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SETD2, an epigenetic tumor suppressor: a focused review on GI tumor

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1. ABSTRACT

Significant progress has been made in our understanding of the role of epigenetic modifiers in many types of human cancer. Here, we review currently available studies on the unique histone methyltransferase, SETD2, which is responsible for H3 lysine 36 tri-methylation (H3K36me3). SETD2 plays pivotal roles in RNA alternative splicing regulation, DNA damage repair, and cytoskeleton protein methylation; inactivation of SETD2 and resultant dysregulation of these functions may lead to tumorigenesis. Despite being a newly discovered tumor suppressor, *SETD2* has been found to be mutated in multiple types of cancer, including gastrointestinal tumor. Some tumors can acquire a selective growth advantage after *SETD2* inactivation, which could happen in different stages in tumor progression. Decreased level of H3K36me3 caused by *SETD2* inactivation has been shown to associate with higher tumor grade, tumor stage, metastasis risk, and shorter survival. Some studies also suggest that *SETD2* mutation is associated with therapy resistance, therefore these *SETD2*-deficient tumors may need different therapeutic strategies.

2. INTRODUCTION

As the basic unit of the chromosome, the bead-like nucleosome consists of 147 base pairs of DNA and eight histone molecules. Post-translational modifications (PTMs) of histone are crucial for genome regulation (1). Lysine methylation of histone is one of those modifications that can regulate the

whole process of transcription. The lysine residues of histone can be methylated by adding 1, 2 or 3 methyls at K4, K9, K27, K36 or K79 of histone H3 and K20 of histone H4 (2). While most of these methylations distributed on promoter or intergenic regions, the enrichment pattern of histone H3 lysine 36 trimethylation (H3K36me3) seems to be quite different and is mainly observed at body regions of active genes (3, 4). However, the function of H3K36me3 remains largely unknown.

SETD2 is an H3K36-specific histone methyltransferase (HMT) that is evolutionarily conserved from yeast to human (5-7), and it is the sole HMT that required for catalyzing H3K36me3 in mammals (8, 9). Full length of SETD2 owns three conserved domains, the SET domain, the WW domain, and the Set2 RNA polymerase II large subunit Rpb1 interacting (SRI) domain (6). The SET domain is the catalytic portion of SETD2 that performs the H3K36me3 transfer. The WW domain, containing two conserved tryptophan residues, can bind to proline-rich proteins, is thus potentially required for some protein-protein interactions. The SRI domain can bind to the phosphorylated C-terminal domain of RNA polymerase II. All these three domains are conserved from yeast to humans. However, recent studies revealed that the yeast Set2 possessed an auto-inhibitory domain (AID) and histone interaction domain, and that these domains can regulate H3K36 methylation (10, 11); whether SETD2 also contains a region with similar function for H3K36me regulation is worth investigating in the future.

To understand the physiological function of SETD2 in normal development, a *Setd2* conventional knockout mouse model was constructed by Hu *et al.*, and they found that *Setd2* deficient mouse is lethal at E10.5-E11.5 due to defects of embryo vascular remodeling (9). Furthermore, conditional knockout of *Setd2* in mouse hematopoietic stem cells (HSCs), intestinal epithelium and mesenchymal stem cells (MSCs) revealed that the *Setd2* deficiency severely impairs self-renewal of HSCs and intestinal stem/progenitor cells (12-14). In addition to affecting self-renewal, deletion of *SETD2* also causes cell differentiation defects. For example, *Setd2* absence leads to HSCs differentiation bias (12), impairs adipocytes differentiation from MSCs (12), inhibition of embryonic stem cell differentiation toward endoderm (15) and repression of myoblasts differentiation to skeletal muscle cells (16).

Interfering with the self-renewal and differentiation of stem/progenitor cells has been broadly regarded as the cellular basis of tumor initiation and progression. Indeed, *SETD2* gene mutations have been frequently reported in clear cell renal cell carcinoma (ccRCC), acute leukemia, gliomas, and lung adenocarcinomas (17-20). *SETD2* mutations also have been reported in some gastrointestinal tumors. As the critical role of SETD2 in the gastrointestinal (GI) tumor has not been reviewed yet, this review aims to examine the current literature about the critical function of SETD2 and to guide the understanding of SETD2 genetic variation in the initiation and progression of gastrointestinal tumors.

