

Staphylococcal nuclease and tudor domain-containing protein 1: An emerging therapeutic target in cancer (Review)

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Abstract. Staphylococcal nuclease and tudor domain-containing protein 1 (SND1) is an oncoprotein that is overexpressed in various types of cancer, including breast, prostate, lung, colorectal and hepatocellular carcinomas, as well as malignant gliomas, especially in cases of advanced and metastatic cancer. SND1 has a significant role in tumour development via its interactions with RNA and partner proteins. SND1 functions as a nuclease within the RNA-induced silencing complex, where small RNAs (such as siRNAs or miRNAs) bind to ribonucleoproteins to mediate RNA interference and silencing of tumour suppressor genes. Metadherin (MTDH) has been identified as an important protein partner of SND1, and the SND1-MTDH interaction has been reported to drive tumour initiation, metastasis and immune evasion in various types of cancer. Therefore, SND1 is considered as a crucial target for cancer therapy, and multiple approaches have been explored to inhibit its nuclease activity or disrupt its interaction with MTDH. In the present review, both the oncogenic functions of SND1 and therapeutic strategies that target either its binding to RNA or its interaction with MTDH are investigated.

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1. Introduction

Cancer remains a leading cause of death globally, with nearly 20 million new cases, and 9.7 million cancer-associated deaths, reported in 2022 (1). However, despite the significant progress that has been made in cancer prevention and early detection, cancer continues to pose a major global health challenge due to its complexity and the diverse mechanisms driving tumorigenesis (2). Major obstacles to successful cancer treatment include multidrug resistance, metastasis and immune evasion. Cancer cells employ various mechanisms that cause either the upregulation or downregulation of specific genes, often rendering current therapeutic strategies ineffective (2). Moreover, even though several of the molecular mechanisms underlying carcinogenesis have been elucidated, numerous factors contributing to cancer progression remain unclear. Therefore, identifying novel cancer-associated proteins is of great clinical significance (2).

Staphylococcal nuclease and tudor domain-containing protein 1 (SND1) protein is a component of the RNA-induced silencing complex (RISC), and is currently recognized as an oncogenic protein. SND1 fulfils a crucial role in gene expression by regulating transcription, RNA splicing, RNA editing and stability, as well as being involved in RNA interference (RNAi) (2). Recent analyses explored the oncogenic role of SND1 across 33 different types of tumour by utilizing data from The Cancer Genome Atlas and Gene Expression Omnibus (3). Elevated levels of SND1 expression have been identified in the majority of cancers, namely 74% cases of hepatocellular carcinoma (HCC), 69.9% cases of colon cancer, 97% cases of prostate cancer and 53.5% cases of breast cancer. SND1 in these types of cancers have been reported to exert a significant role in promoting tumour development, progression, immune cell infiltration and metastasis (2,3).

Wang *et al* (4) identified SND1 as a novel endoplasmic reticulum (ER)-associated protein that facilitates the targeting of the nascent major histocompatibility complex I (MHC-I) heavy chain to the ER-associated degradation (ERAD) pathway. In their study, downregulation of MHC-I on the tumour cell

surface was shown to result in impaired recognition of cancer cells by CD8⁺ T cells. This process was observed in 20-60% of common solid tumours, including lung, breast, prostate and bladder cancers. Reduced expression of MHC-I on the surface of tumour cells helps to create an immune microenvironment that favours cancer growth, allowing tumour cells to evade the immune response (4).

Other research has shown that SND1 interacts with several proteins, including metadherin (MTDH), to exert its oncogenic effects. MTDH, also known as astrocyte elevated gene-1 (AEG-1), is another oncogene that has been implicated in the development of several types of cancer, including breast, prostate, liver, lung, glioma, cervical, bladder, kidney, gastric, colorectal and head and neck cancers (5). In non-cancerous tissues, MTDH is primarily found in the nucleus, although it is translocated to the cytoplasm and cell membrane in malignant tissues, where it engages with critical oncogenic pathways. These pathways include NF- κ B, PI3K/AKT, MAPK and Wnt/ β -catenin as signalling components, all of which contribute to tumour growth and survival (5). Among the various protein partners of SND1, MTDH has been shown to perform a key role in regulating essential processes, including cellular transformation, cancer metastasis and resistance to multiple drugs (6).

The discovery of the MTDH-SND1 protein complex crystal structure (Fig. 1) has paved the way for drug development targeting this crucial protein-protein interaction (PPI) (7). Multiple studies have focused on developing peptide and small-molecule inhibitors to target SND1 with the aim of interrupting its RNA binding and SND1-MTDH interaction (8-12). It has been reported that treating the MDA-MB-231 breast cancer cell line with the small molecule suramin blocked the interaction between SND1 and RNA, thereby resulting in increased levels of the microRNA (miRNA or miR), miR -1-3p. This, in turn, enhanced the chemosensitivity of MDA-MB-231 cells to the Bcl-2 inhibitor navitoclax (9). In addition, silencing of SND1 enhanced cell death induced by cisplatin in breast cancer cells by inhibiting SND1 binding to the 3'-untranslated region (3'-UTR) of glutathione peroxidase 4 (GPX4) mRNA.

Numerous peptides also have been reported to disrupt the MTDH-SND1 interaction and to exhibit antitumour potential in multiple cancers without non-specific toxicity (10). Shen *et al* (11,12) reported the first series of MTDH-SND1 PPI small-molecule inhibitors, and resolved the co-crystal structures of the inhibitors C26-A2 and C26-A6 with SND1. Both C26-A2 and C26-A6 exhibit strong binding affinity for SND1, effectively disrupting the SND1-MTDH interaction. These compounds also inhibited tumour growth and metastasis, thereby leading to an improved chemotherapy response, and have proven to be effective in preclinical models of triple-negative breast cancer (TNBC). The discovery of these small-molecule inhibitors has stimulated the search for more potent inhibitors of the SND1-MTDH protein interaction. Molecular dynamics (MD) simulation-based virtual screening revealed L5 as the top candidate, demonstrating a binding affinity to SND1 with a dissociation constant (K_d) of 2.64 μ M (13). Additionally, this compound exhibited significant anti-proliferative effects in MDA-MB-231 breast cancer cells (13). Another study reported three

promising drug molecules based on virtual screening analyses (BAS_00381028, BAS_00327287, and BAS_01293454), which also exhibited strong binding interactions and a stable binding conformation with the SND1 enzyme (14).

The present review offers an in-depth summary of the current insights into the oncogenic role and clinical relevance of SND1 and its key partners in cancer development and progression. Furthermore, various therapeutic approaches targeting either SND1 alone or its interaction with MTDH are discussed, and future directions that have been proposed for developing potential SND1 inhibitors to prevent cancer are described.

