Introduction

- Puromycin aminonucleoside (PAN) is a podocyte toxin inducing a loss and fusion of podocytes foot processes.
- Repeated PAN injections in rats lead to a direct DNA damage via the production of reactive oxygen species (ROS) and tissue damages, including glomerulosclerosis and interstitial fibrosis.
- c-Jun N-terminal kinase (JNK) is a stress-activated protein kinase which can be induced by various stimuli including ROS and pro-inflammatory cytokines.
- JNK activation seems to play an important role in the development and progression of kidney diseases.

Objective

The aim of this study was to evaluate the preventive and/or curative effect of a JNK inhibitor (XG-102) in a chronic rat model of puromycine aminonucleoside (PAN)-induced nephropathy.

Methods

- **Animals**: rat, Wistar, males (15/group).
- **Nephropathy induction**: PAN was administered i.p. at day 0 (130 mg/kg) and at day 14 (60 mg/kg).
- **Study design**: 2) Hewitson et al., J Saitama Med Univ, 37:1
3) Nakajima et al., J Nephrol, 21:57, 1984
6) Chiara Alfarano et al., J Nephrol, 21:57, 1984

Results

Effect of XG-102 on PAN-induced glomerular damages

**Quantification of glomerular damages**

<table>
<thead>
<tr>
<th>Group</th>
<th>PAN or saline</th>
<th>Treatment</th>
<th>Number of i.v.</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>no</td>
<td>vehicle</td>
<td>7</td>
<td>15</td>
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<tr>
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<td>vehicle</td>
<td>7</td>
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<tr>
<td>3</td>
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<td>XG-102 (1 mg/kg)</td>
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<td>15</td>
</tr>
<tr>
<td>4</td>
<td>yes</td>
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<tr>
<td>5</td>
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<td>XG-102 (4 mg/kg)</td>
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</tr>
</tbody>
</table>

Representative images of HE staining

Compared to untreated rats (A; Group 1), PAN (Group 2) induced:

- B: Focal mesangial cell hypercellularity (circle) with the presence of large and pale cells (arrows);
- C: Thickening of the Bowman’s capsule (arrow) accompanied by glomerular hypercellularity and parietal epithelial hyper trophy/hyperplasia (bracket);
- D: Slight increase in mesangial matrix without mesangial cell increase.

Representative images of HE staining

Effect of XG-102 (i.v.)

Compared to vehicle treated animals (A; Group 2), XG-102 treatment induced:

- No significant effect at 1 mg/kg (B; Group 3):
- A decrease of glomerular damages including both matrix deposition and mesangial hypercellularity (C-D; Group 4, E: Group 5 and F; Group 6) at the doses of 2 and 4 mg/kg, respectively.

Conclusions

The glomerular morphologic and fibrotic changes seen in PAN rats are similar to those observed in human minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS); 4). XG-102 significantly reduced PAN-induced glomerular damages and the beneficial effect of curative treatment is more important than the preventive one. These results suggest that JNK inhibition should represent a good clinical strategy for the treatment of focal segmental glomerulosclerosis in humans.

References

1) Nakajima T et al., J Saitama Med Univ, 37:1-10, 2010
2) Hewitson TD et al., Nephrology, 24:61-67, 1994

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