Role of SMYD2 in gastrointestinal cancer progression (Review)

KUN XIA, YAOXIANG ZHOU, YOUPING XIE and YINZHONG CAI

Department of General Surgery, People's Hospital of Ningxiang City, Ningxiang, Hunan 410600, P.R. China

Received December 13, 2024; Accepted March 21, 2025

DOI: 10.3892/ol.2025.15028

Abstract. Gastrointestinal cancer is one of the most prevalent malignancies in humans and is often associated with a poor prognosis. Understanding the molecular mechanisms underlying cancer progression and severity is essential for the development of effective cancer therapies. Abnormal protein methylation is associated with the occurrence and advancement of cancer, highlighting the importance of protein methyltransferase research. SET and MYND domain-containing protein 2 (SMYD2), a lysine methyltransferase, has emerged as a promising small molecule target for cancer treatment. Notably, SMYD2 is implicated in the pathogenesis of several diseases, including gastrointestinal cancer. SMYD2 is closely associated with the tumorigenesis, proliferation, migration and other biological processes of gastrointestinal cancer, indicating its potential as a novel therapeutic target. The present review offers an in-depth analysis of SMYD2, covering its structural characteristics, regulatory pathways and functional significance. By assessing the biological roles and therapeutic potential of SMYD2, the current review presents fresh insights and perspectives for advancing research in different types of gastrointestinal cancer.

Contents

1. Introduction
2. Structure of SMYD2
3. Biological function of SMYD2
4. SMYD2 and CRC
5. SMYD2 and GC
6. SMYD2 and gastrointestinal stromal tumor (GIST)
7. SMYD2 and liver cancer
8. SMYD2 and pancreatic cancer (PC)
9. SMYD2 and esophageal cancer (EC)
10. Future perspectives
11. Discussion and conclusions

Correspondence to: Dr Yinzhong Cai, Department of General Surgery, People's Hospital of Ningxiang City, 209 North Road of 1st Ring, Ningxiang, Hunan 410600, P.R. China
E-mail: cyzpwk@163.com

Key words: gastrointestinal cancer, SET and MYND domain-containing protein 2, mechanism, biomarker, therapy

1. Introduction

Gastrointestinal cancer ranks among the most common cancer types worldwide. According to 2020 statistics from the World Health Organization, gastrointestinal cancer accounts for ~26% of all cancer cases globally and ~35% of all cancer-related deaths (1). Despite notable advancements in research on gastrointestinal malignancies in recent years, the survival rate remains at only 25-30%, as most patients are diagnosed at advanced or terminal stages of the disease (2,3). At present, the primary clinical interventions for gastrointestinal cancer include surgical resection, chemoradiotherapy and targeted therapies. However, due to the high recurrence and metastatic potential of this cancer type, the clinical prognosis for patients remains unfavorable (4). The exploration of novel diagnostic and therapeutic strategies for gastrointestinal cancer has become a central focus of clinical research. The clinical success of antitumor drugs targeting histone-modifying enzymes, such as histone deacetylase inhibitors, has rendered histone modification an increasingly prominent area of interest in cancer research (5).

SET and MYND domain-containing protein 2 (SMYD2), a lysine methyltransferase, has gained increasing attention due to its dual ability to methylate both histone and non-histone proteins, influencing critical processes such as transcription regulation, cell cycle progression and apoptosis (6-8). The activity of SMYD2 is essential for organismal development and several cellular functions, with mutations of this gene frequently associated with cardiovascular diseases and cancers (9-12). At present, SMYD2 is actively being investigated as a potential target for inhibitors that regulate gene transcription or signal transduction pathways (13,14). The upregulation of SMYD2 is associated with several cancer types, including hepatocellular carcinoma (HCC), colorectal cancer (CRC) and gastric cancer (GC), where it promotes tumorigenesis through both direct protein modification and epigenetic modulation of oncogenic pathways (15). Dysregulation of epigenetic control is widely accepted as a cause of tumor malignancy; therefore, the inhibition of epigenetic enzymes is a highly pursued therapeutic strategy (16,17). SMYD2 inhibitors have shown promising progress in cellular and animal studies across several cancer types (18,19). Despite SMYD2 being regarded as an oncogene, research on specific SMYD2 inhibitors remains limited (20). However, current inhibitors, such as AZ505 and BAY-598, have shown promise in preclinical studies, albeit with challenges related to bioavailability and pharmacokinetics (21).

In the last 10 years, SMYD2 has gained considerable attention in gastrointestinal cancer research, resulting in a growing number of related studies and publications (22). However, to the best of our knowledge, there is currently no comprehensive review specifically addressing the mechanisms of tumorigenesis and treatment strategies associated with gastrointestinal malignancies. Consequently, the present review primarily aims to emphasize the role of SMYD2 as a key lysine methyltransferase and a promising therapeutic target in different types of gastrointestinal cancer. The molecular structure of SMYD2, its biological functions and the mechanisms through which it contributes to the onset and progression of gastrointestinal malignancies, as well as the current therapeutic strategies targeting SMYD2, are thoroughly assessed. Furthermore, the potential of SMYD2-targeted therapies for gastrointestinal cancer and their possible impact on treatment outcomes are evaluated.

2. Structure of SMYD2

The SET and MYND domain-containing protein family, which includes five members (SMYD1-5), is a class of lysine methyltransferases. Among these, SMYD1, SMYD2 and SMYD3 exhibit the highest homology and structural similarity, with their domains organized sequentially as SET, MYND, SET-I, post-SET and C-terminal domain (CTD) (23-25). The SMYD2 gene, located in the 1q32.3 region of the human genome, consists of 12 exons and encodes a protein of 433 amino acids. SMYD2 was first identified by Brown *et al* (6) in 2006.

Similar to other SMYD family members, SMYD2 consists of two major structural components: The N-terminal domain and CTD. The N-terminal domain (residues 1-271) includes four subdomains, N-SET, MYND, SET-I and post-SET, whilst the CTD includes residues 272-433 (26,27). The N-terminal domain contains a mixed structure of α-helices (α1-α6), β-strands (β1-β12) and extended loops, whilst the CTD forms a twisted seven α-helical bundle (α8-α14) (27).

Additionally, SMYD2 undergoes alternative splicing, generating at least two known isoforms. The primary isoform, SMYD2-1, consists of 433 amino acids and is considered the canonical sequence. The alternative isoform, SMYD2-2, differs from the canonical sequence, containing only 272 amino acids due to the deletion of the 273-433 aa segment, resulting in a shorter protein (28). However, detailed descriptions of SMYD2-1 and SMYD2-2 remain limited in the scientific literature. Further research is necessary to improve the understanding of specific SMYD2 isoforms, including SMYD2-1 and SMYD2-2, by investigating alternative splicing events and their functional implications. This may involve transcriptome analysis and protein characterization studies to elucidate the roles of these isoforms in several physiological and pathological contexts.

The SET, SET-I and post-SET domains are essential for the catalytic activity of lysine methyltransferases (29), whilst the MYND domain, with a zinc finger structure, primarily mediates protein-protein interactions (30). Morphologically, the CTD is arranged in antiparallel helices that include a tetratricopeptide repeat (TPR)-like domain (31,32). Together with the SET domain, the CTD contributes to the formation of a two-lobed structure (26). The angle between these lobes creates a 'U'-shaped cavity that binds substrates, with the bottom of this cavity serving as the active site for SET enzyme activity (27). The movement of this structure allows it to reach a specific state, which influences the specificity of SMYD2 for its substrates (27,33,34).

A previous study reported that under activation stress, S-adenosylmethionine binding induced increased elasticity in the CTD, causing SMYD2 to adopt an open conformation that exposed the substrate-binding site (Fig. 1) (35). However, the full mechanisms underlying the function of the CTD remain unclear, and its potential as a drug target site has yet to be explored. Moreover, a recent study identified a novel mixed allosteric site in SMYD2, which exhibited mixed binding characteristics capable of interacting with peptides, proteins, ethylene glycol polymers and small molecules. This allosteric site could serve as a target for future drug design research (36).

3. Biological function of SMYD2

In total, >50 proteins with SET domains are encoded by the human genome and only a small fraction have been reported to methylate histones, with the SMYD protein family being among them (6). The first member of this family, SMYD1, was identified and named by Gottlieb *et al* (37) during the investigation of genes expressed early in mouse heart development. Since then, research on the SMYD protein family has grown. SMYD2 is considered an essential protein for the development of skeletal muscle and cardiac muscle cells in zebrafish (38); however, experiments with mouse models suggest it does not serve a role in cardiac muscle development (39). A previous study reported that SMYD2 exhibits elevated expression levels in the heart, brain, liver, kidneys, thymus and ovarian tissues. By comparison, its expression in the gastrointestinal tract is relatively low, except in the liver, where it is comparatively higher, with its presence detected in both the cytoplasm and nucleus of cells (6). SMYD2 is present in the maternal genome of *Xenopus laevis* embryos and persists until stage 40, with expression localized to the dorsomedial lip, particularly in the face region. Loss-of-function analysis using antisense morpholino oligonucleotide (MO) revealed that *Xenopus laevis* embryos injected with SMYD1MO and SMYD2MO exhibit abnormal somite, abnormal mandibular tissue and severe malformations (40), suggesting that SMYD2 may be involved in the development of multiple systems, including the cardiovascular, nervous, gastrointestinal, musculoskeletal, urinary and reproductive systems.

