学 位 論 文 の 要 旨

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主論文の題名

Antiapoptotic Effect by PAR-1 Antagonist Protects Mouse Liver Against Ischemia-Reperfusion Injury

主論文の要旨

BACKGROUND: Coagulation disturbances in several liver diseases lead to thrombin generation, which triggers intracellular injury via activation of protease-activated receptor-1 (PAR-1). Little is known about the thrombin/PAR-1 pathway in hepatic ischemia-reperfusion injury (IRI). The present study aimed to clarify whether a newly selective PAR-1 antagonist, vorapaxar, can attenuate liver damage caused by hepatic IRI, with a focus on apoptosis and the survival-signaling pathway.

METHODS: A 60-min hepatic partial-warm IRI model was used to evaluate PAR-1 expression in vivo. Subsequently, IRI mice were treated with or without vorapaxar (with vehicle). In addition, hepatic sinusoidal endothelial cells (SECs) pretreated with or without vorapaxar (with vehicle) were incubated during hypoxia-reoxygenation in vitro.

RESULTS: In naïve livers, PAR-1 was confirmed by immunohistochemistry and immunofluorescence analysis to be located on hepatic SECs, and IRI strongly enhanced PAR-1 expression. In IRI mice models, vorapaxar treatment significantly decreased serum transaminase levels, improved liver histological damage, reduced the number of apoptotic cells as evaluated by terminal deoxynucleotidyl transferase dUTP nick end labeling staining (median: 135 versus 25, P = 0.004), and induced extracellular signal-regulated kinase 1/2 (ERK 1/2) cell survival signaling (phospho-ERK/total ERK 1/2: 0.96 versus 5.34, P = 0.004). Pretreatment of SECs with vorapaxar significantly attenuated apoptosis and induced phosphorylation of ERK 1/2 in vitro (phospho-ERK/total ERK 1/2: 0.66 versus 3.04, P = 0.009). These changes were abolished by the addition of PD98059, the ERK 1/2 pathway inhibitor, before treatment with vorapaxar.

CONCLUSIONS: The results of the present study revealed that hepatic IRI induces significant enhancement of PAR-1 expression on SECs, which may be associated with suppression of survival signaling pathways such as ERK 1/2, resulting in severe apoptosis-induced hepatic damage. Thus, the selective PAR-1 antagonist attenuates hepatic IRI through an antiapoptotic effect by the activation of survival-signaling pathways.