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REVIEW

Mechanistic and functional extrapolation of SET and MYND domain-containing protein 2 to pancreatic cancer

Eid Alshammari, Ying-Xue Zhang, Zhe Yang

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal neoplasms worldwide and represents the vast majority of pancreatic cancer cases. Understanding the molecular pathogenesis and the underlying mechanisms involved in the initiation, maintenance, and progression of PDAC is an urgent need, which may lead to the development of novel therapeutic strategies against this deadly cancer. Here, we review the role of SET and MYND domain-containing protein 2 (SMYD2) in initiating and maintaining PDAC development through methylating multiple tumor suppressors and oncogenic proteins. Given the broad substrate specificity of SMYD2 and its involvement in diverse oncogenic signaling pathways in many other cancers, the mechanistic extrapolation of SMYD2 from these cancers to PDAC may allow for developing new hypotheses about the mechanisms driving PDAC tumor growth and metastasis, supporting a proposition that targeting SMYD2 could be a powerful strategy for the prevention and treatment of PDAC.

Key Words: Pancreatic ductal adenocarcinoma; Protein lysine methyltransferase; Histone/non-histone methylation; Oncogenic signaling pathways; Methyltransferase inhibitors

Core Tip: The broad substrate specificity of SET and MYND domain-containing protein 2 (SMYD2) and its involvement in diverse oncogenic signaling pathways in numerous cancers have provided a wealth of information that could be extrapolated to the pancreatic ductal adenocarcinoma (PDAC) research field to expand our understanding of SMYD2 in PDAC development. This review not only discusses the known roles of SMYD2 in PDAC initiation and progression, but also aims to capitalize on a rich body of knowledge with respect to SMYD2's involvement in various signaling cascades to develop new hypotheses about the mechanisms of driving PDAC tumor growth and metastasis.

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INTRODUCTION

Pancreatic cancer is one of the top ten leading causes of cancer-related mortality worldwide, accounting for about 448000 new cases and 441000 deaths in 2017[1]. Pancreatic cancer comprises several types of tumors that arise from the endocrine or exocrine components of the pancreas. The vast majority of pancreatic tumors arise from the exocrine cells, which make up the exocrine gland and the ducts of the pancreas. Pancreatic ductal adenocarcinoma (PDAC) is the most common and aggressive form of pancreatic cancer, which represents about 85% of pancreatic cancer cases[2]. The incidence and mortality rates of pancreatic cancer have dramatically increased over the past few decades and vary considerably across regions and populations, with the highest trends being recorded in developed countries[3]. Although the causes and mechanisms that initiate the formation and development of pancreatic cancer are still largely unknown, the variation in regions and populations may be attributed to the variance in some of the risk factors and the socioeconomic lifestyle identified for this disease, such as obesity, diabetes, and smoking. In the United States, the incidence of pancreatic cancer continues to increase, with an estimation of 60430 new cases and 48200 deaths in 2021, and it has become the fourth leading cause of cancer-related mortality[4]. Pancreatic cancer has the poorest prognosis among the top ten common cancers, with the current 5-year survival (OS) rate of just 10%[4], and it is expected to be the second most common cause of cancer death by 2030[5].

Diagnosis and treatment of PDAC are still challenging due to its multifactorial nature. It is predominantly diagnosed in advanced stages with unresectable tumors due to several reasons, including the lack of early detection methods, the lack of specific PDAC biomarkers and simple examinations, the retroperitoneal location of the pancreas, and the nonspecific symptoms due to its highly metastatic nature early in the disease course[6]. Also, PDAC incidence is significantly associated with age, with the highest incidence rates being in elderly people[1]. Given the poor overall health of the elderly, the surgical resection is not feasible for the majority of elderly PDAC patients, especially for those who have metastatic cancers that have spread to the nearby abdominal vessels and critical organs at diagnosis[7]. Only a small fraction of PDAC patients diagnosed in the early stage have resectable tumors. Although the surgery in combination with adjuvant therapy remains the only cure for PDAC patients, the overall survival rate of PDAC patients is poor, even for those PDAC populations who have undergone surgery [8-10]. PDAC patients, after surgical resection, usually develop acquired chemoresistance, with a high rate of recurrence due to the very heterogeneous biology of PDAC and the aggressive clinical behavior of this disease[6]. These factors may explain the high mortality in PDAC patients; therefore, it is of great importance to identify the molecular mechanism of PDAC pathogenesis and the involved signaling pathways in order to discover novel targets and potential biomarkers for PDAC diagnosis and therapy.

SET and MYND domain-containing protein 2 (SMYD2) has been linked with tumor progression, poor prognosis, or a worse malignant outcome in multiple human cancers including PDAC[11-16]. This protein belongs to a special class of protein lysine methyltransferases and is characterized by a conserved catalytic SET domain split by an MYND domain[11]. The MYND domain of SMYD2 is a zinc finger motif that facilitates the protein-protein interaction, while the SET domain, an evolutionarily conserved motif, catalyzes the transfer of methyl groups to lysine residues of target proteins using S-adenosylmethionine (SAM) as a donor substrate[12]. The carcinogenic potential of SMYD2 is exemplified by its ability to methylate a broad spectrum of proteins involved in cellular signaling, cell cycle control, and cell differentiation and proliferation[17-20]. SMYD2 is an epigenetic regulator that has histone lysine methyltransferase activity and can methylate histones H3K36 and H3K4[11,12]. Through the dimethylation of histone H3 at Lys36 (H3K36me2), SMYD2 was reported to downregulate gene transcription, which is further enhanced by Sin3A-mediated deacetylation to suppress cell proliferation [11]. On the other hand, methylation of histone H3K4 by SMYD2 is usually associated with gene activation, yet the exact underlying mechanism by which this SMYD2-mediated methylation regulates

