



# Tissue factor as a new target for tumor therapy – killing two birds with one stone: a narrative review

Xiaoying Li<sup>1</sup>, Dan Cao<sup>2</sup>, Xiufeng Zheng<sup>1</sup>, Gang Wang<sup>3</sup>, Ming Liu<sup>1</sup>

<sup>1</sup>Gastric Cancer Center/Cancer Center, West China Hospital, Sichuan University, Chengdu, China; <sup>2</sup>Department of Abdominal Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, China; <sup>3</sup>National Engineering Research Center for Biomaterials, Sichuan University, Chengdu, China

*Contributions:* (I) Conception and design: M Liu; (II) Administrative support: D Cao; (III) Provision of study materials or patients: X Li; (IV) Collection and assembly of data: X Zheng; (V) Data analysis and interpretation: G Wang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*Correspondence to:* Ming Liu, PhD. Associate Professor, Gastric Cancer Center/Cancer Center, West China Hospital, Sichuan University, Chengdu 610041, China. Email: liuming629@wchscu.cn.

**Background and Objective:** Cancer is an important disease and can occur anywhere in the body. It is caused by uncontrolled cell growth that spreads to other body parts. This study extensively investigated the transmembrane receptor tissue factor (TF), which is the key motivator of the clotting cascade and plays an essential role in cancer-associated coagulation. TF is considered to be aberrantly expressed in various tumors and appears to promote tumor angiogenesis and metastasis. Therefore, this study was performed to explain the pathological characteristics of TF expression and to discuss future cancer therapies that target TF.

**Methods:** We extensively reviewed the literature on TF published in PubMed, and discussed the effect of TF on tumor progression and TF-targeted therapeutics.

**Key Content and Findings:** This review aimed to uncover how TFs contribute to tumor progression and cancer-associated thrombosis and summarize TF-based targeted therapy. Multiple functions and mechanisms of the TF in cancer-associated thrombosis and tumor progression were discussed.

**Conclusions:** The current literature has confirmed that the TF is involved in the hypercoagulable state of tumors and promotes malignant tumors through coagulation-dependent or non-coagulation-dependent pathways. TF-dependent signaling is also involved in divergent cancer progression. Thus, TF-targeted therapeutics could have broad clinical applicability for the treatment of tumors.

**Keywords:** Tissue factor (TF); tumor therapy; cancer-associated coagulation

Submitted Sep 23, 2022. Accepted for publication Nov 07, 2022.

doi: 10.21037/atm-22-5067

View this article at: <https://dx.doi.org/10.21037/atm-22-5067>

## Introduction

Under physiological conditions, the tissue factor (TF) is constitutively expressed by adventitial cells surrounding blood vessels and released after vascular endothelial injury. It subsequently binds with factor VIIa, forming the TF-FVIIa complex and activating factor X (FX), as well as fibrin deposition and synergistic platelet activation to initiate the subsequent coagulation and hemostatic procedures (1). TF play a prominent role in protective hemostasis, therefore TF is the primary motivator of the extrinsic

coagulation process. Under pathological conditions, TF is aberrantly increased on the surface of tumor cells and vascular endothelial cells in various malignancies, such as pancreatic cancer, acute lymphocytic leukemia, sarcomas, lung cancer, triple-negative breast cancer (TNBC), and glioma. Besides, it is also involved in the occurrence of tumor biological behavior and the formation of the tumor microenvironment (2-7). In addition to the coagulation process, increased TF expression has been observed more often in malignant tissue compared to the adjacent normal

**Table 1** Search strategy summary

Items	Specification
Date of search	21/10/2022
Databases and other sources searched	PubMed database
Search terms used	“Tissue factor”, “Tissue factor” and “cancer coagulopathy”, “Tissue factor” and “cancer”, “Tissue factor” and “tumor neovascularization”, “Tissue factor” and “angiogenesis”, “Tissue factor” and “antibody-drug conjugate”, “Tissue factor” and “oncogene signaling”, “Tissue factor regulation”, “Tissue factor” and “microenvironment”, “Tissue factor” and “metastasis”
Inclusion and exclusion criteria	All English-language literature published on PubMed about the role of tissue factor in cancer progression and TF-directed treatment were included. All study types were included
Timeframe	1999–2022
Selection process	Xiaoying Li and Xiufeng Zheng independently searched the database. Disagreements were resolved by Gang Wang and Ming Liu
Any additional considerations	None

tissue in different organs, including human breast cancer and hepatic carcinoma (HCC) (5). Cancer patients tend to have a procoagulant state and worsened survival for their blood TF levels are higher than healthy people, and TF is a component of extracellular vesicles (EVs), therefore, TF-positive extracellular vesicles (TF+ EVs) may trigger the blood coagulation cascade. Moreover, cancer-associated thrombosis reported to more often in venae, and endothelial TF is associated with arterial thrombosis potential, TF contribute to venous and arterial pathological thrombosis (8–11).

The TF is mainly overexpressed in malignant tumor tissues and affects the prognosis of patients through various biological processes, including thrombosis, angiogenesis, invasion, metastasis, growth, and proliferation (12–14). Higher levels of TF are associated with poor histological differentiation, indicating worse survival (15–17). For example, the activation of protease-activated receptor 2 (PAR2) signaling instead of PAR1 controls endothelial growth factor (VEGF) expression, affecting tumor angiogenesis (18). In addition, a study of human malignant melanoma cell lines reported that the TF regulates VEGF expression via its cytoplasmic tail (19). As mentioned above, TF-targeted therapeutic strategies hold great value in improving cancer management, varieties of preclinical animal models and some clinic trials have been conducted to investigate TF’ role in treatment modalities. Along with TF-targeted antibody-drug conjugate (Tisotumab vedotin) secured US Food and Drug Administration (FDA) approval, establishing a hallmark for guiding direct or indirect inhibition of TF activity and paving the way for precision

therapy (20,21).

In this review, the functions of TF in cancer progression (other than hemostasis and thrombosis) will be discussed in detail. This study aims to discover how TF contributes to tumor progression and cancer-associated thrombosis. Furthermore, this review also focuses on TF-based targeted therapy and explores the likelihood of TF in cancer immunotherapy. We present the following article in accordance with the Narrative Review reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-5067/rc>).

## Methods

We extensively reviewed and analyzed the literature on the role of TF in cancer progression and TF-directed treatment published in PubMed up to October 2022. We performed the literature search using the following keywords: “Tissue factor”, “Tissue factor” and “cancer coagulopathy”, “Tissue factor” and “cancer”, “Tissue factor” and “tumor neovascularization”, “Tissue factor” and “angiogenesis”, “Tissue factor” and “antibody-drug conjugate”, “Tissue factor” and “oncogene signalling”, “Tissue factor regulation”, “Tissue factor” and “microenvironment”, and “Tissue factor” and “metastasis”. The search strategy is summarized in *Table 1*.

## Critical factors affecting TF expression

The TF is a transmembrane glycoprotein that belongs to the class II cytokine receptor superfamily and is involved in

various signal transduction biological processes, including cell adhesion, angiogenesis, and embryonic development (12,13,22). The TF expressed at the protein level includes two isoforms: the membrane-bound full-length TF (flTF) and the soluble alternatively spliced TF (asTF). AsTF plays a vital role in angiogenesis with the assistance of integrin  $\beta 1$  and  $\beta 3$  (23,24), and influences tumor invasion and metastasis processes (25,26). flTF triggers protease-activated receptors (PARs) that affect tumor cell behavior and regulates the function of integrin, which has an independent role in coagulation (27).

