

22 The prolactin family: regulators of Uterine biology

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INTRODUCTION

Pregnancy requires significant changes in the functioning of maternal tissues. Of primary importance is the redirection of resources and nutrients to the uterus, the site of embryonic development. Pregnancy is associated with two key uterine adaptations:

- the differentiation of uterine stromal cells, a process referred to as decidualization
- the modification of the uterine arterial vessels supplying the placenta.

The latter adaptation is directed, at least in part, by invasive trophoblast cells exiting the chorioallantoic placenta. Some of the functions of decidual cells and invasive trophoblast are mediated by their secretion of a family of hormones related to prolactin (PRL).

The purpose of this chapter is to provide a framework for understanding the biology of the PRL family in the context of uterine events contributing to the establishment and maintenance of pregnancy. The discussion focuses primarily on the rat and mouse and, where applicable, on other species for comparative purposes.

ORGANIZATION OF THE UTEROPLACENTAL COMPARTMENT

The uteroplacental compartments of the rat and mouse are similar and they share the same basic organizational plan of other species with hemochorial placentation.^{1,2} Schematic representations of rat uteroplacental anatomy are presented in Figure 22.1

The site where blood enters the uterus determines the orientation of the uteroplacenta. This region is referred to as the mesometrial compartment, and the opposite side is antimesometrial. The uterine mesometrial compartment is composed of stromal cells, blood vessels, immune/inflammatory cells, smooth muscle cells of the myometrium, and trophoblast cells. Cellular composition is dynamic. Following implantation, natural killer cells expand in number, and infiltrate the

mesometrial decidua, located adjacent to the developing chorioallantoic placenta. Decidual cells are derived from uterine stromal cells.^{3,4} A triangular-shaped area rich in blood vessels is situated between the mesometrial decidua and the surface of the uterus and is referred to as the metrial gland, or the mesometrial lymphoid aggregate of pregnancy (MLAP).^{5,6} A subpopulation of trophoblast giant cells represents the earliest extraembryonic invaders of the uterine mesometrial vasculature. While pregnancy progresses, placental and embryonic structures expand in size and the decidua regresses. The chorioallantoic placenta is established in the mesometrial compartment and consists of two functionally distinct regions:

- a junctional zone, an endocrine and invasive tissue, which is composed of trophoblast giant cells, spongiotrophoblast cells, glycogen cells, and the source of an invasive trophoblast cell population
- a labyrinth zone, which is the site of maternal–fetal exchange and the location of syncytial trophoblast, cytotrophoblast, and labyrinthine trophoblast giant cell lineages.

Accompanying the development of the chorioallantoic placenta, natural killer cells vacate the mesometrial decidua and infiltrate the metrial gland where they associate with the resident vasculature. Subsequently, the antimesometrial deciduum and mesometrial-associated natural killer cells degenerate. As natural killer cells vacate, the specialized population of invasive trophoblast cells exits the junctional zone of the chorioallantoic placenta, invades the mesometrial decidua, and associates with the vasculature⁷ (Figure 22.2). In the mouse, trophoblast invasion is limited to the mesometrial decidua; in the rat, trophoblast cells penetrate through the mesometrial decidua and infiltrate the metrial gland.

THE PRL FAMILY

PRL is a hormone initially isolated from the mammalian anterior pituitary with effects on reproduction

