Review Article

Endometriosis, Angiogenesis and Tissue Factor

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Tissue factor (TF), is a cellular receptor that binds the 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 intracellular signaling that utilizes the protease activated receptor-2 (PAR-2). We now review the physiologic expression of TF in the endometrium and its altered expression in multiple cell types derived from eutopic and ectopic endometrium from women with endometriosis compared with normal endometrium. Our findings suggest that TF might be an ideal target for therapeutic intervention in endometriosis. We have employed a novel immunoconjugate molecule known as Icon and were able to eradicate endometrial lesions in a mouse model of endometriosis without affecting fertility. These findings have major implications for potential treatment in humans.

1. Introduction

Normal ovarian functioning requires the coordinated activity of the hypothalamus, which secretes gonadotropin-releasing hormone (GnRH), the pituitary, which secretes the luteinizing hormone (LH) and follicle-stimulating hormone (FSH), the ovary, which secretes estrogens and progesterone, inhibins, activins, and other ovarian modulators [1]. The endometrium in turn responds to estrogen and progesterone [1]. Insulin-like growth factors (IGFs) and their binding proteins (IGFBPs) are important for endometrial development during the menstrual cycle and have mitogenic, differentiative, and antiapoptotic properties and participate in endometrial growth, differentiation, and apoptosis [2].

As a result, the human endometrium undergoes cyclic morphologic as well as molecular changes in preparation for receiving the incoming blastocyst and initiation of pregnancy [3]. If implantation does not occur, the endometrium is shed and menstruation occurs. These events involve extensive tissue remodeling, characterized by waves of endometrial cell proliferation, differentiation, recruitment of inflammatory cells, apoptosis, and tissue breakdown by metalloproteases, menstruation and ultimately regeneration [3]. The ability of ovarian hormones to trigger such diverse physiological responses is foremost dependent upon interaction of activated steroid receptors with specific transcription factors, such as Forkhead box class O (FOXO) proteins, involved in cell fate decisions [4], and HOX genes which encode evolutionarily conserved transcription factors essential to endometrial development, and endometrial receptivity [5]. Furthermore, microRNAs (miRNAs), small noncoding RNAs that function as posttranscriptional regulators of gene expression, have emerged as a major regulator system of steroid hormone responses in the female reproductive tract [4].

Lastly, the constant fluctuations in endometrial growth and shedding require that new vessels be developed. Indeed, the endometrium is one of the few tissues in the adult where physiological angiogenesis occurs [6]. Studies of endometrial angiogenesis are complicated by the continual changes in tissue growth and regression during the menstrual cycle and differences between the two different zones of the endometrium—the functionalis (the endometrial portion that sheds monthly) and basalis which appears to give rise to the new functionalis each month following menses.

Several angiogenic factors have been identified and are believed to be involved in physiologic as well as pathologic angiogenesis in the human endometrium [7]. Vascular endothelial growth factor (VEGF) is considered to be the primary vasculogenic and angiogenic factor [7–9]. However, since the discovery of the angiopoietins [10] it has become clear that the angiogenic process is far more complex than previously thought.

Indeed, tissue factor, the key initiator of the hemostatic cascade, is now also known to play a role in the process of angiogenesis [11, 12]. This subject will be discussed in more detail in the following.

2. Physiological Expression of Tissue Factor in the Endometrium

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 [13, 14]. Consistent with the regulation by progesterone of the decidualization process *in vivo*, medroxyprogesterone acetate (MPA) or other synthetic progestins resulted in a significant induction of TF in primary stromal cell compared to basal levels. This increase paralleled the release of immunoreactive prolactin, a marker of decidualization [13, 14]. Northern analysis of RNA from cultured stromal cells indicated that MPA increased TF mRNA levels approximately 10-fold relative to control levels [13, 14]. In contrast, cultured stromal cell TF protein expression and mRNA levels were unaffected by exogenous estradiol added alone. However, we observed synergistic effect on TF expression after cells were primed with estrogen consistent with its function in elevating the stromal cell progesterone receptor [14]. 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 risks hemorrhage. Therefore, increases in perivascular decidual cell tissue factor expression could serve to promote periimplantational endometrial hemostasis.

3. Endometriosis

Endometriosis is a gynecological disorder characterized by the presence of endometrial tissue outside of the uterus [15–17]. This disease affects up to 10% of all reproductive-aged women and 20%–50% of infertile women [15–18]. Despite its frequency and its impact on quality of life, our understanding of the pathogenesis of endometriosis remains incomplete. Endometrial lesions are primarily located on the pelvic peritoneum and ovaries but can also be found in the pericardium, pleura, lung parenchyma, and rarely the brain [19–21]. Implants can result in substantial morbidity, including pelvic adhesions and pain, allergies, fatigue, bowel problems, and infertility requiring extensive and often ineffective medical and surgical treatments [15–17, 22, 23]. Hence this disease is costly and both physically and psychologically debilitating.

The etiology has been ascribed to retrograde menstruation, coelomic metaplasia, cells hematogenic and lymphogenic spread, remnants of the Mullerian duct, and endometrial stem/progenitor cells [15–17, 24, 25]. However, it also involves a complex interplay of genetic, anatomic, environmental, and immunologic factors [26–29]. Intense macrophage infiltration and excess cytokine expression play

critical roles in the development of endometriosis-related chronic inflammatory processes [18, 30–34]. Endometriotic implant nidation also requires remodeling of the local peritoneal environment mediated by extracellular matrix (ECM) degrading proteases [35]. Matrix metalloproteinases (MMPs) play the dominant role in such tissue remodeling. Endometriotic lesions display enhanced expression of MMP-1, -3, and -7 [35–37].

Many of these same findings have been ascertained in a baboon model of endometriosis [38, 39]. While the molecular mechanisms by which endometriotic lesions persist are not clear, the establishment and progression of endometriosis require angiogenesis providing a target for new therapies.

4. Angiogenesis

While angiogenesis occurs throughout fetal growth and development, in adults it is limited to the endometrium during the menstrual cycle, the ovary during formation of the corpus luteum and in pathological states including wound healing, diabetic retinopathy, tumor growth, and endometriosis [40–44]. This process requires new endothelial cells to sprout and then recruit pericytes to form capillaries or smooth muscle cells to form larger vessels [43, 45]. Subsequent steps include focal ECM degradation, endothelial cell proliferation and migration, organization of endothelial cells into capillary networks and lumen formation [46–50]. Several factors are involved in physiologic as well as pathologic angiogenesis in the human endometrium [6, 20, 51–53].

Vascular endothelial growth factor (VEGF) is the primary vasculogenic and angiogenic factor [46–50, 54]. The VEGF gene contains 8 exons, 7 introns, and a 14 kb coding region. Alternative exon splicing of a single VEGF gene produces 6 different isoforms. These include the predominant isoform VEGF165, as well as VEGF121, VEGF145, VEGF183, VEGF189, and VEGF 206 [55, 56]. The prominent VEGF isoforms are expressed by the endometrium and by primary cultured endometrial stromal cells [6, 55–60]. Binding of VEGF to the Flt-1 and KDR surface receptors activates their tyrosine kinase function resulting in enhanced endothelial cell proliferation, migration, vascular permeability, and protease activity [55, 61].

While VEGF has been considered central to the process of endometrial angiogenesis, we now know that many other factors are critical as well. For example, the angiopoietins also play a crucial role by promoting pericyte recruitment and vascular branching [62–65]. To date, four members of the angiopoietin family have been discovered. The angiopoietins are glycosylated: secreted proteins, which have characteristic protein structures that contain coiled-coil domains in the N-terminal portion and fibrinogen-like domains in the C-terminal portion of the molecule 27, 28. The angiopoietin1/Tie2 receptor system appears to be involved in the secondary stages of blood vessel formation [46–50, 54].

