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REVIEW ARTICLE

The prolactin family and pregnancy-dependent adaptations

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ABSTRACT

The prolactin gene family represents species-specific expansions of hormones/cytokines contributing to the regulation of pregnancy-dependent adaptations. In this review, we discuss the prolactin family expansion in the mouse and rat, its linkage with viviparity and its potential role in regulating adaptations to physiological stressors.

Key words: *gene families, placenta, pregnancy, prolactin.*

INTRODUCTION

Prolactin (PRL) is a protein hormone initially identified from the anterior pituitary that has profound effects on the mammary gland (Stricker & Grueter 1928; Evans & Simpson 1929; Grueter & Stricker 1929; Riddle *et al.* 1933). In the decades following its discovery, PRL has been shown to be a remarkably versatile hormone/cytokine with a myriad of biological actions in vertebrates (Nicoll & Bern 1972; Nicoll 1980; Bole-Feysot *et al.* 1998; Goffin *et al.* 2002). The spectrum of PRL functions includes physiological processes, such as water and electrolyte balance, metabolism, behavior, reproduction and immunoregulation. The versatility of PRL is linked to its structure and ability to activate cellular responses in a wide range of target tissues. The structural features of PRL have also allowed it to serve as a template for the derivation of a diverse family of ligands mediating adaptations to pregnancy.

The *PRL* gene locus has been extensively characterized in the human, mouse, rat and cow. Profound differences in the organization of the locus have been described (Schuler & Kessler 1992; Cooke & Liebhaber 1995; Wiemers *et al.* 2003; Soares 2004; S. M. K. Alam *et al.*, unpubl. data, 2005). In some species, gene duplications have occurred, resulting in the expansion of

the *PRL* locus and the creation of a cluster of related genes encoding for a family of proteins related to PRL (Soares 2004). The mouse and rat possess an expanded *PRL* gene family with similarities in their organization (Wiemers *et al.* 2003; S. M. K. Alam *et al.*, unpubl. data, 2005). An expanded *PRL* gene family also exists in the cow; however, except for *PRL*, its members are not orthologous with members of the rat and mouse *PRL* family genes (Schuler & Kessler 1992; Soares 2004; Takahashi 2006; Ushizawa & Hashizume 2006). In primates, and in humans in particular, the locus contains only a single gene, *PRL* (Cooke & Liebhaber 1995). Unlike the rat, mouse and cow, the human genome has undergone amplification at a related locus, that encoding growth hormone (GH). This is consistent with the evolution of *PRL* and *GH* from a common ancestral gene (Niall *et al.* 1971; Forsyth & Wallis 2002). The human *GH* locus contains a family of five related genes (Cooke & Liebhaber 1995).

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In contrast to rodent and ruminant GH, primate GH possess the dual capacity to activate both PRL and GH receptors, which likely provided plasticity in the choice of templates for the derivation of pregnancy-associated ligands (Soares 2004). To complete the comparative analysis, still other mammalian species may not contain expansions of either the *PRL* or *GH* loci (Talamantes *et al.* 1980; Forsyth & Wallis 2002; Soares 2004).

These observations are noteworthy. No credible scientist would question the importance of PRL and GH as regulators of key physiological processes, but why have some species selectively amplified regions of their genome to create additional ligands related to PRL and GH? Could these 'new' ligands, which do not exhibit cross-species conservation, a 'hallmark' of biological relevance, be important? In this short review, we provide evidence that species-specific gene expansions of the *PRL* family represent adaptive responses to the challenges of pregnancy and the preservation of species-specific reproductive capacities.

