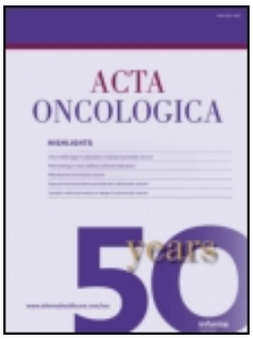

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LETTER TO THE EDITOR

Kinase domain mutation of NTRK3 gene is uncommon in gastric carcinomas

JONG WOO LEE, YOUNG HWA SOUNG, SU YOUNG KIM, SUK WOO NAM, WON SANG PARK, JUNG YOUNG LEE, NAM JIN YOO & SUG HYUNG LEE

Department of Pathology, College of Medicine, The Catholic University of Korea, Seoul, Korea

Protein kinases regulate intracellular signal-transduction pathway mediating cell proliferation, differentiation and survival [1]. Protein kinase family is one of the most frequently mutated gene family found in human cancers and thus are potential therapeutic targets for human cancers [1]. Neurotrophic tyrosine kinase receptor type 3 (NTRK3), also referred to as TrkC, is a receptor tyrosine kinase and plays an important role in the development of neural tissues [2]. NTRK3 expression is not restricted to neural tissues, and various types of tissues, including the gastrointestinal epithelia (stomach, small intestine and colon), have also been shown to express NTRK3 [3]. These data suggest a role of NTRK3 in the growth and maintenance of the gastrointestinal cells.

Recently, Bardelli et al. [4] analyzed 138 tyrosine kinase genes in 147 colorectal cancer tissues for the detection of the somatic mutations. They identified 46 mutations in 14 genes. Of those, seven genes (NTRK3, FES, KDR, EPHA3, NTRK2, MLK4 and GUCY2F) were mutated in more than one tumor. NTRK3 gene mutations were found in six (4.1%) of the 147 colorectal cancers. Of note, the NTRK mutations were exclusively identified in the kinase domain. Because NTRK3 is expressed in gastric epithelium as well as in colorectal epithelium [3], we hypothesized that gastric carcinomas might also harbor NTRK3 mutation. To see whether alteration of NTRK3 gene is involved in the tumorigenesis of gastric carcinoma, we analyzed NTRK3 gene for the detection of somatic mutations in gastric carcinomas by polymerase chain reaction (PCR)-based single strand conformation polymorphism (SSCP) assay.

We analyzed methacarn-fixed tissues of 140 gastric carcinomas. All of the patients of the cancers were Asians (Koreans). The gastric carcinomas consisted of 60 diffuse-type, 49 intestinal-type and 31 mixed-type gastric adenocarcinomas by Lauren's classification, and 25 early and 115 advanced gastric carcinomas according to the depth of invasion. Malignant cells and normal cells from the same patients were selectively procured from hematoxylin and eosin-stained slides using a 30G1/2 hypodermic needle (Becton Dickinson, Franklin Lakes, NJ) affixed to a micromanipulator, as described previously [5]. DNA extraction was performed by a modified single-step DNA extraction method [5]. Because NTRK3 mutations were previously detected only in the exons 15 – 17 [4], we analyzed these three exons in this study. Genomic DNA each from tumor cells and corresponding normal cells were amplified with three primer pairs covering the DNA sequences in the exon 15 – 17 by PCR. Radioisotope ([^{32}P]dCTP) was incorporated into the PCR products for detection by SSCP autoradiogram. Other procedures of PCR and SSCP analysis were performed as described previously [5]. However, the PCR-SSCP analysis and subsequent DNA sequencing of the NTRK3 gene identified no mutation in the 140 gastric adenocarcinomas. We repeated the experiments twice, including PCR, SSCP and sequencing analysis to ensure the specificity of the results, and found that the data were consistent.

Correspondence: Sug Hyung Lee, Department of Pathology, College of Medicine, The Catholic University of Korea, 505 Banpo-dong, Socho-gu, Seoul 137-701, Korea. Tel: +82 2 5901188. Fax: +82 2 5376586. E-mail: suhulee@catholic.ac.kr

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In contrast to the occasional occurrence of the NTRK3 mutations in colorectal cancers, we detected no NTRK3 kinase domain mutation in the gastric carcinoma samples. Our data suggests that the NTRK3 gene mutation is not common in gastric carcinomas and may not contribute to the development of gastric carcinomas. Therapeutically, mutated tyrosine kinases have become rational targets for cancer treatments [1]. The NTRK3 mutation data in the colorectal cancers suggest a possibility of therapeutic targeting of the mutated NTRK3. However, the present data suggested the low possibility of targeting NTRK mutants in the anti-neoplastic therapy against gastric carcinomas.

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