The role of the c-Jun N-terminal kinase (JNK) in insulin resistance

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Inflammation is at the origin and/or the progression of many diseases
Inflammation is at the origin and/or the progression of many diseases.
Metabolism and immunity are closely linked

Obesity is a major risk factor for a vast array of diseases.
Many alterations are found in the hypertrophic adipocyte
JNK is activated by insulin signaling
JNK activation down-regulates insulin signaling.
Exacerbated JNK activation induces insulin resistance
Inflammatory pathway activation in adipocytes and macrophages

The role of the JNK pathway in insulin resistance

* The involvement of JNK in the antidiabetic action of TZD/PPAR$_\gamma$

* *In vivo* effects of JNK activation in pancreatic $\beta$-cells
GC/GR-JNK pathway negative crosstalk

Actions of the nuclear receptor-JNK pathway crosstalk

Ligand

Pro-inflammatory cytokines
Stress

MEKK1

M KK7

JNK

NR

Anti-inflammatory

Anti-diabetic

Inflammation

Caelles et al. (1997) Genes & Dev. 11, 3351-64
Díaz-Delfín et al. (2007) Diabetes 56, 1865-71
TZDs inhibit JNK activation in a PPARγ–dependent manner

A. 3T3L1 adipocytes

<table>
<thead>
<tr>
<th>Treatment</th>
<th>GST-c-Jun</th>
<th>JNK</th>
</tr>
</thead>
<tbody>
<tr>
<td>veh</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF</td>
<td></td>
<td></td>
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<tr>
<td>Rosi/TNF</td>
<td></td>
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<tr>
<td>Rosi</td>
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</table>

Fold increase: 1 4.8 2.2 1.1

B. In vivo

<table>
<thead>
<tr>
<th>Treatment</th>
<th>JNK Activity (fold increase)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosi</td>
<td></td>
</tr>
<tr>
<td>Ob/ob</td>
<td>*</td>
</tr>
<tr>
<td>Lean</td>
<td></td>
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</tbody>
</table>

Díaz-Delfín et al. (2007) Diabetes
JNK1 inhibition mediates TZD insulin-sensitizing action

**Glucose tolerance test**

**WT mice**

**JNK1 KO mice**

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**Díaz-Delfín et al. (2007) Diabetes**
Exacerbated JNK activity induces insulin resistance

Exacerbated JNK activity induces insulin resistance
JNK pathway inhibition mediates TZD/PPAR\textsubscript{γ} insulin-sensitizing action
The role of the JNK pathway in insulin resistance

* The involvement of JNK in the antidiabetic action of TZD/PPAR\(\gamma\)

* *In vivo* effects of JNK activation in pancreatic \(\beta\)-cells
JNK inhibition by TZDs in insulin-secreting cell lines protects from IL-1β-induced apoptosis

Díaz-Delfín et al. (2007) Diabetes
Cre-conditional transgene encoding a constitutively-activated mutant of the JNK MAP2K MKK7

Lanuza et al. (2013) Diabetes
Generation of a transgenic mouse for conditional activation of JNK \textit{in vivo}

Lanuza et al. (2013) Diabetes
JNK activation in pancreatic β cells alter neither the overall islet structure nor their insulin content and does not induce β-cell death.

Normal islet shape and size
Normal α/β cell proportion and distribution
Normal size of the pancreas

Normal pancreatic and islet insulin content
No caspase 3 activation

Lanuza et al. (2013) Diabetes
JNK activation in pancreatic \(\beta\)-cells does not affect basal glycemia or insulinemia

Lanuza et al. (2013) Diabetes
JNK activation in pancreatic β cells leads to glucose intolerance due to impairment of glucose-induced insulin secretion.

Lanuza et al. (2013) Diabetes
JNK activation in pancreatic $\beta$ cells does not interfere with the first phase of glucose-induced insulin secretion.

Lanuza et al. (2013) Diabetes
JNK activation in pancreatic \( \beta \) cells interferes with the second phase/insulin-dependent glucose-induced insulin secretion.
JNK activation blocks insulin signaling in pancreatic β cells 
*in vivo*

<table>
<thead>
<tr>
<th>Control</th>
<th>Glu</th>
<th>Ins</th>
<th>MKK7D</th>
<th>Glu</th>
<th>Ins</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="Pdx-1" alt="Image" /></td>
<td><img src="Insulin" alt="Image" /></td>
<td><img src="Dapi" alt="Image" /></td>
<td><img src="Merge" alt="Image" /></td>
<td><img src="Pdx-1" alt="Image" /></td>
<td><img src="Insulin" alt="Image" /></td>
</tr>
</tbody>
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Lanuza et al. (2013) Diabetes
Rosiglitazone treatment alleviates insulin resistance induced by JNK activation in pancreatic β cells

Lanuza et al. (2013) Diabetes
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