ISSN: 3029-0910

Review Article

Journal of Gynecological & Obstetrical Research

Normal and Abnormal Functions of Tissue Factor. A Review

Graciela Krikun

YALE School of Medicine, Department of OB-GYN and reproductive sciences, USA

Corresponding author
Graciela Krikun, YALE School of Medicine, Department of OB-GYN and reproductive sciences, USA.

Received: April 16, 2025; **Accepted:** April 25, 2025; **Published:** April 30, 2025

Keywords: Tissue Factor (TF), Medroxyprogesterone Acetate (MPA), Extracellular Vesicles, (EVs), Factor VII(a) (VIIa), Protease-Activated Receptor-2 (PAR-2)

Introduction

This review article describes the role of Tissue Factor (TF), the initiator of the coagulation cascade which has the key role in hemostasis, however when aberrantly expressed it can result in pro-thrombotic states and aberrant angiogenesis observed in many diseases including endometriosis [1]. Most TF exists in a cryptic form that is inert. Decryption of TF occurs following a large calcium influx that triggers the exposure phosphatidylserine on cell surfaces and is required for the expression of maximum TF procoagulant activity to form a complex with factor VIIa that rapidly initiates coagulation [2]. Reduction and oxidation of the molecule's Cys186-Cys209 disulfide bond has been proposed to play a central role in the transition between the TF forms [3]. Indeed, aberrant expression has been linked to untoward outcomes such as cardiovascular risks, hypercoagulability often observed in many clinical conditions including proinflammation, diabetes, obesity, cardiovascular diseases, angiogenesis, tumor metastasis including ovarian and breast cancer progression, and endometriosis progression making this molecule a possible target for disease treatment [4-6]. TF, formerly known as thromboplastin and also known as CD142 is the cellular receptor that binds the ligand factor VIIa to initiate the blood coagulation cascade [7]. TF can be detected in the bloodstream; known as circulating TF and has now been shown to be derived in part from extracellular vesicles (EVs) where levels of TF activity are associated with disseminated intravascular coagulation [2]. TF contributes to disease progression in part by promoting angiogenesis, which is the process of forming new blood vessels that carry nutrients and oxygen to tumors [8]. After vessel injury, the TF:FVIIa complex activates the coagulation protease cascade, which leads to fibrin deposition and activation of the coagulation pathway. Although TF is expressed in the mesenchymal and epithelial cells of diverse tissues, endothelial cells and other cells in contact with the circulation do not normally express TF. Following vascular disruption, perivascular cell-bound TF binds to circulating factor VIIa mediates the activation of both factor IX and X and ultimately generates thrombin [9].

Normal TF Expression

TF is a cell membrane bound glycoprotein comprising a hydrophilic extracellular domain, a membrane-spanning hydrophobic domain, and a cytoplasmic tail of 21 residues [10]. Under normal conditions, TF is essential for hemostasis. Importantly cells in contact with blood do not express physiologically active TF [11,12]. It is known that lack of TF results in embryonic lethality death in TF deficient embryonic mice [13]. Tissue factor was first discovered by Yale Nemerson. He isolated the molecule, isolated the DNA and assessed the role of TF in thrombosis and published an article named #My life with tissue factor# Following vascular disruption, perivascular cell-bound TF binds to circulating factor VIIa mediates the activation of both factor IX and X and ultimately generates thrombin [7].

Normal Expression in human Uterine Cells

We previously demonstrated that TF is particularly upregulated at the time of implantation making it a critical factor to protect against excessive bleeding during trophoblast invasion [1]. Endometrial stromal cells from mid- to late secretory phase and decidual cells from gestational human endometrium display prominent immunohistochemical staining for tissue factor (TF). In contrast, no TF expression is observed during the proliferative phase [2]. Consistent with the regulation by progesterone of the decidualization process in vivo, medroxyprogesterone acetate

Citation: Graciela Krikun. Normal and Abnormal Functions of Tissue Factor. A Review. J Gyneco Obstet Res. 2025. 3(2): 1-3.
DOI: doi.org/10.61440/JGOR.2025.v3.28

(MPA) or other synthetic progestins resulted in a significant induction of TF in primary stromal cell compared to basal levels [2]. Northern analysis of RNA from cultured stromal cells indicated that MPA increased TF mRNA levels approximately 10-fold relative to control levels. In contrast, cultured stromal cell TF protein expression and mRNA levels were unaffected by exogenous estradiol added alone [2]. However, we observed synergistic effects on TF expression after cells were primed with estrogen consistent with its function in elevating the stromal cell progesterone receptor. These findings indicate that enhancement of endometrial stromal cell TF content is associated with progesterone induction of the decidualization process. In humans, trophoblastic invasion of the endometrial vasculature during blastocyst implantation may risk hemorrhage, however, TF is particularly upregulated at the time of implantation making it a critical factor to protect against excessive bleeding during trophoblast invasion [1].

Normal TF. Placental and Embryonic Development

TF is required for embryonic and placental development for a successful pregnancy. TF expression in the placenta is believed to have biological effects and maintenance of local placental hemostasis [3].

Abnormal TF and bad Pregnancy Outcomes

While TF is critical for placental and embryonic development, pathologic expression of TF can lead to serious pregnancy complications including recurrent miscarriages, preeclampsia due to a state of hypercoagulability [3].

