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Decidual Hemostasis, Inflammation, and Angiogenesis in Pre-Eclampsia

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Abstract

Invasion of the decidua by extravascular trophoblasts (EVTs) is accompanied by thrombin generation from decidual cell (DC) -expressed tissue factor (TF). This TF protects against hemorrhage as EVTs breach capillaries and subsequently invade and remodel spiral arteries and arterioles. Pre-eclampsia (P-EC) is the world's leading cause of fetal and maternal morbidity and mortality. It is associated with decidual hemorrhage and maternal thrombophilias, which form excess thrombin from DCs, and with maternal infections and other inflammatory conditions that are associated with excess expression of the pro-inflammatory cytokines, interleukin-1 beta (IL-1b) and tumor necrosis factor -alpha (TNF-a). In human first trimester leukocyte-free DCs: 1) thrombin enhances expression of soluble fms-like tyrosine kinase-1 (sFlt-1), a potent inhibitor of angiogenesis; 2) thrombin, IL-1b and TNF-a increase monocyte-recruiting chemokine expression leading to a macrophage excess in the pre-eclamptic decidua. The pathogenesis of P-EC likely stems from shallow EVT invasion leading to impaired decidual vascular remodeling. The resulting reduced uteroplacental blood flow is associated with a hypoxic placenta, which appears to secrete excess sFlt-1 into the maternal plasma. A regulatory role for DCs in vascular remodeling is indicated since impaired decidual vascular remodeling could stem from an aberrant local anti-angiogenic milieu elicited by excess sFlt-1 and/or macrophage inhibited EVT decidual invasion.

Keywords

decidua; tissue factor; hemostasis; angiogenesis; pre-eclampsia

Tissue factor is the primary initiator of coagulation and a mediator of inflammation

Tissue factor (TF) is a transcellular glycoprotein (MW 46 kDa) member of the class-2 cytokine receptor family. It is comprised of a hydrophilic extracellular domain, which acts as a receptor for factor VIIa, a membrane-spanning hydrophobic domain, and a cytoplasmic tail. Endothelial cells do not normally express TF, however, it is constitutively expressed at perivascular sites such as the smooth muscle and adventitia of arteries and veins. There TF

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forms a “hemostatic envelope” that protects against hemorrhage following vascular injury via binding of plasma-derived factor VII.^{1, 2} The coagulation protease cascade depicted in Fig.1 indicates that the TF/VIIa complex activates both Factor (F) X to FXa (extrinsic pathway) and FIX to FIXa (intrinsic pathway) ultimately leading to thrombin generation. Ultimately, following proteolysis of prothrombin to thrombin, the latter activates platelets and promotes hemostasis by cleaving fibrinogen to fibrin.³

Once considered separate phenomena, considerable evidence now reveals the existence of extensive cross-talk between the inflammatory and coagulation pathways in which inflammation activates coagulation factors and coagulation factors promote inflammation.⁴ Among several factors that mediate this two-way hemostasis-inflammation dialogue, TF acting via its effector product thrombin has emerged as the primary initiator of inflammation-induced coagulation.⁴ In experimental models of bacteremia and toxemia, blocking TF activity completely eliminates inflammation-induced thrombin formation.⁵

TF expression is crucial in maintaining pregnancy

In mice and humans, TF expression conforms to a differential, tissue-specific pattern. In tissues that express low levels of TF (*e.g.*, liver, spleen, skeletal muscle and thymus) hemostasis depends primarily on the slower acting intrinsic coagulation pathway.^{2, 6} Conversely, in high TF-expressing tissues (*e.g.*, placenta, skin, heart, lung, brain and uterus) hemostasis is mediated primarily by the faster acting extrinsic coagulation pathway (Fig.1). High TF levels in the latter tissues is consistent with a requirement for additional hemostatic protection against potentially fatal hemorrhage.^{2, 6}

The absence of any human TF deficiency genetic disorder, indicates the importance of TF to human survival but obviates the possibility of direct evaluation of the effects of human TF deficiency.³ Murine TF gene knockouts die *in utero* as a result of bleeding from fragile vessels.⁷ However, incorporation of a human minigene expressing TF at only 1% of the wild type level rescues these TF knockout mice and enables them to produce live pups. Adult low TF-expressing mice suffer from hemostatic defects in the heart, lung, uterus and placenta, which normally express high constitutive levels of TF. In these low TF-expressing mice, blood pools appear in the placental labyrinth and they are highly susceptible to postpartum hemorrhage and death.⁷