Experimental evidence has also reported that SMYD2 specifically methylates the lysine 4 residue of histone H3 (H3K4), lysine 36 residue of histone H3 (H3K36) and lysine 20 residue of histone H4 (H4K20), and these methylation events may alter gene transcription, thereby influencing a range of cellular activities (41). Histone H3 contains the majority of lysine residues targeted by known histone methyltransferases, making it a key pathway member for the regulation of epigenetic mechanisms (6). SMYD2 specifically demethylates H3K36, generating H3K36Me2, which negatively regulates gene expression and thereby inhibits cell proliferation (6). Additionally, in the presence of the chaperone protein, heat shock protein 90α (HSP90α), SMYD2 specifically methylates H3K4, leading to gene activation; conversely, in the absence of

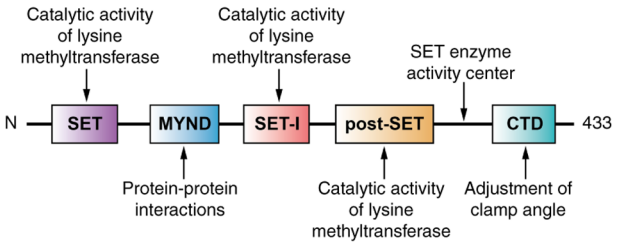

Figure 1. Domain structure of the human SMYD2 protein and the main biological functions corresponding to each part of the structure. SMYD2, SET and MYND domain-containing protein 2; CTD, C-terminal domain.

HSP90α, SMYD2 reverts to its specific methylation of H3K36, resulting in gene repression (31). The SMYD2-mediated methylation of H3K4 is typically associated with gene activation; however, the precise mechanism by which this modification influences cell proliferation has yet to be fully elucidated (41). H4K20 is an unrecognized target of SMYD2, despite a previous study reporting that histone H4 is a more effective substrate for SMYD2 than histone H3 (42). In a large-scale proteomic study of SMYD2-mediated lysine monomethylation, it was reported that H4K20me1 was downregulated in 4/7 cell lines following short hairpin (sh)RNA-mediated knockdown and the use of SMYD2 inhibitors, indicating a more widespread role of SMYD2 in H4K20 monomethylation (43). Moreover, a previous study reported that SMYD2 promoted monomethylation of H4K20 in the human immunodeficiency virus (HIV)-1 promoter region, inhibiting HIV-1 transcription, highlighting its potential in HIV therapeutic strategies (42).

SMYD2 also has a crucial role in the methylation of non-histone proteins within cells (44-46). For example, a previous study reported that SMYD2 methylated p53 and phosphatase and tensin homolog deleted on chromosome ten (PTEN), thereby suppressing their tumor-inhibiting functions (18,47). The retinoblastoma tumor suppressor (RB) can be methylated by SMYD2 at lysine 860, a highly conserved and novel site of modification, thereby influencing cell growth, differentiation and the DNA damage response (48). Furthermore, SMYD2 can methylate the lysine 810 of RB (49). The methylation of RB increases the level of phosphorylation of Ser 807/811 and releases and activates the E2F transcription factor, thereby promoting the cell cycle progression of cancer cells (49). Additionally, SMYD2 suppresses the activity of p53 by monomethylating lysine 370, a function that is dependent on the SMYD2 SET domain as the absence of the conserved SET domain sequence abolishes this methylation (7,31). However, the molecular chaperone HSP90 appears to be unaffected by the SET domain, as the TPR-like domain of SMYD2 interacts with HSP90 to form a chaperone complex, thereby influencing cellular proliferation (50). The dual capacity of SMYD2 to methylate both histone and non-histone proteins impacts key processes such as transcriptional regulation, cell cycle progression and apoptosis (7). The aforementioned findings and further information on histone and non-histone proteins are presented in Table I. These proteins are closely associated with tumor development, underscoring the inextricable link between SMYD2 and cancer.

4. SMYD2 and CRC

CRC ranks third globally in terms of both incidence and mortality. The pathogenesis of CRC is multifactorial, with genetic mutations, lifestyle choices and environmental factors contributing to tumorigenesis. These factors include dietary habits, smoking, alcohol consumption, lack of physical activity and a family history of CRC (51). Previous studies have revealed the association between SMYD2 and CRC. Specifically, multiple investigations have demonstrated elevated levels of SMYD2 mRNA and protein in CRC tissues, which are associated with worse prognoses (52-54).

An *in vitro* study reported that SMYD2 promoted the proliferation and invasion of colon cancer cells, whilst inhibiting apoptosis. Additionally, SMYD2 was reported to enhance Erb-B2 receptor tyrosine kinase 2 (ERBB2) phosphorylation and upregulate fucosyltransferase 4 (FUT4) expression in colon cancer cells (55). Further *in vivo* experiments reported that SMYD2 knockout markedly slowed tumor growth in mice, indicated by the smaller tumor volumes observed in the SMYD2-deficient group. These tumors exhibited reduced expression levels of phosphorylated ERBB2, FUT4 and the proliferation marker, Ki67. Mechanistically, the study demonstrated that SMYD2 mediates colon cancer cell proliferation, invasion and apoptosis through the ERBB2/FUT4 signaling pathway (55). Ren *et al* (56) reported that SMYD2 upregulation in colorectal adenocarcinoma (COAD) tissues is often associated with poor prognosis in patients undergoing oxaliplatin (L-OHP) chemotherapy. *In vitro* and *in vivo* experiments revealed that downregulation of SMYD2 sensitized COAD cells to L-OHP exposure. Moreover, when SMYD2 expression was downregulated, P-glycoprotein (P-gp) levels decreased, whereas its overexpression led to P-gp upregulation, indicating that P-gp serves a role in the SMYD2-mediated resistance to L-OHP (56). P-gp, a membrane-bound transporter, serves as a marker for an unfavorable prognosis in patients with COAD (5,56). Additional research on the role of SMYD2 in L-OHP resistance revealed that its upregulation increased MEK/ERK/activator protein 1 (AP-1) pathway activity, leading to alterations in drug metabolism-associated receptors and signaling cascades, ultimately influencing the responsiveness COAD cells to L-OHP. Consequently, SMYD2 is suggested to facilitate P-gp upregulation via the MEK/ERK/AP-1 pathway, thereby contributing to L-OHP resistance in COAD cells (56). Additionally, SMYD2 has been reported to inhibit the TNF-induced apoptosis and necrosis of colorectal tumor cells by downregulating the receptor-interacting protein kinase 1 phosphorylation signaling pathway, and inhibition of SMYD2 suppresses the growth of colorectal tumors (53).

Bioinformatics analysis has predicted that SMYD2 aberrantly modifies H3K4me3 and acetylated H3K27 (H3K27ac) on long intergenic non-protein coding RNA 1605 (LINC01605) in CRC. Subsequent experiments have reported that SMYD2 promotes LINC01605 expression through H3K27ac and H3K4me3 modifications, thereby influencing the development and progression of CRC (57). Both *in vitro* and *in vivo* experiments demonstrated that knocking down SMYD2 notably suppressed CRC cell proliferation, migration and invasion as well as tumor growth in nude mice, whilst overexpression of SMYD2 produced the opposite effects, indicating its role in

Table I. Function of SET and MYND domain-containing protein 2 histone and non-histone substrates in cancer.

Substrate type	Substrate	Biological function	(Refs.)
Histone	H3K36	Inhibits proliferation	(31)
	H3K4	Gene activation	(41)
	H4K20	DNA repair	(43)
Non-histone	RB	Regulates the cell cycle	(49)
	p53	Promotes proliferation; inhibits apoptosis	(7)
	PTEN	Promotes proliferation and migration	(47)
	Myc	Promotes proliferation	(74)
	EZH2	Promotes proliferation; inhibits senescence	(66)
	Erα	Promotes proliferation	(44)
	HSP90	Promotes proliferation	(50)
	β-catenin	Promotes proliferation, migration and invasion	(59)
	STAT3	Promotes proliferation	(45)
	MAPKAPK3	Promotes proliferation	(12)
	PARP1	Promotes proliferation	(46)

H3K36, histone H3 lysine 36; H3K4, histone H3 lysine 4; H4K20, histone H4 lysine 20; RB, retinoblastoma; p53, tumor protein 53; PTEN, phosphatase and tensin homolog; Myc, v-Myc avian myelocytomatosis viral oncogene homolog; EZH2, enhancer of zeste homolog 2; Erα, estrogen receptor α; HSP90, heat shock protein 90; STAT3, signal transducer and activator of transcription 3; MAPKAPK3, mitogen-activated protein kinase-activated protein kinase 3; PARP1, poly (ADP-ribose) polymerase 1.

promoting CRC progression (58). Further *in vitro* experiments reported that SMYD2 activated Mex-3 RNA binding family member A (MEX3A) transcription by enhancing H3K36me2 modification in the region of its promoter. Silencing MEX3A expression suppressed CRC cell proliferation and growth, as well as reduced tumor growth *in vivo*. Rescue experiments demonstrated that MEX3A silencing restored caudal type homeobox 2 (CDX2) expression, thereby blocking the oncogenic effects of SMYD2. Conversely, silencing CDX2 expression rescued the malignant behavior of CRC cells inhibited by MEX3A silencing. These findings indicate that SMYD2 epigenetically activates MEX3A transcription through H3K36me2 modification, leading to CDX2 downregulation and the promotion of CRC development (58).

