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RESEARCH ARTICLE

Tissue Factor: Factor VIIa Signaling Induces E-cadherin Downregulation in Extra villous Trophoblasts via Parallel MEK and JNK Pathway Activation

Kirthika Manoharan [1], Shanmugam Velayuthaprabhu[2], Jagadish Krishnan[1], Paranitharan Nagarajan [2], Vijaya Anand Arumugam[3], Shenbagam Madhavan [1]*

[1]Department of Biochemistry and Biotechnology, Annamalai University, Chidambaram, India
[2] Reproductive Immunology and Molecular Pathology Laboratory, Department of Biotechnology, Bharathiar University, Coimbatore, India.
[3]Department of Human Genetics and Molecular Biology, Bharathiar University, Coimbatore, India

*Corresponding Author
Dr. M. Shenbagam

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Abstract: Successful human pregnancy is contingent upon the invasion of extravillous trophoblasts (EVTs) into the maternal uterus to establish adequate uteroplacental circulation. This process requires a shift to a migratory phenotype, hallmarked by the downregulation of the cell-cell adhesion molecule E-cadherin. though the importance of E-cadherin loss is established, the upstream signals triggering this event are not fully elucidated. Tissue Factor (TF), the initiator of the extrinsic coagulation cascade, also functions as a signaling receptor when complexed with its ligand, Factor VIIa (FVIIa). This study investigates the hypothesis that TF:FVIIa signaling regulates E-cadherin expression in EVTs. Using the human first-trimester EVT cell line HTR-8/SVneo, we demonstrated that stimulation with FVIIa induces a dose-dependent downregulation of E-cadherin at the mRNA levels. Mechanistically, FVIIa treatment triggers the robust phosphorylation and activation of Mitogen-activated Protein Kinase Kinase (MEK) and c-Jun N-terminal Kinase (JNK). Pharmacological inhibition of the MEK pathway using U0126, or JNK pathway using SP600125, was sufficient to abrogate FVIIa-induced E-cadherin downregulation. These findings reveal a novel, non-hemostatic signaling axis in human trophoblasts where the TF:FVIIa complex orchestrates the suppression of a key epithelial marker through the parallel and co-dependent activation of the MEK and JNK pathways. This pilot study provides a direct link between a coagulation-initiating complex and the molecular machinery of cellular invasion, offering new insights into the regulation of placentation and its potential dysregulation in pregnancy-related disorders.

Keywords: Tissue Factor, Factor VIIa, E-cadherin, Trophoblast, Cell Signaling.

INTRODUCTION

The establishment of a functional placenta is a prerequisite for a healthy pregnancy, mediating the critical exchange of nutrients, gases, and waste between the maternal and fetal systems. Central to this process is the highly specialized function of extra villous trophoblasts (EVTs), which originate from cytotrophoblast progenitor cells in the anchoring villi of the placenta [1-2]. During the first trimester, EVTs invade the maternal decidua and extensively remodel the uterine spiral arteries. This physiological conversion transforms the arteries from narrow, high-resistance vessels into wide, low-resistance conduits, a crucial adaptation for ensuring a sufficient and stable blood supply to the developing fetus. Deficiencies in this invasive process, resulting in shallow placentation, are a primary pathogenic feature of severe pregnancy complications, most notably preeclampsia and fetal growth restriction (FGR) [3-4].

To acquire their invasive capacity, EVTs undergo a precisely regulated cellular transformation analogous to an epithelial-mesenchymal transition (EMT). This process involves the dissolution of stable cell-cell junctions and the adoption of a migratory, mesenchymal-like phenotype [5]. A cornerstone of this transition is the modulation of cell adhesion molecules, particularly E-cadherin (encoded by the *CDH1* gene). As a key component of epithelial adherens junctions, E-cadherin maintains the structural integrity of the trophoblast cell layer. Consequently, its downregulation is a hallmark of EMT and an indispensable step for trophoblast detachment from the villous cell column, enabling the initiation of invasion into the maternal endometrium [6-7]. While the necessity of E-cadherin suppression is well-documented, the specific upstream signals within the uterine microenvironment that trigger this pivotal event remain incompletely understood.

