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Review

The impact of preeclampsia on gene expression at the maternal–fetal interface

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ABSTRACT

Preeclampsia (PE) impacts 8 million mother–infant pairs worldwide each year. This human pregnancy-specific disease characterized by hypertension and proteinuria accounts for significant maternal and neonatal morbidity and mortality. The current theory of the pathogenesis of PE as reviewed by Dr. Christopher Redman and Dr. Ian Sargent is thought to occur as a 2-stage process with poor placentation in the first half of pregnancy resulting in the maternal response in the second half of pregnancy. Our studies have focused on understanding the placental contribution to this serious disease by examining the gene expression profile of the *deciduas basalis* or basal plate, the region of the placenta involved in the "poor placentation". In this review we present summaries of our microarray datasets both of normal placentation and those of gene expression changes resulting in the context of PE. Additionally, we have taken this opportunity to combine the datasets to provide a more comprehensive view of this region of the placenta. As defects in the basal plate are, in part, at the root of the disease process, we believe that understanding the pathobiology that occurs in this region will increase our ability to alter the development and/or course of PE.

1. Normal human placental development

Survival and growth of the fetus requires normal development of the placenta, which in humans involves the formation of a transient organ with both maternal and fetal contributions. During cytotrophoblast (CTB) differentiation, progenitors assume one of the two fates. In floating villi, they fuse to form multinucleate syncytiotrophoblasts (STBs), whose primary functions are transport and hormone production. In anchoring villi, mononuclear CTBs acquire tumor-like properties that enable them to invade the decidua, the endometrium of pregnancy, and the adjacent third of the myometrium (interstitial invasion). They also breach the small uterine vessels they encounter, intercalating within the muscular walls and completely replacing the resident maternal endothelial lining (endovascular invasion). As a result, high-resistance spiral arterioles are transformed into low-resistance, high-capacitance vessels that divert uterine blood flow to the floating villi. This

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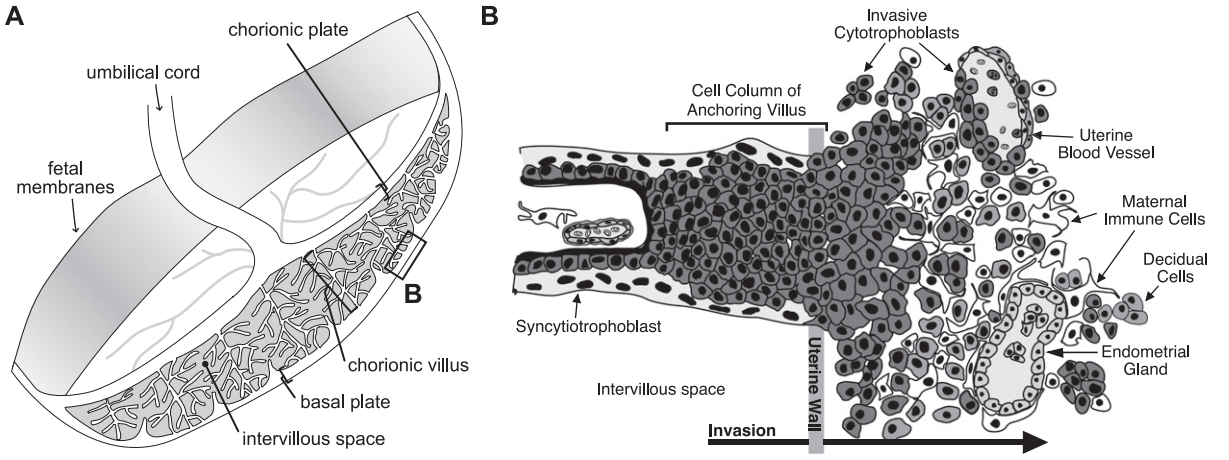