The oncogenic events that drive TF expression as well as K-ras and P53 mutations in colorectal cancer are the leading causes of flTF upregulation and are indicators of the gene mutations associated with TF expression (12,28,29). The TF is also abundantly expressed in vascularized organs such as the kidney, lung, and placenta, subendothelial vessels, adventitia walls, and intermediate smooth muscle cells isolated from blood. Similarly, it is constitutively expressed in cells that surround the abluminal side of the blood vessel and is also expressed in perivascular and epithelial cells in organs and body surfaces, where it forms a hemostatic barrier. Although endothelial cells express minimal TF at baseline, tumor vascular endothelial cells can express TF in a time-dependent manner (7,12,30). Furthermore, cytokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin 1 (IL-1), IL-6, and interferon- $\gamma$  (IFN- $\gamma$ ) can induce TF expression during inflammation (31-33). Conversely, cytokines that exert inhibitory functions, such as IL-4 and IL-10 suppress the expression of TF, which indicates that these cytokines also have anti-atherosclerotic effects (31,34). Furthermore, the bacterial lipopolysaccharide (LPS) can also trigger TF upregulation (35,36).

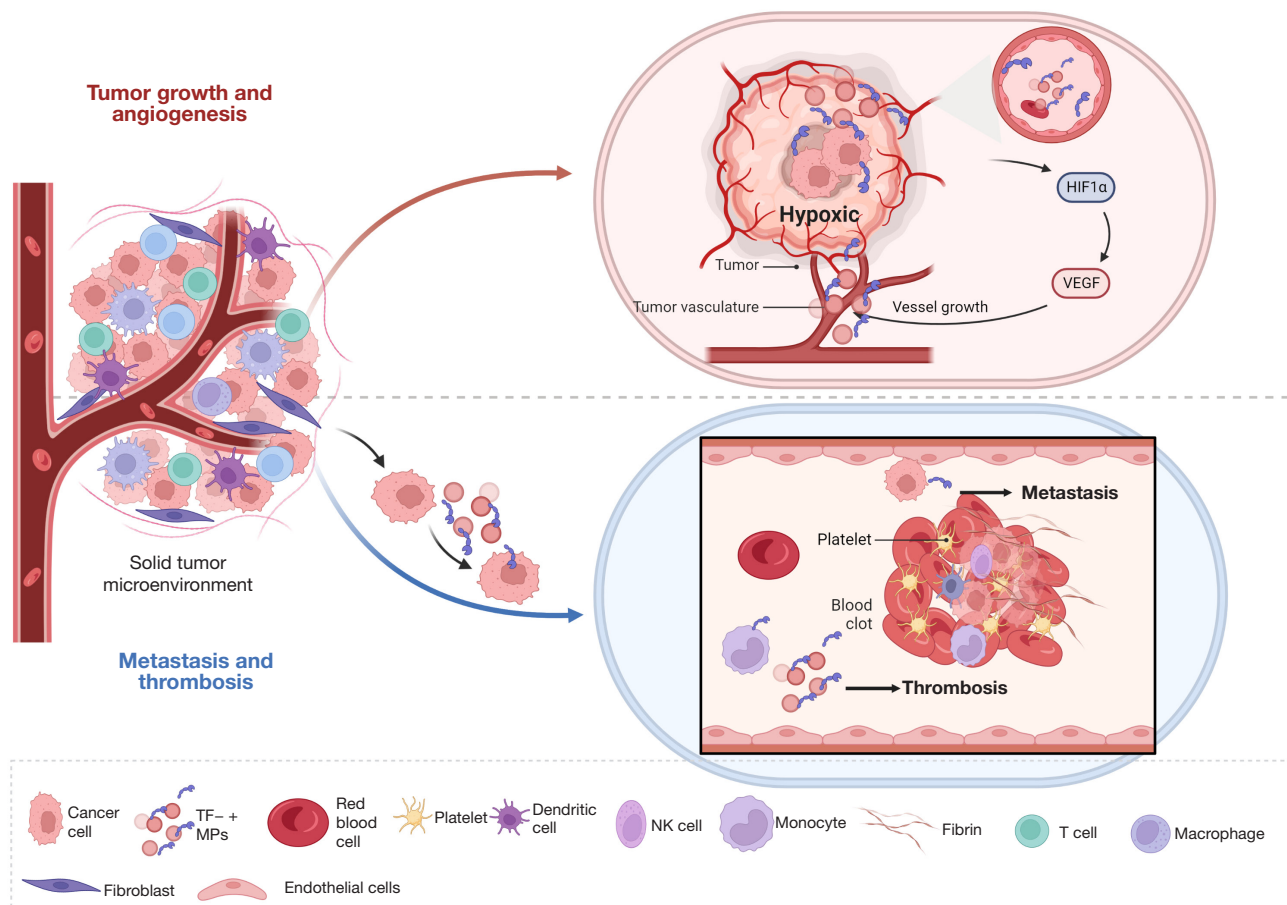
### **Correlation between TF and cancer-associated coagulation disorders**

Patients with malignant tumors are prone to an increased risk of venous thrombosis (VTE) and disseminated intravascular coagulation (DIC), which are considered significant factors of the mortality threat in patients diagnosed with cancer (12,37,38). For example, in ovarian cancer patients, the expression of TF is significantly increased in patients who have developed VTE as compared to those who did not develop VTE. Previous studies have reported on numerous factors that are involved in the occurrence and development of VTE in patients with malignant tumors. The TF plays a vital role in inducing

a hypercoagulable state (38-40). As TF play a pivotal role in disordered coagulation, recently a Phase 2b trial is launched to evaluate the safety of inhibit FVII pathway through nematode anticoagulant protein c2 (NAPc2) in patients requiring inpatient treatment for COVID-19 (NCT04655586) (41).

The role of TF is prominent in the thrombosis of cancer patients. Most tumors overexpress TF and can also secrete microparticles carrying TF. Owing to their procoagulant activity, these TF-positive extracellular microparticles (TF-positive MPs), which are released from tumor cells and act as vehicles for TF, may induce VTE (42,43) (*Figure 1*). To shed light on thrombotic disorders in cancer patients, TF+ EVs from cancer cells followed by association with coagulation factor VII (fVII) can trigger the blood coagulation cascade (9). For example, TF+ EVs induce thrombosis in pancreatic cancer and DIC in cancer patients (44). Furthermore, the TF-positive MPs are considered to indicate poorer survival, and thus, can play a predictive role in VTE risk in cancer patients (17,27,37). Moreover, the production of TF-positive MPs is also dependent on the TF binding of filamin-A and PARs (45). The TF-positive MPs released by pancreatic cancer patients also tend to increase the risk of mortality (46,47). Circulating MPs provide several clues regarding cancer-related VTE (48). TF+/GFAP- MP patients tend to have a higher risk of VTE in high-grade glioma (49). In pancreatic cancer, the activity of TF-positive MPs is also associated with the D-dimer level and future VTE (50). Moreover, under pathologic conditions, cells such as neutrophils, monocytes, platelets, and endothelial cells that flow in the circulatory system can elevate the expression of TF-positive MPs and aggravate TF-positive MPs shedding into the circulation (35) (*Figure 1*).

Meanwhile, different investigations have reported that the TF-positive MPs influence prostate cancer-related DIC, perhaps due to the relationship between platelets and monocytes. The crucial role of the tumor-derived MPs aggravating procoagulant activity to develop VTE in pancreatic cancer patients has also been revealed, meanwhile tumor-derived MPs also accelerates cancer progression (51-54). The content of TF-positive MPs is significantly higher in tumor patients than in non-tumor patients and is associated with an increased risk of VTE in cancer patients. The levels of TF are closely related to the procoagulant activity of MPs in patients who develop cancer-associated thromboembolism (38). Thus, the activity of TF-positive MPs and TF levels could be used as a biomarker of cancer-



**Figure 1** Coagulation disorder and tumor progression based on the TF-mediated process. TF-associated signaling and increased TF expression promote tumor angiogenesis and progression. TF via TF(+) microvesicle motility facilitates metastasis and cancer-associated thrombosis. Figure created with BioRender.com. TF, tissue factor; MPs, microparticles; VEGF, vascular endothelial growth factor; HIF1 $\alpha$ , hypoxia-inducible factor 1 $\alpha$ .

associated VTE owing to its ability to identify procoagulant activity (12,55), while the validation of the potential mechanism will be warranted.

