease mechanisms, and cardiac remodeling [e.g., inflammatory cells (20) and cardiac fibroblasts (21)] and their mechanisms of action is mandatory. This may also foster new ideas and identify new options for improving current therapeutic strategies. Following tissue injury by myocardial infarction the immune system and its cellular protagonists (i.e., monocytes and macrophages) substantially contribute to the initial inflammatory response and subsequent regenerative response. The specific role of monocytes and macrophages during homeostasis and after cardiac ischemic injury is reviewed by Sager *et al.* (22). Cardiac fibroblasts were long an underestimated cell population. However, they have gained more attention in recent years (23). Following the inflammatory phase after myocardial infarction, cardiac fibroblasts proliferate and undergo myofibroblast transdifferentiation to maintain the structural integrity of the impaired ventricle. The role of transforming growth factor-β in this process is reviewed by Frangogiannis (24). Cardiac fibroblasts and their activated forms after injury also represent an interesting novel target population for direct reprogramming techniques (13).

Alternative targets after cardiac injury include non-coding RNAs, e.g., microRNAs and long-non-coding RNAs (25,26). Recent studies have provided additional insights into the roles of non-coding RNAs in heart development and disease [e.g., (27)].

Hoelscher *et al.* (28) review the role of microRNAs in congenital heart disease and further discuss potential therapeutic strategies for such patients based on microRNAs.

Clinical trials with various stem cell resources have recently been performed to treat patients who suffer from acquired heart disease. The results, however, have been highly variable and inconsistent (29). The general consensus is that positive results were mainly triggered by paracrine effects that were mediated by the transplanted cells. The primary positive effect that was observed after cell transplantation was a reduction of scar size after myocardial infarction, but the left ventricular ejection fraction barely improved, if at all (29). Remaining unknown is whether the transplantation of cells into hearts with impaired myocardial function is indeed a curative therapy for affected patients. More recently, clinical trials in children with congenital heart disease, especially with single ventricle morphology, have reported promising results [e.g., (30-32)]. The positive ejection fraction results that were reported after the initial feasibility Phase I trial were maintained in the larger, recently published Phase II trial (32).

Future regenerative approaches will seek to develop patient-specific treatments. The Nobel prize-winning technique that generates induced-pluripotent stem cells from autosomal cells (33,34), combined with elaborate cell purification techniques [e.g., as reported by Miki *et al.* using RNA-switches (35)], offers the unique possibility to treat individual patients with autologous cells. The broad accessibility of whole-genome approaches, such as genome and exome sequencing, also allows precise analyses of patients' genetic backgrounds, thereby allowing the determination of individual drug responses, facilitating the design of personalized health plans, and developing patient-specific treatment options (36,37). This so-called "precision or personalized medicine" will become indispensable for future treatment. It is well recognized that oftentimes drugs and treatments are effect only for some patients.

Intensive innovative research will provide deeper insights into the mechanisms that underlie normal cardiac development, various cardiac diseases, and cardiac aging. The future will reveal which regenerative strategies are appropriate for treating various cardiac impairments that result from a failure of cardiac development, acquired cardiac disease, or the aging process.

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Markus Krane


Karl-Ludwig Laugwitz


Rüdiger Lange


Stefanie A. Doppler

Stefanie A. Doppler[1]
(Email: doppler@dhm.mhn.de)
Rüdiger Lange[1,2]
(Email: lange@dhm.mhn.de)
Karl-Ludwig Laugwitz[2,3]
(Email: laugwitz@mytum.de)
Markus Krane[1,2]
(Email: krane@dhm.mhn.de)
[1]*Department of Cardiovascular Surgery, Division of Experimental Surgery, German Heart Center Munich, Technische Universität München, Munich, Germany;*
[2]*DZHK (German Center for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany;*
[3]*I. Department of Medicine (Cardiology), Klinikum rechts der Isar der Technischen Universität München, Munich, Germany.*
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