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Integrated *in silico* and *in vitro* analyses reveal E-cadherin crosstalk and TF: FVIIa complex-mediated trophoblast motility via MEK/JNK activation

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ABSTRACT

Tissue Factor (TF) is traditionally viewed as a coagulation initiator but increasingly recognized for extra hemostatic functions in cell signaling and migration. In trophoblasts, the TF:FVIIa complex may act as a critical regulator of cell motility during placental development. Yet how TF:FVIIa complex functions to drive human trophoblast migration remains poorly understood. This study investigated whether the TF:FVIIa complex promotes trophoblast migration through MAPK signaling using bioinformatics and functional assays. Genomic analysis of The Cancer Genome Atlas (TCGA) datasets from 657 gynecological samples revealed a significant positive correlation between TF (*F3*) and E-cadherin (*CDH1*) expression across three cohorts ($R = 0.21–0.48$, $p < 0.05$), supporting a partial epithelial-mesenchymal transition model for invasive cells. Protein-protein interaction networks identified MEK and JNK as central intermediates linking TF: FVIIa signaling to adhesion regulation. Functionally, FVIIa stimulation of HTR-8/SVneo trophoblasts induced dose-dependent migration increases (1.90-fold at 4 nM, $p < 0.01$). Inhibition of either MEK (U0126) or JNK (SP600125) completely blocked FVIIa-induced migration, demonstrating that both pathways are required for TF-driven migration. These findings establish TF: FVIIa as a key regulator of trophoblast migration through coordinated MEK/JNK activation, with implications for understanding defects in placental invasion and designing targeted interventions for pregnancy-related disorders.

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INTRODUCTION

Pregnancy success depends fundamentally on establishing a functional placenta through the precisely orchestrated invasion of trophoblast cells from the developing embryo into the maternal uterus. This invasion process requires extravillous trophoblasts (EVTs) to detach from their cellular neighbors, degrade the surrounding tissue barrier, and migrate into the maternal decidua, sometimes penetrating as deep as the inner muscle layer (Gupta *et al.*, 2016). This invasive behavior serves two critical functions: physical anchoring of the placenta to prevent miscarriage and triggering vascular remodeling whereby narrow, muscular maternal blood vessels are transformed into wide, low-resistance conduits that ensure continuous, high-volume blood supply to nourish the developing fetus (Gupta *et al.*, 2016; Knöfler *et al.*, 2019; Pijnenborg *et al.*, 2006). When this carefully regulated invasion process goes awry, serious complications emerge, including preeclampsia, fetal growth restriction, preterm birth, and recurrent miscarriage. These "Great Obstetrical Syndromes" collectively affect a substantial fraction of pregnancies worldwide and represent major health challenges for women and their families (Gupta *et al.*, 2016; Cross *et al.*, 1994; Ives *et al.*, 2020). Understanding the molecular signals that control trophoblast migration is therefore essential for preventing these complications and improving pregnancy outcomes.

Tissue Factor (TF), also known as coagulation factor III or CD142, is a 47 kilodalton transmembrane glycoprotein classically recognized as the primary cellular initiator of the extrinsic coagulation pathway. Traditionally, its function has been understood as a coagulation initiator: when blood vessels are injured, TF binds Factor VIIa (FVIIa) to trigger a cascade of proteolytic reactions that produce thrombin and form a protective fibrin clot (Li *et al.*, 2022; Mackman *et al.*, 2009). Under normal physiological conditions, TF is sequestered in perivascular cells, forming a "hemostatic envelope" that prevents unwanted blood clotting. However, TF is expressed at exceptionally high levels in the placenta, making it one of the most TF-rich organs in the body (Lanir *et al.*, 2003; Gundappa *et al.*, 2022). Emerging evidence over the past two decades reveals that TF plays critical biological functions far beyond hemostasis (Lanir *et al.*, 2003; Gundappa *et al.*, 2022). The TF:FVIIa complex acts as a potent signaling receptor capable of initiating intracellular communication cascades that regulate multiple cellular processes including gene expression, cell proliferation, programmed cell death, blood vessel formation, and cell migration (Ruf *et al.*, 2011). In cancer biology, the TF:FVIIa signaling pathway is well-established as a driver of tumor progression, promoting cancer cell migration, enhancing angiogenesis, and supporting cancer cell survival (Ruf *et al.*, 2011; D'Alessandro *et al.*, 2018). These cancer studies demonstrate that TF signaling activates the same molecular machinery that drives cell invasiveness and metastatic behavior.