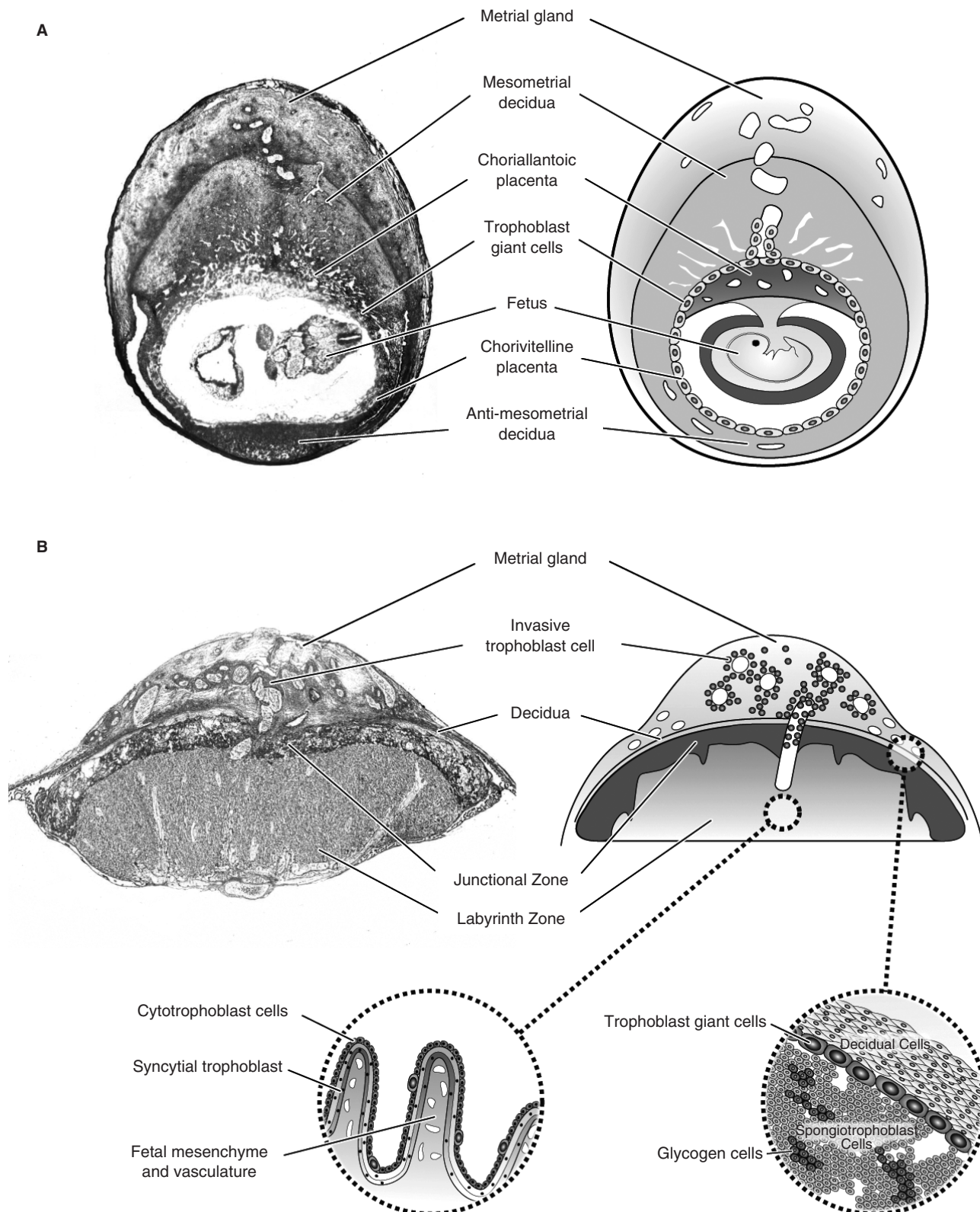


Figure 22.1 Mid and late gestation uteroplacental compartments. (A) Hematoxylin and eosin-stained tissue section of the mid gestation rat uteroplacental compartment (left, day 11 of gestation) and a corresponding schematic diagram (right). (B) Hematoxylin and eosin-stained tissue section of the late gestation rat uteroplacental compartment (left, day 18 of gestation) and a corresponding schematic diagram (right) with highlighted expanded views of the labyrinth and junctional zones (lower panels). (Reproduced in modified form from Ain et al,¹⁰³ with permission from Humana Press.)

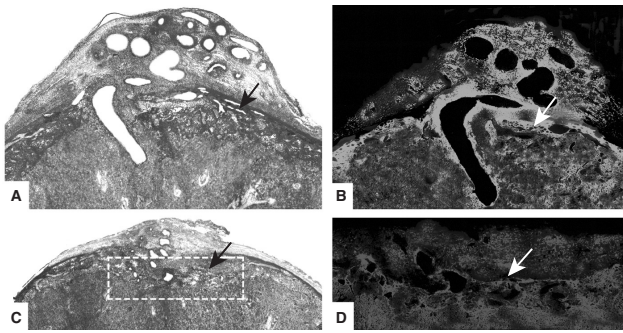


Figure 22.2 Identification of invasive trophoblast cells in the rat and mouse. Rat and mouse placentation sites were recovered at day 18 of gestation, and 10 μ m sections prepared. Trophoblast cells were identified by cytokeratin immunostaining. (A) Hematoxylin and eosin staining of the rat placentation site. (B) Cytokeratin immunolocalization with the rat placentation site. (C) Hematoxylin and eosin staining of the mouse placentation site. (the area shown in the box is present in D). (D) Cytokeratin immunolocalization within the mouse placentation site. All magnifications are at 100 \times . Arrows indicate the trophoblast giant cell boundary between the placenta and decidua. (Reproduced from Ain et al,⁷ with permission from Academic Press.)

and lactation.^{8,9} Subsequent analyses expanded the range of biological actions for PRL to effects on the brain, immune system, and metabolism.¹⁰ Concurrent with these efforts, it also became evident that the PRL locus was expanded in a subset of mammals, including the rat, mouse, and cow; however, PRL loci of other species, as exemplified by the dog and human, have only a single orthologous member, PRL.¹¹ The expanded PRL families, like other gene families, arose via gene duplication and have evolved to their present form by natural selection, resulting in both subfunctionalization and neofunctionalization.¹²

