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Emerging Role of SMYD Family of Proteins in Human Tumorigenesis

(Kemunculan Peranan Famili SMYD Protein dalam Tumorigenesis Manusia)

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ABSTRACT

Protein lysine methylation is a post-translational modification (PTM) that promotes protein complex formation to regulate DNA replication, gene expression, and repair mechanisms. The Su(Var)3–9, Enhancer-of-zeste and Trithorax (SET) and Myeloid, Nervy, and DEAF-1 (MYND) domain-containing proteins SMYD are lysine methyltransferases that catalyze the methylation of various histone and non-histone proteins. There are five members of this SMYD family, and all of these have conserved SET and MYND domains. The SET domain is divided into two segments by the MYND domain (the S-sequence and a core SET domain). SMYD Family performs a key role in numerous biological functions, including growth, development, apoptosis, and proliferation. SMYD family members are associated with skeletal and cardiac muscle physiology and pathology. Several studies have shown that aberrant lysine methylation plays a significant role in oncogenesis. Recently, the SMYD family has gained importance for its role in various mechanisms involved in cancer development and progressions, such as methylation and modification of tumor suppressor proteins (p53 and pRb), transcriptional factors (STAT3, NF-κB), nuclear proteins (PARP1), chaperons (Hsp90), protein kinases (MAPK, ERK), and cell cycle regulatory proteins (CDKN2). SMYD family proteins drive oncogenesis, lead the way to metastasis, and develop chemoresistance, allowing cancer cells to grow, invade the neighboring tissues, and resist therapeutics. In this review, we summarize SMYD family members' role in different cancers by focusing on their histone and non-histone methylation targets and illustrating the mechanism of SMYD family-mediated oncogenesis.

Keywords: Cancer; chemoresistance; oncogenesis; SMYD family; tumor suppressor proteins

ABSTRAK

Pemetilan protein lisin ialah pengubahsuaian pasca translasi (PTM) yang menggalakkan pembentukan kompleks protein untuk mengawal selia replikasi DNA, pengekspresan gen dan mekanisme pembaikan. Protein yang mengandungi domain Su(Var)3–9, Enhancer-of-zeste dan Trithorax (SET) dan Myeloid, Nervy dan DEAF-1 (MYND) ialah lisin metiltransferase yang memangkinkan pemetilan pelbagai protein histon dan bukan histon. Terdapat lima ahli famili SMYD ini dan kesemua mereka telah memulihara domain SET dan MYND. Domain SET dibahagikan kepada dua segmen oleh domain MYND (jujukan S dan domain SET teras). Famili SMYD melaksanakan peranan penting dalam pelbagai fungsi biologi, termasuk pertumbuhan, perkembangan, apoptosis dan percambahan. Ahli famili SMYD dikaitkan dengan fisiologi dan patologi otot rangka dan jantung. Beberapa kajian telah menunjukkan bahawa pemetilan lisin yang menyimpang memainkan peranan penting dalam onkogenesis. Baru-baru ini, famili SMYD telah mendapat kepentingan untuk peranannya dalam pelbagai mekanisme yang terlibat dalam perkembangan dan janjangan kanser, seperti pemetilan dan pengubahsuaian protein penindas tumor (p53 dan pRb), faktor transkrip (STAT3, NF-κB), protein nuklear (PARP1)), chaperon (Hsp90), kinase protein (MAPK, ERK) dan protein pengawalseliaan kitaran sel (CDKN2). Protein famili SMYD memacu onkogenesis, membawa kepada metastasis dan membangunkan rintangan kimia, membolehkan sel kanser berkembang, menyerang tisu jiran dan menentang terapeutik. Dalam ulasan ini, kami meringkaskan peranan ahli famili SMYD dalam kanser yang berbeza dengan memfokuskan pada sasaran pemetilan histon dan bukan histon dan menggambarkan mekanisme onkogenesis pengantara famili SMYD.

Kata kunci: Famili SMYD; kanser; kemoterapi; onkogenesis; protein penindas tumor

Introduction

Cancer is a multifactorial hyperproliferative disease that has been reported as the second major cause of mortalities around the globe (Sharif et al. 2019). The complex biology of cancer is characterized by six fundamental physiological and genetic changes acquired by cancer cells to support tumorigenicity (Sarfraz et al. 2018). These alterations, commonly known as hallmarks of cancer, include limitless replicative capability, resisting apoptosis, metabolic rewiring, angiogenesis, metastasis, evading growth suppressors, tumor inflammation, genomic instability, and avoiding immune destruction (Sarfraz et al. 2020). Numerous pathways in cancer development rely on post-translational modifications, including the methylation of histone and non-histone proteins (Carlson & Gozani 2016).