While TF expression in the placenta is documented and its role in cancer progression is well-characterized, a critical gap exists regarding how TF:FVIIa signaling functionally drives human trophoblast migration. Most previous placental studies have focused on hemostatic functions or have measured gene expression in static conditions, with few studies examining the actual migratory responses of living trophoblast cells to TF:FVIIa stimulation. The signaling function of TF:FVIIa is mediated primarily through protease-activated receptor 2 (PAR-2) (Szklarczyk *et al.*, 2021). When FVIIa binds to TF, this triggers intracellular signaling cascades converging on major Mitogen-Activated Protein Kinase (MAPK) pathways, specifically Extracellular Signal-Regulated Kinase (ERK) and c-Jun N-terminal Kinase (JNK) (Li *et al.*, 2022; Gundappa *et al.*, 2022). These kinase cascades function as central processing hubs, translating signals from the cell surface into changes in gene transcription and cellular behavior (Li *et al.*, 2022). We hypothesized that TF:FVIIa signaling drives trophoblast migration by coordinated activation of the MEK and JNK pathways. To test this hypothesis, we employed a two-tiered approach: genomic bioinformatics analysis to establish whether TF signaling is clinically relevant in invasive tissues

using publicly available data from patients with gynecological cancers that share invasive phenotypes with trophoblasts, and functional migration assays with human trophoblast cells to determine whether FVIIa stimulation directly accelerates cell motility and whether specific MAPK pathways are required. This combined approach provides both clinical relevance and mechanistic detail regarding TF-mediated trophoblast motility.

MATERIALS AND METHODS

Bioinformatics analysis

Data source and rationale

Genomic data were accessed through the Gene Expression Profiling Interactive Analysis 2 (GEPIA2) web server, utilizing publicly available RNA-sequencing data from The Cancer Genome Atlas (TCGA) project. While this study focuses on trophoblasts, large datasets of primary first-trimester placental tissue are limited. Therefore, we selected gynecological malignancies as biological models because they exhibit key invasive traits paralleling trophoblasts: epithelial origin, capacity for tissue invasion, and reliance on similar molecular machinery, including epithelial-mesenchymal transition (EMT) pathways. We analyzed three cohorts: Uterine Corpus Endometrial Carcinoma (UCEC; n=174), Ovarian Cancer (OV; n=426), and Uterine Carcinosarcoma (UCS; n=57). UCEC represents epithelial tumors of the endometrium, the precise tissue site invaded by trophoblasts. OV is a highly aggressive malignancy with documented TF expression and peritoneal invasion. UCS is a mixed tumor exhibiting epithelial-mesenchymal plasticity, modeling the cellular flexibility needed for invasion (Tang *et al.*, 2019).

Correlation analysis

Spearman's rank correlation analysis determined relationships between *F3* (TF gene) and *CDH1* (E-cadherin gene) expression. We calculated correlation coefficients (R) and corresponding p-values to assess monotonic relationships between these variables. To ensure specificity, we also performed correlation analysis between *F3* and *CDH2* (N-cadherin), a different adhesion molecule often associated with the mesenchymal state.

Protein-protein interaction networks

Networks were constructed using the STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) database version 11.5 (Abou-Kheir *et al.*, 2017). We initiated networks with seed nodes (*F3, F7, F2RL1* representing the TF, Factor VII, and PAR-2 genes) and the target node *CDH1* (E-cadherin), querying for connections to MAPK pathway members (MAP2K1, MAPK3, JUN, FOS). Medium confidence interaction scores (≥0.400) were applied, incorporating evidence from experimental data, co-expression patterns, and text-mining analysis.

In vitro functional assays

Cell line and culture conditions

HTR-8/SVneo cells (human extravillous trophoblast cells immortalized with SV40 large T antigen) were selected for this investigation. This cell line maintains the phenotypic characteristics of primary invasive EVTs and is widely accepted as a standard model for studying placental invasion (Haider *et al.*, 2018), (Jung *et al.*, 2022). Cells were cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum and antibiotics (penicillin/streptomycin, 1%) at 37°C in 5% CO_2. Cells were used during logarithmic growth phase (60–80% confluency) to ensure metabolic consistency across experiments.

