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Highlights

• Independent signaling pathways of short form of prolactin receptor are proposed. • Prolactin is important but not essential for follicular development. • An essential role of short form in vascularization and survival of corpus luteum is proposed. • Cooperative and dominant negative actions of short and long form are highlighted.

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Review

Reproductive actions of prolactin mediated through short and long receptor isoforms ☆

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ABSTRACT

Prolactin (PRL) is a polypeptide hormone with a wide range of physiological functions, and is critical for female reproduction. PRL exerts its action by binding to membrane bound receptor isoforms broadly classified as the long form and the short form receptors. Both receptor isoforms are highly expressed in the ovary as well as in the uterus. Although signaling through the long form is believed to be more predominant, it remains unclear whether activation of this isoform alone is sufficient to support reproductive functions or whether both types of receptor are required. The generation of transgenic mice selectively expressing either the short or the long form of PRL receptor has provided insight into the differential signaling mechanisms and physiological functions of these receptors. This review describes the essential finding that both long and short receptor isoforms are crucial for ovarian functions and female fertility, and highlights novel mechanisms of action for these receptors.

Contents

Abbreviations: PRL, prolactin; PRLR, prolactin receptor; GH, growth hormone; PL, placental lactogen; dPRL, decidual prolactin; 20α-HSD, 20alpha-hydroxysteroid dehydrogenase; α2M, alpha 2-macroglobulin; HSD17B-7, 17β hydroxysteroid dehydrogenase; JAK2, janus Kinase 2; STAT, signal transducer and activator of transcription; MAPK, mitogen activated protein kinase; IGFBP1, insulin-like growth factor binding protein 1; VEGF, vascular endothelial growth factor; FRET, fluorescence resonance energy transfer; DUPD1, dual specificity phosphatase and pro isomerase domain containing 1; GALT, galactose-1-phosphate uridylyltransferase.

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1. Prolaction – synthesis and regulation

Prolactin (PRL) is a polypeptide hormone belonging to the PRL/GH/PL family (group I of the helix bundle protein hormones), that includes PRL-like and PRL-related proteins, with which PRL shares structure similarities and sequence homology, as well as overlapping biological properties (Bole-Feysot et al., 1998; Soares, 2004). PRL was originally identified by Stricker and Grueter (1928) as the pituitary factor responsible for milk secretion in rabbits, and almost 70 years later, its cDNA was cloned and characterized by Gabou and colleagues (1996). Today, its presence has been well documented in human (Truong et al., 1984), rat (Gubbins et al., 1979), mouse (Harigaya et al., 1986), guinea pig (Alam et al., 2010), goat (Le Provost et al., 1994), chicken (Harvey et al., 1978), and rainbow trout (Mercier et al., 1989). It is encoded by a six-exon gene, which is located in chromosome 6 in humans (Owerbach et al., 1981; Horseman and Yu-Lee, 1994); chromosome 17 in rats (Rat Genome Sequencing Project Consortium, 2004), and chromosome 13 in mice (Dai et al., 1998). PRL is synthesized as a prohormone containing a signal peptide. The mature protein contains 197–199 amino acid residues depending on the species, with a total molecular mass of approximately 23 kDa (Shome and Parlow, 1977; Bole-Feysot et al., 1998).

PRL is mainly synthesized and secreted by the lactotrope cells of the anterior lobe of the pituitary gland, and released into the blood mainstream enabling transit to different target tissues where it binds to its membrane receptor (PRLR) and acts as a classic endocrine hormone modulator. In addition, several extra-pituitary tissues produce PRL in a cell-specific manner and exert a local autocrine/paracrine response (Review in Ben-Jonathan et al., 1996, 2008). The extra-pituitary sites include the decidua (Gibori et al., 1974; Jayatilak et al., 1985; Prigent-Tessier et al., 1999), breast (Fields et al., 1993; Kurtz et al., 1993; Steinmetz et al., 1993), prostate (Nevalainen et al., 1997; Li et al., 2004), brain (Grattan and Kokay, 2008), skin (Craven et al., 2001; Foitzik et al., 2003, 2006), fat (Hugo et al., 2006) and immune cells (Jurcovicová et al., 1993; Gala and Shevach, 1994). In fact, pioneering investigations into the extra-pituitary production of decidual prolactin (dPRL) in humans and rodents had established a powerful tool by determining the local secretion of this hormone as one of the main markers of decidualization of stromal cells (Maslar and Riddick, 1979; Jayatilak et al., 1985).

Pituitary PRL exhibits a tonic secretion, mainly under the control of hypothalamic inhibitory factors, with dopamine being the best established modulator (reviewed in Ben-Jonathan, 1985; Freeman et al., 2000; Grattan and Kokay, 2008). Dopamine inhibits PRL release by binding to the D2 receptor, an adenylyl cyclase-linked dopamine receptor, on the pituitary lactotroph cells. It has been reported that PRL affects its own secretion by affecting the dopaminergic neurons via a short loop negative feedback (Milenkovic et al., 1990). Using either PRLR knockout or PRLR transgenic models, we and others have shown that disruption of normal PRLR expression causes a significant rise of PRL serum levels, suggesting that PRL/PRLR signaling down-regulates PRL synthesis and/or secretion at the hypothalamic and/or pituitary level (Binart et al., 2000 and Halperin et al., 2008). PRL secretion is pulsatile and is paced by a circadian rhythm. The lowest levels are observed in the morning about 2–3 h after waking up and the highest during sleep (Linkowski et al., 1998). On the other hand, the mechanism of PRL secretion in extra-pituitary sites is not fully understood but appears to be cell type specific and is not necessarily dependent on dopaminergic system (Gellersen et al., 1994; Ben-Jonathan et al., 2008). Ben-Jonathan and colleagues have recently shown expression of functional dopamine receptors in adipocytes that inhibit PRL expression and release after dopamine treatment (Borcherding et al., 2011). However, in other sites such as decidua, secretion of PRL is not dependent on dopamine but rather on transcriptional control, much like other cytokines (Ben-Jonathan et al., 2008).