Additionally, fibroblast growth factors (FGFs), platelet derived growth factors (PDGF), and interleukin-8 (IL-8)

exert more complex effects on angiogenesis [66–70] making this process extremely intricate.

Lastly, TF has now been demonstrated to be involved in angiogenesis [6, 58–60] making it an ideal target in pathologic events. This is discussed in the following.

5. Endometriosis and Angiogenesis

Endometriotic implants require neovascularization to survive, grow, and invade ectopic sites [54, 71–76]. While there are conflicting reports concerning the origin of endometriosis, 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. Just as observed in tumor growth, angiogenesis of the endometriotic cells in implanted places appears to be essential for endometriotic cells survival and development. It has been shown that endometriotic lesions are highly vascularized, and it is now widely accepted that the formation of new blood vessels in implanted places plays a key role in the growth of endometriotic cells [77]. The angiogenic dynamics may provide blood supply to the refluxed menstrual debris, enabling attachment, implantation, and growth of endometrial cells on ectopic places. Indeed, several proangiogenic factors and their corresponding receptors have been found in peritoneal fluid and endometrial tissues from women with endometriosis [77]. As a result, peritoneal fluid from women with endometriosis is highly angiogenic [71–76, 78]. Moreover, specific VEGF blockers suppress the growth of ectopic endometrial explants in a nude mouse model of endometriosis [61, 79, 80]. However, many of these inhibitors have serious untoward effects which may be acceptable in cases such as progressive cancers [81] but would not be advisable for endometriosis, a painful but benign disease.

In addition to the classic angiogenic agents described previously, tissue factor (TF) can mediate angiogenesis using a variety of distinct intracellular signaling pathways, and TF is aberrantly expressed in pathologically growing endothelium [45, 82–86]. Our initial studies suggested that overexpression of TF may be integral for the growth and survival of endometriotic lesions [45].

6. The Role of Macrophages in Endometriosis

Despite the ubiquitous occurrence of retrograde menstruation, most women do not develop endometriosis. In susceptible women, a cytokine-rich peritoneal milieu promotes survival of endometriotic implants [77]. Affected patients display elevated peritoneal concentrations of IL-1β, IL-6, IL-8, IL-10, and TNFα, as well as the potent macrophage (Mφ) chemoattractants: macrophage chemoattractant protein-1 (MCP-1), RANTES, eotaxin, and IL-8 [87, 88]. Implants are also a rich source of Mφ and their recruiting chemokines [88–92]. In turn, activated Mφ also produce proinflammatory mediators, including TNFα, IL-1α, IL-1β, IL-6, IL-8, leukemia inhibitory factor (LIF), interferon-γ (IFN-γ), and MCP-1 [87, 88, 90–92]. These cytokines are known

to induce TF in endothelial cells and/or recruit and activate monocytes/Mφ *in vitro* [93, 94]. Since TF/VIIa/PAR-2 interactions induce cytokine expression [95, 96], we hypothesize the existence of a positive feedback loop whereby the induction of TF perpetuates inflammation. In support of this hypothesis, our studies showed that endometriotic implants display intense TF and PAR-2 expression in Mφ. Thus targeting cells overexpressing TF provides an innovative approach to the treatment of this disease [97].

7. Tissue Factor

TF is a cell membrane-bound glycoprotein (MW 46 kDa) comprised of a hydrophilic extracellular domain, a membrane-spanning hydrophobic domain, and a cytoplasmic tail of 21 residues [98, 99]. Biological activity of the mature protein requires posttranslational modification to include carbohydrate moieties [100–102]. 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 [98, 99, 103]. Tissue factor is expressed in the mesenchymal and epithelial cells of diverse tissues [104–106]. Our laboratory established that in normal endometrium, TF expression is limited to stromal cells of the secretory phase with far lower expression in glandular epithelium [13, 14, 107]. Specifically, we demonstrated that progesterone (P4) enhances endometrial stromal cell TF mRNA and protein expression *in vitro* and that immunohistochemical staining for TF protein and *in situ* hybridization signaling for TF mRNA were greatest in stromal cells from the P4-dominated secretory phase [13, 14]. In contrast, previous studies from our laboratory indicate that in endometriosis, TF is greatly overexpressed in both glandular epithelium and stromal cells irrespective of menstrual phase [45, 108]. Unexpectedly, the most intense TF immunostaining was observed in macrophages infiltrating endometriotic tissues. Even more unusual was the presence of immunoreactive TF in endometriotic endothelial cells [45, 109].

In addition to its role in hemostasis, TF/VIIa binding has important coagulation-independent functions, especially in embryonic and oncogenic angiogenesis, leukocyte diapedesis, and inflammation [110]. Indeed, TF deficiency causes embryonic lethality in the mouse. Thus, TF$^{-/-}$ null embryos die at embryonic day E10.5 and display disorganization of the yolk sac vasculature suggesting that TF plays a pivotal role in vasculogenesis [11, 111, 112]. The absence of reports of TF deficiency in humans suggests a parallel obligatory requirement. While TF/VIIa signaling plays a critical role in angiogenesis, the underlying molecular mechanisms remain controversial. For example, the requirement for concomitant factor Xa binding and the need for phosphorylation as well as the obligatory role of the TF cytoplasmic tail have all been debated [113]. Several recent studies indicate that type-2 protease-activated receptor(PAR-2) is intimately involved in TF-mediated angiogenesis [113–116].

8. Protease-Activated Receptor-2 (PAR-2)

The PAR family consists of four distinct transmembrane G-protein-coupled receptors, with each member playing an important role in inflammation [117]. PAR ligand/agonists are serine proteases that bind to each receptor and then cleave its extended, extracellular N-terminus at a specific site within the protein chain to expose an N-terminal tethered ligand domain [117]. The latter then binds to and activates the cleaved receptor. PARs are "single use" receptors since proteolytic activation is irreversible, and the cleaved receptors are degraded by lysosomes [117]. Thrombin is the primary agonist for PAR-1, the prototypical family member [118]. However thrombin can also activate PAR-3 and PAR-4, whereas PAR-2 is primarily a receptor for trypsin and the trypsin-like enzymes, factors Xa and VIIa [118–122]. Synthetic peptides that mimic the tethered ligand for each receptor activate PARs without the requirement for proteolytic activity [123–125]. These synthetic agonists permit identification of the independent role of individual PARs in a given biologic function. For example, the PAR-2 agonistic peptide (PAR2AP), is specific for PAR-2 but does not activate PAR-1, -3, or -4 [123–125]. A recent report by Shi et al. [126] revealing that the tethered ligand formed by thrombin activated PAR-1 can activate PAR 2 suggests the existence of an unexpected interaction between these two receptors.

In the endometrium, Hirota et al. showed that expression of PAR-2 mRNA is increased between the late secretory and menstrual phases [127, 128]. This group has also shown that activation of PAR-2 enhances IL-8 and MMP-7 production in both endometrial epithelial cells and stromal cells [127, 128]. Mitogen-activated protein kinases (MAPKs) mediate PAR-2-dependent IL-8 secretion [129]. Additionally, inflammatory agents such as tumor necrosis factor-α (TNFα), IL-1β, and lipopolysaccharide (LPS) increase PAR-2 expression in human endothelial cells [130]. Given the potent neutrophils chemotactic and angiogenic effects of IL-8 and its interaction with MMPs to foster endometrial remodeling, PAR-2 activation likely plays a critical role in pathological states in the endometrium [45].

