Emerging role of PR domain containing 5 (PRDM5) as a broad tumor suppressor in human cancers

Xing-sheng Shu

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To the editor,

An excellent article titled “Promoter methylation-mediated downregulation of *PRDM5* contributes to the development of lung squamous cell carcinoma” was published recently in *Tumor Biology*. This study illustrated the epigenetic silencing of *PRDM5* tumor suppressor in lung cancer cells and revealed the potential diagnostic and prognostic value of *PRDM5* methylation for lung cancer patients [1]. This work, together with ours and others’, highlights the emerging role of *PRDM5* as a broad tumor suppressor disrupted by promoter hypermethylation in common cancers (Table 1).

A decade ago, Huang and colleagues isolated the full-length cDNA of *PRDM5* gene, and they showed for the first time that the CpG island within *PRDM5* promoter region was frequently methylated in breast, ovarian, and liver cancers [2]. Since then, epigenetic inactivation of *PRDM5* has been documented in a broad spectrum of solid tumor types, which originate from various organs of the human body, including digestive system tumors (esophageal, gastric, colorectal), respiratory system tumors (nasopharyngeal, lung), gynecologic tumors (ovarian, cervical), as well as liver and breast tumors. These findings strongly implicate that loss of *PRDM5* is a common molecular event during tumorigenesis, and *PRDM5* could be a critical tumor suppressor.

Through independent studies, we and other groups confirmed the causal relationship between *PRDM5* promoter hypermethylation and its downregulation in cancer cells [1–5]. Intriguingly, in addition to DNA methylation, another epigenetic mechanism is also involved in *PRDM5* silencing.

Watanabe et al. found that in colon cancer cells with sparse *PRDM5* methylation, a repressive histone modification, trimethylation of H3K27, was enriched in its promoter region, contributing to its transcriptional silencing [4]. In fact, recent advances in epigenetics field underscore the interplay between DNA methylation and histone modification, in which histone modifications create a “flexible” state around transcription start site while DNA methylation can “lock” the state of transcription permanently [6]. *PRDM5* here gives us an excellent example of this cooperating epigenetic regulation. Apart from epigenetic alterations, classic tumor suppressor genes usually bear genetic abnormalities in cancer. Although no genetic mutation of *PRDM5* in tumor is reported thus far, searching the COSMIC database (catalog of somatic mutation in cancer) did reveal low-frequency point mutations within *PRDM5* gene coding region in most types of cancer, suggesting *PRDM5* mutation may as well contribute to tumor formation. However, the functional relevance of these mutations remains to be delineated.

To understand how *PRDM5* exerts its tumor-suppressive function, Deng and Huang first demonstrated that overexpression of *PRDM5* induced cell cycle G2/M arrest and apoptosis of cancer cells [2]. Further studies showed that inhibition of certain oncogenic pathways, such as Wnt signaling, by *PRDM5* might be a crucial part of its tumor-suppressive activity [3, 7]. As an epigenetic master gene, *PRDM5* does not possess intrinsic histone methyltransferase (HMT) activity, but it can recruit another HMT G9a to the promoter region of target genes and thereby regulates their transcription [8]. In addition, a recent proteomic study revealed *PRDM5* could also interact with insulator factors such as CTCF to modulate chromatin organization of target genome sites [9]. Very recently, a wonderful mouse model work by Lund and colleagues showed knockout of *Prdm5*-accelerated *Apc*^{Min}-driven intestinal carcinogenesis [10]. Furthermore, they

X.-s. Shu (✉)
Institute of Molecular Medicine, Health Science Center, Shenzhen
University, Shenzhen 518060, China
e-mail: shu@szu.edu.cn

Table 1 *PRDM5* methylation in various types of cancer

Type of cancer	Methylation percentage			Reference(s)
	Cell lines	Tumor tissues	Normal tissues	
Esophageal	44.4 % (8/18)	58.1 % (25/43)	42.8 % (3/7)	[3]
Gastric (2007)	80.0 % (4/5)	50.0 % (39/78)	0/15	[4]
Gastric (2011)	76.5 % (13/17)	88.1 % (37/42)	N/A	[3]
Colorectal	50.0 % (1/2)	6.6 % (4/61)	N/A	[4]
Liver (2004)	87.5 % (7/8)	52.8 % (19/36)	0/3	[2]
Liver (2011)	25.0 % (3/12)	63.0 % (29/46)	0/9	[3]
Nasopharyngeal	80.0 % (4/5)	93.5 % (43/46)	28.6 % (2/7)	[3]
Lung	28.6 % (2/7)	73.3 % (22/30)	46.7 % (14/30)	[1, 3]
Breast	80.0 % (8/10)	52.5 % (21/40)	0/3	[2]
Ovarian	83.3 % (5/6)	N/A	N/A	[2]
Cervical	75.0 % (3/4)	40.5 % (17/42)	0/9	[5]

N/A not tested

systematically profiled the genome-wide occupancy of *PRDM5* and identified a subset of metabolic genes as its direct targets, which may function as downstream effectors of *PRDM5*-mediated tumor suppression.

Epigenetic silencing of tumor suppressor genes, especially by promoter hypermethylation, is believed to occur at early stages of tumor development [11], and the power of DNA methylation as biomarker for early detection has been extensively explored [12]. As summarized in Table 1, *PRDM5* methylation is frequently detected in primary tumor tissues (except colorectal cancer). In contrast, the percentages of *PRDM5* methylation in normal tissues are much lower, suggesting it is a potential epigenetic biomarker for these tumors. However, although the detection sensitivity of *PRDM5* methylation is high (above 50 % for most tumors), its specificity in certain types of cancer (esophageal and lung cancers) is poor, and the number of normal tissues tested in these studies is very limited. In addition, methylation-specific PCR (MSP) data of *PRDM5* methylation in the same cancer type (e.g., liver cancer) varies in different studies, probably due to use of different MSP primers (methylation status of individual CpG sites can be different from each other in the same sample) and variable amplification power of different MSP reactions. Thus, including large-scale paired normal/cancer tissues and premalignant samples (if possible) and adopting more accurate and sensitive detection method (e.g., quantitative MSP) in future studies will be very helpful to comprehensively evaluate the value of *PRDM5* methylation as a biomarker.

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Conflicts of interest None.

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