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 cardiacomyocytes 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 rhythmicity 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 diluted 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.

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Vascular remodeling of the endocardium following cardiac infarction secured by arteriogenesis and angiogenesis
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Coronary vasculature is required to maintain cardiomyocyte survival, via delivery of oxygen and nutrients, and consequently myocardial architecture and cardiac function. Ischemic heart disease following myocardial infarction causes irreversible cell loss and scarring and is a major cause of morbidity and mortality. Revascularization of injured, ischemic and regenerating organs is essential to restore organ function and requires the formation of new vessels by the mechanisms of vasculogenesis, angiogenesis or arteriogenesis. With the objective of studying vascular remodeling during myocardial infarction (MI), we have performed permanent left coronary ligation on Connexin60-GFP (Cx60CreERT2) mice. Cx60 encodes a gap junction protein and is expressed in adult endothelial cells of large vessels. In the heart, Cx60-GFP expression is detected in coronary arteries but not in veins, capillaries or endocardium. After two weeks of ligation, MI was detected in left ventricle by echocardiography and anatomical examination of these hearts revealed the presence of an extensive network of GFP-positive vascularization within the infarct area. These vessels follow a tortuous route in the remaining ventricular wall and some communicate with the left ventricular lumen forming a crater covered with GFP and VEGF-R2 positive endothelial cells at the endocardial surface. To determine whether these vessels result from neo-vascularization or coronary artery remodeling, we carried out genetic lineage tracing of coronary endothelial cells using an inducible Cx60Cre allele. Our results show that GFP positive endothelial cells forming the endocardial carters are not always derived from pre-existing coronary arteries, suggesting that endocardium may also contribute to the generation of new vessels during vascular remodeling in the adult heart by angiogenesis.