Epithelial-mesenchymal transition during extravillous trophoblast differentiation

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ABSTRACT
A successful pregnancy depends on the intricate and timely interactions of maternal and fetal cells. Placental extravillous cytotrophoblast invasion involves a cellular transition from an epithelial to mesenchymal phenotype. Villous cytotrophoblasts undergo a partial epithelial to mesenchymal transition (EMT) when differentiating into extravillous cytotrophoblasts and gain the capacity to migrate and invade. This review summarizes our current knowledge regarding known regulators of EMT in the human placenta, including the inducers of EMT, upstream transcription factors that control EMT and the downstream effectors, cell adhesion molecules and their differential expression and functions in pregnancy pathologies, preeclampsia (PE) and fetal growth restriction (FGR). The review also describes the research strategies that were used for the identification of the functional role of EMT targets in vitro. A better understanding of molecular pathways driven by placental EMT and further elucidation of signaling pathways underlying the developmental programs may offer novel strategies of targeted therapy for improving feto-placental growth in placental pathologies including PE and FGR.

KEYWORDS
differentiation; epithelial-mesenchymal transition; invasion; placenta; trophoblast

Introduction
A successful pregnancy is dependent on efficient implantation and placentation. Establishment of an adequate blood supply between mother and fetus is vitally important in the first trimester. Continuous and increasing maternal blood supply throughout gestation supports the nutritional demands of the rapidly growing fetus. The placenta is the key organ of pregnancy, and establishment of the feto-maternal interface is a critical prerequisite to its efficient functioning. The placenta is the primary site of nutrient, waste and gas transfer but it also acts as a barrier protecting the fetus from foreign molecules and infection. Furthermore, the placenta is a dynamic endocrine organ, which produces important hormones throughout gestation that regulate development of the feto-placental unit and alter maternal physiology to support the changing demands of pregnancy. Understanding the development of the placenta in the earliest stages of pregnancy is critical to comprehending the role of the placenta not only in uncomplicated pregnancies but also in pathological pregnancies associated with a malfunctioning placenta. This review was prepared by searching relevant terms in PUBMED.

The development of the placenta is a complex and tightly regulated process. The placenta is the first organ to develop after the attachment of blastocyst to the uterine wall. During implantation, the outer layer of the blastocyst, the trophectoderm, differentiates into the extraembryonic trophoblastic shell, while the inner cell mass of the blastocyst proceeds with embryonic development. The trophoblasts then proliferate and differentiate down either of 2 pathways; the villous or the extravillous pathways. As illustrated in Figure 1, trophoblasts differentiating down the villous pathway fuse to form the multinucleated syncytiotrophoblast, which envelops the chorionic villi and covers the entire surface of the developing placenta, and form the interface between the maternal and fetal blood supplies. The syncytiotrophoblast is also responsible for the production of the majority of placental hormones. Extravillous cytotrophoblasts (EVTs) follow a very different differentiation pathway. They form EVT cell columns at the tips of the chorionic villi.
villi at the tissue interface between the fetal and maternal compartments. The proximal regions of the EVT columns comprise proliferative cells, however at the distal regions of the column the EVT cease to proliferate and instead, they dissociate from the columns and become either migratory (i.e. endovascular trophoblast), or become invasive (i.e., interstitial trophoblast) and penetrate into the maternal decidua basalis (the transformed endometrium of pregnancy) and into the underlying maternal myometrium. Interstitial EVT invasion acts to anchor the placenta into maternal tissues but both endovascular EVTs and interstitial EVTs perform another crucial function; the remodelling the maternal spiral arterioles. The maternal arterioles are transformed into wide calibre, low-resistance channels by replacing the smooth muscle and elastic extracellular matrix of the vessels with a fibrinoid matrix, thereby rendering the vessels unresponsive to maternal vasomotor control. This physiological conversion of the maternal spiral arterioles to low resistance utero-placental vessels is an important step in early pregnancy, as it reduces blood flow resistance and increases placental perfusion, which ultimately facilitates greater nutrient uptake by the fetus.

