Max Planck Institute
for Heart and Lung Research
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Interplay of epigenetic and metabolism in regulation of heart regeneration

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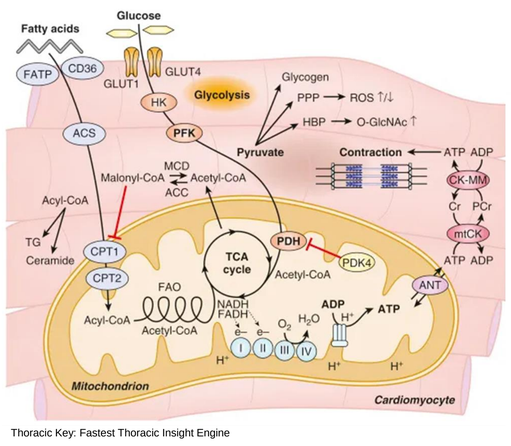
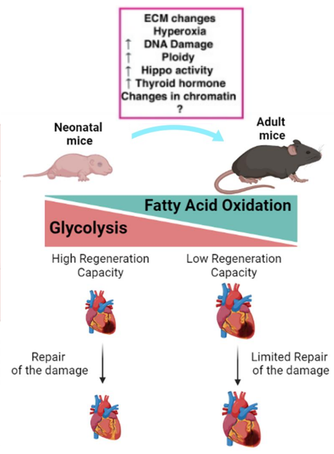
Introduction



Thoracic Key: Fastest Thoracic Insight Engine

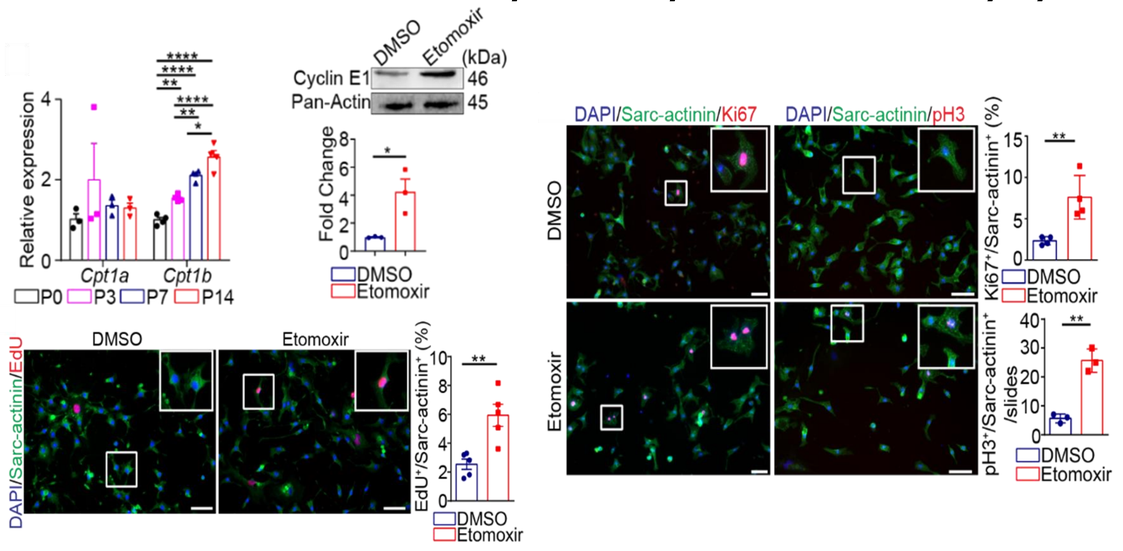


- Cardiomyocytes utilize a variety of nutrients as a source of energy.
- Neonatal mice (p1-p3) retain robust heart regeneration capacity in response to ischemic injury
- Postnatal maturation of cardiomyocytes is characterized by a metabolic switch from glycolysis to fatty acid oxidation (FAO), chromatin reconfiguration, and exit from cell cycle, instating a barrier for adult heart regeneration.
- Changes in the concentration of different metabolites, which serve as essential cofactors or substrates for various chromatin modifiers, potentially couple metabolic processes to the chromatin landscape and gene activity.