SMYD family and their role in epigenetics

The Su(Var)3–9, Enhancer-of-zeste and Trithorax (SET) and Myeloid, Nervy, and DEAF-1 (MYND) domain-containing (SMYD) family of lysine methyl transferases contains 5 members (SMYD1-5) (Rubio Tomás 2021). SET containing methyl transferase is characterized by a split catalytic domain and is prevalent in the cytoplasm and nucleus (Abu-Farha et al. 2008). The SET domain is divided into two segments by the MYND domain (the S-sequence and a core SET domain) (Sirinupong et al. 2010; Tracy et al. 2018). Target proteins' lysine residues receive methyl groups via the core SET domain, whereas the S-sequence may be involved in protein-protein interactions and cofactor binding (Tracy et al. 2018). In particular, the zinc finger motif-containing MYND domain is crucial for protein-protein interactions (Liu et al. 2007). Another characteristic of this family is that all members have post-SET and SET-I domains, but only SMYD1-4 has the C-terminal domain (CTD) (Leinhart & Brown 2011). Among these, all five (SMYD) family members, the most extensively studied lysine methyl transferase is SMYD2 which catalyzes the lysine methylation of H3K36 and H3K4 (Abu-Farha et al. 2008; Brown et al. 2006) as well as non-histone proteins like PARP1, RB, p53, PTEN, ERa, and HSP90AB1 (Donlin et al. 2012; Huang et al. 2006; Nakakido et al. 2015; Piao et al. 2014; Saddic et al. 2010; Zhang et al. 2013). Therefore, it plays a pivotal role in epigenetics by performing gene expression regulation in many biological processes, such as muscle development and physiology, hematopoiesis, and many types of cancer (Rubio-Tomás 2021). Several small-molecule inhibitors of this family members have been developed (Cowen et al. 2016; Jiang et al. 2014), which can be used as potential anti-cancer drugs. However, SMYD2 might be involved in modifying other yet unidentified substrates that mediate cancer development and its poor prognosis thus, can be used as novel drug targets.

Recently, scientists have highlighted the critical role of epigenetic aberrations in cancer development. Chromatin and epigenetic alterations in the cells can confer oncogenic properties and hallmarks of cancer (Flavahan et al. 2017). Cancer epigenetics involves extensive reprogramming of the related machinery, including DNA methylation, histone modifications, post-translational modifications (PTMs), non-coding RNAs, expression, and nucleosome positioning. Interestingly, the reversible nature of epigenetic alterations, unlike genetic mutations, has led to epigenetic therapy's emergence as a promising and therapeutically relevant approach for cancer treatment. Targeting epigenetics has recently progressed with the approval of three epigenetic drugs for cancer (Yoo & Jones 2006).

With the help of post-translational modifications such as glycosylation, phosphorylation, methylation, hydroxylation, ubiquitination, and acetylation, the activity of most eukaryotic proteins is modulated (Mann & Jensen 2003). In the nucleus of eukaryotes, methylation on lysine residues is one of the most common PTM. Methylated lysine on proteins modulates protein complex formation that controls the expression of the genes, DNA replication, and DNA repair mechanisms (Donlin et al. 2012). In the last decade, the SMYD proteins have gained significance due to their essential role in cardiac and skeletal muscle development.

This paper aims to provide an update on the cancer-specific role of SMYD family members to explore their potential as therapeutic targets for cancer treatment. We thoroughly screened the literature for this article via PubMed and Scopus search engines. The keywords used to search data are SMYD Protiens, SMYD (SMYD1, SMYD2, SMYD3, SMYD4, and SMYD5) and cancer.

Historical perspectives of SMYD family members

This section aims to emphasize the historical aspects of the study of the SMYD family from 1964 to till date (Figure 1). The story started in the mid-19th century when Allfrey and Mirsky first identified the methylation of histone proteins (Allfrey & Mirsky 1964). The founding member of the SMYD family, the SMYD1 protein, was first discovered by Hwang and Gottlieb in 1995 in the opposite strand of the CD8b promoter and was initially

named Bop (Hwang & Gottlieb 1995). In 2000, Jenuwein found the first histone methyltransferase (HMT) (Rea et al. 2000), and in 2004, the first histone demethylase was reported (Shi et al. 2004). SMYD3, a gene initially found to be overexpressed in hepatocellular and colon cancer, was identified in 2004 (Hamamoto et al. 2004). In 2006, Tucker reported the identification and characterization of SMYD2, expressed in a range of diseased tissues and tumors (Brown et al. 2006). In 2009, a potential tumor suppressor gene, SMYD4, was identified, which plays a critical role in breast cancer by inhibiting the expression of Pdgfr-alpha (Hu et al. 2009). The first novel and selective inhibitor of SMYD2, AZ505, was discovered in 2011 (Ferguson et al. 2011). In 2015, a small molecule, BCI-121, was found to reduce cancer cells' proliferation and significantly inhibit SMYD3 (Peserico et al. 2015). SMYD3 was demonstrated as a potent enhancer of Ras-driven tumors in 2017 (Huang & Xu 2017). The role of SMYD2 in developing resistance against chemotherapeutic drug (cisplatin) was identified in 2019 (Shang & Wei 2019).

