TRANSPLANTATION

**ADORA2B HELPS TO
BLOCK LIVER INJURY**

Adenosine signalling is known to have a role in protecting the liver from ischaemia–reperfusion injury—a major cause of morbidity and mortality after liver surgery and transplantation. “Adenosine can signal through four receptors (ADORA1, 2A, 2B and 3), but which receptor mediates liver protection is unclear,” explains Holger Eltzschig, corresponding author of this study. Now, Eltzschig and colleagues from the University of Colorado have shown that the Adora2b adenosine receptor has a crucial role in preventing liver injury in mice.

Initial screening studies of human liver biopsy samples revealed that ADORA2B expression was selectively induced after ischaemia–reperfusion injury. Moreover, in a head-to-head comparison of mice with a gene knockout of each adenosine receptor, only Adora2b was found to protect the liver from injury.

The researchers went on to show that treatment of wild-type mice with an Adora2b-selective antagonist triggered enhanced levels of liver injury after ischaemia. By contrast, an Adora2b agonist attenuated liver injury in wild-type mice, but not *Adora2b*^{−/−} mice. Finally, using mice with tissue-specific deletions of Adora2b, Eltzschig *et al.* revealed that hepatocellular-specific Adora2b signalling has a crucial role in protecting mice from ischaemia–reperfusion injury by attenuating NF-κB activation and subsequent liver inflammation.

“We believe that this approach of combining studies in gene-targeted mice, tissue-specific deletions of adenosine receptors and pharmacologic interventions provides a high level of confidence in the data,” says Eltzschig. “Our key finding from this study is the observation that activation of hepatocellular-specific Adora2b adenosine receptors provide liver protection from ischaemia by attenuating liver cell inflammation,” he adds.

“Our next step is to examine an ADORA2B agonist in the treatment of ischaemia–reperfusion injury in humans, such as that which occurs during liver transplantation,” Eltzschig concludes. “We are also considering working towards finding additional compounds that function as ADORA2B agonists, which could be used safely in clinical practice.”

Katherine Smith

Original article Zimmerman, M. A. *et al.* Signaling through hepatocellular A2B adenosine receptors dampens ischemia and reperfusion injury of the liver. *Proc. Natl Acad. Sci. USA* doi:10.1073/pnas.1221733110