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***Invited Review***

# Tissue Factor and Breast Cancer

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## Abstract

*Tissue Factor (TF), a membrane bound glycoprotein, is the cellular initiator of the protease blood coagulation cascade. TF is a component of tissue factor/factor VII (TF/FVII) complex which plays key roles in extrinsic coagulation pathway. According to the traditional view of blood coagulation, although the initial phase of coagulation is triggered by the extrinsic pathway, the amplification of the coagulation cascade is triggered by the intrinsic pathway. Emerging experimental evidences show a broad range of biological functions of TF including hemostasis, thrombosis, hypercoagulability etc. In addition to the role of TF as an initiator of coagulation cascade, TF is also involved in many cancer-related processes like tumor growth, angiogenesis, metastasis etc. It is now widely recognized that a strong correlation exists between TF expression and breast cancer and plasma TF concentration has been found to be up-regulated in primary and recurrent breast cancer patients. TF-induced thrombin can activate several members of the protease activated receptor (PAR) family. Expression of protease activated receptor 1 (PAR1) is both required and sufficient to promote growth and invasion of breast carcinoma cells. Like PAR1, protease activated receptor 2 (PAR2) has also been found to play a critical role in breast cancer cell migration and invasion. Thus, TF plays a very crucial role in breast cancer progression. This review focuses on the role of TF in breast cancer progression based on the evidences available. Better understanding the role of TF in breast cancer will provide considerable clinical benefits associated with breast cancer treatment.*

**Keywords:** *Tissue factor, Breast cancer, Coagulation, Hemostasis, Thrombosis, Angiogenesis.*

## 1. Introduction

Breast cancer is basically one kind of malignant tumor initiated in the breast cells. The cancerous cells of the malignant tumor can invade the surrounding tissues or metastasize to distant parts of the body. Breast cancer occurs almost exclusively in women though men can also get it. It is estimated that an American woman has a one in nine chance of developing breast cancer in her lifetime. Familial breast cancer accounts for about 25% of all the breast cancer cases in women under the age of 30 years. Again, genetic abnormalities of *BRCA1* or *BRCA2* accounts for about 90-95% of familial breast cancer while the remainder is caused by abnormalities of other tumor suppressor genes or oncogenes like *p53*, *RAS (HRAS)*, *hMLH1*, *hMSH2* etc. (Ross *et al.* 2003).

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expressed in a variety of solid tumors of epithelial origin, particularly in carcinomas. There is a strong correlation between expression of TF antigen in cellular components of the stromal compartments and progression to invasive cancer. Basically, the recruitment and/or activation of TF-expressing stromal cells is an early event in the progression to invasive breast cancer. Thus, an association has been found between the TF and the invasiveness of breast cancer (Vrana *et al.* 1996).

## 2. Tissue Factor

### *2.1 Tissue Factor Biology*

TF is a 47 kDa membrane bound glycoprotein consisting of 263 amino acids present on the subendothelial cells. Although the molecular weight for the fully glycosylated protein is 47 kDa, the molecular weight for the polypeptide chain of 263 amino acids is

predicted to be approximately 30kDa (van den Berg *et al* 2012; Panes *et al* 2007). Tissue factor was first purified in 1985. TF was first identified as a constituent of tissue that when added to the plasma activates the clotting cascade. That's why it is named as tissue factor (Broze *et al.* 1985; Macman and Taubman 2009).

TF is also called full-length TF (flTF), coagulation factor III, thromboplastin or CD142 (Han *et al* 2014). Full length TF contains a 219 amino acid extracellular *N*-terminus and a 23 amino acid transmembrane domain followed by an intracellular 21 amino acid *C*-terminus (Chu 2011). The extracellular domain (residues 1-219) representing the $NH_2$ terminal is composed of two fibronectin type III domains and it is involved in the complex formation with activated factor VII (FVIIa). The hydrophobic transmembrane domain (residues 220-242) anchors TF to the membrane. The intracellular *C*-terminal domain (residues 243-263) is involved in signal transduction. There are four potential N-linked carbohydrate attachment sites (Asn$-$Xaa$-\frac{\text{Ser}}{\text{Thr}}$) in the molecule among which three potential N-linked carbohydrate attachment sites occur in the extracellular domain (Butenas 2012; Spicer *et al.* 1987).

