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Review

Roles of Tristetraprolin in Tumorigenesis

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Abstract: Genetic loss or mutations in tumor suppressor genes promote tumorigenesis. The prospective tumor suppressor tristetraprolin (TTP) has been shown to negatively regulate tumorigenesis through destabilizing the messenger RNAs of critical genes implicated in both tumor onset and tumor progression. Regulation of TTP has therefore emerged as an important issue in tumorigenesis. Similar to other tumor suppressors, TTP expression is frequently downregualted in various human cancers, and its low expression is correlated with poor prognosis. Additionally, disruption in the regulation of TTP by various mechanisms results in the inactivation of TTP protein or altered TTP expression. A recent study showing alleviation of Myc-driven lymphomagenesis by the forced expression of TTP has shed light on new therapeutic avenues for cancer prevention and treatment through the restoration of TTP expression. In this review, we summarize key oncogenes subjected to the TTP-mediated mRNA degradation, and discuss how dysregulation of TTP can contribute to tumorigenesis. In addition, the control mechanism underlying TTP expression at the posttranscriptional and posttranslational levels will be discussed.

Keywords: tristetraprolin (TTP); tumorigenesis; posttranscriptional regulation; adenosine and uridine-rich elements (AREs)

1. Introduction

Posttranscriptional regulation of messenger RNA (mRNA) stability is essential for cells to rapidly respond to intracellular and extracellular stimuli [1,2]. The TPA-inducible sequence 11 (TIS11) family of RNA-binding proteins, composed of tristetraprolin (TTP) and butyrate response factors, modulates mRNA stability through direct binding to specific sequences located in the 3′ untranslated region (3′ UTR) of the target mRNA [3]. TTP, also known as TIS11A, G0/G1 switch regulatory protein 24 (GOS24), and growth factor-inducible nuclear protein NUP475, is encoded by the *ZFP36* gene. TTP contains a cysteine–cysteine-cysteine–histidine (CCCH) zinc finger motif for the recognition of cis-acting adenosine and uridine-rich elements (AREs) in the 3′ UTR of target mRNA [4,5]. As illustrated in Figure 1, binding of TTP to AREs generally facilitates the decay of the mRNA by means of recruiting enzymes for the rapid shortening of the poly(A) tail [6]. For instance, TTP interacts with the carbon catabolite repressor protein 4 (Ccr4)-negative on TATA (Not1) deadenylase complex, the exosome components polymyositis/systemic sclerosis 75 (PM/Scl-75), and ribosomal RNA processing 4 (Rrp4) to hydrolyze the poly(A) tail in a processive manner [7]. Alternatively, TTP interacts with poly(A)-binding protein nuclear 1 (PABPN1) in the nucleus to inhibit 3′-polyadenylation of pre-mRNA [8]. The 5′ to 3′ degradation of mRNA is processed by a decapping complex, which includes mRNA-decapping enzyme 2 (Dcp2), enhancer of mRNA-decapping protein 3 (Edc3), and 5′–3′ exoribonuclease (Xrn1), which interact with TTP [9,10].

The physiological importance of TTP in posttranscriptional coordination has been observed in TTP-deficient mice. These mice develop a complex syndrome of inflammatory arthritis, dermatitis,

cachexia, autoimmunity, and myeloid hyperplasia [11]. These symptoms are recapitulated in the wild-type tumor necrosis factor alpha (TNF-α) transgenic and *TNF-α*$^{\Delta ARE}$ mice [12,13]. Indeed, TTP has been shown to accelerate the degradation of *TNF-α* mRNA via direct binding to the ARE in the 3′ UTR of *TNF-α* mRNA [14].

It was revealed that approximately 16% of human protein-coding genes have at least one consensus motif of an ARE in their 3′ UTR [15]. Many of these genes are implicated in immune responses and tumorigenesis [16,17]. Importantly, TTP has been shown to negatively regulate tumorigenesis by destabilizing its target mRNA linked to tumor onset and progression [18,19]. Thus, dysregulation of TTP has been regarded as an important issue in tumorigenesis [20]. In this review, we describe the current understanding of TTP's roles in tumorigenesis, with a particular focus on the roles of TTP's target genes during tumorigenesis. We summarize key oncogenes and tumor-associated genes subjected to TTP-mediated mRNA decay, and discuss how dysregulation of this process potentially contributes to tumorigenesis.