Scratch wound healing assay

Cell migration was quantified using scratch wound healing assay, an established method for studying collective epithelial cell migration. HTR-8/SVneo cells were seeded into 6-well plates and cultured to 95-100% confluency, forming a complete monolayer. A reproducible cell-free gap was created by dragging a sterile 200 µL pipette tip across the well center. Wells were washed twice with sterile PBS to remove floating cellular debris, ensuring that cells subsequently observed in the gap had actively migrated there. Cells were incubated with serum-reduced medium containing vehicle control (DMSO), recombinant human FVIIa (Merck) at concentrations of 1 nM, 2

nM, or 4 nM, or FVIIa with pre-treatment (1 hour) of either the JNK inhibitor SP600125 (5 μM) or the MEK inhibitor U0126 (10.6 μM). Phase-contrast images were captured at T=0 (immediately post-scratch) and T=24 hours using identical field positions. Cell-free gap area was measured using ImageJ software. Migration rate was calculated as percentage of wound closure over 24 hours: Relative Migration Rate (RMR %) = [(relative area of sample / relative area of control) × 100].

Statistical analysis

All functional experiments were performed in independent triplicates. Data are expressed as Mean ± Standard Error of the Mean (SEM). Statistical significance was determined using one-way ANOVA followed by Tukey's post-hoc test using GraphPad Prism software. A p-value < 0.05 was considered statistically significant. Correlation coefficients were calculated using Spearman's rank correlation analysis.

RESULTS

Genomic correlation between TF and E-cadherin in invasive tissues

To establish clinical relevance of TF signaling in invasive tissues, we interrogated TCGA datasets for correlations between *F3* (TF) and *CDH1* (E-cadherin) expression. A statistically significant positive correlation was observed across all three gynecological cohorts (Fig. 1). The strongest correlation appeared in Uterine Carcinosarcoma (R=0.48, p=0.00017, n=57)—a tumor characterized by epithelial-mesenchymal plasticity.

Ovarian Cancer showed a moderate correlation (R=0.28, p=5.10E-09, n=426), while Uterine Corpus Endometrial Carcinoma exhibited a weaker but still significant correlation (R=0.21, p=0.045, n=174).

This positive relationship challenges the classical "cadherin switch" model of invasion, which predicts that cells must lose E-cadherin to become migratory. Instead, our data align with emerging concepts of "partial EMT" or "hybrid epithelial-mesenchymal" states. In this hybrid state, cells acquire migratory properties while retaining epithelial adhesion markers. For trophoblasts, this phenotype offers biological advantages: EVTs invade as cohesive columns, requiring E-cadherin to maintain intercellular communication while utilizing TF signaling to drive migration. To ensure specificity, we analyzed the correlation between TF and N-cadherin (CDH2). No significant correlation was observed between these molecules in any cohort, reinforcing the specificity of the TF-E-cadherin relationship.

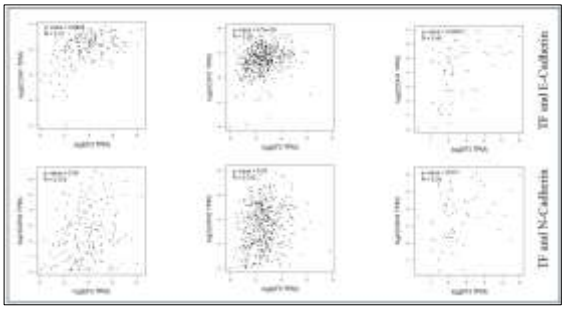

Fig. 1. Spearman's correlation between TF (F3) and E-cadherin (CDH1) across gynecological malignancies. Correlation analysis in (Left) Uterine Corpus Endometrial Carcinoma, (Middle) Ovarian Cancer, and (Right) Uterine Carcinosarcoma. Analysis used RNA-seq data from 657 patient samples from TCGA via GEPIA2 (Tang *et al.*, 2019). R = Spearman's rank correlation coefficient; p < 0.05 considered significant.

Protein-protein interaction network analysis

PPI network analysis identified a multi-tiered signaling hierarchy linking TF to adhesion regulation (Fig. 2). The network revealed high-confidence interactions between the TF:FVIIa complex and PAR-2 (F2RL1), validating PAR-2 as the primary signaling transducer. Robust connections linked PAR-2 to MAP2K1 (MEK1) and MAPK3 (ERK1), positioning MAPK pathways as immediate downstream effectors of the receptor complex.

