

Role and clinical significance of the DNA methylation of 14-3-3 σ in cancer (Review)

DANFENG HE^{1*}, YI HU^{2*} and DI NIU³

¹Department of Pharmacy, The Eighth Hospital of Wuhan, Wuhan, Hubei 430013, P.R. China;

²Department of Dermatology and Venereology, The Eighth Hospital of Wuhan, Wuhan, Hubei 430013, P.R. China;

³Department of Otolaryngology, The Eighth Hospital of Wuhan, Wuhan, Hubei 430013, P.R. China

Received April 14, 2025; Accepted August 4, 2025

DOI: 10.3892/ol.2025.15271

Abstract. The 14-3-3 family of proteins are phosphoserine/phosphothreonine-binding proteins. 14-3-3 σ (SFN) is a subtype of the 14-3-3 family and is widely present in all tissues and organs of eukaryotes. SFN can regulate various biological activities, such as cell growth, cell division, cell death and cell migration, by binding to different client proteins. These diverse biological functions make SFN a candidate protein that may play a notable role in the development of various diseases. However, its mechanism of action remains unclear, and its role in different diseases is still controversial. DNA methylation is an important epigenetic modification. DNA methylation, under the catalysis of DNA-related modification enzymes, affects gene expression regulation, including the silencing of tumor suppressor genes, oncogene activation, genome stability and the tumor microenvironment. In the present review, how SFN DNA methylation promotes or blocks the carcinogenesis and tumor progression of various cancer types is discussed. The potential clinical value of SFN as a tumor suppressor or cancer-promoting factor in different cancer types for precision cancer medicine is also highlighted.

1. Introduction

Cancer has long been a paramount concern in global public health, with the complexity of its pathogenesis extending far beyond initial understanding. At present, clinical treatments for cancer include radiotherapy, chemotherapy and some targeted drugs. However, these treatments still cannot effectively relieve pain or prolong the quality of life of the patient (1,2). Therefore, identifying effective therapeutic targets for precision medicine is of great significance.

The occurrence and development of cancer are inextricably linked to epigenetic modifications, which are influenced by environmental factors (3). Epigenetics has therefore emerged as a research focus. DNA methylation, a key epigenetic modification, refers to the addition of methyl groups to cytosine bases within CpG islands by DNA methyltransferases (DNMTs). CpG islands act as 'clusters of switch buttons' in gene promoter regions, dynamically regulating methylation similar to a light switch for gene expression. Methylation acts as an 'off button,' silencing tumor suppressor genes (4,5). Under normal physiological conditions, DNA methylation accurately regulates gene activation and repression, governing human organ development and contributing to cancer initiation. DNA methylation also plays an important role in cancer development and is often closely associated with the silencing of tumor suppressor genes. When the CpG islands in tumor suppressor genes are highly methylated, the expression of these genes decreases, allowing tumor cells to escape regulation and undergo rampant proliferation and metastasis, which seriously threatens human life and health (6,7). Therefore, in-depth study of the DNA methylation changes in various target genes in cancer not only helps to understand the mechanisms of cancer occurrence and development but is also expected to provide new biomarkers and therapeutic targets for early diagnosis, prognosis assessment and the targeted therapy of cancer (8).

The 14-3-3 gene family has been extensively studied in cancer research (9). The 14-3-3 protein comprises seven isoforms (β , ϵ , γ , η , σ , τ and ζ), each with distinct functions. This family regulates the activity, stability, subcellular localization and interactions of client proteins by mediating direct binding or promoting interactions with other signaling molecules. These regulatory processes govern key cellular pathways, including cell cycle control, apoptosis, proliferation

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Correspondence to: Professor Di Niu, Department of Otolaryngology, The Eighth Hospital of Wuhan, 1288 Jianshe Avenue, Jiangnan, Wuhan, Hubei 430013, P.R. China
E-mail: entniudi1223@126.com

*Contributed equally

Key words: 14-3-3 σ , epigenetics, DNA methylation, cancer

and programmed necrosis, often involving proteins such as p53, cell division cycle 25C (CDC25C) and Bad (9,10). 14-3-3 σ (SFN) is one of the numerous proteins closely associated with cancer. SFN is a dimeric small molecule protein present in all eukaryotes, particularly in epithelial cells (11). First identified in bovine brain tissue, SFN has since been detected in various human organs, including breasts, pancreas, stomach, colorectum, liver and kidneys (12). The diversity of SFN functions makes it a strong candidate as a therapeutic target for a variety of diseases. Drawing from the existing literature on SFN in the fields of epigenetics and cancer, the present review synthesizes the role of the DNA methylation of SFN in different malignancies, dissects its underlying mechanisms and evaluates its potential as a diagnostic or prognostic biomarker and therapeutic target.

2. Structure and biological function of SFN

The SFN protein is composed of 245 amino acids, with a molecular weight of ~28 kDa. Similar to other family members, SFN forms a typical 'U'-shaped dimer structure via an N- and C-terminal α -helix. Each monomer contains nine α -helices, among which helices α_3 , α_4 and α_8 form a conserved phosphopeptide-binding channel similar to a molecular locking structure, which recognize phosphorylated proteins through charge matching (13). Through its unique structure and multifunctional regulatory network, SFN modulates key biological processes, including the cell cycle, DNA damage repair, apoptosis and tumor suppression (14). In recent years, the loss of SFN expression in cancer due to epigenetic modifications (such as DNA methylation) has become a hot topic of research, providing important clues for understanding the tumorigenesis mechanism. The main functional regulatory networks of the SFN protein include: i) Cell cycle arrest and DNA damage response: SFN induces G2/M arrest by sequestering cell cycle regulators (such as CDK2/cyclin E complexes) upon DNA damage, preventing their nuclear translocation. For instance, in p53-dependent responses, SFN maintains G2 arrest by binding phosphorylated CDC25C and inhibiting CDK1 activation (15). ii) Apoptosis regulation and pro-survival function: SFN inhibits apoptosis by binding to the phosphorylated forms of pro-apoptotic proteins such as Bad and Bax, preventing their mitochondrial localization and subsequent cytochrome C release under unstressed conditions (16). However, under conditions of sustained DNA damage or oncogene activation, SFN protein degradation can release the inhibition of apoptotic signals and promote cell clearance (17). iii) Tumor suppressor function: SFN expression is silenced in a variety of epithelial tumors due to hypermethylation of promoter CpG islands. Silencing SFN leads to cell cycle checkpoint defects, genomic instability and apoptotic resistance, thereby promoting tumor progression (18). Restoration of SFN expression has been shown to significantly reduce tumor cell proliferation and metastasis by inhibiting CDK activity and suppressing epithelial-mesenchymal transition (EMT) pathways. The silencing of SFN expression is closely related to tumorigenesis, with promoter methylation being the main regulatory mechanism (19). SFN acts as a molecular scaffold integrating multiple signaling pathways. Studies of its structure-function relationship provide a new

direction for the development of targeted cancer therapies, such as demethylation drugs or phosphatase inhibitors. In the future, it will be necessary to further analyze its interaction network in different tissue microenvironments and explore its clinical application potential as a biomarker or therapeutic target.

3. Relationship between DNA methylation and cancer

Epigenetic modifications (such as DNA methylation, histone modification and non-coding RNA regulation) play a pivotal role in cancer development, with abnormal DNA methylation being one of the most common epigenetic changes in tumor cells. DNA methylation refers to the covalent addition of methyl groups to the 5' position of cytosine in CpG dinucleotides (forming 5-methylcytosine), catalyzed by DNMTs (20). A number of studies have shown that DNA methylation alters chromatin structure, DNA conformation, stability and protein-DNA interactions, thereby regulating gene expression (21-23). In normal cells, DNA methylation regulates gene function through mechanisms such as promoter CpG island hypermethylation and global genome hypomethylation. In cancer, DNA methylation patterns are significantly disrupted, often manifested as: i) Global hypomethylation, which promotes chromosome instability and proto-oncogene activation; and ii) local hypermethylation, which is concentrated in the promoter regions of tumor suppressor genes, resulting in the silencing of their expression (24,25). Different detection methods employ distinct thresholds for defining hypermethylation. For instance, in methylation-specific PCR (MSP), hypermethylation is identified when the intensity of the methylated band exceeds 50% of the unmethylated band. Pyrosequencing defines hypermethylation as either a single CpG site methylation rate >30% or a regional average >50%. Exceeding these hypermethylation thresholds represents the molecular mechanism for the transcriptional silencing of SFN, which correlates with malignancy in specific cancer types (26). DNA methylation affects genome stability and signaling pathway activity by regulating gene expression silencing, making it an important research direction in cancer diagnosis and treatment. Promoter CpG island hypermethylation acts as an epigenetic switch for tumor suppressor genes. DNA methylation forms dense chromatin structures by recruiting methyl-binding proteins (such as methyl-CpG binding protein 2) and histone deacetylases (HDACs), resulting in the transcriptional silencing of genes. For example, in breast and lung cancer, hypermethylation of the SFN promoter leads to defects in G2/M phase arrest and apoptosis resistance, significantly promoting tumor progression (27). O6-methylguanine-DNA methyltransferase is a DNA repair enzyme that protects genomic stability by clearing DNA damage induced by alkylating agents. Hypermethylation of its promoter region leads to gene silencing and loss of repair function, thereby increasing mutation accumulation and promoting tumorigenesis (28). In tumor cells, signal transducers and activators of transcription 5A, involved in cell proliferation and immune regulation, exhibits promoter hypermethylation that suppresses antitumor immune responses (such as T cell activation) and facilitates immune escape (29). The clinical value of DNA methylation is emerging in early diagnosis,

prognosis, therapeutic targeting, drug resistance modulation and immunotherapy synergy. Future challenges in cancer research include identifying actionable methylation targets, developing dynamic methylation regulation strategies, and constructing methylation-driven gene networks.