Human decidual cell-expressed TF promotes hemostasis during gestation

The progression of human pregnancy is associated with increased procoagulant activity in the maternal circulation. This activity reflects reciprocal up-regulation in levels of clotting factors and anti-fibrinolytic mediators with corresponding down-regulation of levels of physiological anticoagulants. While these changes are crucial in meeting the hemostatic challenge of placentation and the third stage of labor, they pose a significant maternal thrombotic risk throughout gestation and in the postpartum period.⁸ Previous studies from our laboratory determined that during the luteal phase of the human menstrual cycle progesterone induces estradiol-primed endometrial stromal cells to undergo decidualization and express TF mRNA and protein. Under continued progesterone stimulation, TF-expressing decidualized stromal cells (decidual cells) spread throughout the late luteal phase and gestational endometrium (decidua).^{9–11}

During human implantation, blastocyst-derived cytotrophoblasts invade the decidua and breach endometrial capillaries embedded in a matrix of decidual cells that express high levels of TF. This invasive process institutes the primordial uteroplacental circulation, and provides the embryo with a vital source of oxygen and nutrients while removing carbon dioxide and other waste products.¹² However, it also risks potential pregnancy-terminating

hemorrhage. In successful pregnancies, cytotrophoblasts continue to traverse the decidua as extravillous trophoblasts (EVTs), which invade and remodel spiral arteries and arterioles.¹³ The occurrence of decidual hemorrhage during this phase of placentation is associated with spontaneous abortion, abruption and preterm birth.^{14, 15} Recently we found that progesterone continues to drive TF expression in human decidual cells at term.¹⁶ Decidual cell TF expression exceeds that of other cell types at the maternal-fetal interface and is localized at the cell membranes¹⁶ where it is positioned to bind to factor VII from the circulation and generate thrombin, thus, protecting against potentially fatal hemorrhage during labor and delivery.

Thrombin promotes inflammation and angiogenesis via cell surface protease activated receptors (PARs)

While its extracellular actions enable thrombin to promote hemostasis, thrombin also mediates several biological effects by binding to and activating members of the protease activated receptor (PAR) family expressed at the surface of several cell types.¹⁷ Mediation by PARs enables thrombin to act as a potent promoter of inflammation¹⁸ and angiogenesis.¹⁹ Of the four members of the PAR family, PAR-1, PAR-3 and PAR-4 serve as thrombin receptors, while PAR-1 can also be activated by the TF-FVIIa complex or by FXa. Although PAR-2 cannot bind thrombin, like PAR-1 it can be activated by TF-FVIIa or FXa.⁴ Previous work from our laboratory indicates that stromal cells from cycling human endometrium express PAR-1.²⁰ Hirota et al. have presented *in vivo* and *in vitro* evidence of endometrial stromal cell PAR-2 expression.²¹

Pre-eclampsia is associated with shallow trophoblast invasion and an exaggerated inflammatory state

EVTs breach decidual arteries and arterioles as endovascular trophoblasts that replace the smooth muscle tunica media and endothelium.¹³ This invasive process is associated with “pseudovasculogenic” transformation of a trophoblast to an endothelial cell-like adhesion molecule phenotype.²² As a consequence high resistance, low capacity vessels are converted to low resistance, high capacity vessels that enhance blood flow to the intervillous space required to supply the growing and developing fetoplacental unit.¹³ In many cases of pre-eclampsia (P-EC), the primary placental defect is believed to be due to shallow EVT invasion of the decidua leading to impaired pseudovasculogenesis,²² incomplete vascular transformation, reduced uteroplacental blood flow and a placenta that becomes ischemic and then hypoxic.^{23, 24}

Pre-eclampsia is a leading cause of fetal and maternal morbidity and mortality worldwide and a major antecedent of intrauterine growth restriction and preterm delivery.²⁵ In normal human pregnancies, maternal-fetal immune interactions create a mild systemic inflammatory state that is clearly evident in the third trimester reflecting activation of vascular endothelium and leukocytes.²⁶ Pre-eclampsia is associated with a further increase in systemic inflammation as well as immune maladaptation at the implantation site associated with aberrant local inflammation.^{26, 27}

Thrombin and inflammatory cytokines may inhibit decidual EVT invasion by promoting local macrophage inflammation

