Cardioprotection by endogenous fibroblast growth factor 2 in cardiac ischemia-reperfusion injury in vivo

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Cardioprotection by Endogenous Fibroblast Growth Factor 2 in Cardiac Ischemia-Reperfusion Injury *In Vivo*

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Fibroblast Growth Factor 2

22 different FGF family members (10 in heart)

FGF2 or basic FGF – first member of the FGF family identified, expressed fairly ubiquitously

FGF2 expressed in all developmental stages of heart; found in cardiomyocytes, fibroblasts, endothelium

FGF2 known functions:
- Hematopoiesis
- Angiogenesis
- Wound Healing
- Mesoderm Induction
- Cell Survival/Death
- Cardiac Hypertrophy
FGF2 Isoforms

FGF2 mRNA (1) (484) (951)

5’ CUG (86) CUG (319) CUG (346) CUG (361) AUG (486) Stop(951) 3’

34 kDa

24 kDa

22.5 kDa

22 kDa

18 kDa

Nuclear localization signal

nuclear

cytoplasmic

Nuclear

LMW

HMW
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
  - reduced infarct size

FGF2-induced cardioprotection mediated through PKC,
  MAPK, and NOS signaling
What is the *in vivo* cardioprotective efficacy of FGF2?
FGF2 Knockout

Targeted ablation of all isoforms of FGF2

Viable and fertile

No difference from wildtype with respect to cardiac morphometry, function, or vessel density
Closed Chest Ischemia-Reperfusion

Instrumentation

90 min Ischemia

7 Days

7 Days Reperfusion

Echo Day 1

Echo Day 7

From Dewald et al. 2004
Echo Determination of Ejection Fraction
Endogenous FGF2 in Cardiac Function Post IR Injury

Endogenous FGF2 in Cardiac Function Post IR Injury

Ejection Fraction %

<table>
<thead>
<tr>
<th></th>
<th>1 day</th>
<th>7 day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wildtype</td>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td>FGF2 KO</td>
<td>40</td>
<td>30</td>
</tr>
</tbody>
</table>

n=6

*p<0.05 vs. wildtype
Echo Analysis of LV Wall Motion Abnormalities

Serial short-axis slices of the LV 1 month post-MI

Kanno et al, JASE 2002;15:601
Echo Analysis of LV Wall Motion Abnormalities

![Graph showing % Infarct Size for Wildtype and FGF2 KO at 1 day and 7 days, with * indicating p<0.05 vs. wildtype.]

n=6

*p<0.05 vs. wildtype
Trichrome Staining of Fibrosis

Wildtype

Fgf2 KO
Picosirius Red Stain of Collagen Fibrils
Endogenous FGF2 Effect on Cardiac Hypertrophy

Heart Wt vs. Body Wt Ratio

Wildtype
FGF2 KO

n=7
Myocyte Area Staining

Wildtype

Fgf2 KO
Myocyte Cross Sectional Area Post IR Injury

n=6
Smooth Muscle Actin Staining

Wildtype

Fgf2 KO
Vessel Density After IR injury

- SMA (# vessels/10X field)
  - Wildtype
  - Fgf2 KO

- Diameter (µm)
  - Wildtype
  - Fgf2 KO

- Vessel Area / 10X field (µm²)
  - Wildtype
  - Fgf2 KO

n=6

*p<0.05 vs. wildtype
Future Directions

Analysis of capillary density and vascular remodeling at early time points post IR injury

Analysis of inflammatory response post IR injury
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