Furthermore, in a previous study, clinical data indicated that high SMYD2 expression was positively associated with tumor diameter in CRC and is a risk factor for tumor metastasis. Further *in vivo* and *in vitro* experiments demonstrated that SMYD2 promoted CRC metastasis by recruiting DNA methyltransferase 1 in CRC cells to suppress adenomatous polyposis coli 2 expression, thereby facilitating epithelial-mesenchymal transition and activating the Wnt/β-catenin signaling pathway (52,59). Another study reported that highly expressed SMYD2 mediated the monomethylation of K422 of heterogeneous nuclear ribonucleoprotein K, which in turn promoted CRC angiogenesis by binding to and stabilizing epidermal growth factor-like domain 7 mRNA. In xenograft experiments, combining a SMYD2 inhibitor (BAY-598) with a VEGFR2 inhibitor (apatinib) inhibited CRC angiogenesis (Fig. 2B). This indicates that targeting SMYD2 is a safe and effective therapeutic strategy that can synergistically enhance the anti-angiogenic effect of apatinib, demonstrating its potential for CRC treatment (54).

5. SMYD2 and GC

GC is one of the most common cancer types worldwide, with the majority of patients diagnosed at the advanced stages of disease and facing poor prognoses. The clinical staging of GC is crucial in determining its prognosis. The 5-year survival rate for early-stage gastric cancer can exceed 90%, whereas for advanced-stage cases, it falls below 30% (60). The pathogenesis of GC is complex and influenced by genetic, environmental and lifestyle factors. Early-stage GC is primarily treated with surgery, whilst advanced cases require chemotherapy, targeted therapy and immunotherapy. Despite advancements in diagnosis and treatment, GC remains a major cause of cancer-related mortality, highlighting the need for further research and improved therapeutic strategies (61).

An analysis of public databases revealed that SMYD2 mRNA expression is notably upregulated in GC, with protein levels consistent with the mRNA levels. Furthermore, SMYD2 expression is negatively associated with both overall survival (OS) and progression-free survival. Additionally, SMYD2 is closely associated with the infiltration of six immune cell types: Uncharacterized cells, $CD8^+$ T cells, $CD4^+$ T cells, macrophages, endothelial cells and B cells. SMYD2 is also markedly positively associated with tumor mutational burden and microsatellite instability in GC (62). An additional analysis of publicly available datasets identified a strong association between SMYD2 mRNA levels and both the occurrence of stomach adenocarcinoma and the mutation status of P53. Moreover, SMYD2 was reported to be negatively associated with $CD8^+$ T cells and dendritic cells (63).

Experimental data demonstrated that both SMYD2 mRNA and protein are highly expressed in GC cell lines, and this expression is independent of the TP53 mutation

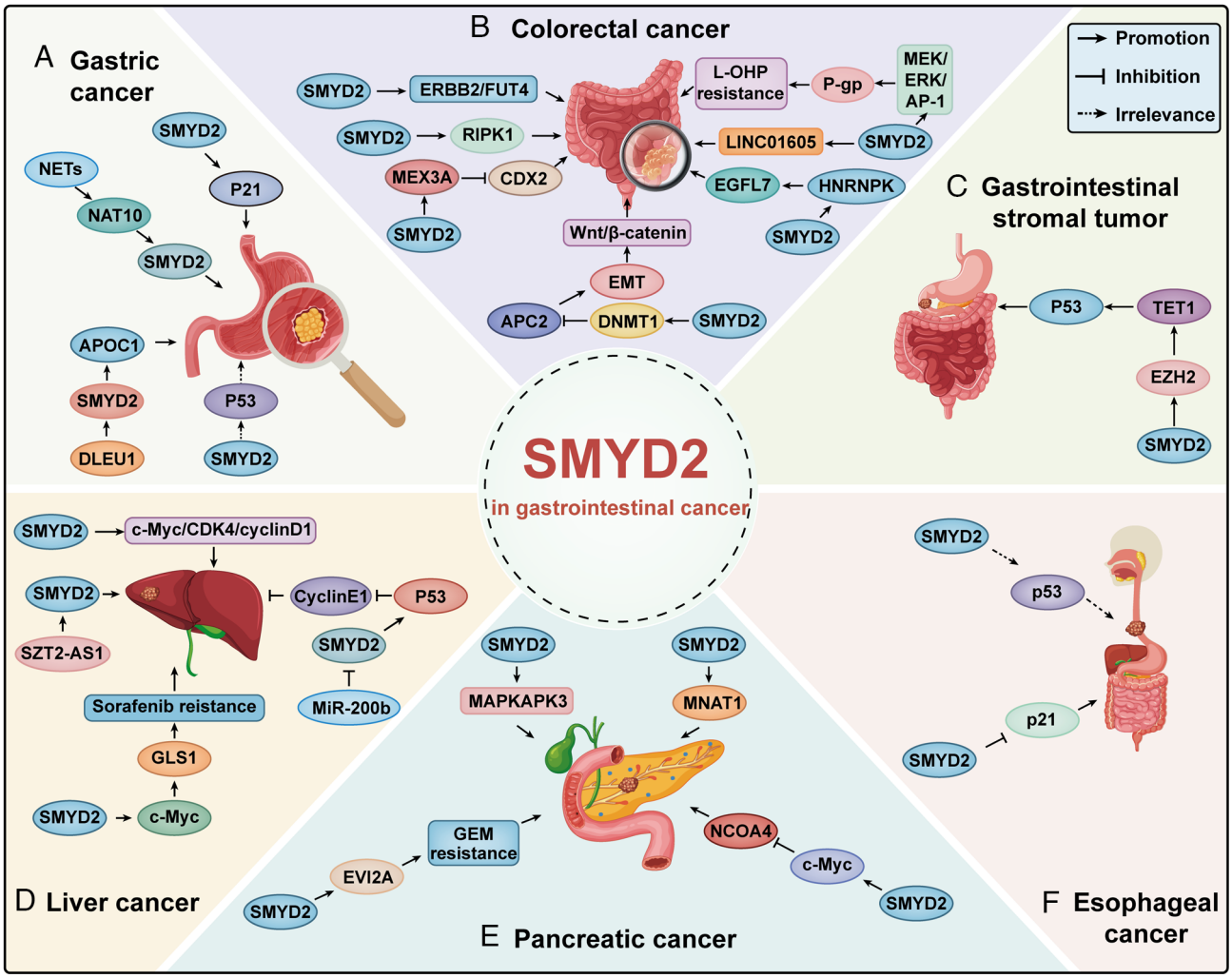

Figure 2. SMYD2 promotes or inhibits the progression of gastrointestinal cancer by targeting related molecules in association with different proteins. (A) Gastric, (B) colorectal, (C) gastrointestinal stromal tumor; (D) liver, (E) pancreatic and (F) esophageal cancers. SMYD2, SET and MYND domain-containing protein 2; NETs, neutrophil extracellular traps; NAT10, N-acetyltransferase 10; DLEU1, deleted in lymphocytic leukemia 1; APOC1, apolipoprotein C1; ERBB2, Erb-B2 receptor tyrosine kinase 2; FUT4, fucosyltransferase 4; L-OHP, oxaliplatin; P-gp, P-glycoprotein; RIPK1, receptor-interacting protein kinase 1; LINC01605, long intergenic non-protein coding RNA 1605; MEX3A, Mex-3 RNA binding family member A; CDX2, caudal type homeobox 2; HNRNPK, heterogeneous nuclear ribonucleoprotein K; EGFL7, epidermal growth factor-like domain 7; DNMT1, DNA methyltransferase 1; APC2, adenomatosis polyposis coli 2; EMT, epithelial-mesenchymal transition; EZH2, enhancer of zeste homolog 2; TET1, ten-eleven translocation methylcytosine dioxygenase 1; CDK4, cyclin-dependent kinase 4; GLS1, glutaminase 1; MAPKAPK3, mitogen-activated protein kinase-activated protein kinase 3; MNAT1, MNAT1 component of CDK activating kinase; NCOA4, nuclear receptor coactivator 4; EVI2A, ecotropic viral integration site 2 A; GEM, gemcitabine.

status and expression levels. Furthermore, downregulation of SMYD2 was reported to inhibit the proliferation, migration and invasion of GC cells (10). *In vitro* experiments revealed that this inhibitory effect was independent of the P53 mutation and expression status, with SMYD2 gene downregulation directly or indirectly inducing p21 expression, leading to G0/G1 cell cycle phase arrest and the subsequent suppression of GC cell proliferation (10). Clinical data analysis subsequently reported that SMYD2 protein expression is associated with tumor size, lymphatic infiltration, lymph node metastasis rate, invasion depth and recurrence rate. Prognostic evaluation demonstrated that patients with elevated SMYD2 expression exhibited significantly worse outcomes than those with lower levels, suggesting that SMYD2 immunoreactivity may serve as an independent prognostic marker for predicting OS in patients with GC (10).

