PGRMC1 and PGRMC2 in uterine physiology and disease

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It is clear from studies using progesterone receptor (PGR) mutant mice that not all of the actions of progesterone (P4) are mediated by this receptor. Indeed, many rapid, non-classical P4 actions have been reported throughout the female reproductive tract. Progesterone treatment of Pgr null mice results in behavioral changes and in differential regulation of genes in the endometrium. Progesterone receptor membrane component (PGRMC) 1 and PGRMC2 belong to the heme-binding protein family and may serve as P4 receptors. Evidence to support this derives chiefly from in vitro culture work using primary or transformed cell lines that lack the classical PGR. Endometrial expression of PGRMC1 in menstrual cycling mammals is most abundant during the proliferative phase of the cycle. Because PGRMC2 expression shows the most consistent cross-species expression, with highest levels during the secretory phase, PGRMC2 may serve as a universal non-classical P4 receptor in the uterus. While the functional importance of PGRMC1/2 in the uterus remains to be fully explored, accumulating evidence suggests that disruption in PGRMC1/2 expression correlates with uterine disease. In this review we will summarize what is known about PGRMC1/2 in uterine physiology and we will provide examples of disrupted expression of these genes in uterine disease states.

Keywords: PGRMC1, PGRMC2, pregnancy, progesterone, uterus

INTRODUCTION

The uterus is a primary target of ovarian-derived progesterone (P4), which acts to prepare the endometrium for embryo implantation. In invasively implanting species such as rodents, rabbits, primates and humans, P4 facilitates and maintains the process of endometrial stromal cell decidualization (i.e., terminal differentiation of stromal cells), a critical event that is required for normal pregnancy. In these species, the embryo significantly modifies or, in some instances, completely invades the maternal uterine vasculature in an effort to gain access to oxygen and nutrients. By regulating stromal cell decidualization, P4 contributes to this process and provides balance to ensure that sufficient, but not excessive, invasion of the embryonic trophectoderm occurs. In most mammals, P4 also promotes uterine growth, modulates the maternal immune system locally so the histocompatibility distinct embryo can survive and suppresses myometrial contractions during pregnancy (Graham and Clark, 1997).

Through pharmacologic approaches and mouse mutagenesis studies, many of the actions of P4 are now known to be mediated by the classical P4 receptor (PGR; Lydon et al., 1996; Mulac-Jericevic and Conneely, 2004; Wetendorf and DeMayo, 2012). Indeed, female mice deficient in PGR are sterile (Lydon et al., 1995) and develop endometrial hyperplasia in response to combined estradiol and progesterone treatment likely due to the unopposed actions of estradiol (Mulac-Jericevic et al., 2000). Since its initial description in rodents (Milgrom and Baulieu, 1970; Milgrom et al., 1970) and then later in humans (Rao et al., 1974), PGR has been characterized as a ligand activated transcription factor that functions to regulate gene expression. However, non-genomic actions are also described for PGR where SRC tyrosine kinase activity and subsequent activation of the MAPK pathway has been demonstrated (Migliaccio et al., 1998; Lange, 2004). These and many other studies have unequivocally established PGR as an important mediator of P4 actions in the female.

In accordance with its elementary role in reproduction, faulty P4 responses have been linked to many reproductive diseases that result in subfertility or infertility including fibroids, breast and endometrial cancers, endometriosis, irregular menstrual bleeding, adenomyosis, miscarriage and preterm labor (Szekeres-Bartho et al., 2001; Wu et al., 2006; Burney et al., 2007; Ehn et al., 2007; Ito et al., 2007; Salazar and Calzada, 2007; Borurban et al., 2008). Conceptions that fail due to faulty communication between the mother and embryo remain a major impediment to successful pregnancy, particularly in an IVF setting. As the uterus is a principal target of P4 responses, it is perhaps not surprising that many causes of infertility stem from disrupted P4 actions in the uterus. Epidemiological studies in humans (Christiansen et al., 2005) and livestock (Inskeep and Dailey, 2005), as well as genetic studies in rodents (Conneely et al., 2002; Wang and Dey, 2006), support the notion that failed pregnancy occurs due to faulty uterine function or miscommunication between the embryo and mother during implantation. An estimated 25–60% of conceptions result in pregnancy failure depending upon the mammalian species. In humans, recurrent pregnancy loss occurs at a rate of 1% and is among the most common complications to pregnancy. Importantly, among pregnancies that fail, most occur as pregnancy is being established, long before the placenta develops.

