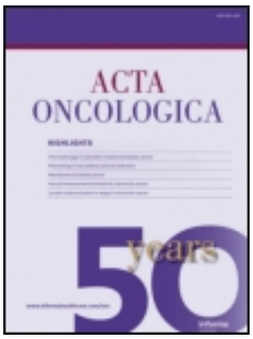

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LETTER TO THE EDITOR

Mutational analysis of *PDPK1* kinase domain in gastric, colorectal and lung carcinomas

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To the Editor

Deregulation of protein kinases involved in modulating cell proliferation and survival is often associated with malignant transformation [1]. 3-phosphoinositide dependent protein kinase 1 (*PDPK1*), also referred to as *PDK1*, is a serine/threonine kinase. *PDPK1* activates diverse downstream molecules, including akt, pka, pkc-zeta, p70s6k and p90s6k, suggesting its functions as a master control point for the activation of a number of signaling pathways involved in cellular proliferation and survival [2]. Recently, Parsons et al. [3] analyzed 340 serine/threonine kinase genes in 204 colorectal cancer tissues for the detection of the somatic mutations. Of them, five genes (*MYLK2, MAP2K4, PDPK1, PAK4* and *AKT2*) were mutated in more than one tumor. *PDPK1* gene mutations were found in three (1.4%) of the 204 colorectal cancers. Of these, two of them were identified in the DNA sequences encoding the kinase domain. Because these downstream molecules of *PDPK1* are frequently activated in cancer cells [4], it could be thought that *PDPK1* acts as an oncogenic protein. Also, *PDPK1* is highly expressed in a many of human cancer cell lines, and retrovirally overexpressed *PDPK1* gene transforms mammary epithelial cells [5,6]. It might be interesting to see whether *PDPK1* kinase domain mutations occur in other types of cancers. In this study, we analyzed 254 cases of common human carcinoma tissues from various origins for the detection of mutations in the kinase domain of *PDPK1* gene.

Methacarn-fixed tissues of 50 gastric carcinomas, 104 colorectal carcinomas and 50 lung adenocarcinomas were analyzed in this study. All of the patients of the cancers were Asians (Koreans). The gastric carcinomas consisted of 22 diffuse-type, 18 intestinal-type and 10 mixed-type gastric adenocarcinomas by Lauren's classification, and five early and 45 advanced gastric carcinomas according to the depth of invasion. The colorectal carcinomas originated from cecum (n = 2), ascending colon (n = 19), transverse colon (n = 6), descending colon (n = 4), sigmoid colon (n = 28) and rectum (n = 45). Tumor 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 by a microdissection. Because the *PDPK1* kinase domain mutations were previously detected only in the exon 10 [3], we analyzed this exon in this study by polymerase chain reaction (PCR) and single-strand conformation polymorphism (SSCP). The primer sequences were as follows (forward 5′- aggttttagatgccacaaag -3′ and reverse 5′- ccagcttacattgccatag -3′). Radioisotope ([^{32}P]dCTP) was incorporated into the PCR products for detection by SSCP autoradiogram.

On the SSCP autoradiograms, all of the PCR products were clearly seen. However, the SSCP from the 204 tumors did not reveal any aberrantly migrating band compared to the wild-type bands from the normal tissues. We repeated the experiments twice, including PCR, SSCP and sequencing

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analysis to ensure the specificity of the results, and found that the data were consistent.

Because genetic alterations of protein kinase-encoding genes profoundly contribute to the development of cancers and could be the therapeutic targets in the treatment of cancer patients, we tried to find *PDPK1* mutations in common human carcinomas in the present study. Moreover, because the previous study showed a modest frequency (2.4%) of *PDPK1* mutation in the colorectal carcinomas, [3] we expected to detect some mutations at least in the colorectal carcinoma samples. However, we detected no *PDPK1* kinase domain mutation in the samples, suggesting that *PDPK1* kinase domain mutation in the exon 10 is rare in common human cancers, including gastric, colon and lung carcinomas.

We compared the incidence of *PDPK1* mutations in colorectal cancers between our data and the earlier data [3]. Statistically, there was no significant difference in the *PDPK1* exon 10 mutation frequencies between the previous study that detected two mutations in 204 samples and our study (0 mutation in the 104 samples) (Fisher's exact test, $p = 0.438$), suggesting that a racial difference between the two studies does not exist.

There is convincing evidence that protein kinases are involved in the development of many human cancers. However, the present data suggest a low possibility of targeting *PDPK1* kinase domain mutation in the anti-neoplastic therapy against gastric, colorectal and lung carcinomas.

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