学位論文審査結果の要旨

所　属	三重大学大学院医学系研究科 甲　生命医科学専攻　臨床医学系講座 肝胆膵・移植外科学分野	氏　名	野口（のぐち）　大介（だいすけ）
審　査　委　員	主　査　竹井　謙之 副　査　西村　有平 副　査　渡邉　昌俊		

（学位論文審査結果の要旨）

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

【主論文審査結果の要旨】

著者らは論文において下記の内容を述べている。

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.

以上のように本論文は、PAR-1 と PAR-1 由来の組織障害シグナルが、肝切除や肝移植に伴い重篤な肝障害の原因となる肝虚血再灌流障害の病態増悪に関連する可能性を示し、更に、PAR-1 の antagonist である vorapaxar を用いて PAR-1 由来シグナルを抑制することで、肝 IRI が制御できることを示した。また、その作用機序として細胞生存シグナルである ERK 1/2 の活性化と、それに続く caspase 9 活性化の抑制という経路を明らかにし、最終的に抗アポトーシス効果がもたらされることを示した論文であり、学術上極めて有益であり、学位論文として価値あるものと認めた。

Journal of Surgical Research
Reserved: 28 May 2019
Accepted: 19 September 2019

Daisuke Noguchi, MD, Naohisa Kuriyama, MD, Takahiro Ito, MD, Takehiro Fujii, MD, Hiroyuki Kato, MD, Shugo Mizuno, MD, Hiroyuki Sakurai, MD, and Shuji Isaji, MD