4. Abnormal methylation of SFN in cancer

Breast cancer (BC). BC is one of the most common malignant tumors, with an increasing incidence among tumors afflicting women. In 2018 alone, 268,670 new cases of BC were reported in the United States (30). As a heterogeneous disease influenced by both genetic and environmental factors, BC remains a significant health burden despite recent therapeutic advances. Current research efforts in personalized treatment (previously guided by disease severity) now focus on underlying biological mechanisms. The search for new targets and treatment strategies is important for patient survival and quality of life.

In recent years, DNA methylation is a major epigenetic modification, and SFN (a tumor suppressor gene) is frequently silenced by this modification in BC (31). Studies have shown that SFN DNA methylation frequency exceeds 90% in BC. Additionally, SFN hypermethylation has been observed in breast hyperplasia samples, while normal tissues remain unmethylated (as determined by MSP assay) (32,33). The downregulation of SFN has been detected in BC samples by serial analysis of gene expression, but no specific gene locus at the SFN site that could account for its downregulation was identified. After the treatment of BC cells with the DNMT inhibitor (DNMTI), 5-Azacytidine, SFN expression was re-detected and found to be activated, indicating that SFN underwent DNA methylation modification mediated by DNMTs. This suggests that DNA hypermethylation of SFN is closely related to the occurrence and development of BC (34). Another study grouped 77 patients with BC (no symptoms of disease) and 34 patients with metastatic BC (symptoms of disease), then DNA methylation in the serum samples from these two groups was detected. The DNA methylation level was higher in the BC group, indicating that SFN may serve as a predictor of BC progression (35). Therefore, SFN can be considered as a biomarker for screening metastatic BC, both in early detection and for monitoring subsequent treatment responses.

The specific mechanism by which SFN affects BC progression is as follows. A study has shown that SFN is a p53-dependent negative regulator of the cell cycle, blocking the G2/M phase by inhibiting the formation of the CDC2-cyclin B1 complex. However, under conditions of hypermethylation, the inactivation of SFN fails to block the cell cycle, thereby promoting cancer progression (36). The hypermethylation of the SFN gene promoter not only facilitates BC diagnosis but also drives the development of new treatments. Inhibiting DNA methylation of SFN is expected to become a potential therapeutic target for BC, and drug design targeting this mechanism could provide a valuable reference for the further clinical treatment of BC.

Lung cancer (LC). LC is the leading cause of cancer-related death worldwide and includes two main subtypes: Small cell LC and non-small cell LC (NSCLC) (37). NSCLC accounts for

~75% of all LC cases (38). Most patients with NSCLC present with advanced disease at diagnosis, as obvious symptoms often emerge in the mid-to-late stages. Current clinical treatments for LC involve a combination of surgery, radiotherapy and chemotherapy (39), yet these approaches fail to sufficiently improve the quality of life for patients with advanced disease. The development of early diagnostic markers and targeted therapeutics for LC remains a critical need. The upregulation of oncogenes and the silencing of tumor suppressor genes are the main causes of LC (40). A study has shown that the loss of SFN expression caused by DNA methylation is correlated with the carcinogenesis and prognosis of LC. SFN methylation has been detected in the serum of 167 patients with NSCLC, with methylation rates ranging from 64.6 to 100% (as determined by MSP assay). Thus, SFN could be used as a marker for the serological testing of NSCLC (41).

As for the specific mechanism of the involvement of SFN in LC progression, current studies mainly focus on cell cycle regulation and drug resistance. For instance, it has been shown that when SFN is hypermethylated and its expression is absent in LC, failure of cell cycle arrest leads to tumor cells escaping constraints on abnormal proliferation, thereby promoting LC progression (34). The therapeutic effect of chemotherapy drugs is often affected by drug resistance. In a cisplatin-treated NSCLC cell line (A549 cells), tripartite motif containing 25-mediated cisplatin resistance is primarily due to the downregulation of SFN, indicating that targeting SFN may be a potential strategy to reverse cisplatin resistance (42). However, rare contradictory reports exist regarding SFN expression in NSCLC. For instance, one study documented that high SFN expression, as a result of SFN hypomethylation, in orthotopic lung adenocarcinoma models is a key driver of early-stage malignant progression (43). The conflicting observations regarding SFN methylation in NSCLC fundamentally reflect the complexity of epigenetic regulation. The methylation status of the same gene across distinct genomic regions may drive tumorigenesis through divergent mechanisms, while sample heterogeneity, technical limitations and co-mutation backgrounds further exacerbate interpretational discrepancies. Future research should integrate spatial methylation profiling, single-cell multi-omics and clinical prospective cohorts to establish dynamic SFN methylation models, potentially uncovering novel epigenetic targets for precision stratified therapy in NSCLC.

Kidney cancer (KC). Worldwide, KC occurs more frequently in men than in women. Although there have been advances in the treatment and diagnosis of KC in recent years, KC remains one of the deadliest malignancies of the urinary system; its incidence is increasing, with an estimated 400,000 new cases per year, according to the most recent data from the World Health Organization. The global mortality rate is close to 175,000 deaths per year (44,45). Risk factors for KC include smoking, obesity, hypertension, poor diet and chronic kidney disease; acute/chronic kidney injury are often precursors of KC (46,47). At present, the main selected treatment for KC is based on the location of the tumor and the stage of the disease. These options can be divided into surgical and non-surgical treatments (48). While improved screening has increased patient survival, rising KC prevalence and stagnant cure rates

highlight the need for early diagnostic markers and targeted small-molecule inhibitors to prevent disease progression. Very little is known about the role of SFN in KC, especially regarding the effects of the DNA methylation of SFN. A study has shown abnormal expression of SFN in 15 (38%) canine KC cases, with a positive association between SFN expression and a significantly reduced survival time observed (11). In human KC, SFN is typically silenced by hypermethylation of its promoter. In a study of 31 patients with KC, methylation levels were found to increase progressively with the malignancy of renal cancer, from normal to cancerous kidney tissue. Among the 16 samples of renal cancer tissues, 87.5% had complete hypermethylation of SFN (as determined by MSP assay) (49). Additionally, SFN can also influence cell cycle regulation, enabling tumor cells to escape DNA damage caused by cisplatin and further promote tumor cell proliferation. These findings indicate that SFN expression, DNA methylation and the treatment of KC are closely related (50). Whether SFN can unlock the mystery of KC development or emerge as a key target for developing KC treatment strategies remains to be further explored by researchers.

Ovarian cancer (OC). OC is the second most common cause of cancer-related death in women worldwide, accounting for ~140,000 deaths annually. This high mortality rate is largely due to a lack of clear early diagnostic markers and delayed treatment (51). Most OC cases are definitively diagnosed at an advanced stage, with a high recurrence rate. The standard treatment for OC includes surgery and combination chemotherapy. In the early stages, the disease can be successfully treated with surgery alone. However, advanced stages require complex chemotherapy regimens, with drugs such as bevacizumab representing newer therapeutic options (52). While these targeted drugs have shown progress in improving the prognosis of OC, it remains the deadliest gynecological cancer in women. OC is generally divided into four main types: Epithelial OC, germ cell tumors, sex cord-stromal tumors and metastatic cancer (53). DNA methylation, histone modification and gene silencing mediated by non-coding RNAs are key processes in the development of OC and represent new targets for cancer detection and treatment (54). In OC, SFN is primarily inactivated by DNA methylation. A study evaluating SFN methylation as a prognostic marker found that it is associated with OC but unable to predict patient outcomes (MSP assay) (55). Hypermethylation of SFN promotes OC progression.

