



Friend or Foe? The fascinating Tudor-SN protein

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Received 23 January 2023, Accepted 14 February 2023, Published online 7 March 2023

Abstract – Tudor-SN (Tudor staphylococcal nuclease), also known as p100 or SND1 (Staphylococcal nuclease and Tudor domain containing 1), is a structurally conserved protein with diverse functions. Emerging evidence indicates that Tudor-SN plays an essential role in both physiological and pathological processes. Under physiological conditions, Tudor-SN regulates DNA transcription, RNA splicing, RNA stability, RNA interference, and RNA editing, and it is essential for a series of cellular biological events, such as cell cycle progression, cell metabolism, and cell survival, in response to harmful stimuli; thus, Tudor-SN functions as a “friend” to the body. However, Tudor-SN is highly expressed in most tumor cells. As an oncoprotein, Tudor-SN is closely associated with the initiation, development, and metastasis of tumors; thus, Tudor-SN functions as a “foe” to the body. What is the potential mechanism by which Tudor-SN switches from its role as “friend” to its role as “foe”? In this study, we review and summarize the available evidence regarding Tudor-SN protein structure, expression, modification, and mutation to present a novel model of Tudor-SN role switching. This review provides a comprehensive insight into the functional significance of the Tudor-SN protein under physiological and pathological conditions as well as corresponding therapeutic strategies that target Tudor-SN.

Key words: Tudor-SN, Expression regulation, Stress, Tumor, Role switching, Targeted intervention.

Introduction

Cells function as the basic units of an organism and perform normal physiological functions; these functions depend on the close cooperation of intracellular nucleic acids, proteins, and other molecular substances. Some cellular biomolecules are vital regulators of normal physiological functions and homeostasis. However, when these molecules undergo abnormal changes in structure, expression, modification, localization, and macromolecule activity, they may promote a transition to pathological conditions and disease development. For instance, the well-known p53 protein is widely considered to be a genetic regulator in cells due to its essential role in regulating multiple aspects of physiological function and in protecting against stress. However, when the p53 gene is mutated, the protein becomes a critical factor that promotes tumorigenesis [1, 2].

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Herein, we introduce a similar multifunctional protein, namely, Tudor-SN, which plays distinct roles under different cellular conditions. The underlying molecular mechanisms warrant attention. We summarize the available evidence regarding the function of Tudor-SN in order to understand the potential mechanism by which this protein switches from its role as a “friend” to its role as a “foe” as well as potential strategies for treating tumors by targeting Tudor-SN.

Discovery and preliminary study

The Tudor-SN protein, also known as p100, SND1, or TSN (Tudor staphylococcal nuclease), shows a certain conservation across different species [3–9]. In 1995, Tong and colleagues first reported that Tudor-SN serves as a transcriptional coactivator of human Epstein–Barr virus nuclear antigen 2 (EBNA2) and has a molecular weight of approximately 100 kDa (originally termed “p100”) [10]. Subsequently, scholars explored the structure and function of Tudor-SN from different

perspectives. In 1997, Callebaut and Morion used hydrophobic cluster analysis to show that Tudor-SN includes four repetitive SN-like (staphylococcal nuclease-like) domains in its N-terminus and a Tudor domain in its C-terminus [11]. Our research group has been paying attention to the Tudor-SN protein for a long time and found for the first time that the C-terminus of Tudor-SN contains a TSN domain that is composed of Tudor and two truncated SN5 (SN5a, SN5b) fragments [12]. Preliminary studies highlighted the role of this protein in gene transcription activation. As a transcriptional coactivator, the fragment (449–554) of the Tudor-SN protein can be phosphorylated by PIM1 kinase, and the PIM1/Tudor-SN complex is essential for the enhancement of c-Myb transcriptional activity [13]. Through a series of experiments, we confirmed that the Tudor-SN protein can function as an essential transcriptional coactivation factor during gene transcription via its SN domain [14–17], and it can also participate in the splicing of pre-mRNAs via its TSN domain [12, 18, 19].

Structure resolution

With the continuous improvement in protein structure analysis techniques, the structural characteristics of different Tudor-SN protein species are becoming clear. As shown in Figure 1, the human Tudor-SN protein is currently believed to consist of N-terminal SN1 ~ SN4 and C-terminal TSN (SN5a–Tudor–SN5b) domains. Based on its different domains, the Tudor-SN protein plays different biological roles in DNA transcription, RNA splicing, RNA stabilization, RNA interference, and RNA editing.

In 2007, we determined the crystal structure of the TSN domain for the first time (Fig. 1), and we observed that it includes an aromatic cage with four conserved residues (Tyr721, Tyr738, Tyr741, and Phe715), which can bind to the methylation groups of U snRNPs (uracil-rich small nuclear ribonucleoprotein bodies) [12]. In 2008, Li et al. [20] observed a crescent-like structure containing SN3/4/5 and Tudor domains and a concave basic surface, which may mediate the specific capture and degradation of highly edited IU- and UI-containing dsRNA (Fig. 1). In 2014, Guo et al. [21] further resolved the high-resolution crystal structure of the human Tudor-SN/MTDH (metadherin) complex and demonstrated that eleven amino acid residues (DWNAPAEEWGN) of MTDH are located in the protein groove between SN1 and SN2; in this region, the W394 and W401 sites of MTDH are critical for the interaction of Tudor-SN with MTDH (Fig. 1). This also provides the molecular basis for functional links between the Tudor-SN/MTDH interaction and breast cancer, liver cancer, colon cancer, and glioma (Table S1).

