Endothelial-specific fibroblast growth factor receptor 1 and 2 deletion impairs vascular remodeling and recovery in an in vivo, closed-chest model of cardiac ischemia-reperfusion injury

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**BACKGROUND AND OBJECTIVES**

Fibroblast growth factor (FGF) signaling is cardioprotective in various models of myocardial infarction. FGF receptors (FGFRs) are expressed in multiple cell types in the adult heart, but the cell type-specific FGFR signaling which mediates different cardioprotective endpoints is currently unknown.

**METHODS**

**Mouse Model of Closed-chest Cardiac Ischemia-Reperfusion Injury:** The mouse model of closed-chest cardiac ischemia-reperfusion injury was performed in the Muscular Cardiomyocyte Phenotyping Core at Washington University in St. Louis School of Medicine. Mice were anesthetized with ketamine/xylazine (100 mg/kg and 5 mg/kg, i.p.) and prepared intracardially through aseptically maintained median sternotomy. Mice were divided into wildtype (WT) and Tie2Cre FGFR1/2 DCKO groups. Controls for these experiments are double fox-2 (Fox-2) and Tie2Cre Fox-2 DCKO mice.

**Echocardiographic determination of baseline functional characteristics of Tie2Cre FGFR1/2 DCKO mice.** There are no alterations in ejection fraction (A), fractional shortening (B), or stroke volume (C) in Tie2Cre FGFR1/2 DCKO mice in the absence of injury. n=5-6.

**Baseline quantification of SMA positive vessel density (A) and capillary density in non-ischemic hearts shows no difference in Tie2Cre FGFR1/2 DCKO hearts compared to wildtype control hearts. n=4.**

**Echocardiographic determination of wall motion abnormalities (A) and LV end-diastolic volume (B) in controls and Tie2Cre FGFR1/2 DCKO hearts after 7 days of reperfusion.** B: Ablation of FGFR1 and FGFR2 in endothelial cells results in decreased capillary density but no change in capillary size after IR injury. n=5-6, *p=0.05 vs. wildtype.

**RESULTS**

**Figure 2:** Echocardiographic determination of baseline functional characteristics of Tie2Cre FGFR1/2 DCKO mice. There are no alterations in ejection fraction (A), fractional shortening (B), or stroke volume (C) in Tie2Cre FGFR1/2 DCKO mice in the absence of injury. n=5-6.

**Figure 3:** Baseline quantification of SMA positive vessel density (A) and capillary density in non-ischemic hearts shows no difference in Tie2Cre FGFR1/2 DCKO hearts compared to wildtype control hearts. n=4.

**Figure 6:** (A) Echocardiographic determination of wall motion abnormalities at 1 day and 7 days after in vivo IR injury. (B) Tie2Cre FGFR1/2 DCKO hearts show increased hypokinetic area compared to wildtype control hearts at 7 days but not 1 day after IR injury. n=5-6, *p=0.05 vs. wildtype.

**Figure 9:** A: Representative images of CD31 staining capillaries in the peri-infarct area of wildtype and Tie2Cre FGFR1/2 DCKO hearts 7 days after 7 days of shortening. B: Ablation of FGFR1 and FGFR2 in endothelial cells results in decreased capillary density but no change in capillary size after IR injury. n=5-6, *p=0.05 vs. wildtype.

**CONCLUSION**

Ablation of FGFR1 and FGFR2 in endothelial cells does not affect the cardiac hypertrophic response to IR injury.

Vascular remodeling after IR injury is impaired in mice with endothelial-specific ablation of FGFR1 and FGFR2.

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