2. Protein structure of SND1

Human SND1 is a protein comprising 910 amino acids. It has four similar staphylococcal nuclease (SN) domains and a fifth domain that combines a Tudor domain and part of a nuclease (TSN) domain (Fig. 2) (15). The SN domains in SND1 are 20-30% similar to those in SN proteins. SNs break down DNA and RNA with the help of calcium. However, the SN domains in SND1 lack the essential amino acid residues required for calcium-dependent catalytic activity. These domains belong to the oligonucleotide/oligosaccharide-binding (OB)-fold superfamily, which encompasses a variety of nucleic acid-binding proteins. Although numerous OB-fold proteins do not exhibit catalytic activity, they do perform other functions, including transcriptional regulation, chromatin modification and DNA repair (16,17). Tudor domains, which are highly conserved across eukaryotes and have been widely studied in *Drosophila*, have roles in DNA binding, epigenetic regulation, gene expression, and in the formation of small nuclear ribonucleoproteins, miRNAs and siRNAs (18). The presence of SN and Tudor domains together provides the SND1 protein with a diverse range of multifunctional properties (Fig. 2).

3. Interacting protein partners of SND1, and their impact on cancer-associated cellular functions

SND1 is a scaffold protein known to interact with different protein partners, including cellular myelocytomatosis viral oncogene homolog (c-Myb), phosphoglycerate mutase family member 5 (PGAM5), protein arginine methyltransferase 5 (PRMT5) and MTDH, to modulate cellular functions, including cell proliferation, cell signaling and cell differentiation. c-Myb is a key factor involved in the differentiation and growth of immature hematopoietic stem cells, and SND1 has been reported to interact with c-Myb in previous studies (19-21). c-Myb and SND1 were both shown to be overexpressed in MCF-7 breast cancer cells, with the SND1 promoter serving as a key site for c-Myb binding. This interaction helps to maintain a positive regulatory loop between c-Myb and SND1, thereby contributing to breast cancer tumorigenesis (22). In addition, the interaction of SND1 with PRMT5 was shown to contribute to oncogenesis in HCC (21). Another study by Liang *et al* (20) demonstrated that localization of SND1 to the mitochondria promoted PGAM5-mediated mitophagy, which, in turn, promoted increased cell proliferation in three HCC cell lines (Hep3B, PLC and HepG2); moreover, tumour growth in an HCC (Hep3B) xenograft model that recruited BALB/c

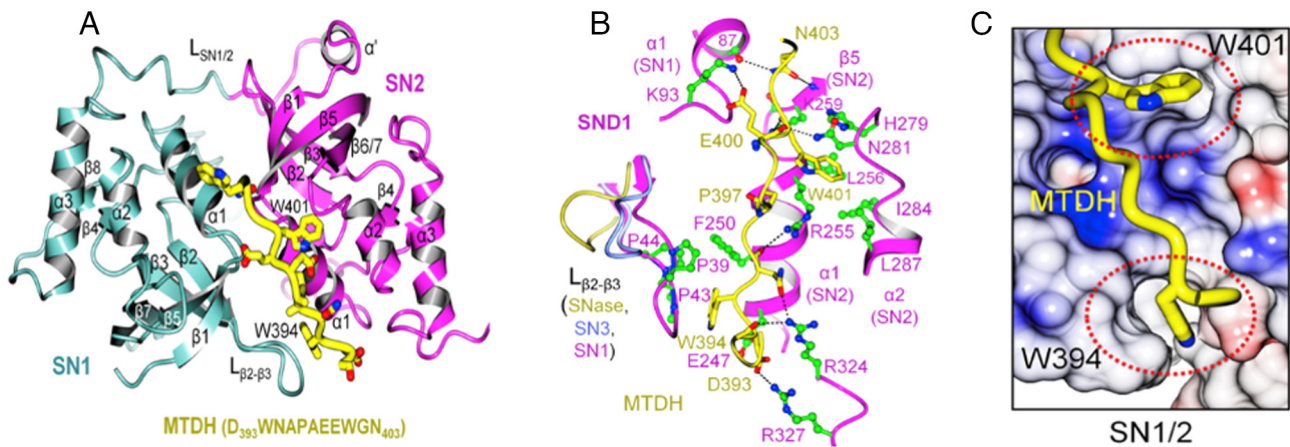


Figure 1. Overall structure of the MTDH-SND1 complex. (A) Two perpendicular views are shown. The SN1 and SN2 domains of SND1 are colored cyan and magenta, respectively, while MTDH is colored yellow. SND1 is displayed as (A) a ribbon diagram and (C) surface representation. MTDH is depicted using a worm (backbone) and cylinder (side chain) representation. (B) A close-up stereo view of the MTDH-SND1 interface. (C) The MTDH peptide (D393WNAPAEWGN403) occupies the shallow groove between SN1 and SN2 domains, with the two tryptophan residues, W394 and W401, forming extensive hydrophobic contacts with two well-defined hydrophobic pockets in SND1 (7). MTDH, metadherin; SND1, staphylococcal nuclease and tudor domain-containing protein 1.

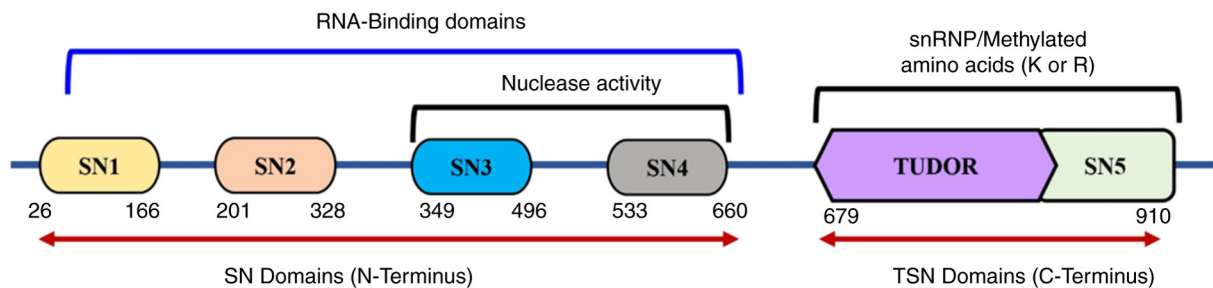


Figure 2. SND1 domains and related functions. SND1, staphylococcal nuclease and tudor domain-containing protein 1.

nude mice was shown to be enhanced. SND1 was also found to interact with long non-coding RNAs (lncRNAs) such as transcription factor 7 (TCF7) and SND1-intronic transcript 1 (IT1), and this interaction participated in the progression of cancer and metabolic disorders (23). Previous studies have identified lncTCF7 as a novel protein partner for SND1, which is essential for the recruitment of the SWI/SNF chromatin remodelling complex to TCF7 promoter region. This interaction activates the expression of TCF7, which enhances the Wnt signalling pathway, thereby promoting cancer progression (24,25). SND1-IT1 is a well-characterized lncRNA located on chromosome 7 at position 7q32.1, which has been reported to be significantly upregulated in gastric cancer tissues (26). It has been shown that SND1-IT1 regulates the expression of collagen, type IV, $\alpha 1$ (COL4A1) by competing with miR-124, a tumour suppressor gene. This competition was found to facilitate TGF- $\beta 1$ -induced epithelial-to-mesenchymal (EMT) transition through the miR-124/COL4A1 axis in HGC-27 gastric cancer cells (26).