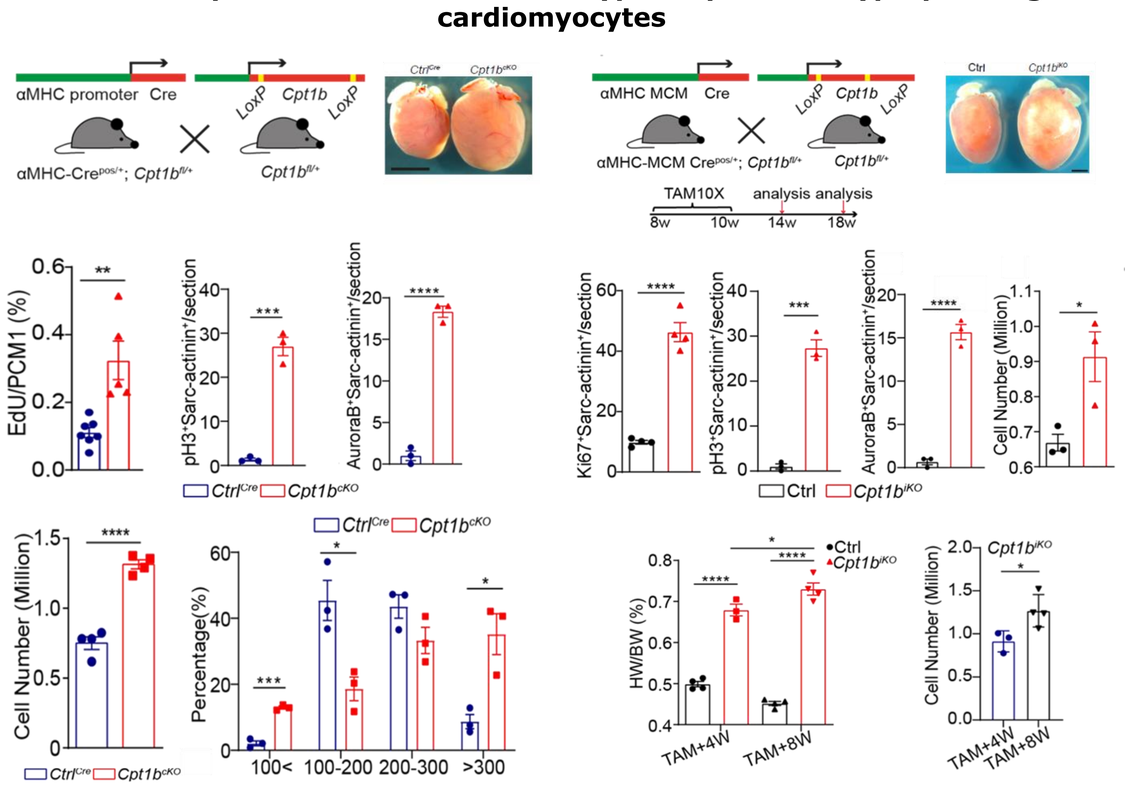
Question:
Whether cardiac metabolic reprogramming by inhibition of fatty acid oxidation affects chromatin configuration, transcriptional profile and heart regeneration following myocardial injury?