Decidual cells are the major cell type encountered by invading EVT at the implantation site. The remainder are predominantly immune cells, of which macrophages comprise 20–25% of the decidual population.²⁸ It has been postulated that they enable trophoblast

invasion by remodeling the implantation site and removing apoptotic cells.²⁹ Observations made in our laboratory³⁰ as well as other laboratories^{29, 31} indicate that the pre-eclamptic decidua contains an excess of macrophages. *In vitro* studies indicate that macrophage-derived tumor necrosis factor- α (TNF- α) inhibits cytotrophoblast invasion by causing them to undergo apoptosis³¹ and by inducing expression of plasminogen activator inhibitor-1 (PAI-1) to inhibit urokinase-type plasminogen activator mediated protease activity at the leading edge of trophoblast invasion.³²

A significant subset of P-EC cases are associated with underlying decidual hemorrhage (abruption)^{33–35} and potentially maternal thrombophilias (reviewed in ²⁷). These conditions generate excess thrombin when circulating factor VII binds to decidual cell-expressed TF as indicated by augmented circulating levels of the thrombin-anti-thrombin complex.³⁶ We evaluated the potential role of thrombin and decidual cells in mediating a local macrophage excess in P-EC. As demonstrated in Figure 2, thrombin significantly enhanced secreted levels of monocyte chemoattractant protein-1 (MCP-1), the primary monocyte chemoattractant and activator, in cultured leukocyte free first decidual cells.³⁷

Maternal infections and other inflammatory conditions such as periodontal disease, obesity and lupus constitute significant risk factors for P-EC [reviewed in ²⁷] and are associated with heightened expression of the classic pro-inflammatory cytokines, interleukin-1 β (IL-1 β and (TNF- α). We found that incubation of leukocyte-free first trimester human decidual cells with these cytokines augmented mRNA and protein expression of MCP-1³⁰ as well as other chemokines known to attract and activate monocytes such as CCL7 (MCP-3), CCL4 (MIP-1 β) and CCL5 (RANTES).^{38, 39} Moreover, immunohistochemical analysis revealed elevated levels of monocyte activating and chemoattracting chemokines localized to decidual cells of sections of pre-eclamptic versus gestationally age-matched control placentas.³⁹ Therefore, both thrombin and pro-inflammatory cytokines can contribute to increased monocyte/macrophage infiltration of the pre-eclamptic decidua to promote its pathogenesis through decidual macrophage inhibition of EVT invasion.

Pre-eclampsia represents an aberrant angiogenic state

The hypoxic human placenta associated with P-EC contains elevated levels of soluble fms-like tyrosine kinase-1 (sFlt-1)⁴⁰, a splice variant of the Flt-1 receptor for vascular endothelial cell growth factor (VEGF), which binds to, and inactivates the angiogenic factors, VEGF and placental growth factor (PlGF). Serum from women with P-EC contains anti-angiogenic activity that is neutralized by adding either VEGF or PlGF. This activity is attributed to abnormally high secretion of sFlt-1 by the hypoxic placenta.^{40, 41} Decreased VEGF and PlGF levels, coupled with elevated sFlt-1 levels in maternal plasma,⁴¹ precede the appearance of pre-eclamptic symptoms. The resulting anti-angiogenic state is hypothesized to promote systemic endothelial activation and hypertension as well as renal dysfunction particularly at level of the glomerulus. This glomeruloendotheliosis leads to proteinuria. Hypertension and proteinuria are the two hallmarks of the maternal syndrome of P-EC [reviewed in ²⁵].

Thrombin may also inhibit EVT invasion by dysregulating angiogenesis

We determined that thrombin significantly enhances secreted levels of sFlt-1 in first trimester leukocyte-free decidual cell monolayers, shown in Figure 3. Corresponding thrombin augmentation of steady state mRNA levels was also observed.⁴² Unlike the marked enhancement of monocyte recruiting and activating chemokine expression elicited by IL-1 β or TNF- α in cultured first trimester decidual cells,^{30, 38, 39} Fig. 3 illustrates that neither of these cytokines affected the levels of sFlt-1. We showed the specificity of the

thrombin enhanced sFlt-1 expression in first trimester decidual cells since no effects are seen in term decidual cells or on VEGF output, whereas PlGF was not detected by ELISA in decidual cell conditioned medium.⁴² Thrombin enhanced sFlt-1 output in first trimester decidual cell cultures was blocked by hirudin thus demonstrating the requirement for active thrombin in inducing this response.