Numerous studies have highlighted the critical role of PPIs between MTDH and its partner proteins in various types of cancer (27-31). The interaction between SND1 and MTDH has also been shown to lead to immune evasion, as well as tumour initiation and metastasis in breast cancer, lung cancer and colorectal cancer (9).

4. Molecular functions of SND1 and its role in cancer

Role of SND1 in RNA-associated processes and gene regulation. Previous studies have shown that SND1 acts as a nuclease within the RISC, where it associates with small RNAs (such as siRNAs or miRNAs) and ribonucleoproteins to facilitate RNAi-mediated gene silencing (32,33). MTDH has been shown to interact with SND1 and other proteins to form a stable RISC complex (2). The overexpression of either MTDH or SND1 has been associated with the downregulation of several tumour suppressor genes that are targeted by onco-miRNAs. These include genes such as PTEN (targeted by miR-221 and miR-21), CDKN1C (also known as p57; targeted by miR-221), CDKN1A (also known as p21; targeted by miR-106b), SPRY2 (targeted by miR-21) and TGFBR2 (targeted by miR-9) (34). The adenomatous polyposis coli (APC) is essential for maintaining cell polarity and cell-cell adhesion, primarily through regulation of the placement of E-cadherin at the plasma membrane. In colon cancer, reduced levels of APC have been linked with the overexpression of SND1, which has been shown to modulate the expression of APC and other cancer-associated genes. Loss of APC was shown to disrupt the degradation of β -catenin via the proteasome, resulting in its stabilization (33). This stabilized β -catenin subsequently activates the transcription of Wnt

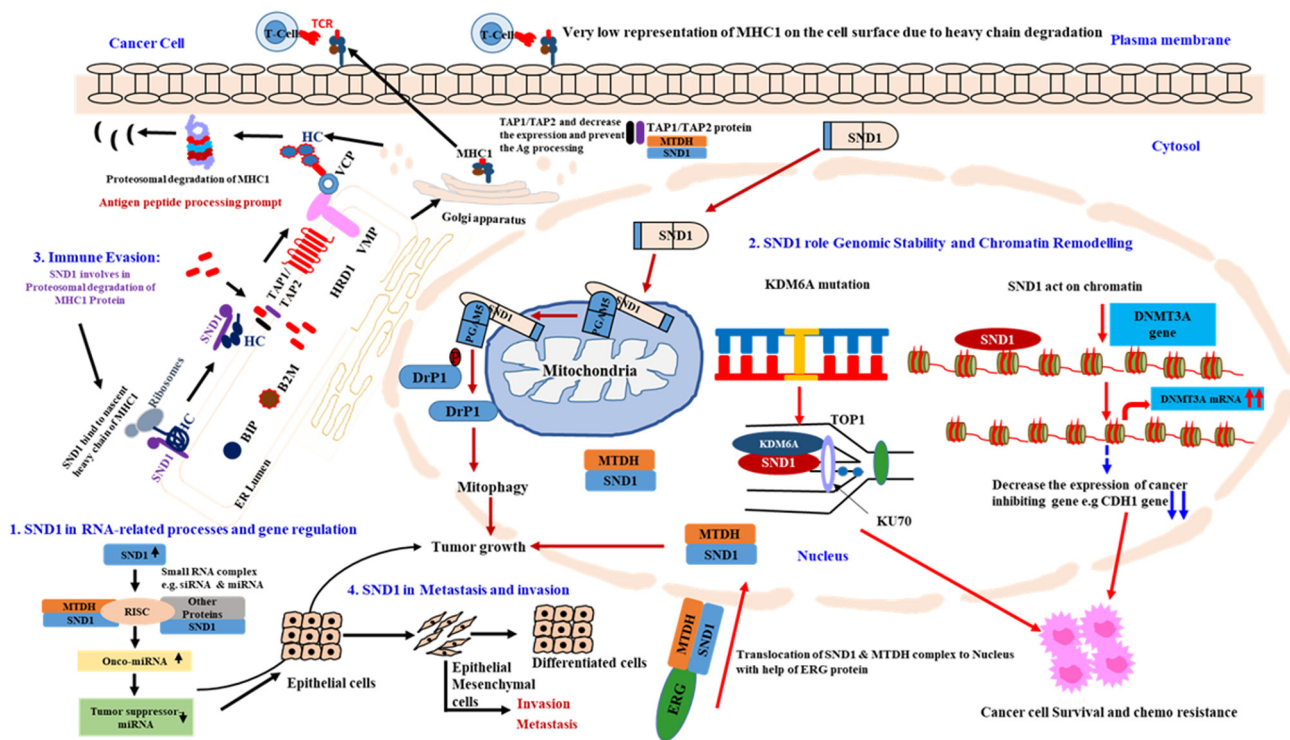


Figure 3. Overall mechanism and role of SND1 in cancer: (1) SND1 role in RNA-related processing and gene regulation. (2) SND1 role in genomic stability and chromatin remodelling. (3) SND1 role in immune evasion and (4) SND1 role in metastasis and invasion. SND1, staphylococcal nuclease and tudor domain-containing protein 1; MTDH, metadherin; MHC1, major histocompatibility complex I; DrP1, dynamamin-related protein 1; KDM6A, lysine demethylase 6A; ERG, ETS transcription factor.

pathway target genes, and this process acts a key driver of tumour progression (35). RNA splicing is a vital process in pre-mRNA maturation, during which non-coding intronic regions are excised, and the exonic regions are joined, thereby producing a mature functional mRNA. The spliceosome complex consists of five dynamic small ribonucleoproteins (U1, U2, U4/U6 and U5), along with several non-coding RNAs. SND1 interacts with U5 spliceosomal RNA, a key component of ribonucleoproteins, which facilitates the formation of the spliceosome. This interaction affects the levels of different splice variants, including the production of a variant form of CD44, which thereby increases the motility and invasive behaviour of prostate cancer cells (36).

Furthermore, SND1 has been shown to augment the stability of certain mRNAs, and this is essential for cellular stress responses (37). Under oxidative stress conditions, SND1 and angiotensin II type 1 receptor (AT1R) mRNA are found to co-localize within the stress granules, where SND1 has a critical role in facilitating efficient protein-RNA complex formation (37). Collectively, these findings have demonstrated that SND1 may increase the stability of specific oncogenic mRNAs.

