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LETTER TO THE EDITOR

Frameshift Mutations of *SMG7* Essential for Nonsense-Mediated mRNA Decay in Gastric and Colorectal Cancers

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To the Editor,

Nonsense-mediated mRNA decay (NMD) is a surveillance pathway that reduces errors in gene expression by eliminating mRNA transcripts that contain premature stop codons [1]. Without the NMD, translation of such aberrant mRNAs could lead to deleterious gain-of-function or dominant-negative activity of the resulting proteins. As for tumors, suppressed NMD can either promote or inhibit tumors depending on the natures of NMD-candidate transcripts. For example, NMD shows a tumor suppressor activity in the cancers with truncated forms of BRCA1 [2]. By contrast, it shows an oncogenic role in those with truncated forms of CDH1 [3]. In humans, NMD depends on UPF1 and six other proteins SMG1, UPF2, UPF3, SMG6, SMG5 and SMG7 [1]. The SMG7 coordinates with UPF1 to degrade NMD-candidate transcripts [4]. NMD-inactivating mutation of *UPF1* gene is common in pancreatic adenosquamous carcinoma [5], indicating that NMD inhibition by somatic mutations of NMD machinery could possibly contribute to tumorigenesis. However, mutational status of the other genes is largely unknown.

There is a mononucleotide repeat (A9) in the coding sequence of *SMG7* that could be a target for frameshift mutation in cancers with microsatellite instability (MSI) such as gastric (GCs) and colorectal (CRCs) cancers [6]. To see whether *SMG7* gene harbored frameshift mutations within the repeat in GC and CRC, we analyzed the A9 repeat in exon 17 of *SMG7* in 34 GCs with high MSI (MSI-H), 45 GCs with microsatellite stable/low MSI (MSS/MSI-L), 79 CRCs with MSI-H and 45 CRCs with MSS/MSI-L by polymerase chain reaction (PCR) and single-strand conformation polymorphism (SSCP) assay as described previously [7]. Radioisotope ([^{32}P]dCTP) was incorporated into the PCR products for detection by autoradiogram. The PCR products were subsequently displayed in SSCP gels. After SSCP, Sanger DNA sequencing reactions were performed in the cancers with mobility shifts in the SSCP as described previously [8].

In the SSCP, we found aberrantly migrating bands in two GCs and six CRCs, but not in their normal samples. DNA sequencing analysis confirmed that the aberrant bands represented *SMG7* somatic mutations, which consisted of frameshift mutations by a deletion (c.2454delA (p. Met849fsx1)) and a duplication (c.2545dupA (p. Met849Asnfsx10)) within the repeat (Fig. 1). The mutations were detected in GCs (2/34, 5.9 %) and CRCs (6/79, 7.6 %) with MSI-H, but not in GCs (0/45) and CRCs (0/45) with MSS/MSI-L (Fisher's exact test, $p = 0.008$). Clinical and histopathological parameters, however, could not distinguish *SMG7* mutation (+) and (−) cancers.

Of the 79 CRCs with MSI-H analyzed, we analyzed multiregional areas in 16 CRCs (96 areas, 4–7 areas per case). One of the 16 CRCs (6.3 %) showed the deletion (c.2454delA) in two of the six regional fragments, indicating intratumoral heterogeneity (ITH) of the *SMG7* frameshift mutation. We could not find any significant histological difference among the ITH regions.

Earlier identification of NMD-inactivating mutation of *UPF1* gene [5] led us to further analyze frameshift mutations of SMG7, another NMD machinery gene. In the present study, we found that eight cases (7.1 %) of GCs and CRCs with MSI-H harbored *SMG7* frameshift mutations, indicating that *SMG7* gene is not uncommon in GCs and CRCs with MSI-H. The N-

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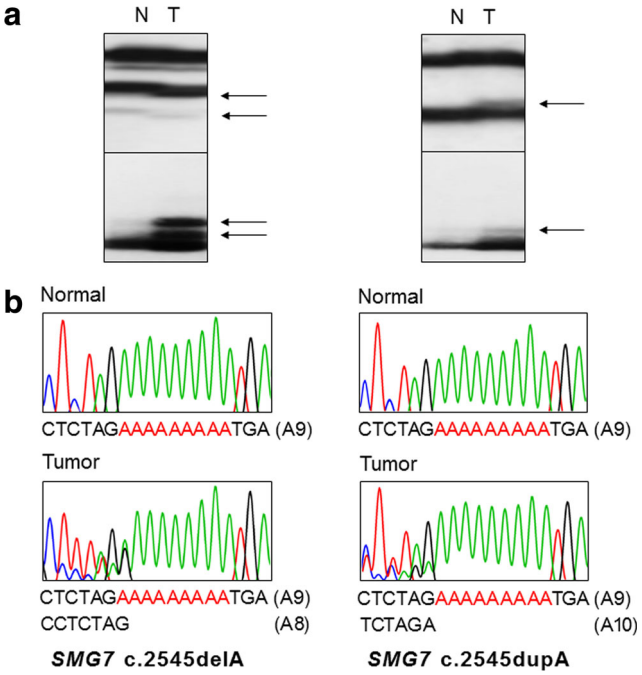

Fig. 1 Representative SSCP and DNA sequencings of repeats of *SMG7* in colon and gastric carcinomas. SSCP (**A**) and DNA sequencing analyses (B) of the A9 repeat in *SMG7* from tumor (Lane T) and normal tissues (Lane N). **a** SSCPs of the PCR products show aberrant bands (arrows in lane T) as compared to SSCP from normal tissues (N). **b** Direct DNA sequencing analyses show a heterozygous A deletion (*left*) and a heterozygous A duplication (*right*) in the A9 in tumor tissues as compared to normal tissues

terminal domain of SMG7 is thought to mediate its association with SMG5 or UPF1 while the C-terminal domain interacts with the mRNA decay complex [1, 4]. The *SMG7* mutations in our study would delete amino acids after the frameshift mutations and hence hamper the interaction with the mRNA decay complex. Interestingly, *UPF1* mutations in pancreatic cancer and *SMG7* mutations in GC and CRC are typical loss-of-function mutations that might inhibit NMD in cancer cells. Whether these are incidental or related to common features of solid tumors remains to be studied. In the present study, we also identified ITH of the *SMG7* mutations in a CRC, suggesting that the *SMG7* mutation occurred during tumor progression rather than as an early event in this case. In summary, our study identified *SMG7* frameshift mutation in GC and CRC that might alter NMD in cancer cells. Together with the previously known *UPF1* gene mutation in pancreatic cancer, our results suggest that somatic mutations encoding the NMD machinery might contribute to cancer pathogenesis.

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Compliance with Ethical Standards

Conflicts of Interest None to declare.

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