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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 and breast cancer progression, endometriosis progression and many others, making this molecule a possible target for disease treatment.

Keywords: Aberrant Tissue Factor; Women's Health; Tissue Factor; cardiovascular Risks; Ovarian and Breast Cancer

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 [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 FVIIa: FIX complex results in the activation of FXa, which participates in the prothrombinase complex (FXa: FXa). This complex converts prothrombin to thrombin, which plays a central role in the coagulation cascade [2]. One crucial mechanism involved in all the diseases mentioned below involves the formation of extracellular vesicles that are positive for TF (TF+EVs) which elevating the risk of thromboembolism [3,4].

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 [5-7]. 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 [8]. In this study we detected the anomalous expression of TF by endothelial cells in endometriotic lesions [8]. 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 [9]. 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. For a review of TF activation and pathogenesis mechanisms have been described by Steffel et al. [10].

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 [11,12] in women with this disease. This is also the case for ovarian cancer [12]. Ovarian cancer is one of the leading causes 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 [13]. Lastly, it has been shown the molecule L-ICON a TF-targeting immunoconjugate (called L-ICON1, for light chain ICON) , which consists of full-length factor VII peptide (406 amino-acid residues, aa) and is fused to the Fc region of IgG1 targets and binds to TF with specificity and high affinity and 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 [14].

TF and Breast Cancer

Breast cancer is the second leading cause of cancer death among women in the United States [15]. As is the case with other cancers, breast cancer is associated with abnormal activation of the coagulation system leading to a prothrombotic state [16]. It has also been demonstrated that TF antigen is detected in both the tumor cells as well as in the endothelial cells lining tumor-associated vessels of infiltrating breast cancer [16]. In support of these findings, the ICON molecule was used to target aberrantly expressed TF in breast cancer. As with ovarian cancer the TF-targeting immuno-conjugate agent known as ICON, was utilized and resulted in destruction of cancer cells in vitro via antibody-dependent cell-mediated cytotoxicity and can be used to treat human and murine model of breast cancer. Treatment of mouse models of breast cancer demonstrated inhibition of tumors with minimal effects on normal tissues [14], again

suggesting that TF may be a good target for tumor regression.

TF and Myocardial Infarction

While there is an increase in awareness regarding myocardial infarction, most people do not realize that heart disease is one of the leading causes 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 [17]. Cardiovascular disease is one of the leading causes of mortality internationally [18]. As per the Centers for Disease Control and Prevention, coronary heart disease is the most common type of heart disease. [19]. 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 [20]. Moreover, it is known that increased levels of TF are observed in patients with cardiovascular risk factors [10]. 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 [10]. At present, research is being conducted to find new ways to prevent heart disease including drug-eluting stents [21].

Conclusion

Tissue Factor is a transmembrane which plays a key physiological role in the initiation of blood coagulation. However, under pathological conditions such as in acute coronary syndrome, cancers, endometriosis as well as several inflammatory diseases it can lead to thrombosis and stroke. In this review we have identified the pathological role of tissue factor in women's health and the possibility that it may be a target to reduce the risk of disease progression.

References

1. Nemerson Y (1992) The tissue factor pathway of blood coagulation. Semin Hematol 29: 170-6.

2. Mann KG, S Butenas, K Brummel (2003) The dynamics of thrombin formation. Arterioscler Thromb Vasc Biol 23: 17-25.

3. Hisada Y, N Mackman (2019) Cancer cell-derived tissue factor-positive extracellular vesicles: biomarkers of thrombosis and survival. Curr Opin Hematol 26: 349-56.

4. Hisada Y, N Mackman (2021) Tissue Factor and Extracellular Vesicles: Activation of Coagulation and Impact on Survival in Cancer. Cancers (Basel) 13.

5. Zondervan KT, CM Becker, SA Missmer (2020) Endometriosis. N Engl J Med 382: 1244-56.

6. Taylor HS (2021) Reimagining Endometriosis. Med 2: 481-5.

7. Giudice LC, LC Kao (2004) Endometriosis. The Lancet 364: 1789-99.

8. Krikun G, et al. (2008) Endometriosis and tissue factor. Ann N Y Acad Sci, 1127: 101-5.

9. Krikun G, et al. (2010) The immunoconjugate "icon" targets aberrantly expressed endothelial tissue factor causing regression of endometriosis. Am J Pathol 176: 1050-6.

10. Steffel J, TF Luscher, FC Tanner (2006) Tissue factor in cardiovascular diseases: molecular mechanisms and clinical implications. Circulation 113: 722-31.

11. Koizume S, Y Miyagi (2022) Tissue factor in cancer-associated thromboembolism: possible mechanisms and clinical applications. Br J Cancer 127: 2099-107.

12. Uno K, et al. (2007) Tissue factor expression as a possible determinant of thromboembolism in ovarian cancer. Br J Cancer 96: 290-5.

13. Arora T, S Mullangi, MR Lekkala (2023) Ovarian Cancer, in StatPearls. 2023: Treasure Island (FL) ineligible companies. Disclosure: Sanjana Mullangi declares no relevant financial relationships with ineligible companies. Disclosure: Manidhar Reddy Lekkala declares no relevant financial relationships with ineligible companies.

14. Hu Z, et al. (2018) Targeting Tissue Factor for Immunotherapy of Triple-Negative Breast Cancer Using a Second-Generation ICON. Cancer Immunol Res, 6: 671-84.

15. Siegel RL, KD Miller, A Jemal (2016) Cancer statistics, 2016. CA Cancer J Clin 66: 7-30.

16. Rella C, et al. (1996) A prothrombotic state in breast cancer patients treated with adjuvant chemotherapy. Breast Cancer Res Treat 40: 151-9.

17. Zbierajewski-Eischeid SJ, SJ Loeb (2010) Recognizing myocardial infarction in women. Nursing 40: 1-7.

18. Keteepe-Arachi T, S Sharma (2017) Cardiovascular Disease in Women: Understanding Symptoms and Risk Factors. Eur Cardiol 12: 10-3.

19. Finegold JA, P Asaria, DP Francis (2013) Mortality from ischaemic heart disease by country, region, and age: statistics from World Health Organisation and United Nations. Int J Cardiol 168: 934-45.

20. Steppich BA, et al. (2009) Plasma TF activity predicts cardiovascular mortality in patients with acute myocardial infarction. Thromb J 7: 11.

21. Senst B, et al. (2023) Drug Eluting Stent Compounds, in StatPearls. 2023: Treasure Island (FL) ineligible companies. Disclosure: Amandeep Goyal declares no relevant financial relationships with ineligible companies. Disclosure: Hajira Basit declares no relevant financial relationships with ineligible companies. Disclosure: Judith Borger declares no relevant financial relationships with ineligible companies.