Genomic stability and chromatin remodelling. Maintaining genomic stability is essential for cell survival and the prevention of cancer. Eukaryotes have evolved complex and tightly regulated mechanisms which maintain genomic stability, thereby ensuring accurate cell division and precise DNA replication (38). Recently, the association between the expression of lysine demethylase 6A (KDM6A) and the DNA damage pathway in normal tissues has been established. The

expression of KDM6A was found to be associated with several key proteins involved in DNA repair, including RAD50, nibrin 1, meiotic recombination 11, DNA polymerase Eta and X-ray repair cross complementing 6 (Ku70). Furthermore, it was demonstrated that the interaction between KDM6A and SND1 facilitates the recruitment of DNA repair factors such as Ku70 and replication protein A to newly synthesized DNA. This study by Wu *et al* (38) also established that an increased interaction between KDM6A and SND1 contributes to chemo-resistance in oesophageal squamous cell carcinoma. Another study revealed that SND1 interacts strongly with another chromatin regulator, namely DNA (cytosine-5)-methyltransferase 3A (DNMT3A) (39). DNMT3A exerts a critical role in the *de novo* methylation of CpG islands in chromatin and also targets hemimethylated DNA for further methylation (40). Furthermore, the overexpression of DNMT3A has been shown to induce aberrant DNA methylation, oncogene activation and the silencing of tumour suppressor genes, resulting in genomic instability and oncogenesis (41-42). SND1 was found to promote the transcription of DNMT3A by functioning as a chromatin architectural regulator (39). Elevated levels of DNMT3A expression lead to gene methylation and the transcriptional silencing of CDH1, thereby facilitating the metastasis of TNBC (Fig. 3) (39). SND1 has also been found to promote malignant glioma phenotypes by epigenetically inducing topological chromatin interactions that activate downstream Ras homolog family member A (RhoA) transcription. RhoA, in turn, influences the expression of key cell cycle regulators, including cyclin D1, cyclin E1, cyclin-dependent kinase 4 (CDK4) and cyclin-dependent kinase inhibitor 1B,

which accelerate the transition from the G₁ to the S phase of the cell cycle, thereby boosting the proliferation of glioma cells (43). In these studies, strong evidence has been provided to suggest that SND1 functions as a novel chromatin architectural modifier, and that it is potentially a promising prognostic marker for cancer and its treatment.

Role of SND1 in tumour immune escape. Tumours are able to evade immune system attacks through various mechanisms, including limiting antigen recognition, suppressing immune responses and promoting T-cell exhaustion (44). One of the key factors contributing to tumour immune escape is the reduced ability of CD8⁺ T cells to recognize tumour cells due to defects in the surface expression of MHC-I molecules. This defect has been observed in 20-60% of common solid tumours, including melanoma and cancers of the lung, breast, kidney, prostate and bladder (5,45,46).

A previous study revealed that SND1 promotes tumour cell immune escape via inhibiting the MHC-I antigen presentation signalling pathway, which leads to an impaired CD8⁺ T cell-mediated antitumour response in the tumour microenvironment (4). This effect is mediated through the downregulation of the MHC-I heavy chain molecule, facilitated by the ERAD pathway. ERAD is responsible for targeting misfolded proteins in the ER for ubiquitination and subsequent degradation by the proteasome. SND1 can capture the nascent MHC-I heavy chain and direct it to the ERAD-mediated proteasomal degradation pathway (4). This process disrupts the proper assembly of the heavy chain with β 2-microglobulin (β 2m) in the ER lumen, thereby impairing antigen presentation. Consequently, tumour cells become less susceptible to immune surveillance, and exhibit a diminished capacity to present antigens to cytotoxic CD8⁺ T cells. Additionally, a decreased expression of the transporter associated with antigen processing (TAP) protein is considered to be one of the key mechanisms of tumour immune evasion (47,48). Two subtypes of the TAP protein (TAP1 and TAP2) have been shown to be mainly associated with other proteins for the purpose of loading the peptides to the MHC class I- β 2m complex, and the antigens are subsequently presented on the cell surface (49-52). A recent study identified that SND1 interacts with TAP1/2 proteins to destabilize the complex with the assistance of the MTDH protein, and this process resulted in a decrease in the expression of TAP1/2 in tumour cells, which were thereby able to evade immune surveillance (12) (Fig. 3). Furthermore, SND1 knockdown in tumour cells led to an increase in TAP1/2 expression levels, which subsequently resulted in an enhanced tumour antigen presentation to CD8⁺ T cells (12). A potential association between immune cell infiltration levels and SND1 gene expression across various cancer types has also been identified through extensive analysis. A negative correlation was observed between CD8⁺ T-cell infiltration and SND1 expression, whereas a positive correlation was identified between cancer-associated fibroblasts and SND1 expression in the majority of different cancer types (3). Recently, epigallocatechin has been reported to block the interaction between SND1-MHC-I, resulting in enhanced MHC-I presentation and an increased CD8⁺ T-cell response within the tumour microenvironment in a xenograft model (53).

Role of SND1 in cancer metastasis, angiogenesis and anti-apoptosis. SND1 performs a crucial role in promoting metastasis and angiogenesis by activating EMT, cell invasion and cell migration, which are essential for its oncogenic function. In the case of colorectal cancer, SND1 interacts with the histone chaperone and transcription elongation factor SPT6 to co-control the expression of human telomerase reverse transcriptase (hTERT) and cell proliferation (54). Briefly, SPT6 and SND1 work in concert to promote cancer progression by targeting hTERT (54). Similarly, in HCC, SND1 has been shown to promote angiogenesis by activating a linear signalling pathway that comprises NF- κ B, miRNA-221, angiogenin and C-X-C motif chemokine ligand 16, and it also promotes EMT via the AT1R and TGF β signalling pathway (55-57).

Mitochondrial dysfunction is a major contributor towards numerous metabolic diseases, including neurodegenerative disorders, aging and cancer. A recent study (20) demonstrated that SND1 promotes liver cancer through PGAM5-mediated dephosphorylation of serine-637 of dynamin-related protein 1 (DRP1) and mitophagy, as shown in Fig. 3. This study revealed that SND1 enhances mitophagy by promoting the interaction between PGAM5 and DRP1 (20). In another study, Shen *et al* (11) employed immunoprecipitation of MTDH followed by mass spectrometric analysis to identify SND1 as a primary interacting partner of MTDH. Their findings revealed that the MTDH-SND1 complex has a critical role in the progression and metastasis of late-stage breast cancer. Furthermore, a different study (58) revealed a functional interaction between SND1 and the ETS transcription factor (ERG) protein in prostate cancer. In prostate organoid models, wild-type SND1 cells exhibited ERG-driven increases in colony size, an effect that was found to be completely eliminated by knockdown of SND1. Collectively, these results suggested that SND1 is a key mediator of ERG-driven organoid growth in prostate epithelial cells.

