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Overcoming MTDH and MTDH-SND1 complex: driver and potential therapeutic target of cancer

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ABSTRACT

Metadherin (MTDH), also known as LYRIC or AEG-1, is an oncogene that enhances tumor progression, metastasis, drug resistance, and immune escape in various cancers by modulating multiple oncogenic pathways, including NF-κB, PI3K/AKT, Wnt/β-catenin, MAPK, and AMPK. Due to the unknown of the complete structure of MTDH, the deep mechanisms of MTDH and selective inhibitors targeting MTDH remain to be explored. The Protein-Protein interaction (PPI) with the Staphylococcal nuclease domain containing 1 (SND1) is a crucial mechanism underlying the function of MTDH. Current studies have demonstrated that inhibitors, including antisense oligonucleotides, peptides, and small molecules targeting MTDH or MTDH-SND1 interactions, provide novel strategies to inhibit the oncogenetic effects of MTDH. This review summarizes and discusses the structure, function, and regulation of MTDH in cancers, providing the potential therapeutic perspectives of MTDH or MTDH-SND1 PPI for drug discovery.

KEYWORDS

MTDH; SND1; Protein-Protein interaction; RNA binding protein; Cancer

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1. Introduction

Malignant tumors are major global health challenges, and according to the statistics released by the American Cancer Society, 1,958,310 new cancer cases and 609,820 cancer deaths are projected for 2023[1]. Bioinformatics, statistical and mathematical methods and public clinical databases such as TCGA and GEO have facilitated the identification of cancer-related genes that affect patient prognosis, cancer stage, and drug resistance mechanisms[2]. Targeting oncogenes at the gene or protein level with highly selective inhibitors is a promising cancer treatment and drug development field. Metadherin (MTDH), also known as Lysine-Rich CEACAM1 Co-Isolated Protein (LYRIC) or Astrocyte Elevated Gene-1 Protein (AEG-1), is an oncogene encoding MTDH protein that promotes various cancers[3], including breast[4], prostate[5], liver[6], lung[7], glioma[8], cervical[9], bladder[10], kidney[11], gastric[12], colorectal[13], and head and neck cancers[14]. Bioinformatic analysis showed that MTDH is overexpressed in various cancers and correlates with poor prognosis[15,16]. Since its cloning over a decade ago[17], MTDH has been found to be involved in various cancer-related signaling pathways. However, the limited knowledge of its structure and function has hampered the development of MTDH-targeted drugs. Recent studies have reported partial functions of MTDH and validated them in various cancers, suggesting that inhibiting MTDH expression by non-conventional small-molecule inhibitors could be an effective strategy for MTDH-based cancer therapy.

This review summarizes the current knowledge on the oncogenic function and clinical significance of MTDH and its vital partner SND1 , discusses therapeutic approaches that target the Protein-Protein interaction (PPI) between MTDH and SND1, and proposes future directions for the development of inhibitors.

2. Structure and localization of MTDH

MTDH is a gene located on human chromosome 8 (8q22) that encodes a protein involved in human immunodeficiency virus (HIV)- and tumor necrosis factor-alpha (TNF-α)-induced signaling and endoplasmic reticulum (ER) localization in primary human fetal astrocytes (PHFAs)[18,19]. MTDH protein, a transmembrane protein of 582 amino acids, comprises intracellular domains with amino acids 1-48, transmembrane domains with amino acids 49-69 anchoring it to the ER membrane, and extracellular domains with amino acids 70-582[20]. The functional domains of MTDH are mainly located in extracellular domains, including RNA binding region 138-350, the region 101-205 interacting with NF-kB p65[21], and the nuclear localization signal (NLS) consisting of three segments with different functions[22–24]. The nuclear localization of MTDH is mainly regulated by the extended NLS-3 motif at C-terminal (amino acids 546-582), while the extended NLS-1 motif (amino acids 78-130) has a minor role in regulating nuclear localization[24]. MTDH can undergo mono-ubiquitination at K486 and K491 through the E3 ubiquitin ligase TOPORS, which catalyzes the mono-ubiquitination of MTDH in the extended NLS-2 motif (amino acids 415-486)[25]. Although the crystal structure of the full-length MTDH has not been reported, Xing et al. identified the crystal structure of the complex between MTDH and SND1, revealing tryptophan at 394 and 401 that are essential for the interaction between MTDH and SND1[25,26]. Srivastava et al. reported that MTDH interacts with and down-regulates the transcription factor retinoid X receptor (RXR) through its LXXLL motif (amino acids 21-25)[27]. Zhu et al. reported that the 49-69 region of MTDH is the binding site for its protein partner protein arginine methyltransferase 5 (PRMT5), and this region is essential for the formation of the MTDH-PRMT5 complex[28]. Moreover, a lung homing domain (LHD) with amino acids 378-440 in mouse or amino acids 381-443 in human, has been identified[29] (Figure 1).

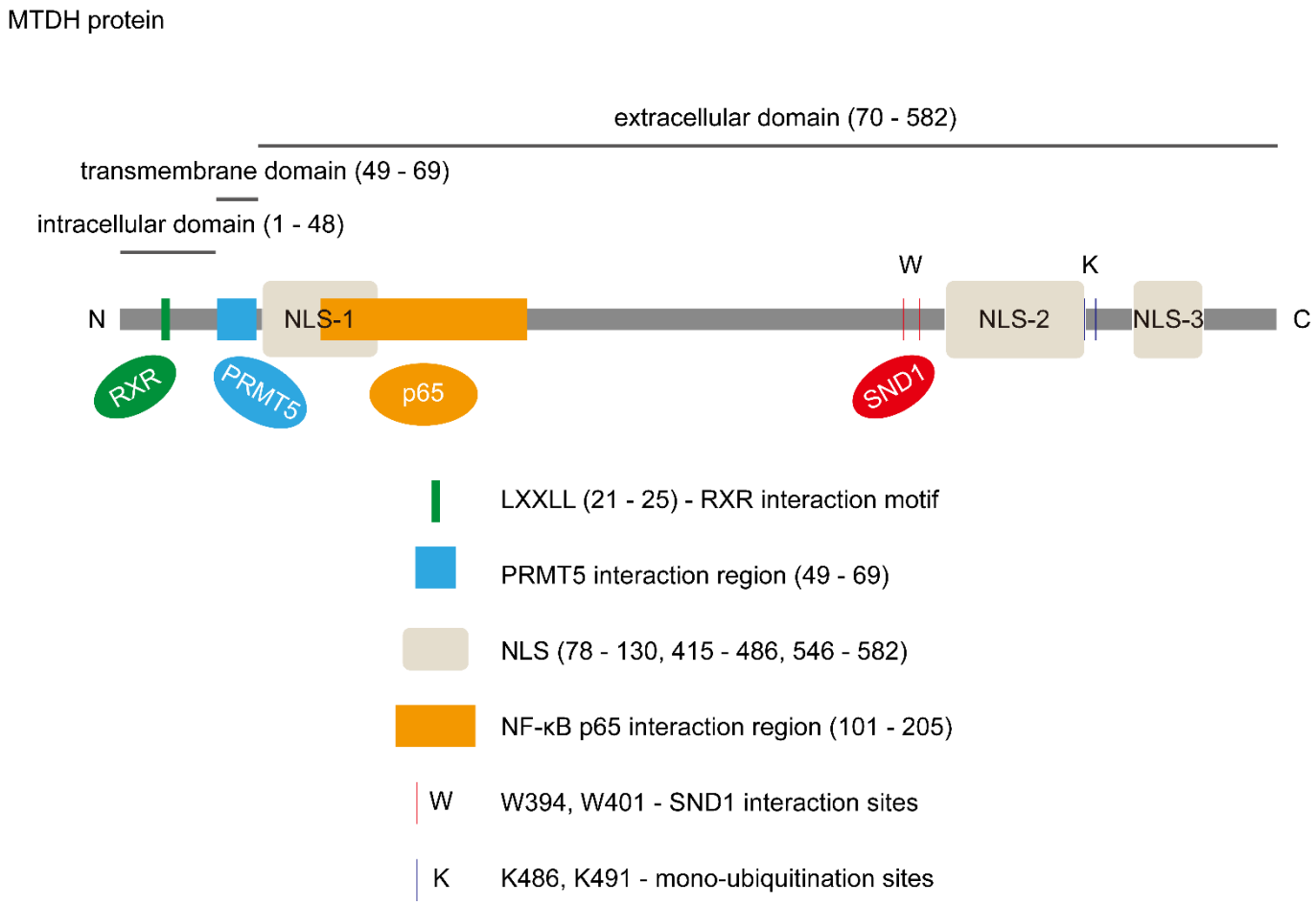


Figure 1. Schematic diagram of MTDH structure. NLS: nuclear localization signal; W: key tryptophan sites of MTDH-SND1 interaction; K: key lysine sites for mono ubiquitination.