The gene of human TF is located on chromosome 1 p21-22 and spans approximately 12.4 kilobases. The coding sequence of TF contains six exons. Exon one corresponds to the translation initiation sites. Exons two to exons five correspond to the sites for the translation of the extracellular domain. Exon six constitutes membrane spanning transmembrane domain and cytoplasmic domain. The sequence of TF reveals a distant homology to the cytokine receptor superfamily and is also a member of the fibronectin type III family (Butenas 2012; Bazan 1990).

### *2.2 Sources of Tissue Factor*

The origin, nature and function of TFs are a controversial issue. The best known function of TF is clotting initiation (Panes *et al.* 2007). In addition to its role in coagulation initiation, it also contributes to a broad range of biological processes (Monroe and Key 2007). The function of TF includes thrombosis and hemostasis (Mackman 2006), hypercoagulability (Trousseau syndrome), tumor growth, angiogenesis, metastasis (Rak *et al* 2006), smooth muscle cell migration (Pyo *et al.* 2004), embryonic blood vessel development (Carmeliet *et al.* 1996), induction of proinflammatory response (Spek 2004) etc.

Blood-borne TF has been reported to be located on blood cells, platelets, microparticles or circulates as a soluble protein. It has been found that blood monocyte is the major source of TF and activation of platelet induces or enhances TF synthesis. Circulating platelets contain enough TF to initiate clotting function. But, resting monocytes express no functional TF because it remains in an encrypted, inactive state. The interaction of monocyte with activated platelets and neutrophils induce the decryption of TF or the release of monocyte derived microparticles carrying the active protein (Panes *et al.* 2007; Butenas 2012).

There is a great debate regarding the localization of TF. It has been found that TF circulates in plasma, largely on microvesicles which can bind activated platelets through mechanisms involving P-selectin glycoprotein ligand 1 (PSGL-1) on the microvesicles and P-selectin on the platelets. TF-bearing microvesicles not only attach to activated platelets but also fuse with them transferring both protein and lipid to the platelet membrane and initiate coagulation (Del Conde *et al.* 2005; Falati *et al.* 2003). But, another report suggests both monocytes and polymorphonuclear (PMN) leucocyte as source of TF that are transferred to platelets (Rauch *et al.* 2000). Again, these findings contrast with studies that show that TF is transferred from platelets to monocytes (Scholz *et al.* 2002; Lösche *et al.* 2004; Panes *et al.* 2007).

### *2.3 Tissue Factor and Coagulation Cascade Model*

The coagulation system can be divided into three pathways: the extrinsic pathway, the intrinsic pathway and the common pathway (Mackman 2009). TF is a very essential mediator of coagulation and also a potent stimulator of extrinsic coagulation cascade. It also enhances cell proliferation and migration (Poll 2008; Han *et al.* 2014).

In the classic concept of coagulation, it is believed that endothelial disruption leads to the exposure of flTF to the bloodstream. Generally, TF is not exposed to the circulating blood in a resting state. But, TF located at the extravascular sites can become exposed to the bloodstream due to the vascular injury or due to the disruption of the endothelium. The exposed flTF can then bind to its natural ligand human zymogen factor VII (FVII) in the presence of calcium ions. FVII then becomes activated serine protease FVII (FVIIa) (van den Berg *et al.* 2012; Poll 2008; Spicer *et al.* 1987). The activation of FVII bound to TF is considered as a key early step in the TF pathway of blood coagulation (Rao and Rapaport 1988). The flTF/FVIIa complex then initiates coagulation activation by converting factor X (FX) to activated factor X (FXa). FXa in turn allows conversion of prothrombin to thrombin (factor IIa) (van den Berg *et al.* 2012). This reaction occurs to a significant extent after the thrombin-induced feedback activation of factors V and VIII. FXa activates prothrombin more than $10^5$-fold more efficiently in conjunction with activated factor V than in absence of activated factor V. Thrombin subsequently activates platelets and converts fibrinogen into fibrin. The activation of platelets and conversion of fibrinogen into fibrin are considered as two important and essential

