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Review: The ADAM metalloproteinases – Novel regulators of trophoblast invasion?

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ABSTRACT

During pregnancy, the extravillous trophoblast (EVT) invades the maternal decidua and remodels spiral arteries reaching as far as the inner third of the myometrium. This process is mandatory to a successful pregnancy since EVTs regulate spiral artery remodeling to achieve maximal vasodilation and thus an adequate nutrient supply to the embryo or communicate with maternal leukocyte populations to guarantee acceptance of the allogeneic conceptus. To achieve this, EVTs undergo a remarkable and unique differentiation process, which yields different phenotypes such as proliferative cell column trophoblasts or growth-arrested, invasive interstitial or endovascular cytotrophoblasts. Matrix metalloproteinases have long been seen as imperative to trophoblast invasion because of their ability to degrade extracellular matrix and therefore allow cellular movement in foreign tissues. However, global gene expression analysis reveals that EVTs also express various members of distintegrin and metalloproteinases (ADAMs). These proteases are associated with the process of proteolytic shedding and activation of surface proteins including growth factors, cytokines, receptors and their ligands rather than extracellular matrix breakdown. While ADAM12 has been associated with chromosomal abnormalities as well as preeclampsia or intrauterine fetal growth restriction, the function of ADAMs in trophoblasts remains elusive. In this article, we review the diverse invasive trophoblast phenotypes, EVT-associated protease systems and related open questions. In addition, we examine recent information about relevant ADAM members and their putative implications for EVT biology.

1. Introduction

Since this review focuses on novel aspects of protease activity in trophoblast motility, we firstly give a short overview of current understanding on different extravillous trophoblast (EVT) phenotypes. Human placentation exhibits, in comparison to all other eutherian mammals, the most pronounced trophoblast-mediated infiltration of the maternal uterus, reaching as deep as the inner third of the myometrium. This unique invasion process is controlled by different EVT subpopulations as noticed by their multifaceted phenotypic appearance, differential gene expression patterns and unique functions. The first step of placental development, which supposedly involves trophoblast motility, occurs upon implantation of the blastocyst. Here, the pre-syncytium invades the underlying uterine endometrium in order to initiate a series of developmental steps leading to the generation of placental chorionic villi. These can be divided into two different types: firstly, floating villi and secondly, relevant to this review, the placental anchoring villus (AV) [1]. The AV attaches to the decidua and forms the trophoblast cell column (CC), a cluster of cells consisting of proliferative, proximal CC trophoblasts and non-cycling, differentiating distal CC trophoblasts. The latter gives rise to various motile trophoblast subtypes, commonly referred to as EVTs. At the distal end of CCs, single trophoblasts start to disseminate from one another in order to invade the decidual stroma as interstitial cytotrophoblasts (iCTBs) [2]. These cells fulfill pivotal functions during pregnancy such as induction of a pregnancy-specific vascular phenotype [2] or crosstalk with decidual cells including maternal leukocytes [3]. iCTBs also appear as multinucleated giant cells (GCs), which are believed to represent endpoints of EVT differentiation due to their numerous appearance late in gestation [4,5]. Although not functionally proven, good evidence exists to suggest that GCs are formed by trophoblast aggregation and are involved in the production of pregnancy-specific hormones such as

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human placental lactogen or alpha chorionic gonadotrophin [6]. Interestingly, iCTBs tend to form trophoblast clusters at more distal parts of the deciuda [7]. Whether such iCTB aggregates represent a precursor state of GCs or comprise a yet to be defined additional invasive iCTB subtype is not known. The tendency to reorganize in epithelial structures might also reflect the reverse process of epithelial to mesenchymal transition (EMT) termed mesenchymal to epithelial transition, which is believed to play an important role in the formation of transient epithelia during embryonic development [8]. Indeed, various epithelial markers such as E-cadherin are downregulated during EVT differentiation [9], whereas iCTB aggregates re-express E-cadherin [7] or certain connexins (Cx) such as Cx40 [10]. As indicated above, invasive iCTBs connect to spiral arteries and induce, in concert with uterine natural killer (uNK) cells and macrophages, the transformation of spiral arteries [11]. This process involves a series of vascular adaptations including disruption and reorganization of the arterial wall as well as trophoblast-mediated replacement of the resident endothelium, which ultimately leads to the generation of a dilated vasculature ensuring adequate blood flow to the growing fetus [12]. Whether iCTBs can cross the vascular basement membrane and thereby generate an additional EVT phenotype, the endovascular trophoblast (eCTB) is still a matter of debate. eCTB-controlled replacement of endothelial cells occurs subsequent to leukocyte-mediated (uNK cells and macrophages) infiltration of the arterial media and is associated with fibrinoid deposits and a progressive dilation of spiral arteries [2,13,14]. In support of iCTB-controlled perivascular invasion, 3D co-cultures of trophoblastic cells and spiral arteries demonstrate that trophoblast-mediated interstitial invasion of spiral arteries does at least occur in vitro [15]. Another invasive route leading to EVT-mediated intraluminal colonization of spiral arteries is suggested to be controlled by migratory CC trophoblasts, originating from AV situated adjacent to distal, vascular openings at the uterine wall (Fig. 1). This process is believed to fulfill two major functions. One is plugging of spiral arteries in order to prevent premature onset of blood flow into the intervillous space and related oxidative stress during early pregnancy [16]. In addition, eCTBs are believed to migrate retrograde to the maternal blood flow to induce intraluminal remodeling of spiral arteries. The notion that these cells constitute the main precursor of eCTBs is supported by the observation that trophoblast-mediated luminal colonization also takes place in the absence of nearby iCTB infiltration [16]. Finally, iCTBs have also been noticed to invade decidual glands [17]. However, no data exist to classify these cells as a separate EVT subpopulation or to assign trophoblast-mediated penetration of glands a functional relevance in humans. Differentiation into these migratory phenotypes of EVTs is believed to be controlled by various autocrine and paracrine factors including numerous growth factors, cytokines, and chemokines as well as by the interaction with resident tissue cells. The latter include decidual stromal cells and specific leukocyte populations of which macrophages and uNK cells represent the most abundant cell types [18,19]. In the light of these diverse EVT phenotypes and related functions, it appears not surprising that failure in trophoblast invasion, manifested for instance in incomplete remodeling of spiral arteries, is associated with severe conditions during pregnancy including preeclampsia [20] or intrauterine fetal growth restriction [21].