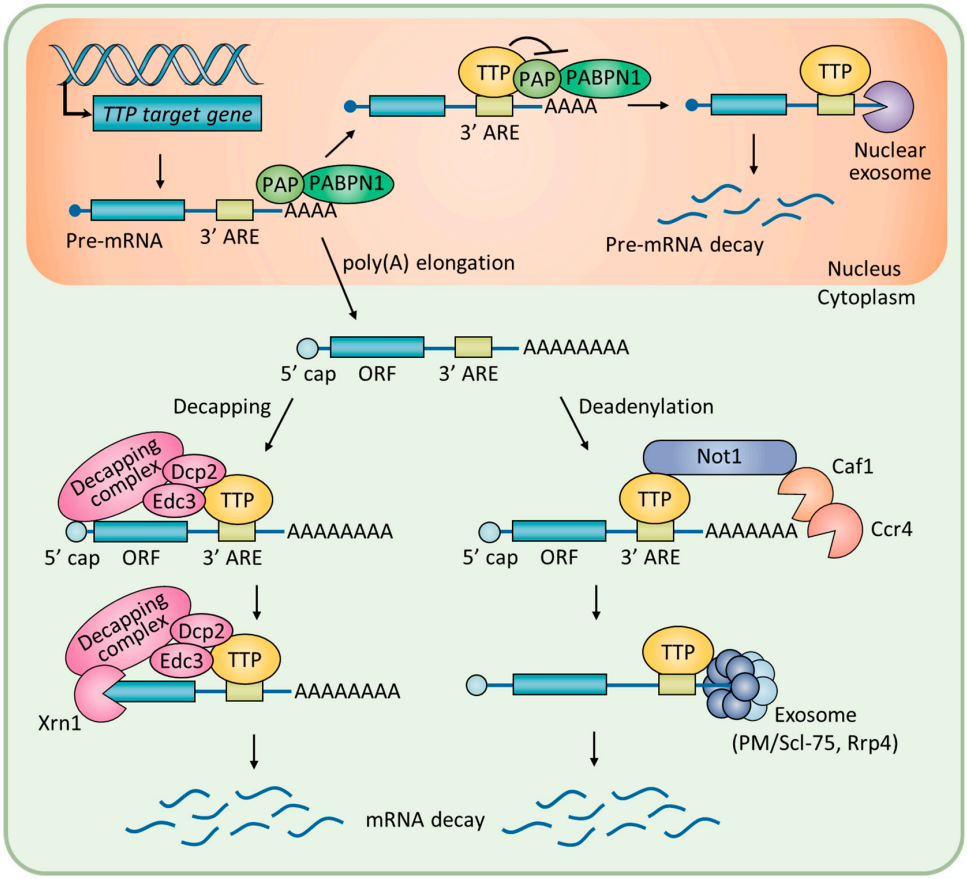

Figure 1. A schematic overview of posttranscriptional regulation of mRNA stability by TTP.

2. Oncogenes and Tumor Suppressor Genes Subjected to TTP-Mediated mRNA Decay

Tumorigenesis can be driven by the uncontrolled proliferation or the inappropriate survival of damaged cells due to the impairment of mRNA stability control of tumor-suppressor genes and oncogenes [21]. Table 1 shows the list of tumor-associated genes and their ARE sequences subjected to TTP-mediated mRNA degradation. The data indicate that TTP's target mRNAs during tumorigenesis are predominantly oncogenes as opposed to tumor suppressors; 21 oncogenes were targets, as compared to three tumor suppressor genes, such as cyclin-dependent kinase inhibitor 1 (*CDKN1A*), large tumor suppressor kinase 2 (*LATS2*), and aryl-hydrocarbon receptor repressor (*AHRR*) [22–24].

Table 1. List of oncogenes and tumor suppressor genes subjected to the ARE-mediated mRNA decay by TTP.

Gene Symbol	ARE Sequences	Regulation by TTP			
		ARE Binding [1]	3′ UTR Binding [2]	mRNA Decay [3]	Ref.
AHRR	TTCTGGCCTCTGGGCATTTATGGATTTAAGACCA GGATGGTATTTCAGAAGCTT	O	O	O	[23]
AKT-1	TTTTTTTACAACATTCAACTTTAGT	O	ND	O	[25,26]
BCL2	ATTTATTTATTTA	ND	O	O	[27]
BIRC3 (*cIAP2*)	TTTGGTTTCCTTAAAATTTTTATTTATTTACAACTC AAAAAACATTGTTTTG	O	O	O	[28,29]
CCNB1 (*cyclin B1*)	TTATTTACTTTTACCACTATTTAAG	O	O	O	[25,30]
CCND1 (*cyclin D1*)	TTATTATATTCCGTAGGTAGATGTG, ACATAATATATTCTATTTTTATACTCT	O	O	O	[25,31]
CDKN1A (*p21*)	TAGTCTCAGTTTGTGTGTCTTAATTATTATTTGTGT TTTAATTTAAACACCTCCT	O	O	O	[24]
CXCL1	TCTTCTATTTATTTATTTATTCATTAGTT	O	O	O	[25,32]
CXCL2 (*MIP-2*)	CACACTCTCCCATTATATTTATTG	O	ND	O	[25,33]
CXCR4	ACTTATTTATATAAATTTTTTTTG	O	O	O	[25,34]
E2F1	CTTTAATGGAGCGTTATTTATTTATCGAGGCC TCTTTG	O	O	O	[29,35]
FOS (*c-Fos*)	TAATTTATTTATT	ND	O	O	[36]
HMGA2	TGTAATTTAATGA	ND	O	O	[37]
IFN-γ	CTATTTATTAATATTTAA	O	O	O	[38]
JUN (*c-Jun*)	TTCTCTATTAGACTTTAGAAA, AGCACTCTGAGTTTACCATTTG	O	ND	ND	[25,39]
LATS2	TTCAAATTAGTATGATTCCTATTTAAAGTGATTTA TATTTGAGTAAAAAGTTCAA	O	O	O	[22]
Lin28A	TTTTATTTATTTG	O	O	O	[29,40]
MACC1	TATAATTTAATAT	ND	O	O	[41]
MYC (*Myc*)	AATTTCAATCCTAGTATATAGTACCTAGTATTAT AGGTACTATAAACCCTAATTTTTTTTATTTAA	O	O	O	[25,31]
PIM-1	CCTGGAGGTCAATGTTATGTATTTATTTATTTATT TATTTGGTTCCCTTCCTATTCC	O	O	O	[42]
PIM-3	TTTAATTTATTTG	ND	O	O	[43]
SNAI1 (*Snail1*)	GTTATATGTACAGTTTATTGATATTCAATAAAGC AGTTAATTTATATATTAAAAA	O	O	O	[44]
XIAP	CAAATTTATTTTATTTATTTAATT	O	O	O	[25,43]

[1] O: experimentally determined ARE sequences; ND: not determined experimentally, the predicted ARE sequences are from ARED-Plus web source; [2,3] O: experimentally confirmed; ND: not determined experimentally.