3. Molecular function of MTDH

3.1. Protein partners

MTDH is a scaffold protein that interacts with various protein partners to modulate cellular processes[19], and numerous reports have identified that the protein-protein interaction between MTDH and protein partners plays an essential role in different types of cancer. SND1 is the most critical protein partner of MTDH, which drives tumor initiation, metastasis, and immune evasion in breast, lung, and colorectal cancer[26] via binding with MTDH in the SN1/SN2 domain. The oncogenic mechanisms of the MTDH-SND1 complex will be discussed in the following sections. MTDH co-expresses with the transcriptional repressor Promyelocytic leukemia zinc finger (PLZF) and reduces PLZF-mediated repression by decreasing the binding of PLZF to the promoters of its target genes, thereby escaping apoptosis and enhancing cell growth. Thirkettle et al. reported that the nuclear interaction between MTDH and PLZF is mediated via the binding of the C-terminal of the RD2 domain in PLZF and both N- and C-terminal domains of MTDH[30]. MTDH was reported to activate NF-κB by degrading IκBα and facilitating p65 translocation from the cytoplasm to the nucleus[31,32]. MTDH acts as an ER-anchored protein that chaperones the NF-κB ubiquitination activators, and it directly binds to the K(63)- or K(48)-linked polyubiquitin chains, with a higher affinity for K(63)-linked polyubiquitin than K(48)-linked polyubiquitin[20]. Studies have shown that the binding of MTDH to BRCA2 and CDKN1A-interacting protein (BCCIPα) leads to the degradation of the latter, and MTDH, which first 169 amino acids at the N-terminal are essential for interaction with BCCIPα, acts as a negative regulator that

binds to BCCIPα[33]. By directly binding to Forkhead box protein M1 (FOXM1) through its N-terminal, MTDH prevents the interaction of cadherin-1 with FOXM1, which would otherwise trigger the proteasomal degradation of FOXM1. The MTDH-mediated stabilization of FOXM1 was abolished when the MTDH-binding sites of FOXM1 were knocked out[34]. Jia et al. reported that MSN and ENO1 proteins are associated with breast cancer progression and bone metastases, and the results of co-immunoprecipitation and siRNA silencing experiments suggested that the effect of MSN and ENO1 may be achieved by binding with MTDH[35]. Han et al. proposed that MTDH could directly interact with PTEN to contribute to cisplatin resistance in ovarian cancer cells[36,37], and the interaction was altered by adding Guizhi Fuling Wan extract (GFWE) sera. DDX17 acts as a transcription factor and protein partner downstream of MTDH to increase EGFR transcription and activate the MEK/pERK pathway, and the binding with MTDH increases the expression of DDX17 by inhibiting its ubiquitination[38].

3.2. RNA binding protein function

RNA binding proteins (RBPs) play essential post-transcriptional regulatory roles in the nucleus and cytoplasm, including RNA splicing, stability, and nuclear localization[39–41]. HSU et al. reported that MTDH, as an integral membrane protein of the ER, was identified in the RNA interactome screen and acted as a selective ER mRNA-binding protein to regulate RNA[19]. Genome-wide analysis of the MTDH-RNA interactome by HIT-CLIP and PAR-CLIP revealed that the MTDH-RNA interactome was enriched for transcripts encoding organelle proteins. Unlike classical RBPs, MTDH-RNA interaction sites were enriched in coding regions and less frequent in 5′ untranslated regions (5′-UTRs). This result identified MTDH as an ER-resident RNA-binding protein that interactome was rich in mRNAs encoding organelle-resident proteins, especially membrane proteins. CLIP analysis suggested that MTDH might achieve ER localization function by interacting with RNA coding regions through low-affinity interactions. In addition, based on algorithm and experimental results, the conserved, highly disordered region of MTDH 138-350 was defined as the RNA-binding domain. They also found that MTDH binds with mRNAs encoding secretory and cytoplasmic proteins, suggesting that MTDH plays multiple roles in regulating ER translation. Meng et al. confirmed that MTDH could form the RNA-induced silencing complex (RISC) with protein partners in endometrial cancer cells and found that MTDH had homology with the RNA-binding protein leucyl-tRNA synthetase and contained several putative RNA-binding domains[42]. By RIP-Chip, the group identified multiple MTDH-associated mRNA targets, and protein levels of PDCD11 and KDM6A increased in MTDH-knockout cells, indicating that cytoplasmic MTDH negatively regulated the translation of these mRNAs.

4. Regulation of MTDH expression

4.1. Genomic regulation on upstream

The expression of MTDH is co-regulated by two widely reported oncogenes, Ha-ras and C-MYC, and Ha-ras can induce the expression of MTDH by transcriptional regulation[32]. From the analysis of MTDH promoter, Zhao et al. identified two E-box elements as the binding sites of C-MYC, and further investigation suggested both positive and negative regulatory regions of MTDH play crucial roles in the activation process of MTDH mediated by Ha-ras. HIF-1α binds the MTDH promoter, enhances its expression, and induces tumor metastasis with up-regulation of MMP2 and MMP9 while inhibiting the expression of E-cadherin and β-catenin in ovarian cancer cell[43]. Chip-sequencing databases suggested that NF-κB p65 subunit binds in the promoter of MTDH, and NF-κB directly enhances the expression of C-MYC and indirectly induces MTDH, forming a feed-forward loop network[44,45]. Furthermore, Heat shock transcription factor 1 (HSF1), an important transcription factor in response under stress condition, could combine with promoter of MTDH and lead to high-expression of MTDH, leading to increased invasion and migration

of Hela cells *in vitro*[46].

4.2. Post-translation modification

Current studies have shown that MTDH is S-palmitoylated at Cys-75, a residue located near the transmembrane domain at the N-terminus, and the modification is catalyzed by zDHHC6, a palmitoyltransferase that regulates the biological activity of MTDH in HCC cell[47]. CRISPR/Cas9-mediated knockout of zDHHC6 resulted in reduced palmitoylation of MTDH and decreased survival of HCC cells both *in vitro* and *in vivo*, suggesting that impaired palmitoylation of MTDH may be a critical risk factor for the progression of DEN-induced HCC[48,49]. The tumor suppressor gene FBXW7 was found to act as an E3 ubiquitin ligase for MTDH, and mediate proteasomal degradation of MTDH. Experimental results confirmed that FBXW7 can negatively regulate MTDH protein stability, inhibit breast cancer cell proliferation, and promote apoptosis by MTDH degradation *in vitro*[50]. Denuc et al. reported that TOPORS, a previously reported E3 ligase that can link ubiquitin and small ubiquitin-like modifier (SUMO) to substrate proteins, was found to have the function of catalyzing MTDH mono-ubiquitination[51]. K486 and K491 located in MTDH NLS2 region are essential sites for MTDH protein mono-ubiquitination, and the mutation of mono-ubiquitination sites resulted in weaker interaction of MTDH with p65 and Importin-b than MTDH-WT, suggesting that the interaction of MTDH with some protein partners may depend on MTDH mono-ubiquitination at the two sites[25]. In addition, cytoplasmic polyadenylation element-binding protein 3 (CPEB3) was identified as a sequence-specific RNA-binding protein, which could suppress MTDH expression at post-transcriptional expression. Further investigation validated that CPEB3 interacts with 3'-UTR of MTDH mRNA to inhibit its translation and progression of HCC[52].

4.3. Non-coding RNA regulation

Depending on localization and specific interaction with mRNA, miRNAs can regulate the stability and translation of cytoplasmic mRNAs and interfere with signaling pathways[53–55]. In recent years, increasing evidence has revealed miRNA's broad expression and regulatory roles associated with MTDH expression and function[56–59]. Saklani et al. reported MTDH as a critical target gene of miRNA-mRNA interaction in gallbladder cancer through analysis of the GSE database[60]. Numerous studies have validated that the involvement of miRNAs modulates MTDH expression in cancer progression. In breast cancer, miR-217-5p may inhibit invasion, migration, epithelial-mesenchymal transition (EMT), and NF-κB pathway activation by targeting MTDH[61]. Jin et al. proposed that circTGA7 could target miR-1471, leading to down-regulation of MTDH and tumor suppression[62]. Jiang et al. reported that TNF-α upregulates miR-21-3p through the NF-κB signaling pathway, and miR-21-3p directly target MTDH 3′-UTR and suppress expression, ultimately inhibiting MTDH-mediated Wnt/β-catenin pathway activation in colorectal cancer[63]. miR-524 and miR-145 were found to have a similar inhibitory effect on MTDH in colorectal and neuroblastoma cancer[64,65]. By targeting MTDH, miRNA can inhibit cancer progression, which has also been reported in breast[57], head and neck cell carcinoma[66], colorectal[67], and bladder[68] cancer, providing a new insight for developing unconventional therapeutic strategies targeting MTDH.

5. Oncogenic mechanisms of MTDH

MTDH has been reported to exert oncogene roles by participating in NF-κB, Wnt/β-catenin, PI3K/AKT, and MAPK[3,69,70], promoting tumor proliferation, metastasis, and autophagy. In this review, we summarized the current studies on the regulatory mechanism of MTDH in cancer-related signaling in the progression of different cancers (Figure 2).