In addition to the human Tudor-SN protein, researchers have also analyzed the structure of the *Drosophila* Tudor-SN protein. In 2009, Friberg and colleagues resolved the crystal structure of the Tudor domain in *D. melanogaster* and observed the existence of a similar aromatic cage consisting of Phe760, Tyr767, Tyr783, Tyr786, and Asn788; this ring specifically binds to sDMA (symmetric demethylation)-modified Sm protein ligands [22]. In 2010, another crystal structure analysis by Liu, H. et al. further confirmed the binding characteristics

of the *Drosophila* Tudor domain with an sDMA-modified Piwi family member, Aubergine protein [23]. In the same year, Liu, K. et al. resolved the mode by which the *Drosophila* Tudor domain binds to another member of the sDMA-modified Piwi family, namely, the PIWIL1 protein [24]. These structural findings indicate a conserved binding pattern of the Tudor domain with sDMA-modified protein ligands in humans and *Drosophila*.

Functional exploration

The structural characteristics of the Tudor-SN protein are the basis of its function. Increasing evidence shows that different functional fragments of the Tudor-SN protein are essential for DNA transcription and RNA metabolism, and Tudor-SN participates in modulating cell proliferation, cell cycle progression, differentiation, apoptosis, stress, metabolism, and other cell biological events. Tudor-SN serves as a “friend” of the body to modulate cellular homeostasis, and this function is essential for cellular growth and survival. Here, we focus on the functional links between Tudor-SN and DNA transcription, RNA splicing, RNA stability, RNA interference, and RNA editing.

DNA transcription

The Tudor-SN protein acts as a coactivator of several transcription factors, including STAT6 [14–16], STAT5 [17], PPAR γ [25], E2F1 [26], and EBNA2 [10], to promote downstream gene transcriptional activation.

We confirmed the transcriptional regulation of DNA by Tudor-SN through a series of experiments (Fig. 2). For instance, as a transcriptional coactivator of STAT6 (signal transducer and activator of transcription 6), the Tudor-SN protein binds the TAD domain of STAT6 via its SN domain and mediates interactions between STAT6 and RNA polymerase II, promoting IL-4/STAT6-mediated I ϵ gene transcription. In addition, Tudor-SN can influence the chromatin modification of IL-4-dependent downstream target gene regions of STAT6 by recruiting acetyltransferase CBP/p300 and RNA helicase A (RHA) [14–16]. We also reported that Tudor-SN can act as a coactivator to enhance the transcriptional activity of STAT5 (signal transducer and activator of transcription 5) and the prolactin-induced transcription of milk protein genes [17]. Cdk 2/4/6 can mediate the phosphorylation of the human Tudor-SN protein at Ser-426/Thr-429, and this phosphorylated form functions as a coactivator of E2F1 to facilitate the G1/S transition during the cell cycle [26]. Tudor-SN also acts as a transcriptional coactivator of PPAR γ , a key transcription factor in adipocyte differentiation, and assists PPAR γ in promoting adipocyte differentiation and lipid droplet formation by enhancing histone acetylation [25]. In addition to binding to transcription factors, Tudor-SN can affect chromatin conformation and regulate gene transcription by recruiting the histone acetyltransferases GCN5 and CBP/p300 or the ATP-dependent chromatin remodeler SMARCA5 [16, 25, 27–31].

Upon X-ray or laser irradiation, Tudor-SN can interact with PARP-1 and be recruited sites of DNA damage in a poly(ADP-ribosylation) modification-dependent manner. Subsequently,

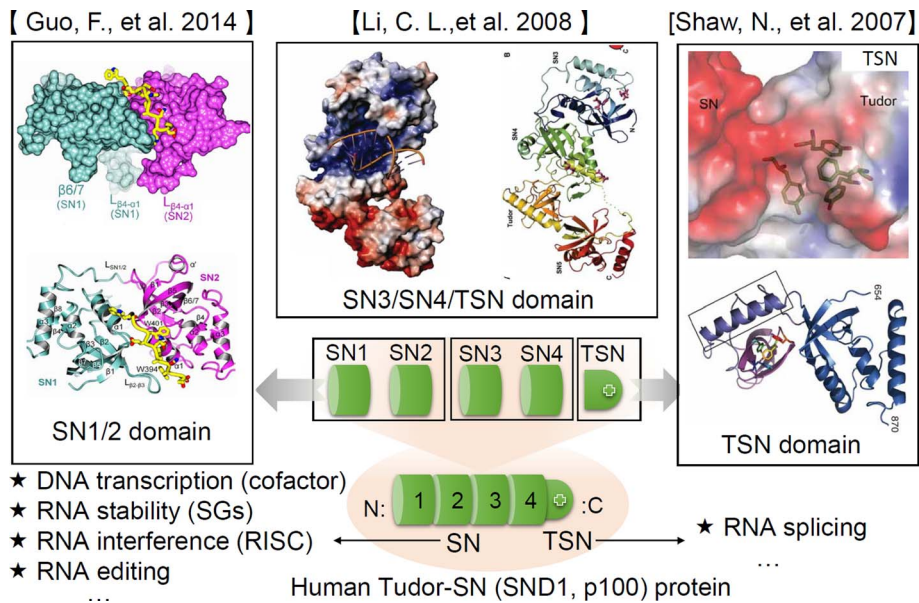


Figure 1. Structural characteristics of the human Tudor-SN protein.

