일반연제 I-2

# Inactivating Mutations of the Siah-1 Gene in Gastric Cancers

가톨릭대학교 의과대학 병리학교실, [1]외과학교실

박원상, 김창재, 박조현[1], 김수영, 남석우, 이석형, 유남진, 이정용

Siah-1 is the mammalian homolog of Drosophila seven in absentia (Sina) and has been identified as a p53-inducible gene upregulated during physiological apoptosis and model systems of tumor suppression. Siah-1 can also induce cell cycle arrest, tumor suppression, and apoptosis through a novel β-catenin degradation pathway. To determine whether genetic alterations of Siah-1 gene is involved in the development and/or progression of gastric cancer, we performed mutational and functional analysis of Siah-1 in 95 unselected gastric cancers. In mutational analysis, we found two missense mutations of the Siah-1 gene, C to T transition at codon 31 and A to C transversion at codon 208, respectively. The effect of Siah-1 on β-catenin degradation was further examined in wild-and mutant-type Siah-1 transfected cells. Interestingly, wild-type Siah-1 promotes downregulation of β-catenin, but two mutants of Siah-1 stabilize β-catenin. To confirm that Siah-1 is a p53-inducible gene, the cytoplasmic levels of β-catenin were analyzed in Siah-1 transfected cells after treatment with adriamycin. Wild-type Siah-1 dramatically reduced cytoplasmic β-catenin level, whereas two mutant-type Siah-1 did not show any difference in the cells before and after adriamycin treatment. These observations indicate that Siah-1 mediate a novel β-catenin degradation pathway linking p53 activation and that inactivating mutations of Siah-1 may contribute to the development of gastric cancer.