PROLACTIN GENE FAMILY EXPANSION IN THE RAT AND MOUSE

Discovery

Research using rats and mice has provided a wealth of information regarding the genetics and biology of the PRL family. These experimental animal models were first used to demonstrate the existence of extrapituitary sites of hormones with biological activities similar to PRL. When pregnant mice and rats were hypophysectomized, their mammary glands and ovaries continued to exhibit pregnancy-dependent changes previously attributed to PRL (Pencharz & Long 1931; Selye *et al.* 1933). The placenta was identified as one of the sources of the extrapituitary lactogenic and luteotropic activities (Astwood & Greep 1938; Cerruti & Lyons 1960). Purification and characterization of the placental hormones and the cloning and characterization of their cDNAs led to the discovery of additional proteins and cDNAs related to PRL (for reviews, see Soares & Linzer 2001; Soares 2004). Characterizations of the rat and mouse genomes through the development of expressed sequence tag databases and direct genomic DNA sequencing (Mouse Genome Sequencing Consortium 2002; Rat Genome Sequencing Project Consortium 2004) led to the delineation of rat and mouse *PRL* family loci (Wiemers *et al.* 2003; S. M. K. Alam *et al.*, unpubl. data, 2005).

Nomenclature

Nomenclature for members of the expanded PRL family is historically based and somewhat cumbersome. Names have been assigned based on biological activities (placental lactogen (PL) and chorionic somatomammotropin) and on structural similarities to PRL (PRL-related protein and PRL-like protein (PLP)). In addition, a transcript induced in proliferating mouse fibroblasts with sequence similarity to PRL was called proliferin (PLF; Linzer & Nathans 1984). PLF and a related protein (PLF-RP) were subsequently shown to be products of the placenta (Linzer & Nathans 1985; Linzer *et al.* 1985). Unfortunately, the scientific literature and databases such as GenBank are not entirely consistent regarding nomenclature for the *PRL* family (see Soares 2004).

Mouse and rat prolactin family loci

The mouse *PRL* family locus contains 26 related genes spanning 1 Mbp on chromosome 13, whereas the rat locus contains at least 25 related genes within a 2.5 Mbp region of chromosome 17 (Wiemers *et al.* 2003; S. M. K. Alam *et al.*, unpubl. data, 2005). The organizational features of the two loci are similar. The *PRL* gene is characteristically situated at one end of each locus. A few additional generalizations are possible: (i) closely related genes are located near each other; (ii) clusters of genes at each end of the locus possess a similar 5'-to 3' orientation and a 5-exon, 4-intron structure; and (iii) genes located mainly in the middle of the locus are aligned in the opposite orientation and have a 6-exon, 5-intron structure. Collectively, these features permit the categorization of members of the *PRL* family into subfamilies (e.g. PL-I, PLP-E/F and PLP-C subfamilies). It is also evident that exceptions exist with each of the rules stated here.

Prolactin family proteins

Genes of the *PRL* family encode proteins possessing a characteristic signal peptide that allows for their secretion and signature configurations of cysteine residues (Soares 2004). Most PRL family ligands enter the circulation; however, some, due to their affinity for extracellular matrix-containing molecules (e.g. heparan sulfate proteoglycan), are largely excluded from dissemination through the vasculature. Posttranslational modifications, including glycosylation, are present on the majority of PRL family ligands but not all (Soares 2004). The addition of carbohydrate to the

PRL family backbone has been shown to modify tissue distribution and biological activities.

LINKAGE OF THE PROLACTIN GENE FAMILY EXPANSION WITH VIVIPARITY

Simply stated, the PRL family is a collection of related hormones/cytokines of pregnancy. Members of the PRL family are produced by the anterior pituitary, uterus and placenta, and current evidence suggests that they participate in the regulation of viviparity.

Expression patterns

Expression of genes of the *PRL* family involves the coordination of maternal, extraembryonic and fetal tissues, and spans the entire duration of pregnancy (Soares *et al.* 1991). Mating activates a neuroendocrine response resulting in twice-daily surges of PRL from the anterior pituitary (Gunnert & Freeman 1983), which promotes survival of the corpus luteum (Bachelot & Binart 2005). These surges of PRL continue for the first half of pregnancy. Luteal steroid hormones, then, together with embryonic signals, are requisites for embryo implantation, the decidualization of the uterine stroma (DeFeo 1967) and its elaboration of a subset of PRL family ligands (Orwig *et al.* 1997; Soares 2004). Finally, the differentiation of the embryo into trophoblast and inner cell mass lineages is the trigger for the development of trophoblast cells and their initiation of *PRL* family gene expression (Soares *et al.* 1996; Soares 2004). Trophoblast cells differentiate into multiple lineages, some of which produce members of the PRL family; among these are trophoblast giant cells, spongiotrophoblast cells and invasive trophoblast cells. These distinct trophoblast cell types can be defined by the unique complement of *PRL* family genes activated.