9. TF/VIIa Signaling through PAR-2

The complex of TF/VIIa with or without factor Xa bound to PAR-2 promotes angiogenesis directly by inducing release of VEGF in multiple cell types via MAPK activation [131]. The TF/VIIa/PAR-2 complex also promotes angiogenesis, inflammation, and tumor cell migration, and invasion and these processes can be blocked by addition of site-inactivated VIIa, as well as by specific antibodies against TF [131]. However, TF/VIIa can also indirectly stimulate angiogenesis by the generation of thrombin [132, 133]. Binding of PAR-1 by thrombin also activates MAPK to enhance VEGF expression [134–136]. Taken together, these data support the hypothesis that TF-VIIa-PAR-2 cell signaling plays a central role in the survival of pathologic cellular growth such as carcinomas as well as more benign conditions such as endometriosis. Hence, blocking TF or PAR-2 may provide another pathway by which to inhibit aberrant angiogenesis.

10. Icon Abolishes Endometriotic Lesions in a Mouse Model of Human Endometriosis

Icon is a novel chimeric antibody-like immunoconjugate molecule (Icon). Icon is composed of a mutated noncoagulation-inducing factor VII (fVII) domain targeting TF and an IgG1 Fc (fVII/IgG1 Fc) effector domain that activates an NK cell cytolytic response against the TF-bearing cells [137–140]. We have shown that Icon eradicates preestablished human endometriotic lesions in an athymic (ATN) mouse model without untoward systemic effects, altered fertility, or subsequent teratogenesis [109]. Specifically, Icon protein was synthesized by stable transfection of Chinese hamster ovary (CHO) cells as previously described [137–139]. To prevent the induction of coagulation following binding of Icon to TF, an amino acid substitution (Lysine 341 to Alanine) was introduced into the Icon fVII domain to block initiation of coagulation without reducing the molecule's strong affinity for TF [137]. The ATN mice were injected with approximately 1.0 mL packed endometrial tissue as previously described [109]. Upon gross morphological examination, 11 out of 15 treated mice had no sign of disease after 4 weekly 10 μg Icon treatment compared to 5 out of 12 mice treated with a 5 μg dose. By contrast, 12 out of 13 mice treated with vehicle control had well-defined endometrial lesions. For those animals treated with Icon and displaying residual lesions, the latter were significantly smaller than those found in control animals. Moreover residual lesions following treatment appeared to be avascular.

Most importantly, unlike antiangiogenic treatments that can only target developing angiogenesis, Icon eliminates preexisting pathological vessels without untoward systemic effects, altered fertility, or subsequent teratogenesis [108].

11. Icon Targets Tissue Factor in Uterine Serous Papillary Carcinoma

Pathological angiogenesis, the formation of new capillary blood vessels from existing blood vessels into diseased tissues, has been previously reported to occur more frequently in endometrial carcinomas developing against a background of endometrial atrophy rather than carcinomas arising from a hyperplastic endometrium [141]. Tissue factor is aberrantly expressed in human cancers and on endothelial cells within the tumor vasculature [142–144]. Importantly, tumor cells characterized by a high production of TF and vascular endothelial growth factor are known to generate solid tumors characterized by intense vascularity and highly aggressive behavior [145, 146]. Consistent with this view, vascular endothelial growth factor expression at the invading tumor front is reported to be 4–10 times higher than in the inner tumor areas and is significantly associated with poor prognosis, particularly with advanced stage endometrial cancer [141].

In a recent study, we evaluated for the first time the *in vitro* potential of Icon as a novel immunotherapeutic agent against biologically aggressive uterine serous tumors (USPC) [147]. Cytoplasmic and/or membrane TF expression was observed in all 16 (100%). USPC samples were tested by immunohistochemistry. High expression of TF was found in 50% (three out of six) of the USPC cell lines tested by real-time PCR and flow cytometry when compared with normal endometrial cells. Uterine serous papillary adenocarcinoma cell lines overexpressing TF were highly sensitive to Icon and demonstrated that this molecule induced strong cytotoxicity against primary chemotherapy-resistant USPC cell lines overexpressing TF. Lastly, it has been demonstrated that Icon could separately induce murine natural killer (NK) cells and activate complement to kill cancer cells *in vitro* via antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) [148].

12. Discussion

Prior studies from our laboratory have shown that in normal endometrium, progestins markedly enhance TF protein and mRNA expression in decidualized stromal cells during the luteal phase [13, 14, 149]. We have also shown that glandular epithelial cells display minimal TF expression throughout the menstrual cycle [13, 14, 149]. Upon discovery of aberrant endometrial TF expression in the endometriotic neovasculature we evaluated whether a novel, immunotherapy targeting endothelial TF could eradicate endometriotic implants. Increased expression of TF in ectopic endometrium from patients with endometriosis compared with controls is a novel finding. It may reflect the known association of endometriosis with increased inflammatory cytokine production [73, 150, 151]. It is well established that IL-1 β and tumor necrosis factor-α acting via the NFκB transcription factor increase TF gene expression in endothelial and other cells types [152]. Increased TF expression in endometrial endothelial cells may also reflect genetic polymorphisms in the promoter region of genes known to regulate TF expression as well as the TF promoter region itself [153–155].

The aberrant expression of TF in ectopic endometrial endothelium suggested that TF might be an ideal therapeutic target for endometriosis. Towards this end, we employed the immunoconjugate molecule, Icon, in a mouse model of endometriosis. Previous studies have demonstrated that Icon targeted TF anomalously expressed on the vasculature of malignant tumors as well as on parenchymal cells within solid tumors [137–139]. Icon also reduced the formation of pathological choroidal neovasculature which is associated with macular degeneration [156, 157]. Thus, Icon takes advantage of endothelial TF expression in pathological neovasculature while having no effects on normal vessels. Icon therapy was shown to eradicate endometriotic lesions in a mouse model of endometriosis [108].

Importantly, because Icon targets not only neo-angiogenesis, but aberrant preexisting vessels, it is the only available compound that could be potentially used to successfully treat preexistent, vascularized lesions. Indeed, women suffering from endometriosis are typically not diagnosed for several years [158, 159] and, thus, would already have established lesions. Although several treatments for endometriosis are available, they are associated with high recurrence rates and considerable side effects [80]. Prior studies have confirmed that Icon treatment does not produce toxicity in various animal strains [137, 139, 156, 157, 160], and we confirm no untoward effects on adult mice treated with Icon. In addition, we now report that treatment does not interfere with subsequent fertility nor does it give rise to teratogenic effects. Hence, Icon may be an ideal drug of choice in the treatment of endometriosis and in particular for reproductive-aged women suffering with this disease who desire subsequent fertility.

References

[1] S. D. Silberstein and G. R. Merriam, "Physiology of the menstrual cycle," *Cephalalgia*, vol. 20, no. 3, pp. 148–154, 2000.

[2] L. C. Giudice and J. C. Irwin, "Roles of the insulinlike growth factor family in nonpregnant human endometrium and at the decidual: trophoblast interface," *Seminars in Reproductive Medicine*, vol. 17, no. 1, pp. 13–21, 1999.

[3] D. Haouzi, H. Dechaud, S. Assou, J. De Vos, and S. Hamamah, "Insights into human endometrial receptivity from transcriptomic and proteomic data," *Reproductive BioMedicine Online*, vol. 24, no. 1, pp. 23–34, 2012.

[4] E. W. Lam, K. Shah, and J. J. Brosens, "The diversity of sex steroid action: the role of micro-RNAs and FOXO transcription factors in cycling endometrium and cancer," *The Journal of Endocrinology*, vol. 212, no. 1, pp. 13–25, 2011.

[5] G. S. Daftary and H. S. Taylor, "Endocrine regulation of HOX genes," *Endocrine Reviews*, vol. 27, no. 4, pp. 331–355, 2006.