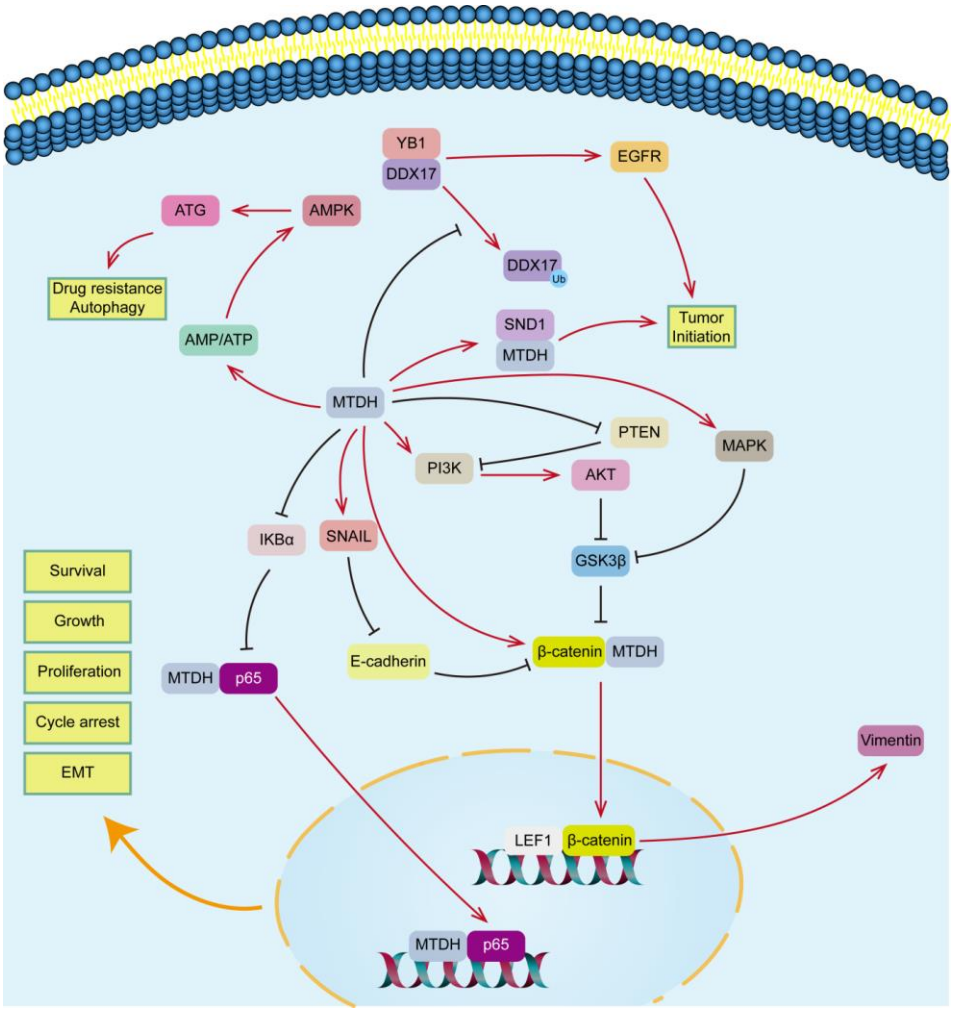


Figure 2. Schematic representation of the cancer-promoting mechanism of MTDH. MTDH promotes tumor initiation tumor survival, growth, cell cycle arrest, EMT, drug resistance, and autophagy via NF-κB, PI3K/AKT, Wnt/β-catenin, MAPK, and AMPK signaling pathway.

5.1. Clinical and prognostic-biomarker

A large number of studies based on clinical data and bioinformatics analysis have confirmed that MTDH is an oncogenic factor closely associated with poor prognosis and cancer progression in various cancers. Yu et al. reported that the expression and transcription of MTDH were significantly upregulated in esophageal cancer cell lines and clinical samples, and immunohistochemical results showed that high expression of MTDH was associated with various clinical stages of esophageal squamous cell carcinoma patients[71]. Multivariate analysis showed that MTDH could serve as an independent prognostic indicator for the survival of esophageal squamous cell carcinoma patients, and Xu et al. reported that the MTDH expression was significantly higher in gastric cancer tissues than in normal tissues[12]. MTDH was significantly associated with TNM stage and Ki-67 proliferation index, as well as poor patient prognosis in gastric cancer. Jung et al. analyzed the relationship between MTDH expression and clinical case parameters and found that the MTDH expression in the clinical liver metastasis group was higher than the non-liver metastasis group[72]. Meanwhile, high expression of MTDH was associated with distant metastasis of colorectal cancer and survival of patients after surgery. Moreover, based on clinical patient samples, a large number of studies have found that high expression of MTDH was significantly associated with postoperative survival rate, tumor metastasis, clinical stage progression and tumor angiogenesis in HCC[73], GBC[60], BRCA[74], NSCLC[32] and GBM[75],

suggesting that MTDH was defined as a clinical and prognostic biomarker in various cancers, and through detection of MTDH expression, timely diagnosis of cancer patients in early stage may be possible.

5.2. Tumor initiation

Tumor initiation is the fundamental challenge for cancer treatment. Wan et al. reported that MTDH is essential for the survival of mammary epithelial cells (MECs) under oncogenic stress, and MTDH knockout inactivates oncogene-induced mammary tumor-initiating cells (TICs) and further inhibits the formation and metastasis of luminal mammary tumors in animal models[76]. Further studies showed that the interaction and stabilization of SND1 with MTDH are essential for the survival of TICs under oncogenic conditions. Jin et al. identified a novel oncogene DDX17, which acts as a transcriptional regulator, interacts with Y-box binding protein 1 (YB1) in the nucleus to drive YB1 binding to its target epidermal growth factor receptor (EGFR) gene promoter, and thereby increases its transcription[38]. Futher investigation suggested that MTDH promoted the occurrence of HCC by upregulating DDX17 expression by inhibiting its ubiquitination.

5.3. Promotion of proliferation and anti-apoptosis

It has been reported that MTDH regulates tumor proliferation through various signaling pathways. For example, CRISPR/Cas9-mediated MTDH knockdown reduced the proliferation of inflammatory breast cancer (IBC) cells, while MTDH overexpression enhanced it. The underlying mechanism may involve the modulation of NF-κB and STAT3, which are key signaling molecules in IBC development[77]. MTDH overexpression also stimulated tumor cell survival and growth by activating the PI3K/AKT pathway, inducing serum-independent cell growth. Conversely, MTDH knockdown leads to G0/G1 cell cycle arrest and apoptosis and inhibits neuroblastoma cell proliferation, which suggests that MTDH expression affects cell proliferation, apoptosis, and cycle[78]. Moreover, the downregulation of miR-98 increased tumor cell proliferation and migration and decreased the apoptotic rate of hypopharyngeal carcinoma cells. The above inhibitor abolished the PTEN effects, suggesting that the miR-98/MTDH axis regulates hypopharyngeal carcinoma by targeting the PTEN/AKT pathway[79].

5.4. Metastasis

Tumor metastasis is a major cause of low five-year and postoperative survival rates in patients with various cancers. MTDH is a crucial factor that promotes tumor metastasis by activating EMT, invasion, and migration, which are essential mechanisms for its oncogenic function. This section reviewed the signaling pathways and molecular mechanisms involved in MTDH-mediated tumor metastasis. MTDH interacts with β-catenin, leading to the down-regulation of phosphorylated β-catenin and E-cadherin and the up-regulation of vimentin[80]. MTDH also promotes EMT development by up-regulating Snail transcription factor and down-regulating E-cadherin through NF-κB-mediated signaling[81]. MTDH promotes Wnt/β-catenin-mediated metastasis by interacting with Glycogen synthase kinase-3 beta (GSK-3β) and CKIδ[82]. The inactivation of GSK-3β results in the up-regulation of Wnt/β-catenin signaling pathway[15]. In gastric cancer, the decreased protein expression levels of E-cadherin and phosphorylated β-catenin and the increased protein level of vimentin and nuclear β-catenin indicated that MTDH upregulates relevant signaling pathways and promotes tumor migration[80]. Moreover, the accumulation of β-catenin in the nucleus suggests that MTDH-induced EMT is closely correlated with the nuclear localization of β-catenin. TGF-β1 treatment increases the protein expression of MTDH, whereas MTDH knockdown strongly suppresses p38 MAPK phosphorylation and reverses TGF-β1-induced EMT[83]. MTDH also binds to the promoter region of Raf kinase inhibitor protein (RKIP) and reduces its expression, leading to the up-regulation of the ERK pathway[84]. In addition, MTDH elevates the expression of p38 in oral squamous cell carcinoma and induces EMT. The above results indicated

that MTDH activates the MAPK pathway, inducing TGF-β1 mediated EMT.