The rat genome contains at least 24 genes related to PRL, spanning approximately 1.7 megabases on chromosome 17.¹³ Organization of the rat PRL family locus is similar to the 1-megabase mouse PRL family locus situated on chromosome 13, which includes at least 26 genes related to PRL.¹⁴ Phylogenetic relationships of rat and mouse PRL families are presented in Figure 22.3. Each PRL family gene encodes for a secretory protein that has been linked to pregnancy.¹¹ All PRL family genes possess five conserved exons. A subset of PRL family genes clustered in the middle of the locus contains an additional exon(s) situated between exon-II and exon-III of the prototypical PRL 5-exon structure.^{13,14} The anterior pituitary, uterine decidual cells,

and various lineages of trophoblast cells all contribute to the production of these ligands. They are elaborated during gestation in specific temporal and spatial profiles. Biological activities of PRL family ligands can be categorized as classical and non-classical.¹¹ Classical actions are mediated by ligand interactions with the PRL receptor and non-classical modes of actions utilize other signaling pathways. PRL and the placental lactogens (PLs) are PRL receptor agonists, and are critical to pregnancy and lactation through their actions on the corpus luteum and mammary gland.¹¹ The remaining members of the PRL family have a broad spectrum of targets, including but not limited to hematopoietic and immune cells and cells of the vasculature. Overviews of PRL family members associated with decidual tissue and those potentially impacting the uterine vasculature are provided below.

DECIDUAL PRL FAMILY

The seminal research leading to the discovery of uterine decidua as a source of PRL related ligands was directed towards elucidation of a decidual factor that promoted corpus luteum survival and function.¹⁵⁻¹⁷ Such biological activities are classified as luteotropic actions and are hallmarks of PRL (see Chapter 17). These investigative efforts culminated in the identification of four PRL family ligands in the deciduum, including PRL-like protein-B (PLP-B), decidual PRL-related protein (dPRP), PLP-J, and PRL. The exact contribution of any of these decidual products to the luteotropic activities intrinsic to decidual tissue is unknown. A couple of generalizations are appropriate for the decidual PRL family ligands: i) expression is most abundant in antimesometrial decidua of pregnancy; and ii) expression is evident in decidual tissue of pseudopregnancy. The decidual PRL family ligands will be discussed in the order of their discovery.

PLP-B

Friesen and co-workers first identified PLP-B in the rat placenta¹⁸ and subsequently demonstrated its expression in rat decidual tissue.¹⁹ PLP-B is encoded by a 5-exon gene with significant homology to the prototypical PRL gene.^{13,14} Temporally, decidual PLP-B production follows the growth, development, and regression of the antimesometrial deciduum.^{19,20} After mid gestation, PLP-B expression shifts to spongiotrophoblast cells of the rat chorioallantoic placenta,

