MINIREVIEW

The Placenta and the Prolactin Family of Hormones: Regulation of the Physiology of Pregnancy

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After fertilization, the next major hurdle for reproduction in eutherian mammals is trophoblast differentiation, which is required for implantation. This in turn is followed lock step by the rapid assembly of these cells into a functional placenta. Although there is a great deal of species-to-species variation in the assemblage process *per se*, the functional results are always the same. For the remainder of gestation, whether an additional 16 days in a mouse or 9 months in a human, the development of the embryo/fetus and the health of the mother critically depend on the placenta. In humans, this fact is graphically illustrated by the spectrum of pregnancy complications that are associated with just one type of pathology, superficial attachment of the placenta to the uterus. In some cases fetal growth stalls, leading to intrauterine growth retardation. In other instances the effects extend to the mother, who may suddenly show signs of widespread vascular damage so severe that death may quickly ensue, hence the name eclampsia (Gk. *eklampsis*, sudden flash or development).

Although the placenta is a transient organ, it has evolved to meet the significant challenge of accommodating the nutritional and growth-regulatory needs of the developing fetus within the overall physiological environment of the mother. Not only must maternal physiology change to meet these needs of the fetus, but changes must also occur to prepare the mother for the distinct needs of the newborn after parturition. For successful reproduction, the physiology of pregnancy in the mother must therefore be significantly different from the physiology of the nonpregnant adult female, with differences in numerous systems, including blood vessel growth, hematopoiesis, immune response, metabolism, steroid hormone production, behavior, and mammary development. The widespread physiological changes that occur during pregnancy must be temporally coordinated among many organs and tissues, an organizational task that typically falls to circulating hormones, and a strong case can be made for the placenta as the most important source of these hormones that reprogram maternal physiology during pregnancy.

The placenta is a rather unique endocrine organ. First, since the hormone-producing placental trophoblast cells are derived from the fertilized egg, the placenta is genetically distinct from the maternal targets of the placental hormones (except, of course, in matings of highly inbred parents, such as inbred strains of mice). Second, the organ is transient, growing and developing during pregnancy but disappearing at parturition. Third, placental hormones are often present in the circulation at concentrations far in excess of what is found for similar hormones in the nonpregnant adult. And fourth, the placenta produces a number of hormones that are not otherwise synthesized in the organism, suggesting that a distinct set of hormones are required to bring about the physiological changes of pregnancy rather than simply producing more of certain hormones. In these properties, the placenta can be seen to resemble a "pharmacological" organ, dispensing high levels of foreign compounds over a restricted time period. The placental hormones almost certainly target receptors and signaling pathways in the mother that exist in the nonpregnant state, again much like pharmaceuticals, and therefore the novel and highly expressed placental hormones may provide valuable probes to identify receptors and signaling pathways that have otherwise remained obscure.

In rodents, ruminants, and primates (including humans), prominent among these placental-specific hor-

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mones are proteins that are closely related in sequence to the pituitary hormones, PRL and GH. In mice and rats, identified PRL-related hormones now number more than a dozen. The first two of these hormones were initially revealed by searches for placental proteins in rats and mice that bind with high affinity to the PRL receptor and that mimic the action of PRL (1). These two hormones have been designated as "placental lactogens" [specifically, placental lactogen I (PL-I), and placental lactogen II (PL-II)] as a reflection of their origin and their activity as lactogenic (inducers of milk production) hormones; a single PL is produced in humans.

As expected for hormones with PRL-like activities, PL-I and PL-II display a wide spectrum of activities on numerous target tissues in addition to the mammary gland. One of the most important targets for these hormones is the ovary, where they act to maintain the corpus luteum of pregnancy and to stimulate luteal progesterone production; early pregnancy depends on pituitary PRL for luteal maintenance and progesterone production, but PL-I functionally replaces pituitary PRL a few days after implantation occurs (2). At midgestation PL-II synthesis begins while PL-I expression declines, and PL-II is therefore the major lactogenic hormone of late pregnancy (2). PL-II maintains positive signaling through the PRL receptor, *e.g*. in mammary development; PL-II has also been shown to enter the fetal compartment (2), where it represents the major ligand for the PRL receptor, which is widely expressed in the developing fetus. More recently, a variant of PL-I has been discovered in the rat, which broadens the list of potential ligands for the PRL receptor in the maternal and fetal compartments (3).