TTP has been shown to prevent malignant proliferation by suppressing the expression of genes for cell-cycle progression and cellular proliferation depicted in Figure 2. Among these, *CCNB1* (cyclin B1) is the key oncogenic driver whose overexpression itself leads to the chronic proliferation of cancer cells [45]. Previous studies reported that high CCNB1 expression levels were detected in various cancers such as breast, colon, and non-small cell lung cancer [46–48]. Ectopic overexpression of TTP suppressed CCNB1 expression but depletion of TTP promoted the accumulation of *CCNB1* mRNA in human lung cancer cells [30]. This is because the ARE motif in *CCNB1* 3′ UTR is subjected to TTP-mediated degradation [25]. High expression of *CCND1* (cyclin D1) also correlates with tumor onset and tumor progression [49]. A recent study showed that treatment with the mechanistic target of rapamycin kinase (mTOR) inhibitor, rapamycin, induced rapid *CCND1* mRNA decay due to the

increased TTP expression in glioblastoma cells [31]. CCND1 binding with cyclin dependent kinase 4 (CDK4) or CDK6 is necessary for the G1/S transition [50]. The active CDK4/6 phosphorylates retinoblastoma 1 (RB), which results in the release of E2F1 [51]. Subsequently, E2F1 initiates the expression of genes required for the cell cycle transition [52]. E2F1 also contains three AREs in its 3′ UTR [35]. In the meantime, the *PIM-1* oncogene is also subjected to TTP-mediated mRNA decay. PIM-1 facilitates cell cycle progression via activating *CDC25a* and *CDC25c* oncogenes [53]. In pancreatic cancer, low TTP expression was correlated with high PIM-1 expression, and patients with such gene expression profiles showed unfavorable survival rates [54].

In addition, by suppressing the expression of lin-28 homolog A (Lin28A), TTP can increase the expression of the tumor suppressor microRNA (miRNA) let-7, whose expression is negatively regulated by Lin28A [29,55]. The miRNA let-7 has been implicated in the regulation of gene transcription including high mobility group A2 (HMGA2) [56]. HMGA2 is frequently upregulated in multiple cancers, and is associated with both malignant and benign tumor formation [57]. The bioinformatic analysis discovered that 3′ UTR of *HMGA2* mRNA contains the hairpin structure termed HMGA2-sh, which is further processed to a HMGA2-sh-3p20 fragment through the action of Drosha and Dicer [37]. Interestingly, HMGA2-sh-3p20 elevated HMGA2 expression in hepatoma cells by means of preventing TTP binding to the *HMGA* mRNA [37]. Thus, HMGA2-sh-3p20 facilitates hepatocarcinogenesis by antagonizing the TTP-mediated decay of *HMGA2* mRNA.

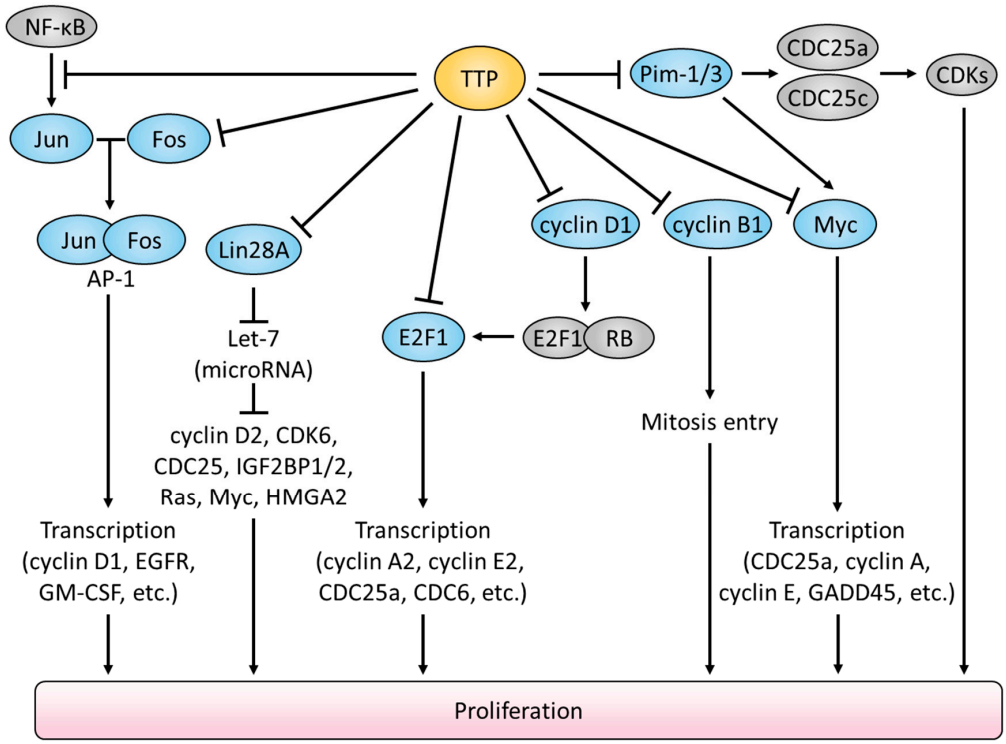

Figure 2. Attenuation of cellular proliferation by TTP-mediated suppression of oncogenic signalings.