Connections extended from MAPKs to AP-1 complex members (JUN, FOS)—known targets of JNK and ERK phosphorylation. The network integrated

interactions between these transcription factors and CDH1, delineating a signaling pathway from the extracellular TF: FVIIa complex to intracellular adhesion regulation: TF:FVIIa → PAR-2 → MEK/JNK → AP-1 → E-cadherin.

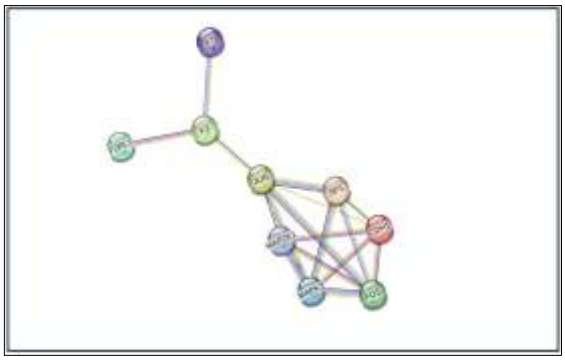

Fig. 2. STRING protein-protein interaction network showing potential linkages between TF: FVIIa signaling and E-cadherin. Network initialized with genes encoding TF signaling components (F3, F7, F2RL1) and MAPK pathway members (MAP2K1, MAPK3, JUN, FOS), queried for connections to CDH1. Network constructed using STRING v11.5 with medium confidence threshold (score ≥0.4) (Abou-Kheir *et al.*, 2017).

FVIIa induces dose-dependent migration in trophoblasts

HTR-8/SVneo cells were subjected to scratch wound assay in the presence of recombinant FVIIa at increasing concentrations (1 nM, 2 nM, 4 nM). Visual inspection of wound areas at 24 hours revealed progressive narrowing of the scratch gap in FVIIa-treated cells compared to controls, which retained wider gaps indicating slower basal motility. Quantitative analysis confirmed statistically significant, dose-dependent increases in relative migration rate (RMR). Control cells displayed approximately 22% basal migration. Treatment with 1 nM FVIIa increased migration to ~35%, while 2 nM and 4 nM FVIIa accelerated migration to approximately 60% and 70%, respectively (Fig. 3). These results demonstrate that FVIIa acts as a potent chemoattractant for trophoblasts, with 4 nM producing maximal migratory response.

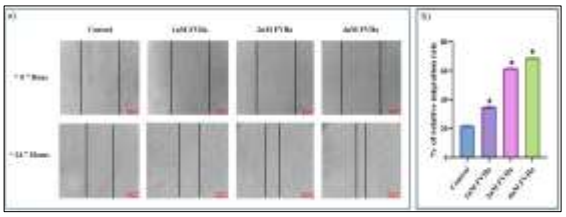

Fig. 3. FVIIa induces dose-dependent migration in HTR-8/SVneo cells. (a) Representative phase-contrast images at T=0 and T=24 hours. (b) Quantification of relative migration rate following FVIIa treatment (1, 2, 4 nM) versus control. Data presented as mean ± SEM; *p < 0.05 vs. control.

JNK signaling is essential for FVIIa-mediated migration

To determine whether JNK acts as a downstream transducer, cells were pre-treated with the selective JNK inhibitor SP600125. SP600125 alone resulted in approximately 28% relative migration rate, slightly lower than untreated controls (~32%) that suggesting basal JNK activity contributes to intrinsic trophoblast motility. Upon FVIIa stimulation, migration rate surged to ~63%. However, pre-treatment with SP600125 significantly reduced this FVIIa-induced response to ~43% (Fig. 4). Visual analysis confirmed these findings: FVIIa-only cells showed near-complete wound closure, whereas SP600125 + FVIIa co-treated cells retained visibly wider gaps resembling control conditions. This partial blockade confirms that JNK signaling is a critical component of the machinery required for full TF:FVIIa pro-migratory effect.

