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LETTER TO THE EDITOR

Mutation and Expression of a Methyl-Binding Protein 6 (MBD6) in Gastric and Colorectal Cancers

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To the editor:

DNA Methylation of cytosine mediates epigenetic regulation and is the best-known DNA modification in eukaryotes [1, 2]. There are several proteins that bind methylated DNA, including methyl-CpG binding domain protein 6 (MBD6). MBD6 regulates Oct4 and involves in cellular stemness [3]. Although alteration of DNA methylation, a crucial epigenetic process, is important in tumorigenesis [1, 2], roles of MBD6 in tumorigenesis remain unknown. In this study, we attempted to find whether *MBD6* gene was mutated and expressionally altered in gastric (GC) and colorectal cancers (CRC).

In a public database, we found that *MBD6* had mononucleotide repeats in the coding sequences (C7 in exon 7 and G8 in exon 9) that might be mutation targets in the cancers with microsatellite instability (MSI) [4]. We analyzed the repeats in 34 GC with high MSI (MSI-H), 45 GC with stable MSI/low MSI (MSS/MSI-L), 76 CRC with MSI-H and 45 CRC with MSS/MSI-L by polymerase chain reaction (PCR) and single-strand conformation polymorphism (SSCP) assay as described previously [5]. We found six frameshift mutations in GC (6/34: 17.6 %) and 15 frameshift mutations in CRC (15/76: 19.7 %) with MSI-H. The mutations were detected in the cancers with MSI-H, but not in those with MSS/MSI-L. All of the mutations were deletion or duplication of bases in the repeats that would cause premature stop codons, which lead to the termination of translation. There was a statistical difference in the frameshift mutation frequencies between the cancers with MSI-H (21/110) and MSS/MSI-L (0/90) (Fisher's exact test, $p < 0.001$).

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Also, to see whether MBD6 protein expression was altered as well, we analyzed the expression in 34 GC and 76 CRC with MSI-H, and 45 GC and 45 CRC with MSS/MSI-L by immunohistochemistry as described previously [6]. Positive expression of MBD6 was observed in 12 GC (35.3 %) and 21 CRC (27.6 %) with MSI-H, and 23 GC (51.1 %) and 24 CRC (53.3 %) with MSS/MSI-L (Table 1). The MBD6 expression was significantly different with respect to the MSI status (MSI-H Vs. MSI-L/MSS) (Fisher's exact test, $p = 0.001$). Of the 21 cancers with *MDB6* frameshift mutations, 17 (80.9 %) showed negative MBD6 immunostaining. There was a significant difference of MBD6 immunostaining between MSI-H cancers with the frameshift mutations and those without the mutations (Fisher's exact test, $p < 0.001$) (Table 1).

In the present study, we have analyzed and found mutational and expressional alterations of *MBD6*, a gene encoding a protein with a methyl-CpG binding domain, in GC and CRC. The GC and CRC with MSI-H harbored both frameshift mutation and expression loss, while those with MSI-L/MSS showed only expression loss of MBD6. To our knowledge, this is the first report that discloses mutational and expressional alterations in MBD family genes. Our findings may provide clues for further researches on MDB family

Table 1 Summary of MBD6 expression in gastric and colorectal cancers

	Positive expression (%)
GC with MSI-H (n=34)	12 (35.3)
CRC with MSI-H (n=76)	21 (27.6)
GC with MSS/MSI-L (n=45)	23 (51.1)
CRC with MSS/MSI-L (n=45)	24 (53.3)
MSI-H GC and CRC with *MBD6* mutation (n=21)	4 (19.0)
MSI-H GC and CRC without *MBD6* mutation (n=179)	76 (42.5)

genes as well as functional implications of MBD6 alterations in cancers.

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