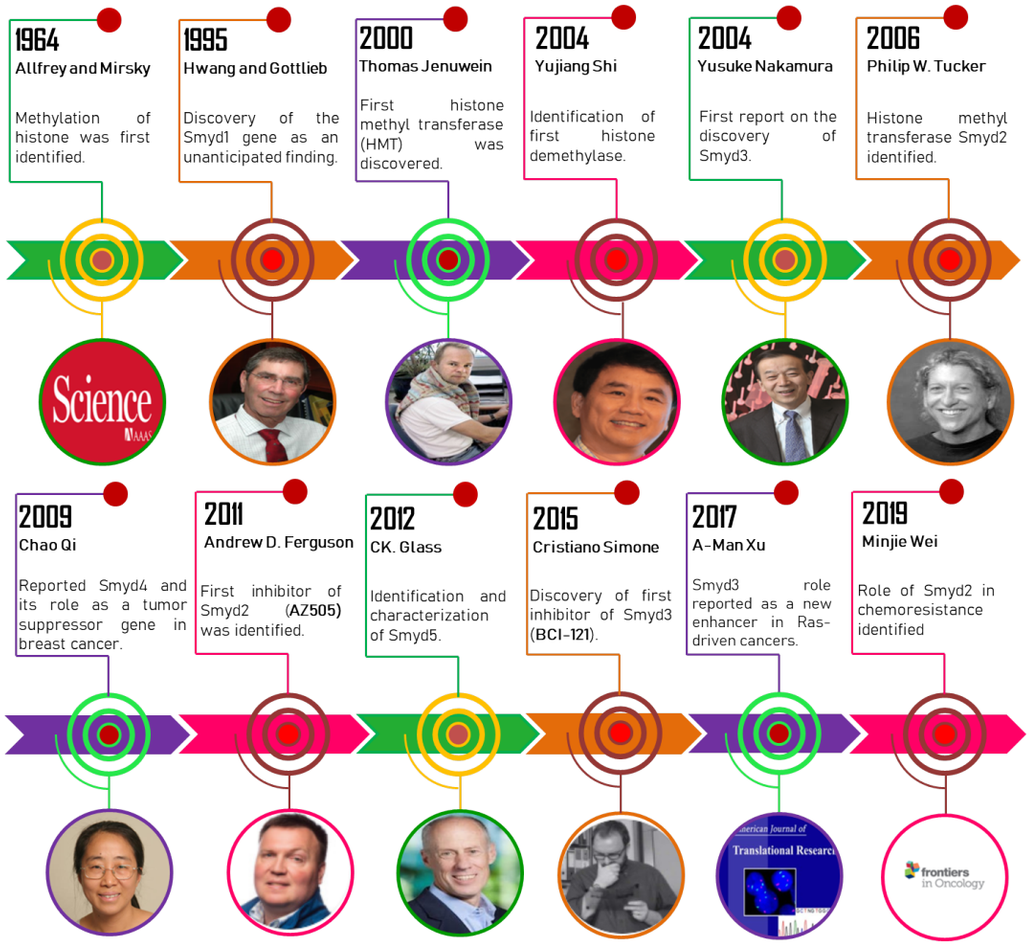

FIGURE 1. Key events in the study of SMYD family proteins

WHAT ARE SMYD PROTEINS?

Recent studies discovered about 60 proteins possessing the SET domain, including the SMYD family in different organisms (Kawamura et al. 2008). SMYD is a SET and MYND (Myeloid translocation protein-8 Nervy-DEAF1) domain-containing family of proteins (Brown et al. 2006). The SET domain contains 130 amino acids and consists of SET-I, pre-SET, and post-SET. The SET domain acts as

a catalytic module (Berger 2007) for the methylation of numerous lysine residues in the presence of S-adenosyl-methionine (SAM)/Ado Met (Kawamura et al. 2008). The SET domain is split by the MYND domain (Brown et al. 2006), a zinc finger motif, which plays a significant role in protein-protein interaction (Liu et al. 2007). After splitting, the SET domain is divided into two parts: S-sequence, which might be significant for the binding of cofactor and protein-protein interaction (Spellman et al. 2015), and a core SET domain (known as ET), which acts as an essential catalytic module. Despite splitting, SET domain topology in SMYD proteins is identical to the topology of other SET domain-containing proteins. C-terminal domain (CTD) is only absent in SMYD5, and its structure is similar to tetratricopeptide repeat (TPR) in other SMYD family members (Allan & Ratajczak 2011; Sirinupong et al. 2011, 2010).

CHARACTERISTICS OF SMYD FAMILY MEMBERS

SMYD1/Bop consists of 490 amino acids and is an imperative regulator of heart development (Gottlieb et al. 2002; Phan et al. 2005). According to the human protein atlas, SMYD1 is involved in cancer development (Song et al. 2019). SMYD2 is a 433-amino acid long protein, and its activity is pH-dependent (Brown et al. 2006). SMYD2 is involved in oncogenesis (Huang et al. 2006), and its overexpression represents a poor prognosis and lower survival rate in cancer patients (Xu et al. 2018; Zuo et al. 2018). SMYD3 is a 428-amino acid long protein and plays an oncogenic role by promoting cell proliferation, invasion, and metastasis in various cancers (Hamamoto et al. 2004). SMYD4 is an 804-amino acid long protein and plays a critical role as a potential tumor suppressor protein (Hu et al. 2009). SMYD5 is a 418-amino acid long protein and plays a significant role in gene regulation, cardiac, and skeletal muscle development (Al-Shar'i & Alnabulsi 2016), and its depletion is involved in enhanced tumor growth (Kidder et al. 2017).