The underlying process leading to the formation of the trophoblastic cell columns is termed epithelial-mesenchymal transition (EMT).

**EMT basics**

EMT describes the process by which an immotile, polarized epithelial cell undergoes a number of biochemical changes to attain mesenchymal cell characteristics, which include the ability to migrate and invade. The ability of cells to transition between the epithelial and mesenchymal states is a fundamental process in the generation of complex body patterns, and is essential for cells to move to and occupy distal sites. EMTs are encountered in distinct biological settings: embryogenesis and development; wound healing and tissue regeneration; and cancer progression and metastasis. While tight regulation and precise orchestration of EMT are observed throughout normal development, the dysregulation of EMT is associated with the pathological processes of tumor metastasis and cancer progression. Nevertheless, despite the dissimilar biological settings in which EMTs occur, these settings are all thought to be governed by a common set of genetic and biochemical elements.

Epithelial cells are characterized by intercellular adhesion complexes, such as adherens junctions, gap junctions, tight junctions and desmosomes. These cells display apical-basolateral polarity, have an organized actin cytoskeleton and do not move away from the epithelial layer. In contrast, mesenchymal cells are not typically associated with a basal lamina, but instead display front-back polarity and a fibroblast-like morphology that enables cell movement. Therefore, in order for a cell to undergo an EMT, a number of phenotypic changes are required including changes in cell shape and changes in polarity and adhesion profiles. Key features enabling an EMT include loss of attachment to the basement membrane as well as attachment to, and degradation of, the extracellular matrix.
EMT in placental development

In early placental development, the EVT lose their organized epithelial phenotype and transition to a migratory and invasive mesenchymal phenotype allowing them to migrate and infiltrate into the maternal decidua and vessels. The cellular mechanisms controlling/underlying EMT in trophoblasts are poorly understood, however attempts have been made to understand these processes by drawing parallels to the larger body of research on EMT from the cancer field. Trophoblast cells and malignant cells share many similar phenotypic properties including extensive proliferation, migration, invasion of neighboring tissues, and the ability to evade the immune system. Furthermore, the 2 cell types are comparable as they express many of the same growth factors, enzymes, hormones and receptors that govern these processes. However, in contrast to the environment of tumor cells, the uterine environment very tightly controls trophoblast behavior in a spatio-temporal manner. This is evident since EVT invasion is restricted to controls trophoblast behavior in a spatio-temporal manner. Furthermore, the ability to undergo terminal differentiation, as seen in the formation of placental bed giant cells, appears to limit the tumor-like properties of the EVTs. With the very tight controls on trophoblast migration and invasion, disruption to their tight homeostasis is also thought to contribute to a number of pregnancy pathologies. For example, shallow invasion is a characteristic feature of pre-eclampsia and fetal growth restriction, while abnormal deep EVT invasion is associated with placenta accreta/increta/percreta and uncontrolled invasion by EVT is associated with choriocarcinoma.

Molecular regulation of EMT

EMTs have been described previously as an “orchestrated series of events”. They are a complex, coordinated sequence of molecular processes that allows a cell to dissociate from its epithelial architecture and migrate to distant sites. A number of inducing signals regulate EMT at the molecular level and these signals are transduced within the cell through key transcriptional factors. These transcription factors in turn regulate downstream target genes that culminate in changes to cellular phenotype that characteristically associated with EMT. Current knowledge of EMT in the human placenta is incomplete in the distribution, expression and functional roles of a number of the well-known EMT markers. However, EMT is a complex process and many important EMT components identified in other human tissues, and in various animal models, have not been investigated in the human placenta.