5.5. Tumor angiogenesis

Tumor angiogenesis is a key feature in cancer, which is driven by high levels of angiogenic factors secreted by tumors[85]. Numerous studies have demonstrated that MTDH is involved in tumor angiogenesis. MTDH[86–88] enhances the anchorage-independent growth of normal immortal cloned rat embryo fibroblast (CREF) cells and induces tumor formation in nude mice[89]. The analysis of angiogenic markers revealed that Ang1, MMP-2, and HIF1-α were highly expressed in CREF-MTDH tumors, which were derived from the injection of CREF-MTDH clones. Further investigation showed that the PI3K/AKT pathway mediated the high vascularization of these tumors. Neeli et al. reported that the histone methyltransferase DOT1L, which catalyzes explicitly the methylation of histone H3K79, could promote the development of triple-negative breast cancer through MTDH-mediated angiogenesis and suggested that MTDH acted as a mediator molecule in the NF-κB pathway, adding a new hypothesis to the classic MTDH-NF-κB pathway[90]. In tongue squamous cell carcinoma, a significant positive correlation between the expression of vascular endothelial growth factor receptor (VEGFR) and MTDH was detected *in vivo* and *in vitro*[88]. Formation of vessel-like structures by invasive tumor cells is associated with tumor metastasis, and Liu et al. reported that macrophages with overexpressed MTDH enhanced the VEGFA-165 expression through β-catenin, thereby activating the VEGFA-165/Flt-1 axis and promoting invasion and metastasis in head and neck squamous cell carcinoma[14].

5.6. Drug resistance and autophagy

Drug resistance is a major obstacle to anti-tumor drug therapy, which severely affects the efficacy of chemotherapeutic drugs in cancer treatment[91–93]. Previous studies have shown that MTDH promotes drug resistance of tumor cells by participating in various pathways[36,94,95]. Autophagy is a cellular survival mechanism, but abnormal autophagy is closely related to the initiation and progression of malignant tumors[96,97]. The autophagy pathway is one of the crucial factors that cause drug resistance and chemotolerance of tumors[98]. Bhutia et al. demonstrated that MTDH could induce cell autophagy by affecting cellular energy consumption, and AMPK was activated when the intracellular AMP/ATP ratio increased. MTDH expression promotes the phosphorylation level of AMPK at Thr-172, enhancing the resistance to doxorubicin[99]. In addition, Pei et al. found that overexpression of MTDH upregulated P-glycoprotein and induced autophagy by regulating ATG-5 expression through phosphorylation of AMPK, increasing 5-FU resistance in gastric cancer cells[100,101]. Zhang et al. proposed that a high level of MTDH expression promoted autophagy and cisplatin chemoresistance in HeLa cells by reducing Caspase-3 cleavage and activating ERK/NF-κB pathway[102]. Anoikis resistance might play a significant role in tumor survival, and Zhu et al. reported that MTDH could promote anoikis resistance and subsequent tumor survival through the protein kinase RNA-like ER kinase (PERK)-eIF2α-ATF4-CHOP signaling axis in HCC, and the process might be dependent on autophagy induced by MTDH[103]. Although some classic theories and novel hypotheses have been reported, the specific process and molecular mechanism of MTDH regulating autophagy remain to be elucidated.

5.7. Immune regulation

Currently, an increasing number of reports focus on the tumor immune behaviors involving MTDH, which mainly pay attention to the regulation of immune checkpoint expression and antigen presentation by MTDH (Figure 3). Studies have shown that MTDH protects tumors by inhibiting CD8+ T cells, and it has been observed that knockout of MTDH can significantly increase the concentration of IFN-γ. The complex formed by MTDH and SND1 down-regulates the level of TAP1/2 mRNA through binding to it, resulting in inhibition of the antigen presentation

process of the tumor and mediation of the immune escape of tumor[104]. MTDH could promote dephosphorylation and nuclear localization of β-catenin, activating Wnt/β-catenin signaling via ERK42/44 activation in tumor cells of hepatomas. Further investigation demonstrated that MTDH regulates the expression of PD-L1 by binding to LEF-1 and forming a ternary transcription complex with β-catenin through the N-terminus of LEF-1[6,105]. At the same time, this study also shows that the nuclear localization region of MTDH plays an indispensable role in the binding of MTDH with LEF-1 and β-catenin. In the K-Ras-induced lung cancer mouse model, Shen et al. found that MTDH knockdown enhanced T cell infiltration into the tumor by reducing PD-1+ CD8+ T cells and PD-L1 expression on tumor cells[104]. These results suggested that MTDH promotes T cell exhaustion and suppresses anti-tumor immunity by upregulating PD-L1 and PD-1. Bioinformatic research revealed that the MTDH/m6A/EMT signature was closely associated with immune infiltration and resistance of immunotherapy[106]. In various tumors, immunosuppressive cells are positively correlated with the expression score of MTDH/m6A/EMT signature, which correlates negatively with immune cells. However, the mechanism of action between MTDH, m6A and immunosuppression remains to be uncovered.

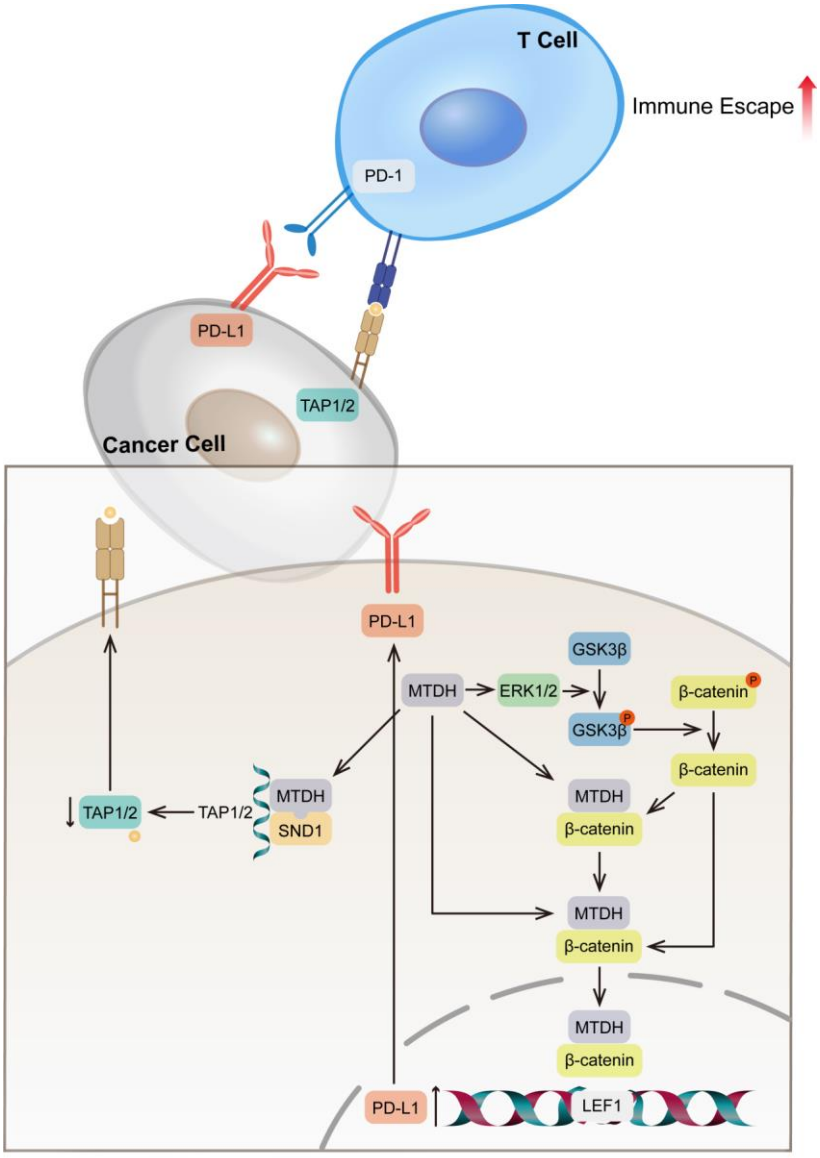


Figure 3. Schematic representation of MTDH promoting immune escape. MTDH promotes the phosphorylation of GSK-3β through ERK1/2, leading to the accumulation of β-catenin to bind to MTDH and promote the transcription of PD-L1; MTDH-SND1 complex binds to the mRNA of TAP1/2, reducing the antigen presentation.

6. Protein-protein interaction with SND1

Among the many protein partners of MTDH, SND1 has been reported to play the most critical role in cancer, and the crystal of the MTDH-SND1 complex has discovered drugs that block the PPI feasible[26]. In the process of cancer development and the signaling pathways involving MTDH, the interaction between of MTDH and SND1 is related to initiation, proliferation, metastasis, and immune evasion in cancer[76]. In this section, we will introduce SND1 and MTDH-SND1 interaction.

6.1. Structure and function of SND1

Staphylococcal nuclease (SN) and Tudor domain containing 1 (SND1), also known as p100, TSN, and Tudor-SN, consists of four SN-like domains at the N-terminal and a fusion domain containing a truncated SN domain and a Tudor domain at the C-terminal[107]. SND1 was identified as a transcription coactivator, which can interact with various transcription factors, such as STAT5/6[108], E2F1[109], EBNA2[110,111,] and c-Myb[112,113]. Recently, several functions of SND1 that are unrelated to RNA transcription have been reported. SND1 can participate in spliceosome assembling and pre-RNA splicing[114,115], and act as a component of RISC[116–118], as well as interact with multiple proteins and serve as a component of stress granules (SGs) under stimulation conditions[119]. Numerous studies have indicated that SND1 plays crucial roles in the promotion and development of tumors through RNA regulation, and the interaction with MTDH was an essential condition for the oncogenetic function of SND1[120].