Tissue Factor (TF), also known as coagulation factor III, is a transmembrane glycoprotein traditionally recognized as the primary initiator of the extrinsic coagulation cascade. However, a growing body of evidence has redefined TF as a multifaceted signaling receptor, capable of initiating intracellular signaling cascades independent of its role in coagulation [8]. This non-hemostatic signaling by the TF:FVIIa complex regulates a wide array of cellular processes, including inflammation, angiogenesis, and cell migration, often through the activation of Mitogen-activated Protein Kinase (MAPK) pathways [9-10]. Given the known roles of TF:FVIIa in promoting migration and the established function of MAPK pathways in this process,

we hypothesized that TF:FVIIa complex formation on the surface of extravillous trophoblasts triggers the downregulation of E-cadherin by activating the MEK and JNK signaling pathways, thereby promoting a molecular switch conducive to invasion.

MATERIAL AND METHODS

2.1 Cell Culture and Reagents

HTR-8/SVneo cells, a well-characterized immortalized human first-trimester extravillous trophoblast cell line obtained from the American Type Culture Collection (ATCC, USA), were maintained under standard cell culture conditions. The cells were cultured in DMEM Ham's F-12 medium supplemented with 10% heat-inactivated FBS and 1% G418 antibiotic selection solution to maintain the selective pressure for transformed cells. Cultures were maintained in a humidified atmosphere containing 5% CO_2 at 37°C in a CO_2 incubator. Regular subculturing was performed using 0.25% trypsin-EDTA solution when cells reached 70-80% confluence to ensure optimal growth conditions and prevent contact inhibition. MDA-MB-231 breast cancer cells were employed as a positive control for comparative tissue factor expression analysis due to their well-documented high tissue factor expression levels.

2.2 Cell treatments to study TF-dependent *E-Cadherin* regulation

HTR-8/SVneo cells were seeded in 6-well plates and grown to approximately 80% confluency. Prior to treatment, cells were serum-starved for 12 hours in RPMI-1640 medium without FBS to minimize basal kinase activity. For dose-response experiments to assess *E-cadherin* expression, cells were treated with FVIIa at concentrations of 1 nM, 2 nM, and 4 nM for 24 hours. For inhibitor studies, cells were pre-treated for 24 hours with either 10.6 µM U0126, 5 µM SP600125, or an equivalent volume of vehicle (DMSO). Following pre-treatment, cells were stimulated with 4 nM FVIIa for 30 minutes to analyze kinase phosphorylation, and for 24 hours to analyze total *E-cadherin* mRNA levels.

2.3 Semi-Quantitative Reverse Transcriptase PCR (RT-PCR)

To investigate the downstream effects of FVIIa treatment, *E-Cadherin* (*CDH1*) gene expression was evaluated using reverse transcription polymerase chain reaction (RT-PCR) analysis. HTR-8/SVneo cells were seeded in T-25 tissue culture flasks and allowed to reach approximately 70% confluence before treatment. Cells were then exposed to recombinant FVIIa (Merck, USA), U0126 (a specific MEK1/2 inhibitor), or SP600125 (a selective JNK inhibitor) according to the experimental design. Following treatment, total RNA was isolated using Trizol reagent (Invitrogen, California, USA) according to the manufacturer's protocol. RNA quality and quantity were assessed, and approximately 2 µg of total RNA was used for complementary DNA (cDNA) synthesis using the PrimeScript 1st strand cDNA synthesis kit (TaKaRa Bio, Japan). PCR amplification was performed using a QIAamplifier 96 thermal cycler (Qiagen, USA) with the following cycling conditions: initial denaturation at 95°C for 4 minutes, followed by 35 cycles of denaturation at 94°C for 1 minute, primer annealing at 58°C for 45 seconds, and extension at 72°C for 1 minute. Gene-specific primer sequences were designed and synthesized as follows: *E-Cadherin* (*CDH1*) forward primer: 5'-TGC CCA GAA AAT GAA AAA GG-3', reverse primer: 5'-GTG TAT GTG GCA ATG CGT TC-3'; *β-actin* forward primer: 5'-CTT GCG GTA TCC ACG AGAC-3', reverse primer: 5'-GCG CCA TAC AGA GCA GAA-3'. *β-actin* (*ACTB*) was employed as an internal housekeeping gene control for normalization of gene expression levels. Each experimental condition was performed in triplicate wells and repeated across three independent experiments to ensure statistical reliability.