cell proliferation is not well understood[12,21]. Several investigations revealed multiple nonhistone substrates of SMYD2, including the tumor suppressor p53, retinoblastomaassociated protein (RB), ERα, HSP90, PARP1, and PTEN (Table 1)[22-27]. For instance, the tumor suppressor p53 is an important nonhistone target that is monomethylated by SMYD2 at Lys370 located in the regulatory domain of p53, repressing the p53's transcriptional regulatory activity and promoting cancer initiation and growth[22]. It has also been shown that through its broad methyltransferase activity on nonhistone proteins, SMYD2 impacts various signaling pathways required for the development and progression of the malignancies [17,28-32]. These pathways include the critical signaling cascade RTK/Ras, the downstream signaling cascades of the RTK/Ras pathway, such as the mitogen-activated protein kinase (MAPK) pathway, and the PI3K/AKT pathway[16,27,28,30,31]. As dysregulation of these signaling pathways is an almost universal phenomenon in cancer, it is not surprising that SMYD2 overexpression has been linked with tumor development and progression in multiple human cancers, such as gastric cancer[33], esophageal squamous cell carcinoma[34], breast cancer[30], bladder cancer[23], colon cancer[31,35], colorectal cancer[36], hepatocellular carcinoma[14], acute lymphoblastic leukemia[37,38], hematopoietic leukemias [39], head and neck squamous cell carcinoma[15], lung adenocarcinoma[13], papillary thyroid carcinoma[40], cervical cancer[41,42], ovarian clear cell carcinoma[43,44], and renal cell carcinoma[45,46] (Table 2).

Because of SMYD2 overexpression in numerous human tumors (Figure 1A), understanding the molecular mechanisms of SMYD2 in cancer initiation and development, and validating its therapeutic potential as a drug target to inhibit abnormal cell proliferation, have gained increasing interest in recent years; currently, SMYD2 is one of the most extensively studied protein lysine methyltransferases in the context of cancer. However, the involvement of SMYD2 in PDAC initiation and progression has not yet been fully explored. The overexpression of SMYD2 has been reported in PDAC by a study that showed methylation of the human MAPK activated protein kinase 3 (MAPKAPK3) by SMYD2 promotes tumor growth and progression[16]. Another investigation identified that the SMYD2 Locus is among the active chromatin sites unique to the genomes of the adenosquamous cancer of the pancreas (ASCP) and is associated with the active H3K4me1 histone mark[47]. These pioneering works, despite being limited in scope, demonstrate that SMYD2-mediated methylation of both histone and nonhistone proteins could also be an important tumorigenic event contributing to PDAC initiation and development. On the other hand, a rich body of knowledge available in many other human cancers with respect to the roles of SMYD2 in cell cycle control and various signaling cascades provides a wealth of information that could be extrapolated to the PDAC research field to expand our understanding of SMYD2 in PDAC development. Here, we review the known roles of SMYD2 in PDAC initiation and progression, and through capitalizing on the current knowledge about its known cancer-related functions in other human cancers, we propose there existing additional SMYD2-mediated methylation events involved in diverse signaling pathways that control and coordinate different cellular processes in PDAC.

CURRENT EVIDENCE OF SMYD2 INVOLVEMENT IN PANCREATIC CANCER

One study aimed to investigate the function of SMYD2 in PDAC using mouse and cellular models found evidence that SMYD2 plays a pivotal role in the development of this deadly pancreatic cancer[16] (Figure 1B). In other human cancers, SMYD2 usually exerts its tumorigenic effects through methylating cell signaling-related proteins and through the effect of such methylation on the targets' activity, stability, or subcellular localization[13,27,42,48]. Such a methylation-oriented mechanism has been instrumental for the initial development of a mechanistic hypothesis of SMYD2 involvement in PDAC and for the subsequent success of establishing a novel link of SMYD2 to promoting PDAC growth and progression[16]. Using an *in vitro* protein-array system, which consists of about 9500 human proteins, 159 proteins were identified as SMYD2 substrates in this study. Among these hits, MAPKAPK3 was selected for further analysis due to being implicated in cancer and being linked to Ras signaling, a key driver of PDAC[16,49-52]. Although the roles of MAPKAPK3, like those of SMYD2, in PDAC were unknown at the time of the study, MAPKAPK3 has been known as a mediator in the MAPK/ERK cascade that is responsible for regulating a wide variety of stimulated cellular processes[53-55]. It has also been shown that MAPKAPK3, phosphorylated by ERK1/2, p38 kinase, and SAPK/JNK, plays a role in inflammation and stress responses[56-59]. Therefore, the identification of MAPKAPK3 as a new SMYD2 substrate suggested a novel regulatory axis in PDAC progression.

