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LETTER TO THE EDITOR

Candidate Tumor Suppressor Gene *EAF2* is Mutated in Colorectal and Gastric Cancers

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To the Editor:

Fusion of *ELL-associated factor 2 (EAF2)* with ELL is related to myeloid leukemia development [1]. Loss of expression and deletion of EAF2 is common in prostate cancer and EAF2 expression blocks prostate cancer growth, suggesting that EAF2 might have tumor suppressor gene (TSG) functions [2]. However, the roles of EAF2 in colorectal (CRC) and gastric (GC) cancers are not known. About one third of CRC and GC have defects in mismatch repair that can cause microsatellite instability (MSI). TSGs are often observed to have mutations at monocleotide repeats in high MSI (MSI-H) GC and CRC [3]. We hypothesize that *EAF2* gene might harbor frameshift mutations at its A8 repeat that would result in inhibition of the EAF functions and play a role in tumor development. For this, we studied the A8 repeat in 79 high MSI (MSI-H) CRCs, 45 microsatellite stable/low MSI (MSS/MSI-L) CRCs, 34 MSI-H GCs and 45 MSS/MSI-L GCs by single-strand conformation polymorphism (SSCP) assay. After SSCP, Sanger DNA sequencings were done in the cancers with mobility shifts in the SSCP to confirm the mutations [4].

We found a type of somatic frameshift mutation in seven CRCs (7/79, 8.9%) and one GC (1/34, 3.0%) with MSI-H phenotype, but there was none in those with MSS/MSI-L (CRCs (0/45) and GCs (0/45)) (Fisher's exact test, $p = 0.001$). The mutation was a deletion (c.334delA (p.Thr112GlnfsX30) in the coding region. We also attempted to find whether there was intratumor heterogeneity (ITH) in the *EAF2* frameshift mutation, which is known to play a role in cancer evolution as well as treatment resistance in cancer. We studied 16 cases of CRCs with 4–7 tissue fragments per CRC. Three of the 16 CRCs (18.8%) showed the deletion mutation (c.334delA) in different tissue regions (Table 1), indicating ITH of the *EAF2* mutation existed in CRC.

In earlier studies, evidence of TSG inactivation in *EAF2* was found in other cancers, but neither in CRC nor GC. In the present study, we found *EAF2* frameshift mutation, and provided evidence of its inactivation in MSI-H CRC and GC. The *EAF2* mutation would produce truncation of EAF2 protein, which resembles a loss-of-function mutation. Truncated EAF2 mutants might inhibit its TSG activities [5] and might contribute to pathogenesis of MSI-H cancers. We identified ITH of *EAF2* frameshift mutation in CRCs, suggesting a possibility that *EAF2* mutation occurred during tumor progression rather than during tumor development. Although ITH is known to influence on clinical outcome of cancer patients, it was not possible to define clinical feature of the cases with ITH due to small

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Table 1 Intratumoral heterogeneity of *EAF2* mutation in colorectal cancers

Case	Regional biopsy sites							Mutation status	ITH status
	#1	#2	#3	#4	#5	#6	#7		
CRC3	WT	WT	WT	WT	WT	WT	n.d.	Wild type	Non-ITH
CRC15	WT	WT	WT	WT	WT	WT	WT	Wild type	Non-ITH
CRC26	c.334delA	WT	n.d.	WT	WT	WT	WT	Mutation	ITH
CRC27	WT	WT	WT	WT	WT	WT	WT	Wild type	Non-ITH
CRC34	WT	WT	WT	WT	WT	WT	WT	Wild type	Non-ITH
CRC35	WT	WT	n.d.	n.d.	n.d.	WT	WT	Wild type	Non-ITH
CRC39	WT	WT	WT	WT	n.d.	WT	WT	Wild type	Non-ITH
CRC41	WT	n.d.	WT	WT	n.d.	WT	WT	Wild type	Non-ITH
CRC43	WT	c.334delA	WT	n.d.	n.d.	c.334delA	n.d.	Mutation	ITH
CRC45	c.334delA	c.334delA	c.334delA	WT	c.334delA	c.334delA	c.334delA	Mutation	ITH
CRC47	WT	WT	WT	WT	WT	WT	WT	Wild type	Non-ITH
CRC48	WT	n.d.	n.d.	WT	WT	WT	WT	Wild type	Non-ITH
CRC49	n.d.	WT	WT	WT	WT	WT	WT	Wild type	Non-ITH
CRC51	WT	WT	WT	WT	n.d.	WT	WT	Wild type	Non-ITH
CRC53	WT	WT	WT	WT	WT	WT	WT	Wild type	Non-ITH
CRC55	WT	WT	n.d.	n.d.	WT	WT	WT	Wild type	Non-ITH

n.d.: not done, ITH: Intratumoral heterogeneity, CRC: colorectal cancer

number of the mutated cases. Based on our preliminary data, further studies are needed to define the clinical implication of *EAF2* mutation.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

References

1. Simone F, Luo RT, Polak PE, Kaberlein JJ, Thirman MJ (2003) ELL-associated factor 2 (EAF2), a functional homolog of EAF1 with alternative ELL binding properties. Blood 101:2355–2362
2. Xiao W, Zhang Q, Jiang F, Pins M, Kozlowski JM, Wang Z (2003) Suppression of prostate tumor growth by U19, a novel testosterone-regulated apoptosis inducer. Cancer Res 63:4698–4704
3. Imai K, Yamamoto H (2008) Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. Carcinogenesis 29:673–680
4. Oh HR, An CH, Yoo NJ, Lee SH (2015) Frameshift mutations of MUC15 gene in gastric and its regional heterogeneity in gastric and colorectal cancers. Pathol Oncol Res 21:713–718
5. Liu JX, Zhang D, Xie X, Ouyang G, Liu X, Sun Y, Xiao W (2013) Eaf1 and Eaf2 negatively regulate canonical Wnt/β-catenin signaling. Development 140:1067–1078