The collapse of the homeostatic balance between cell death and cell proliferation is a hallmark of cancer [58]. Simultaneous overexpression of the anti-apoptotic protein BCL2 and the *Myc* oncogene induces lymphoma [59]. By downregulating the expression of both genes, TTP has been shown to alleviate Myc-driven lymphomagenesis [27,60]. IAP (inhibitors of apoptosis proteins) family anti-apoptotic protein BIRC3 and XIAP are also under control by TTP-mediated mRNA decay [28,43]. Therefore, loss of TTP function would confer resistance to cancer cells against apoptotic stimulus, and promotes cancer cell viability due to the impairment of the destabilizing of anti-apoptotic gene expression.

Aside from its canonical posttranscriptional role, TTP also has been implicated in the regulation of gene expression at the transcriptional level by participating in the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway [39,61,62]. By blocking the nuclear import of NF-κB/p65, TTP suppresses the NF-κB-mediated transcription of oncogenes, including *c-Jun* [63]. c-Jun and c-Fos form the AP-1 early response transcription factor that promotes cell-cycle progression [64]. The stability of *c-Fos* mRNA is subjected to TTP-mediated posttranscriptional control [36]. Thereby, TTP regulates the activity of oncogenic AP-1 both at the transcriptional and posttranscriptional levels.

3. Roles of TTP in Tumor Progression

Recent studies have revealed novel TTP targets involved in the malignancy of tumors, such as epithelial-mesenchymal transition (EMT), invasion, and metastasis (Figure 3). Based on the gene expression profiles from 80 patient samples (23 normal colon mucosa, 30 primary colon carcinoma, and 27 liver metastases), lower TTP expression was detected in primary tumors as compared to normal mucosa [41]. Furthermore, TTP expression was remarkably downregulated in metastatic tumors as compared to primary tumors, suggesting the possibility that TTP is engaged in the EMT process. Consistent with this notion, recent studies have reported that TTP facilitates the mRNA decay of EMT marker genes including *Snail1* (zinc finger protein snail 1), *Twist1* (twist-related protein 1), *ZEB1* (zinc finger E-box binding homeobox 1), *MMP-2* (matrix metalloproteinase 2), and MMP-9 [41,44,65].

The molecular signature of low E-cadherin, high vimentin, and high *N*-cadherin is an indicator of cells undergoing EMT; this feature was also detected in circulating tumor cells [66]. NIH:OVCAR3 (ovarian adenocarcinoma) and HT29 (colorectal adenocarcinoma) cells with high TTP levels exhibited high E-cadherin, low *N*-cadherin, and low vimentin, whereas low TTP-expressing SKOV3 (ovarian adenocarcinoma) and H1299 (non-small lung carcinoma) cells displayed low E-cadherin expression [44]. Snail1, Twist1, and ZEB1 are transcription factors for the transcriptional repression of E-cadherin [67]. TTP binding to the ARE within the 3′ UTR of these three genes triggered their mRNA decay [44]. In the meantime, loss of TTP increased the growth rate and migration capability of colorectal cancer cells due to the upregulation of ZEB1, sex-determining region Y box 9 (SOX9), and metastasis-associated in colon cancer 1 (MACC1) [41]. Furthermore, one of the most significant alterations underlying colorectal cancer is the constitutive activation of the T-cell factor (Tcf)/β-catenin signaling, and the administration of Tcf/β-catenin inhibitor FH535 derepressed TTP expression [41]. Collectively, TTP downregulates Snail1, Twist1, ZEB1, SOX9, and MACC1 expression at the posttranscriptional level to inhibit EMT. Thus, the recovery of TTP expression seems to be promising to suppress EMT in some types of human cancers.

EMT facilitates the reorganization of the extracellular matrix (ECM), since many EMT-inducing factors activate the expression of MMPs [68]. MMPs induce ECM degradation and allow tumor cells to migrate out of the primary tumor to form metastases [69]. Specifically, MMP-1 is an interstitial collagenase that decomposes collagen types I, II, and III, and MMP-13 breaks down type II collagen more efficiently than types I and III [70]. MMP-2, along with MMP-9, cleaves type-IV collagen, which is the most abundant component of the basement membrane of which breakdown is a critical step in the invasion and metastatic progression of cancer cells [70]. An invasion experiment recapitulating the oral mucosa showed that the suppression of TTP activity gives rise to an accelerated invasion rate of head and neck cancer cells due to the secretion of MMP-2, MMP-9, and interleukin-6 (IL-6) [65]. Mechanistically, p38-mediated phosphorylation and the inactivation of TTP upregulated the stability of *MMP-2*, *MMP-9*, and *IL-6* transcripts [65]. Another study showed that ectopic re-expression of TTP in breast cancer cells attenuated the invasion rate because TTP suppressed MMP-1 and MMP-13 expression [71]. Urokinase-type plasminogen activator (uPA) and its specific receptor urokinase plasminogen activator receptor (uPAR) are also implicated in the degradation of the ECM [72]. Overexpression of uPA and uPAR has been observed in invasive glioblastomas [73], and the ectopic expression of TTP alleviated the invasiveness of these cancer cells by suppressing the expression of

both uPA and uPAR [74,75]. In addition, a recent report showed that the upregulated TTP expression led to significant downregulation of uPA and MMP-9 protein expression in breast cancer [76]. Taken together, uPA and uPAR are physiological targets of TTP in various cancer types, and the concept of TTP-mediated downregulation of uPA and uPAR seems to be promising to attenuate the malignancy of tumors [75].

