Preeclampsia: Animal models for a human cure

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Preeclampsia (PE) affects ~5% of human pregnancies and is a leading cause of perinatal mortality, preterm birth, and maternal morbidity (1). Through positive effects on vascular tone and glomerular capillary health, vascular endothelial growth factor (VEGF) and placental growth factor (PGF) are necessary for normal pregnancy (2–4). In PE, these proteins are antagonized by excessive placental production of soluble fms-like tyrosine kinase-1 (sFLT1), a splice variant of the VEGF receptor (2, 3), and in later pregnancy, by soluble endoglin (sENG), a soluble form of a transforming growth factor beta (TGFB1) receptor that prevents binding of TGFB1 to membrane-bound endoglin (5). The report by Kumasawa et al. (6) in PNAS describes the use of a mouse model in which placenta-specific expression of human sFLT1 is present from the time of implantation. The model faithfully reproduces many of the human findings of late-onset PE. The investigators also show that the lipid-lowering drug, pravastatin, ameliorates sFLT1-induced PE in these sFLT mice (6).

The etiology of PE is likely multifactorial and may have several forms. The disease can be characterized by early involvement of some combination of abnormal placental inflammation and hypoxia/reoxygenation injury that is mediated by reactive oxygen and nitrogen species (7, 8). The placental beds of preeclamptic women typically exhibit abnormally shallow trophoblast invasion. It remains unclear whether the invasion abnormalities are the cause or effect of inflammation, hypoxic injury, and changes in angiogenic mediators that are explored in the investigation by Kumasawa et al. (6–8). Problematic in the study of PE is its delayed clinical manifestation until after 26–28 wk gestation (in its severest form) or more commonly, after 34–36 wk (8). Early (10–12 wk gestation) alterations in soluble factors (9) detected in maternal blood can be used to predict those patients who will subsequently develop PE. However, corresponding placental tissues from this stage of gestation are not generally accessible. Study of placental aspects of the disease relies almost exclusively on specimens acquired after delivery, and information gleaned from these placentas is limited to relatively late disease manifestations. Inherent difficulties in the in vivo and in vitro investigations of placental contributions to this human disease require the development of model systems. It is here that Kumasawa et al. (6) have made their most important contribution.