Moreover, a clinical study revealed that the secretion levels of neutrophil extracellular traps (NETs) were notably elevated in 30 patients with GC compared with the healthy control group, with these levels increasing as cancer progressed. Both *in vitro* and *in vivo* experiments further demonstrated that NETs promoted the proliferation, migration and invasion of GC cells (22). Mechanistically, NETs upregulate *N*-acetyltransferase 10 (NAT10), which enhances the mRNA and protein expression levels of SMYD2 by increasing the half-life. Additionally, NAT10 promotes the acetylation of SMYD2, further increasing SMYD2 stability and promoting the proliferation, migration and invasion of GC cells (22). Using a mouse model, it was demonstrated that NETs facilitate the progression of GC and its metastasis to the liver by increasing NAT10 expression (22). These findings suggest that NETs may facilitate GC metastasis through the NAT10-mediated acetylation of SMYD2.

Research by Xu *et al* (64) revealed that SMYD2 promotes the expression of apolipoprotein C1 (APOC1) by regulating the trimethylation of H3K4 at the APOC1 promoter. APOC1 has been identified as a key factor in promoting glycolysis and driving the proliferation of GC cells (64). Additional research into the regulatory mechanisms of SMYD2 in GC revealed that deleted in lymphocytic leukemia 1 (DLEU1) facilitates SMYD2 recruitment to enhance APOC1 expression. Silencing DLEU1 expression disrupted the interaction of SMYD2 with the APOC1 promoter, leading to decreased H3K4me3 enrichment at this site. These results highlight the pivotal role of the DLEU1-SMYD2-APOC1 axis in driving glycolysis and cell proliferation in GC (64) (Fig. 2A). This suggests that targeting this axis may represent a novel therapeutic strategy for GC.

6. SMYD2 and gastrointestinal stromal tumor (GIST)

GIST is the most prevalent mesenchymal tumor of the gastrointestinal tract. GIST can vary in behavior from benign to highly aggressive, depending on factors such as tumor size, mitotic rate and location. Surgical resection is the primary treatment for localized tumors, whilst targeted therapy has markedly improved the outcomes of patients with advanced or metastatic disease. Combining surgery with tyrosine kinase inhibitor therapy has increased the 5-year survival rate for localized GIST to 92%, while it is 50% for metastatic cases (65).

A previous study reported that exposure to LLY-507 and AZ-505 in GIST-T1 cells induced the SMYD2-mediated methylation of enhancer of zeste homolog 2 (EZH2) at K307, which subsequently increased EZH2 stability by facilitating its degradation via the proteasome pathway. Following treatment with LLY-507, there was a notable reduction in demethylation at K307 and the abundance of EZH2, alongside decreased methylation at K310 of p53. These findings indicate that SMYD2 promotes the stability of EZH2 via methylation at K307 (66). Previous research in triple-negative breast cancer also indicated that EZH2 epigenetically regulates ten-eleven translocation methylcytosine dioxygenase 1 (TET1) by mediating H3K27me3, leading to the repression of TET1 expression. This repression inhibited the activation of the p53 tumor suppressor signaling pathway, in which TET1 serves a crucial role (67). Expanding on this, the researchers further reported that EZH2 promoted GIST cell proliferation whilst suppressing senescence, an effect that was achieved by elevating H3K27me3 at the TET1 promoter, thereby inhibiting TET1 expression and disrupting downstream p53 signaling pathways. Furthermore, western blotting revealed an increase in TET1 and p53 expression in GIST-T1 cells treated with sh-EZH2, an effect that was reversed upon sh-TET1 treatment (66). Thus, suppressing EZH2 expression elevated the TET1 and p53 levels, leading to cell cycle arrest and enhanced senescence in GIST-T1 cells, whereas TET1 knockdown counteracted the effects of EZH2 inhibition (66). To further assess the associations between SMYD2, EZH2 and TET1 expression in GIST, immunohistochemistry was employed to analyze their expression levels in tumor samples from patients classified as low, intermediate or high risk. The results revealed a positive association between SMYD2 and EZH2 expression, whilst TET1 expression was negatively associated with EZH2 expression (66). These findings further validated the experimental results but from a clinical perspective. In summary, SMYD2 promotes tumor progression in GIST, whilst it inhibits cellular senescence and apoptosis through modulation of the EZH2/TET1 signaling axis (Fig. 2C). Moreover, inhibitors such as LLY-507 and AZ-505 can downregulate SMYD2 activity, providing new insights for the potential clinical treatment of GIST.

7. SMYD2 and liver cancer

HCC is an aggressive liver cancer characterized by high rates of metastasis and recurrence, leading to a poor prognosis. Over the past two decades, the incidence of liver cancer has risen by 53.7%, while the mortality rate has increased by 48.0%. Despite rapid advancements in comprehensive treatment, primarily centered on surgical resection, the overall 5-year survival rate remains below 20% (68). HCC frequently arises in individuals with chronic liver conditions, including hepatitis B or C infections, alcohol-induced liver injury or non-alcoholic fatty liver disease. Current treatment options include surgical resection, liver transplantation, locoregional therapies and systemic treatments such as targeted therapy and immunotherapy (68).

Previous public database analysis indicated that SMYD2 mRNA levels are positively associated with the incidence rate and clinical staging of patients with HCC, whilst they are negatively associated with OS. Further analysis of immune cell infiltration and immune check sites revealed a positive association between SMYD2 and $CD4^+$ T cells, as well as macrophages (63). Several studies have reported that SMYD2 mRNA and protein levels are markedly elevated in HCC tissues compared with adjacent non-cancerous tissues (69-71). In one study, clinical samples and data from patients with HCC were collected and univariate analysis was performed, which demonstrated that elevated SMYD2 levels were notably associated with a decreased OS. Multivariate analysis revealed that SMYD2 could serve as an independent prognostic marker, indicating a poor prognosis in patients with HCC (69). Functional experiments performed using HCC cell lines demonstrated that silencing SMYD2 expression led to a reduction in cell proliferation and triggered a G0/G1 phase cell cycle arrest, suggesting that SMYD2 promotes HCC cell growth by regulating proliferation and cell cycle progression. Moreover, cyclin D1 expression was markedly reduced upon SMYD2 downregulation, indicating that SMYD2 may influence HCC cell proliferation through the regulation of cyclin D1 (69). However, the precise mechanisms underlying the SMYD2 regulation of cyclin D1 remain unclear and require further investigation.

A study by Xu *et al* (71) demonstrated that SMYD2 expression was positively associated with tumor number, tumor size and patient age. This study also reported that SMYD2 knockdown in HCC cell lines induced G0/G1 phase cell cycle arrest, consistent with previous findings. Additionally, SMYD2 knockdown inhibited the expression of c-Myc, cyclin-dependent kinase (CDK)4 and cyclin D1 (71). Furthermore, the study identified an association between SMYD2 expression and pathways involved in glutamine metabolism. SMYD2 has been reported to facilitate c-Myc methylation, leading to its stabilization and subsequent upregulation of glutaminase 1 (GLS1), an essential enzyme in glutamine metabolism (71).

GLS1 mediates the conversion of glutamine into glutamate, which enters the tricarboxylic acid cycle to generate adenosine triphosphate. This metabolic pathway has been reported to be enhanced by SMYD2 in HCC cells (71). Given the role of glutamine metabolic reprogramming in sorafenib resistance, the study further demonstrated that HCC cells with SMYD2 deletion were more sensitive to sorafenib treatment. These findings suggest that SMYD2 promotes HCC cell growth and enhances chemotherapy resistance to sorafenib (71).

Furthermore, research on the relationship between microRNA (miR)-200b and SMYD2 in HCC demonstrated that miR-200b binds to the 3'-untranslated region of SMYD2, thereby suppressing its transcription. Bioinformatics analysis predicted this interaction, which was subsequently validated through a dual-luciferase reporter assay (70). *In vitro* experiments reported that overexpression of miR-200b reduced SMYD2 protein levels, suppressed cell proliferation, increased p53 expression and decreased cyclin E1 levels in HCC cells. These findings suggest that miR-200b may limit SMYD2 expression, restore p53 levels and induce cell cycle arrest by downregulating cyclin E1 expression (70). Moreover, a recent study reported that hypoxia-induced SZT2 antisense RNA 1 (SZT2-AS1) regulated the levels of H3K4me3 and H3K36me3 in HCC cells. Rescue experiments were performed to assess whether SMYD2-mediated SZT2-AS1 regulates histone methylation, and western blotting revealed that SZT2-AS1-knockdown decreased the levels of H3K4me3 and H3K36me3. These reductions were then rescued by the overexpression of SMYD2 (72). This finding suggests that SZT2-AS1 regulates H3K4me3 and H3K36me3 levels by recruiting SMYD2 in HCC cells under hypoxia, thereby promoting HCC growth, metastasis and angiogenesis (Fig. 2D). In summary, SMYD2 is highly expressed in HCC, where it exerts oncogenic effects and is associated with adverse clinical characteristics and a poor prognosis. Thus, SMYD2 protein levels may act as an independent prognostic indicator of unfavorable outcomes in patients with HCC, making it a potential target for therapeutic intervention.

8. SMYD2 and pancreatic cancer (PC)

PC is often diagnosed at the advanced stages of disease due to its subtle early symptoms, leading to a poor prognosis. Risk factors for PC include chronic pancreatitis, smoking, obesity, diabetes and genetic predisposition. Treatment strategies for PC involve surgical resection for eligible patients, along with chemotherapy, radiation therapy and targeted therapy (73).