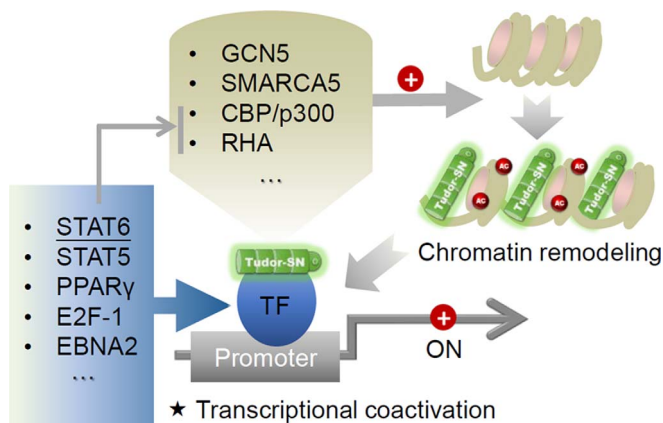


Figure 2. Regulation of DNA transcription by the Tudor-SN protein.

Tudor-SN can recruit SMARCA5 and GCN5 to sites of DNA breaks and regulate the histone modification of the damaged site, resulting in chromatin relaxation and the activation of ATM kinase and downstream DNA repair pathways, which contribute to cell survival [30]. In addition, we found that in SKOV3 cells, Tudor-SN activates SLUG transcription by recruiting the acetyltransferases GCN5 and CBP/p300 to the SLUG promoter proximal region to increase chromatin accessibility, and this process is involved in the regulation of epithelial-mesenchymal transformation in ovarian cancer cells [29]. This evidence indicates that the transcriptional coactivation role of Tudor-SN is essential for IL-4/STAT6 signal transduction, cell cycle progression, adipose differentiation, DNA damage, and other biological events and is one of the key factors in the growth and survival of cells under physiological or even pathological conditions.

RNA splicing

Our findings first highlighted the role of p100 in RNA splicing. Moreover, we reported that the TSN domain of human Tudor-SN can interact with the core protein of U5 snRNP and sDMA (symmetric dimethylation)-modified Sm proteins to facilitate snRNP assembly and pre-mRNA splicing [12, 18, 19].

In eukaryotic cells, pre-mRNAs become mature mRNA molecules through splicing by the spliceosome. The spliceosome is mainly composed of U snRNP, which includes U1, U2, U4/U6, U5 snRNA (small nuclear RNA), and a set of proteins. During the splicing process, the spliceosome functions as a dynamic complex unit. During the process of splicing, the snRNA and protein components of the spliceosome constantly change. For each splicing reaction, the spliceosome must be recombined and activated before the next reaction can be performed. According to the dynamic changes in snRNP components, the spliceosomes at different periods can be named complexes A, B, and C. [32]. In addition to its gene transcription coactivator role, we demonstrated for the first time that the Tudor-SN protein is involved in regulating the splicing of pre-mRNA, promoting complex A formation and the transition of complex A to complex B [12, 18, 19] (Fig. 3a). Tudor-SN can interact with SmB/B'/D1/D3 proteins undergoing symmetric dimethylation through its TSN domain to promote the recruitment of Sm protein to U1 and U2 snRNA to form spliceosome complex A [12, 18, 19]. Tudor-SN also interacts with several U5 snRNP-specific proteins (e.g., U5-116, Prp8) to participate in the cytoplasmic assembly of U5 snRNP and may be involved in promoting the transformation from complex A to complex B [12, 18, 19]. This splicing effect of Tudor-SN can be influenced by mutations in conserved aromatic amino acids in its TSN domain [12, 19] or by caspase-3-mediated Tudor-SN truncation [33]. After the point mutation of four conserved amino acids in the aromatic cage structure of TSN,

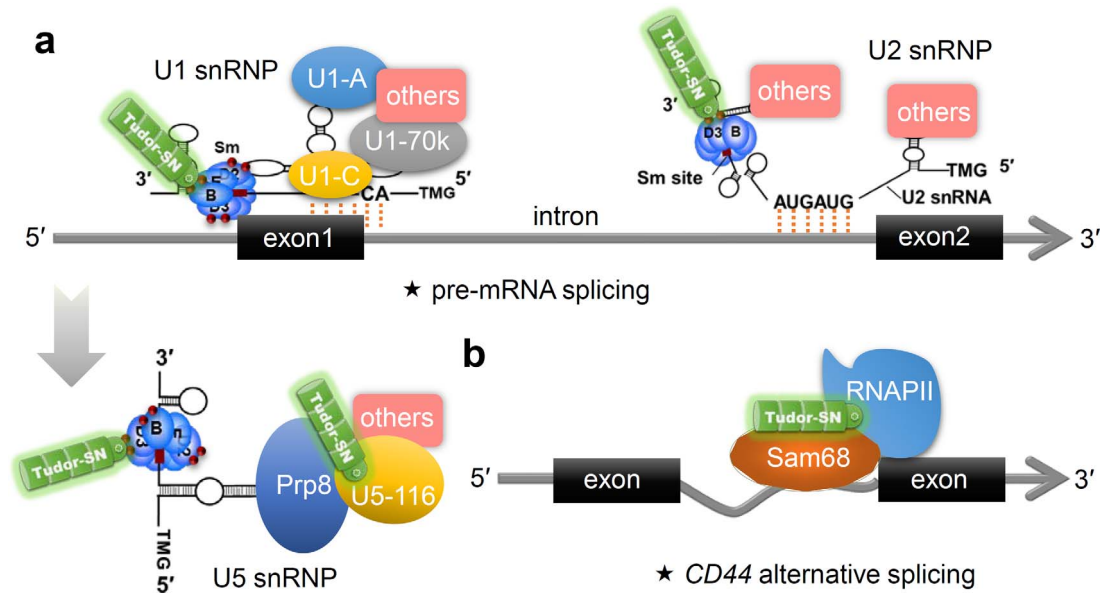


Figure 3. Functional links of Tudor-SN protein and RNA splicing. (a) Pre-mRNA splicing; (b) alternative splicing.