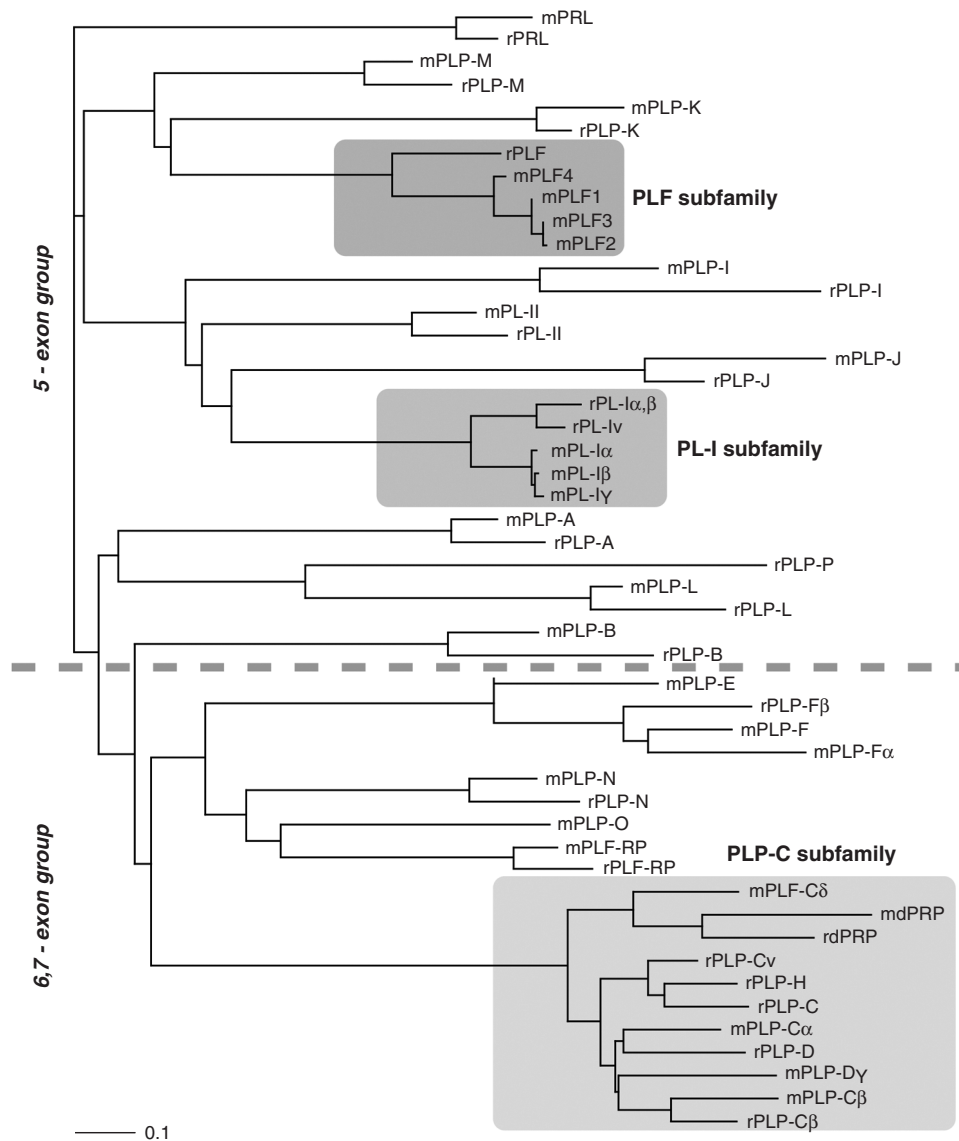


Figure 22.3 Phylogenetic analysis of the PRL family in the rat (*Rattus norvegicus*), and mouse (*Mus musculus*). Multiple amino acid sequence alignments and phylogenetic tree construction were performed using the CLUSTAL X and TREEVIEW software programs.^{104,105} GenBank accession numbers for each member of the rat and mouse PRL family are provided in Table 22.1. The PRL families of the rat and mouse are largely orthologous. The rat and mouse expanded PRL families contain subsets of 5-exon and 6-exon members which can be further subdivided into subfamilies (e.g. PL, PLF, PLP-C). Although the rat and mouse PRL family loci are similar, each possesses some notable unique features (e.g. rat PLP-P, mouse PLP-O, mouse PLP-E, PLF, and some features of the PLP-C subfamily).

where it is expressed at high levels until it declines during the final days of gestation.^{18,20-22} The PLP-B protein is secreted as a glycoprotein by both decidua and placental tissues.²⁰ PLP-B exhibits similar structural features and expression profiles in the mouse.^{23,24} There is some evidence that PLP-B expression is induced by tissue injury, at least in the placenta,²² but there is little information on its biological activities. PLP-B does not effectively bind to PRL receptors, nor

does it activate the PRL receptor signaling pathway;²⁰ thus, it is unlikely to be directly responsible for the luteotropic actions of decidual tissue.

dPRP

dPRP was discovered in an attempt to characterize the PLP-B protein from rat decidual tissue.²⁵ Once

Table 22.1 Rat and mouse PRL families

PRL family ^a	Rat GenBank Accession No.	Mouse GenBank Accession No.	References
PRL	NM_012629	NM_011164	82–84
PL-I α	NM_017363	AF525162	13, 14, 85–87
PL-I β	DQ329283	NM_172155	13, 14
PL-I γ	—	NM_172156	14
PLP-J	NM_031316	NM_013766	34–37
PL-II	NM_012535	M14647	87–89
PLP-I	NM_153736	AF525154	14, 36
PLP-B	M31155	NM_011166	23, 24, 61
dPRP	NM_022846	NM_010088	23, 25, 26
PLP-K	NM_138861	NM_025532	14, 36, 37
PLP-D	NM_022537	—	90
PLP-C ν	NM_020079	—	91
PLP-C	M76537	—	92
PLP-H	NM_021580	—	93
PL-I ν	NM_033233	—	94, 95
PLP-C γ	—	NM_023741	14
PLP-C β	NM_134385	NM_023332	96
PLP-C δ	—	NM_028477	14
PLP-C α	—	NM_011167	97
PLP-N	NM_153738	NM_029355	14, 77
PLP-E	None	NM_008930	98, 99
PLP-F	None	NM_011168	98, 99
PLP-F β	AY741310	—	Unpublished ^b
PLP-F α	NM_022530	—	56
PLP-O	—	NM_026206	14
PLF-RP	NM_053364	NM_011120	50, 56, 78
PLF1	—	NM_031191	49
PLF2	—	K03235	100
PLF3	—	NM_011954	101
PLF4	—	AF128884	102
PLP-M	NM_053791	NM_019991	78
PLF	DQ329281	—	13
PLP-A	NM_017036	NM_011165	61
PLP-L	NM_138527	NM_023746	36, 78
PLP-P	DQ329280	—	13

^aAbbreviations: PRL, prolactin; PL, placental lactogen; PLP, prolactin-like protein; dPRP, decidual prolactin-related protein; PLF, proliferin; PLF-RP, proliferin-related protein.