components of a stable hemostatic plug (Poll 2008; van den Berg *et al*. 2012). The presence of TF is prominent in the perivascular cells which forms a hemostatic barrier and limits the hemorrhage after vessel injury (Liu *et al.* 2011). The TF: FVII/FVIIa complex is called "extrinsic pathway" because exogenous TF is needed for activation of clotting factors in plasma (**Fig. 1**) (Mackman 2009).

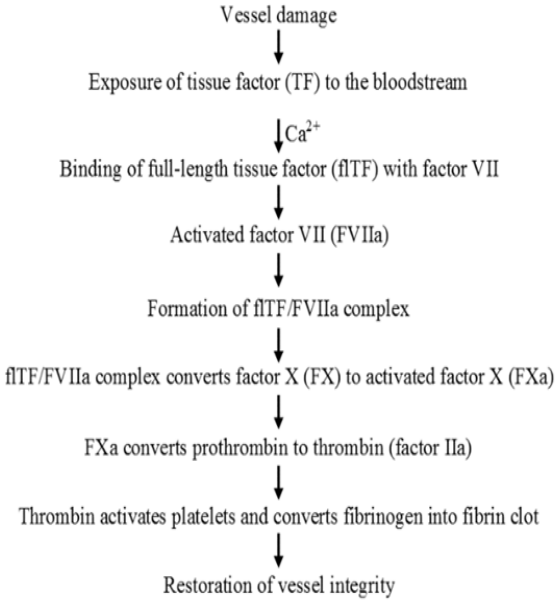


**Fig 1.** Extrinsic coagulation pathway.

Alternatively, coagulation can also be initiated through the "intrinsic pathway". In the early step of intrinsic pathway, factor XII (FXII) becomes activated factor XII (FXIIa) on a charged surface through the process of contact activation. When blood comes into contact with negatively charged surfaces, a series of proteolytic reactions are initiated. The initiation of these reactions results in the activation of FXII, prekallikrein (PK) and factor XI (FXI). It also results in the cleavage of high molecular weight kininogen (HK). These processes are collectively called contact activation reactions (Gailani and Renne´ 2007; Gailani and Renne´ 2007; Kaplan and Silverberg 1987; Colman and Schmaier 1997). Activation of FXII is followed by the activation event of FXI in which FXI becomes activated factor XI (FXIa). Activation of FXI is then followed by the activation event of factor IX (FIX) to activated factor IX (FIXa). The extrinsic and intrinsic pathways converge at the FX activation level (Gailani and Renne´ 2007).

In fact, TF/FVIIa complex of the extrinsic pathway initiates blood coagulation activating both FX and FIX. The activated factor VIII (FVIIIa) then forms a complex with FIXa and FVIIIa/FIXa complex then provides an alternative route to generate FXa. The FXa then in presence of activated factor V (FVa) participates in the prothrombinase complex (FVa/FXa) and activates prothrombin to thrombin. Prothrombinase complex and thrombin are referred to as the common pathway. Thrombin in turn activates FXI which is an alternative way to generate FIXa. It is assumed that thrombin generated early in the clot formation activates FXI, creating a feed-back loop which sustains coagulation. Thrombin also activates factor XIII (FXIII), cleaves fibrinogen and stimulates platelets. Platelets are stimulated by thrombin via the cleavage of protease activated receptors (PARs) (**Fig. 2**) (Mackman 2004; Gailani and Renne´ 2007; Mackman 2009).

