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Endometriosis and Tissue Factor

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Abstract

Tissue factor (TF), is a cellular receptor that binds the ligand factor VII/VIIa to initiate the blood coagulation cascade. In addition to its role as the initiator of the hemostatic cascade, TF is known to be involved in angiogenesis via an interaction with factor VIIa and protease-activated receptor-2 (PAR-2). In this article we review previous studies from our laboratory demonstrating 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. 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. Thus, our studies suggest that TF might be an ideal target for therapeutic intervention in endometriosis.

Keywords

endometriosis; endometrium; tissue factor

Tissue Factor

Tissue factor (TF; also known as coagulation factor III, tissue thromboplastin, or CD142) is a cell membrane–bound glycoprotein (MW 46 kDa) comprising a hydrophilic extracellular domain, a membrane-spanning hydrophobic domain, and a cytoplasmic tail of 21 residues.[1–4] TF is a member of the human class II cytokine receptor family, displaying high homology in secondary and tertiary structure with the interferon-γ receptor.[5,6] Although TF is expressed in the mesenchymal and epithelial cells of diverse tissues,[7,8] 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 to generate thrombin.[1,9–14] The FVI-IIa: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 protease cascade. In particular, thrombin activates FXI, which is an alternative way to generate FIXa. Thrombin also activates FXIII, as well as various cofactors, cleaves fibrinogen, and stimulates platelets via cleavage of protease-activated receptors (PARs). Platelets accelerate the activation of the

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Conflicts of Interest
The authors declare no conflicts of interest.

coagulation cascade by binding FXI and by providing a thrombogenic surface for the assembly of the prothrombinase complex (FVa:FXa).[15,16]

The full TF molecule exists on the cell surface as either a cryptic form that is inert, a coagulant form that rapidly binds factor VIIa to initiate coagulation, and a signaling form that binds FVIIa and cleaves PAR-2, which functions in inflammation, tumor progression, and angiogenesis.[17–19] Thus, detection of immunoreactive TF does not necessarily correspond to TF clotting activity.

The angiogenic function of TF is now known to be mediated through a complex series of intracellular signaling pathways,[20–22] and its absolute requirement has been demonstrated by the embryonic lethality observed in knockout mice.[23–25] Thus, $TF^{-/-}$ null embryos die at embryonic day E10.5 and display disorganization of the yolk sac vasculature.[23–25]

TF in Endometriosis

Endometriosis is a gynecological disorder characterized by the presence of endometrial tissue outside of the uterus.[26] The disease affects up to 10% of all reproductive-aged women and the prevalence rises to 20–50% in infertile women.[27,28] Despite its frequency and its impact on quality of life, our understanding of the pathogenesis of endometriosis remains incomplete and its treatment remains controversial.[29] Endometrial lesions are primarily located on the pelvic peritoneum and ovarie but can also be found in the pericardium, pleura, lung parenchyma, and even the brain.[30,31] Implants can result in substantial morbidity, including pelvic adhesions and pain, allergies, fatigue, bowel problems, and infertility, often requiring extensive medical and surgical treatments.[32–39] Hence, this disease is costly and both physically and psychologically debilitating.

The etiology of the disease likely reflects retrograde menstruation, coleomic metaplasia or both.[27,40–43] However, other theories have been proposed, including a complex interplay of genetic, anatomic, environmental, and immunologic factors.[31] Although reports concerning the origin of endometriosis are conflicting, there is general agreement that endometriosis is associated with a local inflammatory response, and that vascularization at the site of invasion plays a decisive role in the pathogenesis of the disease.[27,40–47]

Because TF has recently been shown to be angiogenic,[48,49] initial studies from our laboratory were conducted to examine the expression of these molecules in eutopic endometrium from control women versus women with endometriosis as well as extrauterine endometriotic lesions.

Prior immunohistochemistry and *in situ* hybridization studies, as well as *in vitro* experiments from our laboratory have shown that, in normal endometrium, progesterone markedly enhances TF protein and mRNA expression in decidualized stromal cells during the luteal phase, whereas glandular epithelial cells display minimal TF expression throughout the menstrual cycle.[50–52] By contrast, this pattern of TF expression is altered in eutopic and ectopic endometrium derived from women with endometriosis. Thus, as previously reported,[53] marked elevation of TF expression was observed in glandular epithelial cells of eutopic or ectopic endometrium derived from women with this disease (Fig. 1). We have also demonstrated that PAR-2, the putative TF receptor believed to regulate intracellular signaling, is highly upregulated in the glandular epithelium of eutopic endometrium (Fig. 2). Hence, both TF and its putative receptor are strategically poised for angiogenic and inflammatory signaling in endometriotic lesions.

Summary

The increased expression of TF in eutopic and ectopic endometrium from patients with endometriosis compared with controls is a novel finding. It may reflect the known association of endometriosis with increased eutopic and ectopic inflammatory cytokine production.[54–58] It is well established that interleukin-1β and tumor necrosis factor-α acting via the NFκB transcription factor increased TF gene expression in multiple cell types.[59–61]

Our findings complement those from previous studies demonstrating an increased activity of the fibrinolytic system in the endometrium and peritoneal fluid of women with endometriosis.[62–64] Hence, the peritoneum possesses an inherent fibrinolytic activity that is responsible for the degradation of the fibrin deposits originated after an injury.[62–64] It is logical, therefore, to expect an upregulation of TF within this milieu of injury. However, increased TF expression in endometrial tissues may also reflect genetic polymorphisms in the promoter region of genes known to regulate TF expression.[65–67]

It is interesting that, in addition to altered localization and expression of TF, we also demonstrated an induction of the putative TF signaling receptor PAR-2 in endometriotic lesions (Fig. 2). It is now known that the interaction of TF with PAR-2 regulates gene transcription, protein translation, cell proliferation, cell motility, and integrin activation.[21,48,59–61,68] We propose that the induction of TF and PAR-2 in endometriotic tissues likely initiates intracellular signaling mechanisms that lead to overexpression of inflammatory cytokines, including Mφ-chemotactants, macrophage metalloproteases (MMPs), vascular endothelial growth factor, and TF. As a result, a pathological feedback cycle of TF expression and intracellular signaling is established, ensuring successful endometriotic nidation and angiogenesis.