The pathogenesis of malignant tumors with VTE is complex due to the interaction between tumor cells and host factors (13). Mechanistically, the overexpression of TF could also cause thrombosis, while TF interacts with tumor development, promoting VTE and also increasing tumor invasion and metastasis (14). Tumor proliferation and invasion compress the blood vessels and slow blood flow stasis, which are predisposing factors for thrombosis (29).

The coagulation/anticoagulation imbalance in the blood induces coagulation-associated disorders in cancer patients (13). It has been reported that androgen deprivation could improve TF expression and also increases the risk of VTE (56). In non-hemostatic processes (other than the

prognostic VTE biomarkers in cancer development), the TF is closely related to atherosclerosis and thrombosis, which may contribute to cardiovascular disorders in pathological coagulation (57).

### Roles of TF in angiogenesis and the tumor microenvironment

The solid tumor microenvironment is hypoxic, probably due to insufficient oxygen supply from the abnormal blood vessels (58). This hypoxia mediates programmed death ligand-1 (PD-L1) upregulation not only in splenic myeloid-derived suppressor cells (MDSCs) but also in macrophages, dendritic cells, and tumor cells (59). Furthermore, the hypoxia-inducible factor (HIF-1 $\alpha$ ) signaling pathway facilitates collagen synthesis and dense extracellular matrix

(ECM) formation, thereby inhibiting the infiltration of CD8<sup>+</sup> cytotoxic T cells (CTLs) (59). Subsequently, immunosuppressive cells such as M2 phenotype tumor-associated macrophages (TAMs), myeloid-derived suppressive cells (MDSCs), and regulatory T-cells (Tregs), and cytokines such as transforming growth factor- $\beta$  (TGF- $\beta$ ) and IL-10 are recruited under hypoxic conditions, which creates a suppressive immune microenvironment.

Previous studies have reported that the TF is expressed in both cancer cells and the tumor vasculature in human breast cancer. Its association with angiogenesis initiation has also been validated via detection of the TF only in the vascular endothelial cells (VECs) of malignant breast tumors and not in the VECs of benign tumors (8,27,60). Similarly, an investigation of human breast cancer cells also indicated that TF expression was upregulated in a cancer-associated hypoxic environment mediated by HIF-1 $\alpha$  by disturbing vascular endothelial growth factor (VEGF) expression (61) (*Figure 1*).

Furthermore, a study has revealed that epithelial tissue-derived cancer cells exhibited higher TF expression than those in non-epithelial-derived malignancies (50). The expression of TF in glioma tissues is significantly increased at both the protein and gene levels and increases with the tumor grade; however, TF is not expressed in normal brain tissue (19). In addition, TF contributes to tumor-associated angiogenesis. The TF found in stromal, vascular, and inflammatory cells interacts with the tumor cells, inducing a procoagulative tumor microenvironment (28). The TF-VIIa binary complex shapes the tumor microenvironment by mediating PAR2 via the induction of a variety of growth factors, including proangiogenic immunomodulatory cytokines and chemokines (62). The interaction between the TF-FVIIa complex and integrin plays a pivotal role in angiogenesis (63). FITF influences angiogenesis through PAR-2 via PAR-dependent pathways, whereas asTF relies on integrin ligation (23).

Angiogenesis is a malignant feature of cancers and an important condition for tumor growth and metastasis. The upregulation of proangiogenic VEGF and downregulation of the anti-angiogenic factor thrombospondin (TSP) are major mechanisms through which TF promotes angiogenesis; it has been reported that VEGF mediates TF expression via early growth response protein 1 (EGR1) (64). This illustrates the important role of TF in angiogenesis. For example, in colorectal cancer, the expression of TF is associated with angiogenesis and TF-positive carcinomas tend to have higher microvessel density (MVD) and VEGF

expression compared to TF-negative tumors. The TF is also considered a key element of the tumor-vascular interface, while the crucial part is expressed by the tumor-associated endothelium, which is also necessary (13). Similarly, transfected cells with high TF expression establish tumors that are highly vascular and accompanied by enhanced VEGF transcription in the tumor cells. However, this effect is weakened after knockdown of the cytoplasmic tail of TF, which indicates that the higher VEGF and TF production is associated with intense vascularity (19).

The TF promotes tumor angiogenesis via the coagulation or non-coagulation pathway-dependent pathways. The coagulation-dependent pathway is mainly related to TF-induced thrombin formation and fibrin cross-linking, while the non-coagulation pathway-dependent pathway is related to TF-mediated signal transduction. The TF can also regulate inflammation and angiogenesis through its cytoplasmic domain. For example, the absence of the TF cytoplasmic domain in mice has a higher peri-infarct vessel density, due to its endothelial cell proliferation, as well as expressing higher amounts of PAR2 and activating proangiogenic pathway factors (65). asTF promotes angiogenesis via the activation of HIF-1 $\alpha$ /VEGF signaling (66).

The TF is an angiogenic-specific receptor on endothelial cells, and TF-targeted therapeutics have been applied in cancer therapy. Also, TF-targeted therapeutics have been used in the treatment of angiogenesis-dependent diseases such as cancer, macular degeneration, and endometriosis (67). Furthermore, the downregulation of TF gene expression with anti-TF antibodies can inhibit the growth and angiogenesis of experimental tumors. However, anti-angiogenic therapy that targets TF-VIIa-PAR2 signaling increases the risk of uncontrollable hemorrhage (62).

### TF signaling pathway

The diverse oncogenic transformations contribute substantially to the overexpression of TF in cancer cells. In addition to the function of TF in hemostasis, TF pathways also exert other functions in cell signaling, especially by mediating the protease-activated receptor (PAR) family. The PAR is a member of the G protein-coupled receptor family, which includes four subtypes: PAR1, PAR2, PAR3, and PAR4. The TF/VIIa complex can activate PAR2 and the TF/FVIIa/FXa complex can activate both PAR2 and PAR1, while PAR1 tends to be involved in tumor cell invasion, growth, and migration (12,62). On the other hand, PAR2, an endogenous receptor, plays an essential role in coagulant

protease VIIa and Xa signaling, migration, and invasion in breast cancer cells (68). Moreover, metastatic tumor cells can activate PAR1 through the ternary TF-VIIa-Xa complex or thrombin signaling, which is an additional signaling network of the coagulation cascade (62).

The (TF)-VIIa protease complex promotes tumor progression through PAR-2 signaling, which is independent of coagulation aspects. The phosphorylation of TF intracellular proteins affects angiogenesis, as it negatively regulates the PAR-2 signaling pathway (14). Furthermore, the relationship between the TF cytoplasmic domain and PAR2 may explain both the TF phosphorylation and tumor recurrence in human breast cancer (69).

Previous studies have confirmed that TF-mediated signal transmission mainly involves the phosphorylation of intracellular proteins and the activation of related signaling pathways, such as mitogen-activated protein kinase kinase (MEK)/mitogen-activated protein kinase (MAPK)-phosphatidylinositol 3'-kinase (PI3K) and NF- $\kappa$ B signaling; therefore, cancers utilize TF-activated pathways to drive their progression (27,70). Similarly, in human colorectal cancer cells, the TF expression is controlled by oncogenic event regulation (i.e., MEK/MAPK/PI3K) to activate the K-ras oncogene and mute the p53 tumor suppressor (70).