Nasopharyngeal cancer (NPC). NPC exhibits a significant geographical clustering, with ~70% of the world's new cases concentrated in Southeast Asia and East Asia. Among these regions, China has the highest incidence of NPC, accounting for 47% of all cases (56). The main risk factors for NPC include Epstein-Barr virus infection, genetic susceptibility, environmental factors and diet (57). Current prevention and control strategies focus on the following areas: Screening of high-risk groups, risk factor intervention and precision epidemiological studies. At present, only one study has shown that SFN promoter methylation occurs in primary NPC tumors, leading to decreased SFN expression; however, promoter hypermethylation has not been detected in normal

nasopharyngeal epithelial cells (MSP-detected methylation rate: 63%). This suggests that SFN expression may also serve as a prognostic marker for NPC (58). SFN is a downstream target gene of miR-597 and miR-675-5p. The downregulation of SFN by miR-597 and miR-675-5p can drive EMT and promote the migration and invasion of NPC (59,60). Additionally, SFN functions as a tumor suppressor *in vitro*, inhibiting NPC cell invasion through the SFN/EGFR/keratin-8 signaling axis (61). Collectively, these findings highlight the research value of SFN in NPC progression.

Squamous cell carcinoma (SCC). SCC can occur in multiple organs, including vulvar SCC (VSCC), esophageal SCC (ESCC) and oral SCC (OSCC), among others. SFN exhibits strong immune reactivity in SCCs from different parts of the body (62). VSCC is commonly found in young women, and the main treatment method is radical surgery. However, the postoperative recurrence rate is relatively high (63). Targeted therapy has attracted attention, driving researchers to identify tumor-associated factors and novel therapeutic markers. In a previous study, SFN CpG methylation was found in ~53% of cases (as determined by MSP assay) (64). In another study of 302 cases of VSCC, it was confirmed that the expression of SFN protein was downregulated, contributing to the development of the disease (63). This indicates that in VSCC, SFN is downregulated as a tumor suppressor through DNA methylation, thereby promoting the progression of the disease.

ESCC is one of the major types of esophageal cancer in Asia and one of the most aggressive gastrointestinal cancer types (65). The absence of symptoms in early ESCC leads to late detection of the disease and poor prognosis. SFN is downregulated in the early stage of ESCC, and this downregulation is associated with a shortened survival period, suggesting that SFN may serve as a biomarker for the early detection of ESCC (66). Abnormal expression of SFN affects the sensitivity of patients with ESCC to chemotherapy drugs, which is the main pathway through which SFN is involved in ESCC (67).

OSCC is a common cancer type and although it accounts for only 1.5% of malignant tumors, its incidence rate is increasing, which deserves attention. Existing studies have shown that SFN is strongly expressed in OSCC, and the survival time of patients with OSCC with high SFN expression is lower than that of patients with low SFN expression, which is different from the expression of SFN in other SCC types (68,69). Inhibition of CpG methylation of SFN may inhibit the progression of SCC.

Gallbladder cancer (GBC) and cholangiocarcinoma. GBC is one of the few cancer types in developing countries with a high mortality rate. The disease presents with almost no obvious symptoms in its early stage, leading to most patients being diagnosed in the middle or late stages, with a poor prognosis (70). Given the epithelial continuity between the gallbladder and bile duct, GBC and cholangiocarcinoma share similar oncogenic and metastatic mechanisms. Current effective treatments for GBC and cholangiocarcinoma include complete tumor resection and adjuvant therapy. However, the prognosis following surgical resection remains poor and incidence has not declined significantly over decades (71). Moreover, there has been little progress in treatment (72).

Therefore, it is urgent to identify therapeutic targets and develop targeted drug therapies. At present, there are few studies on the role and therapeutic significance of SFN dysregulation in cholangiocarcinoma. Epigenetics plays a key role in cancer development; however, there is still no clear understanding of SFN DNA methylation in cholangiocarcinoma and GBC (73,74). As a result, research into new biomarkers for these two cancer types has attracted significant interest from researchers. Only a small number of studies have focused on GBC. In a study, SFN DNA methylation was detected in 45 out of 50 GBC cases, and SFN expression was downregulated in patients with advanced GBC (as determined by MSP assay). These results suggest that low SFN expression, driven by DNA methylation, may promote the progression of GBC (75). Another study confirmed that SFN gene upregulation is associated with an improved prognosis, lower early cancer recurrence rates and reduced distant metastasis after resection (72). This suggests that detecting SFN DNA methylation or SFN expression may represent a new approach in the treatment of GBC. Inhibiting SFN DNA methylation may be a potential therapeutic strategy for GBC; however, the role of SFN in the treatment of cholangiocarcinoma remains unclear.

Pancreatic cancer (PC). PC ranks among the highest in terms of cancer mortality; >90% of patients with PC die due to a non-response to treatment, which is attributed to the lack of effective diagnostic and therapeutic strategies (76). Therefore, it is urgent to identify the pathogenic targets in PC. Whole-genome mapping has offered hope for improving PC management, enabling the development of histological/serological markers and immunotherapies. Through such efforts, SFN has emerged as a key player in PC diagnosis and treatment (77). By analyzing the methylation patterns of SFN, a high incidence of hypomethylation was observed in PC cell lines and primary PC tissues, suggesting that SFN hypomethylation is a common epigenetic event in PC. This study further showed that SFN protein expression is significantly increased in PC (MSP assay), and this elevated expression almost inversely correlated with patients' survival rates (76). This suggests a potential link to PC treatment failure. The mechanism of action of SFN in PC may involve resistance to treatment-induced apoptosis and G2/M cell cycle blockade, thereby causing resistance to anticancer drugs and obstructing their therapeutic effects. For example, gemcitabine is an important anticancer drug used in the treatment of various cancer types, including PC. SFN methylation is regulated by DNMT1, which is involved in the acquisition of gemcitabine resistance (78). Elevated SFN expression also results in resistance to mitoxantrone and doxorubicin, resistance to drug-induced apoptosis and resistance to the G2/M cell cycle blockade (79,80). Therefore, it is considered that SFN may serve as a prognostic indicator to predict the survival of patients with PC, as a biomarker to detect PC in its early stages and as a potential target for therapeutic drugs to guide the clinical treatment of patients. This approach is expected to bring hope in improving the lifespan of patients with PC.

Gastric cancer (GC). GC is a leading cause of cancer-related death worldwide, ranking as the fifth most common cancer and third deadliest globally (81). In China, GC is the second

most prevalent cancer and second leading cause of cancer mortality, with a dismal prognosis (82). Despite recent progress in surgical and pharmacological treatments, the survival rate for patients with GC in China remains very low (~40%) (83). Therefore, it is urgent to identify reliable therapeutic targets or develop small-molecule drugs to treat GC or alleviate the pain it causes. Genetic predisposition may play a key role in the development of GC (84). GC is a disease influenced by environmental epigenetic modifications and often presents with tumors that have a high frequency of abnormal CpG island methylation (85). A study found that abnormally elevated SFN expression is a biomarker of poor prognosis in GC and is associated with shortened survival time in patients with advanced GC (86). Additionally, an analysis of SFN expression in tumor samples from 157 patients who underwent GC resection showed that SFN expression was elevated in 48% of cases and was correlated with p53 expression (86). A study has shown that after SFN knockout, the proliferation and *in vitro* invasion abilities of GC cells are reduced. Additionally, serum levels of SFN are related to the therapeutic status of locally advanced cancer. These findings suggest that SFN plays an important role in the proliferation and metastasis of GC cells and may be a new target for the detection and prevention of GC (87). Another study has shown that SFN expression is increased in the gastric tissue of mice infected with *Helicobacter pylori*. Since *H. pylori* is a recognized factor in the development of GC, these results also indicate that high expression of SFN is closely related to GC (88). Regarding the role of SFN in GC, its effects vary across different stages of the disease. In some human cancer types, SFN is often inactivated due to methylation of the CpG islands, thereby losing its tumor suppressor function. This mechanism may play an important role in undifferentiated GC. The incidence of SFN hypermethylation was found to be 43% in primary GC and higher in poorly differentiated adenocarcinomas, suggesting that SFN hypermethylation is more prevalent in undifferentiated GC than in differentiated GC (as determined by bisulfite-bisulfite-single-strand conformation polymorphism assay (89). In differentiated GC, SFN interacts with p53 to stabilize and enhance its transcriptional activity (87). In another study of 60 GC samples, SFN expression was positive in 64% of cases, with positive staining observed in low, medium and highly differentiated GC cells. This suggests that SFN is involved in the proliferation of GC cells (90). Therefore, these findings indicate that SFN may be a promising target for the treatment of GC.