Unlike sFlt1, first trimester human decidual cells do not appear to express endoglin (unpublished results), another anti-angiogenic factor found to be elevated in the plasma of pre-eclamptic women.⁴³ Decidual cells isolated from placental sections by laser capture microdissection express sFLT-1 mRNA thereby providing evidence that the decidual cells synthesize sFlt-1 *in vivo*.⁴² Taken together, these results suggest that thrombin increases sFlt-1 expression in first trimester decidual cells to create an anti-angiogenic milieu at the implantation site. Since VEGF has been shown to mediate trophoblast migration,⁴⁴ this finding suggests that inhibition of VEGF by sFlt-1 impairs utero-placental blood flow by inhibiting trophoblast-induced pseudovasculogenesis.

Summary and the role of the decidua in initiating pre-eclampsia

The scheme presented in Fig. 4 presents a series of steps in the pathogenesis of P-EC that are initiated in the decidua and end with a series of well-established abnormalities in placental function caused by the resultant reduced uteroplacental blood and hypoxia. The hypoxic placenta in turn secretes into the maternal plasma elevated levels of anti-angiogenic factors, as exemplified by sFlt-1 and soluble endoglin that lower levels of the angiogenic factors PlGF and VEGF. The resulting anti-angiogenic milieu contributes to endothelial cell activation and dysfunction causing the maternal syndrome (hypertension and proteinuria).

The current review has focused on decidual cells in the pathogenesis of subsets of P-EC including those associated with: 1) decidual hemorrhage and maternal thrombophilias, which generate thrombin by binding of plasma-derived factor VII to TF expressed on decidual cell membranes; and 2) maternal infections and aseptic inflammatory conditions, associated with heightened expression of the primary inflammatory mediators IL-1 β and TNF- α . As indicated in Fig. 4, the concerted effects of thrombin, and these inflammatory cytokines induce decidual cells to express an array of monocyte chemoattracting and activating chemokines. Such heightened chemokine expression is consistent with a highly documented chronic infiltration of macrophages into the pre-eclamptic decidua. The resulting macrophage excess is implicated in impaired trophoblast invasion by several mechanisms. The increase in sFlt-1 occurs in the absence of any changes VEGF, whereas PlGF was undetected in these experiments. Shallow EVT invasion and/or an aberrant local anti-angiogenic state could interfere with trophoblast-induced pseudovasculogenesis involved in remodeling of the spiral arteries and arterioles into low resistance, high capacity vessels

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Extrinsic Pathway**Intrinsic Pathway** **Figure 1. The Coagulation Protease Cascade**

The TF-Factor VIIa complex of the extrinsic pathway initiates blood coagulation via direct activation of Factor X directly or by indirectly via activation of Factor IX of the intrinsic pathway. Thrombin plays a central role by activating various proteases and cofactors. Thrombin cleaves fibrinogen to soluble fibrin monomers (SFM), which are cross-linked by Factor XIIIa and it activates platelets to form the fibrin clot. (Reprinted with permission from Lockwood CJ, et al; through John Wiley & Sons, Ann NY Acad Sci. 2008;1127:67-72.)⁴⁵

Figure 2. Effects of thrombin on MCP-1 output by first trimester decidual cell monolayers

Confluent passaged, leukocyte-free first trimester decidual cells were primed for 7 days in estradiol (E₂) plus medroxyprogesterone acetate (MPA) to mimic the steroid milieu of pregnancy then switched to a defined medium with steroid(s) ± 2.5 U/ml thrombin (Th) for 24 hours. Secreted levels of MCP-1 were measured by ELISA and normalized to total cell protein [details in ³⁷]; (n=12, mean ± SEM; p<0.05). * versus E₂ or E₂ + MPA.

Figure 3. Effects of thrombin, TNF- α and IL-1 β on sFlt-1 output by decidual cell monolayers

Confluent passaged, leukocyte-free first trimester and term decidual cells were primed for 7 days in estradiol (E₂) plus medroxyprogesterone acetate (MPA) to mimic the steroid milieu of pregnancy then switched to a defined medium with steroid(s) $\pm$ 2.5 U/ml thrombin (Thr) or 10 ng/ml of TNF- α or for IL-1 β for 24 hours. Secreted levels of sFlt-1 were measured by ELISA and normalized to total cell protein [details in ⁴²]; (n=9 for first trimester; n = 6 for term, mean $\pm$ SEM; p<0.05). Fold change values are shown. * versus corresponding actual E₂ + MPA basal levels.

Decidua Regulates Maternal Syndrome of PE

Figure 4.

Proposed role of decidual cells in mediating pathogenic changes in subsets of pre-eclampsia associated with maternal hemorrhage, thrombophilias, and underlying maternal infections.