Tudor-SN was found to have a reduced ability to bind to its Sm B protein-ligand, which inhibited its function in promoting pre-mRNA splicing [19]. In addition, there is evidence that Tudor-SN can preferentially interact with exon regions that flank introns with high splicing efficiency [34]. Cappellari et al. also reported that Tudor-SN is involved in regulating the selective splicing of *CD44* pre-mRNA in prostate cancer cells by interacting with the SAM68 protein [35] (Fig. 3b). The unique TSN domain allows the Tudor-SN protein to play an important role in cellular RNA splicing, and it is an important domain by which Tudor-SN maintains cell homeostasis.

RNA stability

Cells have evolved various adaptive protective mechanisms to achieve a balance between survival and death when they encounter complex and variable adverse environmental stimuli. SGs (stress granules) and PBs (processing bodies) are two RNA metabolism-related cytosolic granular structures that form during stress [36–38]. Upon cellular stimulation, mRNAs that exist in a translational repression state are released from polyosomes and then maybe sorted and recruited into SGs for protection or selectively delivered to PBs for degradation [36–38]. Increasing evidence shows that the Tudor-SN protein is functionally related to SGs and PBs in different species (Fig. 4). In *Arabidopsis*, Tudor-SN localizes in both SG and PB structures to improve stress tolerance and promote the growth and survival of cells under adverse environmental conditions [7, 39]. Unlike in plant cells, Tudor-SN is localized only to SGs, but not PBs, in animal cells [40–42]. Video 1 shows the SG assembly of RFP-Tudor-SN fusion protein in HeLa cells upon the oxidative stress.

Our findings showed that human Tudor-SN physically binds the G3BP protein via its SN domain and regulates the efficiency of SG assembly [40]. We also reported an essential role of

JNK-mediated Tudor-SN phosphorylation at the Thr-103 site in SG assembly [43]. Furthermore, as a poly(A)⁺ mRNA-binding protein, human Tudor-SN can bind and stabilize *AT1R* mRNA in SGs for protection during stress [41, 44]. Weissbach and Scadden et al. also reported that Tudor-SN binds to the ADAR protein [42] and colocalizes with IU-dsRNA in cellular SG structures, contributing to the inhibition of transcriptional initiation of specific mRNAs under stress conditions [45]. These results suggest that the Tudor-SN protein contributes to cellular survival under stress conditions by binding to specific nucleic acids and proteins to form complexes that affect the stability of specific RNA transcripts.

RNA interference

In 2003, Caudy et al. reported for the first time that the Tudor-SN is a component of the RISC (RNA-induced silencing complex) [46]. Subsequently, there have been several lines of evidence that in multiple species, the Tudor-SN protein can interfere with target mRNA by participating in RISC assembly, but its calcium-dependent nuclease activity is different [9, 46–54]. For instance, the Tudor-SN protein in the RISC of *Arabidopsis* and African trypanosomes possess no or only minor nuclease activity [49–52, 55]. However, in mammals, *Drosophila*, *Caenorhabditis elegans*, ticks, and *Toxoplasma gondii*, the Tudor-SN protein has an enzymatic activity similar to that of other staphylococcal nucleases [8, 9, 46, 47, 54, 56].

RNA editing

During viral infection, Dicer mediates the processing of cytoplasmic dsRNA into siRNA, while Drosha RNase III and Dicer are responsible for the conversion from pri-miRNA to pre-miRNA and then mature miRNA [57, 58]. In the presence of ADAR, dsRNA, and pri-miRNA undergo A to I RNA editing and become IU-dsRNA and IU-pri-miRNA, respectively

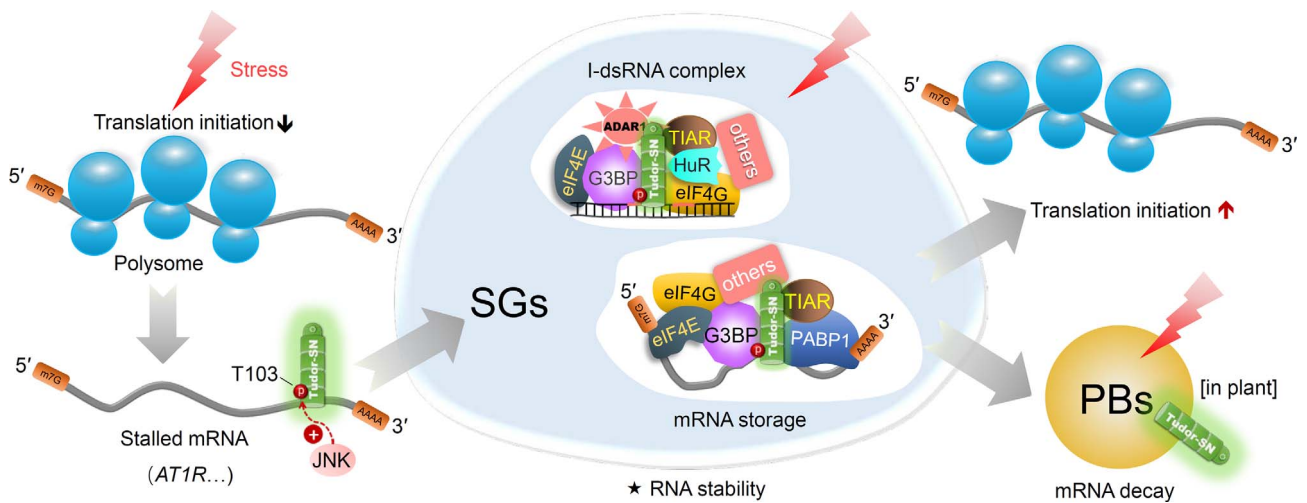


Figure 4. Association between Tudor-SN and cellular stress.



