MicroRNA-21 coordinates human multipotential cardiovascular progenitors' therapeutic potential and post-ischemic revascularization

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Published clinical trials in patients with ischemic diseases show limited benefit of adult stem cell-based therapy, likely due to their restricted plasticity and commitment towards vascular cell lineage. Here, we have uncovered the potent regenerative ability of MesP1/SSEA-1-expressing cardiovascular progenitors enriched from human embryonic stem cells (hESC). Injection of only 10⁶ hESC-derived SSEA-1/Mesp1+ cells, or their progeny obtained after treatment with VEGF-A or PDGF-BB, was effective enough to enhance post-ischemic revascularization in immunodeficient mice with critical limb ischemia (CLI). However, the rate of incorporation of hESC-derived SSEA-1/Mesp1+ cells and their derivatives in ischemic tissues was modest. Alternatively, these cells possessed a unique miR-21 signature that inhibited PTEN thereby activating HIF-1α and the systemic release of VEGF-A. Targeting Dicer or miR-21 limited cell survival in vivo and inhibited their pro-angiogenic capacities both in the Matrigel model and in mice with CLI. Interestingly, we observed an impaired post-ischemic angiogenesis in miR-21 deficient mice suggesting an unrestricted role of miR-21 in this regenerative environment. Notably, amongst the inflammatory cell population, miR-21 was highly expressed in circulating and infiltrated monocytes where it targeted PTEN/HIF-1α/VEGF-A signaling. As a result, miR-21 deficient mice displayed an impaired number of infiltrated monocytes and a defective angiogenic phenotype that could be partially restored by retransplantation of bone marrow-derived cells from wild-type littermates. Hence, hESC-derived SSEA-1/Mesp1+ cells progenitor cells are powerful key integrators of therapeutic angiogenesis in ischemic milieu and miR-21 is instrumental in this process as well as in the orchestration of post-ischemic vessel growth.

Proepicardial prokineticin receptor –1 (PKR1) as a developmental link between heart and kidney

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Methods and Results: Prokineticin receptor-1 (PKR1), signals play critical roles in heart and kidney functions. In particular, the systemic mutation of this receptor results in thinning of the myocardium and hypoplastic kidney. However, the molecular and cellular mechanisms controlled by PKR1 signaling in this process are unclear.

Vascular remodeling of the endocardium following cardiac infarction secured by arteriogenesis and angiogenesis

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Methods and Results: We have analyzed a tissue-restricted mutations of the Prokineticins are potent angiogenic peptides that bind to two G-protein-coupled receptors to initiate their biological effects. We previously
cardiac development is dramatically impaired in mutant mice, including failed expansion of the subepicardial space, blunted invasion of the myocardium, and impaired differentiation of epicardium-derived cells into coronary endothelial and smooth muscle cells. Abnormal mitochondria, lipid accumulation in mutant cardiomyocytes leads to lower contractile response to dobutamine. Impaired proliferation was observed in both Gata5 and Wt1 but apoptosis was observed only Wt1 lineage. Adult mutant hearts had abnormal rhythm and impaired systolic functions. Hypoplastic kidneys at the neonatal mutants were accompanied with deficient glomerular angiogenesis. Outgrown cell from kidney explants had a defective vasculargenic cell differentiation. Atrophy and dilated glomerular structure, abnormal mitochondria, lipid deposition and apoptosis were observed in the adult mutant kidney.

Conclusions: Our findings provide a mechanistic insight into the roles of PKR1 signaling in heart and kidney disorders controlling the maturation of epicardial-derived cell and differentiation in a cell autonomous fashion and affecting cellular communications in a paracrine fashion. Our mouse models recapitulate the complex human heart-kidney disorders.

Non-peptidic prokineticin receptor 1 agonist as a novel cardioprotective therapeutic

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Methods and Results: Prokineticins are potent angiogenic peptides that bind to two G-protein-coupled receptors to initiate their biological effects. We previously