Mutational Analysis of the caspase-10 Gene in Gastric Cancer

Won Sang Park, Jong Heun Lee, Cho Hyun Park¹, Nam Jin Yoo, Jung Young Lee

¹Departments of Pathology and Surgery, College of Medicine, The Catholic University of Korea

**Background** As the concept of cancer as an apoptotic disease is gaining ground, it is important to evaluate the genetic alteration of the apoptosis-associated gene in cancers. Gastric cancer is one of the human tumors with frequent LOH at chromosome 2q33 where the caspase-8 and -10 genes reside. Resistance against Fas-mediated apoptosis may lead to longer survival of affected tumor cells and contribute to the development of lymphoid- and nonlymphoid-lineage malignancies.

**Methods** We have analyzed the genetic alteration of the entire coding region and all splice sites of caspase-8 and -10 genes in ninety-nine gastric cancers by PCR-SSCP-sequencing.

**Results** Three gastric cancers (3%) were found to have the caspase-10 mutation, which were identified in the coding regions of the death effector (DED) domain (codon 147) and the p17 large protease domain (codon 257 and 410), whereas no mutation was detected in caspase-8. We also found LOH of the caspase-8 and -10 in nine (28%) of thirty-two and in four (15%) of twenty-six informative cases, respectively. Interestingly, one case with the caspase-10 mutation showed LOH in the remaining allele, indicating the inactivation of both alleles. In vitro expression studies, all of the mutations impair caspase-10-mediated apoptosis. In addition, coexpression of the caspase mutant, Q257stop, with Fas and DR5 also showed inhibition of apoptosis.

**Conclusion** The data presented here suggest that somatic alterations of the caspase-10 genes might contribute to the pathogenesis in a subset of gastric cancers through the loss of their apoptotic function and that the caspase-10 gene might be possible candidate tumor suppressor genes on 2q33.