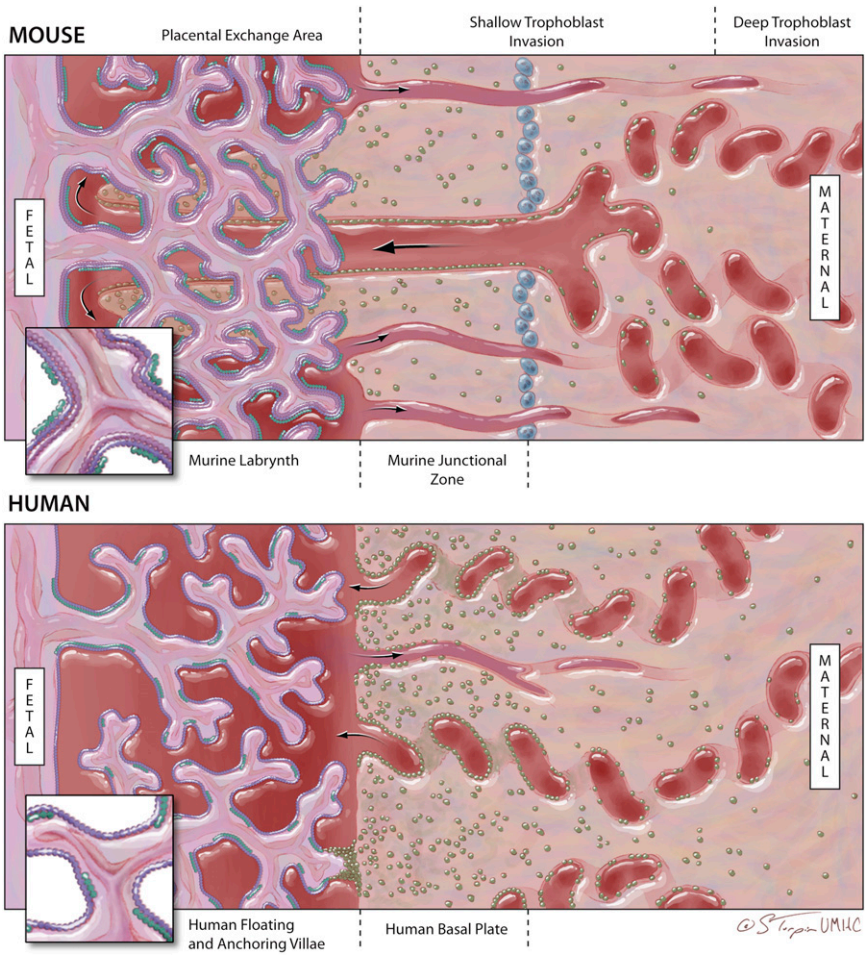

Fig. 1. Mouse (*Upper*) and human (*Lower*) placentas share a discoid shape, hemochorial exchange, and analogous cell types (syncytiotrophoblast, lavender purple; cytotrophoblast/giant cell, turquoise) and cell layers (labyrinth/villi and junctional zone/basal plate). Fetal vessels are bordered by a discontinuous cytotrophoblast layer in both species, but this is surrounded by two continuous syncytiotrophoblast layers in mouse labyrinth and only one in human villi. The exchange surface in the mouse consists of a complex labyrinth of interconnecting villous structures surrounding narrow maternal blood sinuses, whereas that of the human consists of tree-like, branching villous structures, many of which lie free-floating in a continuous pool of maternal blood; however, some traverse the intervillous space to adhere to the maternal decidua (10, 11). In mice, invasion is fairly shallow and mostly limited to those areas of the maternal decidua that lie closest to the fetus (light green and light blue cells), although vascular remodeling is evident far upstream of the most deeply invaded trophoblast (10). In humans, endovascular trophoblast cells (light green) remodel maternal uterine veins and spiral arteries by replacing vasoactive endothelial structures, and interstitial trophoblast cells (light green) invade through at least the inner one-third of the uterine myometrium. [Reproduced with permission from The Curators of the University of Missouri (Copyright 2010, The Curators of the University of Missouri).]

Although the architecture of the murine placenta has remarkable similarities to that of the human, there are several important differences that are outlined in Fig. 1 (10, 11). By transducing murine trophectoderm at the blastocyst stage, Kumasawa et al. (6) drive trophoblast-specific expression of sFLT1 and show that a PE-like disease can be specifically promoted in mice by placentally derived sFLT1. The disease caused by such expression seems to best mimic

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late-onset PE. No effects were seen in livers of mothers carrying hsFLT1 fetuses, and the disease was not accompanied by cranial hemorrhage or other manifestations of severe PE or hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome. The methods described by Kumasawa et al. (6) result in expression of sFLT1 in all layers of murine trophoblast (12), and this pattern of expression may not completely reproduce that in human disease (13). Furthermore, although the authors (6) investigate effects of one placentally derived spliced variant of FLT1, there is emerging evidence that other splice variants may have relevance to PE (14) and that some forms of sFLT1 in preeclamptic placentas arise from protease-mediated cleavage of membrane-bound forms (15). We look forward to further refinement of the authors' (6) techniques that allow for selective gene expression in specific trophoblast cell lineages (e.g., giant cells, glycogen cells, or syncytiotrophoblast) and expanded study of alternate forms of sFLT.

The blastocyst transduction model used in this study is remarkably flexible and should allow these and other investigators to evaluate the effects of a variety of candidate placentally derived mediators of PE in combination and in parallel. In this manuscript, Kumasawa et al. (6) choose totransduce human sFLT1 into murine placenta and are able to show effects of this human-derived molecule in the presence of murine VEGF and murine PGF (6). This clever choice should make their model particularly useful in the study of a variety of potential human therapeutics for PE, including pravastatin, the therapeutic for which the study by Kumasawa et al. (6) presents data. Studies on the effects of statin drugs in animal models of PE have recently been undertaken by several groups (6, 16, 17) with promising findings. Kumasawa et al. (6) show that pravastatin induces PGF and ameliorates preeclamptic changes in their placental sFLT1 model. These results are exciting but must be viewed with care. Increases in sFLT occur during normal pregnancy; in PE, sFLT1 concentrations significantly exceed these normal levels. A treatment that abrogates the effects of sFLT during pregnancy will, therefore, require careful titration (14). Finally, although statins are presently contraindicated in pregnancy, a small prospective cohort study of human pregnancies inadvertently exposed to statins during early gestation showed no increase in teratogenicity or neonatal morbidity among exposed pregnancies (18). Unlike other statin family members, pravastatin is hydrophilic and unlikely to cross the human placenta (18), making pravastatin a promising therapeutic choice for further study in animal models of PE. If shown to have proven benefit in selective and expanded trophoblast-specific PE models based on those described here by Kumasawa et al. (6), this drug may prove an exciting candidate for future human trials.

PE-like disease can be specifically promoted in mice by placentally derived sFLT1.

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