Results

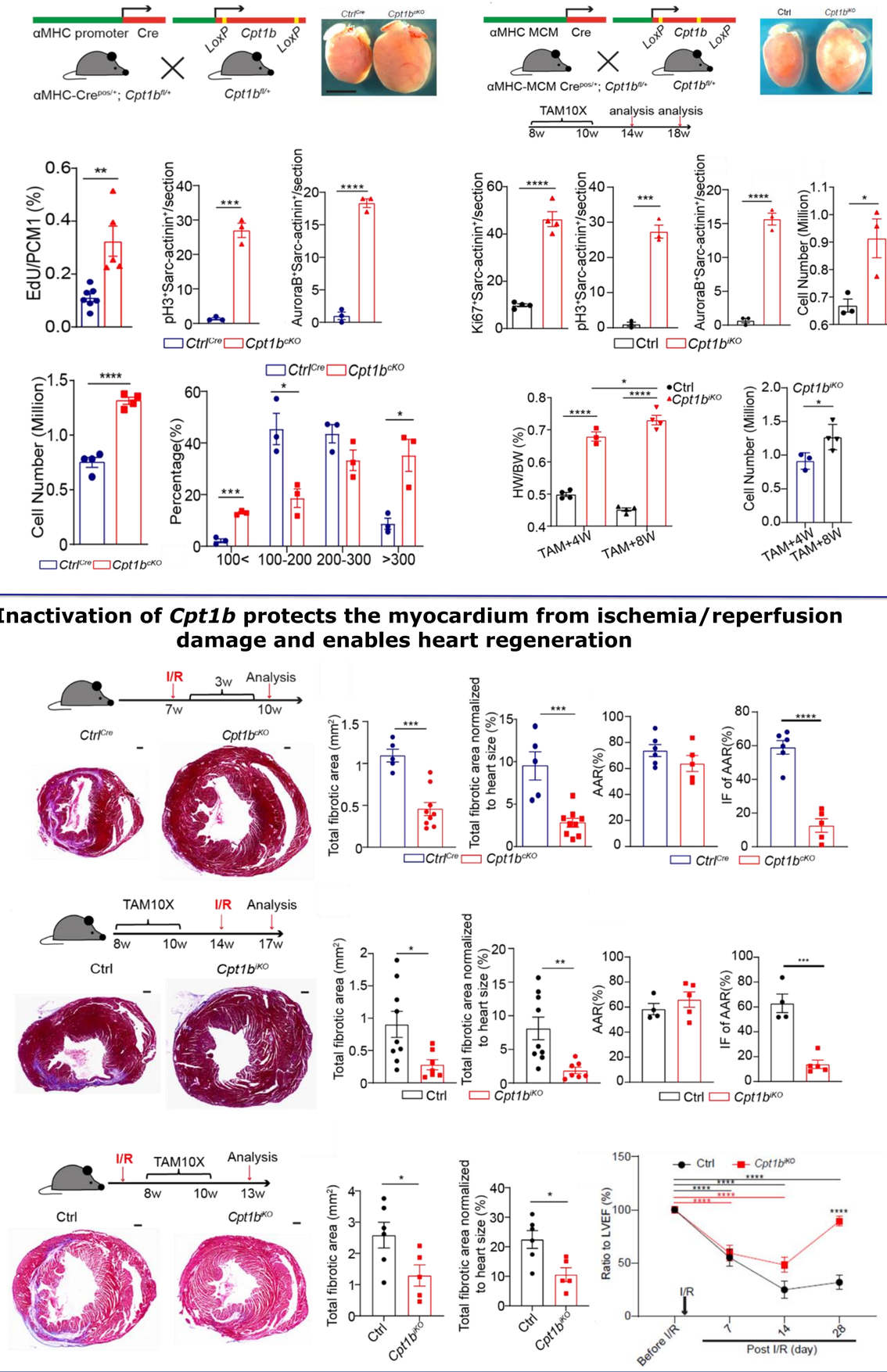
1. Inhibition of CPT1 stimulates cell cycle activity of neonatal cardiomyocytes