3. THE TUMOR SUPPRESSOR FUNCTION OF SETD2 IN GASTROINTESTINAL CANCER

Gastrointestinal tumor (e.g., esophagus, stomach, liver, pancreas and colorectum tumors) incidence and mortality are rapidly growing world-wide (21), yet the reasons remain unclear. As most highly renewing tissues, the gradual accumulation of genetic and epigenetic errors may be a cause. Actually, genetic mutation of epigenetic genes has been broadly studied in tumor initiation, progression, relapse, and so on (22). *SETD2* was reported to have tumor-suppressive function in various human cancers (20, 23, 24). Most frequently detected missense mutations of *SETD2* are located at the SET domain (25). Dalgliesh *et al.* first identified inactivation mutations of *SETD2* in ccRCC in 2010, in which 12 of 407 ccRCC samples had somatic truncating mutations of *SETD2* (17). *SETD2* mutations were also detected in 2 out of 10 primary ccRCC samples by their following investigation using targeted exome-sequencing (26). Another two cohort studies of ccRCC showed that the overall mutation frequency of *SETD2* is around 11% (27, 28). In addition, Zhu *et al.* identified 19 somatic *SETD2* mutations from totally 241 leukemia patients (20). Here, we will

focus on the role of *SETD2* in gastrointestinal tumors.

3.1. Regulation of SETD2 expression level in GI tumors

In a comparison of 168 colorectal cancer (CRC) specimens and 48 normal biopsies, Yuan *et al.* demonstrated that *SETD2* mRNA and protein levels were downregulated, suggesting SETD2 as a tumor suppressor in CRC (13). Similarly, Chen *et al.* reported that *SETD2* mRNA and protein levels are remarkably lower in the gastric cancer samples than in cancer-adjacent tissues indicated by immunohistochemistry, RT-PCR and immunoblotting analyses. 79.7% of primary gastric cancer sample tissues showed a lower expression level of *SETD2* mRNA (29). Recently, non-coding RNA mediated transcriptional and translational regulation have been reported to control *SETD2* expression. For example, since Tang *et al.* found that the long non-coding HOX transcript antisense RNA (HOTAIR) is an oncogenic long noncoding RNA in several tumors (30), a study by Li *et al.* proved that HOTAIR can compete with CREB-P300-RNA Pol II complex and prevents its loading to the *SETD2* promoter, thereby inhibiting SETD2 at transcriptional level and reducing the level of H3K36me3 in the liver cancer sample (31), which implies that the oncogenic function of HOTAIR is partially mediated by down-regulating *SETD2* and decreasing H3K36me3. At the translational level, Xiang *et al.* discovered that the microRNA miR-106b-5p can bind to the 3'-UTR of the *SETD2* mRNA and suppresses *SETD2* expression. Thus, SETD2 protein level was found to be increased by inhibition of miR-106b-5p, resulting in ccRCC cell cycle arrested at G0/G1 phase (31). Furthermore, SETD2 protein stability can also be regulated. Yeast two-hybrid screen and co-immunoprecipitation assays identified SPOP, a key subunit of the CUL3 ubiquitin E3 ligase complex, as a SETD2-interacting protein, which was responsible for SETD2 stability control through polyubiquitination (32). Hence, these transcriptional, translational and post-translational mechanisms for controlling SETD2 expression level and stability are worthy of attention in GI tumors.

3.2. *SETD2* mutations in GI tumors

Huang *et al.* propose that SETD2 is a tumor suppressor for gastrointestinal stromal tumor (GIST), as inactivation of SETD2 is related to the tumor progression. They found that, in patients with high-risk GIST, *SETD2* contains loss-of-function somatic mutations. These mutations can only be detected in patients with high-risk GISTs and metastatic GISTs with a prevalent rate of these mutations around 11%, while they cannot be detected in low or intermediate risk patients. In univariate analysis, the patients with SETD2 loss-of-function were associated hypomethylated heterochromatin and had remarkably shorter relapse-free survival (33).