Inducers of EMT

A wide diversity of EMT inducers exists. Multiple extracellular stimuli such as growth factors, hormones, cytokines, chemokines or cell-matrix contacts, miRNAs initiate signaling upon interaction with receptor tyrosine kinases (RTKs), G-protein-coupled receptors (GPCRs), integrins or others. This ultimately leads to the activation of critical signaling cascades such as mitogen-activated protein kinases (MAPKs), focal adhesion kinase (FAK), the phosphoinositide 3-kinase (PI3K)-Akt pathway or Janus kinase (JAK)-Signal Transducers and Activators of Transcription (STAT) and the whole of Wnt signaling cascades controlling a wide range of biological processes including proliferation, differentiation, migration and apoptosis. Nevertheless, despite the vast range of inducers, many of the signaling pathways have similar end points. These inducers often promote EMT via regulation of downstream transcription factors. A key challenge in establishing the definitive role of any inducing signal of EMT is that the effects of any given EMT inducer are context dependent. Drawing parallels from one field of biology is often difficult, which requires basic research to identify and resolve these context dependent effects. For example, transforming growth factor β (TGFβ) plays multifunctional roles in the regulation of cell behavior, and is implicated in both developmental biology and cancer biology.

TGFβ is noteworthy for its paradoxical actions, having both inhibitory and stimulatory effects on cell growth. In the early stages of cancer, TGFβ acts as a growth inhibitor and tumor-suppressor; but in the later stages, it can act as a potent inducer of EMT. Genetic and molecular changes in malignant cells are thought to alter their responses to signaling molecules. The loss of SMAD3 in choriocarcinomas is responsible for their resistance to TGFβ. Such contradictory roles demonstrate the challenges in comparing different cell types. TGFβ plays crucial roles in regulating trophoblast cell adhesion, proliferation, differentiation, migration and invasion at the maternal-fetal interface. TGFβ exists in 3 different isoforms, with TGFβ1 and TGFβ2 thought to be the most important at the maternal-fetal interface. EVTs within the placental bed express TGFβ2, while extracellular TGFβ1 and cytoplasmic TGFβ2 are localized within the decidua. TGFβ1 and TGFβ2 inhibit trophoblast proliferation, migration and invasion, and increase formation of multinucleated cells. These data suggest that TGFβ is an important growth factor that is secreted by the decidua and has a role in controlling...
trophoblast invasion, while protecting maternal tissues from over-invasion by trophoblast cells.\textsuperscript{32} The role of TGFβ in mediating EMT in trophoblast is not fully elucidated, but there is evidence that TGFβ may play a regulatory role. \textit{In vitro} studies demonstrate that TGFβ1 increases the expression of E-cadherin,\textsuperscript{30} a feature of cells in the epithelial state. TGFβ1 also acts through 2 key transcriptional regulators of EMT in trophoblast cells; SNAIL\textsuperscript{25} and TWIST,\textsuperscript{33} which are discussed in the next section.

Epidermal growth factor (EGF) is another important factor implicated in modulating placental development. EGF and its receptors (EGFRs) play crucial roles in the regulation of various cell functions during early embryonic development, stem cell renewal in normal tissues, and cancer development and progression.\textsuperscript{34} In these biological contexts, EGF acts as an inducer of EMT signaling pathways through its regulatory effects on transcription factors and their downstream target genes.\textsuperscript{9} EGF and EGFR1 are localized in the syncytiotrophoblast and the cytotrophoblast.\textsuperscript{35} EGF expression is most pronounced in the first trimester placenta and is reduced closer to term, suggesting an association of EGF with the early stages of placental development.\textsuperscript{36} EGF promotes trophoblast proliferation and differentiation \textit{in vitro},\textsuperscript{37} and stimulates trophoblast migration in EVT cell lines,\textsuperscript{38,39} which involve pathways such as AKT-mediated signaling.\textsuperscript{40} During EVT formation, cells downregulate EGFR1 and induce ERBB2 (also termed HER-2/neu) in a similar manner to tumor cells.\textsuperscript{41,42} Other studies also demonstrate EGF/EGFR1-induced motility in villous explant cultures and primary cytotrophoblasts.\textsuperscript{38,43} Collectively, these studies provide evidence of EGF and its receptors as important regulators of trophoblast cells.\textsuperscript{44}