Role of SND1 in cancer drug-resistance. Drug resistance presents a major challenge in treating cancer, given that it results in cancer recurrence, cancer dissemination, and death. Transporters, oncogenes, tumour suppressor genes, mitochondrial alteration, DNA repair, autophagy and EMT are involved in the molecular mechanisms underlying multidrug resistance (59-61). The overexpression of SND1 has been demonstrated to be involved in the chemoresistance of various types of cancer. A recent study (62) showed that SND1 binds to the 3'-UTR of GPX4, thereby providing stability, and that this fulfilled an essential role in the development of chemoresistance against cisplatin in bladder cancer. Silencing of SND1 was also found to reverse the cisplatin resistance and trigger cell death via ferroptosis. SND1 has also been shown to be overexpressed in HCC (63), and may be a contributing factor towards the development of resistance in HCC. Another recent study (64) established that the silencing of SND1 expression caused an increase in the protein expression of organic anion transporter 2, which stimulated 5-fluorouracil to inhibit proliferation of the HCC PLC/PRF5 cell line, and PLC/PRF5 cell growth in a xenograft model. Furthermore, Fu *et al* (65) investigated the potential role of SND1 in radio-resistance in cervical cancer. SND1 has been shown to contribute to radio-resistance through preferential activation

of the ATM pathway by affecting cell-cycle checkpoints and DNA repair to promote cell survival upon the cells receiving DNA damage (65-68). Similarly, another recently published study (69) showed that non-small cell lung cancer (NSCLC) is highly resistant to chemo- or radiation therapy due to crosstalk between SND1 and the programmed cell death-4 protein. Chemosensitivity of NSCLC cells to different chemotherapeutic drugs was also found to be increased following the silencing of SND1 (69). Given its consistent overexpression across various types of cancer, SND1 holds promise as a biomarker in the future for the early detection and progression monitoring of malignancies.

5. SND1 as a critical biomarker for cancer diagnosis.

TNBC is a highly invasive form of cancer and ~46% of cases progress to distant metastasis (70-74). In a study involving 144 patients with breast cancer (aged 18-75 years), all were diagnosed with invasive ductal carcinoma with no distant metastasis at the time of surgery; they received standard adjuvant therapy following surgery and the patients were followed for 10 years (75). That study by Gu *et al* (75) investigated the correlation between SND1 protein expression and the clinicopathological features of patients using Chi-square analysis. The results obtained demonstrated that SND1 expression was positively associated with a larger tumour size (>2 cm), higher clinical TNM stage, lymph node metastasis and poorer prognosis. Additionally, high SND1 expression was associated with shorter overall survival and disease-free survival rates compared with patients with low SND1 expression, highlighting its potential as a prognostic biomarker. A different study (43) examined SND1 expression in 58 TNBC tissue samples using immunohistochemical staining and the prognostic relevance of SND1 was evaluated using Kaplan-Meier survival analysis. The results obtained from that study confirmed that overexpression of SND1 was positively associated with increased metastasis and poor prognosis in patients with TNBC.

In addition to breast cancer, SND1 has also been implicated as a potential biomarker in prostate cancer. In a cohort of 174 prostate cancer patients (stratified by age <70 or ≥70 years, PSA levels >20 ng/ml and pathological stages pT2 or pT3), SND1 expression was shown to be significantly correlated with the histological tumour grade, suggesting its utility in improving prostate cancer diagnosis (21). In terms of the underlying mechanism, SND1 regulates the alternative splicing of CD44, thereby contributing to the progression of prostate cancer through the inclusion of pro-oncogenic variant exon v5 (76).

Furthermore, in colon cancer, the co-expression of SND1 and MTDH has been shown to be associated with more advanced disease. Immunohistochemical analysis of 196 cases of colon cancer [with patients stratified according to their age (<60 vs. ≥60 years)] revealed that the cytoplasmic expression levels of both SND1 and MTDH were positively correlated with tumour grade and disease progression and negatively correlated with post-operative survival (77). These findings suggested that the expression of SND1 and/or MTDH may serve as important biomarkers for tumour aggressiveness, metastatic potential and patient prognosis in various types of cancer.

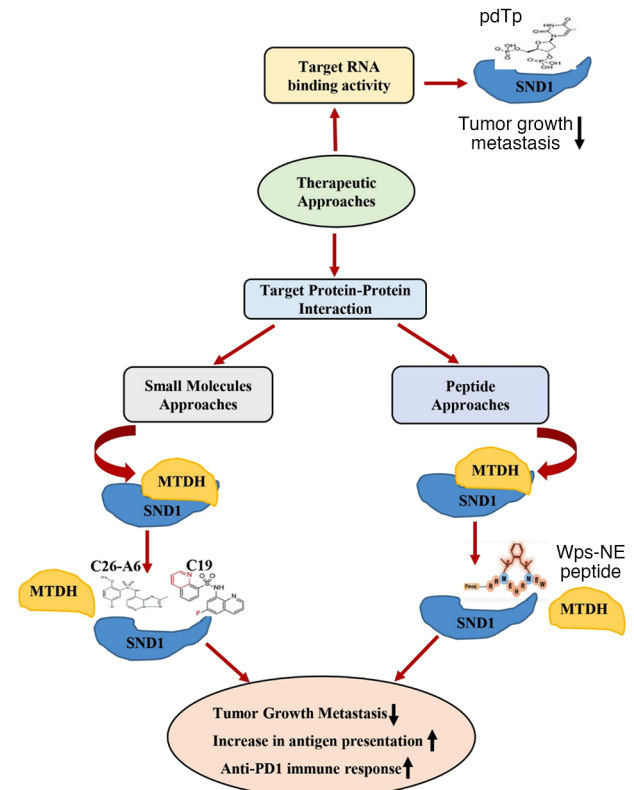


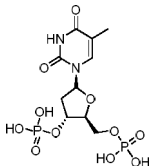
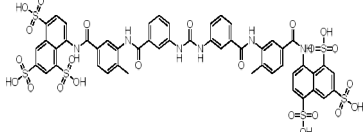
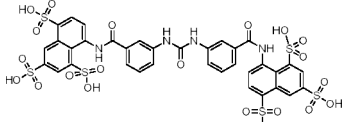
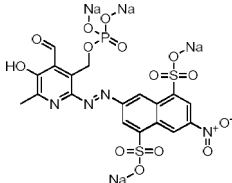
Figure 4. Therapeutic approaches for targeting of SND1. SND1, staphylococcal nuclease and tudor domain-containing protein 1; MTDH, metadherin; pdTp, 3',5'-deoxythymidine bisphosphate.