Colorectal cancer (CRC). Compared with normal colorectal tissues, SFN expression is significantly decreased in CRC tissues. Low expression of SFN is also significantly correlated with low survival rates in patients with CRC (91). SFN influences CRC progression through transcriptional programs regulated by interacting factors (such as Snail, c-JUN, Yes-associated protein 1 and Foxo1), which promote tumorigenesis and growth (92,93). Additionally, LIM and SH3 protein 1 (Lasp1) drives SFN-mediated CRC progression via PI3K/AKT pathway activation. A combination of low SFN and high Lasp1 expression is associated with a poorer overall survival in patients with CRC (94). Notably, there are different viewpoints. The latest research indicates that SFN functions as an oncogene in CRC and is associated with treatment

resistance (9,95). This suggests that SFN may have different effects in different regions of CRC, with upregulation of SFN in the invasive areas promoting tumor progression. Epigenetic silencing of the SFN gene through CpG hypermethylation has been reported in a variety of cancer types; however, this mechanism is not thought to apply to CRC, where SFN hypermethylation and inactivation are considered rare events (96). In invasive CRC zones, the SFN gene regulates cell cycle progression and tumor cell migration, promoting metastasis (9). The contradictory expression patterns of SFN may be attributed to spatial heterogeneity, immune cell exhaustion and dynamic epigenetic regulation. Similar discrepancies between gene expression and function have been documented in other organs and tissues. Cells in distinct anatomical regions not only exhibit divergent gene expression profiles but also display distinct epigenetic signatures and biological functions (29,97-99).

Other cancer types. SFN is also potentially linked to other cancer types, including glioma, endometrial cancer (EC) and prostate cancer (PCa) (34,100,101). In a study of 186 tumor samples from patients with different grades of glioma, higher SFN expression was associated with higher survival rates. SFN inactivation in glioma was also due to its DNA methylation (as determined by MSP assay). Compared with normal tissues, SFN expression in glioma was downregulated, suggesting that targeting SFN DNA methylation may offer a new opportunity to improve outcomes in patients with this disease (100,102).

SFN is expressed in the normal epithelial cells of most organs, and its epigenetic regulation is involved in controlling specific expression in normal cells and gene silencing in cancer cells (34). SFN is often absent in EC and PCa. A study has shown that CpG island methylation of SFN is closely related to its low expression (as determined by MSP assay) (55). Most EC cases are detected early due to vaginal bleeding and the recurrence rate is low after treatment (103). However, a study of 86 cases of EC and 46 cases of normal endometrial tissue found that SFN hypermethylation, low expression and inactivation in EC may be associated with recurrence (as determined by MSP assay) (104). The role of SFN in PCa has not been extensively studied. An early study has shown that SFN is highly expressed in normal prostate tissue, but its expression is significantly reduced in PCa (105). As a cell cycle regulator and tumor suppressor, SFN downregulation in PCa may promote tumorigenesis by bypassing DNA damage checkpoints-possibly independent of p53 (55,106). Detection of SFN CpG methylation could potentially be used for diagnostic and prognostic purposes in the future.

5. Tumor drug development targeting SFN and its epigenetic modifications

Over the past decade, significant progress has been made in the field of epigenetics research in cancer (107). Numerous studies have shown that epigenetic modifications play a crucial regulatory role in the dysregulation of tumor cells. The reversibility of epigenetic modifications offers a chance to rectify their abnormal alterations. Thus, employing epigenome-targeting agents to facilitate the normalization of aberrant methylation in cancer cells will serve as a key strategy for treating

cancer (20). While research in this area has advanced significantly in recent years, new challenges have arisen, including low drug specificity and toxic side effects. Hence, developing gene-specific targeted approaches holds notable scientific and clinical value.

SFN methylation causes chromatin structure to become more compact by recruiting methyl-binding proteins (such as methyl-CpG binding domain protein 2) and HDACs, ultimately inhibiting gene expression and blocking the binding of transcription factors (such as p53) (108,109). The DNA methylation of SFN has the dual potential of both being a therapeutic target and diagnostic marker. As a diagnostic and prognostic biomarker, the SFN methylation status is detectable in body fluids (such as plasma and urine), which provides the possibility for non-invasive cancer screening. For example, SFN methylation in the serum of patients with BC is positively correlated with tumor stage (110). In CRC, the SFN methylation level predicts resistance to 5-FU chemotherapy (111). This 5-FU predictive value not only contributes to the formulation of individualized treatment plans but also provides biomarkers for the efficacy monitoring of epigenetic targeted drugs. Additionally, SFN methylation is also an indicator of the response to demethylation therapy. SFN can work synergistically with other epigenetic drugs, such as HDAC inhibitors. For example, AR42 (OSU-HDAC42), an HDAC inhibitor, shows a negative correlation with SFN expression and collaborates to inhibit tumor growth (112). The current literature reports that DNMTIs (such as 5-Aza-CdR) can reverse SFN methylation and restore its expression, thereby delaying tumor progression. For instance, 5-Aza-CdR restores SFN expression, induces G2/M phase arrest and promotes apoptosis, enhancing radiosensitivity in osteosarcoma and BC cells (113,114). Additionally, 5-Aza-CdR-induced SFN upregulation triggers senescence in melanoma cells, inhibiting tumor progression (115). In EC, SFN-mediated G2/M arrest via 5-Aza-CdR exerts direct antitumor effects. Notably, immunotherapy is a cornerstone of cancer treatment. Recent studies have shown that DNMTIs can potentiate immunotherapy [such as programmed death-ligand 1 (PD-L1) blockade] (116,117). We therefore propose exploring novel molecules integrating methylation reversal and immunomodulation to reactivate SFN and enhance antitumor immunity, with promising translational potential. SFN and microenvironment therapy may also be related to tumor progression. For example, a hypoxic microenvironment contributes to tumor progression, while SFN inhibits metastasis and angiogenesis in CRC induced by tumor hypoxia through regulating hypoxia-inducible factor-1 α (HIF-1 α) (118). Hypoxic regions in gliomas can induce HIF-1 α activation, potentially influencing SFN expression (119). Therefore, SFN may also play a role in mediating responses to microenvironment-targeted therapies. Although DNMTIs can reverse SFN methylation, preclinical and clinical studies have revealed notable limitations: Systemic toxicity, risk of proto-oncogene activation, suboptimal targeting in solid tumors and off-target effects. Most notably, robust clinical evidence supporting their efficacy remains limited (120,121). To date, to the best of our knowledge, there have been no clinical trials directly targeting SFN methylation. In the existing studies, abnormal methylation of SFN has been observed in the majority of cancer types (Table I). Therefore, developing

Table I. Relationship between DNA methylation state and the expression level of 14-3-3σ in different cancer types.

Cancer type	DNA methylation state	Expression of 14-3-3σ	(Refs.)
Breast cancer	High	Low	(31)
Kidney cancer	High	Low	(49)
Ovarian cancer	High	Low	(55)
Nasopharyngeal cancer	High	Low	(58)
Vulvar squamous cell carcinoma	High	Low	(64)
Gallbladder cancer	High	Low	(75)
Glioma	High	Low	(100)
Gastric cancer (primary)	High	Low	(89)
Endometrial cancer	High	Low	(55)
Lung cancer	High/Low	Low/High	(41,43)
Pancreatic cancer	Low	High	(76)
Oral squamous cell carcinoma	/	High	(68)
Prostatic cancer	/	Low	(105)
Esophageal squamous cell carcinoma	/	Low	(66)
Colorectal cancer	/	Low	(91)

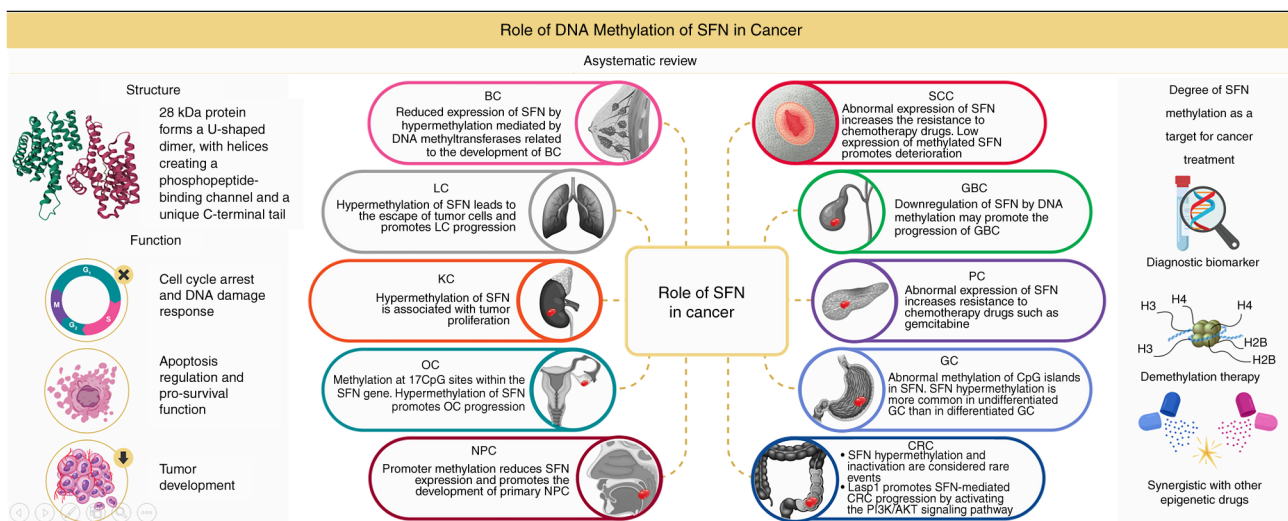


Figure 1. Role of DNA methylation of SFN in cancer. SFN, 14-3-3σ; BC, breast cancer; LC, lung cancer; KC, kidney cancer; OC, ovarian cancer; NPC, nasopharyngeal cancer; SCC, squamous cell carcinoma; GBC, gall bladder cancer; PC, pancreatic cancer; GC, gastric cancer; CRC, colorectal cancer.

antitumor drugs targeting SFN methylation is also a promising strategy. In a very small number of cancer types such as CRC, SFN exhibits a dual role. However, the underlying reasons for these differences are not clear, so further research is needed before conducting in-depth studies on specific targeted treatment strategies.