\textbf{Transcriptional regulation of EMT}

Toward the end of the first trimester, from approximately 10 weeks of gestation, the trophoblast plugs progressively loosen and exposes the developing placenta to maternal blood flow. As a result, the local partial pressure of oxygen increases, whereupon the placenta develops enhanced mechanisms for protection against oxidative damage through activation of Hypoxia-inducible transcription factor, HIF-1α.\textsuperscript{45} It has now become apparent that hypoxia and HIF-1α activation have the potential of modulating the activity of major EMT-triggering pathways by either regulating the expression levels of EMT inducers and their receptors, by affecting the expression levels of pathway associated signaling molecules and downstream effectors, or by a signal enhancing functional interaction with EMT-associated nuclear factors.\textsuperscript{46} In this review, we have specifically focused on the transcription factors that are directly involved in the regulation of EMT signaling therefore we have not discussed hypoxia and HIF-1α in the trophoblast differentiation.

The transcriptional repressor SNAIL, a member of the SNAIL family of zinc-finger proteins, plays an essential role in mesoderm formation and EMT in developmental biology. SNAIL is also a potent inducer of EMT and a regulator of invasion during tumorigenesis. SNAIL achieves its pro-EMT actions primarily through transcriptional repression of E-cadherin,\textsuperscript{47} which is a marker of cells in the epithelial state. The expression of SNAIL induces the acquisition of a more fibroblastic phenotype, distinguished by fewer cell-to-cell contacts and a tighter association of the cells to the cell matrix.\textsuperscript{47} SNAIL may also act as a pro-survival molecule, protecting cells from apoptotic stimuli and promoting survival factors.\textsuperscript{48} Furthermore, SNAIL also down-regulates other molecules such as occludins and claudins, which are responsible for tight junctions in the epithelial architecture.\textsuperscript{49} Despite the important and varied roles that SNAIL plays in epithelial and cancer cells, the roles of SNAIL in trophoblasts and general placental development, is less well known. SNAIL is localized in EVTs within the maternal decidua, but is only weakly detected in the villous trophoblast cells\textsuperscript{50,51} suggesting a primary role for SNAIL in trophoblast invasion. The inverse relationship between SNAIL and E-cadherin observed in epithelial and cancer cells also exists in a number of trophoblast cell lines.\textsuperscript{52,53} Arimoto-Ishida et al.,\textsuperscript{53} investigated the role of SNAIL in trophoblast invasion and showed that down-regulating SNAIL siRNA resulted in decreased invasiveness of trophoblast-derived cell lines. They suggested that during early placentation, low-oxygen tension up-regulates SNAIL in EVT’s, which in turn down-regulates E-cadherin expression and subsequently increases adhesion and invasion.\textsuperscript{53} This preliminary evidence of a role for SNAIL in placental cells is consistent with a potentially important role in early placental development and EMT, which warrants further investigation.

SLUG is another member of the SNAIL family of transcriptional repressors. SLUG, like SNAIL, represses E-cadherin expression in breast cancer cells and in epithelial cell lines, which consequently induces an EMT.\textsuperscript{54,55} Few studies have examined possible functions of SLUG in placental development. Cyclosporin A, an immunosuppressive agent, promotes invasion of the choriocarcinoma-derived JEG-3 trophoblasts through upregulating SLUG and downregulating E-cadherin,\textsuperscript{56} which implicates SLUG in trophoblast regulation. Moreover, trophoblast cells cultured with fibroblast growth factor-4 increased the expression of SLUG and downregulated E-cadherin, which resulted in hyper-invasion of the extracellular matrix.\textsuperscript{57} Nevertheless, the role of SLUG...
in normal placental development and in placental pathologies remains to be fully elucidated.