Transcriptional regulation of pituitary and extra-pituitary PRL expression are under the control of two independent promoter regions: a proximal promoter region modulates pituitary PRL expression (Berwaer et al., 1991), whereas a distal upstream region directs extra-pituitary expression (Berwaer et al., 1994; Featherstone et al., 2012). The proximal promoter region contains multiple binding sites for Pit-1 transcription factor, a member of the POU homeodomain protein. Pit-1 is necessary for transcription of pituitary PRL and mediates its effect by interacting with nuclear hormone receptors and other coregulators (Featherstone et al., 2012; Ben-Jonathan et al., 2008)). As for the extra-pituitary PRL, its expression is proposed to be independent of Pit-1 (Gellersen et al., 1994; Ben-Jonathan et al., 1996). However, recent data suggests that Pit-1 may be involved in the expression of PRL in human breast cell lines and tumors (Ben-Batalla et al., 2010). It is not clear whether this mechanism of regulation is unique to cancer cells or represents a common mechanism in other extra-pituitary PRL producing sites. Nonetheless, the diverse expression profile of the PRL gene in extra-pituitary sites suggests a complex system of regulation enabling cell-specific expression and response to differential regulatory mediators. In the case of the decidua, dPRL is synthesized and secreted by the human endometrium around day 23 of the normal menstrual cycle and depends primarily on levels of progesterone and estradiol (Lockwood and Schatz, 1996). In a fertile cycle, the capacity for dPRL production increases rapidly as implantation progresses. Together with IGFBP1, dPRL is the most dramatically induced genes in the human endometrium during pregnancy. The transcription factor C/EBPβ mediates cAMP induction of dPRL by forming a nucleoprotein complex that binds the proximal dPRL promoter region upon PKA activation in human endometrial stromal cells (Pohnke et al., 1999). Other reports have demonstrated that overexpression of Foxo1A induces a significant increase in dPRL promoter activity by cooperating with C/EBPβ (Christian et al., 2002 and Buzzio et al., 2006) and with HoxA-11 (Lynch et al., 2009), both studies performed in human endometrial stromal cells. Apart from serving as a useful marker of decidualization in endometrial stromal cells, dPRL has also been shown to play an important role in the maintenance of pregnancy, the findings of which are further emphasized in PRL and PRLR knockout mice (Binart et al., 2000; Bao et al., 2007).

2. PRL receptor isoforms

Prolactin receptor (PRLR) is a member of the class 1 cytokine receptor superfamily that lacks intrinsic tyrosine kinase activity (Walker, 2005), and is encoded by a gene located in chromosome 5, 15, or 2 for human (Boutin et al., 1989), mouse (Davis and Linzer, 1989), and rat (Jayatilak and Gibori, 1986; Boutin et al., 1988), respectively. This membrane-anchored protein is composed of an extracellular ligand-binding domain, a single pass transmembrane chain and an intracellular domain responsible for the signal transduction. PRLR was first cloned and characterized in rodents (Boutin et al., 1988; Kelly et al., 1989; Davis and Linzer, 1989, 1990), and almost simultaneously described in human (Boutin et al., 1989), rabbit (Edery et al., 1989), and later in bovine (Scott et al., 1992), chicken (Zhou et al., 1996), frog (Yamamoto et al., 2000), and rainbow trout (Prunet et al., 2000). Although it codes for a single gene product, alternative splicing of its primary transcript or post-translational cleavage can generate multiple variants of the receptor. These various PRLR isoforms share a common extracellular and transmembrane domain, but differ in the length and composition

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of their cytoplasmic domain, and therefore are designated as the long form (PRL-RL) and short form (PRL-RS). The structures of these different isoforms have been discussed at length by several reviews (Bouilly et al., 2012; Ben-Jonathan et al., 2008; Bole-Feysot et al., 1998; Clevenger and Kline, 2001; Freeman et al., 2000). An intermediate form (RI) has also been reported for human PRLR and in the rat NB2 cell line but not in the mouse (Kline et al., 1999; Ali et al., 1991). PRL-RL has been extensively studied and is considered the major isoform through which PRL transmits its signals. The rat PRL-RL has 591 amino acids, of which 357 residues reside within the intracellular domain, whereas mouse PRL-RL is composed of 589 amino acids, with 357 in the intracellular domain. There is a 90% homology between these two species, including conservation of JAK2 binding domain (Ben-Jonathan et al., 2008). As to PRL-RS, it has been cloned in several species, including humans (Hu et al., 2001), rat (Boutin et al., 1988), mouse (Davis and Linzer, 1989), cow, and sheep (Bignon et al., 1997). The rat PRL-RS encodes a small protein of 291 amino acids, of which up to residue 261 is identical to the PRL-RL isoform and differs thereafter (Boutin et al., 1988). Three short isoforms have been reported in mice, known as PR-1, PR-2, and PR-3, with unique C-terminal sequences following the common membrane-proximal residues in the intracellular domain (Davis and Linzer, 1989). Among these, one clone (PR-1) has been identified at protein level and shown to have functional signal transduction capabilities (Binart et al., 2010). PR-1 consists of 303 amino acids, of which the first 280 amino acids are identical to other mouse isoforms, but the last 23 amino acids located within the cytoplamic domain diverge from other isoforms (Davis and Linzer, 1989). This unique sequence may confer its ability to bind to distinct intracellular signaling molecules and independent biological action.