Angiostatic treatments targeting the TF-VIIa signaling pathway may have real potential against neovascular eye diseases and cancer treatment (14). For example, breast tumor cells can inhibit apoptosis via phosphorylation of the p44/42 MAPK and PKB/Akt signaling pathways in a TF-FVIIa-FXa complex-dependent manner instead of a thrombin-independent manner (3). Furthermore, to mediate LPA-induced TF expression in smooth muscle cells, lysophosphatidic acid (LPA1), which is considered an essential receptor for the LPA1- protein kinase D2 axis, induces TF expression through the Jun N-terminal kinases2 (JNK2)-MAPK and p38 $\alpha$  signaling pathways in a protein kinase D (PKD)-dependent manner (71).

Similarly, the NF- $\kappa$ B is a eukaryotic transcription factor that is present in almost all cells and is also involved in the transmission of information, such as cell differentiation, tumor growth, and bodily defense. Transcription factors such as protein-1 and NF- $\kappa$ B can regulate TF expression. It has been reported that gene expression in activated endothelial cells and vascular smooth muscle cells, as well as peptidyl-prolyl isomerase Pin1, modulate the activity of TF by activating protein-1 and NF- $\kappa$ B signaling, thereby increasing procoagulant activity. Therefore, the Pin1-protein-1/NF- $\kappa$ B-TF pathway may offer new avenues

for pathological coagulation (57). The androgen receptor in androgen-dependent prostate tumors facilitates the decreased expression of TF through NF- $\kappa$ B signaling and EGR1, which may account for the androgen deprivation (ADT)-increased risk of VTE for higher TF expression and TF(+) microvesicles in prostate cancer patients (56). Furthermore, under inflammatory conditions, TNF- $\alpha$  increases the TF expression and procoagulant activity through NF- $\kappa$ B, concomitant with the downregulation of vitamin D receptor expression, while the upregulation of TF function may promote a prothrombotic state. Thus, vitamin D may decrease the expression of TF and reduce the risk of cardiovascular disease (72).

The cytoplasmic domain of fTF plays a critical role in non-coagulant signaling. The anti-apoptotic effects of fTF occur due to the suppression of death-associated protein kinase-1 (73) as well as the activation of signaling pathways (PKB/AKT, PI3-kinase/Akt, and JAK/STAT5) that depend on its proteolytic activity (74,75). AsTF ligation with  $\alpha$ 6 $\beta$ 1 or  $\alpha$ V $\beta$ 3 integrins in a non-proteolytic manner demonstrates potent proangiogenic activity, with an improved expression of signals such as FAK, PI3K/AKT, and MAPK. Similarly, the TF can bind to the integrins independent of FVII (23).

### Effect of TF on tumor progression

It has been reported that TF-mediated coagulation is necessary for thrombosis and has non-hemostatic roles in promoting tumor progression. The biology of TF in cancer is highly complex, and thus, TF may not only regulate the exogenous blood coagulation cascade and hemostasis but also exert a variety of non-coagulation functions through PAR-mediated signal transduction pathologic process behaviors, including tumor angiogenesis, invasion, and metastasis (12,22). PAR2, an endogenous receptor, also plays a vital role in coagulant protease VIIa and Xa signaling, migration, and invasion in breast cancer cells (68). Moreover, metastatic tumor cells can activate PAR1 via the ternary TF-VIIa-Xa complex (62). Cancer cells utilize TF procoagulant activity and TF-FVIIa-mediated intracellular signaling pathways for their proliferation.

TF promotes tumor progression by altering signaling, angiogenesis, metastatic capabilities, tumor initiation and growth, as well as cancer-related coagulopathies. Numerous studies have demonstrated elevated TF expression levels in primary colorectal, breast, and pancreatic cancers. TF levels correlate with the invasive phenotype of cancer and promote tumor growth and proliferation (12,27). *In*

*in vivo* colorectal cancer trials involving mice have provided direct evidence that TF promotes tumor growth. It is also confirmed that the controlled reduction of TF expression using small interfering RNA (siRNA) significantly reduces tumor growth (76). Moreover, fTF-MVs promote tumor invasion via their motility (50).

As mentioned, TF is involved in tumor-associated angiogenesis and its expression levels are associated with metastatic potential in various hematologic neoplasms (Figure 1). It promotes tumor cell metastasis by activating both the coagulation cascade and platelets. It also correlates with invasiveness and metastasis because it is predominantly expressed on the tumor border in various liver, breast, pancreas, and lung tissues (77). Studies have further revealed that TF could mediate cell behavior and intracellular gene expression patterns by altering signaling events (22,27). It is also thought to be pro-metastatic and plays a promising role in modulating metastasis, which is critical in the pathogenesis of cancer. For example, TF-positive microparticles, which possess procoagulant ability, released by tumor cells into the circulation may trigger VTE. Similarly, metastasis occurs when TF-positive circulating tumor cells are masked with fibrin, which covers them and evades surveillance from the body's immune system (12,29) (Figure 1).

In conclusion, TF-mediated thrombin generation and intracellular signaling contribute to distal metastasis. TF expression interacts with tumor cells to promote tumor progression, and thus, targeting TF may inhibit several pathologic pathways associated with tumor growth and metastasis.

### TF-based targeted therapy

Due to its high expression in tumor cells, TF has become an attractive target for cancer therapy. The downregulation of TF expression by siRNA, or anti-TF antibodies along with other technologies inhibits tumor growth and metastasis, thereby providing a new way to treat malignant tumors (78). The possibility of TF-targeted therapeutic strategies has been explored. Also, TF antibodies loaded with agents have been studied *in vivo*, including fVII-conjugated photosensitizer factor VII (fVII)-IgG1 Fc, antibody-drug conjugate (ADC) toxins, and radioactive ligands (5,7,29,79,80). A novel TF-specific ADC carries a toxin conjugated to a monoclonal antibody, which exhibits potent antitumor activity in TF: FVIIa-dependent intracellular signaling manner without impacting procoagulant

activity (81). Interestingly, TF-directed antibody-drug conjugate has achieved durable and clinically meaningful responses with a tolerable safety profile (21). The antibody-drug conjugate that targets the TF could be hopeful for ADC targets. Furthermore, asTF is highly expressed in breast cancer and its tumor neovasculature and has been a targeted receptor for its specific expression (5), these novel approaches to anticancer therapy have produced encouraging results, which are attracting more researchers in the field of TF-based targeted therapy.

TF has also been a potential target for immunotherapy development. There are several strategies based on blocking TF signaling. The FVII initiates subsequent coagulation pathways by forming a complex with FX, and both FX and FVII need vitamin K to sustain efficient proteolytic signaling; therefore, vitamin K antagonists can reduce their coagulation activity and expression. For example, vitamin K antagonists (VKAs) have reduced tumorigenesis among VKA-exposed patients (82); these patients are less prone to cancer, especially those with a decreased risk of prostate cancer (83,84). Furthermore, the inhibition of TF-VIIa complex formation using TF pathway inhibitors or theNAPc2 inhibited B16 melanoma growth in mouse model (85). TF-FVIIa inhibitors can block the signaling pathways that decrease angiogenesis and delay tumor development (28). Moreover, the TF cytoplasmic domain-targeted therapy could facilitate intracellular signaling and help control post-infarct left ventricle remodeling without activating coagulation (65). TF, as a tumor-associated antigen (TAA), can be targeted with T-cell engaging bispecific antibody (TCB); TF-TCB can mediate T-cell infiltration by co-targeting CD3 to eliminate TF-positive tumors, demonstrating the efficacy of TF-TCB (86). However, asTF-targeted therapies are rare; the TF-antibody could block the asTF-integrin interaction, suggesting that TF may serve as a target due to the asTF-mediated pathological process (23).

