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LIVER

Purified A1AT holds promise as therapy for acute liver failure

Purified α-1-antitrypsin (A1AT) could be a new therapeutic approach for acute liver failure (ALF), according to a study published in *Hepatology*. By suppressing apoptosis and inflammatory responses in the liver, treatment with A1AT prevented the development of acute liver injury and prolonged survival in several established mouse models of ALF, giving the authors hope that this strategy might also be useful in humans.

ALF has high mortality and limited therapeutic options. Treatment is generally only supportive, with liver transplantation often needed to combat the severe liver damage observed (ALF is characterized by rapid liver cell death with loss of function in 80–90% of liver cells). A1AT had already been shown to have anti-inflammatory activities, with purported anti-apoptotic effects. Author Sabina Janciauskiene, explains: "In recent years, several previously unappreciated functions of A1AT have been discovered, including inhibition of apoptosis". Given the importance of apoptosis in the development of ALF, the researchers reasoned that A1AT might have therapeutic potential.

Janciauskiene and colleagues tested A1AT therapy in three different mouse models of ALF that mimick the forms of the condition in humans, the Jo2 FAS/CD95 antibody model and hepatotoxin poisoning models (induced by paracetomol or α-amantin poisioning). After liver damage had been triggered, treatment with A1AT (either the native or oxidized form) inhibited the development of ALF and prolonged survival in all mouse models tested.

Interestingly, the investigators found that A1AT directly inhibited caspase-3 and caspase-8 activity (both caspases have pivotal roles in the apoptosis signalling cascade) in liver homogenates and *in vitro*. Moreover, A1AT treatment in mice with ALF decreased serum levels of the proinflammatory cytokine TNF, as well as TNF-converting enzyme activity.

"Novel protective effects of A1AT therapy during acute liver injury provides a framework for future studies addressing how exogenous A1AT is internalized by liver cells and delays ALF, and what the optimal doses of the therapy are," says Janciauskiene. Given that A1AT is already commercially available and proven to be well tolerated, Janciauskiene hopes for a "fast translation into clinical use" for ALF of a variety of aetiologies.

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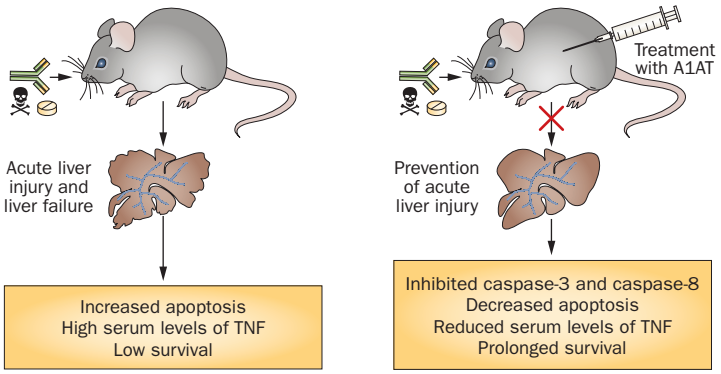

A1AT inhibits acute liver failure in mice. Image developed with S. Wrenger and S. Janciauskiene.

Original article Jedicke, N. *et al.* Alpha-1-antitrypsin inhibits acute liver failure in mice. *Hepatology* doi:10.1002/hep.27024