6.2. MTDH-SND1 interaction promotes the development of cancer

Based on analysis of clinical data, it has been reported that MTDH and SND1 were co-expression in the liver, glioma[121], colon[122], renal[11], and breast[76] cancer, suggesting SND1 may mediate the oncogenetic function of MTDH in the above cancer types. Although the complete protein structure of MTDH has not been reported, the structure of the key region of the interaction between MTDH and SND1 has been studied in detail. GST-pulldown analysis of different truncated forms of MTDH revealed that the MTDH 364-386 region is the site of interaction with the SND1 protein. Guo et al. resolved the crystal structure of the MTDH-SND1 complex and identified the peptide motif of MTDH that contains 11 residues binding to SND1[26]. Because the interaction between synthetic peptide MTDH and SND1 is relatively weak, co-crystallization of SND1 SN1/2 domain and synthetic peptide containing MTDH residues 386-407 failed to produce co-crystals. Fusing the MTDH peptide to the SND1 protein by a 21-residue linker (STGNASDSSSDSSSSEGDGTV) resulted in diffracted crystals of the stable complex. Analyzing the crystal of the MTDH-SND1 complex revealed some structural details of the interaction between MTDH and SND1. The MTDH peptide binds in a shallow groove between the SN1 and SN2 domains of SND1, and its two tryptophan residues, W394 and W401, form extensive hydrophobic interactions with two hydrophobic pockets on SND1. On the other side of the MTDH-SND1 interface, SND1 forms a spiky surface capable of multiple binding modes, and this site may bind to other potential SND1 interaction molecules, including small RNAs, and transcription factors such as STAT5, STAT6, and c-Myb. The structure of the MTDH-SND1 complex has been revealed to provide new possibilities for anti-tumor inhibitors targeting PPI. However, it remains to be revealed whether the MTDH-SND1 PPI plays a dominant role in tumor development and progression in more cancers, which limits the development and application of anti-tumor drugs targeting the MTDH-SND1 complex.

The PPI with MTDH is essential for the stability of SND1, which has been studied extensively, and the PPI between MTDH and SND1 has been implicated in various aspects of carcinoma (Figure 4). The results of bioinformatic analysis based on TCGA and GEO databases and experimental data suggested that MTDH promotes metastasis by activating ERK signaling. Meanwhile, pERK1/2 and the EMT inducer Snail were significantly down-regulated under the knockdown of SND1, indicating that MTDH might cooperate with SND1 to activate ERK and

subsequently augmented the migration and invasion of renal cancer cells (ccRCCs)[11].

The function of MTDH to maintain the stability of SND1 may be a potential mechanism that explains the important roles of the MTDH-SND1 complex in cancer progression. It has been reported that SND1 is a crucial factor that maintains the survival of tumor cells under stress conditions, and Wan et al. demonstrated that the complex formation with SND1 is a necessary prerequisite. The results suggested that MTDH promotes the survival of tumor cells through the stability and binding function of SND1 under stress conditions *in vivo*. Based on a previous study, this hypothesis validates that the complex of MTDH and SND1 activates the diversion of TICs to induce breast cancer[76]. Furthermore, co-immunoprecipitation and co-localization studies confirmed that both MTDH and SND1 are components of RISC in liver cancer[123]. The results of siRNA- and miRNA-mediated silencing of the luciferase reporter gene suggested that the enhanced RNA silencing activity of RISC activated by MTDH and SND1 increase the inhibition of tumor suppressor mRNA. Furthermore, miR-221 is involved in the cancer regulatory signaling mediated by SND1 or MTDH. Angiogenic factors angiogenin and CXCL16 are induced by high expression of miR-221, which is activated through NF-κB, and further investigation discovered that the up-regulation of NF-κB induced by SND1 leads to the induction of miR-221 and its target genes angiogenin and CXCL16[124]. On the other hand, Yoo et al. validated that the promoting effect of RISC in HCC may be achieved by silencing tumor suppressor genes, including PTEN, which targets miR-221[123]. These studies may provide a hypothesis for the synergistic function of MTDH and SND1 in cancer from the perspective of RNA regulation.

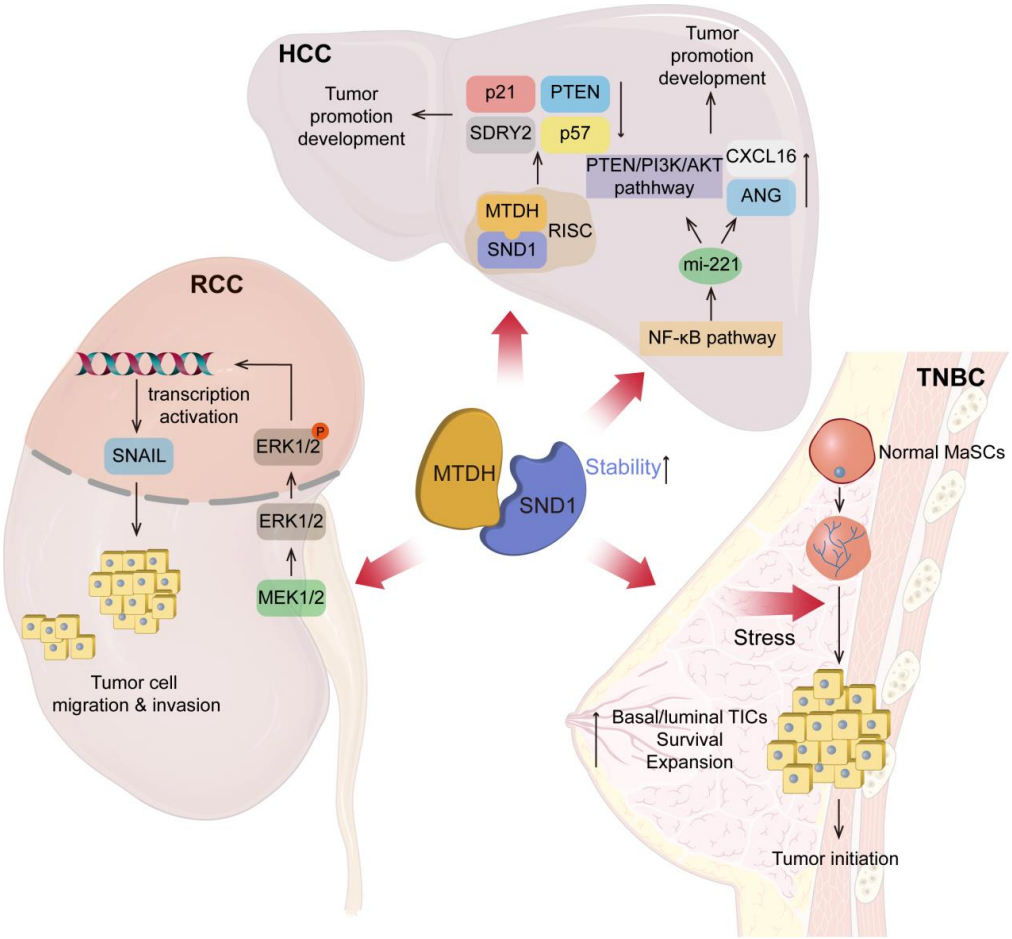


Figure 4. The oncogenic mechanism of MTDH-SND1 PPI in RCC, HCC, and TNBC. MTDH-SND1 PPI promotes tumor through the formation of RISC and NF- κB pathway in HCC; participates in the regulation of MEK1/2 in MAPK pathway to promote transcription and promote tumor metastasis in RCC; activates normal MaSC leading to tumor initiation in TNBC.

7. Therapeutic implications targeting MTDH

As a clinical and prognostic biomarker in various cancers, MTDH regulates downstream biological functions without direct catalytic activity, and due to uncertain of the full-length or relatively complete domain structure of MTDH, the development of small-molecule drugs that directly target MTDH protein remains challenging. Meanwhile, no commercially available or clinically tested small-molecule inhibitors can effectively inhibit MTDH or block the MTDH-SND1 PPI. However, recent studies have reported therapeutic approaches that target MTDH by inhibiting MTDH expression or blocking the MTDH-SND1 protein-protein interaction. We introduced the current status of MTDH therapeutic strategies from three aspects: antisense oligonucleotides targeting MTDH mRNA, modified peptides, and small-molecule inhibitors blocking the PPI (Figure 5).