Hu *et al.* showed that immune cross-linkers composed of murine mutant FVII and Fc domains could specifically bind to TF with high surface affinity in prostate cancer and endothelial cells, simultaneously activating the cytolytic immune responses through Fc domains that inhibit the growth of primary and metastatic tumors for a long time without toxic effects (87). In addition, the designed FVII peptide immunoconjugates (ICON) based on TF targeting in which the mutated fVII was connected to the Fc effector domain of IgG1. A replication-defective adenovirus vector was used to encode immunoconjugates with a

good affinity for TF that lose their coagulating ability and secreted to target tumor cells can induce human tumor xenograft infarction (88). Based on the above findings, Hu *et al.* developed a second-generation immunoconjugate (L-ICON) for triple-negative breast cancer (TNBC) patients because TF was expressed in approximately 50–85% of these patients. Moreover, L-ICON also has demonstrated its efficacy in the treatment of TNBC (5).

There are other methods to block TF expression. Lentivirus-mediated RNA interference reduces the TF expression of activated endothelial cells (ECs) without affecting the extrinsic coagulation pathway, while its downregulation adversely affects EC viability (89). Similarly, siRNA has been used to downregulate TF, suppressing the growth of lung adenocarcinomas that express high levels of TF *in vitro* and *in vivo* (78). Furthermore, a novel siRNA-containing nanoparticle can induce the tumor-specific silencing of TF, demonstrating anti-metastasis efficacy and reducing the risk of thrombotic complications in cancer patients (90).

Chimeric antigen receptor-modified T-cells (CAR T-cells) are a promising therapeutic option for TF-positive cancers. Due to specific binding of TF and FVII, Zhang *et al.* designed a new third-generation CAR (TF-CAR T-cells) to express the FVII light chain, aiming to treat solid tumors that overexpress the TF tumor (79). Their results demonstrated that TF-CAR T biohybrids exhibited specific cytotoxicity in non-small cell lung cancer (NSCLC) and melanoma cells without causing obvious toxicity in mice, highlighting its safety profile (79). Moreover, TF-CAR-engineered natural killer (TF-CAR-NK) cells have also been shown to induce antibody-dependent cellular toxicity (ADCC). The preclinical evidence reported in the TNBC model suggests tumor eradication. In addition, the ADCC effect of L-ICON can boost the efficacy of TF-CAR-NK *in vitro* (80).

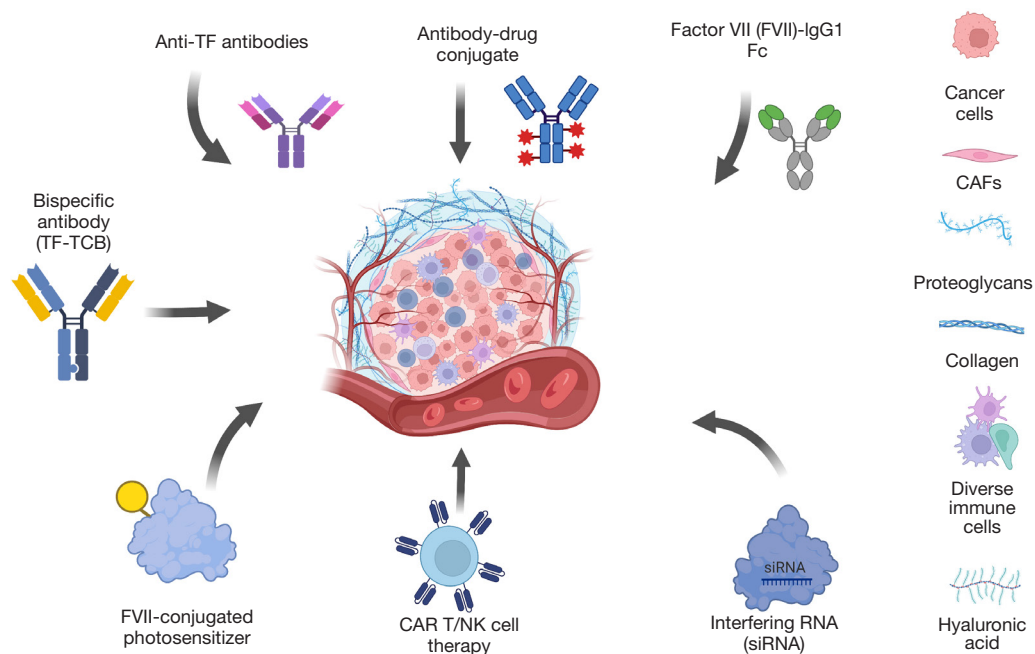
Hu *et al.* attempted to target TF in angiogenic endothelial cells and tumor cells in another way, using FVII-targeted photodynamic therapy (PDT), vascular occlusion, and tumor infarction as potential results. The FVII-Sn(IV) chlorin e6 conjugate FVII, FVII-targeted photodynamic therapy (tPDT) was reported to exhibit durable antitumor immunity for the treatment of breast cancer (91). FVII-tPDT, which combined FVII with the photosensitizer verteporfin, can selectively kill TF-positive breast cancer cells while overcoming the shortcoming of non-targeted PDT due to its poor selectivity and low efficiency, implicating ligand-tPDT as a promising therapeutic option. In addition, the tPDT has excellent

potential in neovascular-targeting therapy (30,92). TF is expressed explicitly in angiogenic vascular endothelial cells (VECs), which make up the inner layer of pathological neovascularization, and is expressed in a time-dependent manner in the vascular system. TPDt can eradicate angiogenic VECs; therefore, targeting TF in tumors, endometriosis, and macular degeneration (i.e., angiogenesis-dependent diseases) is highly anticipated (67).

Given previous studies have established that TF is overexpressed and associated with cancer progression in almost all cancers (ovarian, pancreatic, and prostate colorectal esophageal, gastric, kidney, liver, lung) (27,93), rendering TF more attractive to be clinically exploited. More and more clinic trials are evaluating the efficacy and safety of tissue factor positive advanced or metastatic solid tumors (NCT04843709). In addition, the noninvasive assessment of tumor TF expression status hold a prime position in clinical practice. Based on the mechanism of Factor VII natural binding with TF, providing a promising strategy to noninvasive evaluation of tumor TF expression. Through preclinical models convincingly demonstrated that by labeling derivative of factor VII with <sup>18</sup>F-labeled (64). Cu for non-invasive PET imaging of TF expression in tumor tissue, accelerating the advent of TF-targeted PET radiotracer in humans has been proved to be effective in a phase I clinical trial (NCT03790423) (94-96). Moreover, it has been reported that TF levels were elevated in plasma, and the measurement of plasma activity of the tissue factor to predict VTE in primitive cancer of Lung has completed, but no study results been released for this study (NCT02853188).

The above-described mechanisms and TF-targeted therapeutic agents, including TF-CAR-NK, TF-CAR T cells, TF-antibody, TF-bispecific antibody, (FVII)-IgG1 Fc, and FVII-conjugated photosensitizer exhibited a high efficacy across a broad spectrum of solid tumors (Figure 2). Recently, real breakthroughs has happened with the first TF-targeted antibody–drug conjugate tisotumab vedotin (HuMax<sup>®</sup>-TF-ADC) was approved by the FDA for cervical cancer (20,21). A phase 2 clinical trial was conducted in breast cancer to investigate whether rosuvastatin can influence the number of TF-positive MPs in the blood (NCT01299038). The effect of noxaparine thromboprophylaxis will be investigated in cancer patients with elevated tissue factor bearing microparticles (NCT00908960). Overall, these findings strongly suggest targeting TF using modifying factor VII (FVII) to damage tumor vasculature and cells warrants further clinical study.