TF and Angiogenesis

Angiogenesis, the formation of new blood vessels from existing blood vessels, is a common and critical pathological process in many human diseases including cancer, age-related macular degeneration, endometriosis, rheumatoid arthritis, inflammation, arteriosclerosis, vascular restenosis and different vasculopathies [4-6]. In addition, TF is known to be involved in angiogenesis via an interaction with factor VIIa and protease-activated receptor-2 (PAR-2) [7].

TF and Thrombosis

While TF is required for the initiation of blood coagulation it is also believed to play a key role in both arterial and venous thrombosis by enhancing the procoagulant activity in disease [8].

TF and Cardiac Disease

TF has been recognized to be involved in the pathogenesis of cardiovascular diseases, indeed TF has been recognized to be involved in the pathogenesis of cardiovascular diseases and therapeutic strategies are being developed to specifically interfere with TF and its effectors [9]. TF has been detected in the bloodstream in circulating cells as a component of extracellular vesicles [10]. TF contributes to metastasis via multiple thrombin-dependent and independent mechanisms that include protecting tumor cells from natural killer cells.

TF and Tumor Progression

TF participates in many tumor-related processes that contribute to malignant disease progression [11]. Specifically, TF participates in many tumor-related processes, including tumor angiogenesis, metastasis, hypercoagulability and tumor cell survival; processes that all contribute to malignant disease progression and TF expression in cancer is associated with poor prognosis [11,12].

Endometriosis

Endometriosis is a gynecological disorder characterized by the presence of endometrial tissue outside of the uterus Endometriosis is a major cause of chronic pain, infertility, medical and surgical interventions, and health care expenditures [4]. While non-malignant, endometriosis shares many similarities to cancers. This disease affects up to 10% of all reproductive-aged women and 20%–50% of infertile women While the molecular mechanisms by which endometriotic lesions persist are not clear, the establishment and progression of endometriosis requires angiogenesis, and we previously showed anomalous expression of TF by endothelial cells in endometriotic lesions. Thus, anomalous expression of TF by endothelial cells in endometriotic lesions provides a target for new therapies [4]. We showed that using an athymic mouse model of endometriosis, the TF targeting molecule known as ICON largely destroyed endometriotic implants by vascular disruption without apparent toxicity, reduced fertility, or subsequent teratogenic effects in a mouse model of endometriosis [4].

TF targeting therapies

As aberrant TF expression is involved in the diseases described above, TF may be a good target for therapy. Several therapies include the following:

A. The immunoconjugate molecule (ICON), binds with high affinity and specificity to aberrant endothelial TF. It is known that ICON induces a cytolytic immune response that eradicates tumor and choroidal blood vessels.
B. A recent study by Hu demonstrated that chimeric antigen receptors NK cells (CAR-NK) targeting TF was successful as a cell immunotherapy of triple-negative breast cancer [13].

Conclusions

TF is the primary initiator of coagulation. Although TF is important in maintaining vascular integrity in response to injury, abnormal TF expression has been shown to be involved in a variety of human diseases including disseminated intravascular coagulation in patients with sepsis, cancer, cardiovascular disease and endometriosis. Hence blocking aberrantly expressed TF makes this molecule a target to diminish progression in diseases.

Reference

1. Krikun G, Lockwood CJ, Paidas MJ. Tissue factor and the endometrium: from physiology to pathology. Thromb Res. 2009. 124: 393-396.
2. Krikun G, Schatz F, Mackman N, Guller S, Lockwood CJ. Transcriptional regulation of the tissue factor gene by progestins in human endometrial stromal cells. J Clin Endocrinol Metab. 1998. 83: 926-930.
3. Girardi G. Role of tissue factor in feto-maternal development: a xiphos. J Thromb Haemost. 2011. 9: 250-256.
4. Krikun G, Hu Z, Osteen K, Bruner-Tran KL, Schatz F, et al. The immunoconjugate "icon" targets aberrantly expressed endothelial tissue factor causing regression of endometriosis. Am J Pathol. 2010. 176: 1050-1056.

5. Hu Z. Therapeutic Antibody-Like Immunoconjugates against Tissue Factor with the Potential to Treat Angiogenesis-Dependent as Well as Macrophage-Associated Human Diseases. Antibodies (Basel). 2018. 7.
6. Multhoff G, Radons J, Vaupel P. Critical role of aberrant angiogenesis in the development of tumor hypoxia and associated radioresistance. Cancers (Basel). 2014. 6: 813-828.
7. Mackman N. Role of tissue factor in hemostasis and thrombosis. Blood Cells Mol Dis. 2006. 36: 104-107.
8. Owens AP, Mackman N. Tissue factor and thrombosis: The clot starts here. Thromb Haemost. 2010. 104: 432-439.
9. Steffel J, Luscher TF, Tanner FC. Tissue factor in cardiovascular diseases: molecular mechanisms and clinical implications. Circulation. 2006. 113: 722-731.
10. van Niel G, D'Angelo G, Raposo G. Shedding light on the cell biology of extracellular vesicles. Nat Rev Mol Cell Biol. 2018. 19: 213-228.
11. Bluff JE, Brown NJ, Reed MW, Staton CA. Tissue factor, angiogenesis and tumour progression. Breast Cancer Res. 2008. 10: 204.
12. Cole M, Bromberg M. Tissue factor as a novel target for treatment of breast cancer. Oncologist. 2013. 18: 14-18.
13. Hu Z. Tissue factor as a new target for CAR-NK cell immunotherapy of triple-negative breast cancer. Sci Rep. 2020. 10: 2815.