SPARC (secreted protein acidic and rich in cysteine) knockdown protects mice from acute liver injury by reducing vascular endothelial cell damage

Peixoto E.

Atorrasagasti C.

Aquino J.B.

Militello R.

Bayo J.

Fiore E.

Piccioni F.

Salvatierra E.

Alaniz L.

Garciá M.G.

Bataller R.

Corrales F.

Gidekel M.

Podhajcer O.

Colombo M.I.

Mazzolini G.

Secreted protein, acidic and rich in cysteine (SPARC) is involved in many biological process including liver fibrogenesis, but its role in acute liver damage is unknown. To examine the role of SPARC in acute liver injury, we used SPARC knock-out (SPARC-/-) mice. Two models of acute liver damage were used: concanavalin A (Con A) and the agonistic anti-CD95 antibody Jo2. SPARC expression levels were analyzed in liver samples from patients with acute-on-chronic alcoholic hepatitis (AH). SPARC expression is increased on acute-on-chronic AH patients. Knockdown of SPARC decreased hepatic damage in the two models of liver injury. SPARC-/-mice showed a marked reduction in Con A-induced necroinflammation. Infiltration by CD4+ T cells, expression of

tumor necrosis factor- and interleukin-6 and apoptosis were attenuated in SPARC-/-mice. Sinusoidal endothelial cell monolayer was preserved and was less activated in Con A-treated SPARC-/-mice. SPARC knockdown reduced Con A-induced autophagy of cultured human microvascular endothelial cells (HMEC-1). Hepatic transcriptome analysis revealed several gene networks that may have a role in the attenuated liver damaged found in Con A-treated SPARC-/-mice. SPARC has a significant role in the development of Con A-induced severe liver injury. These results suggest that SPARC could represent a therapeutic target in acute liver injury.