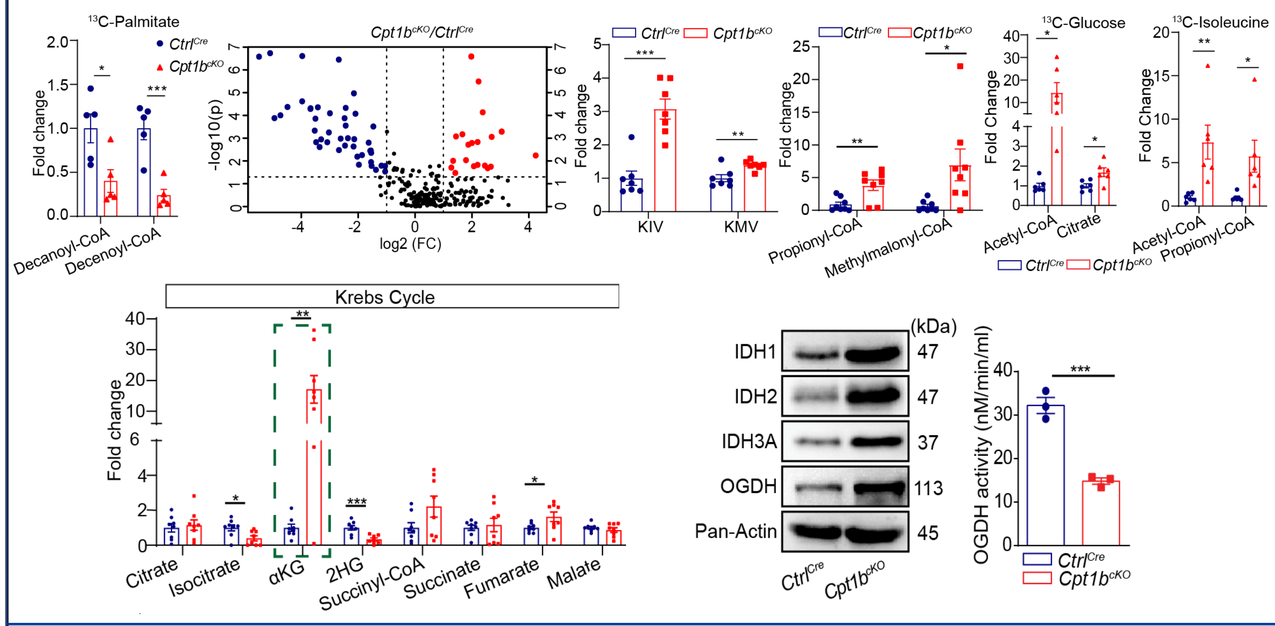
2. Inactivation of *Cpt1b* induces continuous hypertrophic and hyperplastic growth of cardiomyocytes



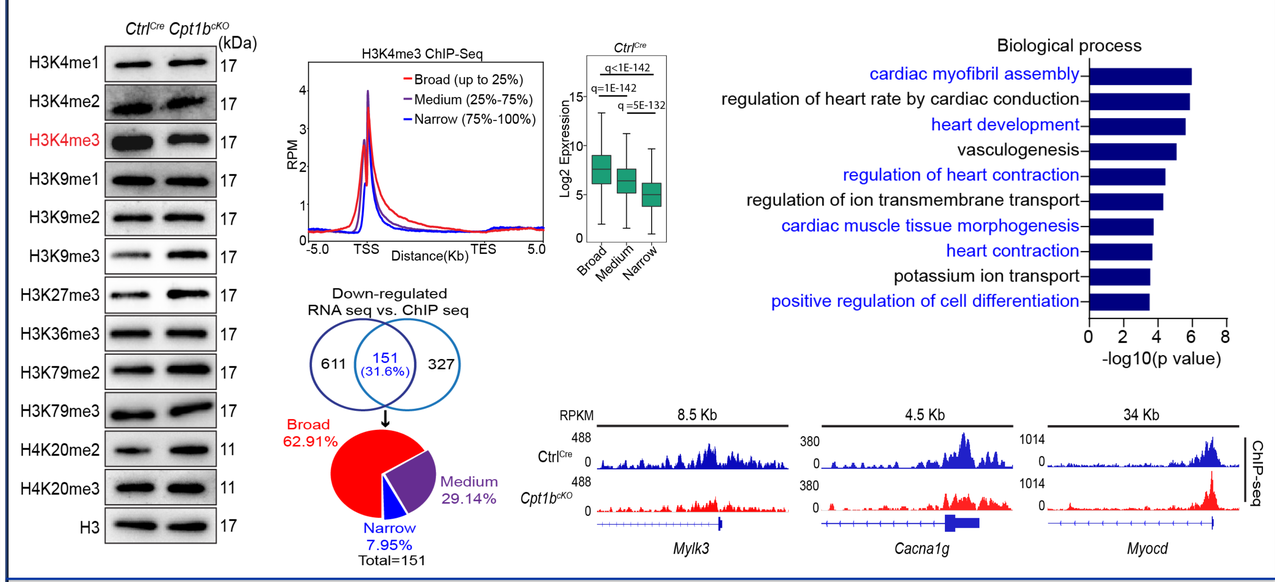
3. Inactivation of *Cpt1b* protects the myocardium from ischemia/reperfusion damage and enables heart regeneration