3. Expression and regulation of PRLR isoforms in reproductive tissues

Expression of PRLR at the transcript level has been shown in the ovary of several species (Kowalewski et al., 2011; Kingston et al., 2008; Picazo et al., 2004; Clarke et al., 1993; Clarke and Linzer, 1993 and Russell and Richards, 1999). In rodents, both PRL-RL and PRL-RS mRNAs are co-expressed in granulosa, interstitial, and luteal cells during the estrus cycle, with PRL-RL being the most dominant isoform along all stages (Clarke et al., 1993). PRLR expression levels vary along the estrus cycle as well as stages of pregnancy. For both isoforms, maximal mRNAs levels were attained during proestrus, followed by a decline during estrus, and then a recovery to maximal levels by late diestrus and early proestrus (Clarke et al., 1993; Clarke and Linzer, 1993). This decrease in PRLR levels presumably plays a role in attenuating PRL actions in a number of periovulatory events over specific ovarian cell types. In addition, the attainment of high PRLR levels in late diestrus coincides with the requirement for PRL to maintain progesterone production in preparation for pregnancy or pseudopregnancy. A sharp increase in PRL-RL expression in preovulatory granulosa cells, as compared with small follicles has been shown by Russell and Richards (1999) and suggested a role for PRL in mature follicles. A similar increase in PRLR expression accompanied by the requirement for progesterone production has been demonstrated in other species as well (Thompson et al., 2011; Picazo et al., 2004).

Expression of both PRL-RL and PRL-RS is further enhanced during luteinization; in particular, a robust increase in PRL-RS transcript level is associated with luteinization (Telleria et al., 1997; Stocco et al., 2007). Interestingly, this increase in PRL-RS is related to enhanced activation of STAT5b in the functional corpus luteum of pregnancy (Russell and Richards, 1999). This suggests an important role for PRL-RS in corpus luteum function either by acting synergistically with PRL-RL or through other independent functions (discussed in Section 7). The mechanisms involved in selective regulation of the different isoforms remains unclear, but perhaps more understanding in the mechanisms of alternative splicing of PRLR will shed light into this differential regulation. The overall up-regulation of PRLR during luteinization in rodents appears to coincide with the LH surge and presumably is important for sustained expression of PRLR (Stocco et al., 2007). There are no significant changes in mRNA levels of either PRL-RL nor PRL-RS in the corpus luteum until day 20 of gestation, whereas a profound decline in PRLR mRNA and protein for both receptor types occurs at the end of pregnancy (Russell and Richards, 1999 and Telleria et al., 1997), an event mediated by prostaglandin F2 α (Stocco et al., 2003, 2000). This drop in PRLR expression is accompanied by a rapid increase in the expression of 20α-hydroxysteroid dehydrogenase (20α-HSD) (Telleria et al., 1997) and decrease in progesterone allowing parturition (Piekorz et al., 2005).

Decidua is another target of PRL function during pregnancy. Expression of PRLR has been demonstrated in many species including human (Jabbour and Critchley, 2001), non-human primates (Frasor et al., 1999), and rodents (Gu et al., 1996 and Reese et al., 2000). Interestingly, decidualization itself does not appear to be a trigger for expression of PRLR, as only 3 days after the induction of decidualization, PRL-RL first detected in the rodent uterus (Gu et al., 1996). Thereafter, mRNAs for both PRL-RS and PRL-RL became detectable in both antimesometrial and mesometrial decidua, although PRL-RL mRNA level is higher than PRL-RS. One study has reported expression of PRLR only in the antimesometrial side in mouse uterus (Reese et al., 2000). This could be due to species difference or due to difference in the sensitivity of the techniques used. In rat, expression of both receptors peak at mid pregnancy, and as embryo development progresses, PRLR mRNA levels decrease (Gu et al., 1996). This decline in PRLR mRNA strongly correlates with expression of activin A and is supported by *in vitro* studies showing that treatment of cultured decidual cells with activin A results in accelerated disappearance of PRLR (Gu et al., 1996; Tessier et al., 2003). In contrast, this inhibitory effect of activin is prevented by expression of alpha 2-macroglobulin (α2 M), an activin binding protein which is highly expressed in mesometrial decidua (Gu et al., 1996). Whether this regulatory mechanism is limited to the uterus or is also present in non-uterine tissues is not clear. However, it is interesting to note that an increase in α2 M expression is also observed during luteinization in the ovary concomitant with an increase in PRLR mRNA levels (Russell and Richards, 1999; Gaddy-Kurten et al., 1989). Taken together, these results suggest that PRLR is expressed in a spatio-temporal manner in reproductive tissues, and the regulation of PRLR expression involves multiple mechanisms mediated by endocrine, paracrine and autocrine factors.

4. PRLR activation mechanisms

Conflicting data have been reported regarding the mechanisms involved in the activation of PRLR. Several investigations proposed a "induced-fit" model given by an obligated-sequential chain of events: PRL binds first to one receptor molecule and induces a conformational change in the ligand, which in turn, favors interaction with a second receptor molecule resulting in the known activated PRLR dimer (Gertler et al., 1996; Sivaprasad et al., 2004; Van Agthoven et al., 2010; Voorhees and Brooks, 2010). However, studies in which PRL-RL was transfected into T47D cells revealed ligand-independent dimerization of the receptor. Moreover, these studies also demonstrated that the addition of PRL to PRL-starved cells did not increase dimer formation, suggesting that part of

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the human PRLR is predimerized in these cell lines (Gadd and Clevenger, 2006). In addition, it was established by FRET and co-immunoprecipitation that two PRLR molecules can dimerize in the absence of PRL, bringing the proximal membrane regions of their intracellular domains into close proximity, forming homo-dimers (PRL-RL – PRL-RL or PRL-RS – PRL-RS) (Tan et al., 2005; Qazi et al., 2006). Activation occurs upon binding of the ligand to this pre-homodimer, forming a one-ligand two-receptor complex. Once the heterotrimeric complex is formed, either by the induced fit model or by binding to a pre-homodimer, a conformational change is induced in the intracellular domain that allows docking of the tyrosine-protein kinase, JAK2, within the membrane-proximal proline-enriched region of each PRLR molecule (Campbell et al., 1994; Rui et al., 1994). Such a region is known as Box 1 and is conserved among all the isoforms of the receptor. JAK2 auto-transphosphorylates and induces phosphorylation of numerous proteins, including the receptor itself, which leads to activation of distinct signaling cascades (Brooks, 2012; Freeman et al., 2000 and Kelly et al., 1991). Interestingly, ligand independent heterodimerization of human PRL-RL and PRL-RS has also been demonstrated (Qazi et al., 2006; Tan and Walker, 2010). Although such heterodimers are competent to bind PRL, subsequent signal transduction events via activation of JAK/STAT, the canonical PRL signaling pathway, is inoperative. Whether heterodimers of PRL-RL and PRL-RS activate other signaling pathways and whether they have functional relevance is not yet clear.

