Frequent Monoallelic Inactivation of the PTEN Tumor Suppressor Gene in Human Gastric Adenocarcinoma

Do-Sun Byun, Sung-Gil Chi

Department of Pathology, College of Medicine, Kyung Hee University, Seoul, Korea

Background Mutational alterations of PTEN are frequently observed in many types of human malignancies and in cancer predisposition syndromes. To explore the implication of PTEN inactivation in gastric tumorigenesis, we characterized PTEN in 121 gastric tissues and cell lines.

Methods Expression and mutation status of PTEN were examined by quantitative polymerase chain reaction (PCR) and single-strand conformation polymorphism analysis. Loss of heterozygosity (LOH) and methylation-specific PCR analyses were performed to define allelic loss and methylation status of the gene.

Results Abnormal reduction of PTEN expression was detected in 2 of 6(33.3%) cell lines and 20 of 55(36.4%) primary carcinomas whereas none of 60 normal and benign tumor tissues showed altered expression. Tumor-specific reduction of PTEN was found in 18 of 48(37.5%) matched sets. Despite a significant LOH(46.4%) of the gene, none of the tumors examined showed homozygous deletion or mutational disruption of the remaining allele. Allelic loss was more frequently observed in advanced tumors compared to early stage tumors and showed a strong association with low expression. Additionally, in some tumors that retain heterozygosity, reduced expression of PTEN was associated with monoallelic hypermethylation of PTEN promoter. Likely LOH tumors, any types of mutations were recognized in PTEN transcripts expressed from the unmethylated alleles in these tumors.

Conclusion We demonstrate that PTEN expression is abnormally reduced in a substantial fraction of gastric carcinomas through the allelic deletion of the gene or monoallelic transcriptional silencing via aberrant hypermethylation. In addition, absence of biallelic inactivation of PTEN in malignant carcinomas strongly suggests that monoallelic inactivation of PTEN might be sufficient for the malignant progression of gastric carcinoma. Collectively, our observations of frequent monoallelic inactivation of the PTEN gene, particularly in advanced stages of tumors suggest that PTEN might play as a tumor suppressor of haploinsufficiency in gastric tumorigenesis.