2.4 Western Blot Analysis

Cells were lysed on ice with RIPA buffer supplemented with protease and phosphatase inhibitor cocktails. Protein concentrations were determined using Lowry's method and equal amounts of protein (30 µg) were separated by SDS-PAGE and transferred to a PVDF membrane. Membranes were blocked for 1 hour at room temperature with 5% non-fat dry milk in Tris-buffered saline with 0.1% Tween-20 (TBST). Membranes were then incubated overnight at 4°C with specific primary antibodies (Table 1). After washing, membranes were incubated with HRP-conjugated secondary antibodies for 1 hour at room temperature. Protein bands were visualized using an enhanced chemiluminescence (ECL) detection system. Densitometric analysis was performed using ImageJ software.

Reagent Type	***Reagent Name***	***Target/Specificity***	***Source & Catalog No.***	***Working Concentration/Dilution***
Recombinant Protein	Recombinant Human FVIIa	Activates Tissue Factor	Merck, USA	1, 2, 4 nM
Inhibitor	U0126	MEK1/2 inhibitor	Sigma-Aldrich	10.6 µM
Inhibitor	SP600125	JNK inhibitor	Sigma-Aldrich	5 µM
Primary Antibody	Anti-pMEK1	Phospho-MEK1 (Ser217/221)	Cell Signaling Technology, 9154T	1:1000
Primary Antibody	Anti-pJNK	Phospho-JNK (Thr183/Tyr185)	Cell Signaling Technology, 4668T	1:1000
Primary Antibody	Anti-E-Cadherin	E-Cadherin (CDH1)	Cell Signaling Technology, 3195T	1:1000
Primary Antibody	Anti-GAPDH	GAPDH	Cell Signaling Technology, 5174	1:2000
Secondary Antibody	HRP-conjugated anti-rabbit	Rabbit IgG	Cell Signaling Technology, 7074	1:2000

Table 1: Detailed Reagents and Antibodies used in this study

2.5 Statistical Analysis

All experiments were performed in triplicate. Data are presented as the mean ± standard error of the mean (SEM). Statistical analysis was performed using GraphPad Prism 10.0. Comparisons between multiple groups were analyzed by one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test. A p-value of less than 0.05 was considered statistically significant.

RESULTS AND OBSERVATIONS:

3.1 Expression and comparative analysis of TF in HTR-8/SVneo

The expression profile of tissue factor (TF) in HTR-8/SVneo cells was evaluated to confirm its presence in this extravillous trophoblast-derived cell line. Reverse transcription-polymerase chain reaction (RT-PCR) analysis demonstrated detectable *TF* mRNA expression in both HTR-8/SVneo cells and the MDA-MB-231 breast cancer cell line, which served as a positive control. Quantitative assessment revealed that TF transcript levels in HTR-8/SVneo cells were approximately 0.5-fold lower relative to MDA-MB-231 cells (Fig.1). mRNA expression data were normalized against *β-actin* as an internal reference. Subsequently, TF protein expression was assessed via western blot analysis. Consistent with the transcript data, TF protein was readily detected in both HTR-8/SVneo and MDA-MB-231 cells (Fig.2). Densitometric quantification of immunoblot bands indicated that TF protein levels in HTR-8/SVneo cells were reduced by approximately 50% compared to MDA-MB-231 cells, following normalization to GAPDH. Collectively, these findings confirm that TF is constitutively expressed at both the mRNA and protein levels in HTR-8/SVneo cells, albeit at a lower abundance compared to MDA-MB-231 cells.

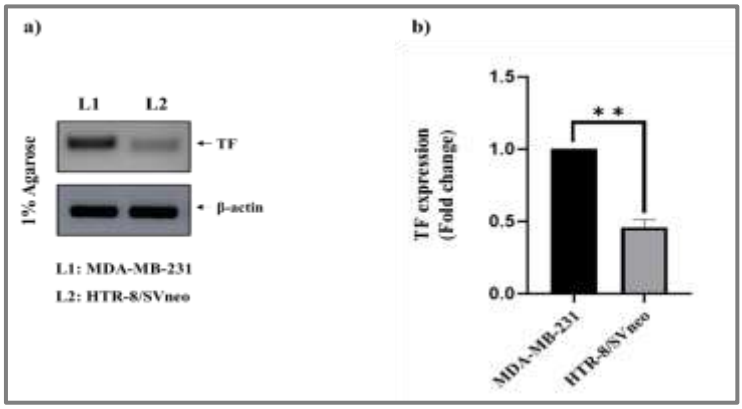

Fig.1. Gene expression and comparative analysis of TF in HTR-8/SVneo: (a) RT-PCR analysis demonstrated TF expression in HTR-8/SVneo trophoblasts and MDA-MB-231 cells, used as a positive control. Graphical representation of TF fold change expression. (b) Data from experiments performed in triplicate were analyzed and presented as Mean ± S.D. The fold change in TF expression was found to be significant at $^{**}p < 0.001$ between HTR-8/SVneo trophoblasts and MDA-MB-231 cells (positive control).