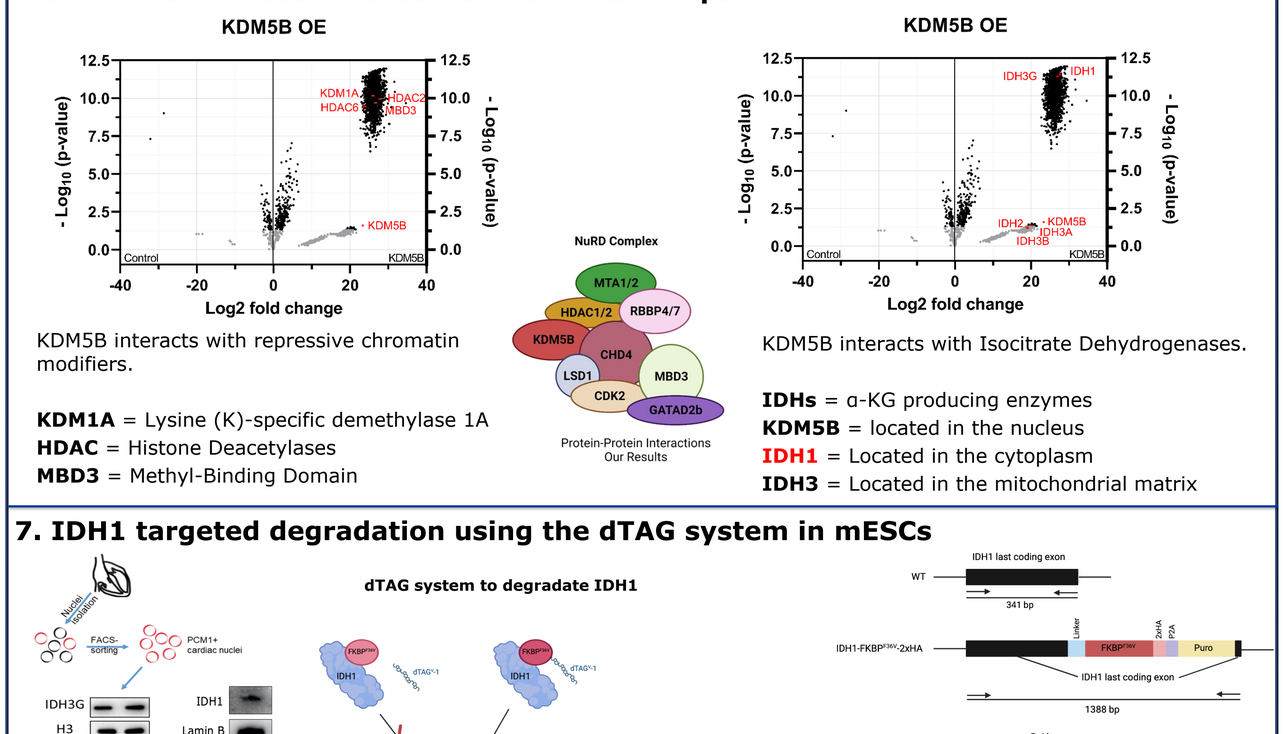
4. Failure of fatty acid import into mitochondria dramatically increases αKG levels