[6] G. Weston and P. A. W. Rogers, "Endometrial angiogenesis," *Best Practice and Research: Clinical Obstetrics and Gynaecology*, vol. 14, no. 6, pp. 919–936, 2000.

[7] C. E. Gargett and P. A. W. Rogers, "Human endometrial angiogenesis," *Reproduction*, vol. 121, no. 2, pp. 181–186, 2001.

[8] A. M. Sharkey, K. Day, A. McPherson et al., "Vascular endothelial growth factor expression in human endometrium is regulated by hypoxia," *Journal of Clinical Endocrinology and Metabolism*, vol. 85, no. 1, pp. 402–409, 2000.

[9] S. K. Smith, "Angiogenesis, vascular endothelial growth factor and the endometrium," *Human Reproduction Update*, vol. 4, no. 5, pp. 509–519, 1998.

[10] N. W. Gale and G. D. Yancopoulos, "Growth factors acting via endothelial cell-specific receptor tyrosine kinases: VEGFs, angiopoietins, and ephrins in vascular development," *Genes and Development*, vol. 13, no. 9, pp. 1055–1066, 1999.

[11] P. Carmeliet, N. Mackman, L. Moons et al., "Role of tissue factor in embryonic blood vessel development," *Nature*, vol. 383, no. 6595, pp. 73–75, 1996.

[12] N. Mackman, "Role of tissue factor in hemostasis, thrombosis, and vascular development," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 24, no. 6, pp. 1015–1022, 2004.

[13] C. J. Lockwood, Y. Nemerson, S. Guller et al., "Progestational regulation of human endometrial stromal cell tissue factor expression during decidualization," *Journal of Clinical Endocrinology and Metabolism*, vol. 76, no. 1, pp. 231–236, 1993.

[14] C. J. Lockwood, Y. Nemerson, G. Krikun et al., "Steroid-modulated stromal cell tissue factor expression: a model for the regulation of endometrial hemostasis and menstruation," *Journal of Clinical Endocrinology and Metabolism*, vol. 77, no. 4, pp. 1014–1019, 1993.

[15] P. A. W. Rogers, T. M. D'Hooghe, A. Fazleabas et al., "Priorities for endometriosis research: recommendations from an international consensus workshop," *Reproductive Sciences*, vol. 16, no. 4, pp. 335–346, 2009.

[16] L. C. Giudice and L. C. Kao, "Endometriosis," *Lancet*, vol. 364, no. 9447, pp. 1789–1799, 2004.

[17] P. Viganò, E. Somigliana, P. Panina, E. Rabellotti, P. Vercellini, and M. Candiani, "Principles of phenomics in endometriosis," *Human Reproduction Update*, vol. 18, no. 3, Article ID dms001, pp. 248–259, 2012.

[18] K. Khoufache, N. Michaud, N. Harir, B. P. Kibangou, and A. Akoum, "Anomalies in the inflammatory response in endometriosis and possible consequences: a review," *Minerva Endocrinologica*, vol. 37, no. 1, pp. 75–92, 2012.

[19] L. C. Giudice, S. I. Tazuke, and L. Swiersz, "Status of current research on endometriosis," *The Journal of Reproductive Medicine*, vol. 43, supplement, no. 3, pp. 252–262, 1998.

[20] M. W. Laschke and M. D. Menger, "In vitro and in vivo approaches to study angiogenesis in the pathophysiology and therapy of endometriosis," *Human Reproduction Update*, vol. 13, no. 4, pp. 331–342, 2007.

[21] N. Saleh and E. Daw, "Endometriosis in non-gynaecological sites," *The Practitioner*, vol. 224, no. 1349, pp. 1189–1195, 1980.

[22] P. Vercellini, M. Meana, L. Hummelshoj, E. Somigliana, P. Viganò, and L. Fedele, "Priorities for endometriosis research: a proposed focus on deep dyspareunia," *Reproductive Sciences*, vol. 18, no. 2, pp. 114–118, 2011.

[23] I. E. Sasson and H. S. Taylor, "Stem cells and the pathogenesis of endometriosis," *Annals of the New York Academy of Sciences*, vol. 1127, pp. 106–115, 2008.

[24] Q.-Y. Jiang and R.-J. Wu, "Growth mechanisms of endometriotic cells in implanted places: a review," *Gynecological Endocrinology*, vol. 28, no. 7, pp. 562–567, 2012.

[25] P. A. W. Rogers, J. F. Donoghue, L. M. Walter, and J. E. Girling, "Endometrial angiogenesis, vascular maturation, and lymphangiogenesis," *Reproductive Sciences*, vol. 16, no. 2, pp. 147–151, 2009.

[26] P. Bellelis, S. Podgaec, and M. S. Abrao, "Environmental factors and endometriosis," *Revista da Associacao Medica Brasileira*, vol. 57, no. 4, pp. 448–452, 1992.

[27] K. Huhtinen, M. Ståhle, A. Perheentupa, and M. Poutanen, "Estrogen biosynthesis and signaling in endometriosis," *Molecular and Cellular Endocrinology*, vol. 358, no. 2, pp. 146–154, 2012.

[28] T. Falcone and D. I. Lebovic, "Clinical management of endometriosis," *Obstetrics and Gynecology*, vol. 118, no. 3, pp. 691–705, 2011.

[29] K. L. Sharpe-Timms, "Endometrial anomalies in women with endometriosis," *Annals of the New York Academy of Sciences*, vol. 943, pp. 131–147, 2001.

[30] G. Weiss, L. T. Goldsmith, R. N. Taylor, D. Bellet, and H. S. Taylor, "Inflammation in reproductive disorders," *Reproductive Sciences*, vol. 16, no. 2, pp. 216–229, 2009.

[31] N. Malhotra, D. Karmakar, V. Tripathi, K. Luthra, and S. Kumar, "Correlation of angiogenic cytokines-leptin and IL-8 in stage, type and presentation of endometriosis," *Gynecological Endocrinology*, vol. 28, no. 3, pp. 224–227, 2012.

[32] S. Defrère, R. González-Ramos, J.-C. Lousse et al., "Insights into iron and nuclear factor-kappa B (NF-κB) involvement in chronic inflammatory processes in peritoneal endometriosis," *Histology and Histopathology*, vol. 26, no. 8, pp. 1083–1092, 2011.

[33] K. N. Khan, M. Kitajima, K. Hiraki et al., "Immunopathogenesis of pelvic endometriosis: role of hepatocyte growth factor, macrophages and ovarian steroids," *American Journal of Reproductive Immunology*, vol. 60, no. 5, pp. 383–404, 2008.

[34] M. Ulukus and A. Arici, "Immunology of endometriosis," *Minerva Ginecologica*, vol. 57, no. 3, pp. 237–248, 2005.

[35] K. G. Osteen, G. R. Yeaman, and K. L. Bruner-Tran, "Matrix metalloproteinases and endometriosis," *Seminars in Reproductive Medicine*, vol. 21, no. 2, pp. 155–163, 2003.

[36] E. M. Wolber, P. Kressin, A. Meyhöfer-Malik, K. Diedrich, and E. Malik, "Differential induction of matrix metalloproteinase 1 and 2 in ectopic endometrium," *Reproductive BioMedicine Online*, vol. 6, no. 2, pp. 238–243, 2003.

[37] K. L. Bruner-Tran, Z. Zhang, E. Eisenberg, R. C. Winneker, and K. G. Osteen, "Down-regulation of endometrial matrix metalloproteinase-3 and -7 expression in vitro and therapeutic regression of experimental endometriosis in vivo by a novel nonsteroidal progesterone receptor agonist, tanaproget," *Journal of Clinical Endocrinology and Metabolism*, vol. 91, no. 4, pp. 1554–1560, 2006.