Further characterization confirmed that the SMYD2-MAPKAPK3 axis is required for efficient PDAC development and that SMYD2-mediated methylation of MAPKAPK3 is a key event during the K-Ras-driven transformation of PDAC cells *in vivo*[16]. Lys355 of MAPKAPK3 was identified as a site of methylation targeted by SMYD2 using a mutagenesis approach and an LC-MS/MS analysis. Specificity analyses using an MS approach showed that the related protein MAPKAPK2, which shares about 75% sequence identity with MAPKAPK3, as well as other MAPKAPK proteins, are not substrates of SMYD2. On the other hand, none of the eight active lysine methyltransferases, including SMYD3 and SET8, could methylate MAPKAPK3 *in vitro*. Co-expression of SMYD2 and MAPKAPK3 in PDAC cells identified MAPKAPK3-K355me1 in a SMYD2-dependent manner, demonstrating that only SMYD2 can

Table 1 Major SET and MYND domain-containing protein 2 nonhistone substrates

Substrate	Methylation site	Methylation effect	Affected pathways	Role of substrates in PDAC	Ref.
ALK	K1451; K1455; K1610	Promotes EML4-ALK phosphorylation and NSCLC cell growth	PI3K/AKT; JAK/STAT; RTK/Ras	ALK rearrangement-positive cancer correlates with better response to chemotherapy	[28, 96]
β-catenin	K133	Promotes β-catenin nuclear translocation	Wnt/β-catenin/TCF	Mediates EMT; promotes cell proliferation, migration, and invasion	[48, 97]
BMPR2	Kinase domain	Stimulates BMPR2 kinase activity; SMAD1/5 phosphorylation; BMP pathway activation	BMP	Promotes tumor growth *via* GRB2/PI3K/AKT pathway	[98, 99]
ERα	K266	Suppresses ERα target gene activation	PI3K/AKT; MAPK-ERK	ERα expression correlates with tumor progression; endocrine therapies	[100, 101]
EZH2	K307	Promotes EZH2 stability; cell proliferation; EMT;invasion in BC	RB-E2F	Linked to an aggressive phenotype	[102, 103]
HSP90AB1	K531; K574	Enhances dimerization; chaperone complex formation of HSP90AB1; promotes cancer cell proliferation	PI3K/AKT	Targeting HSP90 decreases GEM chemores-istance	[25, 104]
MAPKAPK3	K355	Promotes pancreatic ductal adenocarcinoma	RTK/Ras; MAPK-ERK	Interacts with HSP27; mediates gemcitabine toxicity	[16]
p53	K370	Inhibits p53 and p53-mediated transcrip-tional regulation	p53	p53 methylation correlates with aggressive tumors; poor prognosis	[16, 22]
PARP1	K528	Enhances poly (ADP-ribosyl) ation enzymatic activity; promotes apoptotic escape of cancer cells	Base excision repair	Promotes tumorigenesis and resistance	[26, 105]
PTEN	K313	Inactivates PTEN; promotes BC cell prolif-eration	PI3K-AKT	Loss of PTEN enhances activation of PI3K-AKT; NF-κB and MYC; promotes tumor cell growth and survival	[27, 74]
RB	K810; K860	Enhances Ser 807/811 phosphorylation of RB1; enhances E2F transcriptional activity; cell cycle progression	RB-E2F pathway	Reduced expression of RB correlates with cancer progression	[23, 76,78]
STAT3	K685	Activates and phosphorylates STAT3; promotes cell proliferation and survival in triple-negative BC	JAK2/STAT3	Suppress apoptosis *via* regulation of BCL-2 family; promotes tumorigenesis	[30, 106]
P65	K310	Activates and phosphorylation p65; represses tumor cell apoptosis in triple-negative BC	NF-κB pathway	-	[30]

PDAC: Pancreatic ductal adenocarcinoma; MAPKAPK3: Mitogen-activated protein kinase activated protein kinase 3; RB: Retinoblastomaassociated protein; BC: Breast cancer; STAT3: Signal transducer and activator of transcription 3; BCL-2: B cell lymphoma-2.

monomethylate MAPKAPK3 at Lys355 both *in vitro* and *in vivo*. Moreover, depletion of SMYD2 led to a decreased expression of endogenous methylation of MAPKAPK3 at Lys355 in the human SW1990 PDAC cell line, indicating that SMYD2 is required for the physiological levels of MAPKAPK3-K355me1 in these cells. Additional experiments further confirmed MAPKAPK3 as a cancer-relevant cytoplasmic target of SMYD2, as determined by a decreased stromal response and a diminished inflammation in *K-Ras* mutant mice, as well as by the cytoplasmic co-localization of SMYD2 and MAPKAPK3 in human and murine PDAC cell lines[16].

PDAC is one of the Ras-driven carcinomas, where *K-Ras* mutation is a key player in triggering the pancreatic intraepithelial neoplasia (PanIN) and tumor development[16,52]. The overexpression of SMYD2 in PDAC samples, as well as the methylation of the Ras-signaling kinase MAPKAPK3, support the idea that targeting the catalytic activity of SMYD2, or the SMYD2-MAPKAPK3 axis, may be therapeutic in the Ras-driven PDAC. SMYD2 expression was not detectable in normal pancreas tissue sections, while sections from murine and human PanIN and PDAC specimens revealed elevated expression of SMYD2[16]. Notably, an increase in the expression of SMYD2 is correlated with the cancer progression in samples from *K-Ras* mutant mice. Loss of SMYD2 resulted in a reduction in the acinar-to-ductal metaplasia (ADM)[16], an early event in PDAC development triggered by the activation of the RTK/Ras signaling pathway[60]. Consistently, a reduction in the development of the precancerous lesions PanINs and a decreased proliferation ability were also observed upon depletion of SMYD2, as determined by using MUC5AC, pERK1/2, Ki67, cleaved-Caspase-3, and αSMA as markers for PanIN lesions, Ras pathway activation, proliferation, apoptosis, and stromal response, respectively. These