In a whole exome sequencing (WES) analyses of 20 patients with a single nonsyndromic, nonfunctional but with distant metastases pancreatic neuroendocrine tumor (PanNET), Roy *et al.* identified mutations in chromatin-remodeling genes, including *SETD2, ARID1A, CHD8,* and *DNMT1* (34). In a separate analysis of 347 primary PanNETs, disruption of SETD2 function or mutations/deletions of *ARID1A*, *DAXX*, *ATRX,* and *CDKN2A* were found in 81% of primary PanNET patients with distant metastases. In the patients without any of those alterations, 98% of patients had disease-free survival times for 5 years, and 95% of patients had 10 years of disease-specific survival. Among patients with loss functions of any one of these genes, 39% of patients had disease-free survival times for 5 years, and 44% of patients had 10 years of disease-specific survival. The evidence suggests that loss of function of *SETD2*, *ARID1A, ATRX, DAXX*, and *CDKN2A* in primary PanNETs is associated with shorter survival, and impaired function of these genes including *SETD2* may result in metastasis of PanNETs (35).

Similarly, to identify molecular alterations between patients who are older than 65 and patients who are younger than 45 in left-sided colorectal cancers (LCRC), Puccini *et al.* examined the tumor tissue samples from splenic flexure to the rectum of those patients using immunohistochemical approaches and NGS. They found that younger patients more frequently harbor mutations in genes related to cancer-predisposing syndromes, such as *MSH2, MSH6, POLE, NF1, SMAD4,* and *BRCA2*.

They also detected significantly frequent mutation of histone modifier gene: *KMT2A, KMT2C, KDM5C,* and *SETD2*. The mutation frequency of *SETD*2 is relatively higher in LCRC in young patients (3.2% vs. 0.9%, p = .039). In addition, high tumor mutational burden (TMB-H) and high microsatellite instability (MSI-H) were also more frequent in younger patients (36).

Multiregion sequencing revealed that independent *SETD2* mutation occurred at several branching sites of ccRCC clonal evolution (37). Using immunohistochemical analysis, Ho *et al.* found that H3K36me3 levels increased in primary ccRCC in contrast to metastatic ccRCC (38). In a study including 185 ccRCC patients, Hakimi *et al.* observed that *SETD2* mutations were associated with advanced tumor stage (39). The results showed that patients bearing *SETD2* mutations had a higher relapse rate and worse cancer-specific survival, with the median overall survival of 62.7 months in *SETD2* mutated patients comparing 78.2 months in non-mutated patients (40). In addition, Sarakbi *et al.* reported that advanced tumor stages are associated with lower *SETD2* expression levels in breast cancer (24). Fontebasso *et al.* proposed that *SETD2* mutations are essential for the tumorigenesis of high-grade gliomas (19). In their cohort investigation, data of whole exome sequencing (WES) from 183 glioma samples revealed that *SETD2* is mutated in 12.37% high-grade gliomas, while no *SETD2* mutations have been detected in low-grade cases. Table 1 summarizes the currently available data on SETD2 alterations in a variety of human tumors.

4. POTENTIAL MECHANISM OF SETD2 REGULATING GI TUMOR PROGRESSION

Tumor progression is regulated by many different mechanisms, such as genome instability (41), tumor microenvironment (42, 43), immune deregulation (44), metabolic reprogramming (45), chemoresistance (46). A specific morphological transition from the epithelial to the mesenchymal morphology, a process named EMT (epithelial-mesenchymal transition), is a characteristic change during tumor progression (47). Despite a shortage of mechanistic studies of SETD2 that were performed exactly with GI tumors, lesson from other models may also help us to understand how SETD2 may control GI tumor progression through various mechanisms.

4.1. SETD2 and gene transcription

Existing bodies of evidence suggest that H3K36me3 catalyzed by SETD2 plays an important role in transcriptional regulation. In one of the earliest studies, the artificial binding of yeast set2 to promoter indicated that set2 repressed transcription (5). Tandem affinity purification revealed that set2 associated with elongating form of RNA polymerase II, suggesting that set2 couples with transcriptional elongation (48). Setd2 has been reported to regulate *Fgfr3* transcription initiation via H3K36me3 at distal promotor region to influence mouse endoderm differentiation(15). Interestingly, *SETD2* deficiency leads to DNA replication stress (RS) by a similar manner to regulate *RRM2* transcription initiation in ccRCC cell lines(49).