Video 1. Tudor-SN SG assembly in HeLa cells. <https://vcmedpsciences.org/10.1051/vcm/2023001#V1>.

[57, 59, 60]. The Tudor-SN protein participates in the degradation of certainly edited pri-miRNAs, dsRNAs, and specific miRNAs [20, 61–65]. For example, Tudor-SN can mediate the decay of A to I highly edited pri-miR-142 [61]. Tudor-SN specifically binds to and cleaves I-dsRNAs enriched with IU base pairs [62], which is consistent with crystal structure data [20]. The Tudor-SN protein interacts with and mediates the decay of IU-dsRNA and IU-pri-miRNA through its nuclease activity [20, 61–63]. Furthermore, Elbarbary et al. reported that Tudor-SN can directly degrade CA- and UA-rich miRNA substrates through its nuclease activity during the G1/S transition of the cell cycle [64, 65]. These results suggest that Tudor-SN may modulate the steps upstream of the siRNA/miRNA RISC pathway through its RNA editing ability.

Switching from the role of “friend” to the role of “foe”

Expression balance

The orderly temporospatial expression of Tudor-SN is crucial for the normal physiological function of cells. Herein,

we attempt to explore the fine-tuned process of Tudor-SN expression regulation through the mechanisms of “coming” and “going”. Regarding the “coming” mechanism, the transcriptional activity, DNA methylation, RNA stability, protein translation, and stability maintenance of Tudor-SN are analyzed. Regarding the “going” mechanism, the degradation and truncation of Tudor-SN are analyzed at both the mRNA and protein levels.

In terms of the “coming” mechanism, in response to specific stimulation, Tudor-SN is transcriptionally regulated by different transcription factors, such as NF- κ B, Smad2/3, SP1, NF-Y, c-Myb, CEBP/ β , and SREBP-1/2 [25, 66–75]. Tudor-SN is expressed at high levels in most tumor cells, but no DNA hypomethylation is observed in the Tudor-SN promoter region [4]. The potential G-quadruplex structure of the proximal promoter may be involved in the delicate regulation of Tudor-SN expression in both space and time [66]. We observed a TOP structure in the 5' terminal region of *Tudor-SN* mRNA, and the translation activity of Tudor-SN can be regulated by the mTOR signaling pathway [76]. In addition, some protein binding partners (e.g., MTDH) may maintain Tudor-SN protein stability under stress conditions [77, 78].

In terms of the “going” mechanism, multiple miRNAs (e.g., miR-184, miR-361-5p, and miR-320a) [79–81] and the potential G quadruplex structure within the 3'UTR (untranslated region) of *Tudor-SN* [66] may be implicated in the mRNA decay of *Tudor-SN*. Caspase 3 can mediate the truncation of the Tudor-SN protein between the Tudor and SN5 domains by recognizing the DAVD790 motif [33]. In human embryonic diploid cells, overexpression of PIM1 can induce Tudor-SN degradation, which can be blocked by MG132, suggesting the occurrence of ubiquitination-mediated Tudor-SN protein degradation [82]. Additionally, we performed experimental assays to observe the presence of ubiquitination in the Tudor-SN protein and identified ubiquitination signals at multiple sites in Tudor-SN by mass spectrometry (data not shown). Tudor-SN has been reported to directly bind to the ubiquitin-like protein-modified molecule SUMO-2 *in vitro* [83], suggesting that the regulation of Tudor-SN protein stability may involve SUMO modification.

Based on these “coming” and “going” regulatory mechanisms, intracellular expression of Tudor-SN reaches a state of dynamic equilibrium, which matches the functional coordination and effectiveness of Tudor-SN. For instance, the precise caspase 3-mediated truncation of Tudor-SN in time and space may be essential for programmed cell death during normal organismal development [33]. However, when this equilibrium is disrupted, the functional abnormality of Tudor-SN contributes partly to the change in cellular status from physiological to pathological, which is accompanied by the switching of the Tudor-SN protein from its role as “friend” to its role as “foe” of the body. Activation of tumor-associated signaling pathways (TGF β , NF- κ B, TNF- α) can cause the high expression of Tudor-SN through the action of related transcription factors, which facilitate the excessive proliferation and migration of tumor cells.

Role switching model

A series of reports have successively documented the role of Tudor-SN in clinical tumor diseases, such as liver cancer, breast cancer, prostate cancer, and glioma. In this review, we summarized the reported molecular mechanisms by which Tudor-SN functions in diseases in terms of its structural properties, spatiotemporal expression, binding partners, functional alterations, and targeted interventions (Table S1). The potential roles of Tudor-SN in the initiation or progression of several clinical tumors, especially hepatocellular carcinoma (HCC) and breast cancer, have been reported in succession. Herein, we explored the potential mechanism by which Tudor-SN changes its functions related to tumorigenesis. Tudor-SN is more highly expressed in most tumors than in normal control tissues. Therefore, what is the mechanism underlying Tudor-SN overexpression? Under normal physiological conditions, Tudor-SN expression is maintained at equilibrium through the abovementioned “coming” and “going” mechanisms. However, the disruption of this balance between the “coming” and “going” mechanisms may lead to the high expression of Tudor-SN in tumors. For example, in tumor cells, some factors that mediate the transcription of Tudor-SN, including transcription factors (e.g., Smad2/3) and the protein stabilizer MTDH, exhibit a high expression level [21, 73, 84], whereas some miRNAs that induce the decay of Tudor-SN mRNA and are expressed at low levels [79–81].