Table 2 SET and MYND domain-containing protein 2 involvement in human cancers

Cancer type	Findings	Ref.
Acute lymphoblastic leukemia	SMYD2 overexpression; worse OS and EFS; higher WBC counts; a higher percentage of high-risk disease; prognostic factor	[38]
Bladder cancer	Higher expression of SMYD2; promotes cell cycle progression of cancer cells; methylation of RB	[23]
Breast cancer	SMYD2 overexpression; worse RFS; prognostic factor	[107]
	SMYD2 overexpression; poor survival	[30]
Cervical cancer	Higher expression of SMYD2; worse OS; advanced FIGO stage; larger tumor size; poor prognosis	[41]
Chronic lymphocytic leukemia	Higher expression of SMYD2; high WBC counts; complex karyotype; tumor progression	[108]
Clear cell renal cell carcinoma	SMYD2 overexpression; worse OS and DFS; high TNM stage; early tumor relapse	[46]
Colon cancer	SMYD2 overexpression; upregulation MDR1/P-glycoprotein; poor prognosis; enhances oxaliplatin resistance	[31]
Colorectal cancer	SMYD2 overexpression; activates the Wnt/β-catenin pathway; worse OS and DFS; worse oncologic outcomes	[36]
Esophageal squamous cell carcinoma	Higher expression of SMYD2; worse OS; enhances venous invasion; higher pT category and recurrence	[34]
Gastric cancer	SMYD2 overexpression correlates with larger tumor size; aggressive invasion; more lymph node metastasis; recurrence; poor OS	[33]
Hematopoietic leukemias	Higher expression of SMYD2; promote Wnt-β-Catenin signaling; poor OS	[39]
Hepatocellular carcinoma	SMYD2 overexpression correlates with tumor size; vascular invasion; differentiation; TNM stage; worse OS; poor prognosis	[14]
HPV-unrelated, non-multiple head and neck cancer	Higher expression of SMYD2; worse OS; prognostic biomarker	[15]
Lower-grade gliomas	Poor OS; prognostic biomarker	[109]
Lung adenocarcinoma	Overexpressed SMYD2 correlates with shorter OS and DFS; promotes proliferation, migration, and invasion of cancer cells	[13]
Non-small cell lung cancer	Overexpressed SMYD2 enhances cisplatin resistance; downregulates the p53 pathway	[32]
Ovarian clear cell carcinoma	Shorter OS and DSS; prognostic biomarker	[43]
Pancreatic cancer	SMYD2 overexpression; methylation of MAPKAPK3; enhances precancerous lesions; poor OS	[16]
Papillary thyroid carcinoma	SMYD2 overexpression correlates with PTC progression; poor prognosis and DFS; worse clinical outcomes	[40]
Renal cell tumor	Low expression of SMYD2 correlates with shorter DSS and DFS; prognostic biomarker	[45]

SMYD2: SET and MYND domain-containing protein 2; OS: Overall survival; EFS: Event-free survival; DFS: Disease-free survival; DSS: Disease-specific survival.

results have led to pharmacological inhibition experiments aimed to evaluate the therapeutic potential of targeting the SMYD2-MAPKAPK3 axis in Ras-driven pancreatic cancer[16]. The compound PF-3644022, which inhibits the kinase activity of MAPKAPK3, was found to suppress the expansion of PDAC cells in culture[16]. Also, treatment with PF-3644022 caused inhibition of PDAC growth in *K-Ras* mutant mice, as well as resulted in fewer PanIN, reduced cell proliferation, an elevated level of apoptosis, attenuation of the Ras pathway, and a reduced level of inflammatory cytokines. Treatment with the SMYD2 small molecule inhibitor BAY598[61] inhibited the methylation of MAPKAPK3 by SMYD2 and decreased the growth of *K-Ras*/*TP53* mutant PDAC cells, whereas the growth of *K-Ras*/*TP53*/*SMYD2* mutant cells was not significantly impacted. On the other hand, the chemotherapeutic gemcitabine had a stronger inhibitory effect on the clonal expansion of *K-Ras*/*TP53* mutant PDAC cells when combined with BAY598[16]. Gemcitabine also inhibits the growth of *K-Ras*/*TP53*/*SMYD2* mutant cells, suggesting that SMYD2 inhibition along with chemotherapy treatment cooperate to target PDAC cells. Such a notion was further supported by the fact that co-treatment of gemcitabine with either SMYD2 inhibition or its deletion resulted in much greater suppression of the growth of PDAC xenografts in mice when compared with any single-agent treatments. Another combination treatment with low-dose doxorubicin and BAY598 revealed similar results in inhibiting PDAC cell growth[16]. These studies together demonstrated that the efficacy of chemotherapy for the treatment of PDAC patients could be significantly improved by a combination of SMYD2 inhibition and effective chemotherapy agents, underscoring the therapeutic potential of targeting the SMYD2-MAPKAPK3 axis