^bJK Ho-Chen, J Bustamante, MJ Soares, unpublished results.

isolated, dPRP was found to be more closely related to another PRL family member, termed PLP-C, which facilitated its cloning and characterization.²⁵ dPRP is a member of the 6-exon cluster of genes,²⁶ centrally located within the rat and mouse PRL family loci.^{13,14} The temporal and tissue-specific expression profiles for dPRP are similar to PLP-B, except in magnitude.^{25–29} Levels of dPRP production in uterine decidua and the chorioallantoic placenta are inversely related. dPRP expression is abundant in the uterine decidua and modest in the chorioallantoic placenta.²⁹ The dPRP protein is secreted as a glycoprotein but probably resides primarily in the decidual extracellular matrix where it binds with high affinity to heparin-containing molecules.^{28,30}

dPRP exhibits similar structural features and expression profiles in the mouse.^{23,31}

The potential for dPRP as an activator of both classical and known non-classical mechanisms has been examined. dPRP failed to bind to PRL receptors and showed minimal ability to promote the proliferation of the PRL-dependent Nb2 lymphoma cell line.²⁸ Two members of the mouse PRL family, proliferin (PLF) and proliferin-related protein (PLF-RP), are known modulators of angiogenesis through non-classical mechanisms.³² dPRP did not markedly influence the development of vascular structures, as evaluated through both in-vitro and in-vivo assays;²⁸ however, in-vivo analysis indicated that dPRP could facilitate heterologous tissue transplantation into athymic mice.²⁸

Additional experiments with dPRP fusion proteins implicated eosinophils as potential targets for dPRP action.³⁰ These findings suggested that dPRP could potentially contribute to decidual signals responsible for the establishment of pregnancy and prompted the creation and characterization of a dPRP null mouse.

dPRP null mice were made by replacing exons II–VI of the dPRP gene with an inframe enhanced green fluorescent protein gene and a neomycin resistance cassette.³³ Under standard animal husbandry conditions, some modest phenotypic changes were observed, including a decrease in decidual PLP-J expression, but none sufficient to impair the progression of pregnancy. A prominent phenotype was observed when pregnant dPRP null mice were exposed to a physiological stressor. Pregnancies were disrupted when dPRP null mice were exposed to hypoxia. In contrast, wild-type mice adapted to the hypoxic challenge and their pregnancies proceeded. These observations suggest that dPRP may participate in pregnancy-dependent adaptations to physiological stressors. The mechanism underlying dPRP's role in the adaptive response to hypoxia is unknown at present.

PLP-J

Two approaches were used to identify a third decidual mRNA related to PRL:

- screening a decidual cDNA library with a human PRL cDNA³⁴
- inspection of expressed sequence tag (EST) databases for cDNAs with sequence similarity to members of the PRL family.^{35–37}

One of the groups referred to the new gene as PLP-I, whereas the other three termed the new decidual transcript as PLP-J. We refer to the gene as PLP-J, since there is another trophoblast-derived PRL family member with the name PLP-I.^{14,36} The PLP-J mRNA and protein are abundant within the antimesometrial decidua. It is curious that PLP-J is embedded between the PL-I genes and the PL-II gene within the PRL family locus^{13,14} and structurally is also most closely related to the PLs. However, unlike the PLs, PLP-J does not interact with the PRL receptor (S Alam, MJ Soares, unpublished results). Similar to dPRP, PLP-J avidly binds to heparin-containing molecules (S Alam, MJ Soares, unpublished results). We view PLP-J as a potential autocrine/paracrine modulator of the establishment of pregnancy, and/or similar to dPRP, as a contributor to pregnancy-dependent adaptations to physiological stressors.

PRL

The PRL gene has also been shown to be expressed in rat and mouse decidual tissue.^{38,39} The overall abundance of decidual PRL is less than for other members of the decidual PRL family. PRL transcripts in the decidua are most readily detected by reverse transcription-polymerase chain reaction (RT-PCR). PRL signals through the PRL receptor. In the early postimplantation uterus, the PRL receptor is primarily associated with undecidualized stromal cells in the antimesometrial border and a restricted population of mesometrial stromal cells associated with the developing chorioallantoic placenta.⁴⁰ As gestation advances, decidual cell expression of the PRL receptor increases and then declines as the antimesometrial decidua regresses.⁴¹ Local production of PRL by decidual cells may contribute to decidual cell survival.^{38,42} Trophoblast giant cells of the chorioallantoic placenta are situated at the decidual cell-placental interface and produce PL-I and PL-II, which are PRL receptor agonists, and probably also contribute to the modulation of uterine decidual cell function.¹¹

PRL is a prominent product of the uterine decidua in primates, and has been best studied in the human.^{43,44} Human decidual PRL binds to heparin,⁴⁵ a feature it shares with two rodent decidual PRL family members (dPRP and PLP-J), and thus probably accumulates in the decidual extracellular matrix. Targets for human decidual PRL include intrauterine (uterine gland development, angiogenesis, trophoblast cell development, and immune regulation), amniotic, and possibly fetal tissues.^{46,47} The expansion of decidual PRL-related ligands in rodents might represent a subspecialization of biological activities ascribed to PRL in human decidua.

THE PLACENTAL PRL FAMILY AND THE UTERINE VASCULATURE

Establishment of an effective delivery system of nutrients and waste products between the mother and the fetus is imperative for a successful pregnancy.⁴⁸ Trophoblast cells contribute to the remodeling of the uterine vasculature, at least in part, through their secretion of hormones/cytokines, which influence cell types within the uterine mesometrial compartment. PRL family ligands are produced by trophoblast cells as they establish relationships with the uterine mesometrial vasculature.