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



6. Kdm5b interacts with IDH1 and NuRD complex



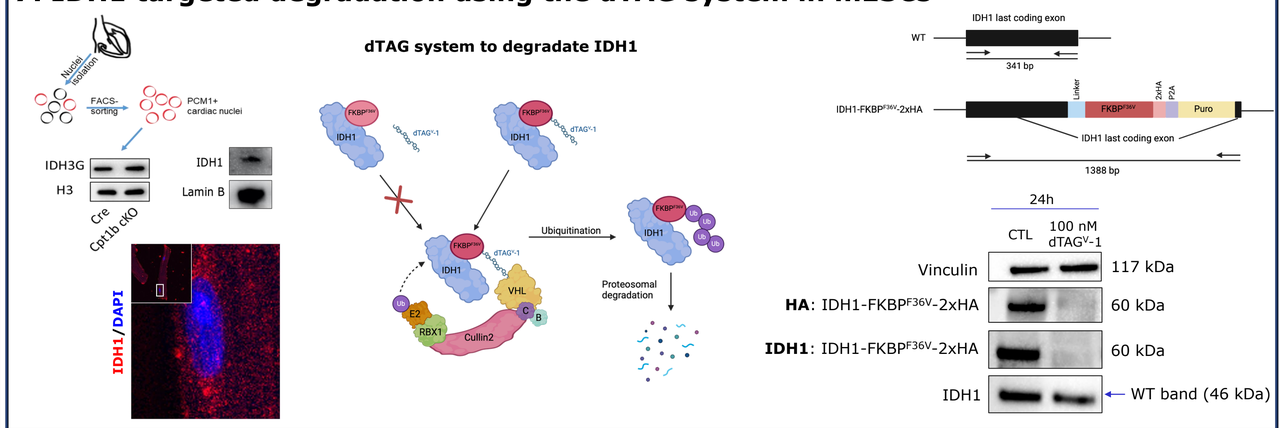
KDM5B interacts with repressive chromatin modifiers.

KDM1A = Lysine (K)-specific demethylase 1A
HDAC = Histone Deacetylases
MBD3 = Methyl-Binding Domain

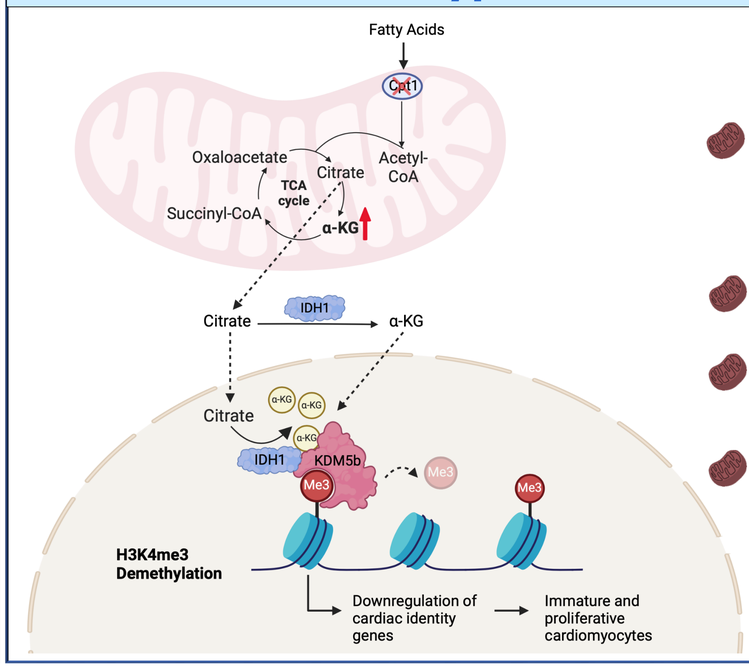
KDM5B interacts with Isocitrate Dehydrogenases.

IDHs = α-KG producing enzymes
KDM5B = located in the nucleus
IDH1 = Located in the cytoplasm
IDH3 = Located in the mitochondrial matrix

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 counting for 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