5. PRLR signaling pathways

5.1. Signaling mechanisms activated by PRL-RL

The most extensively characterized PRLR isoform is PRL-RL, which transduces both mitogenic and differentiative signals. This isoform contains the entire spectrum of signalling entities attributed to PRLR, which include Box1 and Box2 motifs with the variable box (V-box) in between, and an extended Box 2 (X-box) (Reviewed in Clevenger et al., 2003). JAK2 kinase is constitutively associated with Box1 and rapidly activated upon ligand binding (Frasor and Gibori, 2003; Lebrun et al., 1995). Well-known targets of activated JAK2 include the signal transducers and activators of transcription (STAT) transcription factors (Frasor and Gibori, 2003). The two highly related STATs, STAT5a and STAT5b are major mediators of PRL signaling in both mammary gland and ovary (Piekorz et al., 2005). Deficiencies in STAT5b or in both STAT5a and STAT5b result in loss of pregnancy during midgestation, and correlate with an increase in ovarian 20α-HSD expression, and a decrease in serum progesterone (Udy et al., 1997; Teglund et al., 1998). In addition to STAT5, STAT1 and STAT3 are known mediators of PRL signaling and are JAK2 targets (DaSilva et al., 1996). PRL can also activate many kinases other than JAK2/STAT, including phosphoinositide 3-kinase (PI3kinase), Src kinase, MAP kinase and Nek3 kinase (Tessier et al., 2001; Aksamitiene et al., 2011; Sakamoto et al., 2007; Miller et al., 2007). These pathways are presumed to be activated through PRL-RL even though most of the studies were performed using cells which express both PRL-RS and PRL-RL.

5.2. Signaling mechanisms activated by PRL-RS

Conflicting results have been reported over the activation of JAK2/STAT by PRL-RS. It has been proposed that PRL-RS cannot activate JAK2/STAT signalling, as it lacks the distal region on the intracellular domain required for STAT docking (Lebrun et al., 1995; Perrot-Applanat et al., 1997). However, this finding was contradicted by other studies that showed activation of STAT5 through PRL-RS (Bignon et al., 1999; Goupille et al., 1997). These conflicting results could be due to species differences or due to technical issues arising from the use of cell lines expressing both receptors. Using a transgenic mouse model expressing exclusively PRL-RS (PR-1 isoform) in a PRLR−/− background (PRLR−/−RS), we have finally demonstrated that PRL-RS alone does not activate JAK2/STAT signaling in either the ovary or the decidua (Devi et al., 2009a,b). Further controversy exists regarding the physiological function of RS. It was initially thought that PRL-RS played only a dominant-negative role preventing PRL signaling through PRL-RL (Perrot-Applanat et al., 1997, Berlanga et al., 1997; Lesueur et al., 1991). However, this view has been challenged by several groups, including ours (Devi et al., 2009a,b; Halperin et al., 2008; Binart et al., 2003; Huang et al., 2008; Das and Vonderhaar, 1995. Das and Vonderhaar (1995) first proposed a signaling role for PRL-RS in NIH-3T3 fibroblasts by showing that activation of the mouse PRL-RS induced MAPK activity, which ultimately suggested that PRL-RS-signaling may be involved in cell proliferation. The human PRL-RS can also activate MAPK in cultured cells (Huang et al., 2008), although this activation is delayed and prolonged, and therefore a role in differentiation rather than proliferation was suggested. Using a transgenic mouse model, Binart et al. (2003) reported that overexpression of PRL-RS in the PRLR heterozygous background (PRLR+/−RS) could rescue the mammopoiesis defect displayed in the PRLR+/−mice. This led to the conclusion that, in mammary glands, PRL acting through RS may mediate activation of MAPK. Recent data generated using a transgenic mouse model expressing PRL-RS alone (PRLR−/−RS) has at least clarify some of the controversial findings in PRL-RS signaling. Using this mouse model, we have shown that *in vivo* activation of PRL-RS elicits profound effects in the ovary, as it causes a clear defect in follicular development and massive granulosa cell death, leading to premature ovarian failure (Devi et al., 2009a,b; Halperin et al., 2008). In sharp contrast to the mammary gland, PRL signaling through PRL-RS deactivates both ERK1/2 and p38 MAPK in the ovary (Devi et al., 2011). This deactivation was shown to be mediated through a novel phosphatase, DUPD1, which physically associates with both ERK1/2 and p38 MAPK. We have also demonstrated that DUPD1 is exclusively associated with PRL-RS irrespective of ligand binding. Activation of PRL-RS by PRL causes dephosphorylation of a critical threonine site on DUPD1. It has been postulated that this dephosphoryation causes activation of DUPD1 activity, which then dephosphorylates and inhibits MAPK activity (Devi et al., 2011). Furthermore, by using PRLR−/−RS mice we have demonstrated that PRL signaling through PRL-RS represses or stimulates the activity of several transcription factors (Devi et al., 2009a and Halperin et al., 2008), presumably leading to alteration in the expression of genes essential for normal follicular development and survival. Interestingly, co-expression of PRL-RS and PRL-RL could rescue the inhibition of MAPK and transcription factors, and prevent the deleterious effect on follicular development (Devi et al., 2011; Halperin et al., 2008). A simplified model of PRL-RS signaling mechanism leading to premature ovarian failure is shown in Fig. 1.