4.2. SETD2 and mRNA splicing

In a mouse model of CRC, Yuan *et al.* reported that Setd2 can suppress Wnt signaling pathway, and ablation of SETD2 could promote tumorigenesis in mouse intestine (13). Setd2 can modulate the alternative splicing of the genes implicated in tumorigenesis. In their multivariate analysis of transcript splicing study, totally 711 genes showed changes of alternative splicing in the *SETD2*-deficient sample, 198 genes were found to have exon skipping and 279 with intron retention. These alterations of alternative splicing increased disheveled segment polarity protein 2 (DVL2) mRNA, enhanced Wnt/β-catenin signaling and affected intestinal cell differentiation and consequently resulted in tumorigenesis.

SETD2 can also regulate alternative splicing of Human mutL homolog 1 (*hMLH1*). Zhao *et al.* found that the abnormal transcripts of *hMLH1* are associated with the low H3K36me3 status around *hMLH1* exon 10-11 (50). In human gastric carcinoma BGC-823 cells, the alternative splicing pattern of *hMLH1* transcripts changed after *SETD2* inactivation. The researchers proposed that some reader proteins could recognize H3K36me3 and the splicing factors such as SRSF2 was then recruited to the alternative

Table 1. Summary of SETD2 alterations in a variety of human tumors

Tumor type	**Number of cases**	**Major findings**		**References**
Breast cancer	120	Low expression of SETD2 is related to high tumor stage, metastasis, local recurrence and cancer-specific mortality		24
Subgroups	**Case tested**	**SETD2 mRNA (Mean ± SD) (CK19 normalisation)**		
• Normal tissue	33	414434 ± 1106629		
• Tumor tissue	120	20950 ± 37606		
• TNM stage 1	69	8551 ± 29766		
• TNM stage 2	40	8578 ± 24043		
• TNM stage 3	7	174 ± 414		
• TNM stage 4	4	679 ± 1081		
• Disease free	81	12239 ± 43466		
• Alive with Metastasis	7	1983 ± 5142		
• Local recurrence	5	3513 ± 5683		
• Died of disease	20	698 ± 1741		
Tumor type	**Number of cases**	**Major findings**		**References**
Clear cell renal cell carcinoma	146	Decreased H3K36me3 in cancer cell and is associated with metastasis		38
Kidney tissue type	**Case tested**	**Percentage of nuclear staining of H3K36me3**		
• Uninvoloved	30	~ 90%		
• Primary	71	~ 70%		
• Metastases	45	~ 30%		
Tumor type	**Number of cases**	**Major findings**		**References**
Glioma	183	12.37% high-grade gliomas have mutated SETD2. No low-grade gliomas harbor SETD2 mutation		19
Tumor grade	**Wild type**	**Mutated**	**Case tested**	**SETD2 mutation frequency(%)**
• Grade 3-4	122	16	138	12.37
• Pediatric	62	11	73	15
• Adult	60	5	65	8.11
• Grade 2	45	0	45	0
• Pediatric	23	0	23	0
• Adult	22	0	22	0
• Overall	167	16	183	8.7
Tumor type	**Number of cases**	**Major findings**		**References**
Clear cell renal cell carcinoma	185	SETD2 mutation is noted in 7.6% of ccRcc, is associated with higher stage		39
Tumor grade	**Wild type**	**Mutated**	**Case tested**	**SETD2 mutation frequency(%)**
• Stage 3-4	93	11	104	11.8
• Stage 1-2	78	3	81	3.9
• Overall	171	14	185	7.6

