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LETTER TO THE EDITOR

Inactivating Frameshift Mutation of *INPP4B* Encoding a PI3K Pathway Phosphatase in Gastric and Colorectal Cancers

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To the Editor:

The PI3K-AKT pathway regulates crucial cellular processes such as cell proliferation and survival, and is frequently altered in cancers. *PIK3CA* (lipid kinase) and *PTEN* (lipid phosphatase) in this pathway are oncogene and tumor suppressor genes (TSGs), respectively [1]. Another lipid phosphatase INPP4B (inositol polyphosphate-4-phosphatase, type II) in this pathway suppressed PI3K–AKT pathway and exhibited tumor-suppressing activity in cells [1]. Decreased INPP4B expression was found in many cancers [2]. In vivo, INPP4B suppressed development and metastasis of thyroid tumors [3]. Together, these data strongly suggest that INPP4B has TSG functions. However to date, it remains unknown whether somatic mutation of *INPP4B* are common in gastric cancer (GC) and colorectal cancer (CRC).

In a public genome database (http://genome.cse.ucsc.edu/), we found that human *INPP4B* had a mononucleotide repeat that could be a target for frameshift mutation in GC and CRC with microsatellite instability (MSI) [4]. In this study, we analyzed an A7 repeat in the *INPP4B* exon 25 by polymerase chain reaction (PCR)-based single strand conformation polymorphism (SSCP) assay. We used methacarn-fixed tissues of 79 CRCs with high MSI (MSI-H), 53 microsatellite stable (MSS) CRCs, 34 GC with MSI-H and 45 GC with MSS. In cancer tissues, malignant cells and normal cells were selectively procured by microdissection [5]. Radioisotope ([^{32}P]dCTP) was incorporated into the PCR products, which were subsequently displayed in SSCP gels and analyzed with direct DNA sequencing [5].

On the SSCP, we observed aberrant bands of *INPP4B* gene in one GC and two CRCs. DNA from the patients' normal tissues showed no shifts in SSCP compared to tumor DNA, indicating the aberrant bands had risen somatically. DNA sequencing analysis confirmed that the aberrant bands represented a recurrent *PBRM1* somatic mutation, which was an identical frameshift mutation (deletion of one base) in the A7 repeat (c.2452delA) that would result in a frameshift mutation (p.Arg818GlufsX4) (Fig. 1). They were detected in two CRCs (2/79: 2.5 %) and one GC (1/34: 2.9 %) with MSI-H, but not in those with MSS (0/98).

The frameshift mutation detected in the current study would result in a premature stop of amino acid synthesis in INPP4B protein and hence resembles a typical loss-of-function mutation. Based on the earlier data that showed TSG activities of INPP4B in cells [2, 3], the inactivating mutation found in this study could contribute to cancer development by inhibiting the TSG activities. Our data show that GC and CRC with MSI-H could harbor *INPP4B* truncation mutation that might alter PI3K pathway. Such data might provide useful information in evaluating lipid kinase-targeting drugs in cancer patients.

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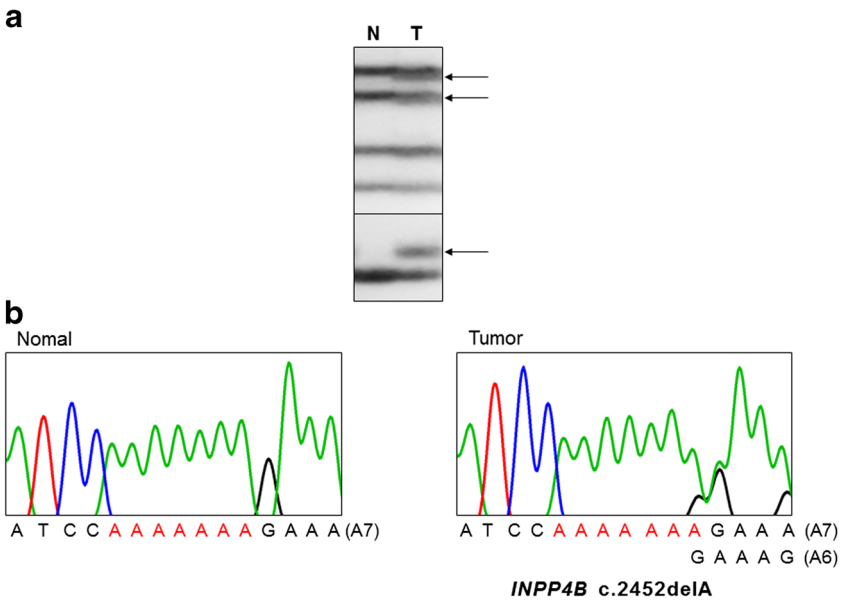

Fig. 1 Representative *INPP4B* A7 mutation in cancer. a PCR product of *INPP4B* exon 25 from a colon carcinoma with MSI-H shows aberrant bands (arrows in lane T) as compared to SSCP from matched normal tissue (N) of the same patient. **b** Direct DNA sequencing analysis of (A) shows a heterozygous A deletion within the A7 in tumor tissue as compare to normal tissue

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Compliance with Ethical Standards

Conflict of Interests The authors declare no competing interests.

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