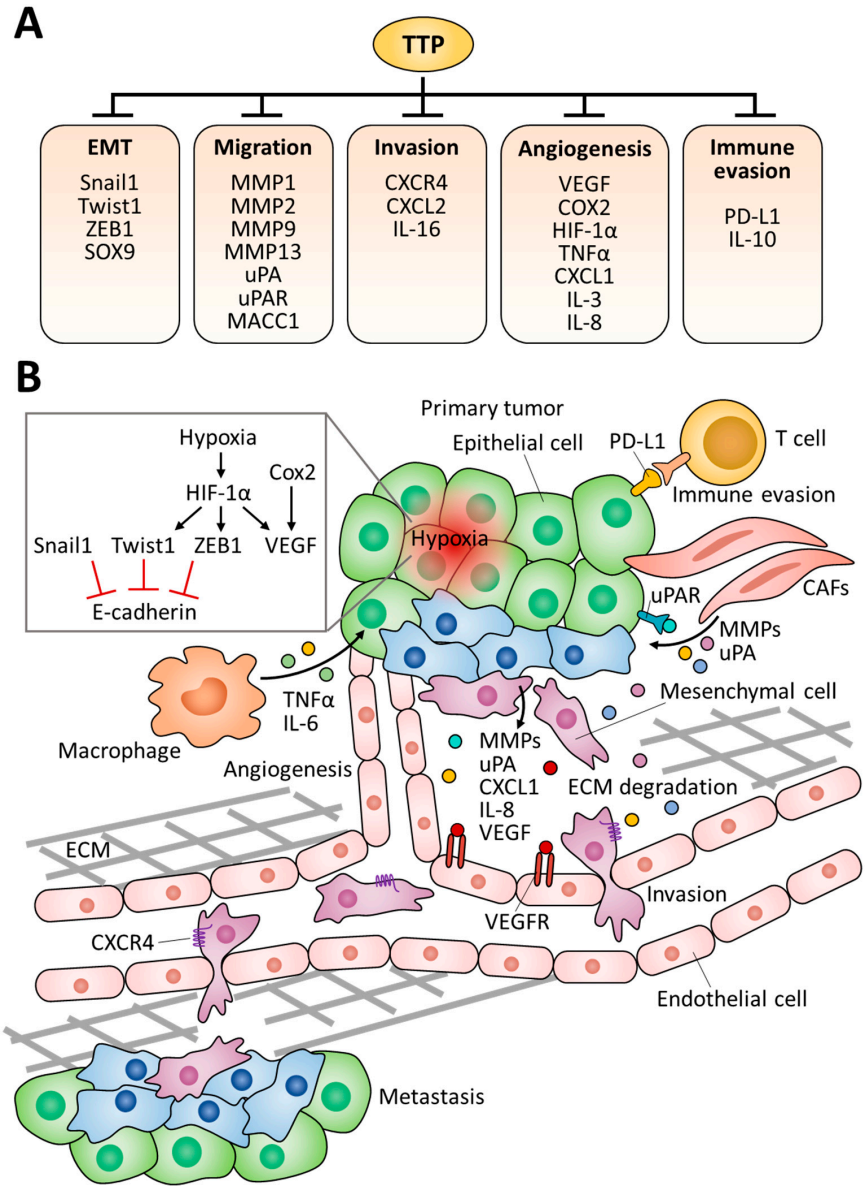

Figure 3. Suppressive roles of TTP in tumor progression. (**A**) TTP targets involved in the malignancy of tumors. EMT; epithelial-mesenchymal transition. (**B**) EMT and metastatic mechanisms driven by TTP target genes. CAFs; carcinoma-associated fibroblasts, ECM; extracellular matrix, VEGFR; vascular endothelial growth factor receptors.

Cancers develop in complex tissue environments known as tumor microenvironments, and these affect the growth and metastasis of tumor cells [77]. Tissues undergoing chronic inflammation due to the deregulation of the microenvironment generally exhibit a high incidence of cancer [78]. According to recent studies, programmed death-ligand 1 (PD-L1) is a novel target for TTP in gastric, lung, and colon cancer cells [79,80]. The expression of PD-L1 is essential for the development and functional maintenance of regulatory T cells [81], and its mRNA stability is negatively regulated by TTP [80]. Consequently, restoration of TTP expression enhanced anti-tumor immunity in a PD-L1-dependent

manner [80]. Neoplastic cells are strongly influenced by the stroma, including surrounding and infiltrating cells. Immune cell infiltration into the tumor is an important determinant of tumor progression, and TTP depletion increases infiltration of monocytes/macrophages into the tumors [82]. IL-16 was identified as a critical TTP-regulated factor that contributes to the migration of immune cells [82]. IL-16 expression was increased in TTP-deficient 3D tumor spheroids, and elevated IL-16 levels enhanced the infiltration of monocytes into tumor spheroids [82]. Apparently, further studies are needed to determine the direct effect of TTP on IL-16 expression, but it seems clear that the loss of TTP allows immune cells within the microenvironment to promote tumor growth.

Tumor cells require a dedicated blood supply to obtain oxygen and nutrients for their maintenance and growth, and vascular endothelial growth factor (VEGF) is a crucial regulator of pathological angiogenesis [83]. TTP can bind to *VEGF* mRNA 3′ UTR and induce *VEGF* mRNA degradation [84]. Higher VEGF levels were detected in colorectal adenocarcinoma, as compared to normal tissues [85]. Cyclooxygenase 2 (COX-2) is also an important mediator of angiogenesis by facilitating the production of VEGF and BCL2 [86]. TTP binds between the nucleotides 3125 and 3232 in the 3′ UTR of *COX-2* mRNA and induces mRNA destabilization [87]. In colorectal cancer cells, low expression of TTP was responsible for the increased expression of COX-2 and VEGF, while overexpression of TTP in colon cancer cells markedly decreased the expression of both genes [88]. Moreover, cytokines related to tumor angiogenesis such as IL-3, IL-8, and TNF-α were reported as TTP targets which are suppressed by the way of ARE-mediated decay [32,89,90]. In contrast, TTP has been shown to increase human inducible nitric oxide synthase (iNOS) mRNA stability. TTP did not bind to human iNOS mRNA directly, but TTP destabilized the KH-type splicing regulatory protein (KSRP), which is responsible for iNOS mRNA decay, by facilitating recruitment of the exosome [91].