6. PRL actions and the role in reproduction

Numerous reports have established a wide spectrum of PRL functions that broadly exceed its traditional role in mammary gland development, differentiation and nurturing of offspring (reviewed in Bole-Feysot et al., 1998). Indeed, PRL-induced effects have been noted in diverse processes that range from electrolyte balance, behavior, immune and stress response, cell growth, differentiation, anti-apoptotic action and breast tumorigenesis. Nonetheless, reproductive processes represent the largest group of functions attributed to this hormone (Bole-Feysot et al., 1998; Bouilly et al., 2012). An essential role of PRL in female reproduction has

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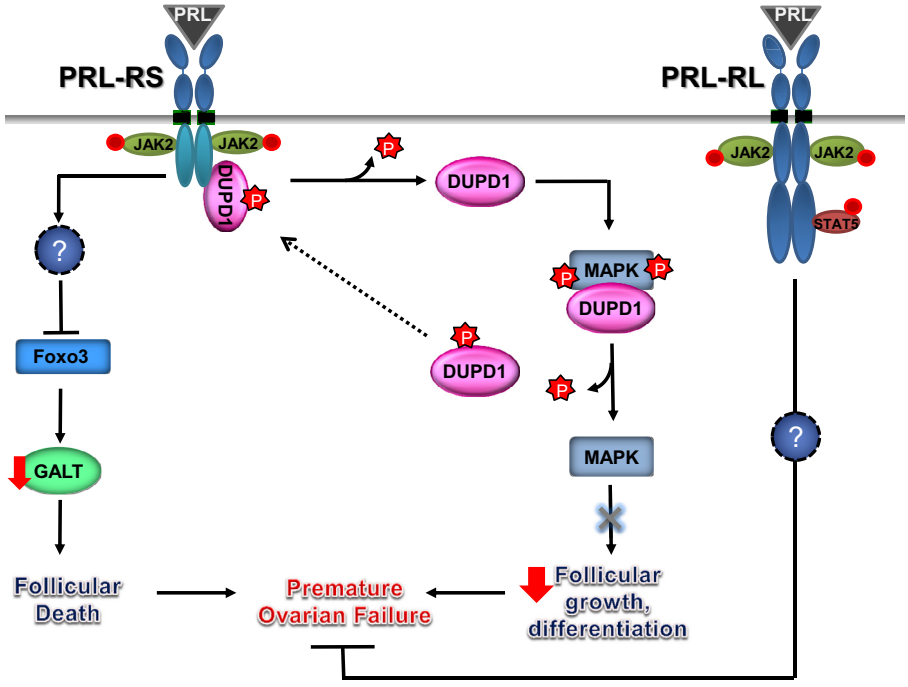

Fig. 1. A proposed model of short form receptor (PRL-RS) signaling in the follicle leading to premature ovarian failure. DUPD1 phosphatase (most likely the phosphorylated inactive form) is constitutively associated PRL-RS. Ligand-mediated activation of PRL-RS causes activation of DUPD1 phosphatase activity through a dephosphorylation process. Activated DUPD1 physically interacts with and dephosphorylates MAPK, causing its inhibition, and prevents downstream signaling. This inhibition negatively affects genes involved in follicular growth and differentiation. On the other hand, PRL signaling through PRL-RS inhibits Foxo3 transcription factor at the protein level by a mechanism yet to be determined. This inhibition causes downregulation of GALT expression, leading to follicular death. The net result of these pathways leads to early depletion of follicles, and ultimately, premature ovarian failure. Recent findings demonstrate that coexpression of long form (PRL-RL) prevents PRL-RS-induced premature ovarian failure by a mechanism(s) yet to be determined.

been well established in rodents, but remains to be determined in human. We have outlined the findings from rodents and human in this section.

6.1. In rodents

PRL was first identified as a key factor for mammary gland development and differentiation (Ormandy et al., 1997; Brisken et al., 1999; Gallego et al., 2001). Although associated with this reproduction-related process, it was not until the generation of PRL−/− and PRLR−/− mice that the vital role of PRL in female fertility became evident (Horseman et al., 1997; Ormandy et al., 1997). Both PRL−/− and PRLR−/− females are totally infertile. One of the major defects seen in PRLR−/− female mice is infertility directly related to insufficient progesterone levels and implantation failure (Ormandy et al., 1997). Two days after mating, the ovaries of female PRLR−/− exhibit corpus luteum undergoing regression, strong DNA cleavage, poor vascularization, impaired steroidogenesis (Ormandy et al., 1997; Grosdemouge et al., 2003; Bachelot et al., 2009). These findings clearly established a critical role of PRL in the maintenance of ovarian corpus luteum and progesterone production for rodent reproduction (Risk and Gibori, 2001; Stocco et al., 2007). Apart from this, PRLR−/− mice also had various reproductive defects, including lack of pseudopregnancy, decreased number of primary follicles, mistimed oocyte release, and impaired oocyte maturation, all signs of disruption in follicular development and possibly atresia (Ormandy et al., 1997). Oocyte maturation is a complex process involving germinal vesicle breakdown, oocyte growth and reinitiating of meiosis in response to gonadotropins. This process requires signals from both oocyte itself and surrounding somatic cells. A large number of oocytes ovulated in PRLR−/− mice still contain intact germinal vesicles, indicating an important role for PRL in normal oocyte maturation. Indeed, expression of PRLR had been shown in oocytes (Kiapekou et al., 2009; Nakamura et al., 2010) and PRL treatment has been shown to improve the rate of oocyte maturation in cultured preantral mouse follicles (Kiapekou et al., 2009). It is unclear, however, whether this defect in oocyte maturation exhibited by PRLR−/− females is due to a lack of PRL signaling in the oocyte, a defect in surrounding granulosa cells, or the combined effect of both. PRL is known to act synergistically with gonadotropins to affect follicular development. Some of the well-established functions of PRL are suppression of FSH-induced aromatase expression and estradiol production while stimulating FSH-induced progesterone production in granulosa cells (Nakamura et al., 2010; Dorrington and Gore-Langton, 1982). In the absence of PRLR, this inhibitory and synergistic affect is abrogated, which may explain why PRLR knockout females exhibit an abnormal increase in the estrogen levels during the estrous cycle and a lack of pseudopregnancy. Although the evidences mentioned above point to an important role for PRL in normal follicular development and ovulation, the absolute requirement for PRL (or PRLR) in these processes could be excluded since PRLR−/− ovaries have mature follicles and are capable of ovulation, albeit with defects.