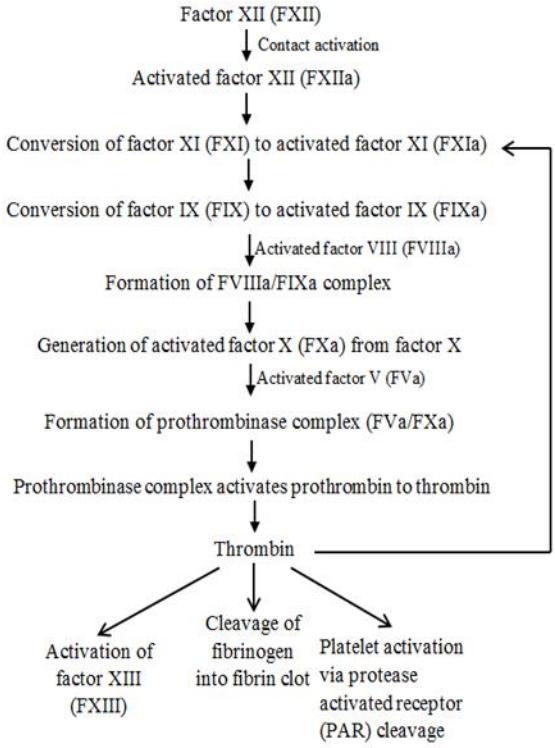


**Fig 2.** Intrinsic coagulation pathway and the common pathway.

### *2.4 Tissue Factor in Hemostasis and Thrombosis*

Hemostasis simply involves the mechanisms that prevent loss of blood from the sites of vascular injury. Thus, it maintains the integrity of the closed, high-pressure circulatory system after vascular injury (Müller *et al.* 2011; Furie and Furie 2008). Again, thrombosis involves the mechanism of formation of blood clotting leading to ischemia. TF has a major role in triggering the hemostasis and thrombosis (Wu 2015). TF is expressed in a tissue specific manner. TF/FVIIa complex regulates hemostasis in a tissue specific manner also and TF-dependent thrombin generation is necessary for hemostasis in many vital organs (Mackman 2009; Mackman 2005). In fact, TF is essential for life because of its central role in

hemostasis. It provides a "hemostatic envelope" in order to limit bleeding after vessel injury. Aberrant TF expression within the vasculature can initiate life-threatening thrombosis in diseases like sepsis, atherosclerosis or even in cancer (Mackman 2004; Mann *et al.* 2006).

Initiation of the coagulation cascade via exposure of TF to blood and the formation of TF/FVIIa complex are essential events for hemostasis and are initial procuagulant signal in thrombosis (Wolberg and Mast 2012). Defects in the regulation of clot formation result in either hemorrhage or thrombosis. Decreased levels of fibrin lead to hemorrhage because of impaired hemostasis. Again, increased levels of fibrin result in intravascular thrombosis (Mackman 2005). According to the traditional view of blood coagulation, the initial phase of coagulation is triggered by the extrinsic pathway whereas amplification of the coagulation cascade is triggered by the intrinsic pathway (Mackman *et al.* 2007).

Recent studies suggest that both FXII and FXI of the intrinsic pathway are very important in thrombosis and FXII-FXI contributes to a greater extent in thrombus formation than to normal hemostasis. It is assumed that FXI contribute to thrombin formation when low amount of TF are present in the environment. But, FXI is comparatively less important in the higher TF environments (Müller *et al.* 2011). Human lacking FXI generally show mild hemostatic defects. Thus, intrinsic pathway can be viewed as important but not as essential for human (Mackman 2009).

## 3. Tissue Factor and Tumor Progression

### *3.1 Tissue Factor and Angiogenesis*

Angiogenesis can be defined as the development of new blood vessel from the existing vasculature. Angiogenesis and hemostasis are two of the most consistent host responses associated with cancer. Generally, TF maintains the vascular integrity upon vessel injury by initiating the coagulation cascade. Again, hypercoagulability contributes to the tumor growth and metastasis by promoting angiogenesis. Thus, angiogenesis and hemostasis are considered as interrelated processes in cancer progression (Bluff *et al.* 2008). It is now accepted that the growth of tumor is angiogenesis dependent because without proliferation of blood vessels the growth of the tumor are limited to 1-2mm$^3$ and can expand rapidly to 1-2 cm$^3$ after vascularization (Folkman 1990).