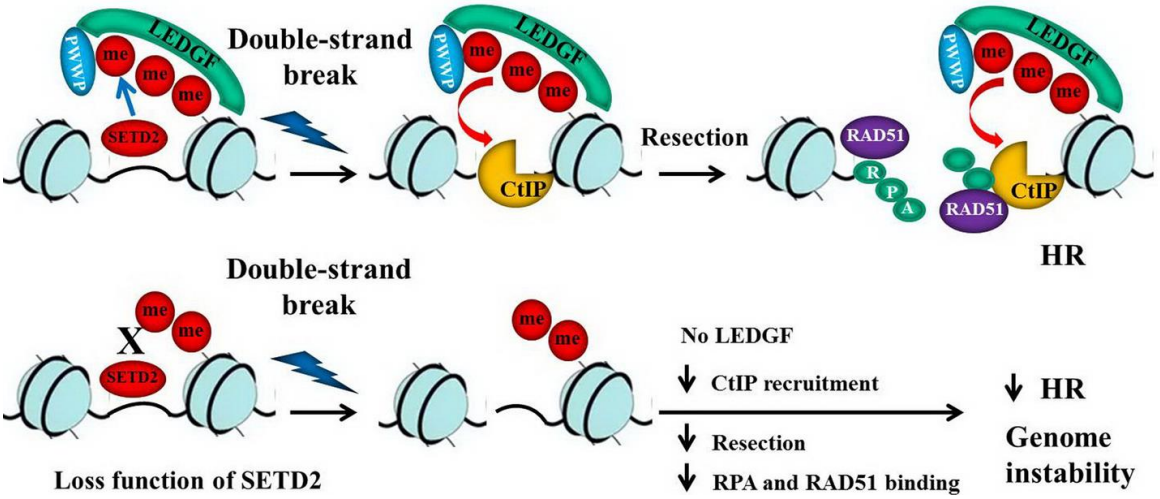

Figure 1. With normal H3K36me3 level surrounding *hMLH1* exon 10–11, medicated by SETD2, SRSF2 can be recruited to the functional splicing sites to enhance normal splicing. With SETD2 inactivation, aberrant splicing happens and this leads to inactivation of *hMLH1* and high-frequency microsatellite instability.

splice sites, resulting in the right splicing pattern which contains *hMLH1* Exon10 and Exon11. Once H3K36me3 was impaired at those alternative splice sites via SETD2 inactivation, aberrant splicing occurred and caused inactivation of *hMLH1*, demonstrated by expressional and translational diversity of hMLH1 protein in gastric cancer, as illustrated in Figure 1. And this explains why some types of gastric cancer carry high-frequency microsatellite instability (MSI).

4.3. SETD2 and DNA replication stress

DNA replication requires high fidelity to ensure the transmission of genetic information from one generation to the next, however, numerous obstacles of both intracellular and extracellular (e.g. limiting nucleotides, DNA lesions, repetitive DNA elements, oncogene-induced stress) cause DNA replication stress, uneffectively repaired RS will lead to aging (51) and genome instability for tumor formation and progression (41). Indeed, loss of function of SETD2 triggers RS to promote renal cancer evolution (52). Recently, Zhang *et al.* showed that conditional knockout of *Setd2* in hematopoietic stem cell results in RS, leading to subsequent genome instability and malignant transformation (12).

4.4. SETD2 and DNA damage repair

The critical roles of SETD2/H3K36me3 are mediated by recruiting some chromatin-associated proteins which have a PWWP domain. The PWWP domain is a protein-protein interaction domain, it has a central core ‘Pro-Trp-Trp-Pro’ motif and is about 70 amino acids length (53). These chromatin-associated proteins include DNA methyltransferase DNMT3b (54), Lens epithelium-derived growth factor (LEDGF) (55) and MSH6 (56). LEDGF and MSH6 have been broadly reported to participate in DNA repair, indicating that beside RS, SETD2 also guard genome stability through DNA repair.

Served as the basic element for HR repair, the PWWP domain of LEDGF can recognize H3K36me3, and facilitate binding of LEDGF to the DNA DSBs of the chromatin. Thereafter, LEDGF recruits C-terminal binding protein interacting protein (CtIP), coupling replication protein A (RPA) and RAD51, and promotes resection, the essential step in HR repair. As illustrated in Figure 2, the impairing of the resection may occur after compromised H3K36me3. However, cells will repair DNA damage via other pathways, such as nonhomologous end-joining and/or microhomology-mediated end-joining. Those