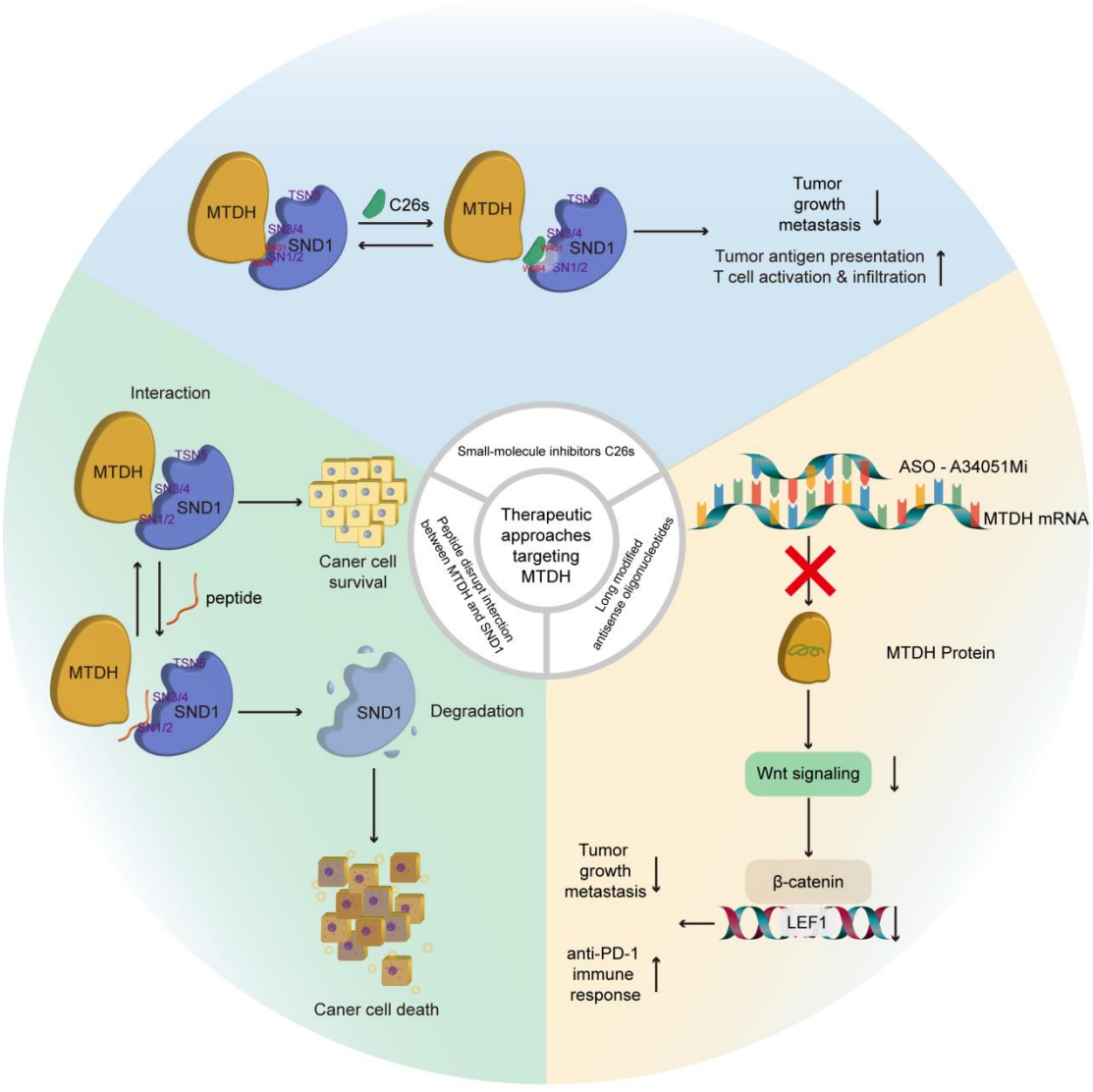


Figure 5. Therapeutic strategies targeting MTDH. Small molecules and peptides inhibit tumor development by targeting the interaction of MTDH-SND1; Antisense oligonucleotide inhibits tumorigenesis and development, activating immune responses by targeting MTDH mRNA.

7.1. Long modified antisense oligonucleotides

Antisense oligonucleotide is a nucleic acid sequences that bind to the target gene or mRNA with sequence specificity to inhibit the gene expression as a molecular drug that regulates the target at the gene level [125,126]. Using silicon-based ASO design and multiple screening, Shen et al. identified ASO A34051Mi that showed high inhibition of MTDH mRNA levels in lung and colorectal cancer cell lines[127]. The suppression of MTDH protein expression by ASO was also validated, and the ASO was found to maintain its inhibitory activity against MTDH expression in animal models with low *in vivo* toxicity. qRT-PCR and western blot results demonstrated MTDH knockdown by ASO *in vitro*, and confirmed that targeting MTDH with ASO effectively inhibited tumor growth and metastasis and downregulated Wnt signaling in tumor tissues of MTDH-specific ASO-treated group compared with the control ASO group. MTDH has been reported to upregulate the transcriptional activity of PD-L1 expression in liver cancer via the β-catenin/LEF-1 signaling pathway, and ASO targeting MTDH enhances the anti-PD-1 immune response and increases the immune infiltration of cytotoxic T cells in PD-1mab-treated tumors[128]. ASO targeting MTDH has the advantage of target specificity, but is not as good as traditional small molecules or peptide inhibitors regarding cell membrane permeability, nucleotidase resistance, and distribution. Meanwhile, the development of inhibitors to block the MTDH-SND1 PPI is a novel potential therapeutic strategy for breast cancer.

7.2. Peptide disrupts the interaction between MTDH and SND1

As discussed above, the interaction between MTDH and SND1 is a crucial pathway for MTDH to exert its tumorigenic functions, therefore, the therapeutic approaches that block the MTDH-SND1 PPI have important research value. Peptides derived from the binding regions of MTDH and SND1 also emerged as an effective strategy to block the MTDH-SND1 complex. Based on the structure of the MTDH template, Chen et al. designed and modified a series of peptides using a cross-linking strategy[129]. By studying the amino acid sequence of MTDH that binds to the SND1 1/2 domain, Dap and iso-Asp were introduced to form the cyclic peptides, and fluorescence polarization (FP) assay confirmed that MS2D with a -WVDE motif had the optimal SND1 KD value. Considering the stability and bioavailability of peptides, they evaluated the antitumor activity of MS2D-cyc4 and MS2D-cyc6 *in vitro*. GST-mediated pull-down assay and co-IP verified the inhibitory activity of the modified peptides on MTDH-SND1 interaction, and the combination treatment of peptide inhibitors and paclitaxel showed significant tumor cell cycle arrest and migration inhibition effects. Although they performed a generalized evaluation of peptide inhibitors *in vitro*, the study lacked *in vivo* experimental data on peptides. Due to peptides' stability, antigenicity, and pharmacokinetic properties, *in vivo* experiments are important for developing peptide anti-tumor inhibitors. Li et al. fused RR-TAT, a hybrid CPP, to construct peptide 4-2 that interacts with the SND1 SN1/2 domain and obtained a selective peptide CPP-4-2 with cell-penetrating ability[130]. CPP-4-2 exhibited significant inhibitory activity with IC50 values of 22.4±1.0, 18.7±0.2, and 15.9±6.2 μmol/L in MDA-MB-231-GFP-Red-FLuc, MCF-7, and MDA-MB-468 cells, respectively. Moreover, mutational analysis of CPP-4-2 revealed that W10 was essential for the SND1 inhibitory activity and cytotoxicity of CPP-4-2, which matched the study of the key binding site of MTDH in the MTDH-SND1 crystal. *In vivo* experiments showed that CPP-4-2 could significantly inhibit tumor volume compared with mutant peptides as controls. Meanwhile, no toxicity symptoms, such as weight loss, were observed in the animal models during peptide treatment[130]. The design of peptides using MTDH as a template opens important areas for the strategies of development for inhibitors of the MTDH-SND1 complex. However, there is still much to be studied for peptide inhibitors targeting the MTDH-SND1 PPI, both in terms of co-crystal structure-based disclosure of the interaction between the peptide inhibitor and SND1 and completeness of *in vivo* experiments.

7.3. Small-molecule inhibitors

Shen et al. constructed a luciferase and fluorescence resonance energy transfer assay and screened a chemical library containing about 50,000 small molecules[131]. The luciferase-based screening system consisted of a firefly luciferase that was cleaved into N- and C-terminal fragments, which had no catalytic activity to produce fluorescence by themselves. The split luciferase fragments were fused to the domains of MTDH and SND1 that interact with each other, and the two luciferase fragments came close and regained the catalytic function to generate luminescence when MTDH formed a complex with SND1. The feasibility of this high-throughput small molecule screening system was verified by co-IP using MTDH-WT as a control. Through the above screening methods, C26 series compounds were found to inhibit MTDH-SND1 PPI, which disrupted the interaction between MTDH and SND1 with IC50 at 2.4μM. Microscale thermophoresis (MST) assay showed that C26-A2 and C26-A6 had binding abilities similar to SND1. The crystals of these two compounds with SND1 confirmed this result and showed that these two small molecules bound to the hydrophobic pocket of SND1 1/2 domain where MTDH W401 binds. Furthermore, they demonstrated that C26-A6 effectively suppressed tumor growth and migration in animal models of TNBC. Meanwhile, C26-A6 combined with paclitaxel significantly inhibited breast cancer tumor volume and lung metastasis *in vivo*, and the inhibitory effect was markedly improved compared with either treatment alone. The group also demonstrated that the MTDH-SND1 complex binds to and destabilizes TAP1/2 mRNA, reducing tumor antigen presentation and impairing T cell activation and infiltration. Based on the synergistic effect of MTDH knockdown and anti-PD-1 treatment on inhibiting breast cancer tumor and lung metastasis *in vivo*, they found that C26-A6 combined with anti-PD-1 treatment showed superior tumor growth and metastasis inhibition than either treatment alone. Further analysis revealed that the combination treatment increased the infiltration and activation of CD8+ T cells in the tumor tissues and reduced the exhaustion of CD8+ T cells[104].