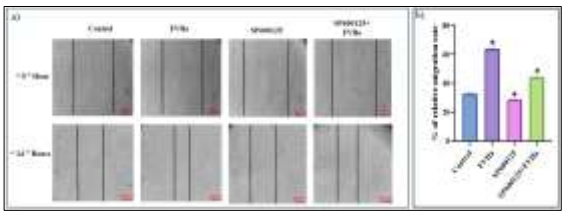

Fig. 4. JNK inhibition reduces FVIIa-induced cell migration. (a) Representative images showing wound closure at T=24 hours. (b) Quantification of relative migration rate with FVIIa, JNK inhibitor SP600125, or combination treatment versus control. Data presented as mean ± SEM; *p< 0.05 vs. control.

MEK pathway inhibition abrogates FVIIa-induced migration

We investigated the MEK/ERK signaling axis using selective MEK inhibitor U0126. Application of U0126 alone profoundly suppressed basal motility, reducing relative migration rate to ~22% compared to ~35% in control groups indicating strong MEK dependence for baseline trophoblast movement. While FVIIa treatment alone robustly stimulated migration to ~60%, this effect was markedly inhibited in U0126-treated cells. Cells co-treated with U0126 + FVIIa exhibited migration rate of ~40%, effectively returning motility to baseline control values (Fig. 5). Morphologically, wounds in the U0126 + FVIIa group remained largely open at 24 hours, contrasting sharply with narrow gaps in FVIIa-only cells. These results demonstrate that MEK signaling is a non-redundant and essential driver of both basal and FVIIa-stimulated trophoblast migration.

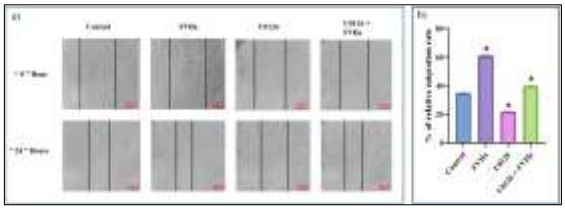

Fig. 5. MEK inhibition abolishes FVIIa-induced cell migration. (a) Representative phase-contrast images at T=24 hours. (b) Quantification of relative migration rate following FVIIa, MEK inhibitor U0126, or combined treatment versus control. Data presented as mean ± SEM; *$p < 0.05$ vs. control.

DISCUSSION

This study provides the first comprehensive functional evidence that the TF:FVIIa complex directly stimulates trophoblast migration through coordinated activation of the MEK and JNK signaling pathways. The dose-dependent acceleration of wound closure upon FVIIa stimulation offers definitive proof that TF signaling drives trophoblast motility, with cellular sensitivity to FVIIa concentration suggesting that *in vivo*, physiological FVIIa gradients originating from maternal blood could serve as chemotactic cues guiding trophoblast invasion into the maternal decidua (Gupta *et al.*, 2016; Knöfler *et al.*, 2019). A striking finding was the positive correlation between *F3* and *CDH1* in invasive tissues, which challenges classical epithelial-mesenchymal transition (EMT) theory predicting that invasion requires loss of E-cadherin (Leung *et al.*, 2022). Our data instead support emerging concepts of "partial EMT" or "hybrid epithelial-mesenchymal" phenotypes (Leung *et al.*, 2022; Gui *et al.*, 2012). In this hybrid state, cells gain migratory capabilities without completely sacrificing epithelial identity, which is biologically advantageous for trophoblasts that invade as cohesive columns or streams, requiring E-cadherin to maintain intercellular connectivity while simultaneously utilizing TF signaling as the molecular engine of invasion (Gui *et al.*, 2012). The positive correlation in TCGA data likely reflects invasive cells that upregulate *F3* to enable migration while maintaining *CDH1* expression to preserve tissue integrity during decidual invasion (Gupta *et al.*, 2016; Knöfler *et al.*, 2019).

Functional migration assays unequivocally demonstrate that TF:FVIIa signaling drives motility through coordinated activation of MEK and JNK pathways, with the critical observation that blocking either pathway results in complete migration failure (Li *et al.*, 2022; Gundappa *et al.*, 2022). This non-redundant requirement suggests a coordinated program where JNK may drive leading-edge cytoskeletal dynamics including actin polymerization and focal adhesion turnover, while MEK/ERK manages adhesion remodeling and metabolic support for sustained migration (Li *et al.*, 2022; Gundappa *et al.*, 2022; Lee *et al.*, 2020; Guo *et al.*, 2020). These pathways integrate multiple signaling inputs through downstream transcription factors and adhesion regulators, indicating that TF: FVIIa functions as a molecular switch operating through integrated signaling cascades rather than parallel backup systems (Ruf *et al.*, 2011; Lee *et al.*, 2020). Recent evidence demonstrates that MAPK pathways play central roles in trophoblast invasion, with ERK1/2 involved in regulating cytoskeletal reorganization and cell matrix interactions (Lee *et al.*, 2020; Gui *et al.*, 2012). The requirement for both MEK and JNK

activation suggests that TF:FVIIa signaling recruits multiple molecular checkpoints to ensure robust regulation of trophoblast motility.