TF can contribute to angiogenesis either directly or indirectly. In the direct regulation of angiogenesis, angiogenesis is thought to be dependent on TF/FVIIa function. The proteolytic activity of TF/FVIIa promotes angiogenesis and tumor growth through a proangiogenic mechanism and does not depend on hemostasis (Hembrough *et al.* 2003). It has been found that angiogenesis mediated by TF/FVIIa signaling is regulated by protease activated receptor 2 (PAR-2) signaling and PAR-2 signaling is sufficient for this proangiogenic effect without the apparent role of protease activated receptor 1 (PAR-1). It is obvious that PAR-2 signaling is tightly controlled by the cytoplasmic domain of TF. Thus, there is a direct contribution of TF in angiogenesis. It is also assumed that the TF/FVIIa might contribute to the angiogenesis simply by stimulating cell division but the mitogenic capacity of TF-FVIIa remains disputable (Uusitalo-Jarvinen *et al.* 2007; Belting *et al.* 2004; Bluff *et al.* 2008).

TF can contribute to the angiogenesis indirectly via clotting dependent mechanisms. Clotting dependent mechanism of tumor angiogenesis is mediated by the TF-induced thrombin and the subsequent deposition of cross-linked fibrin that provides a pro-angiogenic matrix for blood vessel infiltration (Bluff *et al.* 2008). Again, coagulation cascade and PAR-1 signaling can contribute to angiogenesis by modulating endothelial cell function in developing blood vessels. Thrombin's actions on endothelial cells rather than on platelets, mesenchymal cells or fibrinogen can contribute to vascular development and hemostasis (Griffin *et al.* 2001). Also, there is evidence that tissue factor controls the angiogenic properties of tumor cells by altering the production of growth regulators of endothelium by a mechanism distinct from TF activation of the coagulation mechanism (Zhang *et al.* 1994).

### *3.2 Tissue Factor and Metastasis*

Metastasis is the spread of malignant cells from a primary tumor to distant sites and is the main cause of death of cancer patients (Geiger and Peeper 2009). Basically, metastasis is an enormous complex process and by the process of metastasis cancer cells leave the primary tumor and disseminate to anatomically distant sites where they proliferate and form secondary tumor foci (Hunter *et al.* 2008; Brooks *et al.* 2010). The first evidence that thrombin can induce murine tumor cell metastasis was given by Nierodzik and colleagues. They reported that thrombin activation of tumor cells can induce a metastatic phenotype by enhancing tumor cell adhesion to pletelets, subendothelial matrix etc. (Nierodzik *et al.* 1992; Nierodzik *et al.* 1991; Booden *et al.* 2004). Subsequent studies have demonstrated that TF is highly expressed in carcinoma cells and like thrombin it can also contribute to metastasis (Mueller *et al.* 1992; Booden *et al.* 2004; Mueller and Ruf 1998). Tumor cell-associated TF and circulating hemostatic factors contribute to tumor growth by increasing metastatic potential. TF can increase metastatic potential by supporting thrombin-mediated proteolysis. It provides cancer cells a means of directing proteolytic events leading to local thrombin generation and the

formation of tumor cell-associated microthrombi. TF can also contribute to metastasis through TF cytoplasmic domain mediated intracellular signaling events, through activation of PARs mediated by the TF/FVIIa/FXa or through a combination of these processes (Palumbo *et al.* 2007).

## 4. Tissue Factor and Breast Cancer

TF is well known for its essential role in hemostasis. Thus, it plays a great role in pathology associated with hemostasis, triggering the coagulation system in many thrombotic diseases. But, recent studies have also implicated a variety of nonhemostatic role of TF like cell signaling, inflammation, tumor growth and metastasis etc. (Morrissey 2004; Wolberg and Mast 2012). Furthermore, studies have also revealed a correlation between TF expression and breast cancer and plasma TF concentration have been found to be up-regulated in primary and recurrent breast cancer patients (Ueno *et al.* 2000). There is novel experimental evidence that ectopic expression of FVII is frequent in cancer cells of different origin. Ectopic synthesis of FVII was sufficient to drive the migration and invasion of breast cancer cells (Koizume *et al.* 2006). TF expression is very high in breast cancer tissue. Although the detail mechanisms are not very clear, transcriptional activation are thought to be a major mechanism of TF overexpression. Constitutively high expression of *F3* gene is regulated by many transcription factors. Aberrant activation of these factors causes higher TF expression in breast cancer (Koizume and Miyagi 2014).