[38] T. M. D'Hooghe, S. Debrock, C. M. Kyama et al., "Baboon model for fundamental and preclinical research in endometriosis," *Gynecologic and Obstetric Investigation*, vol. 57, no. 1, pp. 43–46, 2004.

[39] A. T. Fazleabas, A. Brudney, D. Chai, D. Langoi, and S. E. Bulun, "Steroid receptor and aromatase expression in baboon endometriotic lesions," *Fertility and Sterility*, vol. 80, supplement 2, pp. 820–827, 2003.

[40] K. Norrby, "Angiogenesis: new aspects relating to its initiation and control," *APMIS*, vol. 105, no. 6, pp. 417–437, 1997.

[41] J. K. Findlay, "Angiogenesis in reproductive tissues," *Journal of Endocrinology*, vol. 111, no. 3, pp. 357–366, 1986.

[42] K.-A. Kim, Y.-J. Shin, J.-H. Kim et al., "Dysfunction of endothelial progenitor cells under diabetic conditions and its underlying mechanisms," *Archives of Pharmacal Research*, vol. 35, no. 2, pp. 223–234, 2012.

[43] O. C. Velazquez, "Angiogenesis and vasculogenesis: inducing the growth of new blood vessels and wound healing by stimulation of bone marrow-derived progenitor cell mobilization and homing," *Journal of Vascular Surgery*, vol. 45, supplement A, pp. 39–47, 2007.

[44] L. Y. Li, K. D. Barlow, and L. J. Metheny-Barlow, "Angiopoietins and Tie2 in health and disease," *Pediatric Endocrinology Reviews*, vol. 2, no. 3, pp. 399–408, 2005.

[45] G. Krikun, F. Schatz, H. Taylor, and C. J. Lockwood, "Endometriosis and tissue factor," *Annals of the New York Academy of Sciences*, vol. 1127, pp. 101–105, 2008.

[46] G. Bellon, L. Martiny, and A. Robinet, "Matrix metalloproteinases and matrikines in angiogenesis," *Critical Reviews in Oncology/Hematology*, vol. 49, no. 3, pp. 203–220, 2004.

[47] T. O. Daniel and D. Abrahamson, "Endothelial signal integration in vascular assembly," *Annual Review of Physiology*, vol. 62, pp. 649–671, 2000.

[48] O. Distler, M. Neidhart, R. E. Gay, and S. Gay, "The molecular control of angiogenesis," *International Reviews of Immunology*, vol. 21, no. 1, pp. 33–49, 2002.

[49] N. Ortéga, F. E. L'Faqihi, and J. Plouët, "Control of vascular endothelial growth factor angiogenic activity by the extracellular matrix," *Biology of the Cell*, vol. 90, no. 5, pp. 381–390, 1998.

[50] C. Rüegg and A. Mariotti, "Vascular integrins: pleiotropic adhesion and signaling molecules in vascular homeostasis and angiogenesis," *Cellular and Molecular Life Sciences*, vol. 60, no. 6, pp. 1135–1157, 2003.

[51] J. Fujimoto, H. Sakaguchi, R. Hirose, H. Wen, and T. Tamaya, "Angiogenesis in endometriosis and angiogenic factors," *Gynecologic and Obstetric Investigation*, vol. 48, supplement 1, pp. 14–20, 1999.

[52] D. I. Lebovic, F. Bentzien, V. A. Chao, E. N. Garrett, Y. G. Meng, and R. N. Taylor, "Induction of an angiogenic phenotype in endometriotic stromal cell cultures by interleukin-1β," *Molecular Human Reproduction*, vol. 6, no. 3, pp. 269–275, 2000.

[53] M. Takehara, M. Ueda, Y. Yamashita, Y. Terai, Y. C. Hung, and M. Ueki, "Vascular endothelial growth factor a and C gene expression in endometriosis," *Human Pathology*, vol. 35, no. 11, pp. 1369–1375, 2004.

[54] R. N. Taylor, J. Yu, P. B. Torres et al., "Mechanistic and therapeutic implications of angiogenesis in endometriosis," *Reproductive Sciences*, vol. 16, no. 2, pp. 140–146, 2009.

[55] N. Ferrara, K. Mayo, J. Cidlowski, N. Kochupillai, and G. Cutler, "Vascular endothelial growth factor and the regulation of angiogenesis," *Recent Progress in Hormone Research*, vol. 55, pp. 15–35, 2000.

[56] C. J. Robinson, S. E. Stringer, and S. E. Stringer, "The splice variants of vascular endothelial growth factor (VEGF) and their receptors," *Journal of Cell Science*, vol. 114, no. 5, pp. 853–865, 2001.

[57] D. S. Torry and R. J. Torry, "Angiogenesis and the expression of vascular endothelial growth factor in endometrium and placenta," *American Journal of Reproductive Immunology*, vol. 37, no. 1, pp. 21–29, 1997.

[58] J. E. Girling and P. A. W. Rogers, "Regulation of endometrial vascular remodelling: role of the vascular endothelial growth factor family and the angiopoietin-TIE signalling system," *Reproduction*, vol. 138, no. 6, pp. 883–893, 2009.

[59] C. J. Lockwood, G. Krikun, M. Hickey, S. J. Huang, and F. Schatz, "Decidualized human endometrial stromal cells mediate hemostasis, angiogenesis, and abnormal uterine bleeding," *Reproductive Sciences*, vol. 16, no. 2, pp. 162–170, 2009.

[60] S. K. Smith, "Vascular endothelial growth factor and the endometrium," *Human Reproduction*, vol. 11, supplement 2, pp. 56–61, 1996.

[61] N. Ferrara, "Vascular endothelial growth factor: basic science and clinical progress," *Endocrine Reviews*, vol. 25, no. 4, pp. 581–611, 2004.

[62] G. Thurston, J. S. Rudge, E. Ioffe et al., "Angiopoietin-1 protects the adult vasculature against plasma leakage," *Nature Medicine*, vol. 6, no. 4, pp. 460–463, 2000.

[63] D. M. Valenzuela, J. A. Griffiths, J. Rojas et al., "Angiopoietins 3 and 4: diverging gene counterparts in mice and humans," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 96, no. 5, pp. 1904–1909, 1999.

[64] S. Davis and G. D. Yancopoulos, "The angiopoietins: Yin and Yang in angiogenesis," *Current Topics in Microbiology and Immunology*, vol. 237, pp. 173–185, 1999.

[65] G. D. Yancopoulos, M. Klagsbrun, and J. Folkman, "Vasculogenesis, angiogenesis, and growth factors: ephrins enter the fray at the border," *Cell*, vol. 93, no. 5, pp. 661–664, 1998.

[66] H. Qiao, K. H. Sonoda, Y. Sassa et al., "Abnormal retinal vascular development in IL-18 knockout mice," *Laboratory Investigation*, vol. 84, no. 8, pp. 973–980, 2004.

[67] J. R. Westphal, R. Van't Hullenaar, R. Peek et al., "Angiogenic balance in human melanoma: expression of VEGF, bFGF, IL-8, PDGF and angiostatin in relation to vascular density of xenografts in vivo," *International Journal of Cancer*, vol. 86, no. 6, pp. 768–776, 2000.

[68] B. Berse, J. A. Hunt, R. J. Diegel et al., "Hypoxia augments cytokine (transforming growth factor-beta (TGF-β) and IL-1)-induced vascular endothelial growth factor secretion by human synovial fibroblasts," *Clinical and Experimental Immunology*, vol. 115, no. 1, pp. 176–182, 1999.

[69] G. Dobrescu, "The role of the endothelium in angiogenesis," *Revista Medico-Chirurgicala a Societatii de Medici si Naturalisti din Lasi*, vol. 101, no. 1-2, pp. 31–39, 1997.