In addition, there is an interactive regulatory mechanism between Tudor-SN and the TGF β , PI3K-AKT-mTOR, and NF- κ B signaling pathways. Tudor-SN is transcriptionally activated by the TGF β and NF- κ B pathways [70, 73, 85] but also participates in the regulation of the gene transcription of TGF β and NF- κ B pathway-related members [28, 86–89]. The PI3K-AKT-mTOR pathway can regulate the translation of the Tudor-SN protein [76], and components of this pathway can also be induced and activated by high Tudor-SN expression [87, 90, 91]. It is thus hypothesized that activation of the TGF β , NF- κ B, and PI3K-AKT-mTOR pathways in tumor cells mediates the overexpression of Tudor-SN by regulating the processes of RNA transcription and protein translation, and the upregulation of Tudor-SN expression, in turn, facilitates

the activation of these signaling pathways. Thus, a positive feedback mechanism is formed.

Emerging evidence suggests functional links between high expression of Tudor-SN and the proliferation, invasion, and migration of tumor cells (Table S1). Thus, is the high expression of Tudor-SN related to tumorigenesis? It was reported that hepatocyte-specific Tudor-SN transgenic mice (Alb/Tudor-SN mice) exhibited partially spontaneous tumor formation after a long period of feeding [87]. In addition, compared with control mice, more aggressive HCC tumors formed in Alb/Tudor-SN mice after exposure to carcinogenic chemicals [87]. Tudor-SN is highly expressed in the tissues of precancerous colon cancer and at the early stages of colon cancer [92]. These results suggest a potential impact of Tudor-SN overexpression on tumorigenesis.

The promoting influence of Tudor-SN on tumor-initiation cell (TIC) formation may partially explain the protumorigenic effect of Tudor-SN [78, 87]. In HCC, high Tudor-SN expression activates the Akt and NF- κ B signaling pathways and facilitates TIC formation [87]. In breast cancer, the Tudor-SN/MTDH complex is implicated in the formation, expansion, and activity maintenance of TICs and tumor metastasis [78]. Thus, we propose a model by which Tudor-SN switches from its role as “friend” to its role as “foe” of the body (Fig. 5); this model includes four stages, namely, “physiological function”, “stress protection”, “tumorigenesis” and “tumor progression”.

The first stage is the “physiological function” stage. Based on the “coming” and “going” mechanisms described above, the expression of Tudor-SN is maintained at intracellular equilibrium. The specific structural properties and spatiotemporal expression patterns contribute to the crucial role of Tudor-SN in normal cellular physiological processes, especially DNA transcription and RNA metabolism. Tudor-SN promotes cell proliferation, differentiation, and tissue development and participates in the maintenance of homeostasis.

The second stage is the “stress protection” stage. When exposed to a certain degree of adverse stimulation, Tudor-SN plays a protective role against the stress through a series of adaptive mechanisms to increase the viability of normal cells. For instance, when Tudor-SN is phosphorylated at the Thr-103 site, it aggregates into the SG structure to protect against stress by interacting with different stress-related proteins and translationally repressed mRNA transcripts. Poly(ADP-ribosyl)ated Tudor-SN binds to PARP-1 and participates in the DNA damage repair process through the ATM signaling pathway.

The third stage is the “tumorigenesis” stage. As the intensity of external adverse stimulation increases or the time of stress increases, the physiological status of cells gradually transforms into a pathological status. The positive feedback transcriptional mechanisms of the TGF β , NF- κ B, and PI3K-AKT-mTOR pathways and the inhibition of specific miRNA-mediated Tudor-SN decay may disrupt the “coming” and “going” equilibrium and result in high expression of Tudor-SN, which partly contributes to the survival of cells under pathological conditions. Furthermore, the genetic mutation of Tudor-SN and the effect of Tudor-SN in facilitating tumor-initiating cell formation are considered drivers of tumorigenesis for specific tumors as well.