PLF and PLF-RP

As indicated above, two members of the mouse placental PRL family (PLF and PLF-RP) modulate blood vessel development.³² PLF was originally discovered as a growth factor regulated gene in serum-starved mouse fibroblasts⁴⁹ and PLF-RP was identified based on its structural relationships with PLF.⁵⁰ PLF is the product of at least four closely related genes in the mouse,¹⁴ whereas in the rat there is only a single PLF gene.¹³ PLFs and PLF-RP are products of the placenta.^{50,51} Trophoblast giant cells contribute significantly to the initial invasion and remodeling of the uterine vasculature and are the source of PLFs.^{52,53} PLF-RP expression differs in the mouse and rat. In the mouse, PLF-RP is a product of the spongiotrophoblast;^{54,55} however, in the rat, PLF-RP is expressed at the leading edge of invasive trophoblast at mid gestation and then within the labyrinth zone during the last week of gestation.⁵⁶ Linzer and his colleagues have demonstrated that PLF is angiogenic and PLF-RP is antiangiogenic.³² These two hormones/cytokines reciprocally influence blood vessel formation as demonstrated by both in-vitro and in-vivo analyses.^{32,57-59} The biological activities of the rat PLF and PLF-RP orthologues have not been reported. Collectively, PLF and PLF-RP represent the major placental factors regulating angiogenesis in the mouse.⁶⁰

PLP-A

PLP-A modulates the establishment of the hemochorial placenta. Rat PLP-A was first discovered as a by-product of the cDNA cloning of PL-II.⁶¹ Subsequently, mouse orthologues were revealed and characterized from EST databases.^{23,24} In the mouse, PLP-A is primarily a product of trophoblast giant cells,^{24,62} whereas in the rat PLP-A is synthesized by trophoblast giant cells, spongiotrophoblast cells, and invasive trophoblast cells.^{7,63} PLP-A is secreted as a glycoprotein hormone,^{24,64,65} circulates in maternal blood as a high molecular mass complex,^{66,67} and specifically interacts with uterine natural killer cells.^{68,69} Uterine natural killer cells are the principal leukocytes of the uterus⁷⁰⁻⁷² and have been implicated in mediating uterine mesometrial inflammatory/immune responses⁷³ and vascular remodeling.⁷⁴ The latter effects on the uterine mesometrial vasculature facilitate nutrient flow to the placenta and fetus⁷⁴ and are proposed to be mediated by interferon γ (IFN γ).⁷⁵ PLP-A is an intermediary in trophoblast cell modulation of natural killer cells, including their production of IFN γ .^{69,76}

The physiology of PLP-A has been further explored in PLP-A-deficient mice.⁷⁶ PLP-A null mice were

made by replacing exons II-V of the PLP-A gene with a neomycin resistance cassette.⁷⁶ As was true for the dPRP gene, the PLP-A gene was also dispensable when mice were maintained under standard animal husbandry conditions. However, when pregnant PLP-A null mice were challenged by exposure to hypoxia, they were not able to adapt and their pregnancies terminated.⁷⁶ Pregnancies failed because of inadequate placentation (Figure 22.4). Exposure to maternal hypoxia disrupted trophoblast cells of the PLP-A-deficient chorioallantoic placenta from establishing connectivity with the uterine mesometrial vasculature. This is in contrast to pregnant mice expressing PLP-A, which successfully adapt to low oxygen and maintain their pregnancies. The potential involvement of natural killer cells in mediating PLP-A-regulated adaptations to maternal hypoxia is unknown.

PRL family and invasive trophoblast cells

During the last week of gestation, invasive trophoblast cells exit the chorioallantoic placenta and enter the mesometrial uterine compartment.⁷ These invasive trophoblast cells possess a unique phenotype, which is distinguished by their elaboration of PRL family ligands. In the rat, invasive trophoblast cells express five members of the PRL family: PLP-A, PLP-L, PLP-M, PLP-N, and PLP-P.^{7,13,77} The structure and function of PLP-A were discussed above. The remaining PRL-related proteins expressed in invasive trophoblast were first identified through searches for PRL-related sequences in rat EST and genomic databases.^{13,36,37,77,78} Orthologues were identified from mouse EST and genomic databases,^{14,37,78} except for PLP-P, which is unique to the rat.¹³ Minimal characterization of the corresponding mRNAs and proteins has been performed beyond tissue expression profiles. In comparison to the junctional zone of the rat chorioallantoic placenta, PLP-A expression in invasive trophoblast cells is weak.⁷ PLP-M and PLP-P are dually expressed in invasive trophoblast cells and in trophoblast cells situated within the chorioallantoic placenta,^{7,13} whereas PLP-L and PLP-N expression is restricted to invasive trophoblast cells.⁷ Rat invasive trophoblast cells expressing genes related to PRL penetrate throughout the uterine mesometrial compartment.⁷ In contrast, mouse invasive trophoblast cells do not penetrate beyond the mesometrial decidual boundary and only prominently express two members of the PRL family (PLP-M and PLP-N).⁷ Invasive trophoblast can replace the endothelium of the uterine arterial vessels