Despite the essential role that PGR plays in female reproduction, not all of the physiological actions of P4 can be explained by activation of PGR. While classical PGR is required for many...
components of female reproductive physiology and also initi-
ates actions in the male (Luetjens et al., 2006), studies using
PGR mutant mice suggest that non-classical P4 signaling me-
chanisms exist (reviewed in Losel et al., 2003), as outlined in greater
detail below. The objective of this perspective article will be to
provide examples of non-classical progesterone signaling events
in vivo and to describe what is currently known about two related
non-classical progesterone receptors called progesterone receptor
membrane component (PGRMC) 1 and PGRMC2.

**EVIDENCE FOR NON-CLASSICAL PROGESTERONE RECEPTOR SIGNALING**

Functional studies in Pgr null female mice, as well as pharma-
cological studies using PGR antagonists (e.g., mifepristone) have
clearly demonstrated a fundamental role for PGR in female fer-
tility (Conneely et al., 2002). However, PGR does not appear to
be the sole receptor mechanism for eliciting P4 actions, as cells
that completely lack expression of PGR are still able to respond
to P4, as well as to non-metabolizable P4 analogs such as R5020
(Peluso, 2006, 2007; Peluso et al., 2009a,b). Non-classical actions
of P4 are historically well-documented in general terms in con-
junction with meiotic maturation (Finidori-Lepicard et al., 1981),
sexual behavior (Frye et al., 2006) and the acrosome reaction
(Foresta et al., 1993; Losel et al., 2004), as well as regulating
ion flux in epithelial cells (Head et al., 1999), neurons (Viero
et al., 2006), and vascular smooth muscle (Barbagallo et al., 2001).
Several laboratories have also shown that P4 modulates immune
cell functions in cells completely devoid of classical nuclear PGR
(Ehring et al., 1998). Interestingly, these examples of responses to
P4 are generally rapid and often do not require gene transcription
(i.e., non-genomic actions). Perhaps the most well-documented
examples of PGR-independent signaling in cells of the female
reproductive system derive from the Peluso lab. Here, studies in
the ovary reveal that granulosa cells lacking PGR are resistant
to apoptosis in response to various forms of stress in the presence
of P4 despite a complete absence of the PGR (Peluso and
Pappalardo, 1998; Peluso et al., 2006, 2008, 2009a,b, 2010).

