Placentation initiates as an invasive phenomenon in which embryo-derived trophoblastic cells progressively integrate into maternal tissues. In this issue of the *Journal* two articles by Zhou et al. demonstrate convincingly that in addition to invasion, placentation involves an apparently novel process of epithelial–endothelial transformation (1, 2). The acquisition of an endothelial cell phenotype by cytotrophoblastic cells has important implications for the management of placental abnormalities and to our current understanding of basic vascular biology.

Early during implantation, trophoblastic cells from the outer layer of the blastocyst invade the endometrium by secretion of matrix-degrading proteases, migration, and rapid proliferation. Trophoblastic cells also differentiate into two layers: the cytotrophoblast and the syncytiotrophoblast. During the first 2 wk of development, nutrients are exchanged by diffusion. Shortly thereafter, columns of cytotrophoblastic cells invade the endometrium (decidua) as sharp lytic fingers, which eventually pierce the maternal vascular wall, a process termed "endovascular invasion." As demonstrated by Zhou et al., cytotrophoblastic cells interdigitate between maternal endothelial cells and acquire endothelial characteristics. These include the expression of PECAM, VE-cadherin, VCAM-1, α_4 and $\alpha_v\beta_3$ integrins, and with concomitant loss of previously expressed epithelial markers. This epithelial–endothelial conversion is restricted to those cytotrophoblastic cells that leave the fetal compartment and not with trophoblastic cells that remain in the placental villi. Therefore, the spatial restriction in trophoblastic phenotype is a consequence of distinct microenvironments, which effect changes in gene expression and are presumed to reflect distinct functional abilities.

Abnormal placentation: When invasion goes wrong

Abnormal placentation can result in loss of the fetus and/or cause severe complications for the mother. Preeclampsia, the most common such defect, affects 7–10% of women during their first pregnancy and manifests clinically as hypertension, proteinuria, and seizures. Analysis of placentas from such patients revealed shallow endometrial invasion and inadequate vascular anchorage. Zhou and colleagues present evidence that these alterations result from a defect in the trophoblastic cells and are accompanied by poor endovascular invasion and lack of epithelial–endothelial transformation (2). When cytotrophoblastic cells were analyzed in an in vitro system that recapitulates certain aspects of their differentiation, cytotrophoblastic cells from preeclamptic placentas showed marked deficiencies in invasion and differentiation. In addition, these cells expressed relatively low levels of VCAM, $\alpha_1\beta_1$, $\alpha_v\beta_3$, and VE-cadherin in situ (2). Are these differences cause or effect? Are they the result of a defective microenvironment or preexisting deficiencies in the cells themselves? Could placentation defects be a manifestation of genetic abnormalities in one or more genes involved in implantation and trophoblast development? If so, would it be possible to use chorionic villus sampling to screen for predisposing alterations?

From correlation to mechanism

Zhou et al. direct us to a rather uncharted area of vascular development, the ability of extravascular cells to convert to endothelium. An important question, yet unanswered, is the mechanism that induces expression of endothelial markers in cytotrophoblastic cells. A tantalizing hypothesis is that local concentrations of growth factors might be involved. Vascular endothelial growth factor (VEGF) and a related gene referred to as placental growth factor (PlGF) are among the possible suspects since they are expressed at high levels during placentation. VEGF has been shown to induce expression of $\alpha_v\beta_3$ on endothelial cells (3), an integrin associated with angiogenic invasion (4). While the best studied effects of VEGF are associated with endothelial cells, VEGF receptors are not entirely unique to the endothelium. In the uterus, for example, myometrial and some stromal cells also express VEGF receptors (Flt-1 and KDR) and respond to VEGF by increased proliferation (5). Furthermore, VEGF receptors are expressed on cytotrophoblastic cells (6). Therefore, VEGF could be an important mediator of this transformation. PlGF also binds to Flt-1 and induces endothelial cell proliferation (7). Investigations on the effect of these factors on cytotrophoblastic cells may bring some light to this problem.

Diversification of endothelial cell precursors and implications for vascular biology

The articles by Zhou et al. demonstrate that cytotrophoblastic cells are plastic and have the ability to acquire endothelial characteristics. Is this unique to the placenta or are there other examples of cells which undergo endothelial conversion? Recently, Asahara and colleagues have demonstrated that circulating CD34-positive cells can differentiate into endothelial cells and become incorporated into mature vessels (8). The ability of specific cell types to convert to endothelium appears to question a central tenet of vascular development, that new vessels arise from only two processes: the in situ differentiation of embryonic mesenchymal cells (vasculogenesis), or by the extension and remodeling of a previously existing vasculature (angiogenesis). While it is likely that most vessels arise from these more traditional processes, the presence of multipotential cells which contribute to the endothelium of adults appears to constitute a distinct process which might be referred to as "endothelial conversion." How many ways are there to form a vasculature? These and other related questions will obviously provide fertile ground for vascular biologists for years to come.

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