Anterior pituitary PRL production is elevated during other physiological events, such as puberty and lactation (Freeman *et al.* 2000), and during certain pathological circumstances, especially those associated with stress (Dorshkind & Horseman 2001). Information on expression of other members of the *PRL* gene family outside of pregnancy is more limited. Two members of the PRL family expressed by trophoblast cells, PLF and PLP-E, are upregulated in extraplacental tissues during disease states, including those involving wound healing, angiogenesis and hematopoiesis (Fassett & Nilsen-Hamilton 2001; Toft *et al.* 2001; Bhattacharyya *et al.* 2002). As we learn more about the biology of the expanded PRL family, we may observe the participa-

tion of still other members contributing to adaptations to disease.

Physiological actions

The biological activities of the PRL family have been classified into two categories: (i) classical; and (ii) non-classical. Classical actions use the PRL receptor signaling pathway; whereas nonclassical activities use other mechanisms of action. A subset of PRL family ligands is capable of stimulating the PRL receptor signaling pathway. These ligands include PRL and PL, and are present throughout gestation. PRL receptors are broadly distributed, including the two classic targets of PRL action, the mammary gland and corpus luteum (Bole-Feysot *et al.* 1998; Goffin *et al.* 2002). Insights into the biology of PRL and the PRL receptor have been gained by characterization of mice with null mutations in each gene (Horseman *et al.* 1997; Ormandy *et al.* 1997). Analyses of these mutant mice have reinforced the importance of PRL as a regulator of the mammary gland and corpus luteum, and have also demonstrated that PRL participates in an even more diverse array of functions, including behavior, bone homeostasis, male fertility and metabolism (Bole-Feysot *et al.* 1998; Goffin *et al.* 2002). The impact of mutations in the *PL* genes on the physiology of pregnancy has not been reported.

Knowledge about the biology of members of the PRL family using nonclassical modes of action is limited. The efforts of Daniel Linzer's group at Northwestern University and others have contributed significantly to our understanding of two pairs of PRL family ligands: (i) PLF and PLF-RP; and (ii) PLP-E and PLP-F. PLF and PLF-RP are products of trophoblast cells, are expressed concurrently and act as regulators of angiogenesis (Jackson *et al.* 1994; Volpert *et al.* 1996; Bengston & Linzer 2000; Toft *et al.* 2001). They possess opposing actions, with PLF promoting blood vessel development and PLF-RP inhibiting the process. Additional evidence suggests that PLF may participate in wound healing (Fassett & Nilsen-Hamilton 2001). PLP-E and PLP-F are expressed sequentially during gestation by mouse trophoblast cells and act to stimulate hematopoiesis, especially megakaryocyte and erythroid lineages (Lin & Linzer 1999; Bittorf *et al.* 2000; Lefebvre *et al.* 2001; Bhattacharyya *et al.* 2002; Zhou *et al.* 2002).

Our research team has made progress in investigating another member of the expanded PRL family, termed PLP-A. This hormone is produced by trophoblast cells and specifically interacts with natural

