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LETTER TO EDITOR

Frameshift Mutations of *TAF7L* Gene, a Core Component for Transcription by RNA Polymerase II, in Colorectal Cancers

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To the Editor:

Transcription initiation by RNA polymerase II that catalyzes precursor mRNA synthesis requires activities of the basal transcription factor TFIID [1]. TFIID is a multisubunit complex comprised of TBP and TBP-associated factors (TAFs). TAF1, the largest subunit of the TFIID, interacts with TAF7 and coordinates gene transcription [1]. TAF7 inhibits the histone acetyltransferase activity of TAF1, subsequently repressing cyclin D1 and cyclin A transcription [2], indicating that TAF7 is a negative regulator of cell cycle progression. In prostate cancer cells, decreased TAF7 expression resulted in resistance to apoptosis [3]. TAF7L is a paralogue of TAF7, but its function is not known well. TAF7L is downregulated in 59 % of acute myelogenous leukemias [4]. These data indicate that both TAF7 and TAF7L are involved in cancer-related pathways and suggest that perturbation of TAF7 and TAF7L functions might be involved in tumorigenesis. However, their implications in cancer development are largely unknown.

In a public genome database (http://genome.cse.ucsc.edu/), we found that human *TAF7* and *TAF7L* had mononucleotide repeats in the coding sequences that could be targets for frameshift mutation in cancers with microsatellite instability (MSI). Frameshift mutation of genes containing mononucleotide repeats is a feature of gastric (GC) and colorectal cancers (CRC) with MSI [5]. To date, however, it is not known whether *TAF7* and *TAF7L* genes are mutationally altered in GC and CRC with MSI. In this study, we analyzed an A7 repeat in the *TAF7* exon 1 and an A7 repeat in the *TAF7L* exon 6 by polymerase chain reaction (PCR)-based single strand conformation polymorphism (SSCP) assay. For this, we used methacarn-fixed tissues of 34 GC with high MSI (MSI-H), 45 GC with stable MSI (MSS), 89 CRC with MSI-H and 45 CRC with MSS. In cancer tissues, malignant cells and normal cells were selectively procured from hematoxylin and eosin-stained slides by microdissection [6]. 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, direct DNA sequencing reactions were performed in the cancers with mobility shifts in the SSCP as described previously [7].

On the SSCP, we observed aberrant bands of *TAF7* gene in a CRC and *TAF7L* in three CRC. DNA from the patients' normal tissues showed no shifts in SSCP, indicating the aberrant bands had risen somatically (Fig. 1). DNA sequencing analysis confirmed that the aberrant bands represented *TAF7* and *TAF7L* somatic mutations. The *TAF7* mutation was a heterozygous frameshift mutation (duplication of one base) in the A7 repeat (c.250dupA) that would result in a frameshift mutation (p.Thr84AsnfsX7). The *TAF7L* mutations were a type of heterozygous frameshift mutation (deletion of one base) in the A7 repeat (c.719delA) that would result in a frameshift mutation (p.Lys240ArgfsX26). They were detected in four of the CRC with MSI-H (4/89: 4.5 %), but not in CRC with MSS. In the cancers with MSI-H, however, there was no correlation between histological features of the tumors (histologic grade, subtypes, mucinous histology, medullary pattern and tumor-infiltrating lymphocytes) and presence of the mutations ($p>0.05$).

The frameshift mutations detected in the present study would result in premature stops of amino acid synthesis in TAF7 and TAF7L proteins and hence resembles a typical loss-

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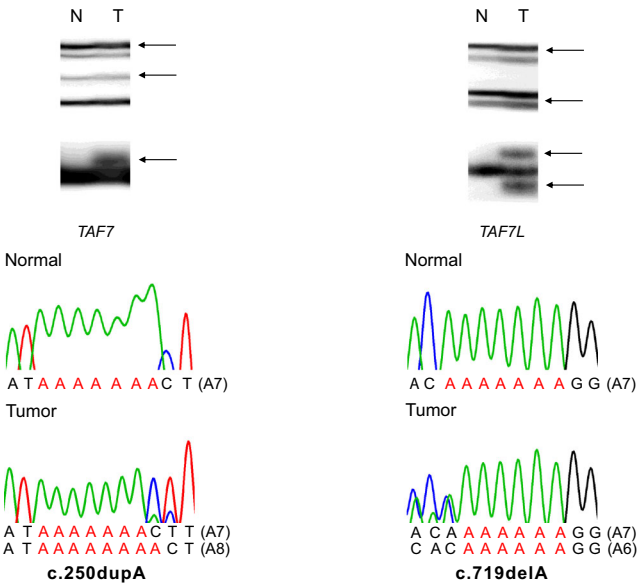

Fig. 1 Mutations of *TAF7* and *TAF7L* frameshift mutations in colon carcinomas with MSI-H. **a**: PCR products of *TAF7* exon 1 from a colon carcinoma and *TAF7L* exon 6 from another colon carcinoma show aberrant bands (*arrows in lane T*) as compared to SSCP from normal tissue (N) of the same patients. **b**. Direct DNA sequence analyses show a heterozygous A duplication within the A7 (*left*) of *TAF7* and a heterozygous A deletion within the A7 (*right*) of *TAF7L* in tumor tissue as compare to normal tissue

of-function mutation. Because earlier data suggested possibilities that both TAF7 (inhibition of cell cycle progression) and TAF7L (loss of TAF7L expression in cancers) possessed tumor suppressor activities, it can be inferred that the inactivating mutations detected in this study might contribute to cancer development by inhibiting the tumor suppressor activities. Despite the low incidence of the mutations detected, our data provide evidence that a core component for transcription by RNA polymerase II, which might affect gene transcription widely, could be mutationally inactivated in CRC.

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References

1. Gegonne A, Devaiah BN, Singer DS (2013) TAF7: traffic controller in transcription initiation. Transcription 4:29–33
2. Kloet SL, Whiting JL, Gafken P, Ranish J, Wang EH (2012) Phosphorylation-dependent regulation of cyclin D1 and cyclin A gene transcription by TFIID subunits TAF1 and TAF7. Mol Cell Biol 32: 3358–3369
3. Fukuchi J, Hiipakka RA, Kokontis JM, Nishimura K, Igarashi K, Liao S (2004) TATA-binding protein-associated factor 7 regulates polyamine transport activity and polyamine analog-induced apoptosis. J Biol Chem 279:29921–29929
4. Yazarloo F, Shirkoohi R, Mobasheri MB, Emami A, Modarressi MH (2013) Expression analysis of four testis-specific genes AURKC, OIP5, PIWIL2 and TAF7L in acute myeloid leukemia: a gender-dependent expression pattern. Med Oncol 30:368
5. Imai K, Yamamoto H (2008) Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. Carcinogenesis 29:673–680
6. Yoo NJ, Kim HR, Kim YR, An CH, Lee SH (2012) Somatic mutations of the KEAP1 gene in common solid cancers. Histopathology 60:943–952
7. Je EM, Kim MR, Min KO, Yoo NJ, Lee SH (2012) Mutational analysis of MED12 exon 2 in uterine leiomyoma and other common tumors. Int J Cancer 131:E1044–E1047