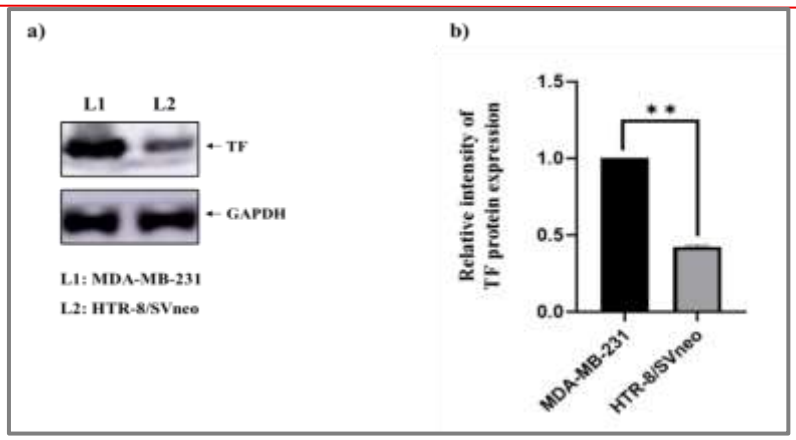

Fig.2. Protein expression and comparative analysis of TF in HTR-8/SVneo: (a) Western blot analysis showing TF expression in HTR-8/SVneo trophoblasts. (b) Densitometry analysis comparing TF expression levels in HTR-8/SVneo and MDA-MB-231 cells. Data were collected from triplicate experiments and are presented as Mean ± S.D. The TF expression in HTR-8/SVneo trophoblasts was significant (**$p < 0.001$) when compared to that of MDA-MB-231 cells (positive control).

3.2 TF:FVIIa Signaling Downregulates E-cadherin Expression in HTR-8/SVneo Cells

To determine if TF:FVIIa signaling dysregulates E-cadherin, HTR-8/SVneo cells were treated with increasing concentrations of FVIIa. Semi-quantitative RT-PCR analysis showed that FVIIa treatment for 24 hours resulted in a dose-dependent decrease in *CDH1* mRNA (*E-cadherin*). As shown in figure 3, densitometric analysis revealed approximately 0.1-fold, 0.4 -fold, and 0.7-fold decrease in *CDH1* mRNA levels at 1, 2, and 4 nM FVIIa, respectively, compared to the untreated control ($p<0.05$). This finding indicates that activation of TF signaling transcriptionally represses the E-cadherin gene in trophoblast cells.

