EFFECTS OF JNK INHIBITOR ON PUROMYCIN AMINONUCLEOSIDE-INDUCED NEPHROPATHY IN RATS

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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:

  - Experimental groups:

    | Group | PAN (i.p.) | Treatment (i.v.) | Number of i.v. administrations | n |
    |-------|------------|------------------|------------------------------|---|
    | 1     | no         | vehicle          | 7                            | 15 |
    | 2     | yes        | vehicle          | 7                            | 15 |
    | 3     | yes        | XG-102 (1 mg/kg) | 7                            | 15 |
    | 4     | yes        | XG-102 (2 mg/kg) | 7                            | 15 |
    | 5     | yes        | XG-102 (4 mg/kg) | 7                            | 15 |
    | 6     | yes        | XG-102 (4 mg/kg) | 4                            | 15 |

- Histology: glomerular damages evaluation by score system on Periodic Acid Schiff (PAS) and hematoxilin/eosin (HE) staining of kidney sections.

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). 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 Satsuma Med Univ, 37:1-10, 2010

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