Although the precise mechanisms that determine the directional movement of tumor cells to distant sites are not well understood, this movement pattern seems similar to the chemokine-mediated leukocytes movement [92]. The expression of C-X-C motif chemokine receptor 4 (CXCR4) is low or absent in normal tissues, while it is highly expressed in various types of cancer, including colorectal cancer, ovarian cancer, and breast cancer [93,94], and the CXCR4 level was inversely correlated with TTP expression [34]. It has been revealed that CXCR4 is a TTP target containing a functional ARE in its 3′ UTR, and thus, induction of TTP results in the compromised CXCR4-mediated invasion and migration [34]. Furthermore, TTP depletion increased the production of several chemokines, such as C-X-C motif chemokine ligand 1 (CXCL1), CXCL2, and CXCL8 (also known as IL-8), which are involved in melanoma pathogenesis and angiogenesis [32,33,95]. Taken together, TTP has the ability to repress tumor metastasis by regulating chemokine-mediated migratory signaling.

As the tumor grows, consumption of nutrients and oxygen around it lead to a state of nutrient and oxygen deprivation [96]. Subsequently, hypoxia induces hypoxia-inducible factor 1α (HIF-1α), an important transcription factor involved in angiogenesis, leading to angiogenesis that allows nutrients to the microenvironment around tumor tissue [97]. Importantly, TTP expression was induced in hypoxic cells, and the overexpression of TTP repressed the hypoxic induction of HIF-1α protein in colorectal cancer cells [98]. Thus, it was proposed that cancer cells may benefit from the downregulation of TTP, which subsequently increases HIF-1α expression and assists with the adaptation of cancer cells to hypoxia.

4. Regulation of TTP Expression in Normal and Cancer Cells

Recent research has demonstrated that TTP is abnormally expressed in various human malignancies [60,85,99–105]. TTP was initially identified as a member of immediate early response genes that are rapidly induced by the stimulation of insulin [106], serum [107], or mitogen [108,109] in quiescent fibroblasts. Serum-stimulated *TTP* mRNA induction was dependent on consensus binding sites for several transcription factors, such as early growth response protein 1 (EGR1), specificity protein 1 (SP-1), and activator protein 1 (AP-2) in the 5′-proximal region of the TTP promoter [110]. A few studies have shown that transcription of *TTP* was induced by growth-inhibitory cytokines

during an inflammatory response. For instance, transforming growth factor beta 1 (TGF-β1)-induced TTP transcription was mediated by the binding of Smad3/4 transcription factors to the putative Smad-binding elements of the TTP promoter in human T cells [111]. Parallel to this, TTP expression was necessary for TGF-β1-dependent growth inhibition in normal intestinal epithelium [112]. In addition, the TTP promoter contains putative binding sites for signal transducer and activator of transcription (STAT) proteins. Indeed, STAT1, STAT3, and STAT6 were recruited to these sites, and induced *TTP* gene transcription under stimulation by different cytokines. Interferon gamma (IFN-γ)-induced STAT1 phosphorylation promoted *TTP* gene transcription [113]. IL-10-activated STAT3 or IL-4-activated STAT6 induced TTP expression through the janus kinase 1 (JAK1) pathway [114,115]. Interestingly, *TTP* mRNA is highly unstable, and the rapid turnover of *TTP* mRNA is due to an auto-regulatory negative feedback loop [116,117].

TTP expression is often deficient in several cancer types (Figure 4). Rounbehler and colleagues [60] found that TTP was expressed at low levels in Myc-expressing cancers including breast, colorectal, and metastatic prostate cancer. The 5′-proximal region of the *TTP* gene includes a putative initiator element (Inr) near the TATA box [110]. Myc directly inhibits the transcription of *TTP* through direct binding to the Inr. In contrast, the tumor suppressor p53 activates *TTP* mRNA expression in human cancer cells [55]. Wild-type p53 stimulated by the DNA-damaging agent doxorubicin was recruited to the TTP promoter to activate *TTP* transcription, whereas mutant p53 failed to induce *TTP* transcription [55]. The epigenetic gene silencing of the TTP promoter has been shown as an alternative way to regulate TTP expression [105,118,119]. For instance, TGF-β1-dependent Smad-binding region located in the TTP promoter has a specific single CpG site. In hepatocellular carcinoma cell lines, TTP expression was attenuated frequently by methylation of the CpG site [105]. MicroRNA-29a (miR-29a) targets the 3′ UTR of *TTP* mRNA, leading to the degradation of *TTP* mRNA in cancer cells [101,120]. In pancreatic and breast cancer, miR-29a-mediated *TTP* mRNA degradation was associated with EMT, and promoted tumor growth, invasion, and metastasis [101,120].