PARs are G protein-coupled receptors (GPCRs) which are uniquely activated by proteolysis. PARs are predominantly expressed in vascular cells, immune cells, epithelial cells etc. PAR family is comprised of four members: Protease activated receptor 1 (PAR1), Protease activated receptor 2 (PAR2), Protease activated receptor 3 (PAR3) and Protease activated receptor 4 (PAR4) (Soh *et al.* 2010). PAR1, PAR3 and PAR4 can be activated by TF-induced thrombin. On the other hand, PAR2 can be activated by trypsin, tryptase as well as FVIIa and Xa, but not by thrombin. PAR1 is activated when thrombin cleaves its amino-terminal extracellular domain or exodomain at specific site. This cleavage unmasks a new N terminus which then serves as a tethered ligand and effect transmembrane signaling (Coughlin 2000).

PAR1 expression is found to be minimal or absent in normal breast epithelial tissue. But, increased expression of PAR1 has been correlated with invasion of breast carcinoma cell (Booden *et al* .2004; Henrikson *et al.* 1999). Expression of PAR1 is both required and sufficient to promote growth and invasion of breast carcinoma cells. The degree of invasiveness is directly correlated with PAR1 expression levels. It has been found that invasive breast cancer cell line expresses very high levels of PAR1, PAR2 and PAR4. But, minimally invasive cells have no PAR1 and low levels of PAR2 and PAR4 (Boire *et al.* 2005; Cancino *et al.* 2007).

Activated PAR1 trafficking is severely altered in metastatic breast carcinoma cells but not in nonmetastatic or normal breast epithelial cells. Alteration in trafficking of activated PAR1 causes persistent signaling and contributes to breast carcinoma cell invasion. The proteolytic activation of PAR1 by thrombin is the cause of this continued signaling and the signaling can also be continued even after the withdrawal of thrombin (Booden *et al.* 2004; Even-Ram *et al.* 1998). Proteolytic activation of PAR1 by thrombin promotes cell invasion stimulating the induction of persistent epidermal growth factor receptor (EGFR) and ErbB2/HER2 and subsequently, a prolonged ERK1/2 signaling (Ohshiro *et al.* 2013). The mechanism by which PAR1 persistently transactivates EGFR and ErbB2 includes $G\alpha_{i/o}$ signaling, metalloprotease activity and release of heparin-binding epidermal growth factor (HB-EGF) ligand. PAR1-stimulated EGFR and ErbB2 transactivation leads to prolonged extracellular signal-regulated kinase 1 and signal-regulated kinase 2 signaling in breast carcinoma cell invasion. It is important to note that ErbB2/HER2 is overexpressed in approximately 20-30% of human invasive breast cancers. ErbB2/Her2 overexpression is also correlated with increased metastatic potential and increased patient death. But, the mechanism by which activated PAR1 induces prolonged ERK1/2 signaling is not known (Arora *et al.* 2008).

Like PAR1, PAR2 has also been found to play a critical role in breast cancer cell migration and invasion. The mechanism by which PAR2 promotes cancer cell migration and invasion is poorly understood. But, there is experimental evidence suggesting the role of PAR2 in mediating FVIIa and FXa-induced signaling, migration and invasion of breast cancer cells (Morris *et al.* 2006). Again, there is evidence that thrombin-mediated PAR3 activation leads to extracellular signal-regulated kinase (ERK) 1/2 phosphorylation and increased interleukin 8 production. But, PAR-3 from the human origin is largely unexplored and its role in breast cancer is not obvious (Ostrowska and Reiser 2008).