SMYD2 is highly expressed in both PC tissues and cell lines. SMYD2 mediates the methylation of c-Myc, promoting its ubiquitination and subsequent degradation, which in turn reduces c-Myc expression in PC (74). Previous research has identified nuclear receptor coactivator 4 (NCOA4) as a specific receptor for ferritin, serving a crucial role in ferritinophagy. This process facilitates iron release from ferritin, contributing to iron homeostasis and the regulation of ferroptosis (75). The regulation of ferroptosis is achieved through c-Myc, which influences NCOA4 levels (76). Based on these findings, the c-Myc/NCOA4 axis was further assessed and it was reported that c-Myc inhibited NCOA4 expression by binding to NCOA4 mRNA, whilst a reduction in c-Myc led to an increase in NCOA4 expression (74). Furthermore, in mouse experiments, knockdown of SMYD2 expression in PC tumor tissues was associated with a notable reduction in tumor volume. SMYD2 knockdown in PC tumor tissues also led to decreased c-Myc levels, increased NCOA4 levels and heightened levels of ferritinophagy and ferroptosis (74). Therefore, targeting SMYD2 may promote ferritinophagy-dependent ferroptosis through the c-Myc/NCOA4 axis, potentially inhibiting PC development.

Adenosquamous carcinoma of the pancreas (ASCP) is a relatively rare histological subtype that includes both pancreatic adenocarcinoma (PAAD) and pancreatic squamous cell carcinoma. In a study by Lenkiewicz *et al* (77), whole-genome copy number variation analysis of patient-derived xenografts (PDXs) from 3 patients with ASCP and 3 patients with pancreatic ductal adenocarcinoma (PDAC) revealed that SMYD2 displays distinct chromatin activity in ASCP PDX samples, specifically targeting the active chromatin marker, H3K4me1. Compared with PDAC, the specificity of SMYD2 for H3K4me1 in ASCP may serve as a distinguishing feature and a potential biomarker for differentiating ASCP from PDAC (77).

PAAD accounts for ~85% of PCs and has a poor prognosis, with nearly 80% of patients experiencing postoperative recurrence and a 5-year survival rate of just 6% (78). An analysis of The Cancer Genome Atlas database indicated that SMYD2 levels are markedly elevated in PAAD tissues compared with adjacent normal tissues, with its expression closely associated with patient prognosis. Further research revealed that SMYD2 upregulates the MNAT1 component of CDK activating kinase (MNAT1) expression in PAAD cells by modifying the H3K36me2 marker in the region of the MNAT1 promoter. Silencing MNAT1 expression inhibits the aggressive characteristics of PAAD cells. Furthermore, rescue experiments demonstrated that overexpression of MNAT1 restored the activity of PAAD cells suppressed by sh-SMYD2 (79). MNAT1 functions as a substrate specificity determining factor, as well as an assembly factor of cyclin-dependent kinase-activating kinase (CAK) to promote CAK stability and activation, which further leads to the phosphorylation and activation of CDKs to ensure cell cycle progression. It has been reported that the phosphorylation of PI3K and AKT in PAAD cells can be inhibited by sh-SMYD2 but restored by overexpression of MNAT1, indicating that the SMYD2-MNAT1 axis is at least partially involved in the activation of PI3K/AKT, thereby promoting PAAD cell proliferation, migration and invasion (79). However, the exact mechanistic link between MNAT1 and the PI3K/AKT pathway remains unclear, necessitating further investigation. Another study reported that SMYD2 increases ecotropic viral integration site 2A (EVI2A) expression in PAAD cells via H3K36me2 modification. Elevated EVI2A expression induced M2-like macrophage polarization, which inhibited T-cell effector activation and promoted gemcitabine (GEM) resistance and immune evasion in PAAD cells (80). These findings highlight the critical role of SMYD2 in regulating PAAD invasiveness through mechanisms involving GEM resistance and immune evasion.

Clinically, PDAC tends to originate from the pancreatic ducts. A previous study reported that SMYD2 promoted PDAC cell growth by methylating K355 of mitogen-activated protein kinase-activated protein kinase 3 (MAPKAPK3) (12). Notably, SMYD2 expression is undetectable in normal

pancreatic tissue, but it is elevated in pancreatic intraepithelial neoplasia (PanIN) tissues and PDAC specimens from both mice and humans. In K-Ras mutant mouse models, increased SMYD2 expression was associated with cancer development and its deletion reduced acinar-to-ductal metaplasia and inhibited PanIN development (12). Further research indicated that suppressing SMYD2-driven MAPKAPK3 methylation using the small-molecule inhibitor, BAY598, slowed the proliferation of PDAC cells harboring K-Ras/TP53 mutations, whereas those with mutations in K-Ras/TP53/SMYD2 had a minimal response (12). Additionally, the combination of GEM and BAY598 markedly inhibited the growth of K-Ras/TP53 mutant PDAC cells, whilst GEM alone inhibited the growth of K-Ras/TP53/SMYD2 mutant PDAC cells (12). These findings suggest that combining SMYD2 inhibitors with GEM could enhance therapeutic efficacy in patients with PDAC (41) (Fig. 2E), highlighting the potential value of targeting the SMYD2-MAPKAPK3 axis in PDAC treatment.

9. SMYD2 and esophageal cancer (EC)

EC is the eleventh most common cancer worldwide and the seventh leading cause of cancer-related deaths, accounting for 2.6% of all new cancer cases and 4.6% of cancer deaths. Despite significant advancements in the diagnosis and treatment of EC in recent years, the 5-year survival rate remains only around 20%. Esophageal squamous cell carcinoma (ESCC) accounts for ~90% of all EC cases and is characterized by a high recurrence rate and poor long-term prognosis (81). Due to its asymptomatic early stages of disease, most ESCC cases are diagnosed at an advanced stage, limiting treatment options. Current therapeutic approaches include surgery, chemotherapy, radiotherapy and emerging targeted and immunotherapy strategies (81).

Public database analysis revealed that SMYD2 mRNA expression in EC is notably associated with incidence, clinical stage, TP53 mutation status, OS and recurrence-free survival. Furthermore, correlation analysis of immune cell infiltration and immune checkpoints indicated a negative correlation between SMYD2 and $CD4^+$ T cells (63). Further experiments demonstrated that SMYD2 is highly expressed in ESCC cell lines and tissues, with its protein levels markedly associated with clinical features such as sex, venous invasion, pathological tumor stage (depth of tumor invasion) in the TNM classification and recurrence status (82). Multivariate analysis reported that patients with ESCC harboring high SMYD2 expression had a worse OS compared with those harboring low SMYD2 expression, and SMYD2 positivity was independently associated with a worse prognosis (82). Knockdown of SMYD2 expression using specific small interfering RNAs suppressed the proliferation of ESCC cell lines overexpressing SMYD2, largely independent of TP53 mutation status (82). Moreover, SMYD2 downregulation primarily arrested cells in the G0-G1 phase, and p21 protein was detected in the KYSE790 cell line, in a previous study (82). This suggests that the oncogenic role of SMYD2 in ESCC may involve the regulation of cell cycle proteins such as p21, independent of p53 (Fig. 2F). However, the aforementioned study did not explore the precise mechanism through which SMYD2 influences cell proliferation via p21, indicating the need for further investigation. Overall, studies on SMYD2 in ESCC remain limited and its precise mechanisms of action require further investigation.

10. Future perspectives

Epigenetic modifications, such as DNA methylation and histone modifications, have a crucial role in cancer progression. The SMYD protein family of lysine methyltransferases is integral to epigenetic regulation, with SMYD2 being a key member. SMYD2 catalyzes the methylation of both histone and non-histone proteins, influencing several cellular processes. Structural studies of SMYD2 have provided valuable insights into its functional domains: The SET domain drives its catalytic activity, whilst the MYND domain facilitates protein-protein interactions. SMYD2 methylates H3K4, H3K36 and H4K20, exerting distinct effects on gene expression. The oncogenic properties of SMYD2 primarily arise from its ability to methylate tumor suppressor proteins, including p53, RB and PTEN, thereby inhibiting their function and promoting tumor development. Numerous studies have reported that SMYD2 is upregulated in several gastrointestinal cancer types, including colorectal, gastric and liver cancer, with specific effects depending on the cancer type (Table II).

The present review assessed the multifaceted role of SMYD2 in the progression of gastrointestinal cancer, its contribution to drug resistance and emerging therapeutic strategies aimed at inhibiting its activity. Several small molecule inhibitors targeting the catalytic activity of SMYD2, such as AZ505 and BAY-598, have demonstrated potent antitumor effects in preclinical models, particularly when combined with other anticancer agents such as GEM and the VEGFR2 inhibitor, apatinib. However, challenges persist in improving the pharmacokinetics and cellular permeability of these inhibitors to enhance their efficacy. Developing more selective SMYD2 inhibitors is crucial to minimize off-target effects and improve therapeutic outcomes. Additionally, identifying biomarkers to predict SMYD2 inhibitor sensitivity is essential for patient stratification and personalized treatment approaches. Future research should focus on optimizing SMYD2 inhibitors and exploring combination therapies targeting SMYD2 alongside other oncogenic pathways. Despite the progress made with SMYD2 inhibitors in the treatment of a number of diseases, especially cancer, no safety or efficacy evaluations of SMYD2 inhibitors have been performed in clinical trials to date, to the best of our knowledge. Ongoing research into the molecular mechanisms of SMYD2, alongside the advancement of innovative inhibitors, will be crucial for translating these discoveries into effective cancer treatments.