METHYLATION TARGETS OF SMYD FAMILY MEMBERS

SMYD proteins are crucial in histone and non-histone protein methylations (Table 1). SMYD1/Bop methylates histone 3 lysine 4 (H3K4) (Berkholz et al. 2015; Tan et al. 2006), and non-histones skNAC (skeletal and heart muscle-specific variant of the nascent polypeptide-associated complex), TRB3 (tribbles homolog 3) (Rasmussen et al. 2015; Tracy et al. 2018). SMYD2 methylates histone3 lysine36 (H3K36) (Brown et al. 2006), H3K4 (Abu-Farha et al. 2008), and non-histones p53 (Huang et al. 2006), retinoblastoma (RB) (Cho et al. 2012; Saddic et al. 2010), heat shock protein 90 (Hsp90)-α (Abu-Farha et al. 2011; Donlin et al. 2012), Estrogen receptor alpha (ERα) (Zhang et al. 2013), Poly(ADP-ribose)-polymerase1 (PARP1) (Piao et al. 2014), phosphatase and tensin homolog (PTEN) (Nakakido et al. 2015), Six1 (sine oculis homeobox 1), Six2, SIN3B, DHX15 (Lanouette et al. 2015), MAPKAPK3 (Reynoird et al. 2016), AHNAK (desmoyokin), AHNAK2 (AHNAK nucleoprotein 2) (Olsen et al. 2016), STUB1 (STIP1 homology and U-box containing protein 1), and eEF2 (eukaryotic elongation factor 2) (Ahmed et al. 2016). SMYD3 methylates H3K4 (Hamamoto et al. 2004), histone4 lysine20 (H4K20) (Foreman et al. 2011), histone4 lysine5 (H4K5) (Van Aller et al. 2012), and non-histones vascular endothelial growth factor receptor 1 (VEGFR1) (Kunizaki et al. 2007), MAP3K2 (Mazur et al. 2014). Histone and non-histone methylation targets of SMYD4 are still unknown. SMYD5 methylates H4K20 (Stender et al. 2012), and the non-histone methylation target of SMYD5 is still unknown (Table 1). SMYD family plays essential functions in the development of muscles and cellular differentiation by methylation of histone and non-histone proteins (Du, Tan & Zhang 2014). This review has summarized how SMYD proteins play a significant role in different cancers by methylation of numerous protein lysine residues.

ROLE OF SMYD FAMILY MEMBERS IN DIFFERENT CANCERS

Modulation of SMYD family members has been reported in different cancers (Figure 2). SMYD2 is reported as a novel oncogene that promotes the progression of numerous cancers (Table 2) (overexpression of SET and MYND domain containing protein 2 (SMYD2) is associated with poor prognosis in pediatric B lineage acute lymphoblastic leukemia), renal cell carcinoma (inhibition of SMYD2 suppresses tumor progression by down-regulating microRNA-125b and attenuates multi-drug resistance in renal cell carcinoma. Furthermore, overexpression of SMYD2 represents poor prognosis in cancer patients (Xu et al. 2018; Zuo et al. 2018). Children with acute lymphoblastic leukemia (ALL) have a higher level of SMYD2 mRNA expression level. Significantly after complete remission, this mRNA expression level of SMYD2 decreased significantly and the patients with higher white blood cell count has a higher percentage of risk of acute lymphoblastic leukemia (Song et al. 2019).

TABLE 1. Methylation targets of SMYD members

SMYD Protein	Histone targets	Non-histone targets	Protein length	Percentage homology (HMR)
SMYD1	H3K4 (Tan et al. 2006, Berkholz et al. 2015)	skNAC, TRB3 (Rasmussen et al. 2015, Tracy et al. 2018)	490	91 (Tracy et al. 2018)
SMYD2	H3K4 (Abu-Farha et al. 2008), H3K36 (Brown et al. 2006)	P53 (Huang et al. 2006), RB (Saddic et al. 2010), PARP1 (Piao et al. 2014), Hsp90α (Donlin et al. 2012), PTEN (Nakakido et al. 2015), MAPKAPK3 (Reynoird et al. 2016), AHNAK, AHNAK2, PDAP1, BTF3 (Olsen et al. 2016), ERα (Zhang et al. 2013), MAPT, NCOA3, STUB1, CCAR2, UTP14A, eEF2 (Ahmed et al. 2016), six1,six2, DHX15, SIN3B (Lanouette et al. 2015)	433	93 (Tracy et al. 2018)
SMYD3	H3K4 (Hamamoto et al. 2004), H4K5 (Van Aller et al. 2012), H4K20 (Foreman et al. 2011)	MAP3K2 (Mazur et al. 2014), VEGFR1 (Kunizaki et al. 2007)	369	94 (Tracy et al. 2018)
SMYD4	Unknown	Unknown	804	68 (Tracy et al. 2018)
SMYD5	H4K20 (Stender et al. 2012)	Unknown	418	88 (Tracy et al. 2018)

SMYD2 activates STAT3 by lysine methylation which further leads to its translocation into nucleus, a hallmark of cancer cell proliferation. Methylation of NFκB by SMYD2 results in the suppression of apoptosis in cancer cells. Moreover, SMYD2, NFκBp65, and STAT3 have synergistic effects in TNBC (Li et al. 2018). SMYD3 is also reported as an oncogene that promotes the proliferation and metastasis of numerous cancers (Table 3). Furthermore, overexpression of SMYD3 is involved in aggressive cancer phenotype, and it might indicate poorer prognosis and survival rates (Huang & Xu 2017). SMYD4 overexpression is associated with tumor suppressor activity in breast cancer (Han et al. 2019; Hu et al. 2009). SMYD5 primarily gains importance in embryonic stem (ES) cell differentiation but SMYD5 depletion in human colon cancer and lung cancer results in enhancing the growth of tumors (Kidder et al. 2017b).