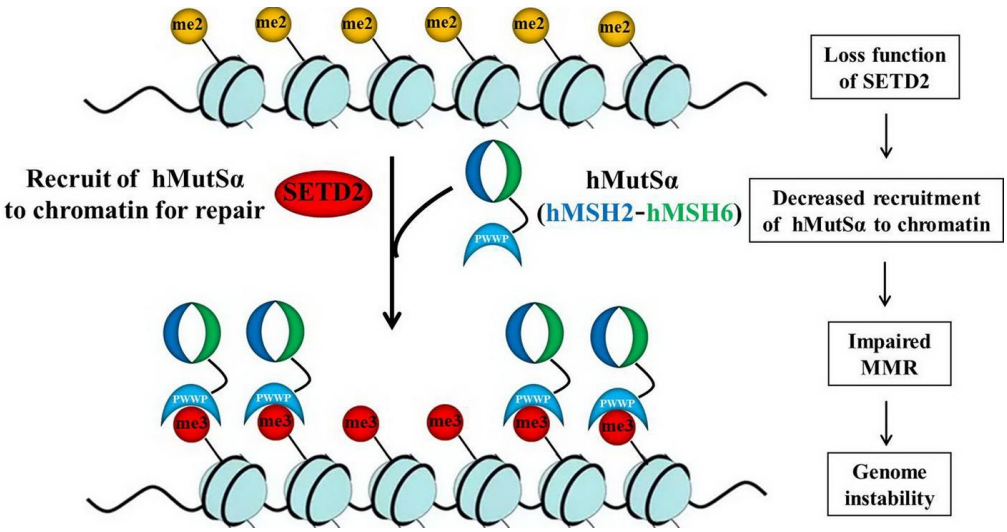

Figure 2. PWWP domain of LEDGF can recognize H3K36me3, through which LEDGF can be recruited to DSBs to initiate DNA repair. LEDGF recruits CtIP, RPA, and RAD51, which promotes resection, an essential step in HR repair. Without H3K36 trimethylation, chromatin LEDGF association could be compromised, CtIP, RPA, and RAD51 cannot be recruited, which will impair resection and HR, leading to deletions and subsequent genome instability and tumorigenesis.

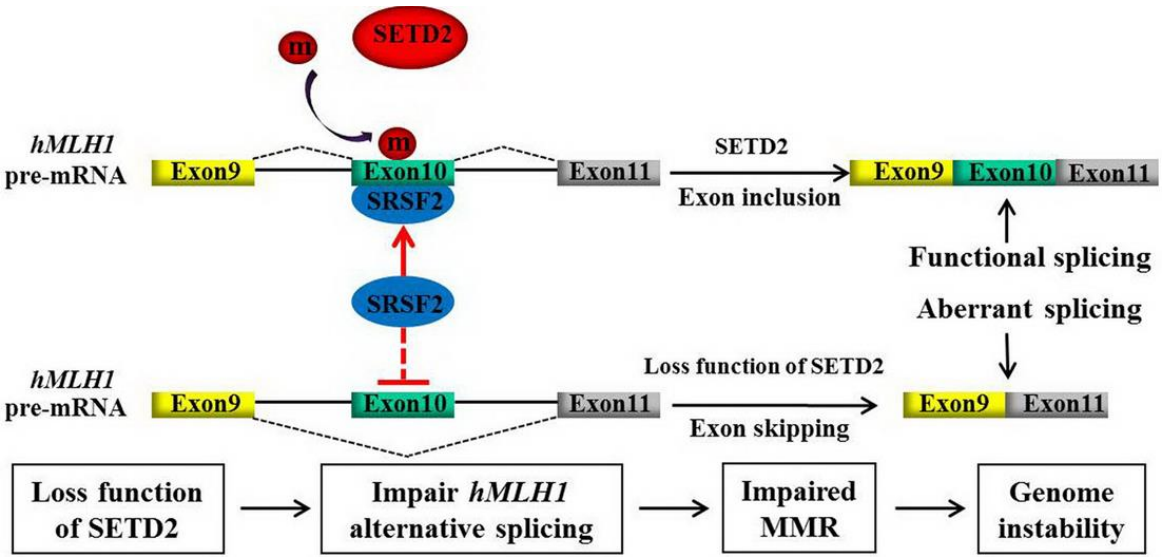

Figure 3. SETD2 mediated H3K36me3 is essential to attract the hMutS-alpha (hMSH2-hMSH6) complex to the damaged DNA sites through recognizing between H3K36me3 and PWWP domain of hMSH6. Depletion of SETD2 will compromise this interaction and the subsequent localization, leading to a DNA MMR deficiency.

alternative mechanisms are fallible and could lead to genomic instability and subsequent tumorigenesis (57).