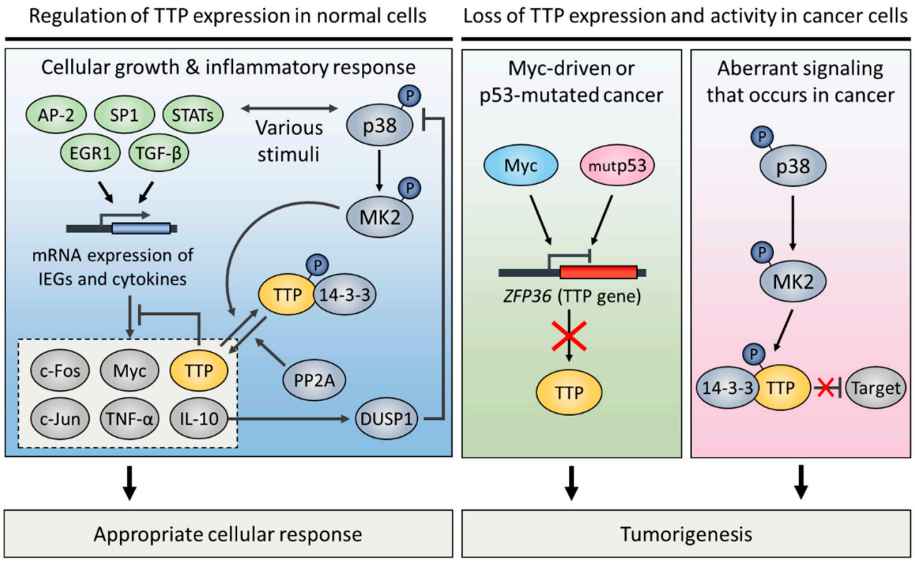

Figure 4. Regulation of TTP expression and activity in normal and cancer cells.

In addition to the loss of TTP expression, cells can become TTP deficient through a loss in TTP activity. Inactivation of TTP has been predominantly associated with its phosphorylation status. TTP can be phosphorylated by several kinases, including extracellular signal-regulated kinases (ERK) [121], p38 [121,122], c-Jun N-terminal kinases (JNK) [121], and v-akt murine thymoma viral oncogene (AKT) [31]. Among these, the p38 pathway is a major determinant for TTP activity but does not affect the protein level of TTP. p38 kinase phosphorylates and activates MAPK-activated protein kinase 2 (MK2); subsequently, MK2 phosphorylates TTP at serine 60 and 186 [123]. Subsequently, 14-3-3

proteins interact with phosphorylated TTP and inactivate it [31,124–126]. The TTP-14-3-3 complex cannot recruit the Ccr4-Not1 deadenylase complex, but has no impact on the binding affinity of ARE [124,125]. In addition, the interaction with 14-3-3 is required for cytoplasmic accumulation of TTP [126], which results in the inhibition of TTP's role in the nucleus. Cytoplasmic TTP promotes the decay of mRNA containing AREs [18], whereas nuclear TTP functions as a transcriptional corepressor of NF-κB [39,127] and several nuclear receptors [128,129]. In breast cancer cells, ectopic overexpression of TTP was capable of repressing the transactivation activity of nuclear receptors, including estrogen receptor alpha (ERα), progesterone receptor (PR), glucocorticoid receptor (GR), and androgen receptor (AR), via physically interacting with these factors [128]. Mechanistically, nuclear TTP attenuates ERα transactivation by disrupting its interaction with steroid receptor coactivator 1 (SRC-1) [129].

The phosphorylation-induced TTP inactivation is reversed by two phosphatases. Protein phosphatase 2A (PP2A) directly dephosphorylates and reactivates TTP, but this results in a decrease in TTP protein stability [130–134]. Another phosphatase for TTP reactivation is dual specificity phosphatase 1 (DUSP1), that indirectly regulates TTP activity through the dephosphorylation of p38, which results in the inactivation of p38 kinase activity [135]. Several reports have indicated that a high level of the phosphorylated, inactive form of TTP was found in head and neck [65] and brain cancer cells [99,136]. Thus, the pharmacological application of a p38 inhibitor against these cancers may provide new ways to treat cancers containing hyperphosphorylated TTP.

The first p38 inhibitors were identified in a screen for compounds that inhibited expression of TNF-α in human monocytic leukemia cell line [137]. In multiple myeloma and head and neck squamous cell carcinoma, p38 inhibitors were successfully used to limit tumor growth and angiogenesis, due indirectly to TTP-mediated inhibition of cytokine secretion [138,139]. p38 inhibitor also attenuates progression of malignant gliomas by inhibition of TTP phosphorylation [99]. Dufies and colleagues reported that p38 inhibitors may be a promising adjuvant therapy in cancer. Sunitinib, known as a first-line treatment for metastatic renal cell carcinoma, leads to patient relapse by p38 activation. While sunitinib mainly targets the host blood vessels via the inhibition of VEGF receptors, the mechanism of patient relapse is associated with increased lymphangiogenesis and lymph node metastasis via induction of *VEGFC* mRNA expression through p38-mediated inactivation of TTP. In renal cancer cells, the p38 inhibitor reduces the sunitinib-dependent increase in the *VEGFC* mRNA [140]. Several independent groups have identified effective drug candidates targeting TTP for anticancer therapies. For instance, Sorafenib targeting v-Raf murine sarcoma viral oncogene homolog B (B-Raf) kinase triggers re-expression of TTP in melanoma cells via the inhibition of B-Raf-dependent ERK activity [95]. Gambogic acid, the main active compound of *Gamboge hanburyi*, also induces upregulation of TTP expression through ERK inactivation, and efficiently inhibits the progression of colorectal cancer cells [141]. Histone deacetylase (HDAC) inhibitors in colorectal cancer cells induce TTP expression through activation of EGR1, which promote its binding affinity to ARE, and thus, reduce cell growth and angiogenesis [118,119]. Resveratrol, a natural polyphenolic compound present in many plant species, including grapes, peanuts, and berries, inhibits cell growth through TTP upregulation in several cancers, including breast [142], colorectal [29] and brain cancer [74]. Molecular activators of PP2A enhance the anti-inflammatory function of TTP in lung cancer cells, and thus, provide pharmacotherapeutic strategies to chronic inflammation-mediated cancer [133]. In addition, treatment with MK2 inhibitor triggers apoptosis in hepatocellular carcinoma. TTP knockdown rescued these cells from apoptosis in the presence of MK2 inhibitor, suggesting that the MK2-mediated TTP inactivation plays a role in cell survival of hepatocellular carcinoma [26]. These studies increase the understanding of the anti-cancer effects of various compounds and the molecular basis for further applications of therapeutic agents targeting TTP in clinical cancer therapy.

