— S-107 —

Heat shock protein 90 억제제의 간성상세포 활성 및 생존에 미치는 영향

서울대학교 의과대학 내과학교실, 간연구소

*김보현 · 명선정 · 김원 · 장자준 · 이성희 · 이수미 · 윤정환 · 이효석 · 김정룡

Background/Aims : Activated hepatic stellate cells (HSCs) are major participants in hepatic fibrosis, and thus, the induction of HSC apoptosis has been proposed as an anti-fibrotic treatment. Heat shock protein (Hsp) 90 is a molecular chaperone that maintains the stability of major signal transduction proteins, and its inhibitor has anti-tumor activity since cancer cells are particularly dependent on Hsp90 for their survival. In this study, the susceptibility of HSCs to Hsp90 inhibitor was evaluated by examining if this inhibitor may induce HSC apoptosis and attenuate HSC activation. **Methods :** LX-2 cells, an immortalized human HSC line, 17-(allylamino)-17-demethoxygeldanamycin (17AAG), an Hsp90 inhibitor, and monensin, an acidic sphingomyelinase inhibitor, were used in this study. Cellular apoptosis was quantified by DAPI staining, and signaling cascades were explored using immunoblot and immunoprecipitation techniques. NFkB activity was evaluated by immunofluorecent microscopyand ELISA method. Collagen 1 and α-smooth muscle actin expression was examined with real time RT-PCR and immunoblot, respectively. **Results :** Hsp90 inhibitor induced HSC apoptosis. In particular, caspase 8 cleavage preceded downstream activation of apoptotic signaling cascades. This caspase 8 activation was dependent on acidic sphingomyelinase activity, which is responsible for ceramide generation. In addition, Hsp90 inhibitor prevented NFkB nuclear translocation and activation, specifically by inducing complex formation of NFkB and glucocorticoid receptor. Accordingly, NFkB-dependent cFLIP expression level was decreased following Hsp90 inhibitor treatment. Finally, Hsp90 inhibitor down-regulated collagen 1 and α-smooth muscle actin expression levels in HSCs prior to inducing apoptosis. **Conclusions :** These results demonstrate that Hsp90 inhibitor induces HSC apoptosis via sphingomyelinase- and NFkB-dependent mechanism. Since this inhibitor also reduces HSC activation prior to apoptosis, 17AAG treatment might therapeutically be useful as an anti-fibrotic strategy in a variety of liver diseases.

— S-108 —

A remnant cystic duct cancer presenting as a duodenal submucosal tumor

Department of Internal Medicine, Pusan National University School of Medicine, Busan, Korea

*Jae Sup Eum, MD, Gwang Ha Kim, MD, Chan Ho Park, MD ·

A 45-year-old man was referred to our institution because of a submucosal tumor (SMT) of the duodenum, which was detected incidentally by gastroduodenoscopy. He had a history of a cholecystectomy because of cholecystolithiasis 20 years previously. During the gastroduodenoscopy, a SMT-like lesion, covered by white exduates, was observed at the duodenal bulb.The EUS examination revealed a 2.4 cm x 1.5 cm hypoechoic mass with an irregular margin on the remnant cystic duct that extended to the common bile duct and duodenum.The abdominal CT scan showed an abnormal soft tissue mass in the distal portion of remnant cystic duct. A total resection of the extrahepatic bile duct and remnant cystic duct was performed. On the gross examination of the surgical specimen, a poorly demarcated irregular firm mass (2.0 cm x 1.5 cm x 0.8 cm) was identified with its center located in the remnant cystic duct. Histopathologically the tumor was composed of poorly differentiated adenocarcinoma with no lympho-vascular invasion.The final diagnosis was a remnant cystic duct cancer. After removal of the tumor,the patient was well and without recurrence at the last six-month follow-up.