11. Discussion and conclusions

SMYD2 has gained recognition as a crucial regulator of several cellular functions, including the cell cycle and differentiation, and has been implicated in several pathological conditions, particularly cancer and cardiovascular diseases. SMYD2 is highly expressed in tissues such as the heart, brain, liver, kidneys, thymus and ovaries, suggesting its involvement in the development of the cardiovascular, nervous, gastrointestinal, musculoskeletal, urinary and reproductive

Table II. Function of SET and MYND domain-containing protein 2 in gastrointestinal cancer.

Cancer type	Expression	Role	Targets	Biological function	(Refs.)
Colorectal	Up	Oncogene	ERBB2/FUT4	Promotes proliferation and invasion; inhibits apoptosis	(55)
		/	MEK/ERK/ AP-1; P-gp	Enhances the L-OHP resistance of CRC cells	(56)
	Up	Oncogene	RIPK1	Inhibits apoptosis and necrosis	(53)
	Up	Oncogene	LINC01605	Promotes proliferation, migration and invasion	(57)
	Up	Oncogene	MEX3A; CDX2	Promotes proliferation, migration and invasion	(58)
	Up	Oncogene	DNMT1; APC2; Wnt/β-catenin	Promotes proliferation, migration and invasion	(52)
	Up	Oncogene	HNRNPK; EGFL7	Promotes angiogenesis	(54)
Gastric	Up	Oncogene	p21	Promotes proliferation, migration and invasion	(10)
	Up	Oncogene	APOC1	Promotes glycolysis and proliferation	(64)
Gastrointestinal stromal tumor	Up	Oncogene	EZH2; TET1; p53	Promotes proliferation; inhibits senescence	(66)
Liver	Up	Oncogene	c-Myc/CDK4/ cyclinD1	Promotes proliferation	(71)
		/	c-Myc; GLS1	Enhances the sorafenib resistance of HCC cells	(71)
	Up	Oncogene	p53; cyclinE1	Promotes proliferation	(70)
Pancreatic	Up	Oncogene	c-Myc; NCOA4	Promotes proliferation; inhibits ferroptosis	(75)
	Up	Oncogene	MNAT1	Promotes proliferation, migration and invasion	(79)
		/	EVI2A	Enhances the GEM resistance of PAAD cells	(80)
	Up	Oncogene	MAPKAPK3	Promotes proliferation; enhances the GEM resistance of PDAC cells	(12)
Esophageal	Up	Oncogene	p21	Promotes proliferation	(82)

ERBB2, Erb-B2 receptor tyrosine kinase 2; FUT4, fucosyltransferase 4; AP-1, activator protein 1; P-gp, P-glycoprotein; L-OHP, oxaliplatin; CRC, colorectal cancer; RIPK1, receptor-interacting protein kinase 1; LINC01605, long intergenic non-protein coding RNA 1605; MEX3A, Mex-3 RNA binding family member A; CDX2, Caudal type homeobox 2; DNMT1, DNA methyltransferase 1; APC2, adenomatosis polyposis coli 2; HNRNPK, heterogeneous nuclear ribonucleoprotein K; EGFL7, epidermal growth factor-like domain 7; APOC1, apolipoprotein C1; EZH2, enhancer of zeste homolog 2; TET1, ten-eleven translocation methylcytosine dioxygenase 1; p53, tumor protein 53; CDK4, cyclin-dependent kinase 4; GLS1, glutaminase 1; HCC, hepatocellular carcinoma; NCOA4, nuclear receptor coactivator 4; MNAT1, MNAT1 component of CDK activating kinase; EVI2A, ecotropic viral integration site 2A; GEM, gemcitabine; PAAD, pancreatic adenocarcinoma; PDAC, pancreatic ductal adenocarcinoma; MAPKAPK3, mitogen-activated protein kinase-activated protein kinase 3.

systems. Mechanistically, SMYD2 acts as a methyltransferase, specifically methylating H3K4, H3K3 and H4K20, as well as non-histone proteins, thereby regulating key signaling pathways in tumor cells and influencing the transcription and expression of downstream target genes. Clinically, SMYD2 has been identified as an independent biomarker for the diagnosis and prognosis of gastrointestinal malignancies. Studies have reported that the aberrant regulation of SMYD2 is associated with chemotherapy resistance and poor clinical outcomes in certain patients with cancer, whilst its loss can sensitize patients to chemotherapy and immunotherapy. This suggests that SMYD2 antagonists may serve as potential adjuvants in cancer treatment. SMYD2 is upregulated in several human tumors, and increasing attention is being paid to understanding its molecular mechanisms in tumorigenesis and to assessing its viability as a therapeutic target for restricting tumor cell growth.

Despite the limited scope of research, pioneering studies have demonstrated that SMYD2-mediated methylation of histone and non-histone proteins serves a notable role in the development and progression of gastrointestinal cancer types. Ongoing research continues to explore the role of

SMYD2 in these cancer types, although challenges remain. These challenges include the need for a more comprehensive understanding of the biological functions of SMYD2, the development of small-molecule inhibitors and probes, as well as clarification on the specific mechanisms by which SMYD2 influences tumor development and treatment. Furthermore, a critical challenge in SMYD2-targeted therapy is the development of highly selective and potent inhibitors, as poor bioavailability continues to limit their clinical efficacy. In summary, SMYD2 serves as a crucial factor in the onset and advancement of gastrointestinal malignancies, influencing both treatment strategies and patient prognosis, making it a promising therapeutic target.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

KX and YC contributed to the conceptualization and design of this study and took responsibility for the integrity of the work as a whole, from inception to published article. KX collected the literature and wrote the article. YZ was involved in drafting the manuscript. YX involved in revising it critically for content. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Arnold M, Abnet CC, Neale RE, Vignat J, Giovannucci EL, McGlynn KA and Bray F: Global burden of 5 major types of gastrointestinal cancer. Gastroenterology 159: 335-349.e15, 2020.
2. Zhang FF, Luo YH, Wang H and Zhao L: Metastasis-associated long noncoding RNAs in gastrointestinal cancer: Implications for novel biomarkers and therapeutic targets. World J Gastroenterol 22: 8735-8749, 2016.
3. Grady WM: Epigenetic alterations in the gastrointestinal tract: Current and emerging use for biomarkers of cancer. Adv Cancer Res 151: 425-468, 2021.
4. Wang DK, Zuo Q, He QY and Li B: Targeted immunotherapies in gastrointestinal cancer: From molecular mechanisms to implications. Front Immunol 12: 705999, 2021.
5. Cao Z, Shu Y, Wang J, Wang C, Feng T, Yang L, Shao J and Zou L: Super enhancers: Pathogenic roles and potential therapeutic targets for acute myeloid leukemia (AML). Genes Dis 9: 1466-1477, 2022.
6. Brown MA, Sims RJ III, Gottlieb PD and Tucker PW: Identification and characterization of Smyd2: A split SET/MYND domain-containing histone H3 lysine 36-specific methyltransferase that interacts with the Sin3 histone deacetylase complex. Mol Cancer 5: 26, 2006.
7. Huang J, Perez-Burgos L, Placek BJ, Sengupta R, Richter M, Dorsey JA, Kubicek S, Opravil S, Jenuwein T and Berger SL: Repression of p53 activity by Smyd2-mediated methylation. Nature 444: 629-632, 2006.
8. Zeng Y, Qiu R, Yang Y, Gao T, Zheng Y, Huang W, Gao J, Zhang K, Liu R, Wang S, *et al*: Regulation of EZH2 by SMYD2-mediated lysine methylation is implicated in tumorigenesis. Cell Rep 29: 1482-1498.e4, 2019.
9. Sajjad A, Novoyatleva T, Vergarajauregui S, Troidl C, Schermuly RT, Tucker HO and Engel FB: Lysine methyltransferase Smyd2 suppresses p53-dependent cardiomyocyte apoptosis. Biochim Biophys Acta 1843: 2556-2562, 2014.
10. Komatsu S, Ichikawa D, Hirajima S, Nagata H, Nishimura Y, Kawaguchi T, Miyamae M, Okajima W, Ohashi T, Konishi H, *et al*: Overexpression of SMYD2 contributes to malignant outcome in gastric cancer. Br J Cancer 112: 357-364, 2015.
11. Hamamoto R, Toyokawa G, Nakakido M, Ueda K and Nakamura Y: SMYD2-dependent HSP90 methylation promotes cancer cell proliferation by regulating the chaperone complex formation. Cancer Lett 351: 126-133, 2014.
12. Reynoird N, Mazur PK, Stellfeld T, Flores NM, Lofgren SM, Carlson SM, Brambilla E, Hainaut P, Kaznowska EB, Arrowsmith CH, *et al*: Coordination of stress signals by the lysine methyltransferase SMYD2 promotes pancreatic cancer. Genes Dev 30: 772-785, 2016.
13. Eggert E, Hillig RC, Koehr S, Stöckigt D, Weiske J, Barak N, Mowat J, Brumby T, Christ CD, Ter Laak A, *et al*: Discovery and characterization of a highly potent and selective aminopyrazoline-based in vivo probe (BAY-598) for the protein lysine methyltransferase SMYD2. J Med Chem 59: 4578-4600, 2016.
14. Hamamoto R, Saloura V and Nakamura Y: Critical roles of non-histone protein lysine methylation in human tumorigenesis. Nat Rev Cancer 15: 110-124, 2015.
15. Zheng Q, Zhang W and Rao GW: Protein lysine methyltransferase SMYD2: A promising small molecule target for cancer therapy. J Med Chem 65: 10119-10132, 2022.
16. Copeland RA: Protein methyltransferase inhibitors as precision cancer therapeutics: A decade of discovery. Philos Trans R Soc Lond B Biol Sci 373: 20170080, 2018.
17. Copeland RA: Epigenetic medicinal chemistry. ACS Med Chem Lett 7: 124-127, 2015.
18. Tang M, Chen G, Tu B, Hu Z, Huang Y, DuFort CC, Wan X, Mao Z, Liu Y, Zhu WG and Lu W: SMYD2 inhibition-mediated hypomethylation of Ku70 contributes to impaired nonhomologous end joining repair and antitumor immunity. Sci Adv 9: eade6624, 2023.
19. Meng J, Yang W, Li C and Li F: Synergistic anticancer effects of SMYD2 inhibitor BAY-598 and doxorubicin in non-small cell lung cancer. Heliyon 10: e32015, 2024.
20. Razmi M, Yazdanpanah A, Etemad-Moghadam S, Alaeddini M, Angelini S and Eini L: Clinical prognostic value of the SMYD2/3 as new epigenetic biomarkers in solid cancer patients: A systematic review and meta-analysis. Expert Rev Mol Diagn: 1-15, 2022 (Epub ahead of print).
21. Rubio-Tomás T: Novel insights into SMYD2 and SMYD3 inhibitors: From potential anti-tumoural therapy to a variety of new applications. Mol Biol Rep 48: 7499-7508, 2021.
22. Liu D, Yang X and Wang X: Neutrophil extracellular traps promote gastric cancer cell metastasis via the NAT10-mediated N4-acetylcytidine modification of SMYD2. Cell Signal 116: 111014, 2024.
23. Carr SR, Akerley W, Hashibe M and Cannon-Albright LA: Evidence for a genetical contribution to non-smoking-related lung cancer. Thorax 70: 1033-1039, 2015.
24. Spellmon N, Holcomb J, Trescott L, Sirinupong N and Yang Z: Structure and function of SET and MYND domain-containing proteins. Int J Mol Sci 16: 1406-1428, 2015.
25. Leinhart K and Brown M: SET/MYND lysine methyltransferases regulate gene transcription and protein activity. Genes (Basel) 2: 210-218, 2011.