Based on the discovery of C26 series molecules and the evaluation of anti-tumor activity, Xu et al. discovered 7 small molecules that could bind to SND1 protein with KD value less than 15μM from 1.2 million molecules by molecular docking and various molecular dynamics simulations[132]. Among them, compound L5 had an IC50 value of 57 μM for MDA-MB-231 cell proliferation and immunofluorescence (IF) assay verified that L5 inhibited the PPI of MTDH-SND1 in cells. The protein-protein inhibition activity of compound L5 must be further verified by split-luciferase or FRET experiments, and the in vivo activity of small-molecule inhibitor needs further confirmation. Meanwhile, researchers reported that the hydrogen bond interactions between C26s and SND1 R255 contributed significantly to the binding of the ligands to SND1, based on their molecular dynamics simulation[132,133]. These studies supplemented the research on the binding mode of MTDH-SND1 small molecule inhibitors with SND1 and guided further small molecule development.

The discovery of the first small molecule inhibitor disrupting the interaction of MTDH and SND1 revealed the binding model of the effective group with the hydrophobic pocket of SND1. Co-crystal structure data showed that C26-A2 and C26-A6 both bind to a pocket on the surface of the SND1 protein formed by key residues (Figure 6). These compounds are positioned closely in the R255 side chain, and two direct hydrogen bonds between N and N2 atoms of the triazole and pyridylamine part of C26-A2 or the methyltriazole and pyridylamine part of C26-A6 respectively, with R255 N and NH2 stabilize the interaction. The chloromethoxyphenyl part positioned the space between residues R255, N281, and I284, occupying the MTDH peptide W401 side chain position. Besides C26-A2 and C26-A6, which have been revealed with co-crystal data, other C26 series compounds provide structure-activity relationships of MTDH-SND1 PPI inhibitors. Based on the luciferase complementation assay data, C-26, C-26-A1, C-26-A2 and C26-A6 have similar inhibitory activity against MTDH-SND1 PPI (Table1). These compounds share a similar scaffold structure: A fragment consisting of chloromethoxyphenyl and B fragment consisting of triazolopyridine. The methoxy group of the A fragment contributes significantly to the PPI inhibition activity, and changing the substitution position of the methoxy group leads to reduced activity. The activity of the linked A-B

fragment depends on the sulfonamide part, which is crucial for PPI inhibition. The aromatic fused ring of the B fragment is essential for activity, and saturating or opening the triazolopyridine leads to loss of inhibition activity. Changing the linkage position of the amine and substituting the N atom of the triazolopyridine in the B fragment simultaneously results in a significant decrease in inhibition activity, suggesting that the linkage mode between the A and B fragments and the alpha N of the triazolopyridine may be important structural affecting the binding of small molecule inhibitors to SND1. Although no direct hydrogen bond between the sulfonamide group and the SND1 pocket was observed from the co-crystal structure, Xu et al. suggested that the sulfonamide group, rather than the methyltriazolopyridinamine part, might form a hydrogen bond with SND1 R255 based on molecular dynamics simulation study of C26-A6[132]. The reports of compound C26 series as well as two SND1 co-crystals validate the hydrophobic pocket in the MTDH-SND1 complex with potential binding ability to small molecule inhibitors. At the same time, differences in the activities of C26 series also provide part of the structure-activity relationship. Previous studies on C26 series have not focused on the structural and physicochemical properties of small molecules, which means that developing novel small molecule inhibitors targeting the MTDH-SND1 complex is still to be explored in these aspects.

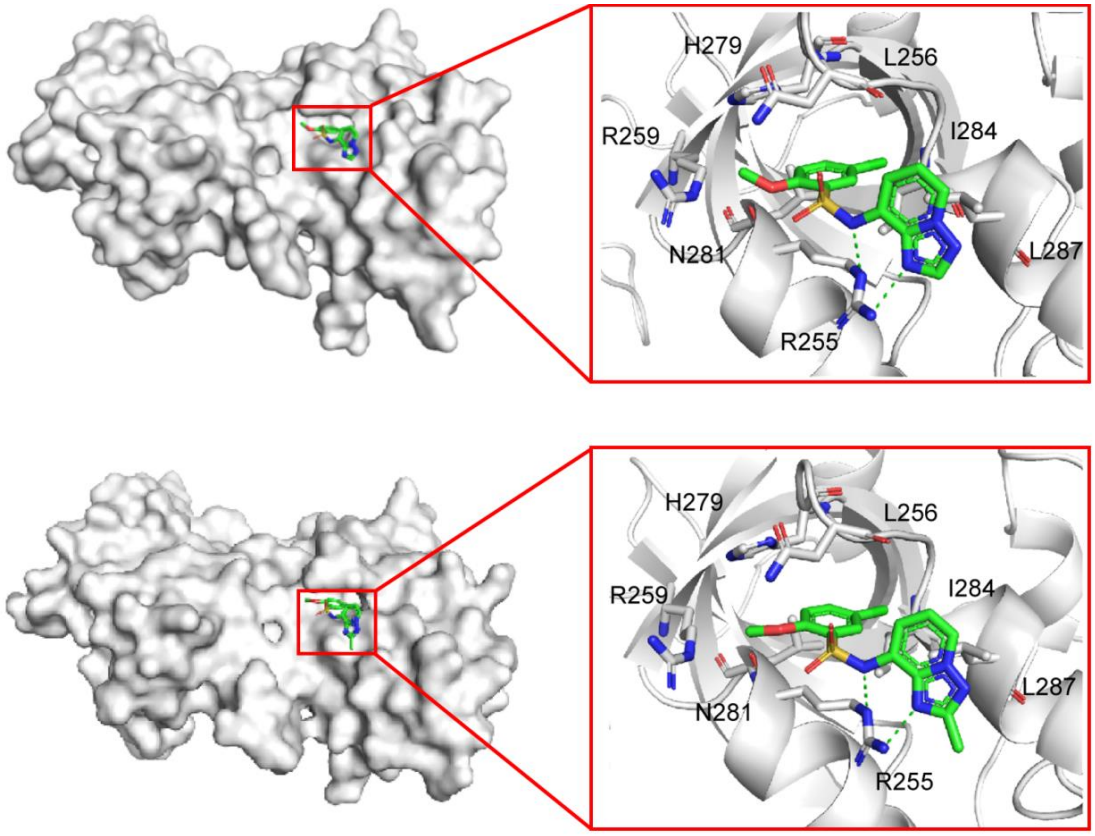


Figure 6. Cocrystal structures of C26-A2(PDB:7KNW, top) and C26-A6(PDB:7KNX, bottom) with SND1. SND1 R255, L256, R259, H279, N281, I284, and L287 form the hydrophobic pocket binding with C26s; two direct hydrogen bonds formed between N and N2 atoms.

8. Conclusion and perspectives

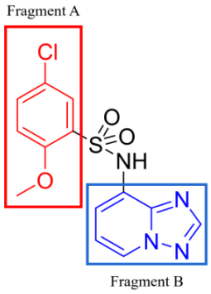
Novel therapies targeting oncogenes have become essential in diagnosing malignant tumors, inhibiting tumor progression, and improving patient prognosis[134,135]. Bioinformatics analysis and experimental studies have revealed that MTDH is a critical biomarker in cancer, and that MTDH is implicated in various aspects of cancer

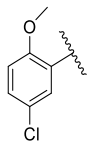
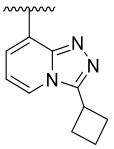
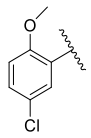
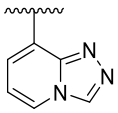
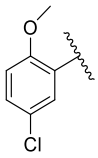
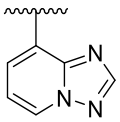
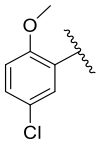
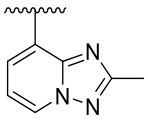
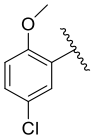
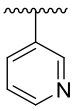
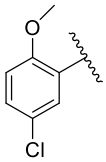
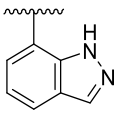
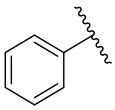
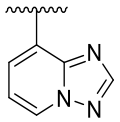
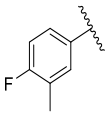
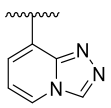
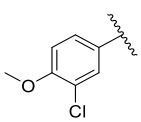
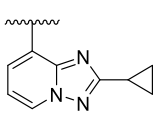
biology, including initiation[76], invasion[82], migration[83], drug resistance[103,] and immune escape[104]. However, the molecular mechanisms and protein interactions of MTDH are still under investigation.