Table 1 Mouse and rat prolactin families

Member	Abbreviation	Maternal–fetal interface source	Targets	Species
Prolactin	PRL	Decidua	PRL-R	Mouse and rat
Placental lactogen-I α	PL-I α	TGC	PRL-R	Mouse and rat
Placental lactogen-I β	PL-I β	TGC	?	Mouse and rat
Placental lactogen-I γ	PL-I γ	TGC	?	Mouse only
Placental lactogen-I variant	PL-Iv	TGC, SpT	PRL-R	Rat only
Placental lactogen-II	PL-II	TGC, LZ-T	PRL-R	Mouse and rat
Proliferin	PLF	TGC	?	Rat only
Proliferin-1	PLF-1	TGC	Endothelial cells	Mouse only
Proliferin-2	PLF-2	TGC	?	Mouse only
Proliferin-3	PLF-3	TGC	?	Mouse only
Proliferin-4	PLF-4	TGC	?	Mouse only
Proliferin-related protein	PLF-RP	TGC, SpT, LZ-T	Endothelial cells	Mouse and rat
PRL-like protein-A	PLP-A	TGC, SpT, Inv-T	NK cells	Mouse and rat
PRL-like protein-B	PLP-B	SPT	?	Mouse and rat
PRL-like protein-C	PLP-C	TGC, SpT	?	Rat only
PRL-like protein-C variant	PLP-Cv	TGC, SpT	?	Rat only
PRL-like protein-C α	PLP-C α	TGC, SpT	?	Mouse only
PRL-like protein-C β	PLP-C β	TGC, SpT	?	Mouse and rat
PRL-like protein-C γ	PLP-C γ	TGC, SpT	?	Mouse only
PRL-like protein-C δ	PLP-C δ	TGC, SpT	?	Mouse only
PRL-like protein-D	PLP-D	TGC, SpT	?	Rat only
PRL-like protein-H	PLP-H	TGC, SpT	?	Rat only
Decidual PRL-related protein	DPRP	Decidua, TGC, SpT	Heparin, eosinophils	Mouse and rat
PRL-like protein-E	PLP-E	TGC	Hematopoietic cells	Mouse only
PRL-like protein-F	PLP-F	SpT	Hematopoietic cells	Mouse only
PRL-like protein-F β	PLP-F β	SpT	?	Rat only
PRL-like protein-F α	PLP-F α	TGC	?	Rat only
PRL-like protein-I	PLP-I	TGC, SpT	?	Mouse and rat
PRL-like protein-J	PLP-J	Decidua	Heparin	Mouse and rat
PRL-like protein-K	PLP-K	TGC, SpT, LZ-T	?	Mouse and rat
PRL-like protein-L	PLP-L	Inv-T	?	Mouse and rat
PRL-like protein-M	PLP-M	Inv-T, TGC, SpT	?	Mouse and rat
PRL-like protein-N	PLP-N	Inv-T	?	Mouse and rat
PRL-like protein-O	PLP-O	LZ-T	?	Mouse only
PRL-like protein-P β	PLP-P β	TGC, SpT	?	Rat only
PRL-like protein-P α	PLP-P α	Inv-T	?	Rat only

Inv-T, invasive trophoblast; LZ-T, labyrinth zone trophoblast; SpT, spongiotrophoblast; TGC, trophoblast giant cells; ?, unknown.

killer (NK) cells (Müller *et al.* 1999; Ain *et al.* 2003a). During pregnancy, NK cells are the principal leukocytes of the uterus (Croy *et al.* 1996; Moffett-King 2002; Dosiou & Giudice 2005). They accumulate in the uterine mesometrial region, which is conspicuous in serving as the major site for the delivery of blood to the conceptus. At midgestation, the mesometrial vasculature is surrounded by NK cells. As gestation progresses, the NK cells disappear and are replaced, in part, by trophoblast cells exiting the chorioallantoic placenta (Ain *et al.* 2003b). NK cells stimulate changes in the uterine mesometrial vasculature, facilitating nutrient flow to the placenta and

fetus (Croy *et al.* 2000). These vascular remodeling effects of NK cells are mediated by interferon- γ (IFN- γ ; Ashkar & Croy 2001). PLP-A is an intermediary in trophoblast cell modulation of NK cells, including their production of IFN- γ (Ain *et al.* 2003a, b). The physiology of PLP-A has been further explored in PLP-A-deficient mice (Ain *et al.* 2004; see following section). Information about the biology of other members of the expanded PRL family is fragmentary or not available.

Collectively, the cellular targets for the expanded PRL family of ligands are compelling and precisely those requiring adjustments during pregnancy.

