

Myocardial Research



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Growth control and regeneration pathways in the heart

Heart failure ensues as the final common pathway of cardiac diseases, most frequently as a sequel of myocardial infarction. Despite improvements in patient outcome with state-of-the-art therapy, which includes neurohormonal modulation and devices, it still represents a leading cause of death and hospitalization. The recent recognition of intrinsic regenerative capacities in the adult heart that are thought to participate in organ homeostasis, but to be insufficient to compensate for cell loss after injury, provides now a basis for novel therapeutic strategies that aim at the strengthening of endogenous regeneration pathways and the use of cardiac progenitor cells (CPCs). A major interest of our laboratory is to decipher signaling and gene regulatory networks that are involved in tissue homeostasis and cell replacement in the heart, and to elucidate how they regulate the delicate balance between the proliferation of immature precursor and progenitor cells and their differentiation and maturation.

The microenvironment is an important regulator of cell fate and provides cues from the extracellular matrix (ECM) as well as soluble factors. We are particularly interested in how information from the ECM is transduced into a cell fate-regulatory response. We recently found that the differential regulation of YAP and of the cell cycle regulator Plk2 in response to ECM proteins either maintains proliferation of CPCs, thus contributing to their amplification, or directs them towards lineage commitment and differentiation, whereby Plk2 appears to act as an inverse link between cell cycle and fate decision. YAP and Plk2 are part of a developmentally regulated pathway, which is gradually shut down in the postnatal heart, thus allowing for terminal differentiation and maturation of cardiac cells. Such master regulators of cardiac cell fate could be therapeutically targeted to promote regeneration of the injured heart.

In a related line of studies with focus on the role of stem cell-regulatory factors in the heart, we recently uncovered an unexpected function of the hematopoietic cytokine Flt3 ligand and its receptor Flt3 as gatekeepers of CPC quiescence. We have previously shown that Flt3 is upregulated in the ischemically injured heart and that its pharmacological activation confers cytoprotection, hence improving remodeling and function after myocardial infarction. Flt3 is part of the cancer kinome and cardiomyopathies have been observed in patients under Flt3-targeting receptor tyrosine kinase inhibitor (TKI) therapy. Using functional analyses and relating them to whole transcriptome profiling, we are also studying how targeted cancer therapeutics, specifically TKIs, affect cardiac function. Results from these studies will not only provide a mechanistic rationale for cancer drug-related cardiotoxicity, but also help identify key effectors of cardiac growth and regeneration pathways.

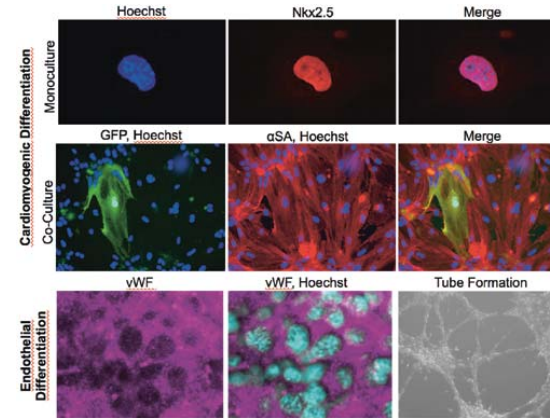


Fig. 1:
Cardiomyogenic and endothelial differentiation of cardiac progenitor cells (CPCs).
Top: Expression of cardiomyogenic transcription factors (shown Nkx2.5) after three weeks in monoculture. Expression of α -sarcomeric actinin (α SA) in a green-fluorescent protein (GFP)-expressing CPC-derived cell after three weeks in co-culture with cardiomyocytes. Bottom: Expression of von Willebrand Factor (vWF) protein after three weeks in endothelial differentiation medium. Such cells exhibit an endothelial cell phenotype with the capacity of tube formation in Matrigel.

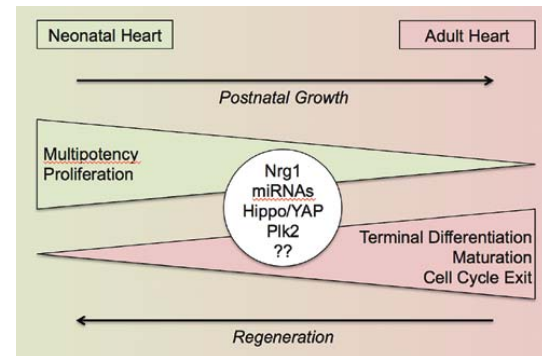


Fig. 2:
Relationship between regenerative capacities and organ/cell maturation in the heart.
The regenerative capacities of the mouse heart are lost within the first week after birth, when key pathways balancing cell cycle regulation and differentiation during development are shut down. Nrg1: neuregulin-1; miRNAs: micro RNAs; YAP: yes-associated protein; Plk2: polo-like kinase 2; ?? : others and yet to be identified.

Selected Publications

- Mochizuki M, Lorenz V, Ivanek R, Della Verde G, Gaudiello E, Marsano A, Pfister O, Kuster GM. (2016) Polo-like kinase 2 is dynamically regulated to coordinate proliferation and early lineage specification downstream of YAP in cardiac progenitor cells.
- Kuster GM, Liao R. (2016) Fortune favors the prepared: Safety and efficacy of allogeneic hypoxia preconditioned mesenchymal stromal cells in primates. Circulation research 118, 908–910
- Kuster GM, Della Verde G, Liao R, Pfister O. (2016) Cell therapy for cardiac regeneration. In Translating regenerative medicine to clinics, J. Laurence, M. Van Beusekom, P. Baptista, and A. Atala, eds. (United States of America: Academic Press, Elsevier Inc.), pp. 266–283
- Pfister O, Della Verde G, Liao R, Kuster GM. (2014a) Regenerative therapy for cardiovascular disease. Translational Research 163, 307–320
- Pfister O, Lorenz V, Oikonomopoulos A, Xu L, Hauselmann SP, Mbah C, Kaufmann BA, Liao R, Wodnar-Filipowicz A, Kuster GM. (2014b) FLT3 activation improves post-myocardial infarction remodeling involving a cytoprotective effect on cardiomyocytes. Journal of the American College of Cardiology 63, 1011–1019