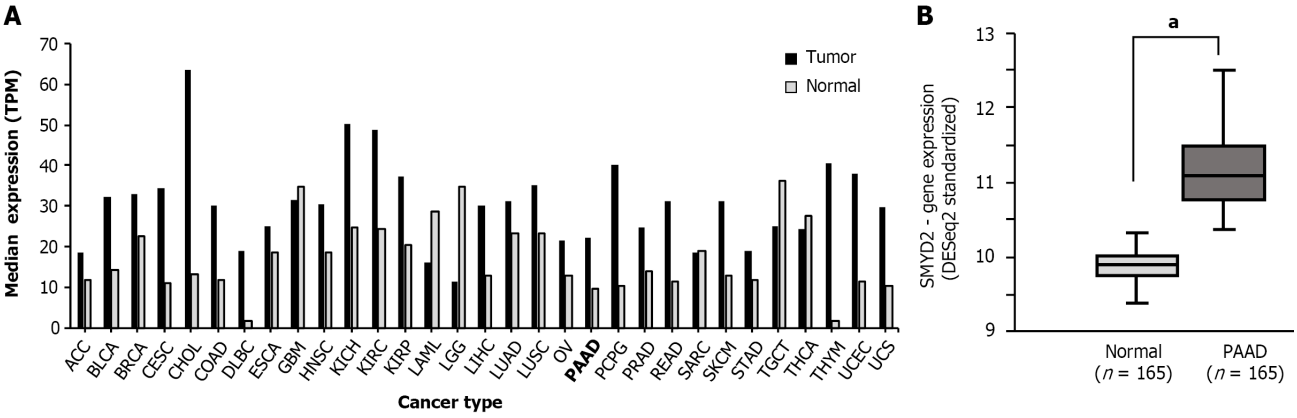

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Figure 1 SET and MYND domain-containing protein 2 gene expression in cancer. A: The gene expression profiles of SET and MYND domain-containing protein 2 (SMYD2) across 31 types of tumor samples and paired normal tissues from the Cancer Genome Atlas (TCGA) and the Genotype-Tissue Expression (GTEx) project, the analysis was performed using the Gene Expression Profiling Interactive Analysis (GEPIA2); B: Differences in SMYD2 expression between pancreatic ductal adenocarcinoma tissues and paired normal tissues. TPM: Transcripts per kilobase of exon per million mapped reads; ACC: Adrenocortical carcinoma; BLCA: Bladder urothelial carcinoma; BRCA: Breast invasive carcinoma; CESC: Cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL: Cholangiocarcinoma; COAD: Colon adenocarcinoma; DLBC: Lymphoid neoplasm diffuse large B-cell lymphoma; ESCA: Esophageal carcinoma; GBM: Glioblastoma multiforme; HNSC: Head and neck squamous cell carcinoma; KICH: Kidney chromophobe; KIRC: Kidney renal clear cell carcinoma; KIRP: Kidney renal papillary cell carcinoma; LAML: Acute myeloid leukemia; LGG: Lower grade glioma; LIHC: Liver hepatocellular carcinoma; LUAD: Lung adenocarcinoma; LUSC: Lung squamous cell carcinoma; OV: Ovarian serous cystadenocarcinoma; PAAD/PDAC: Pancreatic ductal adenocarcinoma; PCPG: Pheochromocytoma and paraganglioma; PRAD: Prostate adenocarcinoma; READ: Rectum adenocarcinoma; SARC: Sarcoma; SKCM: Skin cutaneous melanoma; STAD: Stomach adenocarcinoma; TGCT: Testicular germ cell tumors; THCA: Thyroid carcinoma; THYM: Thymoma; UCEC: Uterine corpus endometrial carcinoma; UCS: Uterine carcinosarcoma; *n*: Number of samples. [a]$P < 0.001$ is indicated by three asterisks.

in PDAC.

FUNCTIONAL EXTRAPOLATION OF SMYD2 FROM OTHER CANCERS TO PANCREATIC CANCER

SMYD2 involvement in many other human cancers (Table 2) through regulating the oncogenic signaling pathways provides a conceptual foundation for extrapolating the known functions of SMYD2 to the less studied pancreatic cancer. SMYD2 is highly expressed in breast tumor tissues relative to normal breast tissues[30]. Inhibition of SMYD2 by RNAi-mediated knockdown or through the specific inhibitor AZ505 significantly decreased tumor growth *in vivo*, indicating that SMYD2 may be involved in the initiation and development of breast cancer (BC) *via* methylation of proteins required for BC cell survival. Indeed, the contribution of SMYD2 to BC development depends on its ability to methylate four protein targets including the NF-κB p65 subunit, signal transducer and activator of transcription 3 (STAT3), histone H3, and PTEN; the activation/inactivation of these protein targets by the methylation affects a wide range of cancer cell behaviors, including cell proliferation, migration, invasion, and survival (Figure 2). SMYD2-mediated methylation of the NF-κB p65 subunit resulted in NF-κB activation and repressed apoptosis of human breast cancer cells[30]. SMYD2-mediated methylation of STAT3 contributes to STAT3 activation in triple-negative breast cancer cells, which in turn increases SMYD2 expression, leading to increased methylation of H3K4 and H3K36 by SMYD2, thereby linking SMYD2 to several BC-associated signaling cascades, including JAK2/STAT3, ERK, and AKT signaling[11,27,30,62]. SMYD2-mediated methylation of PTEN at Lys313 was shown to downregulate the expression of PTEN and to suppress PTEN activity through inducing phosphorylation at serine 380 of PTEN[27,30]. PTEN is a dual lipid and protein phosphatase; as a negative regulator of PI3K/AKT signaling, it downregulates signal transduction initiated by growth factors and hormones through dephosphorylating phosphatidylinositol 3,4,5-triphosphate (PIP3) produced by PI3K[63]. Since PI3K/AKT signaling is a crucial intracellular pathway in human cancers and is frequently upregulated in multiple types of cancer including PDAC[64], the link of SMYD2 to this signaling pathway *via* the methylation-induced repression of PTEN activity suggests a possible new mechanism by which SMYD2 contributes to PDAC development. Several reports have shown the constitutive activation of Ras/ERK and PI3K/AKT signaling and PTEN downregulation being involved in the pathogenesis and progression of pancreatic cancer[65-70]. PTEN was shown to be abundantly expressed in the cytoplasm of non-tumor pancreatic tissues but to be significantly downregulated in PDAC tissues[71]. The downregulation of PTEN has been associated with a high rate of tumorigenesis and a poor prognosis for PDAC patients[71-73]. One important mechanism by which aberrant PTEN expression contributes to PDAC development is the activation of