A number of studies have demonstrated non-classical P4
responses in the uterus. For example, the effect of P4 on uterine
sensitivity to oxytocin involves direct, but non-classical action
of P4 on the uterine oxytocin receptor (Grazzini et al., 1998; Dunlap
and Stormshak, 2004; Duras et al., 2005; Bishop and Stormshak,
2006). The details of these studies are discussed in an accompany-
ing review in this edition. DeMayo and colleagues demonstrated
that while PGR is important for mediating changes in the expres-
sion of many P4-regulated genes in the murine uterus, many other
genes are regulated by P4 by a PGR-independent mechanism.
Indeed, 44 genes were shown to be differentially regulated in the
uteri of Pgr null mice in response to P4 treatment (Jeong et al.,
2005). Interestingly, these data were derived from mouse U74av2
microarrays which were spotted with only 6000 known genes
along with 6000 ESTs. Collectively, this only constitutes about one
third of the entire mouse genome. As such, it is likely that many
more genes are regulated by P4 in a PGR-independent manner. In
support of this, Matumoto et al. established that P4 up-regulates
the Indian Hedgehog (IHH) signaling pathway (Matumoto et al.,
2002). This pathway plays an integral role in coordinating uterine
epithelial-mesenchymal interactions during embryo implant-
ation. In their study, ovariectomy of wild type mice followed 1
week later with a single injection of P4 resulted in transcriptional
up-regulation of Ihh mRNA. Ihh mRNA was shown by in situ
hybridization to be up-regulated within 6 h. The same treat-
ment was given to Pgr null mice, and surprisingly Ihh was also
up-regulated within 6 h despite a complete absence of PGR from
the uterus. Similar results were found for other members of the
IHH pathway like Patched-1 (Ptc1), as well as the downstream
IHH target homeobox gene A10 (Hoxa10). The important con-
clusion from these studies is that the transcriptional effects of P4
on Ihh, Ptc, and Hoxa10 in the uterus are mediated in part by a
PGR-independent mechanism.

These data clearly illustrate that P4 actions are mediated by
multiple signaling pathways that involve both PGR and other, as
yet, undefined pathways. Two families of non-classical membrane
receptors have been identified and these include the Progestin and
AdipoQ receptor (PAQR) and Progesterone Receptor Membrane
Component (PGRMC) families (Tang et al., 2005; Cahill, 2007;
Peluso, 2007; Thomas, 2008; Thomas and Pang, 2012). Members
of the PAQR family with purported P4 binding activity belong to
the G protein-coupled receptor superfamily and include mem-
brane progestin receptors α, β, and γ, (also called PAQR VII,
VIII, and V, respectively). Each gene has been cloned and partially
characterized in mammals (Zhu et al., 2003). While these recep-
tors have been shown to have biological actions in vitro (Karteris
et al., 2006), others have challenged the validity of the mPRs as
bona fide progestin receptors (Krietsch et al., 2006). In addition,
two distinct proteins with progestin binding activity have been
described and these are referred to as PGRMC1 and PGRMC2.
These genes were originally cloned as hem-1 domain protein or
HPR6.6 and Dg6, respectively (Falkenstein et al., 1996; Meyer
et al., 1996; Gerdes et al., 1998). The function of each of these
genes has been outlined in two recent review articles (Cahill, 2007;
Wendler and Wehling, 2013).

**PGRMC1 AND PGRMC2 EXPRESSION AND FUNCTION IN THE UTERUS**

PGRMC1 and PGRMC2 are highly expressed in female reproduc-
tive tissues of the mouse (Zhang et al., 2008), rat (Peluso et al.,
2006; Intlekofer and Petersen, 2011; Lodde and Peluso, 2011),
monkey (Keator et al., 2012), cow (Luciano et al., 2010, 2011;
Slonina et al., 2012), and human (Engmann et al., 2006; Zhang
et al., 2008; Peluso et al., 2009a,b).

PGRMC1

The first report of PGRMC1 expression in the uterus derives from
a microarray study in which Pgrmc1 mRNA was found to be
down-regulated from the proliferative (i.e., epithelial cell cycle
progression, mucosal edema and angiogenesis) to the secretory
(i.e., mitosis blockade, cellular differentiation and mucosal secre-
tion) phase of the human menstrual cycle (Kao et al., 2002).
This was later confirmed with microarray data in the primate
(Ace and Okulicz, 2004) and a proteomics-based study in women
(Chen et al., 2009). Beyond this, very little is known about
PGRMC1 expression in the human endometrium. Keator et al.
recently demonstrated that PGRMC1 mRNA and protein are

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*Note: The text continues with more detailed scientific content.*
highly expressed in the proliferative phase in an artificial menstrual cycle model in monkeys, but then becomes down-regulated to the point of not being detected during the late secretory phase (Keator et al., 2012). Expression of PGRMC1 during the proliferative phase was most evident in the stroma, glandular epithelium and luminal epithelium of the inner-most aspect of the endometrium (i.e., functionalis). Given that PGRMC1 is most abundant during the proliferative phase of the human and monkey menstrual cycle, it may serve a role in regulating the cell cycle. PGRMC1 is also expressed and highly regulated in the human decidua at the maternal:fetal interface, as well as in the embryonic/fetal trophectoderm (Zhang et al., 2008). In each of these cases, the subcellular localization of PGRMC1 was most abundant in the peri-nuclear region.