Some of the effects of SNAIL and SLUG on EMT are triggered by the formation of T-cell factor (TCF)/β-catenin-dependent complexes, which were shown to transcriptionally activate EMT-promoting TGF-β3 expression. The TCF/β-catenin complex is the key regulatory transcription factor of the Wnt signaling pathway, promoting multiple processes such as embryonic development, stem cell maintenance, differentiation and tumorigenesis. EVT formation is associated with activation of canonical Wnt signaling, with localization of nuclear TCF-4 and β-catenin expression in the distal regions of the trophoblast cell columns and in invasive EVTs. Autocrine Wnt signaling promotes trophoblast motility, while gene silencing of TCF-4 decreases trophoblast migration, as well as expression of EVT/EMT markers such as ITGA1, ITGA5 or SNAIL. These data suggest that TCF-4/β-catenin could be part of a complex network of EMT-factors controlling EVT differentiation.

Another emerging transcription regulator of EMT in trophoblast cells, which does not belong to the SNAIL family of proteins is TWIST. TWIST increases the expression of mesenchymal markers vimentin and N-cadherin, and significantly decreases the expression of E-cadherin; a combination of events that ultimately leads to an EMT. Two studies demonstrated roles of TWIST in trophoblast differentiation, fusion and invasion through modulation of cadherin proteins.

Clearly, further studies are needed to determine spatial and temporal expression, as well as the particular roles of transcription factors in normal and pathological placental development. A recent study implicated abnormal placental SNAIL and TWIST expression in molar pregnancies, where aberrant trophoblast differentiation is a key feature.

**Downstream gene targets/cell-adhesion molecules in EMT**

Downstream target genes of transcriptional regulators are responsible for maintaining cellular phenotype. Molecules that are responsible for cell adhesion complexes, such as adhesion junctions and tight junctions, play an integral role in the maintenance of a cell’s epithelial phenotype. In contrast, molecules responsible for cellular polarity determine whether a cell will display apico-basal polarity or front-back polarity. Therefore, molecules that modulate cellular adhesion and cell polarity are critical for not only the maintenance and organization of cellular architecture and structure, but also play a crucial role in supporting the specific functions of different tissue components.

The cadherins are a group of transmembrane glycoproteins responsible for the induction of cell-cell contacts and adherens junctions. They are potentially important in embryonic development and tissue formation, since their spatio-temporal patterns correlate with the establishment of cellular polarity.

Epithelial-cadherin (E-cadherin), one of the more extensively studied adhesion molecules, is a key phenotypic marker of cells in the epithelial state. It is the major cadherin expressed by epithelial cells and the loss of functional E-cadherin is a hallmark of EMT. E-cadherin is a tumor-suppressor, as its loss correlates with metastasis and poor prognosis in the cancer setting. E-cadherin is present in villous cytotrophoblasts and is reduced in the distal regions of the EVT cell columns and in migrating and invading EVT within the decidua in first and second trimester placental tissues. Floridon et al., reported a transient down regulation of E-cadherin expression in migratory and invasive EVT that was restored when trophoblasts aggregated in the decidua to form giant cells, and in the vessel wall after completion of trophoblast migration and invasion. In vitro evidence demonstrated that knock-down of E-cadherin significantly increased invasiveness of the EVT cell line JEG-3 and of isolated second trimester trophoblast cells. This evidence suggests E-cadherin is important in the maintenance of an epithelial phenotype in trophoblasts, and reduced E-cadherin expression is associated with trophoblasts acquiring a migration and/or invasion potential. In this respect, trophoblast cells behave in a similar manner to other epithelial cell types and cancer cells.

