Pathology - Research and Practice 215 (2019) 152579

Contents lists available at ScienceDirect

Pathology - Research and Practice

journal homepage: www.elsevier.com/locate/prp

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Somatic frameshift mutations of cancer-related genes *KIF3C* and *BARD1* in colorectal cancers

To the Editor

Kinesin superfamily proteins (KIFs) are microtubule-dependent motor proteins that play roles in many cellular processes, including intracellular transportations, cell migration and division [1]. KIF3C confers anti-cancer docetaxel resistance in breast cancers [1], while it inhibits tumor growth and metastasis in breast cancers [2], suggesting its functions vary depending on cellular contexts. BRCA1-associated RING domain 1 (BARD1) binds with BRCA1 that functions as a tumor suppressor gene (TSG) [2]. Knock-out of *Bard1* in mice results in mammary carcinomas, indicating that BARD1 is a TSG [3]. BARD1 is overexpressed and performs TSG functions in some cancers including leukemias [4], suggesting that BARD1 possesses both TSG and oncogene functions in tumor pathogenesis. Cancer-related genes are frequently categorized into either proto-oncogene or TSG. However, many genes as shown in the cases of KIF3C and BARD1, exhibit both TSG and oncogene functions during tumorigenesis.

Approximately one third of colorectal cancers (CRCs) display impaired DNA mismatch repair and are classified as high microsatellite instability (MSI-H) cancers that show hypermutation [5]. MSI-H cancers can have frameshift mutations at monocleotide repeats in the coding region, which may inactivate TSGs. However, it has not been well studied whether a gene with both TSG and oncogene functions have frameshift mutations in MSI-H cancers as well. In the human genome database, we observed that *KIF3C* and *BARD1* genes have nucleotide repeats in coding sequences that might be mutated in MSI-H CRCs. In the present study, we analyzed a G7 repeat in *KIF3C* and two A7 in *BARD1* coding sequences by polymerase chain reaction (PCR)-based single strand conformation polymorphism (SSCP) analysis. We studied 100 CRC with MSI-H and 45 CRCs with microsatellite stable (MSS). In cancer tissues, malignant cells and normal cells were selectively procured by microdissection [6]. Radioisotope ([^{32}P]dCTP) was incorporated into the PCR products, which were subsequently displayed in SSCP gels and analyzed with direct DNA sequencing [6].

We detected frameshift mutations of *KIF3C* in 5 (5%) CRCs and *BARD1* in 3 (3%) CRCs (Table 1). DNA from matched normal tissues did not show any evidence for mutation in Sanger sequencing, indicating the frame mutations had risen somatically. These mutations were deletion or duplication of one base in nucleotide repeats that would result in frameshift of amino acid translation. The mutations were detected in 8 cancers (8/100: 8.0%) with MSI-H, but not in those with MSS (0/90) ($P < 0.01$).

The frameshift mutations identified in the present study would translate immature premature stops in KIF3C and BARD1 and thus resemble a typical inactivating mutation. TSG functions of *KIF3C* and *BARD1* [1–4] might be inactivated by the mutations, which could contribute to cancer development. As for the oncogenic functions, however, the consequences of the frameshift mutations remain to be clarified in the pathogenesis of MSI cancers. Of note, the frameshift mutations were detected in CRCs with MSI-H, but not with MSS, which exhibited a significant difference in the prevalence between the cancers with MSI-H and MSS/MSI-L, indicating that the gene mutations were MSI-H-specific.

Declaration of Competing Interest

None to declare.

Acknowledgement

This work was supported by a grant from National Research Foundation of Korea (2019R1A5A2027588).

https://doi.org/10.1016/j.prp.2019.152579
Received 28 June 2019

Table 1
Summary of *KIF3C* and *BARD1* mutations in colorectal cancers.

Gene	Wild type	Mutation	MSI status of the mutation cases (n)	Incidence in MSI-H cancers (%)	Nucleotide change (predicted amino acid change)
KIF3C	G7	G6	MSI-H (1)	Colorectal: 1/100 (1.0)	c.996delG (p.Asn333MetfsX7)
		G8	MSI-H (4)	Colorectal: 4/100 (4.0)	c.996dupG (p.Asn333GlufsX19)
PA2G4	A7	A6	MSI-H (1)	Colorectal: 1/100 (1.0)	c.513delA (p.Asp172MetfsX40)
	A7	A8	MSI-H (2)	Colorectal: 2/100 (2.0)	c.623dupA (p.Lys209GlufsX5)

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