Interestingly, despite the dynamic regulation of PGRMC1 in the primate and human, PGRMC1 expression does not change during the estrous cycle in the cow (Luciano et al., 2011; Kowalik et al., 2013). However, in the mouse PGRMC1 expression is highest when female mice are exposed to P4 during either the estrous cycle or following ovariectomy and subsequent P4 supplementation (Zhang et al., 2008). Within the endometrium, PGRMC1 expression is highly regulated and dependent on the stage of the estrous cycle, pregnancy status and steroid hormone supplementation following ovariectomy (Zhang et al., 2008). Specifically, the PGRMC1 expression pattern changed from mainly the glandular and luminal epithelium during preestrus to then also include stromal cells during metestrus. As seen with granulosato-luteal cell differentiation in the ovary, the cellular localization of PGRMC1 changes during stromal cell decidualization of early pregnancy in which the protein transitions from the plasma membrane of undifferentiated endometrial stromal cells to the nuclei of stromal cells undergoing differentiation. Upon terminal stromal cell differentiation (i.e., decidualization), PGRMC1 becomes localized throughout the cell, particularly in the peri-nuclear space. Because of the observed nuclear localization, we speculate that PGRMC1 regulates expression of a unique set of genes distinct from those regulated by the classical PGR. In support of this, PGRMC1 was recently shown to regulate expression of genes associated with apoptosis (Peluso et al., 2010), as well as activity of the TCF/LEF transcriptional unit in granulosa cells (Peluso et al., 2012). Alternatively, PGRMC1 may participate in cell cycle regulation given that nuclear localization occurs at a time when proliferative stromal cells transition to terminally differentiated decidual cells. A role for PGRMC1 in regulating cell cycle progression has been proposed in granulosa cells (Lodde and Peluso, 2011).

PGRMC2
Considerably less information is available on PGRMC2 expression and function. Recently, Albrecht et al. (2012) demonstrated in SKOV-3 cancer cells that PGRMC2 may function to inhibit cell migration (Wendler and Wehling, 2013). Within the uterus, Pgrmc2 mRNA is up-regulated by P4 in both mice and monkeys. In the mouse, uterine PGRMC2 expression is elevated during metestrus, as well as in response to P4 treatment following ovariectomy (Zhang et al., 2008). Similarly, PGRMC2 expression increases substantially during the secretory phase of an artificial menstrual cycle in macaques (Keator et al., 2012). In this model, PGRMC2 mRNA and protein localize strongly to the functionalis layer, particularly the glandular and luminal epithelial compartments. This corresponds to a time when PGRMC1 and the classical PGR are absent. As such, while several studies have demonstrated that the stromal compartment indirectly mediates the actions of P4 on the epithelium via paracrine signaling, P4 may also directly signal in epithelial tissue at the time of embryo implantation via PGRMC2-mediated signaling. A significant increase in PGRMC2 was also observed in the human chorionic decidua of term and pre-term pregnancies (Shankar et al., 2010).

The expression studies reveal two important points regarding PGRMCs. First, uterine expression of PGRMC1 and PGRMC2 is regulated by endocrine factors. This is evident from the dynamic patterns of PGRMC1 and PGRMC2 expression under physiological conditions and in response to steroid hormones. Second, much work is clearly needed, particularly in humans, to fully characterize the pattern of PGRMC1 and PGRMC2 expression in the mammalian uterus and to establish a functional role for these genes in female reproduction. The most recent overview of general PGRMC1 and PGRMC2 functions is outlined in a recent review (Wendler and Wehling, 2013).