6. Therapeutic strategies to target SND1

SND1 has been shown to have oncogenic functions by controlling gene expression through multiple pathways, including those associated with transcription activation, regulating mRNA stability and degradation, modulating ubiquitination and controlling alternative splicing (36). Different pharmacological approaches have been adopted to inhibit SND1 binding to either RNAs or other proteins for the treatment of cancer. Various therapeutic strategies designed to disrupt the interaction between SND1 and its RNA or protein partners are highlighted in Fig. 4.

Inhibition of nuclease or RNA binding activity. Crystal structure analyses have shown that the SN domains of SND1 are responsible for nuclease activity, whereas the Tudor domain is involved in RNA binding (7,15). A primitive inhibitor, 3',5'-deoxythymidine bisphosphate (pdTp), was identified as a competitive inhibitor that targets the SN domain to inhibit the RNA-protein interactions of SND1 in *Plasmodium* (Table I). A previous study showed that pdTp inhibits the growth of both chloroquine-sensitive and chloroquine-resistant strains of *P. falciparum* at concentrations ranging from 100-200 μ M (78). Moreover, upon treating cells of an HCC cell line (QGY-7703) with pdTp, a significant reduction in cell viability was noted, as well as a decrease in colony-forming potential (79). Furthermore, the administration of different doses of pdTp in human HCC cells (of the QGY-7703 cell line) in a xenograft NSG™ mouse model resulted in the observation of a significant inhibitory effect on tumour progression compared with vehicle

Table I. Inhibitors reported to inhibit nuclease activity or RNA binding of SND1.

Compounds	Structures	Mechanism of action	Biochemical activity (IC ₅₀ in μ M)	<i>In vivo</i> activity (mg/kg)	(Refs.)
pdTp		Inhibitor against SN domain to inhibit RNA interaction of SND1	200	0.8	(63)
Suramin		Inhibition of RNA binding and increased expression of miR-1-3p	0.6 $\pm$ 1.0	N/A	(9)
NF023		Inhibition of RNA binding and increased expression of miR-1-3p	1.6 $\pm$ 1.0	N/A	(9)
PPNDS		Inhibition of RNA binding and increased expression of miR-1-3p	0.5 $\pm$ 1.0	N/A	(9)

SND1, staphylococcal nuclease and tudor domain-containing protein 1; pdTp, 3',5'-deoxythymidine bisphosphate; N/A, not applicable; miR, microRNA.

and no toxicity was observed. Recently, Lehmusvaara *et al* (9) identified the top three most effective inhibitors (suramin, NF 023 and PPNDS) of SND1 and RNA-binding activity using a fluorescence polarization-based competitive assay (Table I). Among the identified compounds, suramin proved to be the most potent, inhibiting RNA binding to SND1 with an IC₅₀ of 0.6 μ M (9). Inhibition of SND1 binding to RNA by suramin led to an increased expression of the miRNA miR-1-3p and sensitization of SW480 colon cancer cells to navitoclax (a Bcl-2 inhibitor). However, effective and specific molecules that block the interaction of SND1 with RNA have yet to be identified, and subsequent studies should focus on developing novel and more effective compounds for this purpose.

Targeting of the SND1-MTDH interaction. In recent years, SND1 has attracted significant attention due to the identification of interacting partner proteins and its role in cancer prognosis. Although multiple protein interactions have been reported, the interaction between SND1 and MTDH has been identified with markedly high oncogenic potential in different types of cancer (80). The identification of the SND1-MTDH interaction paved the way for the development of potent and specific inhibitors to block this interaction and to prevent cancer progression (Tables II and III). This progress was facilitated by elucidating the crystal structure of the MTDH-SND1 complex, which revealed a distinct interface between the SN1 and SN2 domains of SND1 and a MTDH peptide motif. The SND1 protein contains

two deep pockets that specifically interact with two tryptophan residues of MTDH. Notably, the large and hydrophobic side chains of Trp-394 and Trp-401 of MTDH were found to fit deeply into the two hydrophobic binding pockets of SND1 (11). The following approaches have been reported and proposed to prevent the SND1-MTDH interaction.

Specific small-molecule inhibitors. The interaction between MTDH and SND1 is crucial for breast cancer progression, and targeting this interaction with small chemical compounds may offer therapeutic potential (6,11). A high-throughput screening analysis performed by Shen *et al* (11) led to the identification of specific inhibitors that can disrupt the SND1-MTDH interaction. Of the three identified compounds (A26, A32, and A36), A26 was further modified, deriving the compounds C26-A2 and C26-A6. C26-A6 has been identified as the first small-molecule inhibitor that specifically targets the interaction between SND1 and MTDH. In *in vitro* studies, C26-A6 demonstrated strong inhibitory effects in SCP28 breast cancer cells that expressed a split-luciferase reporter system, and this was used to monitor the SND1-MTDH interaction. Furthermore, *in vivo* experiments in a breast cancer xenograft model showed that C26-A6 significantly suppresses tumour growth. These experiments were performed in 8-week-old female mice across multiple strains, including immunocompromised (NSGTM and nude) and immunocompetent (FVB and BALB/c) mice (Table II).

Table II. Small molecule inhibitors reported to inhibit SND1 interaction with partner proteins.

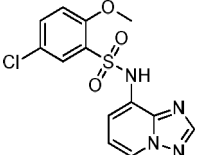
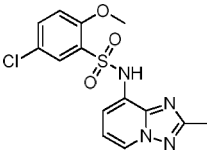
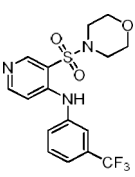
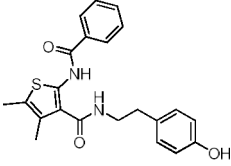
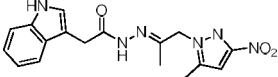
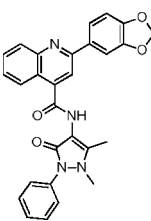
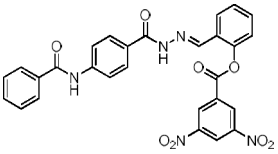
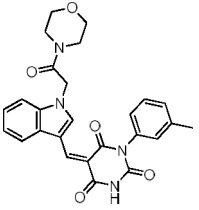
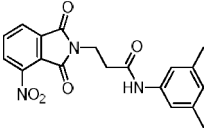
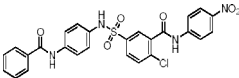
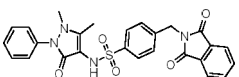
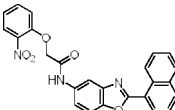
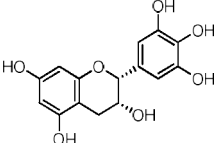
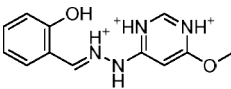
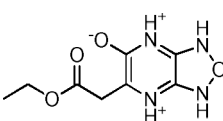
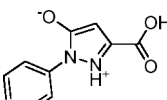
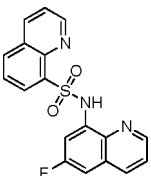
Compounds	Structures	Mechanism of action	<i>In vitro</i> activity		<i>In vivo</i> activity (mg/kg)	(Refs.)
			Biochemical (IC ₅₀ in μ M)	Anticancer (IC ₅₀ in μ M)		
C26-A2		Binds to SN1/2 domain of SND1 and prevents SND1-MTDH interaction	9	38.7	15	(11,12)
C26-A6		Binds to SN1/2 domain of SND1 and prevents SND1-MTDH interaction	5.8	12.3	15	(11,12)
L1		Binds to SN1/2 domain of SND1 and prevents SND1-MTDH interaction	467±87.1	N/A	N/A	(13)
L2			N/A	N/A	N/A	
L3			194±37.4	N/A	N/A	
L4			11.3±2.10	N/A	N/A	
L5			2.64±0.36	57	N/A	
L6			5.53±0.30	N/A	N/A	
L7			4.36±1.38	N/A	N/A	
L8			0.214±0.002	N/A	N/A	
L9			29.8±19.6	N/A	N/A	