PRL also plays an important role in fertilization and development of the pre-implantation embryos. Fertilization rates are reduced in PRLR−/− females compared to wild type controls, and most of the fertilized eggs fail to develop correctly (Ormandy et al., 1997). Majority of oocytes arrest at the single cell stage immediately after fertilization and only 19% of blastocyst-stage embryos can be recovered on day 3.5 of pregnancy in the uterus of PRLR−/− animals. The presence of PRLR mRNA during all stages of mouse pre-implantation embryos have been demonstrated (Kiapekou et al., 2005), and PRL has been shown to accelerate pre-implantation mouse embryo development *in vitro* (Yohkaichiya et al., 1988). However, oocyte PRLR does not appear to be essential for the development of the pre-implantation embryo, since embryos from PRLR−/− mother that are transplanted into the oviduct of PRLR+/+ foster mothers develop normally. Expression of PRLR has been observed in the oviduct of both mouse and human (Shao

et al., 2008) where it may play a role in the development of pre-implantation embryo. These findings highlight the important role of PRL not only in ovarian function but also elsewhere in the reproductive tract. Intriguingly, the defects in pre-implantation egg development and implantation seen in PRLR−/− mice can also be rescued by supplementation of progesterone from day 0.5 of pregnancy (Reese et al., 2000; Binart et al., 2000). Of note, the PRL-induced progesterone surge does not occur until day 2.5 of pregnancy whereas the defect in pre-implantation embryos of PRLR−/− females occurs earlier (between days 0.5 and 1.5) and at a time when progesterone levels are normal in PRLR−/− females. This suggests that PRL and progesterone may have redundant functions during post-fertilization events and the PRL deficit may be compensated for by progesterone. However, the quality of embryos developed in such progesterone supplemented animals (PRLR−/−) have not been thoroughly examined. Interestingly, a large number of embryos were lost from mid-gestation and only 22% of the embryos remained viable till term (Binart et al., 2000). This observation could be either due to quality of embryos being compromised during preimplantation development or upregulation of detrimental factors in the uterus in the absence of PRLR, or a combined effect of both factors. Decidual PRL is known to act locally and inhibit detrimental factors such as IL-6 and 20α-HSD during gestation (Bao et al., 2007) and upregulation of these factors may be a plausible reason for fetal loss at mid-pregnancy.

6.2. In humans

While a critical role of PRL in female reproduction in rodents has been established, it remains unclear whether PRL plays a similar essential role in human reproduction. This is partly due to the overlapping functions of PRL with placental lactogen and human growth hormone, both of which can bind and elicit signaling through PRLR (Cunningham et al., 1990 and Lowman et al., 1991). Moreover, there is no known homozygous inactivating mutation of PRLR or PRL gene in human that could confirm the role of PRL/PRLR in human reproduction. Hyperprolactinemia is currently the best known PRL-related pathology that affects human fertility and is defined as abnormally high levels of circulating PRL. Hyperprolactinemia causes galactorrhea, amenorrhea, and infertility in women, mainly due to inhibition of hypothalamic GnRH pulsatility, suppression of the preovulatory gonadotropin surge, and its consequent inhibition of ovarian function (Kaiser, 2012). Hyperprolactinaemia is found in 30% of women with secondary amenorrhoea, and 75% of women with both amenorrhoea and galactorrhoea (Prabhakar and Davis, 2008). Although hyperprolactinemia has been proposed to block ovulation through inhibition of GnRH release, the mechanisms involved in this process are poorly understood. Using a mouse model of continuous PRL infusion, a recent report demonstrated that hyperprolactinemia significantly decreased kisspeptin mRNA and peptide staining, induced anovulation, and reduced GnRH and gonadotropin secretion (Sonigo et al., 2012). Furthermore, kisspeptin administration restored gonadotropin secretion and ovarian cyclicity, suggesting that kisspeptin neurons play a major role in hyperprolactinemic anovulation.

7. Differential and cooperative functions of PRLR isoforms: Lessons from transgenic mice selectively expressing PRL-RS or PRL-RL

Studies from PRL−/− and PRLR−/− mice have undoubtedly highlighted a critical role of PRL/PRLR in various reproductive functions. Although PRL-RL has been always assumed to be the main isoform involved in the regulations of those functions, neither PRL nor PRLR knockout mice models could clarify which receptor isoform is essential for these functions. We are able to address some of these issues with the generation of transgenic mice, which selectively express either PRL-RS or PRL-RL. These mice allow us to investigate the specific physiological role of each receptor type and the signals activated exclusively of one isoform in the absence of others. We have identified novel signaling pathways mediated by each receptor isoform and established that PRL-RS has an important physiological role beyond the alleged dominant-negative function. Transgenic mice expressing PRL-RS in a PRLR null background (PRLR−/−RS) were generated by mating fertile transgenic PRLR+/−RS females with PRLR−/−males. The PRLR−/−RS females were not only infertile, but also exhibited severe defects in follicular development characterized by accelerated follicular recruitment followed by massive granulosa cell death, collapsed zona pellucida, and ultimately exhausting all follicular pool leading to premature ovarian failure (Halperin et al., 2008). Furthermore, *in vitro* transfection of PRL-RS in granulosa and luteal cell lines lacking endogeneous PRLR die after PRL treatment (Devi et al., 2009b). These results strongly suggest that PRL-RS can signal on its own and has a physiological role independent of PRL-RL. Gene expression profiling and analysis of transcription factors have revealed that PRL-RS signaling can affect the expression of several genes as well as the activity of transcription factors involved in multiple critical pathways (Halperin et al., 2008; Devi et al., 2009a,b). Of particular interest was the inhibition of expression and activity of transcription factors involved in oxidative stress and cell death, namely Sp1 and FOXO3. In recent years, Sp1 has been shown to play a critical role in multiple cellular responses beyond the traditional view as a constitutive activator of housekeeping genes and other TATA-less genes (Wierstra, 2008). Indeed, Sp1 was shown to stimulate survival in cells under oxidative stress (Dorrington and Gore-Langton, 1982; Ryu et al., 2003; Lee et al., 2006). Our observation that cells expressing PRL-RS as the only form of the receptor die after PRL treatment, concomitant with the loss of Sp1, suggesting that this transcription factor is critical for cell survival in the ovary and that expression of PRL-RS alone disrupts this pathway.