6. Conclusions and perspectives

The SFN protein is a core molecule in cell cycle regulation and the DNA damage response, and its functional inactivation is closely related to cancer initiation and progression. In the present review, the epigenetic regulation mechanisms and clinical significance of this protein in various tumor types were systematically summarized (Fig. 1 and Table SI). Silencing of SFN expression is not only caused by gene mutation or

deletion but also by abnormal hypermethylation of promoter CpG islands. This epigenetic silencing shows tissue-specific patterns in BC, PCa and LC and is positively associated with tumor aggressiveness. Although the degree of DNA methylation varies among different cancer types, SFN methylation leads to G2/M checkpoint failure and apoptotic resistance, thereby promoting genomic instability. There are also some specific mechanisms. These findings suggest the pivotal role of SFN in precision therapy.

At present, to the best of our knowledge, there are no clinical guidelines incorporating SFN methylation detection. Through a literature review, we conclude that SFN methylation, as a prognostic marker, holds certain clinical significance. SFN methylation precedes abnormal protein expression, in contrast to prostate-specific antigen/CA-125 that often serve as late-stage indicators. SFN methylation is prognostically

relevant across multiple cancer types (such breast and lung cancer), supporting the development of pan-cancer screening strategies. Additionally, SFN methylation directly mediates resistance to cisplatin/gemcitabine, a mechanism unaddressed by traditional markers. Thus, we consider that SFN methylation profiling holds significant clinical utility as a biomarker.

The existing challenges and breakthroughs highlight the need for in-depth mechanistic research. At present, to the best of our knowledge, the upstream driving factors of SFN methylation have not been fully analyzed. The synergistic mechanisms between methylation and other epigenetic modifications need to be clarified through multi-omics integration analyses. The technical bottleneck in clinical transformation lies in the insufficient sensitivity of existing detection technologies for low-abundance methylated circulating tumor DNA. At present, there is a lack of specific SFN methylation inhibitors, and methyltransferase inhibitors also have some unresolved clinical challenges. Systemic off-target effects of DNMTIs, such as decitabine, may result from the activation of proto-oncogenes. Therefore, further exploration of tumor-targeted delivery strategies is needed. There is room for innovation in therapeutic strategies. ‘Pulsed administration’ based on methylation dynamics may balance demethylation efficacy and toxicity. Combining epigenetic editing with immune checkpoint blocking may break tumor immune tolerance. With the development of single-cell epigenomics and spatial multi-omics techniques, it will be possible to analyze the role of SFN methylation in the evolution of tumor heterogeneity. We therefore propose that the development of bi-functional molecules with both methylation reversal and immune regulation functions, such as DNMT-PD-L1 dual-target inhibitors, may provide a new paradigm for overcoming therapeutic resistance. SFN is expected to become a signature target in the field of cancer epigenetic therapy in these new modalities. Other epigenetic modifications also need the attention of researchers, such as RNA modifications and histone modifications, which may drive cancer progression through synergistic or independent effects. In the future, research should focus on multi-modification interactions, dynamic regulation and precise intervention strategies, combined with technological innovation and clinical validation, to provide new targets and paradigms for cancer treatment.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

DH, YH wrote the main manuscript text and DN was involved in drafting the manuscript and revising it critically for important intellectual content. All authors read and approved the

final version of the 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. de Visser KE and Joyce JA: The evolving tumor microenvironment: From cancer initiation to metastatic outgrowth. *Cancer Cell* 41: 374-403, 2023.
2. Arafeh R, Shibue T, Dempster JM, Hahn WC and Vazquez F: The present and future of the cancer dependency map. *Nat Rev Cancer* 25: 59-73, 2025.
3. Mathers JC, Strathdee G and Relton CL: Induction of epigenetic alterations by dietary and other environmental factors. *Adv Genet* 71: 3-39, 2010.
4. Gupta MK, Peng H, Li Y and Xu CJ: The role of DNA methylation in personalized medicine for immune-related diseases. *Pharmacol Ther* 250: 108508, 2023.
5. Bergstedt J, Azzou SAK, Tsuo K, Jaquaniello A, Urrutia A, Rotival M, Lin DTS, MacIsaac JL, Kobor MS, Albert ML, *et al*: The immune factors driving DNA methylation variation in human blood. *Nat Commun* 13: 5895, 2022.
6. Zeng Y and Chen T: DNA methylation reprogramming during mammalian development. *Genes (Basel)* 10: 257, 2019.
7. Tolmacheva EN, Vasilyev SA and Lebedev IN: Aneuploidy and DNA methylation as mirrored features of early human embryo development. *Genes (Basel)* 11: 1084, 2020.
8. Klutstein M, Nejman D, Greenfield R and Cedar H: DNA methylation in cancer and aging. *Cancer Res* 76: 3446-3450, 2016.
9. Huang Y, Yang M and Huang W: 14-3-3 σ : A potential biomolecule for cancer therapy. *Clin Chim Acta* 511: 50-58, 2020.
10. Iwahori S, Umaña AC, Kalejta RF and Murata T: Serine 13 of the human cytomegalovirus viral cyclin-dependent kinase UL97 is required for regulatory protein 14-3-3 binding and UL97 stability. *J Biol Chem* 298: 102513, 2022.
11. Suárez-Bonnet A, Lara-García A, Stoll AL, Carvalho S and Priestnall SL: 14-3-3 σ protein expression in canine renal cell carcinomas. *Vet Pathol* 55: 233-240, 2018.
12. Gu Q, Cuevas E, Raymick J, Kanungo J and Sarkar S: Downregulation of 14-3-3 proteins in Alzheimer's disease. *Mol Neurobiol* 57: 32-40, 2020.
13. Obsil T, Ghirlando R, Klein DC, Ganguly S and Dyda F: Crystal structure of the 14-3-3 ζ :serotonin N-acetyltransferase complex. A role for scaffolding in enzyme regulation. *Cell* 105: 257-267, 2001.
14. Mhawech P: 14-3-3 proteins-an update. *Cell Res* 15: 228-236, 2005.
15. Hermeking H and Benzinger A: 14-3-3 Proteins in cell cycle regulation. *Semin Cancer Biol* 16: 183-192, 2006.
16. Henry RE, Andrysk Z, Paris R, Galbraith MD and Espinosa JM: A DR4:tBID axis drives the p53 apoptotic response by promoting oligomerization of poised BAX. *EMBO J* 31: 1266-1278, 2012.
17. Pozuelo-Rubio M: 14-3-3 Proteins are regulators of autophagy. *Cells* 1: 754-773, 2012.
18. Lodygin D and Hermeking H: The role of epigenetic inactivation of 14-3-3 σ in human cancer. *Cell Res* 15: 237-246, 2005.
19. Raychaudhuri K, Chaudhary N, Gurjar M, D'Souza R, Limzerwala J, Maddika S and Dalal SN: 14-3-3 σ gene loss leads to activation of the epithelial to mesenchymal transition due to the stabilization of c-Jun protein. *J Biol Chem* 291: 16068-16081, 2016.
20. Sun L, Zhang H and Gao P: Metabolic reprogramming and epigenetic modifications on the path to cancer. *Protein Cell* 13: 877-919, 2022.