**Figure 2** Overview of TF-associated therapy. TF-directed treatment based on blocking the function of TF or modifying factor VII (FVII) or by conjugating the TF antibody with novel agents, as well as TF-CAR-engineered NK/T therapy. Figure created with BioRender.com. TF, tissue factor; CAR, chimeric antigen receptor; NK, natural killer.

## Discussion and future perspectives

The current study has confirmed that TF is involved in the hypercoagulable state of tumors and is highly expressed in a variety of malignant tumors through coagulation- or non-coagulation-dependent pathways, mediating a variety of signals transduction pathways that disturb tumor growth, metastasis, and neovascularization. Moreover, it is involved in rapid hemostasis when organ damage occurs and is considered to be a biomarker for recurrent VTE. Reports have shown that physiological hemostasis can be maintained with only a little TF expression (31). Similarly, antibody-drug mixtures that target TF have been applied in numerous related studies to treat a variety of solid tumors (81,97).

The TF has gradually been recognized as a target for cancer therapy. TF-targeted therapy involves FVII engineering, such as conjugating ADC drugs, photosensitizers, and the regulation of TF expression by siRNA or anti-TF antibodies. However, the main challenge for antitumor treatment is the lack of interference with the procoagulant capacity. Future investigations will focus on the TF isoforms and the non-hemostatic aspects of TF activity, which simultaneously targets downstream signaling

while retaining the hemostatic ability. Therefore, TF-based targeted therapy seems to be a potential option for improving the management of malignant diseases.

The mechanisms through which tumor cells control these divergent functions of TF remain to be elucidated. Given the established actual practices of targeting TF in preclinical efficacy studies, when the risk of uncontrollable hemorrhage is effectively controlled, TF-targeted therapies may have a significant potential for treating cancer and should be investigated in future clinical trials.

## Acknowledgments

*Funding:* This work was supported by 1.3.5 Project for Disciplines of Excellence, West China Hospital, Sichuan University (No. ZYJC21043), the National Natural Science Foundation of China (No. 31971390), and Sichuan Science and Technology Program (No. 2021YFH0142).

## Footnote

*Reporting Checklist:* The authors have completed the Narrative Review reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-5067/rc>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-5067/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

*Open Access Statement:* This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

## References

- Mackman N, Tilley RE, Key NS. Role of the extrinsic pathway of blood coagulation in hemostasis and thrombosis. *Arterioscler Thromb Vasc Biol* 2007;27:1687-93.
- Nadir Y, Brenner B, Zetser A, et al. Heparanase induces tissue factor expression in vascular endothelial and cancer cells. *J Thromb Haemost* 2006;4:2443-51.
- Jiang X, Guo YL, Bromberg ME. Formation of tissue factor-factor VIIa-factor Xa complex prevents apoptosis in human breast cancer cells. *Thromb Haemost* 2006;96:196-201.
- Guan M, Jin J, Su B, et al. Tissue factor expression and angiogenesis in human glioma. *Clin Biochem* 2002;35:321-5.
- Hu Z, Shen R, Campbell A, et al. Targeting Tissue Factor for Immunotherapy of Triple-Negative Breast Cancer Using a Second-Generation ICON. *Cancer Immunol Res* 2018;6:671-84.
- Khorana AA, Ahrendt SA, Ryan CK, et al. Tissue factor expression, angiogenesis, and thrombosis in pancreatic cancer. *Clin Cancer Res* 2007;13:2870-5.
- Cheng J, Xu J, Duanmu J, et al. Effective treatment of human lung cancer by targeting tissue factor with a factor VII-targeted photodynamic therapy. *Curr Cancer Drug Targets* 2011;11:1069-81.
- Witkowski M, Witkowski M, Friebe J, et al. Vascular endothelial tissue factor contributes to trimethylamine N-oxide-enhanced arterial thrombosis. *Cardiovasc Res* 2022;118:2367-84.
- Koizume S, Miyagi Y. Tissue factor in cancer-associated thromboembolism: possible mechanisms and clinical applications. *Br J Cancer* 2022;1-9.
- Zelaya H, Rothmeier AS, Ruf W. Tissue factor at the crossroad of coagulation and cell signaling. *J Thromb Haemost* 2018;16:1941-52.
- Khorana AA, Mackman N, Falanga A, et al. Cancer-associated venous thromboembolism. *Nat Rev Dis Primers* 2022;8:11.
- Kasthuri RS, Taubman MB, Mackman N. Role of tissue factor in cancer. *J Clin Oncol* 2009;27:4834-8.
- Rak J, Milsom C, May L, et al. Tissue factor in cancer and angiogenesis: the molecular link between genetic tumor progression, tumor neovascularization, and cancer coagulopathy. *Semin Thromb Hemost* 2006;32:54-70.
- Belting M, Dorrell MI, Sandgren S, et al. Regulation of angiogenesis by tissue factor cytoplasmic domain signaling. *Nat Med* 2004;10:502-9.
- Kakkar AK, Lemoine NR, Scully MF, et al. Tissue factor expression correlates with histological grade in human pancreatic cancer. *Br J Surg* 1995;82:1101-4.
- Nitori N, Ino Y, Nakanishi Y, et al. Prognostic significance of tissue factor in pancreatic ductal adenocarcinoma. *Clin Cancer Res* 2005;11:2531-9.
- van den Berg YW, Osanto S, Reitsma PH, et al. The relationship between tissue factor and cancer progression: insights from bench and bedside. *Blood* 2012;119:924-32.
- Versteeg HH, Schaffner F, Kerver M, et al. Protease-activated receptor (PAR) 2, but not PAR1, signaling promotes the development of mammary adenocarcinoma in polyoma middle T mice. *Cancer Res* 2008;68:7219-27.
- Abe K, Shoji M, Chen J, et al. Regulation of vascular endothelial growth factor production and angiogenesis by the cytoplasmic tail of tissue factor. *Proc Natl Acad Sci U S A* 1999;96:8663-8.
- Mullard A. First-in-class tissue factor-targeted antibody-drug conjugate secures FDA approval. *Nat Rev Drug Discov* 2021;20:806.
- Coleman RL, Lorusso D, Gennigens C, et al. Efficacy and safety of tisotumab vedotin in previously treated recurrent or metastatic cervical cancer (innovaTV 204/GOG-3023/ENGOT-cx6): a multicentre, open-label, single-arm, phase 2 study. *Lancet Oncol* 2021;22:609-19.
- López-Pedraza C, Barbarroja N, Dorado G, et al. Tissue factor as an effector of angiogenesis and tumor