In addition to the flTF, identification of a form of human TF generated by alternative splicing has been reported. This alternatively spliced TF (asTF) is soluble in nature and circulates in blood. When asTF is exposed to phospholipids, it exhibits pro-coagulant activity. asTF contains most of the extracellular domain of TF. But, it lacks a transmembrane domain and terminates with a unique peptide sequence (Bogdanov *et al.* 2003). Recent experimental evidence suggests that asTF is abundantly

expressed in breast cancer cells and contribute to breast cancer cell proliferation. asTF acts as a autocrine factor and promotes breast cancer growth in a β1 integrin-dependent manner. Again, asTF can induce angiogenesis independent of PAR2 activation, by acting as an integrin ligand. This, flTF and asTF contribute in cellular signaling via distinct mechanisms (Kocatürk *et al.* 2013).

Progression of breast cancer is dependent on sex hormone. Thus, proliferation of breast cancer is found to be induced by progesterone metabolites. It has been found that progesterone potently upregulate TF in breast cancer cells. This progesterone-upregulated TF contribute to breast cancer via TF-dependent pathway (Kato *et al.* 2005; Henriquez *et al.* 2011).

## 5. Conclusion

Breast cancer is one of the leading cause of cancer death in women worldwide. TF is highly expressed in breast cancer cells. TF/FVII complex plays key roles in extrinsic coagulation pathway. As FVII are profoundly found in the cancer cells, TF-FVII complex can also be formed in absence of injury. It is now well established that TF/FVIIa complex can stimulate many malignant phenotype like angiogenesis, metastasis etc. Angiogenesis is thought to be dependent on TF/FVIIa function. The proteolytic activity of TF/FVIIa promotes angiogenesis and tumor growth through a proangiogenic mechanism. Again, Tumor cell-associated TF and circulating hemostatic factors contribute to tumor growth by increasing metastatic potential. TF can also contribute to metastasis through TF cytoplasmic domain mediated intracellular signaling events, through activation of PARs mediated by the TF/FVIIa/FXa or through a combination of these processes. Thus, TF/FVIIa complex has become an attractive target in breast cancer treatment. The exact mechanism by which TF is involved in breast cancer is not well understood. Co-factors and other proteins involved in induction of TF activity during angiogenesis and metastasis are needed to be explored. Exploring transcription factors which are involved to induce the function of TF could give concrete idea to develop TF as a biomarker in breast cancer. Again, it is necessary to explore the role of TF to other genes which are involved in tumor angiogenesis and metastasis. The development of inhibitors which suppress the TF/FVIIa activity in pathological angiogenesis but do not affect the coagulation function can help in the specific drug design essential for breast cancer treatment. Ectopic expression of FVII also contributes to breast cancer progression. So, inhibition of FVII expression can also represent a valuable therapeutic mechanism is breast cancer treatment. In addition to the flTF, asTF also plays a major role in breast cancer cell proliferation. So, understanding the detailed regulatory mechanism of flTF as well as asTF will enable us in the development of newer therapeutic strategies in the treatment of breast cancer.

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## Conflict of interest

We declare that we have no conflict of interest

## Abbreviations

TF: Tissue Factor, flTF: Full-length Tissue Factor, FVIIa: Activated Factor VII, PSGL-1: P-Selectin Glycoprotein Ligand 1, PMN: Polymorphonuclear, FVII: Factor VII, FX: Factor X, FXa: Activated Factor X, FXII: Factor XII, FXIIa: Activated Factor XII, FXI: Factor XI, PK: Prekallikrein, HK: Kininogen, FXIa: Activated Factor XI, FIX: Factor IX, FIXa: Activated Factor IX, FVIIIa: Activated Factor VIII, FVa: Activated Factor V, FXIII: Factor XIII, PAR: Protease Activated Receptor, PAR-2: Protease Activated Receptor 2, PAR-1: Protease Activated Receptor 1, GPCR: G protein-coupled receptor, PAR-3: Protease Activated Receptor 3, PAR-4: Protease Activated Receptor 4, EFGR: Epidermal Growth Factor Receptor, HB-EGF: Heparin-binding Epidermal Growth Factor, asTF: Alternatively Spliced Tissue Factor**.**

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