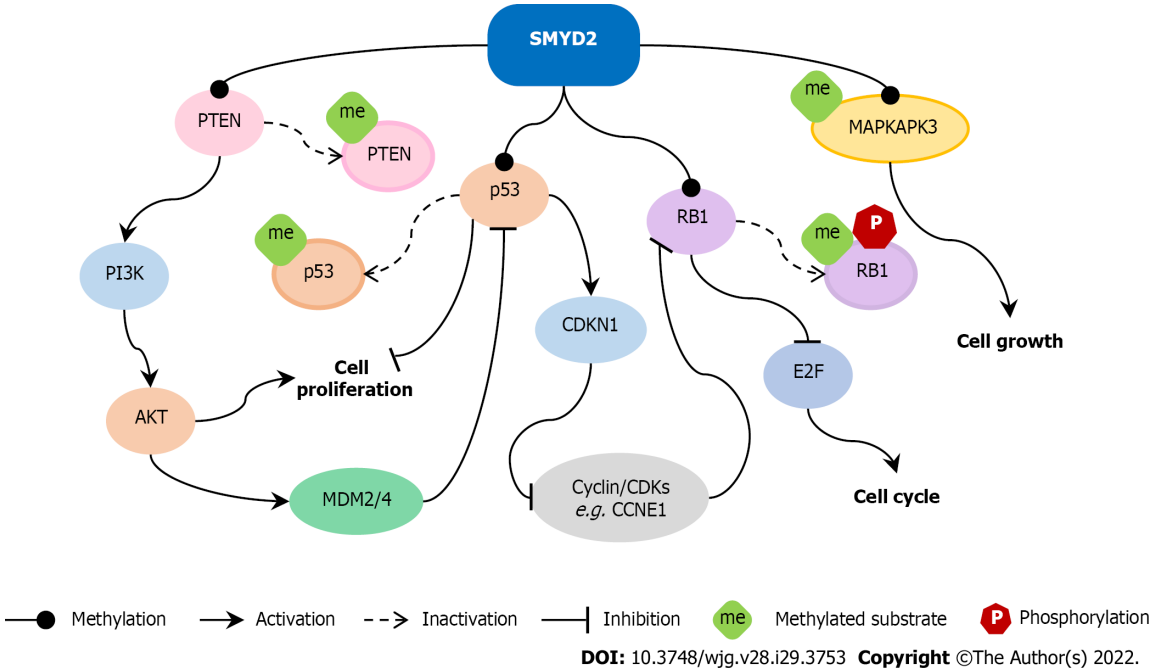

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Figure 2 A schematic model for SET and MYND domain-containing protein 2 driving pancreatic cancer development *via* methylation of nonhistone proteins. SET and MYND domain-containing protein 2 (SMYD2) can methylate several nonhistone proteins that may be involved in pancreatic cancer tumorigenesis, including p53, PTEN, retinoblastomaassociated protein (RB), and mitogen-activated protein kinase activated protein kinase 3 (MAPKAPK3). SMYD2 methylates and inactivates p53 to promote cell proliferation. PTEN is downregulated by SMYD2-mediated methylation, which promotes cell proliferation through activation of PI3K signaling. Methylation of RB by SMYD2 enhances RB phosphorylation, which allows E2F to disassociate from the RB-E2F complex and enhances E2F activity to promote cell cycle progression. SMYD2 impacts the RTK/Ras pathway through methylation of MAPKAPK3 to promote cell growth. MAPKAPK3: Mitogen-activated protein kinase activated protein kinase 3; RB: Retinoblastoma-associated protein.

the PI3K/AKT signaling pathway, which promotes PDAC cell growth, survival, and angiogenesis[74,75]. Therefore, in addition to promoting PDAC growth *via* methylation of MAPKAPK3, it is possible that the tumor-promoting activity of SMYD2 in PDAC is attributable to its methyltransferase activity on PTEN, which subsequently causes the activation of the oncogenic PI3K/AKT signaling pathway. In order to prove this hypothesis, future investigation should be directed towards assessing whether Lys313 of PTEN, which is methylated by SMYD2 in BC, can be methylated by SMYD2 in the context of PDAC, and whether such methylation represses the tumor-suppressor activity of PTEN, leading to the activation of PI3K/AKT signaling.