4 **Table 2** Pregnancy-associated species-specific gene expansions

Gene family	Function	Species	References
Cathepsin	Cysteine protease	Mouse, rat	Deussing <i>et al.</i> (2002); Mason <i>et al.</i> (2002); Sol-Church <i>et al.</i> (2002)
Chorionic gonadotropin (β -subunit)	Ligand	Primates	Maston and Ruvolo (2002)
Growth hormone	Ligand	Primates	Cooke and Liebhaber (1995)
Interferon- τ	Ligand	Bovine, ovine	Roberts <i>et al.</i> (2003)
Kunitz domain proteins	Protease inhibitor	Bovine, ovine	MacLean <i>et al.</i> (2003)
Pregnancy-associated glycoproteins	Unknown	Bovine, ovine	Xie <i>et al.</i> (1997); Hughes <i>et al.</i> (2003)
Pregnancy-specific glycoproteins	Ligand	Mouse, rat, primate	McLellan <i>et al.</i> (2005a, b)
Prolactin	Ligand	Mouse, rat, bovine	Schuler and Kessler (1992); Wiemers <i>et al.</i> (2003); S. M. K. Alam <i>et al.</i> , unpubl. data, 2005
Rhox family	Transcription	Mouse	MacLean <i>et al.</i> (2005)

EXPANDED PROLACTIN FAMILY GENES AND PREGNANCY-DEPENDENT ADAPTATIONS TO PHYSIOLOGICAL STRESSORS

Evidence is emerging that the PRL family participates in the regulation of adaptations to physiological stressors. The most convincing data have been generated with three lines of mutant mice: one possessing a null mutation in the *PRL* gene (Horseman *et al.* 1997), the second a null mutation in the *PLP-A* gene (Ain *et al.* 2004) and the third a gain-of-function mutation resulting in the constitutive expression of PLP-E (Zhou *et al.* 2005). Experiments with PRL-deficient mice have led to the conclusion that PRL is a critical regulator of immune system adaptations to stress (Dorshkind & Horseman 2001; Dugan *et al.* 2002, 2004). Although PRL signaling is not essential to the development of the immune system (Horseman *et al.* 1997; Bouchard *et al.* 1999), it is pivotal for the regulation of myelopoietic responses to a stress event (Dugan *et al.* 2002). Complementary insights have been achieved with PLP-A-deficient mice. As we characterized the phenotype of PLP-A null mice, it became evident that the *PLP-A* gene was 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 (Ain *et al.* 2004). Pregnancies failed because of inadequate placentation. This is in contrast to pregnant mice expressing PLP-A, which successfully adapt to low oxygen conditions and maintain their pregnancies. The final supporting evidence comes from the demonstration that mice constitutively expressing PLP-E recover

faster from chemically induced thrombocytopenia and neutropenia than do control mice (Zhou *et al.* 2005). Thus, at least three members of the PRL family contribute to homeostatic responses to environmental insults. The involvement of other members of the PRL family in adaptive responses to physiological stressors remains to be determined.

SPECIES-SPECIFIC GENE FAMILY EXPANSION

PRL is not the only example of a species-specific expanded gene family. Twenty-five expanded gene families were identified in the mouse genome, where only single corresponding members were present in the human genome (Mouse Genome Sequencing Consortium 2002). Most of the expanded gene families appear to be associated with reproduction or immune defense, and some specifically with events transpiring at the maternal–fetal interface. Examples of the latter exist in the mouse and rat, including the cathepsins (Deussing *et al.* 2002; Mason *et al.* 2002; Sol-Church *et al.* 2002), the Rhox transcription factor family (MacLean *et al.* 2005) and pregnancy-specific glycoproteins (*Psg*; McLellan *et al.* 2005a, b). The *Psg* gene family is similarly expanded in humans, but is not orthologous (McLellan *et al.* 2005b). Cattle and sheep possess a number of expanded gene families associated with placentation: the *PRL* family (Schuler & Kessler 1992; Takahashi 2006; Ushizawa & Hashizume 2006), the Kunitz family of serine proteinase inhibitors (MacLean *et al.* 2003), pregnancy-associated glycoproteins (aspartic proteinase family; Xie *et al.* 1997; Hughes *et al.* 2003) and the interferon- τ family (IFN- τ ; Roberts *et al.* 2003). In addition to the *Psg* gene