Table II. Continued.

Compounds	Structures	Mechanism of action	In vitro activity		In vivo activity (mg/kg)	(Refs.)
			Biochemical (IC ₅₀ in μ M)	Anticancer (IC ₅₀ in μ M)		
L10			3±0.10	N/A	N/A	
Epigallocatechin (EGC)		Binds to K490-containing sites of SND1 and inhibits SND1-MHC-I complex	3.2	0.16	100	(53)
BAS_00381028		<i>In silico</i> studies show binding to SN1/2 domain of SND1	N/A	N/A	N/A	(13)
BAS_00327287			N/A	N/A	N/A	
BAS_01293454			N/A	N/A	N/A	
C19		Binds to SN1/2 domain of SND1 and prevents SND1-MTDH interaction	0.48±0.99	0.626±0.27	60	(82)

SND1, staphylococcal nuclease and tudor domain-containing protein 1; MTDH, metadherin; N/A, not applicable.

The discovery of C26-A6 has encouraged researchers to develop additional inhibitors with higher affinity and efficacy. Subsequent all-atom MD simulations in solution revealed that C26-A6 binds more strongly to SND1 compared with C26-A2, since C26-A2 undergoes a 180° directional shift during the simulation process (81). Furthermore, C26-A6 was shown to reduce tumour growth and metastasis, while also enhancing the sensitivity of TNBC preclinical models to the chemotherapeutic agent paclitaxel when combined with C26-A6 (12). In addition, the MTDH-SND1 complex was shown to suppress tumour antigen presentation and to prevent the infiltration of CD8⁺ T cells within the tumour microenvironment (11). Disrupting the MTDH-SND1 interaction with C26-A6 boosted the immune response, thereby improving the effectiveness of anti-programmed cell death protein 1 (anti-PD-1) therapy in a preclinical metastatic breast cancer model (11).

Another approach utilizing MD simulations was performed to screen over 1 billion compounds from the ZINC15 database, aiming to identify novel small-molecule inhibitors that could inhibit the SND1-MTDH interaction (13). The top 12 potential candidates were identified through virtual screening, and subsequently tested for their ability to bind to SND1 using a

surface plasmon resonance-based assay (Table II). Among the 10 best SND1 binders, L5 and L8 were the top hit compounds, with K_d values of 2.64 and 0.2 μ M, respectively. Subsequent analysis of L5 for anticancer activity in MDA-MB-231 breast cancer cells revealed an IC₅₀ value of 57 μ M.

In addition, structure-based virtual screening was performed to target the known active site of the SND1 enzyme, which resulted in the identification of three promising lead molecules (BAS_00381028, BAS_00327287 and BAS_01293454) from the Asinex library (<https://www.asinex.com/>) (Table II). The binding energy score was calculated and compared with the reference compound C26-A6. These molecules exhibited excellent binding to the SND1 enzyme, and maintained stable docked conformations during MD simulations. Furthermore, the pharmacokinetic properties were also elucidated, and favourable drug-like properties were predicted that could be used in experimental investigations to study their SND1 inhibition potential (14). A MD approach was performed by Shen *et al* (11), which revealed a novel series of inhibitors for the SND1-MTDH interaction. Using 293 cells stably expressing SND1-Nluc and Cluc-MTDH, this research group identified a markedly potent inhibitor, C19, which disrupted the

Table III. Peptide inhibitors reported to inhibit SND1-MTDH protein-protein interaction.

Peptides	Structures	Mechanism of action	<i>In vitro</i> activity (μM)		<i>In vivo</i> activity (mg/kg)	(Refs.)
			Biochemical (K_d in μM)	Anticancer (IC_{50} in μM)		
CPP-4-2	RRRKRRRQRRR-QFDYDHFLMWYS	Binds to SN1/2	3.1	23.6 $\pm$ 2.6	50	(83)
MS2D-cyc4	DW-cyclo(isoDAPDap)EEWGNWVDE	domain of SND1	0.074 $\pm$ 0.007	50	N/A	(10)
MS2D-cyc6	cyclo(isoDRRDap)DWNAPAEWGNWVDE	and prevents	0.0824 $\pm$ 0.005	50	N/A	
NS-E	cyclo(isoDNSDap)DWNAPAEWGNWVDE	SND1-MTDH interaction	0.0234 $\pm$ 0.002	121	8	(84)

SND1, staphylococcal nuclease and tudor domain-containing protein 1; MTDH, metadherin; N/A, not available.

MTDH-SND1 interaction according to a split-luciferase assay (IC_{50} =487 $\pm$ 99 nM). C19 was also shown to inhibit MCF-7 breast cancer cell proliferation, invasion and migration, to arrest the cell cycle, and to induce apoptosis (Table II). Furthermore, C19 has demonstrated promising levels of tumour growth inhibition in MCF-7 xenograft models (82).

Specific peptide inhibitors. Trp-394 and Trp-401 are two crucial tryptophan residues in MTDH that have been found to occupy the binding pocket of SND1, and these tryptophan residues are critical in the SND1-MTDH interaction to promote breast cancer initiation and progression (Fig. 1) (7). A 12-mer (CPP-4-2-2) high-affinity MTDH-like peptide was discovered through utilizing phage display technology to target the MTDH-SND1 complex (Table III). CPP-4-2-2 was found to exert anticancer effects, both *in vitro* in MDA-MB-231, MCF-7 and MDA-MB-468 breast cancer cell lines and *in vivo* in an xenograft BALB/c nude mice model via interacting with the SN1/2 domain of SND1 and disrupting the SND1-MTDH interaction, which resulted in SND1 degradation (83). However, the linear peptide CPP-4-2-2 contains a number of notable limitations, including its having an unstable secondary structure, low serum stability, weak cell permeability and poor druggability.