- progression in hematological malignancies. *Leukemia* 2006;20:1331-40.
23. van den Berg YW, van den Hengel LG, Myers HR, et al. Alternatively spliced tissue factor induces angiogenesis through integrin ligation. *Proc Natl Acad Sci U S A* 2009;106:19497-502.
  24. Matiash K, Lewis CS, Bogdanov VY. Functional Characteristics and Regulated Expression of Alternatively Spliced Tissue Factor: An Update. *Cancers (Basel)* 2021;13:4652.
  25. Kocatürk B, Versteeg HH. Tissue factor isoforms in cancer and coagulation: may the best isoform win. *Thromb Res* 2012;129 Suppl 1:S69-75.
  26. Ünlü B, Versteeg HH. Effects of tumor-expressed coagulation factors on cancer progression and venous thrombosis: is there a key factor? *Thromb Res* 2014;133 Suppl 2:S76-84.
  27. Unruh D, Horbinski C. Beyond thrombosis: the impact of tissue factor signaling in cancer. *J Hematol Oncol* 2020;13:93.
  28. Ruf W, Disse J, Carneiro-Lobo TC, et al. Tissue factor and cell signalling in cancer progression and thrombosis. *J Thromb Haemost* 2011;9 Suppl 1:306-15.
  29. Eisenreich A, Bolbrinker J, Leppert U. Tissue Factor: A Conventional or Alternative Target in Cancer Therapy. *Clin Chem* 2016;62:563-70.
  30. Hu Z, Rao B, Chen S, et al. Targeting tissue factor on tumour cells and angiogenic vascular endothelial cells by factor VII-targeted verteporfin photodynamic therapy for breast cancer in vitro and in vivo in mice. *BMC Cancer* 2010;10:235.
  31. Witkowski M, Landmesser U, Rauch U. Tissue factor as a link between inflammation and coagulation. *Trends Cardiovasc Med* 2016;26:297-303.
  32. Bastarache JA, Sebag SC, Grove BS, et al. Interferon- $\gamma$  and tumor necrosis factor- $\alpha$  act synergistically to up-regulate tissue factor in alveolar epithelial cells. *Exp Lung Res* 2011;37:509-17.
  33. Grignani G, Maiolo A. Cytokines and hemostasis. *Haematologica* 2000;85:967-72.
  34. Kamimura M, Viedt C, Dalpke A, et al. Interleukin-10 suppresses tissue factor expression in lipopolysaccharide-stimulated macrophages via inhibition of Egr-1 and a serum response element/MEK-ERK1/2 pathway. *Circ Res* 2005;97:305-13.
  35. Østerud B, Bjørklid E. Sources of tissue factor. *Semin Thromb Hemost* 2006;32:11-23.
  36. Eisenreich A, Rauch U. Regulation and differential role of the tissue factor isoforms in cardiovascular biology. *Trends Cardiovasc Med* 2010;20:199-203.
  37. Owens AP, 3rd, Mackman N. Microparticles in hemostasis and thrombosis. *Circ Res* 2011;108:1284-97.
  38. Kobayashi S, Koizume S, Takahashi T, et al. Tissue factor and its procoagulant activity on cancer-associated thromboembolism in pancreatic cancer. *Cancer Sci* 2021;112:4679-91.
  39. Abu Saadeh F, Norris L, O'Toole S, et al. Tumour expression of tissue factor and tissue factor pathway inhibitor in ovarian cancer- relationship with venous thrombosis risk. *Thromb Res* 2013;132:627-34.
  40. Frangou E, Chrysanthopoulou A, Mitsios A, et al. REDD1/autophagy pathway promotes thromboinflammation and fibrosis in human systemic lupus erythematosus (SLE) through NETs decorated with tissue factor (TF) and interleukin-17A (IL-17A). *Ann Rheum Dis* 2019;78:238-48.
  41. Hess CN, Capell WH, Bristow MR, et al. Rationale and design of a study to assess the safety and efficacy of rNAPc2 in COVID-19: the Phase 2b ASPEN-COVID-19 trial. *Am Heart J* 2022;246:136-43.
  42. Grover SP, Mackman N. Tissue Factor: An Essential Mediator of Hemostasis and Trigger of Thrombosis. *Arterioscler Thromb Vasc Biol* 2018;38:709-25.
  43. Dvorak HF, Quay SC, Orenstein NS, et al. Tumor shedding and coagulation. *Science* 1981;212:923-4.
  44. Hisada Y, Satchetto ATA, Mackman N. Circulating tissue factor-positive extracellular vesicles and their association with thrombosis in different diseases. *Immunol Rev* 2022;312:61-75.
  45. Koizume S, Ito S, Yoshioka Y, et al. High-level secretion of tissue factor-rich extracellular vesicles from ovarian cancer cells mediated by filamin-A and protease-activated receptors. *Thromb Haemost* 2016;115:299-310.
  46. Khorana AA, Francis CW, Menzies KE, et al. Plasma tissue factor may be predictive of venous thromboembolism in pancreatic cancer. *J Thromb Haemost* 2008;6:1983-5.
  47. Thaler J, Ay C, Mackman N, et al. Microparticle-associated tissue factor activity in patients with pancreatic cancer: correlation with clinicopathological features. *Eur J Clin Invest* 2013;43:277-85.
  48. Date K, Ettelaie C, Maraveyas A. Tissue factor-bearing microparticles and inflammation: a potential mechanism for the development of venous thromboembolism in cancer. *J Thromb Haemost* 2017;15:2289-99.
  49. Sartori MT, Della Puppa A, Ballin A, et al. Circulating microparticles of glial origin and tissue factor bearing in high-grade glioma: a potential prothrombotic role. *Thromb Haemost* 2013;110:378-85.

50. Thaler J, Ay C, Mackman N, et al. Microparticle-associated tissue factor activity, venous thromboembolism and mortality in pancreatic, gastric, colorectal and brain cancer patients. *J Thromb Haemost* 2012;10:1363-70.
51. Woei AJFJ, Tesselaar ME, Garcia Rodriguez P, et al. Tissue factor-bearing microparticles and CA19.9: two players in pancreatic cancer-associated thrombosis? *Br J Cancer* 2016;115:332-8.
52. Tesselaar ME, Romijn FP, Van Der Linden IK, et al. Microparticle-associated tissue factor activity: a link between cancer and thrombosis? *J Thromb Haemost* 2007;5:520-7.
53. van Es N, Hisada Y, Di Nisio M, et al. Extracellular vesicles exposing tissue factor for the prediction of venous thromboembolism in patients with cancer: A prospective cohort study. *Thromb Res* 2018;166:54-9.
54. van Doormaal F, Kleinjan A, Berckmans RJ, et al. Coagulation activation and microparticle-associated coagulant activity in cancer patients. An exploratory prospective study. *Thromb Haemost* 2012;108:160-5.
55. Wang M, Huang X, Zhu M, et al. High concentration of the plasma microparticles for venous thromboembolism associated with lung cancer. *Clin Respir J* 2020;14:481-7.
56. Hoesel B, Mussbacher M, Dikorman B, et al. Androgen receptor dampens tissue factor expression via nuclear factor- $\kappa$ B and early growth response protein 1. *J Thromb Haemost* 2018;16:749-58.
57. Kurakula K, Koenis DS, Herzik MA Jr, et al. Structural and cellular mechanisms of peptidyl-prolyl isomerase Pin1-mediated enhancement of Tissue Factor gene expression, protein half-life, and pro-coagulant activity. *Haematologica* 2018;103:1073-82.
58. Rankin EB, Nam JM, Giaccia AJ. Hypoxia: Signaling the Metastatic Cascade. *Trends Cancer* 2016;2:295-304.
59. Gilkes DM, Bajpai S, Chaturvedi P, et al. Hypoxia-inducible factor 1 (HIF-1) promotes extracellular matrix remodeling under hypoxic conditions by inducing P4HA1, P4HA2, and PLOD2 expression in fibroblasts. *J Biol Chem* 2013;288:10819-29.
60. Contrino J, Hair G, Kreutzer DL, et al. In situ detection of tissue factor in vascular endothelial cells: correlation with the malignant phenotype of human breast disease. *Nat Med* 1996;2:209-15.
61. Sun L, Liu Y, Lin S, et al. Early growth response gene-1 and hypoxia-inducible factor-1 $\alpha$  affect tumor metastasis via regulation of tissue factor. *Acta Oncol* 2013;52:842-51.
62. Schaffner F, Ruf W. Tissue factor and PAR2 signaling in the tumor microenvironment. *Arterioscler Thromb Vasc Biol* 2009;29:1999-2004.
63. Rothmeier AS, Liu E, Chakrabarty S, et al. Identification of the integrin-binding site on coagulation factor VIIa required for proangiogenic PAR2 signaling. *Blood* 2018;131:674-85.
64. Mechtcheriakova D, Wlachos A, Holzmüller H, et al. Vascular endothelial cell growth factor-induced tissue factor expression in endothelial cells is mediated by EGR-1. *Blood* 1999;93:3811-23.
65. Chong SY, Zharkova O, Yatim S, et al. Tissue factor cytoplasmic domain exacerbates post-infarct left ventricular remodeling via orchestrating cardiac inflammation and angiogenesis. *Theranostics* 2021;11:9243-61.
66. Giannarelli C, Alique M, Rodriguez DT, et al. Alternatively spliced tissue factor promotes plaque angiogenesis through the activation of hypoxia-inducible factor-1 $\alpha$  and vascular endothelial growth factor signaling. *Circulation* 2014;130:1274-86.
67. Hu Z, Cheng J, Xu J, et al. Tissue factor is an angiogenic-specific receptor for factor VII-targeted immunotherapy and photodynamic therapy. *Angiogenesis* 2017;20:85-96.
68. Morris DR, Ding Y, Ricks TK, et al. Protease-activated receptor-2 is essential for factor VIIa and Xa-induced signaling, migration, and invasion of breast cancer cells. *Cancer Res* 2006;66:307-14.
69. Schaffner F, Versteeg HH, Schillert A, et al. Cooperation of tissue factor cytoplasmic domain and PAR2 signaling in breast cancer development. *Blood* 2010;116:6106-13.
70. Yu JL, May L, Lhotak V, et al. Oncogenic events regulate tissue factor expression in colorectal cancer cells: implications for tumor progression and angiogenesis. *Blood* 2005;105:1734-41.
71. Hao F, Liu Q, Zhang F, et al. LPA(1)-mediated PKD2 activation promotes LPA-induced tissue factor expression via the p38 $\alpha$  and JNK2 MAPK pathways in smooth muscle cells. *J Biol Chem* 2021;297:101152.
72. Martinez-Moreno JM, Herencia C, Montes de Oca A, et al. Vitamin D modulates tissue factor and protease-activated receptor 2 expression in vascular smooth muscle cells. *Faseb J* 2016;30:1367-76.
73. Aberg M, Johnell M, Wickström M, et al. Tissue Factor/FVIIa prevents the extrinsic pathway of apoptosis by regulation of the tumor suppressor Death-Associated Protein Kinase 1 (DAPK1). *Thromb Res* 2011;127:141-8.
74. Aberg M, Wickström M, Siegbahn A. Simvastatin induces apoptosis in human breast cancer cells in a NF $\kappa$ B-dependent manner and abolishes the anti-apoptotic signaling of TF/FVIIa and TF/FVIIa/FXa. *Thromb Res* 2008;122:191-202.