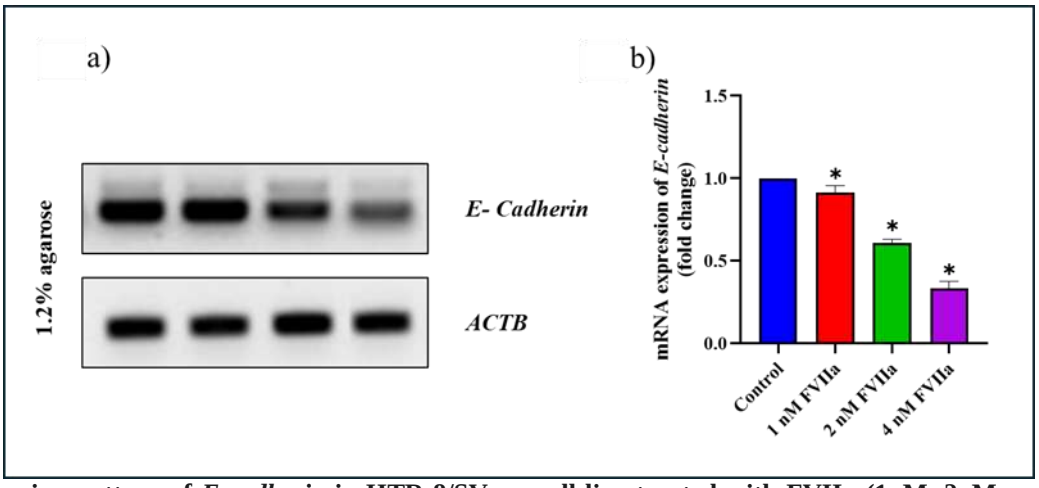

Fig.3. Expression pattern of *E-cadherin* in HTR-8/SVneo cell line treated with FVIIa (1nM, 2nM and 4nM): (a) Gene expression patterns of *E-cadherin.* (b) Graphical representation of *E-Cadherin* fold change expression. Data from experiments performed in triplicate were analyzed and presented as Mean ± S.D. The fold change in *E-cadherin* expression was found to be significant when compared to control sample (*$p < 0.05$).

3.3 The MEK Pathway is Required for TF:FVIIa-Mediated E-cadherin Downregulation

To investigate the involvement of the MEK/ERK pathway, we assessed its activation status and the effect of its inhibition on E-cadherin expression. As shown in the representative Western blots in **Figure 4**, treatment with 4 nM FVIIa led to a significant increase in the phosphorylation of MEK1/2 (upper panel). Densitometric analysis showed a 0.2-fold increase in MEK phosphorylation compared to control cells ($p<0.01$). This activation was blocked by pre-treatment with the specific MEK1/2 inhibitor, U0126. Concurrently, FVIIa treatment markedly reduced E-cadherin protein expression to 0.6-fold of control levels (middle panel, $p<0.01$). Importantly, pre-treatment with U0126 significantly reversed this effect, restoring E-cadherin protein expression to near control levels, even in the presence of FVIIa. The loading control (GAPDH) confirmed equal protein loading across all lanes (lower panel). These results demonstrate that the MEK pathway is a critical downstream mediator of TF:FVIIa-induced E-cadherin suppression.

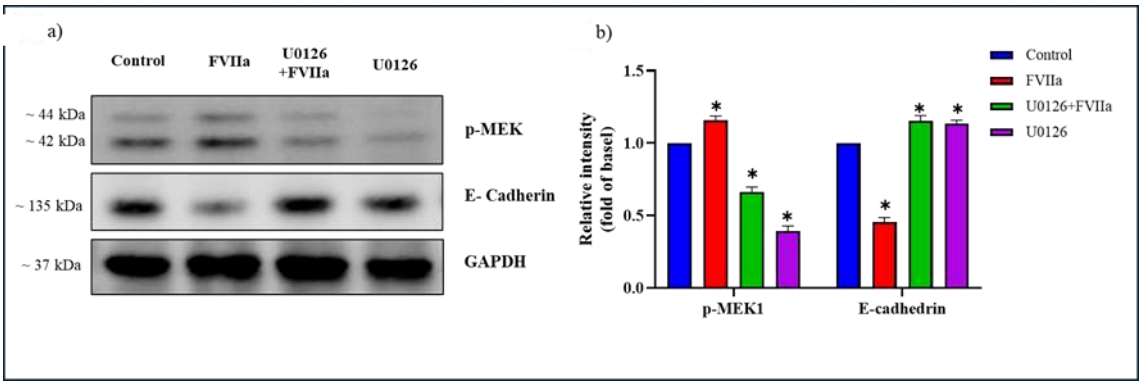

Fig.4. Tissue factor-dependent MEK signaling transduction and E-cadherins regulations in HTR-8/SVneo cell line: (a) Western blot analysis of pMEK1 and E-cadherin expression in HTR8/SVneo cells treated with FVIIa (4 nM) or/and U0126 (10.6 µM). The upper panel shows the expression pattern of pMEK1 in HTR8/SVneo cells. Middle panel shoes the expression of E-Cadherin and lower panel shows the expression of GAPDH. Statistical analysis was performed in graph pad prism. (b) Graphical representation of relative intensity of respective protein expression. Data were obtained & analysed from experiments carried out in triplicates, expressed as Mean ± SD and the values were significant at *p < 0.05.

3.4 TF:FVIIa-Induced E-cadherin Suppression is Dependent on JNK Pathway Activation

We next explored the role of the JNK pathway in this process. As shown in Figure 5, stimulation of HTR-8/SVneo cells with 4 nM FVIIa induced a rapid and robust phosphorylation of JNK (upper panel). Quantification revealed a 0.6-fold increase in p-JNK levels compared to the control ($p<0.01$). This FVIIa-induced JNK activation was effectively prevented by pre-treatment with the JNK inhibitor SP600125. In parallel, FVIIa treatment led to a significant downregulation of E-cadherin protein (middle panel). Inhibition of the JNK pathway with SP600125 substantially rescued this FVIIa-mediated decrease in E-cadherin, maintaining its levels near those of the control group. The loading control ensured equal protein loading (lower panel). This result indicates that, similar to the MEK pathway, the JNK pathway is an essential component of the signaling cascade linking TF:FVIIa to E-cadherin regulation.