RELATIONSHIPS BETWEEN DISRUPTED PGRMC1 AND PGRMC2 EXPRESSION AND THE DEVELOPMENT OF DISEASE STATES
Several recent studies have suggested that PGRMC1 and PGRMC2 are important for maintaining normal reproductive functions. For instance, Pgrmc1 levels are reduced in peripheral blood cells in women with polycystic ovarian syndrome (Schuster et al., 2010) and in some women with premature ovarian failure (Mansouri et al., 2008; Schuster et al., 2010). In contrast PGRMC1 over-expression is associated with impaired follicular development in women induced to undergo ovulation as part of their infertility treatment (Ellassar et al., 2012). Antral follicle development is impaired in mice in which the Pgrmc1 gene has been conditionally knocked out (cKO) of granulosa cells (Pru unpublished).

As noted above, PGRMC2 expression is increased by P4 in the luminal and glandular epithelia of the secretory endometrium in the macaque (Keator et al., 2012). In contrast, the level of PGRMC2 is reduced and its cellular localization disrupted in a primate model of endometriosis (Keator et al., 2012). Importantly, this phenotype is recapitulated in women with endometriosis (Bunch et al., 2013). This suggests that aberrant PGRMC2 expression may contribute to P4 refractoriness commonly found in endometriosis. Within the ovary, Pgrmc2 expression is elevated in granulosa cells of young women with diminished ovarian reserve. Previously unpublished data from our lab reveal that PGRMC1 deficiency in the murine endometrium results in development of cystic glandular hyperplasia by as early as 3 months of age (Figure 1). By 6 months of age, greater than 80% of the female mice exhibit the phenotype. While control female mice display with expectedly normal endometrium, female mice in which Pgrmc1 was conditionally deleted from mesenchymal tissue (i.e., stroma and myometrium) of the uterus...
using the anti-Müllerian hormone type II receptor-cre recombinase (Amhr2-cre) transgenic mouse develop hyperplastic and enlarged glands. The glandular hyperplasia is accompanied by the presence of many epithelial cells with pyknotic nuclei indicative of apoptosis, infiltration of immune cells, heavily vacuolated epithelial cells, and disruption of the transitional zone between the epithelium and underlying stromal tissue. Interestingly, many cross sections obtained from Pgrmc1 cKO mice harbor multiple glandular structures that are larger than even the luminal space. This accounts for the approximate 2-fold increase in cross-sectional volume compared with control sections. This is important and clinically relevant roles in regulating female reproductive tissues when normal expression is disrupted in Pgrmc1 cKO mice. In the very least, it is clear that stromal PGRMC1 is necessary for cross-talk between the mesenchymal and epithelial compartments. These cumulative findings clearly demonstrate that PGRMC1 and PGRMC2 play important and clinically relevant roles in regulating female reproductive functions and in the manifestation of disease states in female reproductive tissues when normal expression is disrupted.

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**FIGURE 1 | Female Amhr2cre+/-; Pgrmc1fl/fl conditional knockout (cKO) mice develop uterine cystic hyperplasia.** Shown are uterine cross-sections of control (Amhr2cre+/-;Pgrmc1fl/fl, A) and Pgrmc1 cKO (Amhr2cre+/-;Pgrmc1fl/fl, B and C) female mice at 6 months of age (40X). Extensive cystic hyperplasia is evident in glandular tissue in sections from cKO mice. Higher magnification images (600X) reveal normal glandular tissue in control (D) sections, with development of vacuoles in glandular epithelium in sections from cKO mice (E). Epithelial cells with pyknotic nuclei consistent with apoptosis, disruption of the transitional zone between epithelial and stromal tissues and infiltration of immune cells are also evident in sections obtained from cKO female mice (F).
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