Methylation of RB by SMYD2[76], which is involved in the development of bladder cancer[77], suggests another potential mechanism by which SMYD2 contributes to PDAC progression. SMYD2 is overexpressed in bladder cancer cell lines and primary bladder tumor samples and plays a role in promoting bladder cancer cell proliferation[23]. One mechanism for the SMYD2's bladder cancer-promoting role is the methylation of the tumor suppressor RB, which contributes to the hyperphosphorylation of RB, leading to RB inactivation, and thereby bypassing the regulatory action of RB on cell proliferation[23]. In the case of pancreatic cancer, RB protein levels were significantly lower in PDAC tumor tissues than those in adjacent normal tissues; the low protein levels of RB have been associated with PDAC progression[78]. Another study showed that RB depletion promotes PanIN and rapid malignant transformation in *K-Ras*-induced PDAC, being associated with an impaired p53 activity[79]. This result suggests the importance of RB function in suppressing PDAC progression through mediating the cellular senescence and enhancing p53 function. However, little is known about the methylation status of RB in pancreatic cancer, how such posttranslational modification regulates RB activity, and what are the downstream effects of the methylation on cellular functions and PDAC progression. Given the role of the SMYD2-mediated RB methylation in bladder cancer, one can speculate that there might exist an analogous cancer-promoting mechanism, where SMYD2 mediates the inactivation of RB through direct methylation of RB, resulting in bypassing cell cycle restrictions and promoting PDAC cell growth.

Because of the broad substrate specificity of SMYD2 (Table 1), with most of its substrates being tumor suppressors or oncogenic proteins, the mechanistic link of SMYD2 to PDAC proliferation is expected to be complex, involving the interconnected signaling pathways that regulate the cell cycle, apoptosis, as well as energy metabolism. The tumor suppressor p53 is another important methylation target of SMYD2[22], and this methylation has been shown to promote the tumorigenesis of cervical cancer through an alternative metabolic strategy, shifting the major production of cellular metabolism to lactate production[42]. p53 exerts its tumor-suppressive function in response to severe DNA damage and

inhibits the onset and progression of tumors[80]. p53 is a master regulator of the cell cycle and apoptosis and is involved in the regulation of metabolic pathways to maintain the metabolic homeostasis of cells [81,82]. It has been reported that SMYD2 monomethylates p53 at Lys370, which led to p53 inactivation by decreasing the binding activity of p53 to its target genes[22]. Loss-of-function and gain-of-function experiments revealed that SMYD2 depletion not only significantly reduced the p53K370me level but also increased the p53 reporter activity in cervical cancer cell lines; in contrast, overexpression of SMYD2 in the same cell lines led to an increased level of p53K370me[42]. It has also been shown that the knockdown of p53 in SMYD2-overexpressing cervical cancer cells compromised the increase in glucose uptake and lactate production induced by SMYD2[42]. Moreover, hijacking tumor glycolysis by the glucose analog 2-deoxy-D-glucose (2-DG) significantly repressed SMYD2-dependent tumor growth. These findings together indicate that SMYD2 is a positive glycolytic mediator and plays a promoting role in enhancing tumor growth in a glycolysis-dependent manner, likely through SMYD2-mediated methylation of p53 to promote aerobic glycolysis and tumorigenesis in cervical cancer[42]. Although the role of SMYD2-mediated p53 methylation in PDAC has not yet been explored, dysregulation of the p53 pathway is one of the primary molecular pathological events in PDAC, which promotes the development and progression of pancreatic tumors[83]. In a cohort of 272 PDAC patients, an aberrant alteration rate of the *TP53* gene was about 38%[84], consistent with earlier reports demonstrating 40% and 47% of PDAC samples having p53 mutations[85,86]. It was shown that the inactivation of p53 occurs during the progression of PanIN to invasive tumors[87], while activation of the mitochondrial p53 was shown to restore the apoptotic pathway and inhibit PDAC growth *in vitro* and *in vivo*[88]. These studies demonstrate that p53 dysfunction has a strong association with the progression of pancreatic cancer. As an upstream regulator of the p53 pathway, SMYD2 monomethylates p53 and deactivates the transcriptional activity of p53, and it is thus possible that its ability to block the p53-tumor suppressor activity is another mechanism by which SMYD2 contributes to PDAC progression. It would also be interesting to investigate whether SMYD2-mediated silencing of p53 is also involved in the metabolic reprogramming of pancreatic tumors and promotes the aerobic glycolysis of cancer cells.