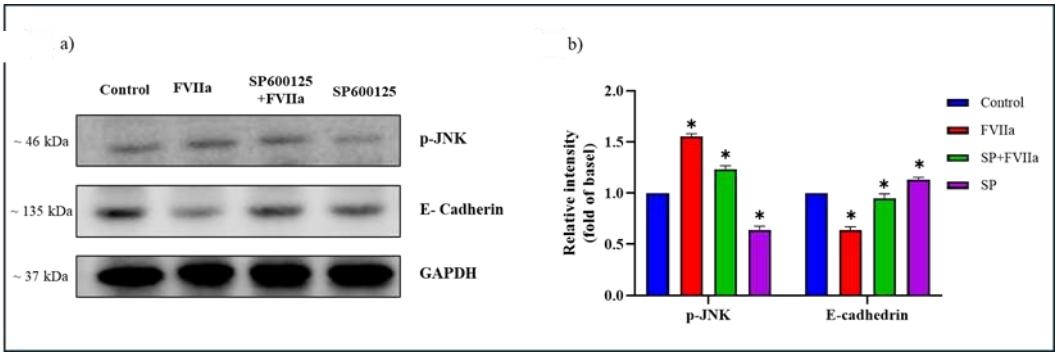

Fig.5. Tissue factor-mediated JNK signaling transduction and its importance in E-cadherins regulations in HTR-8/SVneo cell line: (a) The images represent the WB analysis carried out for the expression of p-JNK and E-cadherin in HTR8/SVneo cells with FVIIa or JNK inhibitor (SP600125; 5 µM) with or without FVIIa. GAPDH used as a positive control. The upper panel shows the expression pattern of JNK in HTR8/SVneo cells. Middle panel shoes the expression of E-Cadherin and lower panel shows the expression of GAPDH. (b) Graphical representation of relative intensity of respective protein expression. Data were obtained & analysed from experiments carried out in triplicates, expressed as Mean ± SD and the values were significant at *p < 0.05.

DISCUSSION

The development of the placenta represents one of the most remarkable biological processes in human reproduction, characterized by intricate cellular and molecular mechanisms that ensure successful pregnancy outcomes. This highly dynamic organ undergoes continuous remodeling through well-coordinated processes including trophoblast differentiation, invasion, vascular remodeling, and immune regulation. Understanding these fundamental mechanisms is crucial for identifying and managing pregnancy-related complications that affect maternal and fetal health.

Trophoblast invasion into maternal tissues constitutes a critical step in successful implantation and placentation. While tissue factor (TF) has been extensively studied in coagulation and cancer biology, its specific roles in

trophoblast cells and placental functions remain inadequately understood. Yamakage et al. demonstrated that TF expression is upregulated during early pregnancy and plays a crucial role in trophoblast invasion into maternal tissues [9]. However, limited evidence exists regarding TF expression and its influence on cellular adhesion molecules, particularly cadherins, in HTR-8/SVneo cells, despite significant implications for placental development and pregnancy-related disorders.

Our investigation aimed to examine the crosstalk between TF and E-cadherin in HTR-8/SVneo cells, using MDA-MB-231 cells as a positive control due to their constitutive TF expression, which contributes to cancer-associated thrombosis [11]. Importantly, our findings confirmed robust TF expression in HTR-8/SVneo cells at both gene and protein levels, with expression patterns consistent between these two analytical approaches. These results align with previous findings that confirmed TF presence and expression in human trophoblast cells [12].

The formation of the TF-FVIIa complex represents a pivotal molecular event with implications beyond hemostasis. Recent studies have demonstrated that the Tissue Factor (TF):Factor VIIa complex can upregulate the expression of adhesion molecules, such as integrins, through activation of the MAPK signaling pathway. This suggests a potential role for TF:FVIIa signaling in modulating cell adhesion and promoting cellular interactions with the extracellular matrix, which may contribute to processes like invasion and metastasis. [10]. Given the critical importance of the TF-FVIIa complex in both cancer biology and placental function, our study focused on investigating the molecular link between this complex and E-cadherin regulation in trophoblast cells.