Neuronal cadherin (N-cadherin) is another member of the cadherin transmembrane glycoprotein family, which plays an important role in the formation of cell-cell contacts. In contrast to the situation with E-cadherin, N-cadherin promotes a less adhesive phenotype in some cell types, and is implicated in tumor cell motility and invasion. N-cadherin promotes the downregulation of E-cadherin and cellular adhesion, which reveals an inverse relationship between N-cadherin and E-cadherin in some cell types. Such cadherin switching is now considered a feature of EMT, supporting the transition from an epithelial to an invasive phenotype. N-cadherin is absent from first-trimester human placenta, but is expressed in first trimester EVTs. N-cadherin may also play an important role in trophoblast invasion, as in vitro knockdown of this gene limits the invasiveness of the HTR-8/SVneo EVT cells. Furthermore, N-cadherin promotes cancer cell adhesion to the vascular endothelium, thereby aiding passage through the
vasculature.\(^{68}\) Such actions may be important in early placental development and remodeling of maternal spiral arterioles. Given the strong evidence that N-cadherin has a role in cell migration, invasion and adhesion to vasculature, further study of N-cadherin in trophoblast function is justified. Vascular endothelial-cadherin (VE-cadherin) is responsible for the cadherin-mediated cell-cell junctions observed in endothelial cells,\(^{64}\) and is critical for vascular development.\(^{73}\) VE-cadherin is absent from villous trophoblast but is expressed in the trophoblast cell columns, interstitial EVT and spiral artery endothelial cells (unmodified vessels).\(^{65}\) VE-cadherin shows an inverse relationship with E-cadherin in trophoblasts, and switching cadherin phenotype from an epithelial to vascular endothelial phenotype may allow trophoblasts to invade and interact with maternal vessels.\(^{65}\) Subsequently, VE-cadherin was shown to facilitate the passage of endovascular trophoblasts across the endothelium.\(^{74}\) Thus, the various cadherins play important roles in cell biology and particularly, also have important functions in placental biology. Tight junctions play a role in the maintenance and support of tissue structure and function, by preserving epithelial and endothelial barriers, and by the regulation of epithelial differentiation.\(^{75}\) Occludins, claudins and zona occludens-1 (ZO-1) are just a few of the molecules responsible for the induction/maintenance of tight junction cellular contacts. In normal tissues, these molecules are essential for the establishment of epithelial cell architecture. As is the case with E-cadherin, these molecules are under the control of transcription factor SNAIL.\(^{49}\) In normal placentae, ZO-1 and occludin are localized to the syncytiotrophoblast and villous trophoblast, but are not expressed in EVT.\(^{76}\)

The present literature as well as published mRNA expression data,\(^{77}\) which are available at GEO profiles (accession number GDS3523[ACCN]), also suggests that many features of EMT such as downregulation of junction proteins (CLDN1/4, OCLN, MPP5, ZO1), and upregulation of EMT-associated and -promoting genes (ITGA5, ITGB1, FSP1, SPARC, HSP47, SNAI1, TCF-4, FN1) occur during EVT differentiation of cytotrophoblasts (CTB) (Fig. 2). However, the EMT program in EVTs might not be fully accomplished since the prime marker of epithelial trophoblasts, cytokeratin 7, is not downregulated during differentiation. Similarly, the marker gene of mesenchymal cells that underwent EMT, vimentin, is not induced during EVT formation. It is known that during development epithelial cells may only lose some of the genes associated with cell adhesion and polarity and only acquire a few features of mesenchymal cells depending on the cellular context and the signaling cascades in place.\(^{16}\) This situation, termed partial EMT, may also apply to EVT differentiation.

In summary, the present data suggest that similar to EMT processes during development or cancerogenesis,
EVT differentiation is associated with the induction of key transcription factors of EMT such as SNAIL (Fig. 3) controlled by upstream signaling cascades such as FGF, TGFβ and Wnt.

EMT is implicated in pathological pregnancies

Pre-eclampsia (PE) and fetal growth restriction (FGR) are 2 clinically significant complications of human pregnancy. The more severe forms of early-onset PE and idiopathic FGR are thought to originate as a consequence of impaired trophoblast function, with limited EVT invasion into maternal decidua and underlying myometrium in the early stages of pregnancy. Defective trophoblast differentiation and shallow invasion of trophoblasts are key lesions commonly observed in PE placentae. Placentae from FGR pregnancies show reduced trophoblast cell proliferation, reduced villous vascularisation and elevated vascular impedance. Failure to create low-resistance utero-placental arterioles leads to placental hypo-perfusion and failure to achieve the local and systemic adaptations required for pregnancy, which interact with the underlying maternal factors, ultimately manifest in these disorders.