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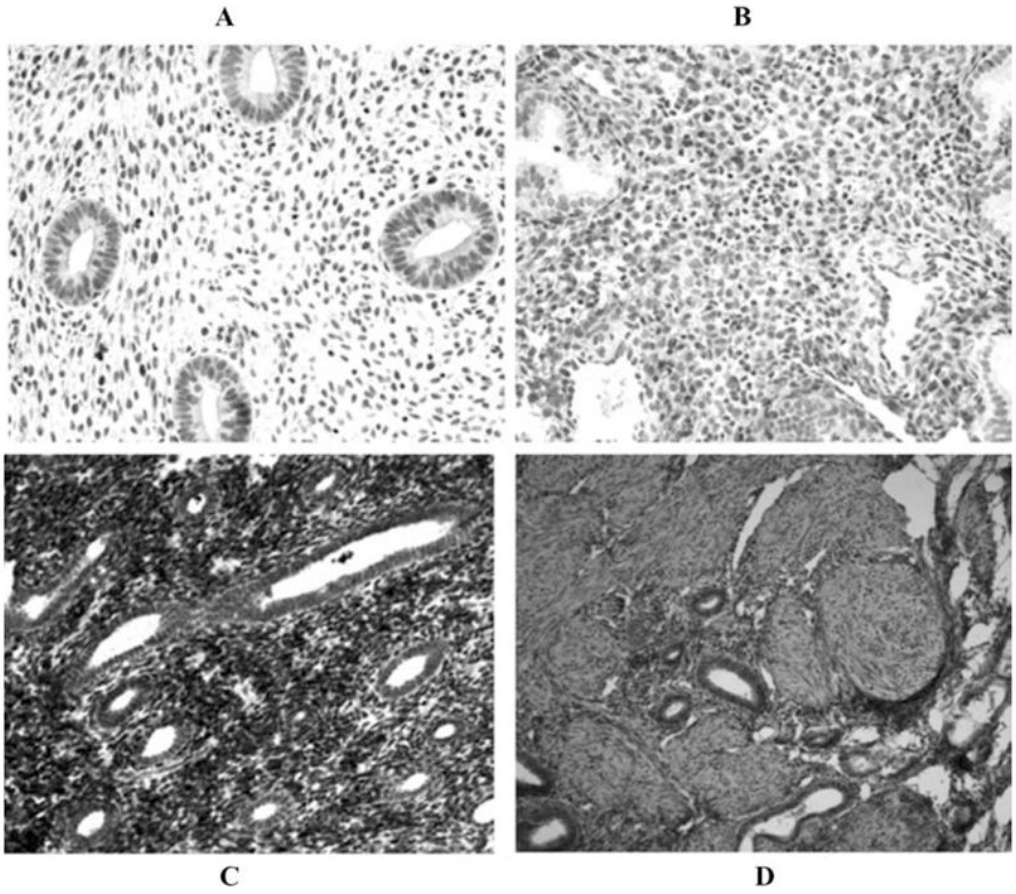

FIGURE 1.
TF immunohistochemistry. **(A)** Normal proliferative endometrium showing low to no TF staining in glands or stromal cells. **(B)** Normal secretory endometrium showing decidualized stromal cell staining. **(C)** Ectopic endometriotic implant from proliferative phase endometrium with glandular staining. **(D)** Eutopic late proliferative phase endometrium from patients with endometriosis with glandular staining (×20).

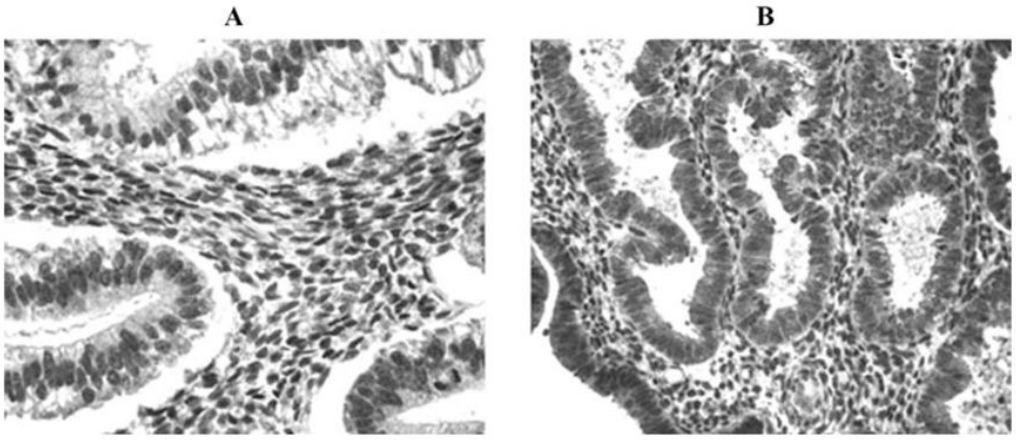

FIGURE 2.

Expression of PAR-2 by normal versus eutopic endometrium of women with endometriosis. Endometria were immunostained as previously described.[51] **(A)** Normal early secretory eutopic endometrium. **(B)** Eutopic mid-secretory endometrium from a patient with endometriosis.