This study identifies a novel signaling pathway in human extra villous trophoblasts where the non-hemostatic TF:FVIIa complex orchestrates the downregulation of E-cadherin. The central finding is that this regulation is mediated through the parallel and co-dependent activation of two distinct MAPK arms: the MEK and JNK pathways. These results provide a direct mechanistic link between a coagulation-initiating factor and the molecular machinery that governs the trophoblast's invasive/migration phenotype, a process fundamental to successful placentation.

The controlled invasion of EVTs into the maternal decidua is a tightly regulated process that shares molecular hallmarks with cancer cell metastasis, including the requirement for EMT. The downregulation of E-cadherin is a critical initiating step, permitting cells to lose their tight epithelial connections and become motile [13]. Our preliminary findings position the TF:FVIIa complex as a key upstream regulator of this event. At the fetal-maternal interface, EVTs are in direct contact with maternal blood and vasculature. Localized inflammation or micro-injury could lead to the generation of FVIIa, which would then bind to TF expressed on trophoblasts. This interaction may serve as a physiological cue, signaling to the EVTs that they are in the correct microenvironment to initiate their invasive program. In this context, TF:FVIIa signaling acts as a sensor and transducer, converting information from the maternal vascular state into a specific cellular response essential for placental development.

This mechanism of E-cadherin suppression acts in concert with other pro-migratory pathways initiated by TF signaling. Our previous research has established that the TF:FVIIa complex also enhances the migratory capacity of HTR-8/SVneo cells by upregulating the expression of several integrins, which are crucial for cell-matrix adhesion and motility [12]. Therefore, TF:FVIIa signaling appears to comprehensively reprogram the trophoblast's adhesive properties, shifting the balance from stable, epithelial cell-cell adhesion (via E-cadherin downregulation) towards dynamic cell-matrix interactions (via integrin upregulation) required for invasion.

The signaling axis elucidated here TF:FVIIa activating MEK and JNK pathways to promote an invasive phenotype is remarkably similar to pathways that drive metastasis in multiple cancers [14-15]. This study reinforces the concept that the molecular toolkits for physiological development and pathological progression are often shared, with the critical distinction lying in the stringency of their regulation. In placentation, this pathway is harnessed for a spatially and temporally restricted invasive process that is vital for pregnancy. In cancer, the same pathway is co-opted and dysregulated, leading to uncontrolled invasion and metastasis. These parallel highlights the importance of understanding the regulatory mechanisms of TF signaling. Dysregulation of this axis in trophoblasts could plausibly contribute to placental pathologies. Insufficient signaling could lead to the shallow invasion seen in preeclampsia, while excessive or prolonged signaling could contribute to the over-invasive phenotype observed in conditions like placenta accreta [16].

This study has several limitations. The findings are based on the HTR-8/SVneo immortalized cell line, which may not fully recapitulate the biology of primary EVTs. Furthermore, while we demonstrate a clear molecular change in E-cadherin expression, the study does not include functional assays, such as migration or invasion assays, to directly connect this molecular event to a change in cellular behavior. Future studies should aim to validate these findings in primary human trophoblast cultures and utilize functional invasion assays to confirm that MEK and JNK inhibition blocks FVIIa-induced trophoblast invasion.

CONCLUSION

In summary, this work elucidates a key molecular mechanism by which TF:FVIIa signaling regulates the invasion and migratory properties. We demonstrate that TF:FVIIa complex, acting in a non-hemostatic capacity, induces the downregulation of E-cadherin through the necessary and parallel activation of the MEK and JNK signaling pathways. These findings deepen our understanding of the molecular control of placentation and highlight a potential signaling nexus that, when dysregulated, could contribute to severe pathologies of pregnancy.

Credit authorship contribution statement

Kirthika Manoharan: Writing - original draft, Methodology, Investigation, Formal analysis. Shanmugam Velayuthaprabhu: Conceptualization, Writing - original draft, Methodology, Investigation, Formal analysis. Paranitharan Nagarajan: Methodology, Investigation, Reviewing. Jagadish Krishnan: Investigation, Formal analysis. Shenbagam Madhavan: Supervision, Conceptualization.

Declaration of competing interest

The authors declare no competing interests.

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Data availability: All data are contained within the article

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