MTDH lacks catalytic activity and domain and thus belongs to "undruggable targets[69]". Therefore, developing inhibitors that down-regulate MTDH expression or block the interactions between MTDH and its partner proteins is a promising strategy to inhibit MTDH function in cancer. Recent studies have uncovered the novel mechanisms and pathways by which non-coding RNAs regulate MTDH expression, advancing the understanding of the regulation of MTDH at the nucleic acid level[57,136]. Moreover, several non-coding RNAs that are inversely correlated with MTDH expression have been identified, offering the possibility of suppressing MTDH expression and cancer progression by modulating these non-coding RNAs. Targeting MTDH and relevant signaling pathways, thereby inhibiting the oncogenic functions of MTDH, may be a future direction for cancer therapy. Modified ASOs can target MTDH and inhibit MTDH expression, thereby achieving anti-tumor effects, but the druggability and stability of ASO *in vivo* limit the clinical application of this type of drug for targeting MTDH in cancer treatment.

Although previous studies have shown that multiple residues at the interface of two proteins are involved in the PPI process, not all residues on the interaction surface are indispensable for PPI[137]. Unlike traditional small-molecule inhibitors targeting MTDH or SND1, inhibitors that inhibit the PPI between MTDH and SND1 do not require them to have catalytically orthosteric binding sites, which makes it possible to develop small-molecule inhibitors that indirectly block the main oncogenic functions of MTDH. Recently, two reports of peptides that block MTDH-SND1 PPI showed that modified peptides could occupy the binding site of MTDH on the surface of SND1, thereby disrupting MTDH-SND1 interaction[129,130]. However, due to the lack of modified peptides in peptide toxicity, bioavailability, and stability, novel highly selective small-molecule inhibitors are still the preferred choice for targeting MTDH-SND1 protein interaction therapy. In 2021, the first small-molecule inhibitors C26s that disrupt the binding of MTDH to SND1 were reporeted[131]. This finding is a milestone discovery in the study of MTDH in cancer, and provides valuable insights for the development of small-molecule inhibitors targeting MTDH-related protein interaction. Further studies showed the multiple values of these molecules in combination with chemotherapy and immunotherapy. Recently, computational chemistry studies on the binding mode of the optimal molecule C26-A6 with SND1 protein have been reported, which complemented the structure-activity relationship studies of C26s compounds and provided a favorable basis for further development of small-molecule inhibitors disrupting MTDH-SND1 PPI. At the same time, the group obtained several small molecules that were determined to have binding ability with SND1 through comprehensive computer-aided drug design (CADD), which provided structural references for the design and modification of novel PPI small molecules. With the development of computer technology, screening and optimization of small molecules by CADD has become an important field in medicinal chemistry and an essential method for drug development[138,139]. Although ASO, peptides, or small molecule inhibitors targeting MTDH or MTDH-SND1 PPI have been reported, the inhibitors still faces tremendous challenges as excellent drugs for cancer treatment. Current research reports are in the stage of animal models in the form of peptides or small molecule inhibitors, and there is no comprehensive evaluation data in terms of safety and pharmacokinetic properties, there is still much work to be done before clinical trials. At the same time, the development of novel, efficient, and safe inhibitors targeting the MTDH-SND1 complex is still in the investigational stage due to the limited number of reports of peptide and small molecule inhibitors. In addition, traditional Chinese medicine is a valuable compound resource, and combining computer-aided drug design technology to screen, modify, and optimize natural product structures may become a potential research and development idea for novel small-molecule inhibitors targeting MTDH-SND1 PPI.

Table 1. Structures and MTDH/SND1 interaction blocking abilities of representative C26s compounds.



Compd.	Fragment A	Fragment B	MTDH/SND1 interaction blocking ability(50μM)
C-26			**0.76**
C-26-A1			**0.75**
C-26-A2			**0.77**
C-26-A6			**0.95**
C-26-A7			**-0.03**
C-26-A10			**-0.10**
C-26-A3			**0.06**
C-26-A4			**0.02**
C-26-A14			**0.23**

Tumor immunology is a subfield of immunology that focuses on the interaction between tumor cells and the immune system[140]. MTDH is a multifunctional protein that plays a role in tumor immune escape and immune resistance. Although several studies on MTDH have increased in recent years, the molecular mechanism of MTDH in modulating immune responses remains poorly understood. Single-cell sequencing technology is a powerful tool to explain the heterogeneity and dynamics of immune cells[141]. With applying single-cell sequencing approaches, identifying the pathways and regulatory processes mediated by MTDH in different immune cell types and thus uncovering novel MTDH-related immune mechanisms and potential therapeutic targets could be a future direction of anti-tumor treatment.

In summary, this review highlighted the significance of MTDH and MTDH-SND1 PPI in cancers, and introduced current therapeutic strategies. We offered an insight into the mechanisms of tumor initiation and progression and guided the development and application of drug targeting MTDH and MTDH-SND1 PPI.

Abbreviations

AEG-1	Astrocyte Elevated Gene-1
AKT	protein kinase B
AMPK	5-adenosine monophosphate-activated protein kinase
ASO	Antisenseoligonucleotide
ATG-5	autophagy related gene5
BCCIPα	BRCA2 and CDKN1A-interacting protein
BRCA	Breast invasive carcinoma
CADD	computer-aided drug design
ccRCC	Clear cell renal cell carcinoma
CPEB3	cytoplasmic polyadenylation element-binding protein 3
CREF	cloned rat embryo fibroblast
CXCL16	CXC chemokine ligand 16
DDX17	DEAD-box helicase 17
DOT1L	DOT1-like, histone H3 methyltransferase
E2F1	E2F Transcription Factor 1
EBNA2	EBV Nuclear Antigen2
EGFR	epidermal growth factor receptor
EMT	epithelial-mesenchymal transition
ENO1	Enolase 1
ER	Endoplasmic Reticulum
ERK	extracellular-signal-regulated kinase
ESCC	Esophageal Squamous Cell Carcinoma
FBXW7	F-box and WD repeat-domain containing 7
FOXM1	Forkhead box protein M1
FP	fluorescence polarization
FRET	Fluorescence resonance energy transfer
GBC	Gallbladder Cancer
GBM	Glioblastoma multiforme
GEO	Gene Expression Omnibus
GFWE	Guizhi Fuling Wan extract
GSK-3β	Glycogen synthase kinase-3 beta

HCC	Hepatocellular Carcinoma
HIT-CLIP	high-throughput sequencing of RNA isolated by crosslinking immunoprecipitation
HIV	human immunodeficiency virus
HSF1	Heat shock transcription factor 1
IBC	inflammatory breast cancer
IF	immunofluorescence
KDM6A	Lysine demethylase 6A
LEF-1	Lymphoid enhancer-binding factor 1
LHD	lung homing domain
LYRIC	Lysine-Rich CEACAM1 Co-Isolated Protein
MAPK	mitogen-activated protein kinase
MEC	mammary epithelial cell
MMP2	matrix metalloproteinase 2
MMP9	matrix metalloproteinase 9
MSN	Moesin
MST	Microscale thermophoresis
MTDH	Metadherin
NF-kB	nuclear factor-k-gene binding
NLS	nuclear localization signal
NSCLC	Non-Small-Cell Lung Cancer
PAR-CLIP	photoactivatable ribonucleoside-enhanced crosslinking and immunoprecipitation
PD-1	programmed cell death protein 1
PDCD11	programmed cell death protein 11
PD-L1	Programmed cell death 1 ligand 1
PHFA	primary human fetal astrocytes
PI3K	Phosphoinositide-3 kinase
PLZF	Promyelocytic leukemia zinc finger
PPI	Protein-Protein interaction
PRMT5	protein arginine methyltransferase 5
PTEN	phosphatase and tensin homolog deleted on chromosome ten
RBP	RNA-binding protein
RIP-Chip	RNA binding protein immunoprecipitation-Chip
RISC	RNA-inducing silencing complex
RKIP	Raf kinase inhibitor protein
RXR	retinoid X receptor
SG	stress granule
SN	Staphylococcal nuclease
SND1	Staphylococcal nuclease domain containing 1
STAT3	signal transducer and activator of transcription 3
SUMO	small ubiquitin-like modifier
TCGA	The Cancer Genome Atlas
TGF-β1	transforming growth factor beta 1
TIC	mammary tumor-initiating cell
TNBC	triple-negative breast cancer

TNF-α	Tumor Necrosis Factor alpha
TOPORS	TOP1 binding arginine/serine rich protein
VEGFR	vascular endothelial growth factor receptor
YB1	Y-box binding protein 1
zDHHC6	zinc finger, DHHC-type containing 6

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Conflict of interest

The authors declare no competing interests.

Author contributions

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