Figure 1. Diagram of the human maternal–fetal interface. (A) Representation of the human placenta after delivery. The placental surface that was adjacent to the uterine wall is termed the basal plate. The boxed area denotes the region biopsied for these studies. (B) View of the basal plate at the cellular level. This chimeric region of the placenta is composed of both maternal and fetal cells: cytotrophoblasts (dark grey), decidual cells (light grey), remodeled vasculature (both invasive CTBs and maternal endothelium) and maternal immune cells (white). (Reproduced with permission from Endocrinology along with associated text [13].)

invasion process is most active during 10–20 weeks of gestation. This region where maternal and fetal cells coexist is termed the basal plate or maternal–fetal interface, and its proper formation and function are required for normal pregnancy outcome (Fig. 1).

At a molecular level, many unusual processes occur in this area. For example, invasive CTBs execute a novel epithelial-to-mesenchymal transition that enables vascular mimicry, required for establishing blood flow to the placenta [1,2]. Perhaps most remarkably, the maternal immune system tolerates the invasion of the hemi-allogeneic fetal cells for the duration of pregnancy.

Over the past several decades, a great deal of information has been gained about placental development by taking a candidate molecule approach [3]. For example, the fact that endovascular CTBs function as endothelial cells prompted investigators to study the role of vasculogenic/angiogenic molecules, including adhesion receptors, at the maternal–fetal interface [4,5]. As in many tumors, CTBs use matrix metalloproteinases for the purpose of invasion [6,7]. Interestingly, CTBs express several molecules involved in leukocyte function, including TOLL-like receptors, which are involved in the response to infections, and L-selectin, which mediates a novel type of rolling adhesion [8,9].

However, there are also numerous examples of seemingly novel mechanisms that are unique to placental development. For example, trophoblasts in all locations lack major histocompatibility class (MHC) II expression, and upon allocation to the invasive pathway, CTBs upregulate HLA-G, a nonclassical MHC class I molecule, in the absence of HLA-A and B expression [10,11]. In addition, many lines of evidence suggest that CTBs have unusual responses to hypoxia, likely a reflection of the fact that the fetus resides in a physiologic state of lower oxygen tension [12]. Furthermore, very little is known about gene expression during the embryonic and fetal stages of human development. Accordingly, unbiased analyses, such as microarray approaches, are also crucial for obtaining new insights into the mechanisms that are required for normal basal plate formation and function during pregnancy. Determining the gene expression profile of this critical region also provides an important foundation for investigations of the basal plate region in pathologic conditions such as preeclampsia.

2. Gene expression profiling at the human maternal–fetal interface over gestation

Basal plate biopsy specimens were obtained from 36 placentas (14–40 weeks) from women who had normal pregnancies. RNA was isolated, processed and hybridized to HG-U133A and HG-U133B Affymetrix GeneChips. Surprisingly, the expression of very few genes was modulated during the 14- to 24-week interval. In contrast, hundreds of genes, including those already known to be regulated over gestation, were modulated between mid-pregnancy (14–24 weeks) and term. These data allowed us to identify molecules that play potentially important roles in the formation of the maternal–fetal interface during the second trimester or in the preparation of this area for parturition.

Our analysis revealed a total of 418 genes/expressed sequence tags that were differentially regulated between term and mid-gestation. A heat map of the top 25 up and down regulated genes is shown (Fig. 2; complete heat map and data [13]). Based on GO annotations, the differentially expressed genes were involved in a variety of biological processes. At least one sixth of the probesets were expressed sequence tags or hypothetical proteins and thus lacked annotations. Of the known differentially expressed genes, 17 were related to lipid metabolism, 10 were involved with formation or regulation of the extracellular matrix (ECM), 21 were immune effectors or modulators, 24 were transcription factors, and 6 had angiogenic/vasculogenic functions.

Ingenuity Pathway Analysis (IPA) software was used to further evaluate the participation of the differentially expressed genes in metabolic and signaling pathways. Analysis of genes with at least a twofold change highlighted two