IGFBP-3 aggravates post-ischemic liver injury

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IGF-IGFBP axis

High-affinity IGF binders

- IGFBP-1
- IGFBP-2
- IGFBP-3
- IGFBP-4
- IGFBP-5
- IGFBP-6

150kD complex
130kD complex

Low-affinity IGF binders

- IGFBP-rPs
- IGFBP proteolyzed fragments

IGFBP protease

M6P

IGFBP(s) receptor(s)

αα

Type I IGF receptor

Type II IGF receptor

IGFBP-rP(s) receptor(s)

Hwa V et al., Endocrine Reviews (1999)
IGF/IGF-1R-dependent and –independent actions of IGFBP-3
Nuclear localization of IGFBP-3

- IGFBP-3 endocytic entry into cell via transferrin and caveolin
- Phosphorylation of IGFBP-3 at S156 by DNA-PK
- NLS on IGFBP-3 allows importin β to transport IGFBP-3 to the nucleus

(A) Heterodimerization of RXRα/Nur77 regulates transcriptional activities in the nucleus
(B) IGFBP-3 binds to RXRα and induces translocation of Nur77 to the mitochondria

Jogie-Brahim S. et al., *Endocrine Reviews* (2009)
Mechanisms involved in hepatic I/R injury

HC  Ca\textsuperscript{2+}  iNOS

Plts  KC  Cytokines  ROS  ET  NO

Serotonin

Leukotrienes  PAF

Adhesion molecules  Complement

ATP  PMNs
Hepatic ischemia-reperfusion model

- Ad-IGFBP-3
- Ad-mtIGFBP-3
  - IGFBP-3^{GGG}
  - devoid of IGF binding affinity
Hepatic IGFBP-3 protein expression after I/R injury
IGFBP-3 expression after adenovirus injection

A

<table>
<thead>
<tr>
<th>Ad-IGFBP-3 (day)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGFBP-3</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-actin</td>
<td></td>
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</tbody>
</table>

B

Sham | Saline | Ad-LacZ | Ad-IGFBP-3 | Ad-mtiIGFBP-3

C

Ad-LacZ

Ad-IGFBP-3

Ad-mtiIGFBP-3
Increase of hepatic I/R injury by IGFBP-3

The graph shows the enzyme activities (AST and ALT) in different groups. The bars represent the mean ± standard error of the mean (SEM) for each group. The groups are as follows:

- Sham
- Saline
- Ad-LacZ
- Ad-IGFBP3
- Ad-mtIGFBP3

The y-axis represents the enzyme activity in IU/L, while the x-axis represents the different groups with I/R indicated. The asterisks (*) and double asterisks (##) indicate statistical significance compared to the Sham group.
Increase of hepatic I/R injury by IGFBP-3

<table>
<thead>
<tr>
<th>Sham</th>
<th>Saline</th>
<th>Ad-LacZ</th>
<th>Ad-IGFBP3</th>
<th>Ad-mtIGFBP3</th>
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</thead>
<tbody>
<tr>
<td><img src="image1" alt="Sham" /></td>
<td><img src="image2" alt="Saline" /></td>
<td><img src="image3" alt="Ad-LacZ" /></td>
<td><img src="image4" alt="Ad-IGFBP3" /></td>
<td><img src="image5" alt="Ad-mtIGFBP3" /></td>
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</table>
Increase of neutrophil infiltration by IGFBP-3
Inhibition of NF-κB activation by IGFBP-3
Inhibition of NF-κB activation by IGFBP-3

Sham

Saline

Ad-LacZ

Ad-IGFBP-3

Ad-mtIGFBP-3

Positive/total hepatocytes (%)
Increased levels of proinflammatory cytokines

**A**

- **ICAM-1/GAPDH**
  - Sham
  - Saline
  - Ad-LacZ
  - Ad-IGFBP-3
  - Ad-mtIGFBP-3

- **TNF-α/GAPDH**
  - Sham
  - Saline
  - Ad-LacZ
  - Ad-IGFBP-3
  - Ad-mtIGFBP-3

- **IL-1β/GAPDH**
  - Sham
  - Saline
  - Ad-LacZ
  - Ad-IGFBP-3
  - Ad-mtIGFBP-3

**B**

- **TNF-α (pg/mL)**
  - Sham
  - Saline
  - Ad-LacZ
  - Ad-IGFBP-3
  - Ad-mtIGFBP-3

- **IL-1β (pg/mL)**
  - Sham
  - Saline
  - Ad-LacZ
  - Ad-IGFBP-3
  - Ad-mtIGFBP-3
Elimination of the protective effect of IPC

A

- Virus injection
- EMSA Western RT-PCR
- AST, ALT Cytokine
- Histology
- Ischemia
- Reperfusion

B

- Saline
- Ad-LacZ
- Ad-IGFBP-3
- Ad-mtIGFBP-3

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>I/R</td>
<td></td>
<td>AST</td>
<td>ALT</td>
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<td>IPC</td>
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Summary

1. Overexpression of IGFBP-3 aggravated hepatic I/R injury.

2. The aggravation was associated with NF-κB suppression, increased production of proinflammatory cytokines and neutrophil infiltration.

3. IGFBP-3 has these effects mainly in a ligand-independent manner because Ad-mtIGFBP-3 also had the similar effects as compared with Ad-IGFBP-3.
감사합니다