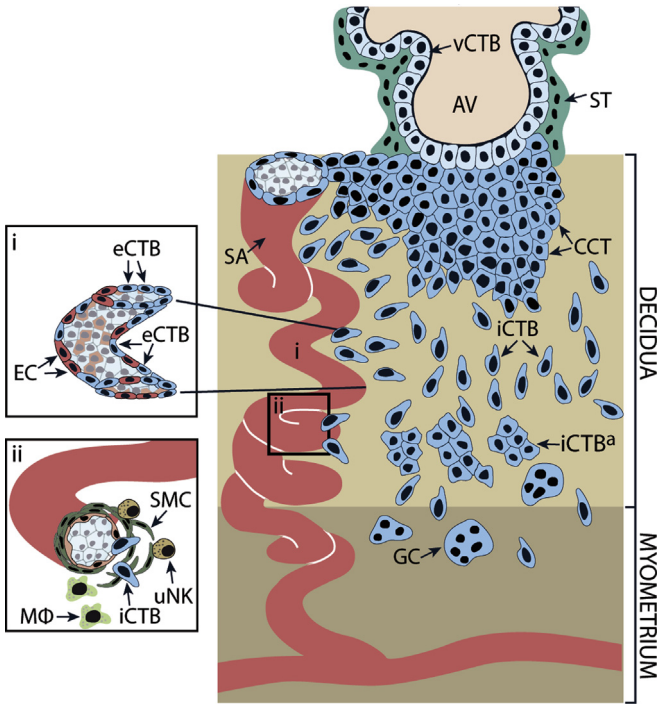

Fig. 1. Extravillous trophoblast subpopulations. Anchoring villi form cell columns, attach to the maternal decidua and give rise to various motile trophoblast subpopulations. Cell column trophoblasts exit the cell cycle and differentiate into highly invasive interstitial cytotrophoblasts or migrate towards spiral arteries in order to colonize the vascular lumen by the formation of endovascular cytotrophoblasts (i). Interstitial cytotrophoblasts either associate to spiral arteries and regulate vascular remodeling in concert with uterine killer cells and macrophages (ii), or differentiate to multinucleated giant cells. In addition, interstitial cytotrophoblasts re-organize in epithelial aggregates. AV, anchoring villus; CCT, cell column trophoblast; GC, giant cell; iCTB, interstitial cytotrophoblast; iCTB^a, interstiatial cytotrophoblast aggregate; MΦ, macrophage; SMC, smooth muscle cell; ST, syncytiotrophoblast; uNK, uterine natural killer cell; vCTB, villous cytotropholast.

2. Proteolytic activity during trophoblast invasion – known and novel aspects

Similar to other processes which require cellular movement in foreign tissues, including cancer progression, angiogenesis or embryonic development, trophoblast invasion into the decidual stroma is accompanied by the upregulation of proteolytic enzymes. These include matrix metalloproteinases (MMPs), cathepsins and the serine protease urokinase-type plasminogen activator (uPA). Among those, MMP2 and -9 represent the best-characterized proteases in the context of trophoblast invasion. Both metalloproteinases are expressed and secreted by cultivated trophoblasts [22,23] and the addition of tissue inhibitors of metalloproteinases (TIMPs) or specific blocking antibodies down regulates trophoblast invasion in vitro [22,24]. In addition, factors that either promote or inhibit trophoblast invasion have been associated with regulatory effects on MMP2 and/or -9 activity. For instance, epidermal growth factor (EGF)-mediated induction of trophoblast invasion is characterized by increased expression and activity of both MMP2 and -9 [25,26] whereas the anti-invasive effect of transforming growth factor beta (TGFβ) on trophoblasts is accompanied by the induction of TIMP2 secretion [27]. Along those lines, a recent study suggests that MMP9 deficiency in mice mimics a preeclampsia-associated phenotype by impairing trophoblast differentiation and invasion [28]. Other MMP members found to be expressed by trophoblasts include MMP3, -7 or -12; the latter was recently described to execute elastolysis during uterine spiral artery remodeling [29]. Moreover, uPA and its receptor uPAR are believed to play a pivotal role in trophoblast motility [30]. For instance, tumor necrosis factor alpha (TNFα)-mediated suppression of trophoblast motility is controlled by the upregulation of the uPA inhibitor plasminogen activator inhibitor-1 [31]. Interestingly, uPA might also execute pro-migratory function in trophoblasts independent of its proteolytic activity [32]. While all human cathepsins (CTS) are expressed in the