Cellular homeostasis and lineage maintenance during cardiac regeneration

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Mammalian hearts only regenerate during neonatal stages. Effort has been made to identify the healing factors responsible for early resilience, but absent in mature mammalian hearts. The paired-like homeodomain transcription factor 2 (Pitx2) is essential for cardiac development and homeostasis. Our previous studies showed a role of Pitx2 in myocardial regeneration after ischemic injury. Loss of Pitx2 specifically in cardiomyocytes predisposes atrial fibrillation, and compromises the neonatal regenerative capacity by causing persistent scarring three weeks after myocardial infarction (MI). Pitx2 gain-of-function in mature cardiomyocytes is protective, and promotes heart repair, however the underlying mechanisms are not entirely understood. Our further research characterized long-term myocardial phenotype after MI in Pitx2 conditional knockout (Pitx2CKO) mice, and observed adipose-like tissue in Pitx2CKO hearts at 60 days after surgery-induced MI, performed at postnatal day (P) 2. The histological phenotype mimics arrhythmogenic right ventricular cardiomyopathy (ARVC), an inherited disease characterized by fibro-fatty replacement of myocardium. Molecular and cellular analysis showed onset of adipogenic signaling in mutant hearts after MI. ES cell differentiation assay showed the requirement of Pitx2 during cardiomyocyte lineage commitment. However, the lineage tracing experiments showed a non-cardiomyocyte origin of the de novo adipose-like tissue. The current findings indicate a novel role of Pitx2 in the maintenance of composition and homeostasis of cardiac cell types during heart regeneration. Future studies will focus on the interaction between different cell types in injured myocardium.