Interplay of epigenetic and metabolism in regulation of heart regeneration

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Introduction

1. Inactivation of Cpt1b induces continuous hypertrophic and hyperplastic growth of cardiomyocytes

2. Inactivation of Cpt1b protects the myocardium from ischemia/reperfusion damage and enables heart regeneration

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4. Failure of fatty acid import into mitochondria dramatically increases αKG levels

5. Increased αKG level provokes H3K4me3 demethylation and decreases expression of cardiomyocyte identity genes

6. Kdm5b interacts with IDH1 and NuRD complex

7. IDH1 targeted degradation using the dTAG system in mESCs

Hypothesis and Aims

Aims

- Determine the existence of TCA enzymes localized in healthy neonatal and adult cardiomyocytes as well as in our hypertrophic or Cpt1b mutant heart models using mass spectrometry.
- Dissect the mechanisms coupling nuclear translocation of metabolic enzymes.
- Investigate the effects of rapid targeted degradation of IDH1 on cardiomyocyte differentiation and maturation ex vivo.
- Generate knock-in mouse models using dTAG technology to dissect the effect of global degradation of IDH1 on heart development, maturation and function.

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