THE MECHANISM OF SMYD FAMILY-DERIVED CANCER DEVELOPMENT AND PROGRESSION

The role of SMYD1 in cancer has not been reported yet. On a large scale, proteomic studies have demonstrated

TABLE 2. SMYD2 associated cancers

Type of cancer	References
esophageal squamous cell carcinoma (ESCC)	(Komatsu et al. 2009)
bladder carcinoma	(Cho et al. 2012)
pediatric acute lymphoblastic leukemia (ALL)	(Sakamoto et al. 2014)
gastric cancer	(Komatsu et al. 2015)
HPV-unrelated head and neck squamous cell carcinoma's (HNSCCs)	(Ohtomo-Oda et al. 2016)
pancreatic ductal adenocarcinoma (PDAC)	(Reynoird et al. 2016)
(Reynoird et al. 2016), non-small cell lung carcinoma (NSCLC)	(Wang et al. 2017)
colon cancer	(Deng et al. 2017)
hepatocellular carcinoma (HCC)	(Zuo et al. 2018)
(Zuo et al. 2018), triple-negative breast cancer (TNBC)	(Li et al. 2018)
papillary thyroid carcinoma	(Xu et al. 2018)
cervical cancer	(Sun et al. 2019)
high-grade serous ovarian carcinomas (HGSOCs)	(Kukita et al. 2019)

that the oncogenic protein SMYD2 methylates various key cancer-associated histone and non-histone proteins, which leads to either repression or activation of transcription (Tracy et al. 2018). p53 is one of the non-histones proteins which is regulated by Symd2-mediated lysine methylation. SMYD2-mediates the methylation of p53 at two sites: lysine 372 (K372) and lysine 370 (K370). SMYD2-mediated methylation of p53 at K372 prevents cell death in cardiomyocytes; thus, SMYD2 acts as a cardioprotective protein (Sajjad et al. 2014). However, p53 methylation at K370 is repressive for p53 dependent regulation of transcription compared to p53 methylation at K372. SMYD2-mediated methylation of p53 on K370 leads to the repression of tumor-suppressive functions of p53. Thus, SMYD2 acts as a putative oncogene. It has also been found that SET9 dependent methylation of p53 at K372 inhibited the SMYD2 associated methylation of p53 at K370, providing cross-talk between PTMs (Huang et al. 2006).

SMYD2 can potentially methylate RB (retinoblastoma tumor suppressor) at lysine 860 (K860) in cells. This methylation helps to bind the methyl binding domain of L3MBTL1 to methylated RB (Saddic et al. 2010). SMYD2-derived methylation of RB1 at K810 enhances the level of p-RB1. The transcriptional activity of E2F is accelerated by methylated RB1, which promotes cell division progression. So, SMYD2 associated RB methylation at K810 plays a critical role in cancer progression (Cho et al. 2012).

TABLE 3. SMYD3 associated cancers

Type of cancer	References
breast cancer	(Chen et al. 2017, Fenizia et al. 2019, Hamamoto et al. 2006, Kim et al. 2009, Luo et al. 2014, Ma et al. 2018, Ren et al. 2011)
HCC	(Chen et al. 2007, Fei et al. 2017, Li, Tang, et al. 2018, Yang et al. 2009, Zhou et al. 2019, Zhu et al. 2017)
cervical carcinoma	(Wang, Luo, et al. 2008)
ESCC	(Dong et al. 2014, Liu et al. 2017, Wang, Liu, et al. 2008, Zhang et al. 2018, Zhu et al. 2016)
cholangiocarcinoma	(Guo et al. 2011, Zeng et al. 2012)
gastric cancer	(Liu, Liu, Kong, et al. 2015, Liu, Deng, et al. 2015a, Liu, Liu, Luo, et al. 2015b, Liu, Luo, et al. 2015c, Wang, Wang, et al. 2017)
prostate cancer (PrC)	(Lobo et al. 2018, Vieira et al. 2015)
human glioma	(Dai et al. 2015)
bladder cancer	(Shen et al. 2016)
chronic lymphocytic leukemia (CLL)	(Lin et al. 2019, Oliveira-Santos et al. 2016)
colorectal cancer	(Li et al. 2018)
pancreatic cancer	(Zhu & Huang 2019)
ovarian cancer	(Jiang et al. 2019, Lyu et al. 2019, Zhang et al. 2019a)