21. Meng H, Cao Y, Qin J, Song X, Zhang Q, Shi Y and Cao L: DNA methylation, its mediators and genome integrity. *Int J Biol Sci* 11: 604-617, 2015.
22. Dai X, Ren T, Zhang Y and Nan N: Methylation multiplicity and its clinical values in cancer. *Expert Rev Mol Med* 23: e2, 2021.
23. Suo XG, Wang JN, Zhu Q, Zhang MM, Ge QL, Peng LJ, Wang YY, Ji ML, Ou YM, Yu JT, *et al*: METTL3 mediated m6A modification of HKDC1 promotes renal injury and inflammation in lead nephropathy. *Int J Biol Sci* 21: 3755-3775, 2025.
24. Nishiyama A and Nakanishi M: Navigating the DNA methylation landscape of cancer. *Trends Genet* 37: 1012-1027, 2021.
25. Kulis M and Esteller M: DNA methylation and cancer. *Adv Genet* 70: 27-56, 2010.
26. Ku JL, Jeon YK and Park JG: Methylation-specific PCR. *Methods Mol Biol* 791: 23-32, 2011.
27. Horie-Inoue K and Inoue S: Epigenetic and proteolytic inactivation of 14-3-3sigma in breast and prostate cancers. *Semin Cancer Biol* 16: 235-239, 2006.
28. Jayaprakash C, Radhakrishnan R, Ray S and Satyamoorthy K: Promoter methylation of MGMT in oral carcinoma: A population-based study and meta-analysis. *Arch Oral Biol* 80: 197-208, 2017.
29. Liang WW, Lu RJ, Jayasinghe RG, Foltz SM, Porta-Pardo E, Geffen Y, Wendl MC, Lazcano R, Kolodziejczak I, Song Y, *et al*: Integrative multi-omic cancer profiling reveals DNA methylation patterns associated with therapeutic vulnerability and cell-of-origin. *Cancer Cell* 41: 1567-1585.e7, 2023.
30. Barzaman K, Karami J, Zarei Z, Hosseinzadeh A, Kazemi MH, Moradi-Kalbolandi S, Safari E and Farahmand L: Breast cancer: Biology, biomarkers, and treatments. *Int Immunopharmacol* 84: 106535, 2020.
31. Gheibi A, Kazemi M, Baradaran A, Akbari M and Salehi M: Study of promoter methylation pattern of 14-3-3 sigma gene in normal and cancerous tissue of breast: A potential biomarker for detection of breast cancer in patients. *Adv Biomed Res* 1: 80, 2012.
32. Luo J, Feng J, Lu J, Wang Y, Tang X, Xie F and Li W: Aberrant methylation profile of 14-3-3 sigma and its reduced transcription/expression levels in Chinese sporadic female breast carcinogenesis. *Med Oncol* 27: 791-797, 2010.
33. Umrbricht CB, Evron E, Gabrielson E, Ferguson A, Marks J and Sukumar S: Hypermethylation of 14-3-3 sigma (stratifyn) is an early event in breast cancer. *Oncogene* 20: 3348-3353, 2001.
34. Lodygin D and Hermeking H: Epigenetic silencing of 14-3-3sigma in cancer. *Semin Cancer Biol* 16: 214-224, 2006.
35. Zurita M, Lara PC, del Moral R, Torres B, Linares-Fernández JL, Arrabal SR, Martínez-Galán J, Oliver FJ and Ruiz de Almodóvar JM: Hypermethylated 14-3-3-sigma and ESR1 gene promoters in serum as candidate biomarkers for the diagnosis and treatment efficacy of breast cancer metastasis. *BMC Cancer* 10: 217, 2010.
36. Ko S, Kim JY, Jeong J, Lee JE, Yang WI and Jung WH: The role and regulatory mechanism of 14-3-3 sigma in human breast cancer. *J Breast Cancer* 17: 207-218, 2014.
37. Thai AA, Solomon BJ, Sequist LV, Gainor JF and Heist RS: Lung cancer. *Lancet* 398: 535-554, 2021.
38. Petrella F, Rizzo S, Attili I, Passaro A, Zilli T, Martucci F, Bonomo L, Del Grande F, Casiraghi M, De Marinis F and Spaggiari L: Stage III non-small-cell lung cancer: An overview of treatment options. *Curr Oncol* 30: 3160-3175, 2023.
39. Giaccone G and He Y: Current knowledge of small cell lung cancer transformation from non-small cell lung cancer. *Semin Cancer Biol* 94: 1-10, 2023.
40. Ansari J, Shackelford RE and El-Osta H: Epigenetics in non-small cell lung cancer: From basics to therapeutics. *Transl Lung Cancer Res* 5: 155-171, 2016.
41. Raungrut P, Petjaroen P, Geater SL, Keerattichananont W, Phuakoloun M, Suwiwat S and Thongsuksai P: Methylation of 14-3-3σ gene and prognostic significance of 14-3-3σ expression in non-small cell lung cancer. *Oncol Lett* 14: 5257-5264, 2017.
42. Qin X, Qiu F and Zou Z: TRIM25 is associated with cisplatin resistance in non-small-cell lung carcinoma A549 cell line via downregulation of 14-3-3σ. *Biochem Biophys Res Commun* 493: 568-572, 2017.
43. Radhakrishnan VM, Jensen TJ, Cui H, Futscher BW and Martinez JD: Hypomethylation of the 14-3-3σ promoter leads to increased expression in non-small cell lung cancer. *Genes Chromosomes Cancer* 50: 830-836, 2011.
44. Bahadoram S, Davoodi M, Hassanzadeh S, Bahadoram M, Barahman M and Mafakher L: Renal cell carcinoma: An overview of the epidemiology, diagnosis, and treatment. *G Ital Nefrol* 39: 2022-vol3, 2022.
45. Cirillo L, Innocenti S and Becherucci F: Global epidemiology of kidney cancer. *Nephrol Dial Transplant* 39: 920-928, 2024.
46. Bukavina L, Bensalah K, Bray F, Carlo M, Challacombe B, Karam JA, Kassouf W, Mitchell T, Montironi R, O'Brien T, *et al*: Epidemiology of renal cell carcinoma: 2022 Update. *Eur Urol* 82: 529-542, 2022.
47. Chow WH, Dong LM and Devesa SS: Epidemiology and risk factors for kidney cancer. *Nat Rev Urol* 7: 245-257, 2010.
48. Hancock SB and Georgiades CS: Kidney cancer. *Cancer J* 22: 387-392, 2016.
49. Liang S, Xu Y, Shen G, Zhao X, Zhou J, Li X, Gong F, Ling B, Fang L, Huang C and Wei Y: Gene expression and methylation status of 14-3-3sigma in human renal carcinoma tissues. *IUBMB Life* 60: 534-540, 2008.
50. Vasko R, Mueller GA, von Jaschke AK, Asif AR and Dihazi H: Impact of cisplatin administration on protein expression levels in renal cell carcinoma: A proteomic analysis. *Eur J Pharmacol* 670: 50-57, 2011.
51. Penny SM: Ovarian cancer: An overview. *Radiol Technol* 91: 561-575, 2020.
52. Konstantinopoulos PA and Matulonis UA: Clinical and translational advances in ovarian cancer therapy. *Nat Cancer* 4: 1239-1257, 2023.
53. O'Shea AS: Clinical staging of ovarian cancer. *Methods Mol Biol* 2424: 3-10, 2022.
54. Thi HV, Ngo AD and Chu DT: Epigenetic regulation in ovarian cancer. *Int Rev Cell Mol Biol* 387: 77-98, 2024.
55. Mhaweche P, Benz A, Cerato C, Greloz V, Assaly M, Desmond JC, Koeffler HP, Lodygin D, Hermeking H, Herrmann F and Schwaller J: Downregulation of 14-3-3sigma in ovary, prostate and endometrial carcinomas is associated with CpG island methylation. *Mod Pathol* 18: 340-348, 2005.
56. Dee EC, Wang S, Ho FDV, Patel RR, Lapen K, Wu Y, Yang F, Patel TA, Feliciano EJG, McBride SM and Lee NY: Nasopharynx cancer in the United States: Racial and ethnic disparities in stage at presentation. *Laryngoscope* 135: 1113-1119, 2025.
57. Su ZY, Siak PY, Lwin YY and Cheah SC: Epidemiology of nasopharyngeal carcinoma: Current insights and future outlook. *Cancer Metastasis Rev* 43: 919-939, 2024.
58. Chan SY, To KF, Leung SF, Yip WW, Mak MK, Chung GT and Lo KW: 14-3-3 sigma expression as a prognostic marker in undifferentiated nasopharyngeal carcinoma. *Oncol Rep* 24: 949-955, 2010.
59. Xie L, Jiang T, Cheng A, Zhang T, Huang P, Li P, Wen G, Lei F, Huang Y, Tang X, *et al*: MiR-597 targeting 14-3-3σ enhances cellular invasion and EMT in nasopharyngeal carcinoma cells. *Curr Mol Pharmacol* 12: 105-114, 2019.
60. Zhang T, Lei F, Jiang T, Xie L, Huang P, Li P, Huang Y, Tang X, Gong J, Lin Y, *et al*: H19/miR-675-5p targeting SFN enhances the invasion and metastasis of nasopharyngeal cancer cells. *Curr Mol Pharmacol* 12: 324-333, 2019.
61. Huang WG, Cheng AL, Chen ZC, Peng F, Zhang PF, Li MY, Li F, Li JL, Li C, Yi H, *et al*: Targeted proteomic analysis of 14-3-3sigma in nasopharyngeal carcinoma. *Int J Biochem Cell Biol* 42: 137-147, 2010.
62. Nakajima T, Shimooka H, Weixa P, Segawa A, Motegi A, Jian Z, Masuda N, Ide M, Sano T, Oyama T, *et al*: Immunohistochemical demonstration of 14-3-3 sigma protein in normal human tissues and lung cancers, and the preponderance of its strong expression in epithelial cells of squamous cell lineage. *Pathol Int* 53: 353-360, 2003.
63. Wang Z, Tropè CG, Suo Z, Trøen G, Yang G, Nesland JM and Holm R: The clinicopathological and prognostic impact of 14-3-3 sigma expression on vulvar squamous cell carcinomas. *BMC Cancer* 8: 308, 2008.
64. Gasco M, Sullivan A, Repellin C, Brooks L, Farrell PJ, Tidy JA, Dunne B, Gusterson B, Evans DJ and Crook T: Coincident inactivation of 14-3-3sigma and p16INK4a is an early event in vulvar squamous neoplasia. *Oncogene* 21: 1876-1881, 2002.
65. Okumura H, Kita Y, Yokomakura N, Uchikado Y, Setoyama T, Sakurai H, Omoto I, Matsumoto M, Owaki T, Ishigami S and Natsugoe S: Nuclear expression of 14-3-3 sigma is related to prognosis in patients with esophageal squamous cell carcinoma. *Anticancer Res* 30: 5175-5179, 2010.
66. Qi YJ, Wang M, Liu RM, Wei H, Chao WX, Zhang T, Lou Q, Li XM, Ma J, Zhu H, *et al*: Downregulation of 14-3-3σ correlates with multistage carcinogenesis and poor prognosis of esophageal squamous cell carcinoma. *PLoS One* 9: e95386, 2014.
67. Lai KKY, Chan KT, Choi MY, Wang HK, Fung EYM, Lam HY, Tan W, Tung LN, Tong DKH, Sun RWY, *et al*: 14-3-3σ confers cisplatin resistance in esophageal squamous cell carcinoma cells via regulating DNA repair molecules. *Tumour Biol* 37: 2127-2136, 2016.