5. Conclusions

The role of TTP as a key factor in posttranscriptional gene regulation has been established, especially with regard to its function in promoting mRNA decay of ARE-containing genes, including

oncogenes and cancer-related cytokines. What has become more obvious is that TTP participates extensively in gene regulatory networks for tumor suppression. Cumulative evidence was provided that the loss of TTP expression or function was closely related with tumor onset and tumor progression, and presented poor outcomes of cancer patients. Based on current knowledge, many factors and signal pathways have been identified to regulate TTP at the transcriptional, posttranscriptional, and posttranslational level. The abnormal expression or activity of these factors consequently affected TTP's expression or function. Therefore, endeavors for searching molecular pathways or chemical compounds upregulating TTP expression or activity will pave the way for potentially attractive therapeutics for cancer treatment.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

3′ UTR	3′ untranslated regions
AHRR	Aryl-hydrocarbon receptor repressor
AKT-1	AKT serine/threonine kinase 1
AP-1	Activator protein 1
AR	Androgen receptor
AREs	Adenosine and uridine-rich elements
BCL2	B-cell CLL/Lymphoma 2
BIRC3	Baculoviral IAP repeat containing 3
B-Raf	v-Raf murine sarcoma viral oncogene homolog B
CAFs	Carcinoma-associated fibroblasts
CCCH	Cysteine–cysteine-cysteine–histidine
CCNB1	Cyclin B1
CCND1	Cyclin D1
Ccr4	Carbon catabolite repressor protein 4
CDC25A	Cell division cycle 25 homolog A
CDK4	Cyclin dependent kinase 4
CDK6	Cyclin dependent kinase 6
CDKN1A	Cyclin dependent kinase inhibitor 1A
COX-2	Cyclooxygenase 2
CXCL1	C-X-C motif chemokine ligand 1
CXCL2	C-X-C motif chemokine ligand 2
CXCR4	C-X-C motif chemokine receptor 4
Dcp2	mRNA-decapping enzyme 2
DUSP1	Dual specificity phosphatase 1
E2F1	E2F transcription factor 1
ECM	Extracellular matrix
EGR1	Early growth response protein 1
Edc3	Enhancer of mRNA-decapping protein 3
EMT	Epithelial-mesenchymal transition
ERK	Extracellular signal-regulated kinases
ERα	Estrogen receptor alpha
FOS	FBJ murine osteosarcoma viral oncogene homolog
GOS24	G0/G1 switch regulatory protein 24
GR	Glucocorticoid receptor
HDAC	Histone deacetylase

HIF-1α	Hypoxia-inducible factor 1α
HMGA2	High mobility group A2
IAP	Inhibitors of apoptosis proteins
IFN-γ	Interferon gamma
IL-6	Interleukin-6
iNOS	inducible nitric oxide synthase
Inr	Initiator element
JAK1	Janus kinase 1
JNK	c-Jun N-terminal kinases
JUN	v-jun avian sarcoma virus 17 oncogene homolog
KSRP	KH-type splicing regulatory protein
LATS2	Large tumor suppressor kinase 2
Lin28A	Lin-28 homolog A
MACC1	Metastasis associated in colon cancer 1
MAPK	Mitogen-activated protein kinase
miR-29a	MicroRNA-29a
MK2	MAPK-activated protein kinase 2
MMP-13	Matrix metalloproteinase 13
MMP-2	Matrix metalloproteinase 2
MMP-9	Matrix metalloproteinase 9
mRNA	Messenger RNAs
Myc	v-myc avian myelocytomatosis viral oncogene homolog
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
Not1	Negative on TATA 1
NUP475	Growth factor-inducible nuclear protein NUP475
PABPN1	Poly-A-binding protein nuclear 1
PD-L1	Programmed death-ligand 1
PIM-1	Proto-oncogene serine/threonine-protein kinase pim 1
PM/Scl-75	Polymyositis/systemic sclerosis 75
PP2A	Protein phosphatase 2A
PR	Progesterone receptor
RB	Retinoblastoma 1
Rrp4	Ribosomal RNA processing 4
SNAI1	Zinc finger protein snail 1
SOX9	Sex-determining region Y box 9
SP-1	Specificity protein 1
SRC-1	Steroid receptor coactivator 1
STAT	Signal transducer and activator of transcription
Tcf	T-cell factor
TGF-β1	Transforming growth factor beta 1
TIS	12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced sequence
TNF-α	Tumor necrosis factor alpha
TTP	Tristetraprolin
Twist1	Twist-related protein 1
uPA	Urokinase-type plasminogen activator
uPAR	Urokinase plasminogen activator receptor
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptors
XIAP	X-linked inhibitor of apoptosis
Xrn1	5′-3′ exoribonuclease
ZEB1	Zinc finger E-box binding homeobox 1
ZFP36	Zinc finger protein 36

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