family, humans possess two other expanded gene families whose expression profiles and activities are associated with pregnancy: the chorionic gonadotropin β -subunit family (CG- β ; Maston & Ruvolo 2002) and the GH family (Cooke & Liebhaber 1995). CG- β and IFN- τ have well-established regulatory roles ensuring corpus luteum function during the establishment of pregnancy (Devoto *et al.* 2002; Roberts *et al.* 2003; Spencer & Bazer 2004). However, the biological significance of expanded families for each these ligands is not fully appreciated. Interestingly, Kaplan and Grumbach (1981) proposed that members of the primate placental GH family serve as regulators of adaptations to physiological stressors, especially those associated with increased metabolic demands. It is appealing to speculate that the species-specific gene expansions cited here may be involved in pregnancy-dependent adaptive responses to physiological stressors; however, such a hypothesis is yet to be examined. It is likely that this hypothesis will be tested in animal models that can be genetically manipulated, such as a mouse model.

GENE AMPLIFICATION AND ADAPTATION

Gene families, including the *PRL* family, arose by gene duplication and natural selection (Ohno 1970; Taylor & Raes 2004; Francino 2005). Francino (2005) has proposed a model for the origin of expanded gene families that is particularly attractive given the discussion earlier in this review. The core of the model is based on experimentation with bacteria, yeast and mammalian cell lines, and includes two concepts: (i) adaptive DNA amplification; and (ii) selection resulting in neofunctionalization or subfunctionalization. Gene amplification represents a common adaptive feature of prokaryotic and eukaryotic cells to environmental insults. The acquisition of additional copies of a gene is an effective way to increase production of a protein product. When increased availability of the protein product improves survival under challenging conditions, then the cell, or potentially the organism, has successfully adapted. We propose that environmental pressures led to gene amplification within the ancestral *PRL* locus. Enhanced production of the ancestral *PRL* improved survival of the species. Subsequent relaxation of the environmental forces removed the need for increased ancestral *PRL*. The surplus copies of the ancestral *PRL* gene would then be available to mutate when subjected to new selective pressures,

resulting in the acquisition of new functions (neofunctionalization) or further specialization (subfunctionalization). Although simplistic, this theory is provocative, and interesting questions surface. What was the environmental insult that led to gene amplification within the ancestral *PRL* locus? What was the key function of the ancestral *PRL* that permitted enhanced survival? How many times did gene amplification occur within the *PRL* family locus? What is so special about *PRL* or at least the ancestral *PRL* locus? What were the selective pressures that resulted in the derivation of the *PRL* family paralogs? How did acquisition of the paralogs facilitate adaptation? Can we find new insights about the *PRL* family locus through comparative species analysis?

PROLACTIN GENE FAMILY EXPANSION IS NOT UNIVERSAL

It is apparent that not all mammalian species possess an expanded *PRL* gene family. This does not necessarily indicate that the expanded *PRL* family lacks relevance. We offer here some thoughts on this matter. First of all, some species, as exemplified by humans, may utilize other related templates (e.g. GH) to produce *PRL*-related ligands critical to viviparity. Second, alternate means of expanding the diversity of *PRL*-related ligands may be implemented by other species, such as through alternative splicing of mRNA (Hwang *et al.* 2000), proteolysis (Clapp *et al.* 1988; Corbacho *et al.* 2002), phosphorylation (Oetting *et al.* 1986; Wicks & Brooks 1995) and glycosylation (Markoff *et al.* 1988). Finally, the increase in the variety of *PRL*-related ligands in rodents might be related to their reproductive success. Few mammalian species have evolved reproductive strategies that are as effective as those exhibited by rodents. The expansion of the *PRL* gene family may represent a mechanism that allows rodents to effectively reproduce in a wide range of habitats and during exposure to an assortment of environmental challenges.

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