68. Hayashi E, Kuramitsu Y, Fujimoto M, Zhang X, Tanaka T, Uchida K, Fukuda T, Furumoto H, Ueyama Y and Nakamura K: Proteomic profiling of differential display analysis for human oral squamous cell carcinoma: 14-3-3 σ protein is upregulated in human oral squamous cell carcinoma and dependent on the differentiation level. *Proteomics Clin Appl* 3: 1338-1347, 2009.
69. Laimer K, Blassnig N, Spizzo G, Kloss F, Rasse M, Obrist P, Schäfer G, Perathoner A, Margreiter R and Amberger A: Prognostic significance of 14-3-3sigma expression in oral squamous cell carcinoma (OSCC). *Oral Oncol* 45: 127-134, 2009.
70. Wang S, Zheng R, Li J, Zeng H, Li L, Chen R, Sun K, Han B, Bray F, Wei W and He J: Global, regional, and national lifetime risks of developing and dying from gastrointestinal cancers in 185 countries: A population-based systematic analysis of GLOBOCAN. *Lancet Gastroenterol Hepatol* 9: 229-237, 2024.
71. Hu Z, Wang X, Zhang X, Sun W and Mao J: An analysis of the global burden of gallbladder and biliary tract cancer attributable to high BMI in 204 countries and territories: 1990-2021. *Front Nutr* 11: 1521770, 2024.
72. Sirivatanauskorn V, Dumronggittigule W, Dulnee B, Srisawat C, Sirivatanauskorn Y, Pongpaibul A, Masaratana P, Somboonyosdech C, Sripinitchai S, Kositamongkol P, *et al*: Role of stratifin (14-3-3 sigma) in adenocarcinoma of gallbladder: A novel prognostic biomarker. *Surg Oncol* 32: 57-62, 2020.
73. Sharma A, Sharma KL, Gupta A, Yadav A and Kumar A: Gallbladder cancer epidemiology, pathogenesis and molecular genetics: Recent update. *World J Gastroenterol* 23: 3978-3998, 2017.
74. Nakaoka T, Saito Y and Saito H: Aberrant DNA methylation as a biomarker and a therapeutic target of cholangiocarcinoma. *Int J Mol Sci* 18: 1111, 2017.
75. Singh TD, Gupta S, Shrivastav BR and Tiwari PK: Epigenetic profiling of gallbladder cancer and gall stone diseases: Evaluation of role of tumour associated genes. *Gene* 576: 743-752, 2016.
76. Li Z, Dong Z, Myer D, Yip-Schneider M, Liu J, Cui P, Schmidt CM and Zhang JT: Role of 14-3-3 σ in poor prognosis and in radiation and drug resistance of human pancreatic cancers. *BMC Cancer* 10: 598, 2010.
77. Rodriguez JA, Li M, Yao Q, Chen C and Fisher WE: Gene overexpression in pancreatic adenocarcinoma: Diagnostic and therapeutic implications. *World J Surg* 29: 297-305, 2005.
78. Qin L, Dong Z and Zhang JT: Reversible epigenetic regulation of 14-3-3 σ expression in acquired gemcitabine resistance by uhrf1 and DNA methyltransferase 1. *Mol Pharmacol* 86: 561-569, 2014.
79. Dim DC, Jiang F, Qiu Q, Li T, Darwin P, Rodgers WH and Peng HQ: The usefulness of S100P, mesothelin, fascin, prostate stem cell antigen, and 14-3-3 sigma in diagnosing pancreatic adenocarcinoma in cytological specimens obtained by endoscopic ultrasound guided fine-needle aspiration. *Diagn Cytopathol* 42: 193-199, 2014.
80. Qin L, Dong Z and Zhang JT: 14-3-3 σ regulation of and interaction with YAP1 in acquired gemcitabine resistance via promoting ribonucleotide reductase expression. *Oncotarget* 7: 17726-17736, 2016.
81. Venneman K, Huybrechts I, Gunter MJ, Vandendaele L, Herrero R and Van Herck K: The epidemiology of Helicobacter pylori infection in Europe and the impact of lifestyle on its natural evolution toward stomach cancer after infection: A systematic review. *Helicobacter* 23: e12483, 2018.
82. Zhu Y, Jeong S, Wu M, Zhou JY, Jin ZY, Han RQ, Yang J, Zhang XF, Wang XS, Liu AM, *et al*: Index-based dietary patterns and stomach cancer in a Chinese population. *Eur J Cancer Prev* 30: 448-456, 2021.
83. Zhang Y, Li Y, Lin C, Ding J, Liao G and Tang B: Aberrant upregulation of 14-3-3 σ and EZH2 expression serves as an inferior prognostic biomarker for hepatocellular carcinoma. *PLoS One* 9: e107251, 2014.
84. Kim W, Kidambi T, Lin J and Idos G: Genetic syndromes associated with gastric cancer. *Gastrointest Endosc Clin N Am* 32: 147-162, 2022.
85. Chen YZ, Guo F, Sun HW, Kong HR, Dai SJ, Huang SH, Zhu WW, Yang WJ and Zhou MT: Association between XPG polymorphisms and stomach cancer susceptibility in a Chinese population. *J Cell Mol Med* 20: 903-908, 2016.
86. Muhlmann G, Ofner D, Zitt M, Müller HM, Maier H, Moser P, Schmid KW, Zitt M and Amberger A: 14-3-3 Sigma and p53 expression in gastric cancer and its clinical applications. *Dis Markers* 29: 21-29, 2010.
87. Jung JY, Koh SA, Lee KH and Kim JR: 14-3-3 Sigma protein contributes to hepatocyte growth factor-mediated cell proliferation and invasion via matrix metalloproteinase-1 regulation in human gastric cancer. *Anticancer Res* 42: 519-530, 2022.
88. Nagappan A, Park HS, Park KI, Hong GE, Yumnam S, Lee HJ, Kim MK, Kim EH, Lee WS, Lee WJ, *et al*: Helicobacter pylori infection combined with DENA revealed altered expression of p53 and 14-3-3 isoforms in Gulo-/- mice. *Chem Biol Interact* 206: 143-152, 2013.
89. Suzuki H, Itoh F, Toyota M, Kikuchi T, Kakiuchi H and Imai K: Inactivation of the 14-3-3 sigma gene is associated with 5' CpG island hypermethylation in human cancers. *Cancer Res* 60: 4353-4357, 2000.
90. Li YL, Liu L, Xiao Y, Zeng T and Zeng C: 14-3-3 σ is an independent prognostic biomarker for gastric cancer and is associated with apoptosis and proliferation in gastric cancer. *Oncol Lett* 9: 290-294, 2015.
91. Young GM, Radhakrishnan VM, Centuori SM, Gomes CJ and Martinez JD: Comparative analysis of 14-3-3 isoform expression and epigenetic alterations in colorectal cancer. *BMC Cancer* 15: 826, 2015.
92. Winter M, Rokavec M and Hermeking H: 14-3-3 σ functions as an intestinal tumor suppressor. *Cancer Res* 81: 3621-3634, 2021.
93. Shao Q, Duong TN, Park I, Orr LM and Nomura DK: Targeted protein localization by covalent 14-3-3 recruitment. *J Am Chem Soc* 146: 24788-24799, 2024.
94. Shao Z, Cai Y, Xu L, Yao X, Shi J, Zhang F, Luo Y, Zheng K, Liu J, Deng F, *et al*: Loss of the 14-3-3 σ is essential for LASP1-mediated colorectal cancer progression via activating PI3K/AKT signaling pathway. *Sci Rep* 6: 25631, 2016.
95. Lonare A, Raychaudhuri K, Shah S, Madhu G, Sachdeva A, Basu S, Thorat R, Gupta S and Dalal SN: 14-3-3 σ restricts YY1 to the cytoplasm, promoting therapy resistance, and tumor progression in colorectal cancer. *Int J Cancer* 156: 623-637, 2025.
96. Ide M, Nakajima T, Asao T and Kuwano H: Inactivation of 14-3-3sigma by hypermethylation is a rare event in colorectal cancers and its expression may correlate with cell cycle maintenance at the invasion front. *Cancer Lett* 207: 241-249, 2004.
97. Ben-Moshe S and Itzkovitz S: Spatial heterogeneity in the mammalian liver. *Nat Rev Gastroenterol Hepatol* 16: 395-410, 2019.
98. Postwala H, Shah Y, Parekh PS and Chorawala MR: Unveiling the genetic and epigenetic landscape of colorectal cancer: New insights into pathogenic pathways. *Med Oncol* 40: 334, 2023.
99. Klemm SL, Shipony Z and Greenleaf WJ: Chromatin accessibility and the regulatory epigenome. *Nat Rev Genet* 20: 207-220, 2019.
100. Deng J, Gao G, Wang L, Wang T, Yu J and Zhao Z: Stratifin expression is a novel prognostic factor in human gliomas. *Pathol Res Pract* 207: 674-679, 2011.
101. Ito K, Suzuki T, Akahira J, Sakuma M, Saitou S, Okamoto S, Niikura H, Okamura K, Yaegashi N, Sasano H and Inoue S: 14-3-3sigma in endometrial cancer-a possible prognostic marker in early-stage cancer. *Clin Cancer Res* 11: 7384-7391, 2005.
102. Liang S, Shen G, Liu Q, Xu Y, Zhou L, Xiao S, Xu Z, Gong F, You C and Wei Y: Isoform-specific expression and characterization of 14-3-3 proteins in human glioma tissues discovered by stable isotope labeling with amino acids in cell culture-based proteomic analysis. *Proteomics Clin Appl* 3: 743-753, 2009.
103. Iavazzo C, Gkegkes ID and Vrachnis N: Early recurrence of early stage endometrioid endometrial carcinoma: Possible etiologic pathways and management options. *Maturitas* 78: 155-159, 2014.
104. Nakayama H, Sano T, Motegi A, Oyama T and Nakajima T: Increasing 14-3-3 sigma expression with declining estrogen receptor alpha and estrogen-responsive finger protein expression defines malignant progression of endometrial carcinoma. *Pathol Int* 55: 707-715, 2005.
105. Evren S, Dermen A, Lockwood G, Fleshner N and Sweet J: mTOR-RAPTOR and 14-3-3 σ immunohistochemical expression in high grade prostatic intraepithelial neoplasia and prostatic adenocarcinomas: A tissue microarray study. *J Clin Pathol* 64: 683-688, 2011.
106. Lodygin D, Diebold J and Hermeking H: Prostate cancer is characterized by epigenetic silencing of 14-3-3sigma expression. *Oncogene* 23: 9034-9041, 2004.
107. Chu DT, Ngo AD and Wu CC: Epigenetics in cancer development, diagnosis and therapy. *Prog Mol Biol Transl Sci* 198: 73-92, 2023.