Preeclampsia is fundamentally a disease of shallow trophoblast invasion, and this study positions the TF: FVIIa axis as a potential pathological locus in preeclampsia-related complications (Gupta *et al.*, 2016; Ives *et al.*, 2020; Hod *et al.*, 2015). If TF signaling is required for EVT migration, then any disruption whether from reduced ligand availability, receptor dysfunction, inflammatory mediator interference, or pathway inhibition could precipitate the shallow invasion phenotype underlying preeclampsia and fetal growth restriction (Gupta *et al.*, 2016; Ives *et al.*, 2020; Hod *et al.*, 2015). Understanding this axis may identify therapeutic targets for enhancing trophoblast function in pregnancy disorders and for developing selective TF:FVIIa-PAR2 antagonists that could offer novel therapeutic approaches for complications arising from excessive trophoblast invasion such as placenta accreta or from insufficient invasion such as preeclampsia (Ives *et al.*, 2020; Hod *et al.*, 2015; Redecha *et al.*, 2008). The striking parallels between trophoblast invasion and cancer cell metastasis reveal that both processes share fundamental molecular machinery including proteolytic degradation of tissue barriers, coordinated migration, and interaction with host vasculature (Ruf *et al.*, 2011; D'Alessandro *et al.*, 2018; Lee *et al.*, 2020). Cancer may represent a pathological reactivation of the dormant physiological program of placental implantation, with both contexts relying on TF-mediated signaling as a driver of invasiveness (Ruf *et al.*, 2011; D'Alessandro *et al.*, 2018). This biological kinship suggests that insights from placental biology may inform cancer therapy and vice versa, and future studies should investigate whether TF:FVIIa-PAR2 signaling dysregulation contributes to both pregnancy complications and metastatic disease (Ruf *et al.*, 2011; D'Alessandro *et al.*, 2018; Redecha *et al.*, 2008).

A strength of this investigation is the combined approach integrating genomic correlation analysis, protein-protein interaction network mapping, and functional migration assays to establish clinical relevance, identify mechanistic pathways, and provide direct evidence of biological function. However, limitations warrant discussion. First, cancer cell datasets were used as proxies for invasive tissues; while gynecological malignancies share key features with trophoblasts, they are not identical models (Tang *et al.*, 2019). Second, the HTR-8/SVneo cell line, while well-established and widely accepted for studying placental invasion, is a finite cell line rather than primary tissue (Haider *et al.*, 2018; Jung *et al.*, 2022). Future studies using primary EVT cells or tissue explants would strengthen these findings. Third, this study focused on MEK and JNK pathways; other MAPK members including ERK5 and p38, as well as non-MAPK pathways such as phosphoinositide 3-kinase (PI3K)/AKT signaling, may also contribute to TF-mediated migration (Mackman *et al.*, 2009; Lee *et al.*, 2020; Gui *et al.*, 2012). Future investigations should examine crosstalk between MEK and JNK signaling, identify specific downstream targets of these kinases relevant to migration such as focal adhesion remodeling and cytoskeletal dynamics, investigate whether TF:FVIIa signaling influences trophoblast differentiation or syncytialization in addition to migration, and conduct comparative analysis of TF expression and signaling in preeclamptic versus normal placentae to determine whether TF pathway dysregulation contributes to placental insufficiency (Gupta *et al.*, 2016; Ives *et al.*, 2020; Hod *et al.*, 2015).

CONCLUSION

This study establishes the TF: FVIIa complex as a critical regulator of trophoblast motility through coordinated MEK/JNK pathway activation, redefining Tissue Factor as a dual-purpose molecule at the feto-maternal interface that simultaneously serves as a guardian of hemostasis and a molecular engine of trophoblast invasion. By elucidating this mechanism, the study provides a foundation for understanding pathological conditions of placentation and for developing targeted

interventions addressing these major causes of maternal and fetal morbidity.

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