DNA mismatch repair (MMR) ensures replication fidelity by correcting insertion/deletion loops and base-base mismatches generated during DNA replication. hMutS-alpha (MSH2-MSH6) complex plays a pivotal role in MMR. Li *et al.* reported that the hMSH6 PWWP domain as a histone

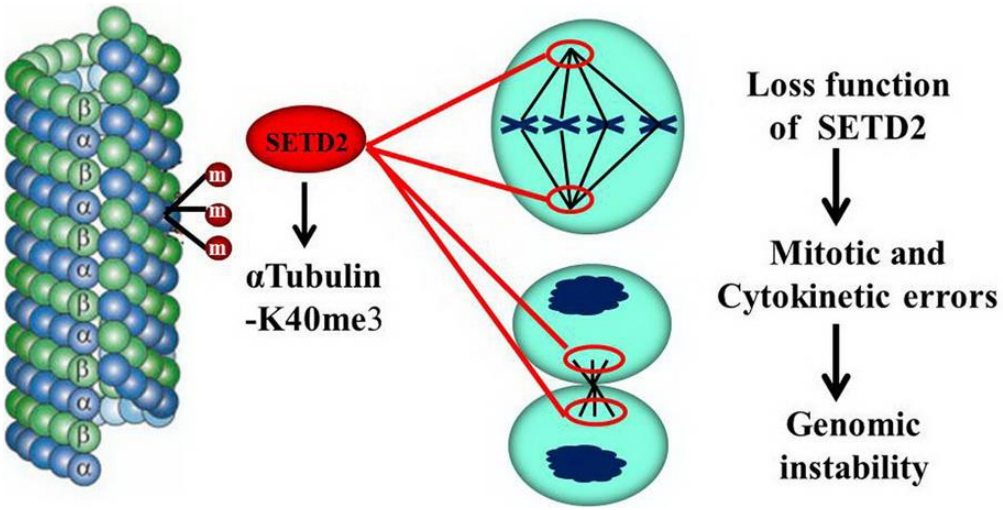

Figure 4. During mitosis and cytokinesis, SETD2 can trimethylate alpha-tubulin on lysine 40 (alpha-TubK40me3), and ablation of SETD2 causes mitotic spindle and cytokinesis defects, micronuclei, and polyploidy, which causes genomic instability and tumorigenesis.

modification reader and can interact directly with H3K36me3. Thus, hMutS-alpha complex is recruited to the chromatin. Once SETD2 is inactivated, the recruitment of hMutS-alpha to the damaged DNA sites will be decreased (58). As illustrated in Figure 3, this finding explained why some MSI-positive cancer cells do not bear mutations of the well-studied MMR genes.

4.5. SETD2 regulation of mitosis by tubulin methylation

A recent discovery by Park *et al.* showed that SETD2 can maintain genomic stability by keeping the proper function of α-tubulin during mitosis and cytokinesis. SETD2 can tri-methylate α-tubulin on lysine 40 (α-TubK40me3), and ablation of SETD2 causes defects of mitotic spindle and cytokinesis, micronuclei, and polyploidy. This study suggested that the genomic unstable oncogenic phenotypes of *SETD2*-mutated cells may be caused by tubulin defects during cytokinesis and mitosis, as illustrated in Figure 4 (58). Nevertheless, this mechanism leading to chromosomal instability in colorectal cancer remains to be determined.

4.6. SETD2 and immune deregulation

Tumor cells often form an immunosuppressive niche that can promote tumor progression, a non-biased high-throughput RNAi screening found that SETD2 as a critical effector molecular to promote IFNα-mediated cellular response against HBV replication via directly methylated STAT1 like tubulin methylation (59). Whether the progressive stage of GI tumor with *SETD2* mutation also exists IFNα pathway inhibition is a worthy research direction in the future.