The deleterious phenotype observed in PRLR−/−RS females could be attributed in large part to diminished expression of FOXO3 in the ovary. An essential role for FOXO3 in follicular development has been well established. FOXO3 is part of the inhibitory machinery controlling oocyte growth during primordial follicle activation (Liu et al., 2007; Reddy et al., 2008; John et al., 2008). In fact, FOXO3 knockout mice exhibit an ovarian phenotype of accelerated follicular activation, cell death, and premature ovarian failure (Castrillon et al., 2003 and Hosaka et al., 2004) similar to that seen in PRLR−/−RS. Whether there is a link between single-nucleotide polymorphisms or mutations in FOXO3 gene with idiopathic premature ovarian failure in women is currently being investigated by several groups (Wang et al., 2010; Gallardo et al., 2008). Interestingly, we have identified a novel cellular target of FOXO3, an enzyme known as galactose-1-phosphate uridyltransferase (GALT) in the PRLR−/−RS mice. *In vitro* analysis of the GALT promoter confirmed that FOXO3 exerts a significant up-regulation on GALT expression. GALT is an enzyme that participates in normal galactose metabolism and deficiency of this enzyme leads to cell toxicity and death due to increased accumulation of the metabolites gal-1P and galactitol in a disease known as galactosemia. More than 180 mutations in the GALT gene have been identified in people with the classic form of galactosemia (Gort et al., 2006). Intriguingly, women with this disease are fertile early in life, but later exhibit a strong depletion of follicles, which eventually leads to premature ovarian failure (Kaufman et al., 1981). The negative impact of galactosemia on ovarian function has been also well demonstrated in animal models, e. g. high galactose diet in rats led to a decrease follicular development (Liu et al., 2006) and an increase in apoptosis of maturing follicles (Lai et al.,

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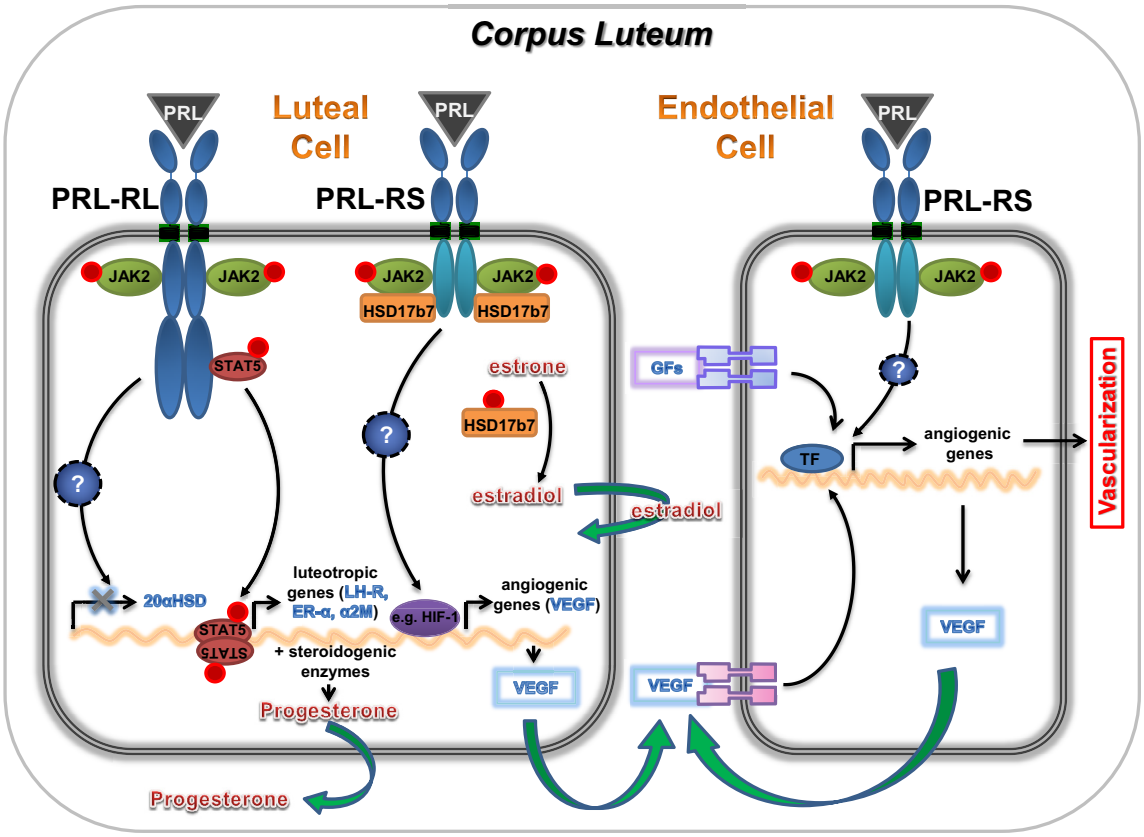