108. Devailly G, Grandin M, Perriaud L, Mathot P, Delcros JG, Bidet Y, Morel AP, Bignon JY, Puisieux A, Mehlen P and Dante R: Dynamics of MBD2 deposition across methylated DNA regions during malignant transformation of human mammary epithelial cells. *Nucleic Acids Res* 43: 5838-5854, 2015.
109. Feng L, Pan M, Sun J, Lu H, Shen Q, Zhang S, Jiang T, Liu L, Jin W, Chen Y, *et al*: Histone deacetylase 3 inhibits expression of PUMA in gastric cancer cells. *J Mol Med (Berl)* 91: 49-58, 2013.
110. Ye M, Huang T, Ying Y, Li J, Yang P, Ni C, Zhou C and Chen S: Detection of 14-3-3 sigma (σ) promoter methylation as a noninvasive biomarker using blood samples for breast cancer diagnosis. *Oncotarget* 8: 9230-9242, 2017.
111. Sakai A, Otani M, Miyamoto A, Yoshida H, Furuya E and Tanigawa N: Identification of phosphorylated serine-15 and -82 residues of HSPB1 in 5-fluorouracil-resistant colorectal cancer cells by proteomics. *J Proteomics* 75: 806-818, 2012.
112. Balch C, Naegeli K, Nam S, Ballard B, Hyslop A, Melki C, Reilly E, Hur MW and Nephew KP: A unique histone deacetylase inhibitor alters microRNA expression and signal transduction in chemoresistant ovarian cancer cells. *Cancer Biol Ther* 13: 681-693, 2012.
113. Li Y, Geng P, Jiang W, Wang Y, Yao J, Lin X, Liu J, Huang L, Su B and Chen H: Enhancement of radiosensitivity by 5-Aza-CdR through activation of G2/M checkpoint response and apoptosis in osteosarcoma cells. *Tumour Biol* 35: 4831-4839, 2014.
114. Wang L, Zhang Y, Li R, Chen Y, Pan X, Li G, Dai F and Yang J: 5-aza-2'-Deoxycytidine enhances the radiosensitivity of breast cancer cells. *Cancer Biother Radiopharm* 28: 34-44, 2013.
115. Schultz J, Ibrahim SM, Vera J and Kunz M: 14-3-3sigma gene silencing during melanoma progression and its role in cell cycle control and cellular senescence. *Mol Cancer* 8: 53, 2009.
116. Yang Z, Chu B, Tu Y, Li L, Chen D, Huang S, Huang W, Fan W, Li Q, Zhang C, *et al*: Dual inhibitors of DNMT and HDAC remodels the immune microenvironment of colorectal cancer and enhances the efficacy of anti-PD-L1 therapy. *Pharmacol Res* 206: 107271, 2024.
117. Huang W, Zhu Q, Shi Z, Tu Y, Li Q, Zheng W, Yuan Z, Li L, Zu X, Hao Y, *et al*: Dual inhibitors of DNMT and HDAC induce viral mimicry to induce antitumour immunity in breast cancer. *Cell Death Discov* 10: 143, 2024.
118. Liu S, Guo R, Xu H, Yang J, Luo H, Yeung SJ, Li K, Lee MH and Yang R: 14-3-3 σ -NEDD4L axis promotes ubiquitination and degradation of HIF-1 α in colorectal cancer. *Cell Rep* 42: 112870, 2023.
119. Bai J, Zhao Y, Shi K, Fan Y, Ha Y, Chen Y, Luo B, Lu Y, Jie W and Shen Z: HIF-1 α -mediated LAMC1 overexpression is an unfavorable predictor of prognosis for glioma patients: Evidence from pan-cancer analysis and validation experiments. *J Transl Med* 22: 391, 2024.
120. Parker WB and Thottassery JV: 5-Aza-4'-thio-2'-deoxycytidine, a new orally bioavailable nontoxic 'best-in-class': DNA methyltransferase 1-depleting agent in clinical development. *J Pharmacol Exp Ther* 379: 211-222, 2021.
121. Traube FR, Brás NF, Roos WP, Sommermann CC, Diehl T, Mayer RJ, Ofial AR, Müller M, Zipse H and Carell T: Epigenetic anti-cancer treatment with a stabilized carbocyclic decitabine analogue. *Chemistry* 28: e202200640, 2022.



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