The existence of placental hormones related to PRL but distinct from the PLs was first realized with the identification of proliferin (4). Although found as a growth-regulated mRNA and protein in mouse fibroblast cell lines, proliferin expression *in vivo* is restricted to placental trophoblast giant cells (5), the terminally differentiated cells of the placenta that form intimate connections with maternal decidual tissue. Proliferin was named both for its specific expression in proliferating cells (in culture) and for its relationship to PRL, but hypothesized PRL-like actions of this placental hormone have not been detected. Instead, proliferin was found to target endothelial cells and to induce endothelial cell migration (6); another function attributed to proliferin (referred to as "mitogen-regulated protein" by these investigators) is the stimulation of midgestation uterine cell proliferation (7).

The ability of proliferin to act on endothelial cells suggests that this hormone may play an important role in the vascularization of the implantation site (Fig. 1). Indeed, the majority of the soluble angiogenic activity secreted by the midgestation placenta, as measured in an endothelial cell chemotaxis assay, is attributable to proliferin (6). Furthermore, disruption of a gene for the GATA-2 transcription factor, a factor essential for proliferin expression *in vivo*, results in a significant

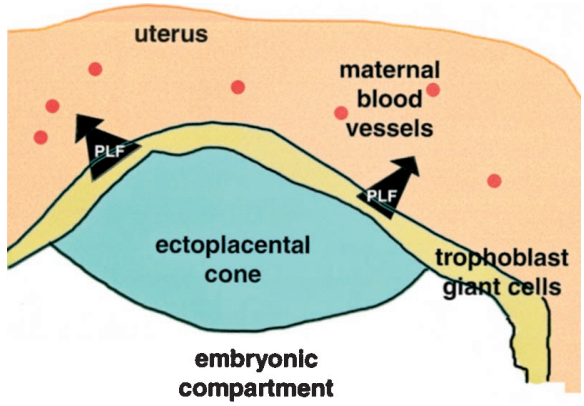

Fig. 1. Model of Proliferin Action

Proliferin (PLF) is secreted specifically by the trophoblast giant cells (*yellow*) from early- through midgestation in mice. The resultant gradient of proliferin extending from the giant cells into the uterus would act as a chemoattractant for endothelial cells in maternal uterine blood vessels to migrate toward the implantation site. As these vessels reach the trophoblast cell layer, the giant cells displace the endothelial cells and establish direct contacts between the trophoblasts and maternal blood.

decrease in the amount of angiogenic activity secreted by the placenta and an implantation site that displays markedly reduced vascularization (8). Since proliferin is expressed by all of the trophoblast giant cells, which form a thin layer completely surrounding the embryo and other extraembryonic layers, it seems likely that a primary function for proliferin is to stimulate reorganization and growth of maternal blood vessels in the decidual tissue toward implantation sites; the close apposition of maternal blood vessels with the trophoblasts is essential for the establishment of efficient nutrient/waste and gas exchange between the maternal and embryonic compartments. The mechanism of proliferin action is not completely understood, but proliferin is able to bind to endothelial cells through the insulin-like growth factor 2/mannose 6-phosphate receptor, and binding to this receptor is required for proliferin-induced cell migration (9), but how this receptor participates in the transduction of ligand binding into an intracellular signal cascade has not been well established.

The detection of the proliferin mRNA in a placental cDNA library also led to the discovery of another placental-specific hormone, designated proliferin-related protein or PRP (10). This hormone was named to reflect the observation that the proliferin and PRP cDNAs hybridize to each other, but upon inspection of the cDNA sequences it became clear that the region of identity only included the 5′-untranslated region and a portion of the signal-sequence coding region; the remainder of the coding regions for these two hormones was similar, but no more similar than for proliferin or PRP compared with PRL or to the PLs. With the finding that proliferin was an angiogenic hormone, the effect of PRP on endothelial cells was also examined. Sur-

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prisingly, PRP was found to have the opposite effect of proliferin, *i.e.* it inhibited endothelial cell migration (6). PRP was found to block endothelial cell migration in response to several angiogenic factors, not just to proliferin, and thus may act by inducing a signaling pathway that targets a common and essential step in chemotactic cell movement.

