Fibroblast growth factor receptor signaling in endothelium mediates post-ischemic vascular remodeling and functional recovery in an in vivo, closed-chest model of acute myocardial infarction

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FGF2 and Cardioprotection

Isolated work-performing global low-flow IR injury-
  *Fgf2* KO have worsened post-ischemic function
  Cardiac-specific human FGF2 Tg have improved post-ischemic cardiac function and reduced infarct size
  Recombinant FGF2 treatment during early reperfusion improved cardiac function, reduced apoptosis and reduced infarct size

*In vivo* model of regional IR injury-
  Post-IR injury, *Fgf2* KO have worse cardiac function, increased infarct size, increased apoptosis, impaired hypertrophic response, and impaired vascular remodeling
What are the cellular targets of FGF2 in the heart?

How does FGF signaling in different cardiac cell types affect acute IR injury and cardiac remodeling?

Use a genetic approach to remove FGFR1 and FGFR2 in either endothelium, cardiomyocytes, or fibroblasts
Cre-lox System

**Cre Mouse**

**LoxP (Floxed) Mouse**

**Cre LoxP Mouse**

**F₀ Generation**

**F₁ Generation**

Original gene function is disrupted, a reporter gene is transcribed instead.

Original gene function is untouched.

Tie2Cre Promoter

Cre Recombinase

Lox P  FGFR1  Lox P

Lox P  FGFR2  Lox P
Targeting Endothelium

Tie2Cre FGFR1/2 DCKO, mTmG

In the absence of Cre expression:
- Lox P
- TdTomato
- Lox P
- GFP

In the presence of Cre expression:
- Lox P
- GFP
- TdTomato
Baseline Echo Parameters

- **Ejection Fraction %**
  - Wildtype
  - Tie2Cre FGFR1/2 DCKO

- **Fractional Shortening %**
  - Wildtype
  - Tie2Cre FGFR1/2 DCKO

- **Stroke Volume (ml)**
  - Wildtype
  - Tie2Cre FGFR1/2 DCKO

n=5-6
Baseline Vessel Density

- #SMA vessels/10X field
- Number of Capillaries/Nuclei

Wildtype
Tie2Cre FGFR1/2 DCKO

Baseline Vessel Density

n=4
Closed Chest Ischemia-Reperfusion

Instrumentation → 90 min Ischemia → 7 Days Ischemia → 7 Days Reperfusion → Day 1 → Day 7
Echo Analysis of Function Post IR Injury

**Ejection Fraction (%):**
- **Wildtype:** Comparison between 1 day and 7 day post IR injury.
- **Tie2Cre FGFR1/2 DCKO:** Same comparison as above.

**Fractional Shortening (%):**
- **Wildtype:** Comparison between 1 day and 7 day post IR injury.
- **Tie2Cre FGFR1/2 DCKO:** Same comparison as above.

**Stroke Volume (μL):**
- **Wildtype:** Comparison between 1 day and 7 day post IR injury.
- **Tie2Cre FGFR1/2 DCKO:** Same comparison as above.

*\( *p < 0.05 \) vs. wildtype, n=5-6
Echo Analysis of LV Wall Motion Abnormalities
Echo Analysis of Wall Motion Abnormalities

Infarct Size %

Wildtype

Tie2Cre FGFR1/2 DCKO

1 day 7 day

* p<0.05 vs. wildtype, n=5-6
Hypertrophic Response Post-IR Injury

Wildtype

Tie2Cre FGFR1/2 DCKO

Remote

Peri-infarct

Myocyte Cross Sectional Area ($\mu$m$^2$)

Wildtype

Tie2Cre FGFR1/2 DCKO

WGA

DAPI

n=6-8
Smooth Muscle Actin Containing Vessels Post-IR Injury

Wildtype

Tie2Cre FGFR1/2 DCKO

* p<0.05 vs. wildtype, n=5-6
Capillary Density Post-IR Injury

Capillary Size (um²)

Wildtype
Tie2Cre FGFR1/2 DCKO

CD31
DAPI
FITC

*p<0.05 vs. wildtype, n=5-6
Summary

Endothelial-specific ablation of FGFR1 and FGFR2:

No effect in cardiac function or vessel density in the absence of injury

Worsened functional recovery at 7 days after IR

Increased wall motion abnormalities at 7 days after IR

No effect on post-IR cardiac hypertrophic response

Impaired vascular remodeling for both arterioles and capillaries after IR injury
Future Directions

Determine if impaired vascular remodeling is due to increased vascular loss or reduced neovascularization.

Determine endothelial-specific signaling which mediates these effects.

Study effect of FGF signaling in other cardiac cell types and optimize delivery of recombinant FGF2 during reperfusion or remodeling to elicit cardioprotection.
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