CURRENT CHALLENGES IN THE MOLECULAR THERAPEUTIC TARGETING OF SMYD2

Because of the tumor-promoting role of SMYD2 in numerous cancers including PDAC, the development of selective small-molecule inhibitors against SMYD2 could offer a substantial opportunity for targeted medicine with a broad therapeutic benefit. Great progress in crystal structure analysis of SMYD2 has allowed for the development of multiple selective and potent SMYD2 inhibitors over the past decade [89]. The first SMYD2 inhibitor AZ505 was identified in 2011 after screening over one million-compound library[90]. AZ505 is a competitive inhibitor and has high selectivity for SMYD2, with an inhibitory potency at IC_{50} of 0.12 μM. This landmark discovery opened avenues for structure-based drug discovery for SMYD2 and led to the development of more potent SMYD2 inhibitors. A systematic structure-activity relationships (SAR) study on the AZ505 structure has identified the small molecule A893 as a highly selective SMYD2 inhibitor and being more potent in inhibiting p53 methylation than AZ505[91]. LLY507, another selective SMYD2 inhibitor, was developed and validated not only by a biochemical assay but also by the cell-based assays, and this inhibitor was found to strongly inhibit SMYD2-mediated p53 methylation in several cancer cell lines[92]. Using a modified high-throughput binding assay, BAY598 was identified as one of the most selective and potent SMYD2 inhibitors, with promising pharmacokinetic properties and capable of inducing SMYD2 inhibition *in vivo*[61]. BAY598 showed more than 100-fold selectivity towards SMYD2 relative to other SMYD proteins, and it had a preferred binding to the SMYD2-SAM substrate complex. In cell-based assays, BAY598 was able to inhibit the methylation of p53 by SMYD2, and it can also lead to a slight reduction of tumor area in mice[61]. Further studies identified additional potent and selective inhibitors with suitable pharmacokinetic properties, namely AZ931 and AZ506, though these inhibitors showed no effect on the proliferation of either *TP53* wild-type or *TP53*-deficient cell lines[93]. Recent studies presented new SMYD2 inhibitors, including EPZ033294, EPZ032597, MTF1497, and MTF9975[89,94]. It is noteworthy that EPZ033294 was the first SMYD2 inhibitor acting as a non-competitive inhibitor for the substrate peptide, with a low nanomolar inhibitory activity[94]. However, all these SMYD2 inhibitors are still at a research level and have not undergone clinical trials as therapeutic agents against tumors.

It is widely accepted that the cancer-promoting role of SMYD2 is dependent on its ability to methylate histone and nonhistone proteins, which has significant functions in the development and progression of malignancies. However, targeting the methyltransferase activity of SMYD2 has not yet achieved great outcomes in current cancer studies. This lack of success may be attributed to traditional SMYD2 inhibitors that usually inhibit the evolutionarily conserved cofactor binding site, as well as the complexity of the SMYD2 broad substrate specificity and its involvement in multiple signaling pathways that are essential for both normal and cancerous cells. Targeting the cofactor binding site of SMYD2 is a straightforward strategy, as the methyltransferase activity of SMYD2 relies on the methyl donor SAM being bound at the cofactor binding site. However, the highly conserved nature of this SAM binding site across the entire SET domain-containing protein lysine methyltransferase superfamily

makes designing a highly selective inhibitor with minimum cross-reactivity a challenge. Although a great selectivity has been achieved by some SMYD2 inhibitors, the current specificity analysis is limited to a handful number of SET domain-containing proteins that are closely related to SMYD2, and the full spectrum of the specificity profiles of these inhibitors across the genome is unknown. Consequently, some reports pointed out a potent inhibition of cell proliferation by some of the SMYD2 inhibitors, such as LLY507, being independent of SMYD2 inhibition, rather targeting several other unrelated enzymes to exert their inhibitory effects[94]. Similar conflicting data was also obtained about the effect of the SMYD2 inhibitor BAY598[61]. As a result of these conflicting data, some reports concluded that SMYD2 might not be required for *in vitro* cell line proliferation, though such a claim needs to be further studied [94]. The broad substrate specificity of SMYD2 represents another significant challenge in targeting SMYD2 for cancer therapy. In the past two decades, many nonhistone substrates of SMYD2 have been reported, suggesting that the functional impact of inhibiting SMYD2 will be very complex, involving different mechanisms and affecting various cellular pathways in both normal and pathological conditions. The lack of understanding of how SMYD2 inhibition affects the physiological behavior of normal cells is a major issue of current SMYD2 inhibitors. Another issue is that, for example, SMYD2 inhibition leading to the restoration of the p53 tumor suppressor activity has been well characterized, but how this inhibition affects the function of p53 gain-of-function mutants is unknown. Many mutant p53 proteins promote tumorigenesis through the gain-of-function mechanism[95]. The activity of such p53 mutants could be enhanced by targeting SMYD2 in a similar way as it does to wild-type p53, leading to unwanted outcomes and adverse effects. This is consistent with the evidence that SMYD2 is not always a poor prognostic marker for cancer patients, and the overexpression of SMYD2 has been shown to be a favorable prognostic marker for patients with renal cell tumors[45]. Nonetheless, given that the cancer-promoting role of SMYD2 has been confirmed in multiple types of cancers, it is worthwhile to continue to exploit SMYD2 as a drug target for cancer treatment, with more attention being paid to new inhibition strategies, such as targeting protein-protein interactions and targeting additional functional sites that are less conserved but have substrate-specific functions.

CONCLUSION

In the past few decades, there have been huge improvements in our understanding of the complex molecular nature of pancreatic cancer and progress in the available therapy options, including surgery, chemotherapy, radiotherapy, immunotherapy, and targeted therapies. Although these therapy options have resulted in a slight improvement in the overall 5-year survival rate of patients, pancreatic cancer remains a difficult disease to treat. SMYD2 could be a promising target for the development of a novel PDAC therapy, given its involvement in diverse oncogenic signaling pathways to control multiple cellular processes like cell proliferation, apoptosis, and energy metabolism (Figure 2). SMYD2 is overexpressed in PDAC and serves as an important regulatory molecule through the interplay with the RTK/Ras signaling pathway and the PI3K-AKT signaling pathway to drive PDAC cell growth and metastasis. The projected role of SMYD2 in repressing the activity of the tumor suppressors p53 and PTEN in PDAC development further implies that SMYD2 is a key player in promoting the cell cycle, cell growth, and cell survival. Therefore, targeting SMYD2 could be a powerful strategy for the prevention and treatment of PDAC, in particular with consideration of tumor subtypes and genetic backgrounds.

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