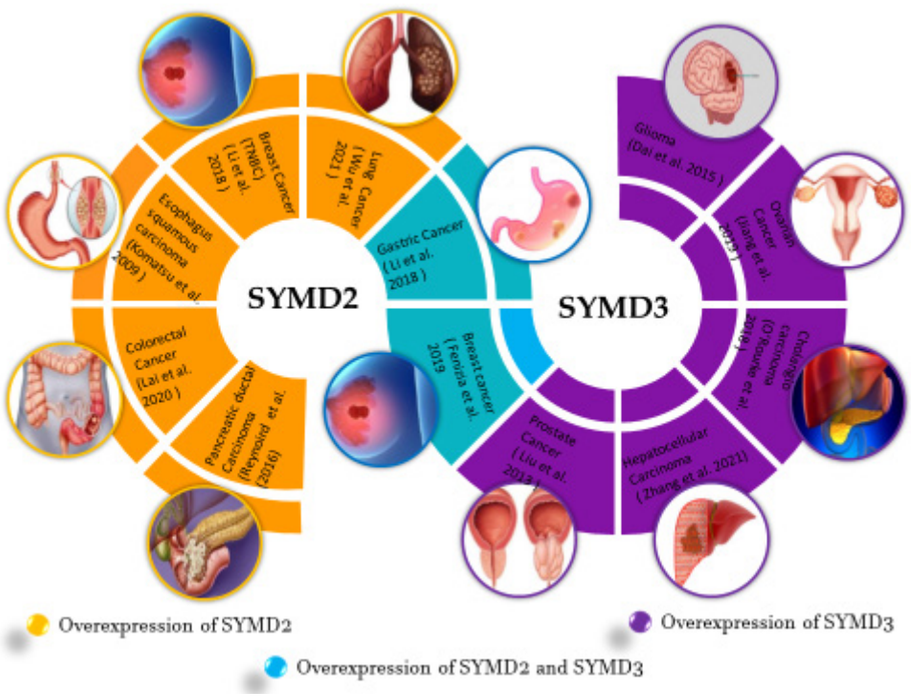

FIGURE 2. Role of SMYD2 and SMYD3 in different cancer types

SMYD2 methylates *Hsp90* at K209/615 on the nucleotide-binding and dimerization domain (Abu-Farha et al. 2011). SMYD2 also methylates *Hsp90*AB1 at K531/574, which are novel sites for chaperone-complex formation and dimerization of *Hsp90*AB1. Hsp90 chaperon machinery is a crucial facilitator of oncogenesis, which protects oncoproteins from degradation and misfolding. Thus, SMYD2 plays a role in accelerating cancer cell proliferation by methylation of Hsp90 (Hamamoto et al. 2014).

SMYD2 mediated methylation of ERα at lysine 266 *in vivo* and *in vitro*, which represses expression of ERα target gene. SMYD2 mediated methylation of ERα is important in regulating estrogen signaling through the repression of ERα mediated transactivation. Estrogen signaling governs numerous developmental processes and has a critical role in cancer (Jiang et al. 2014; Zhang et al. 2013).

SMYD2 methylates PARP1 at K528, which enhances its enzymatic activity in cancerous cells. PARP1 has been found upregulated in numerous human cancers; the overexpression of PARP1 allows the maintenance of genome integrity, DNA repair, and chromatin modification (Piao et al. 2014). This study provides a peculiar mechanism of PARP1 activation in cancer via SMYD2-mediated methylation.

SMYD2 mediated methylation of PTEN at K313, which inhibited its tumor suppressor activity by inducing phosphorylation of the PI3K-AKT signaling pathway, which accelerated cancer cell proliferation (Nakakido et al. 2015). SMYD2 is overexpressed in PDAC and performs a key role in cancer progression and chemoresistance via targeting MAPKAPK3 (Reynoird et al. 2016). Nuclear translocation of β-catenin and Wnt signaling activation is promoted by SMYD2 dependent methylation of β-catenin at K313. Wnt/β-catenin pathway is activated by the nuclear translocation of β-catenin, which drives oncogenesis (Deng et al. 2017). Thus, inhibiting SMYD2 has the potential to block β-catenin and Wnt signaling in cancer (Figure 3). Apart from its role in normal growth, survival and transformation of hematopoietic leukemias, SMYD2 has an oncogenic role in leukemias resulting from defective hematopoietic stem cells (HSC). Loss of SMYD2 normal function affects hematopoiesis and its downstream targets of HSC via apoptotic loss and transcriptional deregulation of HSC proliferation and disturbance in Wnt-β-Catenin pathway (Brown et al. 2020). SMYD2 decreased the sensitivity of oxaliplatin in colon cancer by regulating MDR1/P-glycoprotein through MEK/ERK/AP-1 signaling pathway, providing a potential strategy to sensitize chemotherapy by SMYD2-OE knockdown in colon cancer treatment (Ren et al. 2019). PTEN phosphorylation was also induced by SMYD2-mediated methylation, thereby inhibiting the tumor suppressor function in the PI3KAKT pathway and promoting cancer cell growth (Zhang et al. 2020). SMYD2 directly methylates zeste homolog 2 (EZH2) at lysine 307 (K307) and increases its constancy, which can be reassured by the histone H3K4 demethylase lysine-specific demethylase 1 (LSD1). SMYD2 facilitated EZH2 methylation plays an important role in fine-tuning of EZH2 functions in chromatin recruitment and transcriptional repression (Zeng et al. 2019).