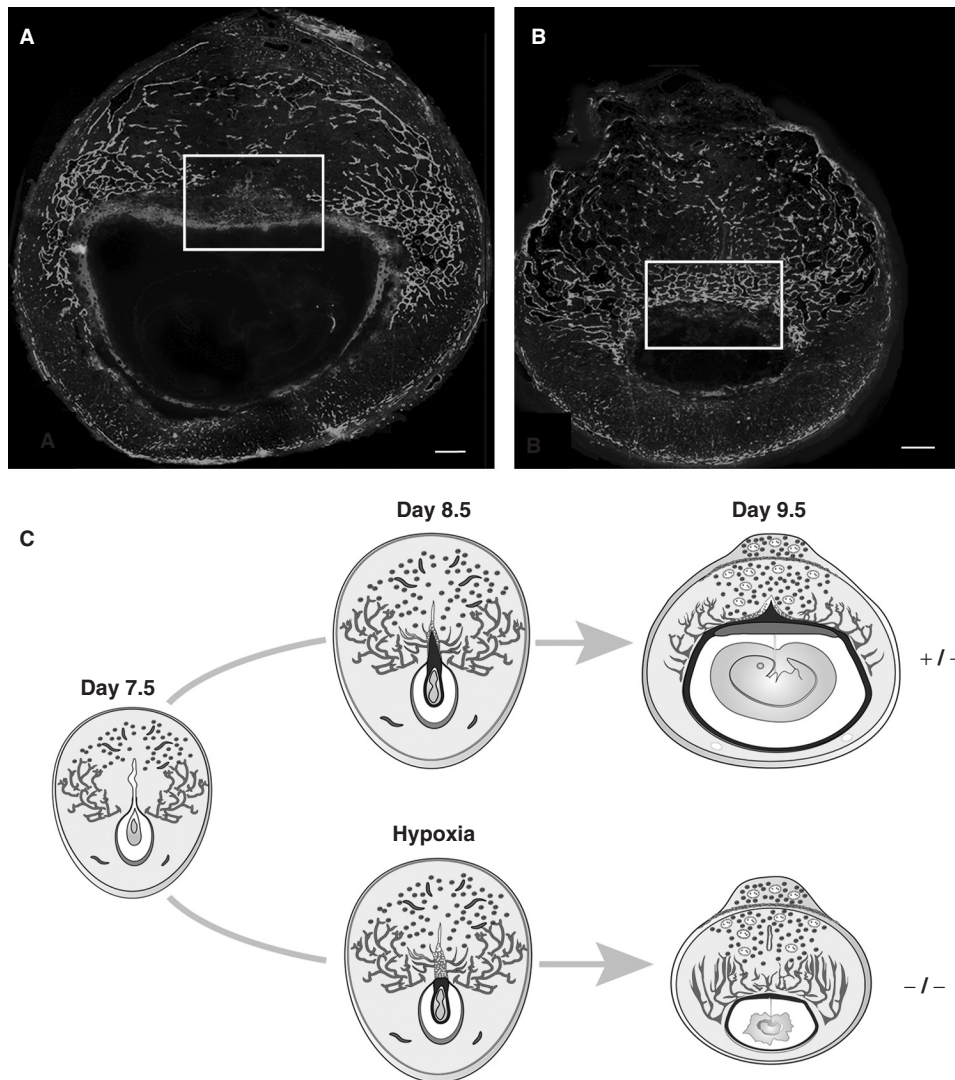


Figure 22.4 Defect in hemochorial placentation and trophoblast-vascular interactions in PLP-A null mutant mice exposed to hypoxia. Double immunohistochemical staining for trophoblast cells by using a cytokeratin-8-specific antibody (TROMA-1) and for endothelial cells by using an endoglin antibody within implantation sites of wild-type and PLP-A null mutant mice after 48 hours (A and B) of hypoxia starting on gestation day 7.5 (scale bars = 250 μ m). (C) Cellular dynamics at implantation sites of wild-type and PLP-A null mutant mice exposed to hypoxia for 48 hours starting on gestation day 7.5. Note the lack of trophoblast expansion into the mesometrial chamber on days 8.5 and 9.5 of pregnancy in PLP-A null mutant mice after exposure to hypoxia. Also note the aberrant vasculature and underdeveloped placentas at the implantation sites on day 9.5 of pregnancy in PLP-A null mutant mice exposed to hypoxia. (Reproduced in modified form from Ain et al,⁷⁴ with permission from the National Academy of Sciences of the USA.)

(endovascular) and accumulate around the vessels (interstitial), where their presence is associated with the disappearance of vascular smooth muscle.^{7,79,80} These changes impact the permeability and distention properties of the vessels and alter their delivery of cellular and molecular components of maternal blood. A distant relative of the PRL family, growth hormone variant (also known as placental growth hormone), is a known autocrine/paracrine stimulator of invasiveness in human trophoblast.⁸¹ Whether the different

PRL family expression patterns in invasive trophoblast cells of the rat and mouse are responsible for the species difference in the depth of trophoblast invasion remains to be determined.