26. Ferguson AD, Larsen NA, Howard T, Pollard H, Green I, Grande C, Cheung T, Garcia-Arenas R, Cowen S, Wu J, *et al*: Structural basis of substrate methylation and inhibition of SMYD2. Structure 19: 1262-1273, 2011.
27. Xu S, Zhong C, Zhang T and Ding J: Structure of human lysine methyltransferase Smyd2 reveals insights into the substrate divergence in Smyd proteins. J Mol Cell Biol 3: 293-300, 2011.
28. 'SMYD2-SET and MYND domain-containing protein 2'. UniProt, Geneva, 2024. https://www.uniprot.org/uniprot/Q9NRG4
29. Herz HM, Garruss A and Shilatifard A: SET for life: Biochemical activities and biological functions of SET domain-containing proteins. Trends Biochem Sci 38: 621-639, 2013.
30. Wu J, Cheung T, Grande C, Ferguson AD, Zhu X, Theriault K, Code E, Birr C, Keen N and Chen H: Biochemical characterization of human SET and MYND domain-containing protein 2 methyltransferase. Biochemistry 50: 6488-6497, 2011.
31. Abu-Farha M, Lambert JP, Al-Madhoun AS, Elisma F, Skerjanc IS and Figeys D: The tale of two domains: Proteomics and genomics analysis of SMYD2, a new histone methyltransferase. Mol Cell Proteomics 7: 560-572, 2008.
32. Spellmon N, Sun X, Sirinupong N, Edwards B, Li C and Yang Z: Molecular dynamics simulation reveals correlated inter-lobe motion in protein lysine methyltransferase SMYD2. PLoS One 10: e0145758, 2015.
33. Xu S, Wu J, Sun B, Zhong C and Ding J: Structural and biochemical studies of human lysine methyltransferase Smyd3 reveal the important functional roles of its post-SET and TPR domains and the regulation of its activity by DNA binding. Nucleic Acids Res 39: 4438-4449, 2011.
34. Sirinupong N, Brunzelle J, Ye J, Pirzada A, Nico L and Yang Z: Crystal structure of cardiac-specific histone methyltransferase SmyD1 reveals unusual active site architecture. J Biol Chem 285: 40635-40644, 2010.
35. Chandramouli B and Chillemi G: Conformational dynamics of lysine methyltransferase Smyd2. insights into the different substrate crevice characteristics of Smyd2 and Smyd3. J Chem Inf Model 56: 2467-2475, 2016.
36. Zhang Y, Alshammari E, Sobota J, Spellmon N, Perry E, Cao T, Mugunamalwaththa T, Smith S, Brunzelle J, Wu G, *et al*: Structure of the SMYD2-PARP1 complex reveals both productive and allosteric modes of peptide binding. bioRxiv [Preprint]: 2024.12.03.626679, 2024.
37. Gottlieb PD, Pierce SA, Sims RJ, Yamagishi H, Weihe EK, Harriss JV, Maika SD, Kuziel WA, King HL, Olson EN, *et al*: Bop encodes a muscle-restricted protein containing MYND and SET domains and is essential for cardiac differentiation and morphogenesis. Nat Genet 31: 25-32, 2002.
38. Sesé B, Barrero MJ, Fabregat MC, Sander V and Izpisua Belmonte JC: SMYD2 is induced during cell differentiation and participates in early development. Int J Dev Biol 57: 357-364, 2013.
39. Diehl F, Brown MA, van Amerongen MJ, Novoyatleva T, Wietelmann A, Harriss J, Ferrazzi F, Böttger T, Harvey RP, Tucker PW and Engel FB: Cardiac deletion of Smyd2 is dispensable for mouse heart development. PLoS One 5: e9748, 2010.
40. Kawamura S, Yoshigai E, Kuhara S and Tashiro K: smyd1 and smyd2 are expressed in muscle tissue in *Xenopus laevis*. Cytotechnology 57: 161-168, 2008.
41. Alshammari E, Zhang YX and Yang Z: Mechanistic and functional extrapolation of SET and MYND domain-containing protein 2 to pancreatic cancer. World J Gastroenterol 28: 3753-3766, 2022.
42. Boehm D, Jeng M, Camus G, Gramatica A, Schwarzer R, Johnson JR, Hull PA, Montan M, Sakane N, Pagans S, *et al*: SMYD2-mediated histone methylation contributes to HIV-1 latency. Cell Host Microbe 21: 569-579.e6, 2017.
43. Olsen JB, Cao XJ, Han B, Chen LH, Horvath A, Richardson TI, Campbell RM, Garcia BA and Nguyen H: Quantitative profiling of the activity of protein lysine methyltransferase SMYD2 using SILAC-based proteomics. Mol Cell Proteomics 15: 892-905, 2016.
44. Weirich S, Schuhmacher MK, Kudithipudi S, Lungu C, Ferguson AD and Jeltsch A: Analysis of the substrate specificity of the SMYD2 protein lysine methyltransferase and discovery of novel non-histone substrates. Chembiochem 21: 256-264, 2020.
45. Li LX, Fan LX, Zhou JX, Grantham JJ, Calvet JP, Sage J and Li X: Lysine methyltransferase SMYD2 promotes cyst growth in autosomal dominant polycystic kidney disease. J Clin Invest 127: 2751-2764, 2017.
46. Piao L, Kang D, Suzuki T, Masuda A, Dohmae N, Nakamura Y and Hamamoto R: The histone methyltransferase SMYD2 methylates PARP1 and promotes poly(ADP-ribosyl)ation activity in cancer cells. Neoplasia 16: 257-264, 264.e2, 2014.
47. Nakakido M, Deng Z, Suzuki T, Dohmae N, Nakamura Y and Hamamoto R: Dysregulation of AKT pathway by SMYD2-mediated lysine methylation on PTEN. Neoplasia 17: 367-373, 2015.
48. Saddic LA, West LE, Aslanian A, Yates JR III, Rubin SM, Gozani O and Sage J: Methylation of the retinoblastoma tumor suppressor by SMYD2. J Biol Chem 285: 37733-37740, 2010.
49. Cho HS, Hayami S, Toyokawa G, Maejima K, Yamane Y, Suzuki T, Dohmae N, Kogure M, Kang D, Neal DE, *et al*: RB1 methylation by SMYD2 enhances cell cycle progression through an increase of RB1 phosphorylation. Neoplasia 14: 476-486, 2012.
50. Obermann WMJ: A motif in HSP90 and P23 that links molecular chaperones to efficient estrogen receptor α methylation by the lysine methyltransferase SMYD2. J Biol Chem 293: 16479-16487, 2018.
51. Ji K, Jia H, Liu Z, Yu G, Wen R, Zhang T, Peng Z, Man W, Tian Y, Wang C, *et al*: New insight in immunotherapy and combine therapy in colorectal cancer. Front Cell Dev Biol 12: 1453630, 2025.
52. Meng F, Liu X, Lin C, Xu L, Liu J, Zhang P, Zhang X, Song J, Yan Y, Ren Z and Zhang Y: SMYD2 suppresses APC2 expression to activate the Wnt/β-catenin pathway and promotes epithelial-mesenchymal transition in colorectal cancer. Am J Cancer Res 10: 997-1011, 2020.
53. Yu YQ, Thonn V, Patankar JV, Thoma OM, Waldner M, Zielinska M, Bao LL, Gonzalez-Acera M, Wallmüller S, Engel FB, *et al*: SMYD2 targets RIPK1 and restricts TNF-induced apoptosis and necroptosis to support colon tumor growth. Cell Death Dis 13: 52, 2022.
54. Zhang Y, Zhou L, Xu Y, Zhou J, Jiang T, Wang J, Li C, Sun X, Song H and Song J: Targeting SMYD2 inhibits angiogenesis and increases the efficiency of apatinib by suppressing EGFL7 in colorectal cancer. Angiogenesis 26: 1-18, 2023.
55. Lai Y and Yang Y: SMYD2 facilitates cancer cell malignancy and xenograft tumor development through ERBB2-mediated FUT4 expression in colon cancer. Mol Cell Biochem 477: 2149-2159, 2022.
56. Ren H, Wang Z, Chen Y, Liu Y, Zhang S, Zhang T and Li Y: SMYD2-OE promotes oxaliplatin resistance in colon cancer through MDR1/P-glycoprotein via MEK/ERK/AP1 pathway. Onco Targets Ther 12: 2585-2594, 2019.
57. Yue M, Liu T, Yan G, Luo X and Wang L: LINC01605, regulated by the EP300-SMYD2 complex, potentiates the binding between METTL3 and SPTBN2 in colorectal cancer. Cancer Cell Int 21: 504, 2021.
58. Pan L, Fan Y and Zhou L: SMYD2 epigenetically activates MEX3A and suppresses CDX2 in colorectal cancer cells to augment cancer growth. Clin Exp Pharmacol Physiol 49: 959-969, 2022.
59. Deng X, Hamamoto R, Vougiouklakis T, Wang R, Yoshioka Y, Suzuki T, Dohmae N, Matsuo Y, Park JH and Nakamura Y: Critical roles of SMYD2-mediated β-catenin methylation for nuclear translocation and activation of Wnt signaling. Oncotarget 8: 55837-55847, 2027.
60. Ma X, Xu W, Qi L, Zhang Q, Sun X and Zhang S: Clinical outcome of non-curative endoscopic submucosal dissection for early gastric cancer. J Gastrointest Oncol 15: 566-576, 2024.
61. Liu Z, Xu H, You W, Pan K and Li W: Helicobacter pylori eradication for primary prevention of gastric cancer: Progresses and challenges. J Natl Cancer Cent 4: 299-310, 2024.
62. Liu D, Liu M, Wang W, Li X, Shi E, Zhang C, Wang Y, Zhang Y, Wang L and Wang X: SMYD family members serve as potential prognostic markers and correlate with immune infiltrates in gastric cancer. J Oncol 2023: 6032864, 2023.
63. Liu D, Wang X, Shi E, Wang L, Nie M, Li L, Jiang Q, Kong P, Shi S, Wang C, *et al*: Comprehensive analysis of the value of SMYD family members in the prognosis and immune infiltration of malignant digestive system tumors. Front Genet 12: 699910, 2021.
64. Xu H, Ba Z, Liu C and Yu X: Long noncoding RNA DLEU1 promotes proliferation and glycolysis of gastric cancer cells via APOC1 upregulation by recruiting SMYD2 to induce trimethylation of H3K4 modification. Transl Oncol 36: 101731, 2023.