[70] R. F. Nicosia, S. V. Nicosia, and M. Smith, "Vascular endothelial growth factor, platelet-derived growth factor, and insulin-like growth factor-1 promote rat aortic angiogenesis in vitro," *American Journal of Pathology*, vol. 145, no. 5, pp. 1023–1029, 1994.

[71] J. Gilabert-Estellés, L. A. Ramón, F. España et al., "Expression of angiogenic factors in endometriosis: relationship to fibrinolytic and metalloproteinase systems," *Human Reproduction*, vol. 22, no. 8, pp. 2120–2127, 2007.

[72] M. Y. Wu and H. N. Ho, "The role of cytokines in endometriosis," *American Journal of Reproductive Immunology*, vol. 49, no. 5, pp. 285–296, 2003.

[73] R. N. Taylor, D. I. Lebovic, and M. D. Mueller, "Angiogenic factors in endometriosis," *Annals of the New York Academy of Sciences*, vol. 955, pp. 89–100, 2002.

[74] A. Akoum, C. Lawson, S. McColl, and M. Villeneuve, "Ectopic endometrial cells express high concentrations of interleukin (IL)-8 in vivo regardless of the menstrual cycle phase and respond to oestradiol by up-regulating IL-1-induced IL-8 expression in vitro," *Molecular Human Reproduction*, vol. 7, no. 9, pp. 859–866, 2001.

[75] J. McLaren, "Vascular endothelial growth factor and endometriotic angiogenesis," *Human Reproduction Update*, vol. 6, no. 1, pp. 45–55, 2000.

[76] S. Matsuzaki, M. Canis, C. Darcha, P. Dechelotte, J. L. Pouly, and M. A. Bruhat, "Angiogenesis in endometriosis," *Gynecologic and Obstetric Investigation*, vol. 46, no. 2, pp. 111–115, 1998.

[77] Q.-Y. Jiang and R.-J. Wu, "Growth mechanisms of endometriotic cells in implanted places: a review," *Gynecological Endocrinology*, vol. 28, no. 7, pp. 562–567, 2012.

[78] P. R. Koninckx, S. H. Kennedy, and D. H. Barlow, "Endometriotic disease: the role of peritoneal fluid," *Human Reproduction Update*, vol. 4, no. 5, pp. 741–751, 1998.

[79] K. L. Bruner-Tran, D. Webster-Clair, and K. G. Osteen, "Experimental endometriosis: the nude mouse as a xenographic host," *Annals of the New York Academy of Sciences*, vol. 955, pp. 328–339, 2002.

[80] A. Mihalyi, P. Simsa, K. C. Mutinda, C. Meuleman, J. M. Mwenda, and T. M. D'Hooghe, "Emerging drugs in endometriosis," *Expert Opinion on Emerging Drugs*, vol. 11, no. 3, pp. 503–524, 2006.

[81] L. S. Rosen, "Clinical experience with angiogenesis signaling inhibitors: focus on vascular endothelial growth factor (VEGF) blockers," *Cancer Control*, vol. 9, supplement 2, pp. 36–44, 2002.

[82] C. Reinhardt, M. Bergentall, T. U. Greiner et al., "Tissue factor and PAR1 promote microbiota-induced intestinal vascular remodelling," *Nature*, vol. 483, no. 7391, pp. 627–631, 2012.

[83] M. Belting, M. I. Dorrell, S. Sandgren et al., "Regulation of angiogenesis by tissue factor cytoplasmic domain signaling," *Nature Medicine*, vol. 10, no. 5, pp. 502–509, 2004.

[84] N. Mackman, "The many faces of tissue factor," *Journal of Thrombosis and Haemostasis*, vol. 7, supplement 1, pp. 136–139, 2009.

[85] J. Yu, L. May, C. Milsom et al., "Contribution of host-derived tissue factor to tumor neovascularization," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 28, no. 11, pp. 1975–1981, 2008.

[86] R. Pawlinski, B. Pedersen, J. Erlich, and N. Mackman, "Role of tissue factor in haemostasis, thrombosis, angiogenesis and inflammation: lessons from low tissue factor mice," *Thrombosis and Haemostasis*, vol. 92, no. 3, pp. 444–450, 2004.

[87] J. Halme, S. Becker, and S. Haskill, "Altered maturation and function of peritoneal macrophages: possible role in pathogenesis of endometriosis," *American Journal of Obstetrics and Gynecology*, vol. 156, no. 4, pp. 783–789, 1987.

[88] K. N. Khan, H. Masuzaki, A. Fujishita, M. Kitajima, I. Sekine, and T. Ishimaru, "Differential macrophage infiltration in early and advanced endometriosis and adjacent peritoneum," *Fertility and Sterility*, vol. 81, no. 3, pp. 652–661, 2004.

[89] T. Harada, T. Iwabe, and N. Terakawa, "Role of cytokines in endometriosis," *Fertility and Sterility*, vol. 76, no. 1, pp. 1–10, 2001.

[90] N. Santanam, A. A. Murphy, and S. Parthasarathy, "Macrophages, oxidation, and endometriosis," *Annals of the New York Academy of Sciences*, vol. 955, pp. 183–198, 2002.

[91] N. Sidell, S. W. Han, and S. Parthasarathy, "Regulation and modulation of abnormal immune responses in endometriosis," *Annals of the New York Academy of Sciences*, vol. 955, pp. 159–173, 2002.

[92] R. Gazvani and A. Templeton, "Peritoneal environment, cytokines and angiogenesis in the pathophysiology of endometriosis," *Reproduction*, vol. 123, no. 2, pp. 217–226, 2002.

[93] C. T. Esmon, "Possible involvement of cytokines in diffuse intravascular coagulation and thrombosis," *Bailliere's Best Practice and Research in Clinical Haematology*, vol. 12, no. 3, pp. 343–359, 1999.

[94] M. L. von Brühl, K. Stark, A. Steinhart et al., "Monocytes, neutrophils, and platelets cooperate to initiate and propagate venous thrombosis in mice in vivo," *The Journal of Experimental Medicine*, vol. 209, no. 4, pp. 819–835, 2012.

[95] U. Bavendiek, P. Libby, M. Kilbride, R. Reynolds, N. Mackman, and U. Schönbeck, "Induction of tissue factor expression in human endothelial cells by CD40 ligand is mediated via activator protein 1, nuclear factor κB, and Egr-1," *Journal of Biological Chemistry*, vol. 277, no. 28, pp. 25032–25039, 2002.

[96] J. C. Williams and N. Mackman, "Tissue factor in health and disease," *Frontiers in Bioscience*, vol. 4, pp. 358–372, 2012.

[97] M. B. Donati and R. Lorenzet, "Coagulation factors and tumor cell biology: the role of tissue factor," *Pathophysiology of Haemostasis and Thrombosis*, vol. 33, supplement 1, pp. 22–25, 2003.

[98] D. Kirchhofer and Y. Nemerson, "Initiation of blood coagulation: the tissue factor/factor VIIa complex," *Current Opinion in Biotechnology*, vol. 7, no. 4, pp. 386–391, 1996.

[99] W. H. Konigsberg and Y. Nemerson, "Molecular cloning of the cDNA for human tissue factor," *Cell*, vol. 52, no. 5, pp. 639–640, 1988.

[100] S. Higashi, H. Nishimura, S. Fujii, K. Takada, and S. Iwanaga, "Tissue factor potentiates the factor VIIa-catalyzed hydrolysis of an ester substrate," *Journal of Biological Chemistry*, vol. 267, no. 25, pp. 17990–17996, 1992.