FINAL THOUGHTS

The PRL family is an intriguing example of the evolution of a set of genes directed towards the regulation

of viviparity and species-specific reproductive success. At this juncture, we possess a modicum of knowledge on the evolution of the PRL family but we do have enough insights from the few mammalian species that have been studied to know that conservation is not the rule. The lack of species conservation would direct some scientists elsewhere. However, based on emerging gene targeting experimentation, this would be an unfortunate oversight.^{33,76} Evolution of the PRL family and its various expansions did not occur in the laboratory setting. The PRL family expanded in the mouse and rat to ensure pregnancy-dependent adaptations to environmental challenges. These challenges might have included nutrient availability, exposure to pathogens, and temperature excesses. The ability to reproductively adapt to environmental challenges provides a selective advantage for a species, ensuring its survival.

The insights discussed in the preceding paragraph are based on the phenotypic analysis of mice with disruptions in two mouse PRL family genes, dPRP and PLP-A.^{33,76} The physiological relevance of the remainder of the mouse PRL family locus is unknown. If the mouse PRL family locus was modified to resemble the human locus, consisting of only PRL, what would be the impact on pregnancy? The generation of new genes by gene duplication and natural selection results in a purification process, leading to subspecialization from the ancestral gene (subfunctionalization) or the development of new functions not previously attributed to the ancestral gene (neofunctionalization). Have rodent PRL family ligands undergone subfunctionalization and/or neofunctionalization? Are mouse PRL and human PRL functionally equivalent or have they undergone specialization? These questions can be addressed through chromosomal engineering and gene replacement experiments and will provide important information about the evolution of the PRL family locus.

Finally, it is important to emphasize that we gain insights about human pregnancy from studying rodent pregnancy and the rodent PRL family. Pregnancy is characterized by adaptive responses to physiological stressors. Appropriate adaptive responses result in successful progression of gestation and healthy offspring, whereas ineffective adaptations compromise pregnancy and the health of the fetus and newborn. Insights into the mechanisms controlling pregnancy-dependent adaptations to physiological stressors are essential to understanding the etiology of pregnancy-related diseases, such as preeclampsia and intrauterine growth restriction. The rodent PRL family provides a means for identification of key cellular and molecular participants in pregnancy-dependent adaptations.

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Soares et al side panel

Background

- In rats and mice, the uterus is bicornuate with a mesometrial vascular supply.
- The chorioallantoic placenta develops at the mesometrial pole.
- Above the basal decidua is a triangular area rich in blood vessels known as the metrial gland or the mesometrial lymphoid aggregate of pregnancy (MLAP).
- Uterine natural killer (uNK) cells are abundant in the metrial gland at mid gestation.
- The placenta comprises two anatomically distinct regions: the junctional zone, an endocrine and invasive tissue; and the labyrinth, which is the site of maternal–fetal exchange.
- Prolactin (PRL) is a polypeptide hormone with effects on reproduction, lactation, the brain, immune system, and metabolism in rodents, humans, and other mammals.
- Members of the PRL family are produced by the anterior pituitary, the decidua, and the placenta.

Basic Science

- In mid pregnancy in the rat a subpopulation of trophoblast exits the junctional zone and infiltrates the metrial gland and its blood vessels. This coincides with the degeneration of the uNK cell population.
- In the mouse, trophoblast infiltration is restricted to the mesometrial decidua.
- A subset of mammals, including the rat, mouse, and cow have genes encoding numerous PRL family members, while other species, such as dogs and humans, have only a single orthologous member, PRL.
- The PRL family seems to have expanded in the mouse and rat to enable adaptations to environmental challenges during pregnancy. These challenges might have included nutrient availability, exposure to pathogens, or changes in atmospheric conditions or temperature.
- The anterior pituitary, uterine decidual cells, and various lineages of trophoblast cells all contribute to the production of these ligands.
- PRL and the placental lactogens (PLs) are PRL receptor agonists.
- They are critical to pregnancy and lactation through their actions on the corpus luteum and mammary gland.
- Human decidual PRL binds to heparin and probably accumulates in extracellular matrix at the maternal–fetal interface.
- Its targets in the uterus may include epithelial glands, angiogenesis, trophoblast development, and immune cells. In addition, it may target amniotic and possibly fetal tissues.
- The remaining members of the PRL family have a broad spectrum of targets, including but not limited to hematopoietic precursor cells and immune cells and cells of the vasculature. PLP-A produced by trophoblast binds receptors on uNK cells.
- Expression of decidual PRL family ligands is most abundant in antimesometrial decidua in the mouse and the rat.
- Gene ablation studies in the mouse have demonstrated that two family members, dPRP and PLP-A, are both dispensable under normal breeding conditions but their absence renders mice susceptible to hypoxia-induced pregnancy failure.

Clinical

- Insights into the mechanisms controlling pregnancy-dependent adaptations to physiological stressors may be useful in understanding the etiology of pregnancy-related diseases such as preeclampsia and intrauterine growth restriction.