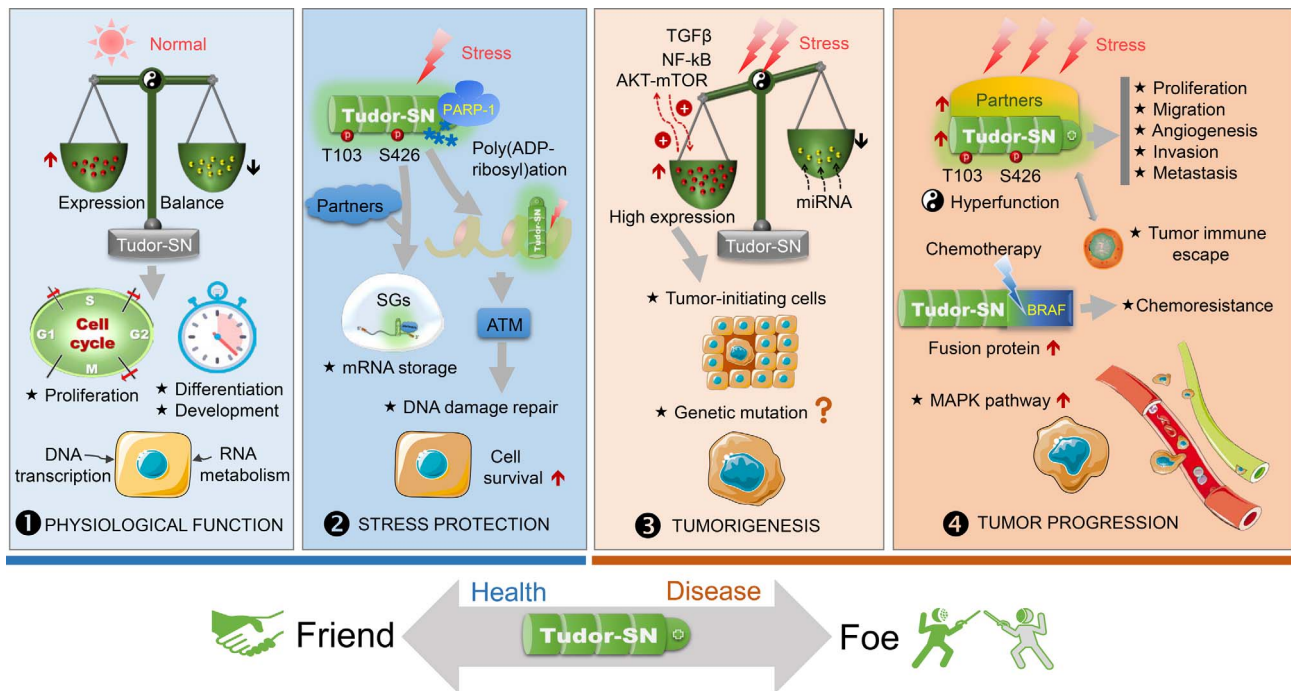


Figure 5. Model of Tudor-SN role switching.

The fourth stage is the “tumor progression” stage. Tumor cells with high Tudor-SN expression are hyper-functional and exhibit enhanced resistance to strong external stress pressure. The effects of Tudor-SN on promoting the proliferation, invasion, migration, metastasis, angiogenesis, and immune escape of tumor cells significantly contribute to the implication of Tudor-SN in tumor progression. When exposed to repeated stimulation by certain chemotherapeutic agents, some tumor cells may also acquire the fusion mutation of Tudor-SN: BRAF, which is accompanied by the activation of the MAPK pathway. This adaptive change protects the tumor cells from the killing effect of the drugs.

Of note, Tudor-SN tends to promote the survival of cells in either the “Health” (physiological health) status of the first/second stages or the “Disease” (pathological disease) status of the third/fourth stages. The synergistic abnormalities in the expression or protein structure of many biomolecules (e.g., p53, Tudor-SN) contribute to the carcinogenesis of cells. Tudor-SN may help to enhance the stress resistance and proliferation of cells with cancerous tendencies. This may be the crucial link in the switching of Tudor-SN from its role as “friend” to its role as “foe”.

Exploration of targeted interventions

Considering the potential mechanism underlying the role-switching of Tudor-SN, the exploration of possible Tudor-SN-targeting intervention strategies may benefit the diagnosis and treatment of Tudor-SN-related clinical diseases, particularly tumors. Tudor-SN exerts an anti-apoptotic effect, and Tudor-SN depletion enhances cellular sensitivity to chemotherapeutic agents and radiation [93–95]. A small molecule called suramin can inhibit the RNA binding ability of Tudor-SN and then

enhance the miR-1-3p expression level, leading to an increased sensitivity of colon carcinoma cells to navitoclax [96]. The expression of different types of Tudor-SN: BRAF fusion proteins was observed in pancreatic alveolar cell carcinoma, lung adenocarcinoma, prostate cancer tissues, thyroid cancer, and c-Met inhibitor-resistant gastric cancer strain GTL16 (Table S1). Thus, the specific tumor characteristics and mutation patterns should be fully considered in the development of synergistic personalized treatment approaches that include Tudor-SN-targeting treatments and related radiotherapy. Herein, we will summarize the available evidence and describe potential Tudor-SN-targeting intervention strategies from four aspects, including enzyme activity, Tudor-SN/MTDH, Tudor-SN/HLA-A, and Tudor-SN/AT1R (Fig. 6).

Enzyme activity inhibition

The potential nuclease activity of Tudor-SN may contribute to the regulation of RNA metabolism and be reported to be inhibited by a drug called pdTp (3',5' – deoxythymidine bisphosphate, 3',5' – deoxythymidine bisphosphate) [8, 97, 98]. Evidence from HCC cell and mouse models suggests a link between pdTp treatment and tumor inhibition [87, 99], suggesting that the inhibition of Tudor-SN nuclease activity by pdTp can be considered a potential treatment strategy for HCC.

Tudor-SN/HLA-A

Several lines of evidence suggest functional links between Tudor-SN and the immune response of organisms [4, 87, 100–103]. Our findings showed that in tumor cells, highly expressed Tudor-SN cells could target nascent HLA-A for