SMYD2 positively regulates the expression Cyclin-dependent kinases 4 and 6 (CDK4/6), while (CDK4/6) also completely controls the phosphorylation and enzymatic activity of SMYD2. The higher level of SMYD2 and CDK4/6 with inhibitors results in the restoration of the primary cilium in tumor and cystic cells of breast cancer and autosomal dominant polycystic kidney disease (ADPKD) (Li et al. 2020). SMYD2 expression was screened in ovarian clear cell carcinoma (OCCC) and significant upregulation of SMYD2 expression was seen in clinical samples. Symd2 knockdown decreased the cell viability, induced apoptosis and the ratio of cells in the sub-G1 phase increased due to SMYD2 inhibition by LLY-507 in OCCC (Kojima et al. 2020). Adenosquamous cancer of the pancreas (ASCP) is a subtype of pancreatic cancer and it has a worse prognosis and more potential for metastatis than more common pancreatic ductal adenocarcinoma (PDAC). SMYD2 and pancreatic stem cell regulator (RORC) genes were found in all three ASCPs, (Lenkiewicz et al. 2020). SMYD2 is highly expressed in clear cell renal cell carcinoma (ccRCC) and the knockdown of SMYD2/miR-125b/DKK3 pathways via AZ-505 suppressed the growth and invasion of ccRCC cells (Yan et al. 2019).

SMYD3 drives oncogenesis by interacting with RNA polymerase II and trans-activating several genes such as oncogenes and cell-cycle regulatory genes in colorectal and liver cancers (Hamamoto et al. 2004). SMYD3 has also been reported to be involved in breast carcinogenesis by directly modulating the expression of the proto-oncogene, WNT10B (Hamamoto et al. 2006). SMYD3 induced MMP-9 (matrix metalloproteinase-9) expression in transformed fibrosarcoma cells and upregulated MMP-9-stimulated migration of cancer cells; thus, SMYD3 played a peculiar role in metastasis (Hamamoto et al. 2006). Later on, the synergy between the overexpression

of SMYD3 and MMP-9 was also found in stomach cancer (Liu et al. 2015a; Sampieri et al. 2010).

SMYD3 overexpression has the inhibitory effects on the tumor suppressor activity of retinoblastoma-interacting zinc-finger protein 1 (RIZ1). Thus, a low level of RIZ1 is associated with proliferation (Dong et al. 2014). SMYD3 overexpression is found to be positively correlated with the expression of transforming growth factor (TGF-β1) and STAT3 (Liu et al. 2015b). SMYD3 overexpression gained importance in regulating and stimulating lysyl oxidase like 2 (LOXL2) and Ezrin (EZR) transcription through direct binding with promoter site. EZR overexpression is associated with cell proliferation and invasion. LOXL2 overexpression is closely linked with the survival of tumor cells and metastasis (Zhu et al. 2016).

SMYD3 methylates promoter of Ras association domain family 1 isoform A (RASSF1A). Thus, the higher expression of SMYD3 results in the lower expression of tumor suppressor RASSF1A and the lower level or inactivation of RASSF1A is involved in cancer cell proliferation (Guo et al. 2011). SMYD3 is a transcriptional co-activator of ER and also promotes ER-dependent transcription. Hence, SMYD3 overexpression is associated with ER's transcriptional regulation, which is an important regulator for developmental processes and is involved in cancer development (Kim et al. 2009).

SMYD3 overexpression enhances the Myocardin-related transcription factor-A (MRTF-A) dependent upregulation and activation of Myosin light chain 9 (MYL9), which is involved in cancer progression and migration (Luo et al. 2014). SMYD3 promotes the progression of prostate cancer through its methyltransferase enzymatic activity (Vieira et al. 2015). SMYD3 overexpression modulates tumor suppressor activity of p53, which promotes the progression and proliferation of gliomas (Dai et al. 2015). SMYD3 enhances cancer proliferation, partially by increasing the expression of BCL2-associated transcription factor 1 (BCLAF1) and induction of autophagy (Shen et al. 2016). SMYD3 enhances cancer progression via modulation of the SMYD3-H4K20me3-CDKN2A pathway (Jiang et al. 2019). In pancreatic and lung cancers, SMYD3 potentiates oncogenic Ras/ERK signaling by methylating MAP3K2 kinase, thus, promoting Ras-driven cancers (Mazur et al. 2014).

SMYD3 overexpression in bladder cancer increases H3K4 activity to modulate cell proliferation, cell migration and invasion ability (Wu et al. 2019). Colon adenocarcinoma (COAD) malignancy starts from the digestive tract and it is tested that SMYD3 affects the cell proliferation, apoptosis and the cell cycle of COAD *in vitro* and promotes cancer growth *in vivo* (Yue et al. 2020). SMYD3 overexpressed in non-small cell lung cancer (NSCLC) and cancer cells become more resistant to cisplatin and SMYD3 silencing makes the cancer cells more sensitive to the drug, and SMYD3 knockdown upregulates Bim, Bak, and Bax and downregulates Bcl2, Bcl-xl, MMP-2 and MMP-9 in NSCLC (Li et al. 2020).

It is a known fact that von Hippel-Lindau/hypoxia-inducible factor α (VHL-HIFα) and epidermal growth factor receptor (EGFR) play important roles in the carcinogenesis of renal cell carcinoma (RCC). SMYD3 collaborates with SP1 to transcriptionally increase EGFR expression, and accelerate its downstream signaling activity. So, SMYD3 is an important prognostic marker in renal cell carcinoma (Liu et al. 2020). SMYD3 as an independent prognostic factor identified in pancreatic cancer (Zhu & Huang 2020). Overexpression of SMYD3 decreases p53 protein stability and brings epithelial mesenchymal transition in epithelial ovarian cancer (Zhang et al. 2019b). STAT3 and SMYD3 up-regulation in chronic lymphocytic leukemia promotes cell proliferation and prevents the expression of apoptotic genes. STAT3 inhibition by WP1066 prevents the binding of STAT3 to SMYD3 promoter, resulting in decreased SMYD3 transcription (Lin et al. 2019).

