Rapamycin suppresses astrocytic and microglial activation and reduces development of neuropathic pain after spinal cord injury in mice.

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The mammalian target of rapamycin (mTOR)

【mTOR signaling pathway】

Growth factors → PI3K → Akt → Rheb → mTOR

Effect of rapamycin

- Immunosuppression
- Anti angiogenesis
- Anti cancer
- Extended aging
- Promote autophagy
- Neuroprotection
- Neuroregeneration

Metabolism
Proliferation
Survival
Autophagy
Background

- Rapamycin reduces neural tissue damage and locomotor impairment after SCI in mice. 
  (Sekiguchi, J Neurotrauma. 2011)

- Rapamycin reduces peripheral neuropathic pain in rats 
  (Geranton SM, J Neurosci. 2009)

Rapamycin reduces neuropathic pain after SCI?

Objective

To examine whether rapamycin reduces neuropathic pain after SCI in mice
SCI model

- C57BL/6 mouse (Female, 10-12 weeks)
- Spinal cord contusion injury: Modified NYU Impactor (T10 segment: 10 g rod, height 3 mm)

Rapamycin administration

- Rapamycin-treated group (n=5) (4 hours after SCI, 1 mg/kg, BW)
- Vehicle-treated group (n=5)
Experimental analysis

Behavioral analysis (0-42 days)

- Locomotor function:
  Basso mouse scale (BMS) score, subscore
- Mechanical allodynia: von Frey test
- Thermal allodynia: Hargreaves’ test

Histological analysis (42 days, L2/3)

- Microglia: Iba-1
- Astrocyte: GFAP
- Activation of p38 MAPK: p-p38
- Double-staining: Iba-1 and p-p38

Quantification of immunoreactivity

The box (100 x100 μm) was placed onto areas of the lateral, central and medial superficial dorsal horn of the lumbar spinal cord sections. The total pixels of the stained area were expressed as the immunodensity.
Rapamycin significantly improved locomotion.
Mechanical and Thermal allodynia

Rapamycin significantly improved mechanical and thermal allodynia
Rapamycin significantly suppressed activation of microglia

Activation of astrocytes were relatively reduced by rapamycin
Rapamycin significantly suppressed activation of p38 MAPK.

Rapamycin decreased p-p38 positive cells in microglia.
Discussion

Rapamycin treatment for SCI

Previous study

- Neural tissue damage ↓
- Locomotor function ↑

(Sekiguchi, J Neurotrauma. 2011)

This study

- Mechanical and thermal allodynia ↓
- Activation of glial cells and p38 MAPK in the lumbar spinal cord ↓

Rapamycin reduces neuropathic pain after SCI
Therapeutic mechanism

**Previous study**

- Neuroprotective treatment for acute SCI improved neuropathic pain
  - (Gris, J. Neurosci. 2004)
  - (J. Voda, Neurosci. Res. 2007)
  - (Bao, J Neurotrauma. 2011)

- Rapamycin for SCI in acute phase
  - Neuroprotective effect
  - (Sekiguchi, J Neurotrauma. 2011)

**This study**

- Rapamycin reduced neuropathic pain after SCI

Neuroprotective effect of rapamycin in acute phase improved neuropathic pain after SCI
Conclusions

• Rapamycin significantly improved not only locomotor function but also mechanical and thermal allodynia after SCI.

• Rapamycin significantly attenuated glial activation in the lumbar spinal cord.

• Rapamycin treatment has a significant therapeutic potential to reduce neuropathic pain after SCI.

Disclosure declaration
None of the authors has any potential conflict of interest