

Aberrant Tissue Factor Expression and Women's Health- A Review

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ABSTRACT

Tissue Factor (TF) is the initiator of the coagulation cascade, however if aberrantly expressed can result in pro-thrombotic action. Indeed, aberrant expression has been linked to untoward outcomes such as cardiovascular risks, hypercoagulability often observed in many clinical conditions which expands its role in proinflammation, diabetes, obesity, cardiovascular diseases, angiogenesis, tumor metastasis including ovarian cancer progression, endometriosis progression and many others, making this molecule a possible target for disease treatment.

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Introduction

Tissue Factor (TF), also known as CD142 is a transmembrane cellular receptor that binds the ligand factor VII/VIIa to initiate the blood coagulation cascade via an interaction with factor VIIa and protease-activated receptor-2 (PAR-2) [1].

In addition to its role as the initiator of the hemostatic cascade, TF plays a critical role in promoting thrombosis and is known to be involved in aberrant angiogenesis, cancer development and progression, endometriosis progression to name a few. Normally, endothelial cells and other cells in contact with the circulation do not express TF. However, following vascular disruption, perivascular cell-bound TF binds to circulating factor VIIa to mediate the activation of both factor IX and X and ultimately generate thrombin. The FVIIIa:FIXa complex of the intrinsic pathway provides an alternative route to generate FXa, which participates in the prothrombinase complex (FVa:FXa). This complex converts prothrombin to thrombin, which plays a central role in the coagulation cascade [2].

TF and Endometriosis

Endometriosis is a gynecological disorder characterized by the presence of endometrial tissue outside of the uterus. The disease affects up to 10% of all reproductive-aged women and the prevalence rises to 20–50% in infertile women [3]. Previous studies from our laboratory demonstrated that the pattern and level of TF expression is altered in multiple cell types derived from eutopic and ectopic endometrium from women with endometriosis compared with normal endometrium [4]. In a previous study from our laboratory, we detected the anomalous expression of TF by endothelial cells in endometriotic lesions. 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. However, following vascular disruption, perivascular cell-bound TF binds to circulating factor VIIa to mediate the activation of both factor IX and X and ultimately generate thrombin. In a previous study from our laboratory, we

detected the anomalous expression of TF by endothelial cells in endometriotic lesions [5]. We posit that the inflammatory environment that occurs in ectopic and eutopic endometrium from patients with disease results in high TF expression that in turn, signals via PAR-2 to further produce inflammatory cytokine or chemokine production and macrophage recruitment suggesting that TF might be an ideal target for therapeutic intervention in endometriosis.

TF and Ovarian Cancer

As in many other cancers TF is involved in disease progression and risk of thromboembolism in several cancers and it is reported that as such there is an increased risk of thromboembolism in women with this disease. This is also the case for ovarian cancer [6,7]. Ovarian cancer is the leading cause of death in women diagnosed with gynecological cancers. Unfortunately most of the cases are diagnosed at an advanced stage, which leads to poor outcomes of this disease [8]. Lastly, it has been shown the molecule L-ICON a TF-targeting immunoconjugate (called L-ICON1, for light chain ICON) induces strong cytotoxicity against primary chemotherapy-resistant ovarian cancer in cell lines overexpressing TF and may represent a novel therapeutic agent for the treatment of ovarian tumors refractory to standard treatment modalities [9].

TF and Myocardial Infarction

While there is an to increase awareness regarding myocardial infarction, most people do not realize that heart disease is now the leading cause of death for women. Because many cardiac symptoms experienced by women are atypical, many women are unable to link their symptoms to heart disease, which often leads them to delay seeking treatment which leads to death [10]. Cardiovascular disease is a leading cause of mortality internationally [11]. As per the Centers for Disease Control and Prevention, coronary heart disease is the most common type of heart disease [12]. In addition, atherothrombosis, characterized by a disruption of atherosclerotic lesions superimposed with thrombus formation, is the major cause of acute coronary syndromes and

cardiovascular death [13]. Moreover, it is known that levels of TF are observed in patients with cardiovascular risk factors. Thus, studies targeting TF have been carried out to determine if this can reduce the rate of mortality in patients with heart disease. One study determined the administration of a monoclonal anti-TF antibody which reduced infarct size in a rabbit coronary artery ligation model as the result of reduced chemokine expression and leukocyte infiltration [14]. At present there continuous to be research conducted to find new ways to prevent heart disease including drug-eluting stents [15].

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