PRP is expressed a few days later than proliferin, and PRP is expressed in a broader swath of cells that includes both the giant cells and the spongiotrophoblasts, diploid cells within the placenta that lie directly under the giant cells (11, 12). The antiangiogenic effect of PRP may have several physiological consequences (Fig. 2). First, PRP may simply be the "brake pedal" that slows down vessel growth in response to proliferin and other angiogenic factors. Second, endothelial cells at the ends of the maternal blood vessels that reach the placenta are displaced by trophoblasts, resulting in the direct contact of the trophoblasts with maternal blood in spaces referred to as blood sinuses (13); PRP may be important for preventing endothelial cells from resealing the ends of the vessels. And third, PRP is perfectly positioned to generate a barrier zone to prevent maternal blood vessels extending from the uterus and fetal vessels growing out into the placenta from criss-crossing; without such a barrier to vessel growth, maternal vessels might be able to deliver immune cells into the fetal compartment where they would recognize paternal antigens, and fetal vessels might grow into the uterus with the potentially disastrous result of excessive bleeding at parturition.

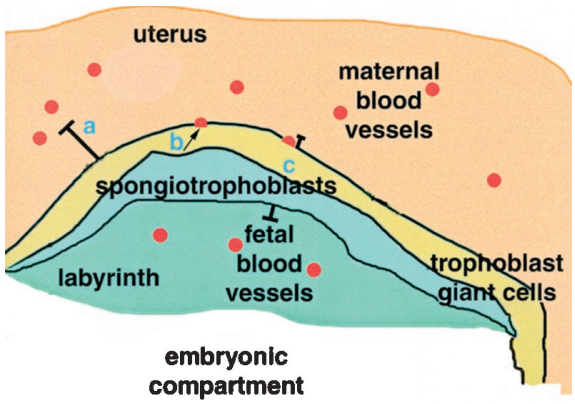

Fig. 2. Model of PRP Action

PRP is synthesized by both the giant cells (*yellow*) and the underlying spongiotrophoblasts (*blue*) during the second half of gestation in mice. Note that the cell layers and placental structure are different between early pregnancy, as shown in Fig. 1, and later pregnancy, as shown here. The antiangiogenic action of PRP is postulated to lead to three physiological effects: a) inhibiting migration of maternal blood vessels toward the placenta after midgestation (the temporal "brake pedal"), b) preventing endothelial cells from resealing vessels that are contacting the trophoblast layer (thus enabling the trophoblasts to maintain direct contact with maternal blood), and c) forming a barrier zone that keeps maternal vessels from growing into the embryonic compartment and fetal vessels from extending into the uterus.

The functions of the many other placental hormones related to PRL are only now beginning to be identified. Consistent with the categorization of these hormones as members of the cytokine superfamily, preliminary findings have identified specific hematopoietic cell populations, including natural killer cells (14), preerythrocytes (15), and megakaryocytes (J. Lin and D. Linzer, manuscript in preparation), as targets for other placental hormones in the PRL family. Furthermore, the PRL receptor, the target of PL-I and PL-II as well as of PRL, is also an important signaling receptor on lymphocytes (16). Thus, a common theme appears to be developing for the actions of the placental PRL family of hormones, *i.e* that these hormones contribute to the broad array of alterations in angiogenesis, hematopoiesis, and lymphocyte function that occur during pregnancy.

Mammalian pregnancy, from mice to humans, is characterized by blood vessel growth (in the uterus and placenta, as well as in the fetus), by large increases in blood volume (with corresponding increases in hematopoiesis required to keep blood cell concentrations near the optimal levels in the mother, while hematopoiesis is also being initiated in the fetus), and by alterations in the immune system (at least in part to protect the fetus from attack by the mother's lymphocytes). In rodents, it seems likely that many of these changes in the blood system in the mother and fetus during pregnancy can be attributed to the effects of the placental hormones in the PRL family. Other than a placental lactogen, homologs for these hormones have not yet been identified in humans, but since pregnancy-specific changes in vascularization and hematopoiesis also occur in human pregnancy, similar placental factors may also be involved. Whether or not human homologs of the rodent PRL-like placental hormones are eventually detected, their molecular and cellular targets and the resultant downstream signaling pathways may well be conserved, and thus an analysis of the effects and mechanisms of action of the rodent PRL-like placental hormones should provide important insights into how the physiology of pregnancy is regulated in humans.

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