Subsequently, Chen *et al* (10) utilized a terminal aspartic acid cross-linking strategy (TD method) to overcome the issues associated with linear peptides. This research group effectively created a range of stabilized peptides derived from the MTDH sequence using structure-based design and optimization. Ultimately, they identified the peptides MS2D-cyc4 (K_d =74 nM) and MS2D-cyc6 (K_d =82 nM), which demonstrated exceptional binding affinities, efficient cellular uptake and enhanced serum stability (Table III). Further study of MS2D-cyc4 and MS2D-cyc6 revealed that these peptides possessed appreciable bioactivity in TNBC cells (10). Additionally, a more potent cyclized peptide, NS-E, exhibiting a K_d value of 23.4 nM, was developed, which possessed a 4-fold greater activity compared with MS2D-cyc4 and MS2D-cyc6 (84). In spite of its enhanced activity, however, this NS-E exhibited poor cell penetration efficiency, and also demonstrated antitumour effects at relatively high concentrations, with an IC_{50} value exceeding 100 μM in MDA-MB-231 and 4T1 cells (Table III). To overcome these limitations, a stabilized peptide delivery system was developed

which utilized a reversible sulfonium-based peptide carrier (Wpc) to improve the cell permeability of NS-E. The IC_{50} of the nanomaterial-conjugated peptide (Wpc/NS-E) was found to be reduced to 20 μM in cell-based assays (Table III). The Wpc/NS-E peptide effectively blocked the MTDH-SND1 interaction by targeting SND1, with enhanced delivery into tumour cells. Consequently, the Wpc/NS-E peptide induced apoptosis and significantly inhibited the proliferation, migration and invasion of human MDA-MB-231 and mouse 4T1 TNBC cells. Moreover, the Wpc/NS-E peptide demonstrated exceptional antitumour activity in a 4T1-TNBC mouse model (84).

7. Conclusions and future perspectives

SND1 has been found to be overexpressed in several different types of cancer, including breast, colon, prostate, lung cancer and glioma. Due to its positive correlation with cancer progression and metastasis, SND1 has recently emerged as a potential biomarker and a novel therapeutic target (85). It has been shown to influence global gene expression, regulating a variety of mechanisms that operate at both the transcriptional and post-transcriptional levels. As discussed in the present review, numerous efforts have been made to develop inhibitors that are able to block SND1 binding to RNA, and thereby inhibit its nuclease function. However, the SND1 inhibitors developed thus far have proven to be less potent in preclinical studies, and none of them have advanced to clinical trials. Recently, the SND1-MTDH interaction emerged as a target with great cancer therapeutic potential, as a small molecule C26-A6 was reported to block the SND1-MTDH interaction by binding to SND1 (11). Subsequently, disruption of the SND1-MTDH interaction by C26-A6 was demonstrated to reduce tumour growth and metastasis, and enhanced CD8⁺ T-cell infiltration was identified in the tumour microenvironment in a TNBC mouse model (13).

A recent review described how MTDH lacks catalytic activity, suggesting that developing inhibitors to reduce MTDH expression or block its interaction with protein partners, such as SND1, may offer a promising strategy for targeting different types of cancers (86). Therefore, developing SND1 inhibitors (either small molecules or peptides) may offer a more effective strategy to disrupt the oncogenic SND1-MTDH interaction, given that SND1 has a well-defined binding pocket. In this context, both linear and structurally stabilized peptides are

being optimally designed, with a view to enhancing their binding affinities, which should result in the peptides ultimately exhibiting improved anti-tumour activity. However, to date, the majority of the peptide- and small-molecule-based inhibitors that have been developed have experienced the setback of poor cellular permeability (11,13), which has limited their ability to attain therapeutic concentrations in systemic circulation or within tumour tissues. Going forwards, this reduced bioavailability poses a major barrier to achieving effective anticancer responses.

MD simulation-driven approaches or computer-aided drug design approaches have yielded several SND1-specific compounds, although these have exhibited poor potency in cell-based assays (13). The emergence of artificial intelligence (AI), along with the availability of extensive biological and chemical datasets, has significantly transformed small-molecule drug discovery. In particular, machine learning (ML) and, more recently, deep learning (DL) approaches have accelerated the identification and optimization of potential anticancer compounds (87). Several studies have successfully integrated ML models with MD-based virtual screening methods to identify inhibitors for critical cancer-associated proteins, including CDK4/6, PI3K, histone deacetylase and VEGF (88-91). Additionally, advanced techniques such as quantitative structure-activity relationship (QSAR)-guided ligand-based virtual screening have shown considerable promise. QSAR is widely utilized for hit-to-lead optimization, whereas ML algorithms, such as random forest and support vector machines, are routinely employed to predict absorption, distribution, metabolism, excretion and toxicity (ADMET) properties, enabling the early elimination of unsuitable drug candidates (92). Collectively, these AI-driven approaches have the potential to overcome the limitations of previously identified SND1 inhibitors, and their implementation should accelerate the development of effective cancer therapeutics.

Additionally, proteolysis-targeting chimeras (PROTACs) are bifunctional molecules that consist of a ligand for the protein of interest (POI), a linker that connects the components, and another ligand that binds to an E3 ubiquitin ligase (such as VHL, MDM2 or CRBN), thereby facilitating the degradation of the POI. Unlike conventional inhibitors that block specific protein functions, PROTACs induce complete degradation of the target protein via the ubiquitin-proteasome system (93). This approach has shown promise in targeting challenging protein classes, such as transcription factors, nuclear proteins and scaffolding proteins. PROTACs such as ARV-110 and ARV-471 have already demonstrated encouraging efficacy in Phase II clinical trials (94). It is suggested that the development of SND1-targeting PROTACs by conjugating known SND1 inhibitors (as shown in Tables I, II and III) with appropriate linkers and E3 ligase ligands should be encouraged. These SND1-PROTACs would promote the degradation of both the SN1/2 and Tudor domains, thereby disrupting SND1 interactions with partner proteins and enabling more effective inhibition of its oncogenic functions.

Overall, SND1 has been demonstrated to be a multifunctional protein that contributes to tumour immune evasion and immune resistance. One of the key factors behind resistance to immunotherapy, especially immune checkpoint blockade therapy, is low immunogenicity, which leads to limited immune cell infiltration. It is proposed that targeting the

SND1-MTDH interaction could represent a novel strategy for improving the effectiveness of immunotherapy in cancers that are characterized by low immunogenicity, often due to impaired tumour-associated antigen presentation.

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Authors' contributions

SKR and AK were involved in the conception and design of the present review. MIK AP, RK, RIP and SD contributed substantially to the literature search and data collection. SKR, MIK and RK also performed the critical analysis of findings from the reviewed literature. The draft manuscript was prepared by MIK and RK. Data authentication is not applicable. All authors read and approved the final manuscript.

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.

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