65. He C, Wang Z, Yu J, Mao S and Xiang X: Current drug resistance mechanisms and treatment options in gastrointestinal stromal tumors: Summary and update. Curr Treat Options Oncol 25: 1390-1405, 2024.
66. Ji Y, Xu X, Long C, Wang J, Ding L, Zheng Z, Wu H, Yang L, Tao L and Gao F: SMYD2 aggravates gastrointestinal stromal tumor via upregulation of EZH2 and downregulation of TET1. Cell Death Discov 8: 274, 2022.
67. Yu Y, Qi J, Xiong J, Jiang L, Cui D, He J, Chen P, Li L, Wu C, Ma T, *et al*: Epigenetic co-deregulation of EZH2/TET1 is a senescence-countering, actionable vulnerability in triple-negative breast cancer. Theranostics 9: 761-777, 2019.
68. Hwang SY, Danpanichkul P, Agopian V, Mehta N, Parikh ND, Abou-Alfa GK, Singal AG and Yang JD: Hepatocellular carcinoma: Updates on epidemiology, surveillance, diagnosis and treatment. Clin Mol Hepatol 31 (Suppl): S228-S254, 2025.
69. Zuo SR, Zuo XC, He Y, Fang WJ, Wang CJ, Zou H, Chen P, Huang LF, Huang LH, Xiang H and Liu SK: Positive expression of SMYD2 is associated with poor prognosis in patients with primary hepatocellular carcinoma. J Cancer 9: 321-330, 2018.
70. Fang W, Song L, Li Z, Meng P, Zuo S and Liu S: Effect of miRNA-200b on the proliferation of liver cancer cells via targeting SMYD2/p53 signaling pathway. Zhong Nan Da Xue Xue Bao Yi Xue Ban 47: 1303-1314, 2022 (In English, Chinese).
71. Xu K, Ding J, Zhou L, Li D, Luo J, Wang W, Shang M, Lin B, Zhou L and Zheng S: SMYD2 promotes hepatocellular carcinoma progression by reprogramming glutamine metabolism via c-Myc/GLS1 axis. Cells 12: 25, 2022.
72. Liu R, Guo Y, Wang L, Yin G, Tuo H, Zhu Y, Yang W, Liu Q and Wang Y: A novel hypoxia-induced lncRNA, SZT2-AS1, boosts HCC progression by mediating HIF heterodimerization and histone trimethylation under a hypoxic microenvironment. Cell Death Differ: Nov 22, 2024 (Epub ahead of print).
73. Jiang Z, Zheng X, Li M and Liu M: Improving the prognosis of pancreatic cancer: Insights from epidemiology, genomic alterations, and therapeutic challenges. Front Med 17: 1135-1169, 2023.
74. Tan J, Liao S, Yuan B, Liu X, Yu W, Zhan H, Jiang Y and Liu Y: Targeting SMYD2 promotes ferroptosis and impacts the progression of pancreatic cancer through the c-Myc/NCOA4 axis-mediated ferritinophagy. Biochim Biophys Acta Gen Subj 1868: 130683, 2024.
75. Mancias JD, Wang X, Gygi SP, Harper JW and Kimmelman AC: Quantitative proteomics identifies NCOA4 as the cargo receptor mediating ferritinophagy. Nature 509: 105-109, 2014.
76. Jin Y, Qiu J, Lu X and Li G: C-MYC inhibited ferroptosis and promoted immune evasion in ovarian cancer cells through NCOA4 mediated ferritin autophagy. Cells 11: 4127, 2022.
77. Lenkiewicz E, Malasi S, Hogenson TL, Flores LF, Barham W, Phillips WJ, Roesler AS, Chambers KR, Rajbhandari N, Hayashi A, *et al*: Genomic and epigenomic landscaping defines new therapeutic targets for adenosquamous carcinoma of the pancreas. Cancer Res 80: 4324-4334, 2020.
78. Zhao Q, Ye Y, Zhang Q, Wu Y, Wang G, Gui Z and Zhang M: PANoptosis-related long non-coding RNA signature to predict the prognosis and immune landscapes of pancreatic adenocarcinoma. Biochem Biophys Rep 37: 101600, 2023.
79. Xu Z, Liu Y, Pan Z and Qin L: Epigenetic upregulation of MNAT1 by SMYD2 is linked to PI3K/AKT activation and tumorigenesis of pancreatic adenocarcinoma. Histol Histopathol 39: 263-277, 2024.
80. Jin L, Qian D, Tang X, Huang Y, Zou J and Wu Z: SMYD2 imparts gemcitabine resistance to pancreatic adenocarcinoma cells by upregulating EVI2A. Mol Biotechnol 66: 2920-2933, 2024.
81. Jiang W, Zhang B, Xu J, Xue L and Wang L: Current status and perspectives of esophageal cancer: A comprehensive review. Cancer Commun (Lond) 45: 281-331, 2025.
82. Komatsu S, Imoto I, Tsuda H, Kozaki KI, Muramatsu T, Shimada Y, Aiko S, Yoshizumi Y, Ichikawa D, Otsuji E and Inazawa J: Overexpression of SMYD2 relates to tumor cell proliferation and malignant outcome of esophageal squamous cell carcinoma. Carcinogenesis 30: 1139-1146, 2009.