75. Sorensen BB, Rao LV, Tornehave D, et al. Antiapoptotic effect of coagulation factor VIIa. *Blood* 2003;102:1708-15.
76. Nakasaki T, Wada H, Shigemori C, et al. Expression of tissue factor and vascular endothelial growth factor is associated with angiogenesis in colorectal cancer. *Am J Hematol* 2002;69:247-54.
77. Poon RT, Lau CP, Ho JW, et al. Tissue factor expression correlates with tumor angiogenesis and invasiveness in human hepatocellular carcinoma. *Clin Cancer Res* 2003;9:5339-45.
78. Xu C, Gui Q, Chen W, et al. Small interference RNA targeting tissue factor inhibits human lung adenocarcinoma growth in vitro and in vivo. *J Exp Clin Cancer Res* 2011;30:63.
79. Zhang Q, Wang H, Li H, et al. Chimeric antigen receptor-modified T Cells inhibit the growth and metastases of established tissue factor-positive tumors in NOG mice. *Oncotarget* 2017;8:9488-99.
80. Hu Z. Tissue factor as a new target for CAR-NK cell immunotherapy of triple-negative breast cancer. *Sci Rep* 2020;10:2815.
81. Breij EC, de Goeij BE, Verploegen S, et al. An antibody-drug conjugate that targets tissue factor exhibits potent therapeutic activity against a broad range of solid tumors. *Cancer Res* 2014;74:1214-26.
82. Schulman S, Lindmarker P. Incidence of cancer after prophylaxis with warfarin against recurrent venous thromboembolism. Duration of Anticoagulation Trial. *N Engl J Med* 2000;342:1953-8.
83. Pengo V, Noventa F, Denas G, et al. Long-term use of vitamin K antagonists and incidence of cancer: a population-based study. *Blood* 2011;117:1707-9.
84. Pottgård A, Friis S, Hallas J. Cancer risk in long-term users of vitamin K antagonists: a population-based case-control study. *Int J Cancer* 2013;132:2606-12.
85. Huang FY, Mei WL, Tan GH, et al. Cytochalasin D promotes pulmonary metastasis of B16 melanoma through expression of tissue factor. *Oncol Rep* 2013;30:478-84.
86. Pan Z, Chen J, Xiao X, et al. Characterization of a novel bispecific antibody targeting tissue factor-positive tumors with T cell engagement. *Acta Pharm Sin B* 2022;12:1928-42.
87. Hu Z, Garen A. Targeting tissue factor on tumor vascular endothelial cells and tumor cells for immunotherapy in mouse models of prostatic cancer. *Proc Natl Acad Sci U S A* 2001;98:12180-5.
88. Hu Z, Sun Y, Garen A. Targeting tumor vasculature endothelial cells and tumor cells for immunotherapy of human melanoma in a mouse xenograft model. *Proc Natl Acad Sci U S A* 1999;96:8161-6.
89. Osterholm C, Li S, Ekberg H, et al. Downregulation of tissue factor (TF) by RNA interference induces apoptosis and impairs cell survival of primary endothelium and tumor cells. *Cell Tissue Res* 2008;334:93-102.
90. Liu S, Zhang Y, Zhao X, et al. Tumor-Specific Silencing of Tissue Factor Suppresses Metastasis and Prevents Cancer-Associated Hypercoagulability. *Nano Lett* 2019;19:4721-30.
91. Hu Z, Rao B, Chen S, et al. Selective and effective killing of angiogenic vascular endothelial cells and cancer cells by targeting tissue factor using a factor VII-targeted photodynamic therapy for breast cancer. *Breast Cancer Res Treat* 2011;126:589-600.
92. Gomez S, Tsung A, Hu Z. Current Targets and Bioconjugation Strategies in Photodynamic Diagnosis and Therapy of Cancer. *Molecules* 2020;25:4964.
93. Rondon AMR, Kroone C, Kapteijn MY, et al. Role of Tissue Factor in Tumor Progression and Cancer-Associated Thrombosis. *Semin Thromb Hemost* 2019;45:396-412.
94. Loft M, Christensen C, Clausen MM, et al. First-in-Human PET Imaging of Tissue Factor in Patients with Primary and Metastatic Cancers Using (18)F-labeled Active-Site Inhibited Factor VII ((18)F-ASIS): Potential as Companion Diagnostic. *J Nucl Med* 2022. [Epub ahead of print]. doi: 10.2967/jnumed.122.264068.
95. Nielsen CH, Erlandsson M, Jeppesen TE, et al. Quantitative PET Imaging of Tissue Factor Expression Using 18F-Labeled Active Site-Inhibited Factor VII. *J Nucl Med* 2016;57:89-95.
96. Nielsen CH, Jeppesen TE, Kristensen LK, et al. PET Imaging of Tissue Factor in Pancreatic Cancer Using 64Cu-Labeled Active Site-Inhibited Factor VII. *J Nucl Med* 2016;57:1112-9.
97. de Bono JS, Concin N, Hong DS, et al. Tisotumab vedotin in patients with advanced or metastatic solid tumours (InnovaTV 201): a first-in-human, multicentre, phase 1-2 trial. *Lancet Oncol* 2019;20:383-93.

**Cite this article as:** Li X, Cao D, Zheng X, Wang G, Liu M. Tissue factor as a new target for tumor therapy—killing two birds with one stone: a narrative review. *Ann Transl Med* 2022;10(22):1250. doi: 10.21037/atm-22-5067