4.7. SETD2 and chemoresistance

Several studies have reported a high frequency of *SETD2* mutation in the relapse of acute leukemia (18) and hepatosplenic T-cell lymphoma (60), suggesting that SETD2 mutation promotes chemoresistance. Using CRISPR/Cas9 to knockout *SETD2* in leukemia cell lines, Mar *et al.* found SETD2 impaired DNA damage recognition to induce resistance to DNA-damaging chemotherapy (61). To further clarify the mechanism of chemoresistance in leukemia, *Mll-Af9* knock-in leukemia mouse model in *Setd2* mutant was constructed, the authors demonstrate that SETD2 loss of function mutations confer chemoresistance on AL to DNA-damaging treatment by S and G2/M checkpoint defects (62). In other solid tumors, SETD2 also confer chemoresistance, Kim *et al.* found that SETD2

mediated H3K36me3 is critical for cellular sensitivity to cisplatin, and *SETD2* inactivation may lead to cisplatin resistance. They reported that knockdown of *SETD2* and ectopic expression of mutated *SETD2* both can confer cisplatin resistance by inhibiting H3K36me3-ERK pathway in non-small cell lung cancer cells (63). Jiang *et al.* found that low expression of *SETD2* was observed in osteosarcoma tissue, osteosarcoma cell growth can be inhibited both *in vitro* and *in vivo* by ectopic *SETD2*. Additionally, through regulating Wnt/β-catenin signaling, SETD2 can increase cisplatin-mediated apoptosis in osteosarcoma cells, and this was mediated by enhancing GSK-3β expression through increasing H3K36me3 level at the GSK-3β promoter, which resulted in β-catenin degradation and downregulation of its downstream gene cyclin D1, c-myc, and CD133 (64).

5. CONCLUSION AND PERSPECTIVES

This review summarizes the currently available studies on the alterations of SETD2, a histone methyltransferase, in the tumorigenesis of human malignancies, especially in the gastrointestinal tumors. Not only *SETD2* mutation but also downregulation expression occurs in GI tumor. Notably, these changes appear almost exclusively in the progressive phase and associate with poor prognosis. We mainly discuss the potential mechanism of GI tumor progression caused by SETD2 mutation, with some lessons learned from other cancer types. SETD2 mediated H3K36me3 can be recognized by effector protein, which connects critical tumor suppressor function of SETD2 to several critical biological processes in tumorigenesis, including mRNA alternative splicing, methylation of α-tubulin, and recruitment of the LEDGF protein or the hMutS-alpha complex during DNA damage repair. Once mutations of *SETD2* occurs with a resultant low level of H3K36me3, the effector proteins cannot be recruited to their right location to maintain the genomic stability and integrity. Although genomic instability caused by *SETD2* mutation acts as a driver for tumor progression, several recent studies fortunately revealed that some inhibitors can selectively kill *SETD2*$^{-/-}$ cells. For example, Yang *et al.* have found four chemical compounds in the database of Genomics of Drug Sensitivity in Cancer (GDSC) which can selectively inhibit *SETD2*$^{-/-}$ cell growth, and two of them target P13Kβ (65). Feng *et al.* reported that AZD6482 can also selectively inhibit *SETD2*$^{-/-}$ ccRCC cell lines (66). In the study conducted by Pfister *et al.*, the G2-M cell cycle checker WEE1 inhibitor AZD1775 can inhibit H3K36me3-deficient renal cancer cell growth (49). This study suggests that WEE1 inhibitors may be a promising drug for H3K36me3-deficient tumors treatment. Future research on elucidating the functional consequences of *SETD2* mutations, including discovering more H3K36me3 readers, may help identify novel targets for therapeutic intervention in patients with *SETD2* mutant-harboring gastrointestinal cancers.

6. ACKNOWLEDGMENTS

Ming Hu and Mu Hu contributed equally to this article, Ming Hu, Mu Hu, Qin Zhang developed the original idea and wrote the manuscript, Jinping Lai and Xiuli Liu contributed to the critical revision of the manuscript for important intellectual content.

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