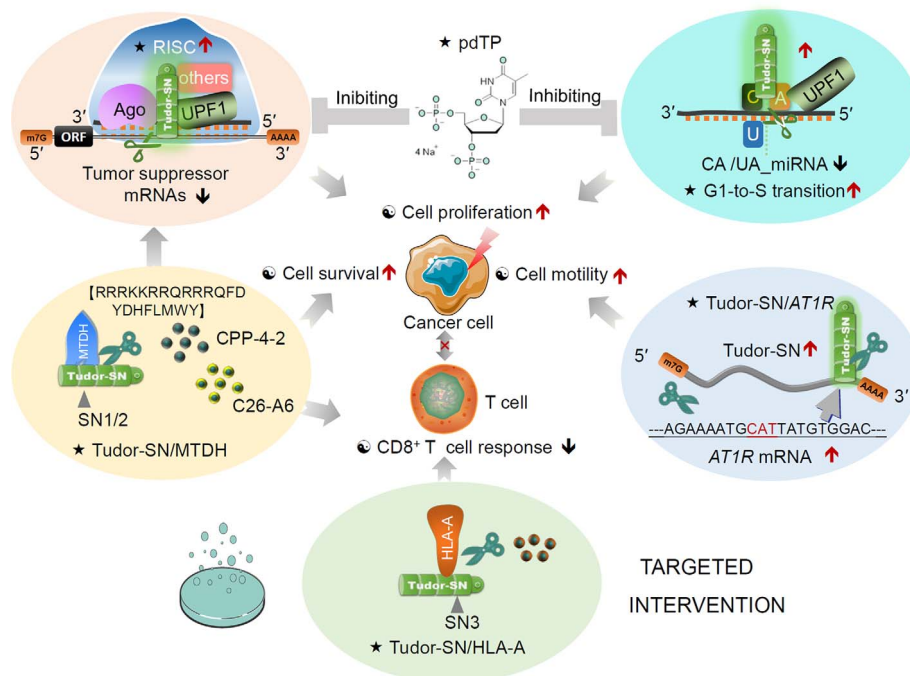


Figure 6. Tudor-SN-targeting tumor intervention strategies.

endoplasmic reticulum-associated degradation [100]. The subsequent reduction in HLA-A expression on the surface of tumor cells suppresses tumor antigen presentation, leading to decreased recognition and killing abilities of CD8⁺ T cells [100]. Further screening of potential inhibitors that interfere with the binding of Tudor-SN and HLA-A will be helpful for suppressing tumor immune escape and investigating possible synergistic therapeutic effects with other immune checkpoint drugs.

Tudor-SN/MTDH

Both Tudor-SN and MTDH are highly expressed in tumor tissues, and MTDH contributes to the stabilization of the Tudor-SN protein under stress conditions. Decreased expression of MTDH may lead to the loss of the anti-apoptotic and pro-survival effects of Tudor-SN [78, 104]. Additionally, Tudor-SN/MTDH exerts a protumorigenic effect by modulating the formation of tumor-initiating cells for breast cancer [78]. Li et al. identified a small peptide called CPP-4-2 through a phage display screening approach, and this peptide can interfere with the Tudor-SN/MTDH interaction and trigger Tudor-SN degradation and breast cancer cell death [77]. Another small-molecule compound, C26-A6, was shown to disrupt the binding of Tudor-SN and MTDH, leading to increased immune surveillance and a synergistic effect with anti-programmed cell death protein 1 treatment in metastatic breast cancer [105]. Additionally, Tudor-SN/MTDH degrades mRNAs that are associated with the tumor inhibition response in HCC cells (e.g., PTEN, p57, p21, etc.) through the nuclease activity of RISC [99, 106]. The use of Tudor-SN/MTDH blockers in conjunction with pdTp may yield a better synergistic antitumor effect for the treatment of HCC.

Tudor-SN/AT1R

As described above, Tudor-SN can bind to the 3'URT of *AT1R* mRNA and promote its stability [107, 108]. With the assistance of Tudor-SN, *AT1R* mRNA is transported into the SG structure and protected under stress conditions [44]. Furthermore, Tudor-SN reportedly enhances the invasion and migration of HCC cells by increasing the stability of *AT1R* mRNA and activating the downstream ERK and TGFβ signaling pathways [109]. Considering the potential antitumor efficacy of AT1R blockers and angiotensin-converting enzyme inhibitors [110], it would be interesting to investigate a treatment strategy that combines Tudor-SN/AT1R-targeting drugs.

Nontumor clinical diseases

In addition to tumors, there are other Tudor-SN-related clinical diseases, such as autism, autosomal dominant polycystic kidney disease, burn skin keloids, and septic sweat glands (Table S1). For instance, the small de novo copy number variants of *Tudor-SN* may be linked to the risk of autism [111]. Under specific stress conditions, the nucleic acid variation of *Tudor-SN* may lead to changes in the protein structure or in the physiological function of Tudor-SN, which may contribute to the pathogenesis of these nontumor clinical diseases. These may also partly contribute to the switching of Tudor-SN from its role as “friend” to its role as “foe”.

Conclusions

Tudor-SN acts as a “friend” of the body, and it is important for cellular physiological function and stress defense; however, it also acts as a “foe”, and it is implicated in or facilitates

tumorigenesis or tumor progression. In this study, we summarize the available evidence and examine the potential mechanism by which Tudor-SN changes its functional role in terms of four stages. Nevertheless, some issues remain unresolved. For instance, are there differences or similarities in the possible mechanisms underlying the protumorigenic effects of Tudor-SN in different tumors? Are relatively low-frequency Tudor-SN mutations involved in its role-switching mechanism? What kind of Tudor-SN interaction network exists in the tumor microenvironment? How can appropriate Tudor-SN-targeting intervention and synergistic treatments with other antitumor agents be developed for different tumors? All these possibilities warrant more in-depth investigations by more scholars.

Supplemental material

Supplementary material is available at <https://vcm.edp-sciences.org/10.1051/vcm/2023001/olm>

Table S1. Tudor-SN-associated clinical diseases.

Conflicts of interest

The authors declare that they do not have any conflicts of interest.

Acknowledgements. This work was supported in part by grants from the National Nature Science Foundation of China (32271201, 32070724), Tianjin Natural Science Foundation Project (20JCYBJC00470), and the Excellent Talent Project of Tianjin Medical University. We would like to thank Xiaoteng Cui, Chao Su, Jinzheng Ma, Yuankun Chen, Yan Zhao, and Xinxin Zhang for their contributions to the material arrangement and collection. We also thank American Journal Experts (AJE) for the English language editing service and Figdraw for the figure drawing.

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Cite this article as: Gao X, Xin L, Yao Z, Silvennoinen O, Yang J, Friend or Foe? The fascinating Tudor-SN protein. *Visualized Cancer Medicine*. 2023; 4, 5.