[101] A. Guha, R. Bach, W. Konigsberg, and Y. Nemerson, "Affinity purification of human tissue factor: interaction of factor VII and tissue factor in detergent micelles," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 83, no. 2, pp. 299–302, 1986.

[102] Y. Nemerson, "Biological control of factor VII," *Thrombosis et Diathesis Haemorrhagica*, vol. 35, no. 1, pp. 96–100, 1976.

[103] A. Breitenstein, G. G. Camici, and F. C. Tanner, "Tissue factor: beyond coagulation in the cardiovascular system," *Clinical Science*, vol. 118, no. 3, pp. 159–172, 2010.

[104] N. Mackman, "Regulation of the tissue factor gene," *Thrombosis and Haemostasis*, vol. 78, no. 1, pp. 747–754, 1997.

[105] M. Z. Cui, G. C. N. Parry, P. Oeth et al., "Transcriptional regulation of the tissue factor gene in human epithelial cells is mediated by Sp1 and EGR-1," *Journal of Biological Chemistry*, vol. 271, no. 5, pp. 2731–2739, 1996.

[106] N. Mackman, "Regulation of tissue factor gene expression in human monocytic and endothelial cells," *Haemostasis*, vol. 26, supplement 1, pp. 17–19, 1996.

[107] C. J. Lockwood, G. Krikun, and F. Schatz, "The decidua regulates hemostasis in human endometrium," *Seminars in Reproductive Endocrinology*, vol. 17, no. 1, pp. 45–51, 1999.

[108] G. Krikun, Z. Hu, K. Osteen et al., "The immunoconjugate "icon" targets aberrantly expressed endothelial tissue factor causing regression of endometriosis," *American Journal of Pathology*, vol. 176, no. 2, pp. 1050–1056, 2010.

[109] G. Krikun, Z. Hu, K. Osteen et al., "The immunoconjugate "icon" targets aberrantly expressed endothelial tissue factor causing regression of endometriosis," *American Journal of Pathology*, vol. 176, no. 2, pp. 1050–1056, 2010.

[110] H. H. Versteeg, M. P. Peppelenbosch, and C. A. Spek, "Tissue factor signal transduction in angiogenesis," *Carcinogenesis*, vol. 24, no. 6, pp. 1009–1013, 2003.

[111] T. H. Bugge, Q. Xiao, K. W. Kombrinck et al., "Fatal embryonic bleeding events in mice lacking tissue factor, the cell-associated initiator of blood coagulation," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 93, no. 13, pp. 6258–6263, 1996.

[112] J. R. Toomey, K. E. Kratzer, N. M. Lasky, J. J. Stanton, and G. J. Broze, "Targeted disruption of the murine tissue factor gene results in embryonic lethality," *Blood*, vol. 88, no. 5, pp. 1583–1587, 1996.

[113] L. G. van den Hengel and H. H. Versteeg, "Tissue factor signaling: a multi-faceted function in biological processes," *Frontiers in Bioscience*, vol. 3, pp. 1500–1510, 2011.

[114] E. C. Gabazza, O. Taguchi, H. Kamada, T. Hayashi, Y. Adachi, and K. Suzuki, "Progress in the understanding of protease-activated receptors," *International Journal of Hematology*, vol. 79, no. 2, pp. 117–122, 2004.

[115] M. D. Hollenberg, "Physiology and pathophysiology of proteinase-activated receptors (PARs): proteinases as hormone-like signal messengers: PARs and more," *Journal of Pharmacological Sciences*, vol. 97, no. 1, pp. 8–13, 2005.

[116] R. Pawlinski and N. Mackman, "Tissue factor, coagulation proteases, and protease-activated receptors in endotoxemia and sepsis," *Critical Care Medicine*, vol. 32, no. 5, pp. S293–297, 2004.

[117] C. Dale and N. Vergnolle, "Protease signaling to G protein-coupled receptors: implications for inflammation and pain," *Journal of Receptors and Signal Transduction*, vol. 28, no. 1-2, pp. 29–37, 2008.

[118] K. Borensztajn, M. P. Peppelenbosch, and C. A. Spek, "Factor Xa: at the crossroads between coagulation and signaling in physiology and disease," *Trends in Molecular Medicine*, vol. 14, no. 10, pp. 429–440, 2008.

[119] E. Sokolova and G. Reiser, "Prothrombin/thrombin and the thrombin receptors PAR-1 and PAR-4 in the brain: localization, expression and participation in neurodegenerative diseases," *Thrombosis and Haemostasis*, vol. 100, no. 4, pp. 576–581, 2008.

[120] T. E. Golde, M. S. Wolfe, and D. C. Greenbaum, "Signal peptide peptidases: a family of intramembrane-cleaving proteases that cleave type 2 transmembrane proteins," *Seminars in Cell and Developmental Biology*, vol. 20, no. 2, pp. 225–230, 2009.

[121] A. Russo, U. J. K. Soh, and J. Trejo, "Proteases display biased agonism at protease-activated receptors: location matters," *Molecular Interventions*, vol. 9, no. 2, pp. 87–96, 2009.

[122] F. Schaffner and W. Ruf, "Tissue factor and PAR2 signaling in the tumor microenvironment," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 29, no. 12, pp. 1999–2004, 2009.

[123] B. Al-Ani, M. Saifeddine, A. Kawabata, and M. D. Hollenberg, "Proteinase activated receptor 2: role of extracellular loop 2 for ligand-mediated activation," *British Journal of Pharmacology*, vol. 128, no. 5, pp. 1105–1113, 1999.

[124] D. J. Lerner, M. Chen, T. Tram, and S. R. Coughlin, "Agonist recognition by proteinase-activated receptor 2 and thrombin receptor: importance of extracellular loop interactions for receptor function," *Journal of Biological Chemistry*, vol. 271, no. 24, pp. 13943–13947, 1996.

[125] N. Vergnolle, W. K. Macnaughton, B. Al-Ani, M. Saifeddine, J. L. Wallace, and M. D. Hollenberg, "Proteinase-activated receptor 2 (PAR2)-activating peptides: identification of a receptor distinct from PAR2 that regulates intestinal transport," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 95, no. 13, pp. 7766–7771, 1998.

[126] X. Shi, B. Gangadharan, L. F. Brass, W. Ruf, and B. M. Mueller, "Protease-activated receptors (PAR1 and PAR2) contribute to tumor cell motility and metastasis," *Molecular Cancer Research*, vol. 2, no. 7, pp. 395–402, 2004.

[127] Y. Hirota, Y. Osuga, T. Hirata et al., "Activation of protease-activated receptor 2 stimulates proliferation and interleukin (IL)-6 and IL-8 secretion of endometriotic stromal cells," *Human Reproduction*, vol. 20, no. 12, pp. 3547–3553, 2005.

[128] Y. Hirota, Y. Osuga, T. Hirata et al., "Evidence for the presence of protease-activated receptor 2 and its possible implication in remodeling of human endometrium," *Journal of Clinical Endocrinology and Metabolism*, vol. 90, no. 3, pp. 1662–1669, 2005.

[129] D. Guo, H. Zhou, Y. Wu et al., "Involvement of ERK1/2/NF-κB signal transduction pathway in TF/FVIIa/PAR2-induced proliferation and migration of colon cancer cell SW620," *Tumor Biology*, pp. 921–930, 2011.

[130] S. Nystedt, V. Ramakrishnan, and J. Sundelin, "The proteinase-activated receptor 2 is induced by inflammatory mediators in human endothelial cells: comparison with the thrombin receptor," *Journal of Biological Chemistry*, vol. 271, no. 25, pp. 14910–14915, 1996.