As PE and FGR are considered to be conditions of trophoblast and placental dysfunction, unravelling the complex mechanisms that underlie the key functions of trophoblasts will ultimately help us to understand defects that contribute to these conditions. The principal trophoblast functions, proliferation, migration, invasion, and differentiation, are cellular functions that also underpin the EMT. Abnormal trophoblast invasion may therefore reflect failure of trophoblasts to acquire phenotypic changes required for the mesenchymal migratory/invasive phenotype.

Altered expression of EMT inducers, transcription factors and adhesion molecules in pathological pregnancies

TGFβ and EGF are EMT inducers believed to be involved in the pathogenesis of PE and FGR through inhibition of trophoblast differentiation into an invasive phenotype. TGFβ1 is present at higher concentrations in the plasma and placenta of women with PE compared with that of normotensive controls. A similar finding was also reported for TGFβ2, but other studies have produced contradictory results. Numerous studies have also linked EGF and EGFR to placental dysfunction and to the pathophysiology of PE and FGR. EGF can attenuate hypoxia-induced apoptosis in human cultured trophoblast cells, and may thus protect the placenta from hypoxic injury in pregnancies complicated by placental hypo-perfusion. EGFR mRNA expression is significantly lower in FGR placentae than that of healthy controls; but in FGR and PE placentae, there is significantly increased expression of the truncated form of EGFR. Furthermore, maternal EGF deficiency causes fetal hypoglycaemia and FGR in mice. Together these data suggest an important role for EGF and EGFR in the regulation of placental development and fetal growth. Nevertheless, whether the disorder-associated dysregulations of TGFβ1 and EGF are involved in the pathogenesis through modifying the EMT process in trophoblasts or are as a consequence of the disorder remains to be investigated.

Studies of differential expression of transcription factor SNAIL in PE placentae compared with normotensive controls have yielded contradictory results. Blechschmidt et al. found SNAIL expression to be significantly increased in the EVT from PE pregnancies in third-trimester, whereas another study reported the level of SNAIL-positive nuclei and SNAIL protein to be significantly lower in PE placentae compared with normotensive controls. The transcription factors SLUG and TWIST have not yet been implicated in the pathogenesis of PE or FGR and further studies are needed to determine their roles in normal and pathological placental development.
In PE, E-cadherin is highly expressed in the villi, decidua and on EVT that penetrate superficial portions of uterine arterioles. Increased E-cadherin expression in PE may reflect excessive trophoblast proliferation, or impaired trophoblast differentiation, either of which could have adverse consequences. E-cadherin protein levels are also significantly higher in PE placentae compared with normotensive placentae. Thus, it was also suggested that cadherin modulation is defective in PE, as it was shown that VE-cadherin was not adequately upregulated in trophoblasts for interaction with maternal vessels.

Conclusions and future directions

Our current understanding of EMT in the human placenta is rudimentary. Trophoblasts are unique in that while they undergo extensive proliferation, migration and invasion, there are intrinsic and extrinsic mechanisms that precisely control these functions. Determining the spatial and temporal expression of important EMT markers and establishing their roles in the placenta are essential to understanding trophoblast regulation and placental development in early pregnancy. Trophoblast functions, particularly proliferation, migration and invasion are likely to be influenced by EMT regulators. Furthermore, unravelling the complex pathways and interactions that characterize the EMT in normal placental development will provide important clues in our understanding of how a deregulated EMT contributes to the pathogenesis of pregnancy complications such as PE and FGR.

Abbreviations

EGF epidermal growth factor
EMT epithelial-mesenchymal transition
EVT extravillous trophoblast
FGR fetal growth restriction
PE pre-eclampsia
TGF β transforming growth factor β

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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