SMYD3 serum level and SMYD3 mRNA expression was found high as compared to the control group in hepatitis B virus (HBV) patients (Binh et al. 2020). SMYD3 suppression in bladder cancer (BC) resulted in decreased AKT/mTOR signaling pathway which directed bladder cancer cells to die (Wang et al. 2020).

The role of SMYD3 is shown in the expression and regulation of more than 80 genes that result in breast, colorectal, and hepatocellular carcinomas. While the inhibition of SMYD3 restores the normal function of genes and prevents proliferation (Alshiraihi et al. 2020). SMYD3 expression was also checked in gall bladder cancer and its presence was compared with the cholelithiasis group. SMYD3 expression was high in cancer patients than in cholelithiasis patients (Chandra et al. 2021). In hepatocellular carcinoma (HCC), tumor growth is halted by targeting SMYD3 via next generation antisense oligonucleotides (SMYD3-ASO) to modulate its mRNA level *in vivo* (Kontaki et al. 2021). In neointimal hyperplasia, SMYD3 binds with the parp16 promoter and enhanced the H3K4me3 to initiate host gene transcription which leads to UPR (unfolded protein response) and

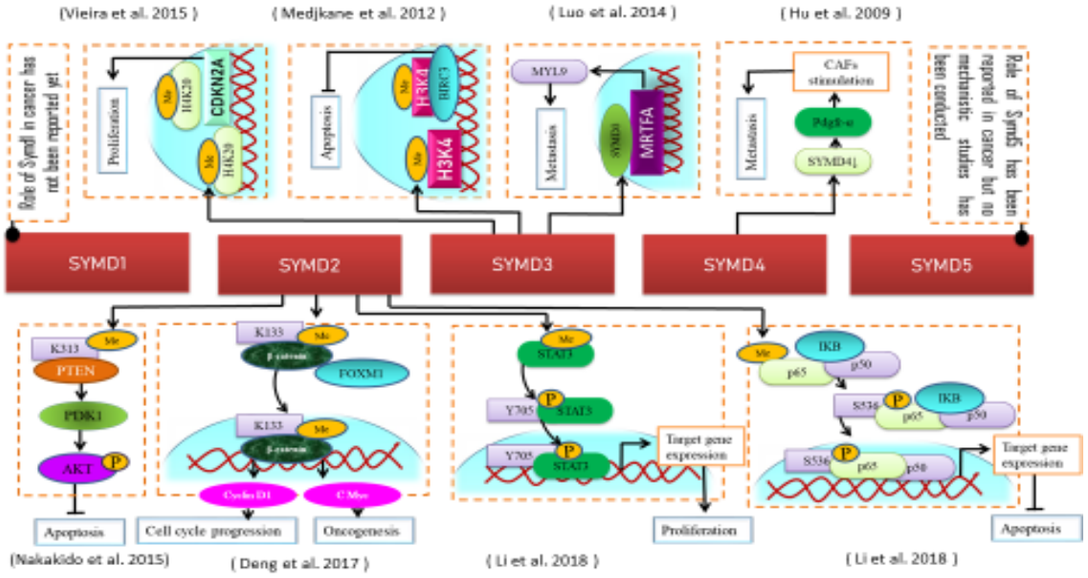

FIGURE 3. Representation of molecular mechanism of SMYD family-derived cancer development and progression

proliferation of smooth muscle cells (SMCs). Targeting of SMYD3 and parp16 reduces the ER stress (Yang et al. 2020). Dislodging of cancer cells from the primary source and formation of spheroids in ascites is required for the establishment of metastasis. Knockdown of SMYD3 inhibits metastasis in epithelial ovarian cancer (Lyu et al. 2020).

SMYD4 overexpression is associated with the reduced expression of platelet-derived growth factor receptor alpha (Pdgfr-α). Pdgfr-α is involved in the survival and development of breast tumors. By inhibiting the expression of Pdgfr-α, the proliferation of breast cancer can be significantly controlled (Figure 3). Thus, SMYD4 potentially acts as a tumor suppressor protein in breast cancer (Han et al. 2019). SMYD5 depletion in human colon cancer and lung cancer led to enhanced tumor growth while its up-regulation is associated with colon cancer and lung cancer (Kidder et al. 2017b).

Conclusion and Future Perspectives

To the best of our knowledge, there is no report on the role of SMYD1 in cancer development; thus, future studies should explore the expression and activity of SMYD1 in various tumors. Overexpression of SMYD2 and SMYD3 is associated with oncogenesis and metastasis through the modulation of different signaling molecules. SMYD2 and SMYD3 could serve as prognostic and diagnostic markers for cancer. While on the other hand, overexpression of SMYD4 is associated with tumor suppressor activity in breast cancer and could serve as a novel target for cancer therapy against breast tumors. SMYD5 depletion was found consistent with multiple human cancers. We anticipate that further mechanistic studies on various molecular signaling pathways derived by SMYD family members and their functional role as novel pharmacological drug targets should be done to provide better therapeutics to control carcinogenesis.

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