[131] W. Ruf, J. Disse, T. C. Carneiro-Lobo, N. Yokota, and F. Schaffner, "Tissue factor and cell signalling in cancer progression and thrombosis," *Journal of Thrombosis and Haemostasis*, vol. 9, supplement 1, pp. S306–S315, 2011.

[132] H. H. Versteeg and W. Ruf, "Emerging insights in tissue factor-dependent signaling events," *Seminars in Thrombosis and Hemostasis*, vol. 32, no. 1, pp. 24–32, 2006.

[133] W. Ruf and M. Riewald, "Tissue factor-dependent coagulation protease signaling in acute lung injury," *Critical Care Medicine*, vol. 31, supplement 4, pp. S231–S237, 2003.

[134] U. M. Chandrasekharan, M. Waitkus, C. M. Kinney, A. Walters-Stewart, and P. E. Dicorleto, "Synergistic induction of mitogen-activated protein kinase phosphatase-1 by thrombin and epidermal growth factor requires vascular endothelial growth factor receptor-2," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 30, no. 10, pp. 1983–1989, 2010.

[135] Y. Furukawa, Y. Kawano, J. Fukuda, H. Matsumoto, and H. Narahara, "The production of vascular endothelial growth factor and metalloproteinase via protease-activated receptor in human endometrial stromal cells," *Fertility and Sterility*, vol. 91, no. 2, pp. 535–541, 2009.

[136] C. M. Kinney, U. M. Chandrasekharan, L. Mavrakis, and P. E. DiCorleto, "VEGF and thrombin induce MKP-1 through distinct signaling pathways: role for MKP-1 in endothelial cell migration," *American Journal of Physiology, Cell Physiology*, vol. 294, no. 1, pp. C241–C250, 2008.

[137] Z. Hu and A. Garen, "Intratumoral injection of adenoviral vectors encoding tumor-targeted immunoconjugates for cancer immunotherapy," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 97, no. 16, pp. 9221–9225, 2000.

[138] Z. Hu and A. Garen, "Targeting tissue factor on tumor vascular endothelial cells and tumor cells for immunotherapy in mouse models of prostatic cancer," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 98, no. 21, pp. 12180–12185, 2001.

[139] Z. Hu, Y. Sun, and A. Garen, "Targeting tumor vasculature endothelial cells and tumor cells for immunotherapy of human melanoma in a mouse xenograft model," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 96, no. 14, pp. 8161–8166, 1999.

[140] K. G. Osteen, K. L. Bruner-Tran, O. N. G. David, and E. Eisenberg, "Paracrine mediators of endometrial matrix metalloproteinase expression: potential targets for progestin-based treatment of endometriosis," *Annals of the New York Academy of Sciences*, vol. 955, pp. 139–146, 2002.

[141] O. Abulafia and D. M. Sherer, "Angiogenesis of the endometrium," *Obstetrics and Gynecology*, vol. 94, no. 1, pp. 148–153, 1999.

[142] J. Contrino, G. Hair, D. L. Kreutzer, and F. R. Rickles, "In situ detection of tissue factor in vascular endothelial cells: correlation with the malignant phenotype of human breast disease," *Nature Medicine*, vol. 2, no. 2, pp. 209–215, 1996.

[143] W. Ruf and B. M. Mueller, "Tissue factor in cancer angiogenesis and metastasis," *Current Opinion in Hematology*, vol. 3, no. 5, pp. 379–384, 1996.

[144] Y. Zhang, Y. Deng, T. Luther et al., "Tissue factor controls the balance of angiogenic and antiangiogenic properties of tumor cells in mice," *Journal of Clinical Investigation*, vol. 94, no. 3, pp. 1320–1327, 1994.

[145] M. Suzuki, K. Hori, S. Saito et al., "Functional characteristics of tumor vessels: selective increase in tumor blood flow," *Science*

Reports of the Research Institutes Tohoku University. Series C, vol. 36, no. 1–4, pp. 37–45, 1989.

[146] K. Abe, M. Shoji, J. Chen et al., "Regulation of vascular endothelial growth factor production and angiogenesis by the cytoplasmic tail of tissue factor," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 96, no. 15, pp. 8663–8668, 1999.

[147] E. Cocco, Z. Hu, C. E. Richter et al., "HI-con1, a factor VII-IgGFc chimeric protein targeting tissue factor for immunotherapy of uterine serous papillary carcinoma," *British Journal of Cancer*, vol. 103, no. 6, pp. 812–819, 2010.

[148] Z. Hu and J. Li, "Natural killer cells are crucial for the efficacy of Icon (factor VII/human IgG1 Fc) immunotherapy in human tongue cancer," *BMC Immunology*, vol. 11, article no. 49, 2010.

[149] G. Krikun, F. Schatz, N. Mackman, S. Guller, R. Demopoulos, and C. J. Lockwood, "Regulation of tissue factor gene expression in human endometrium by transcription factors Sp1 and Sp3," *Molecular Endocrinology*, vol. 14, no. 3, pp. 393–400, 2000.

[150] A. Arici, E. Seli, H. B. Zeyneloglu, L. M. Senturk, E. Oral, and D. L. Olive, "Interleukin-8 induces proliferation of endometrial stromal cells: a potential autocrine growth factor," *Journal of Clinical Endocrinology and Metabolism*, vol. 83, no. 4, pp. 1201–1205, 1998.

[151] R. N. Taylor, I. P. Ryan, E. S. Moore, D. Hornung, J. L. Shifren, and J. F. Tseng, "Angiogenesis and macrophage activation in endometriosis," *Annals of the New York Academy of Sciences*, vol. 828, pp. 194–207, 1997.

[152] G. C. N. Parry and N. Mackman, "Transcriptional regulation of tissue factor expression in human endothelial cells," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 15, no. 5, pp. 612–621, 1995.

[153] J. L. Reny, I. Laurendeau, P. Fontana et al., "The TF-603A/G gene promoter polymorphism and circulating monocyte tissue factor gene expression in healthy volunteers," *Thrombosis and Haemostasis*, vol. 91, no. 2, pp. 248–254, 2004.

[154] Y. Shinohara, H. Iwasaki, N. Ota et al., "Novel single nucleotide polymorphisms of the human nuclear factor kappa-B 2 gene identified by sequencing the entire gene," *Journal of Human Genetics*, vol. 46, no. 1, pp. 50–51, 2001.

[155] X. F. Sun and H. Zhang, "NFKB and NFKBI polymorphisms in relation to susceptibility of tumour and other diseases," *Histology and Histopathology*, vol. 22, no. 12, pp. 1387–1398, 2007.

[156] P. S. Bora, Z. Hu, T. H. Tezel et al., "Immunotherapy for choroidal neovascularization in a laser-induced mouse model simulating exudative (wet) macular degeneration," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 100, no. 5, pp. 2679–2684, 2003.

[157] T. H. Tezel, E. Bodek, K. Sönmez et al., "Targeting tissue factor for immunotherapy of choroidal neovascularization by intravitreal delivery of factor VII-Fc chimeric antibody," *Ocular Immunology and Inflammation*, vol. 15, no. 1, pp. 3–10, 2007.

[158] R. S. Schenken, "Delayed diagnosis of endometriosis," *Fertility and Sterility*, vol. 86, no. 5, pp. 1305–1306, 2006.

[159] R. Hadfield, H. Mardon, D. Barlow, and S. Kennedy, "Delay in the diagnosis of endometriosis: a survey of women from the USA and the UK," *Human Reproduction*, vol. 11, no. 4, pp. 878–880, 1996.

[160] Y. Tang, P. Borgstrom, J. Maynard et al., "Mapping of angiogenic markers for targeting of vectors to tumor vascular endothelial cells," *Cancer Gene Therapy*, vol. 14, no. 4, pp. 346–353, 2007.