Fig. 2. A proposed and simplified model of coordinated action of PRL-RS and PRL-RL in the corpus luteum. Based on both previous and recent findings, we propose a model of PRL-RS and PRL-RL signaling pathways in the corpus luteum involving two cell compartments, namely endothelial cells and steroidogenic luteal cells. PRL mediated activation of PRL-RS causes activation of transcription factors (TF) e.g. HIF-1 and induction of angiogenic genes such as VEGF. In conjunction with other growth factors (GFs), VEGF acts upon endothelial cells to induce vascularization, which is critical for corpus luteum survival. Since PRL-RS is expressed by both endothelial and luteal cells, this receptor may mediate its action in both cell types. PRL-RS also physically associates with HSD17β-7, an enzyme that converts estrone to estradiol, bringing it in close proximity to JAK2 allowing phosphorylation and stabilization of HSD17β-7; thus contributing to local estradiol synthesis. This locally produced estradiol, in turn, acts on the luteal cells to induce hypertrophy and VEGF expression. On the other hand, PRL-mediated activation of PRL-RL in luteal steroidogenic cells is critical for induction of luteal genes involved in progesterone production and inhibition of 20αHSD. Activation of Jak2/STAT5 is crucial for these PRL-mediated functions; however, other signaling pathways may also be involved. These results strongly suggest that the coordinated actions of both receptors are required for survival and maintenance of corpus luteum. However, the precise signaling mechanism remains to be explored.

2003). We believe there is a close relation between GALT and PRL-RS as ovaries from PRLR−/−RS females exhibit a dramatic loss of GALT mRNA and overexpression of PRL-RS in culture strongly represses GALT transcriptional activity (Halperin et al., 2008). This loss of GALT is presumably a major factor in early follicular depletion and premature ovarian failure phenotype of PRLR−/−RS mice (summarized in Fig. 1).

In spite of the many defects in follicular development observed in PRLR−/−RS ovaries, some follicles do escape atresia and manage to ovulate in young females. However, the corpus luteum rapidly degenerates and these females never become pregnant. Since expression of PRL-RS could not prevent the luteal failure induced by the deletion of PRLR gene (Ormandy et al., 1997; Halperin et al., 2008), activation of PRL-RL was thought to be the sole receptor responsible for the luteotropic effect of PRL. In an attempt to study the role of PRL-RL in mediating the luteotropic effect of PRL in the corpus luteum, two novel transgenic mouse models which selectively express PRL-RL either ubiquitously or in a corpus luteum specific manner (PRLR−/−RL) were developed by Gibori and colleagues (Le et al., 2012). Surprisingly, both of these transgenic females are infertile and exhibit low progesterone levels despite the activation of JAK2/STAT5 signaling, suggesting that expression of PRL-RL alone is not sufficient to rescue infertility. Closer analysis revealed a defect in luteal cell hypertrophy and steroidogenic capacity. Interestingly, the luteal cells derived from PRLR-/-RL transgenic mice are perfectly normal in culture, suggesting extrinsic factor(s) may be involved in this luteinization defect. Expression of VEGFA, a key regulator of angiogenesis and vascularization is dramatically reduced in PRLR−/−RL mice. Furthermore, PRLR−/−RL females exhibit aberrant expression of collagen IV, a marker for the basal lamina of endothelial cells and a discordant organization of endothelial cells in the corpus luteum (Le et al., 2012), suggesting that PRL-RS may be necessary for proper expression of these factors. We have recently shown that PRL activation of PRL-RS robustly stimulated the activity of HIF-1 transcription factor (Devi et al., 2009a), which is a key inducer of VEGF expression (Alam et al., 2009). All these results strongly suggest that PRL-RS plays an essential role in vascularization of pregnancy corpus luteum. This notion is further supported by the fact that (1) PRL-RS is the predominant isoform in endothelial cells derived from CL (Ricken et al., 2007), (2) a robust increase in the expression of PRL-RS is observed during luteinization in normal ovary (Russell and Richards, 1999; Telleria et al., 1997), (3) PRL induces endothelial cell proliferation and vascularization in corpus luteum (Chen et al., 2002; Gaytan et al., 1997), (4) mice expressing only one allele of PRLR (RS) in the PRL-RL transgenic background (PRLR+/−RL) are fertile and have normal corpus luteum. Furthermore, PRL-RS could be also involved in luteal cell hypertrophy which is a critical step preceding proliferation of vascular endothelial cells in the corpus luteum (Tamura and Greenwald, 1987). It is well known that

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estradiol stimulates luteal cell hypertrophy (McLean et al., 1990). PRL-RS was shown to be physically associated with HSD17B-7, a key enzyme in estradiol biosynthesis, in the corpus luteum (Risk et al., 2005; Duan et al., 1996, 1997). This association appears to stabilize and increase expression of HSD17B-7, which in turn stimulates estradiol biosynthesis. Fig. 2 depicts a proposed model of PRL-RS and PRL-RL signaling in corpus luteum. Although the precise signaling mechanism is still unclear, these findings strongly advocate an important role of PRL-RS in angiogenesis and a coordinate action with PRL-RL for proper maintenance of functional corpus luteum and fertility.

8. Concluding remarks

PRL impacts a large number of ovarian functions including follicular development and the maintenance of functional corpus luteum. PRL actions on each ovarian cell type and which receptor isoform is important for these functions remains a deeply debated area. This became more complicated by the fact that both long and short isoform of the receptor are expressed in varying concentrations in many cell types throughout the estrus cycle and during gestation. The long form has been viewed as the predominant receptor with active and positive signaling whereas the physiological role as well as signaling of the short form remains controversial. However, recent and compelling evidences suggest that the short form can interact with signaling molecules, activates specific signaling pathways, and can cooperate with or inhibits the long form signaling. The function and the differential signaling mechanisms elicited exclusively by one type of receptor are beginning to unravel with the help of transgenic mice, which selectively express either the short or the long form receptor. Contrary to previous beliefs that the short form is a sole dominant negative receptor, these recent findings have clearly demonstrated that either long or short form can act as dominant negative to each other and prevent excessive signaling of one isoform. On the other hand, their concerted cooperative actions are required for survival of the corpus luteum. What remains to be explored is the manner in which these isoforms cross talk with each other and mediate differential or cooperative signaling. This review highlighted important findings on novel PRL signaling though different isoforms of receptor and discussed their implications in normal reproductive function and reproductive pathologies.

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