# Nuclear Receptors in Ovarian Function

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**Abstract**

The ovary undergoes cycles of hormone production that regulate physiological changes necessary for folliculogenesis, ovulation and luteinisation, ultimately contributing to female reproductive success. Crucial to these biological processes is stage-specific nuclear receptor signalling. While the transcriptional regulatory roles of steroid receptors in female fertility and especially ovarian functions have long been documented, non-steroid receptors also play an important part in regulating gene expression at various stages of ovarian development. The recent application of high-throughput genomic and transcriptomic technologies has begun to shed light on the molecular mechanisms underlying ovarian nuclear receptor actions and pointed to a complex interplay between highly specific transcription co-regulators as well as between nuclear receptors in mediating mutual as well as unique target genes. Interrelationships between nuclear receptors as well as the involvement of context-specific protein and non-protein co-regulators are likely keys to the precise and specific nuclear receptor action in the ovary. Leveraging such knowledge on the nuclear receptor network is especially valuable in the development of novel fertility treatments as well as female contraceptives.

**Keywords**

Reproductive biology · Steroid receptor · Nuclear receptor · Ovary · Ovulation · Female reproduction

## 3.1 Introduction

The ovary is responsible for ensuring female reproductive success through the generation of viable oocytes for fertilisation and development as well as the production of hormones that coordinate the reproductive cycle and support pregnancy and lactation. Critical ovarian functions include follicle development (folliculogenesis), oocyte maturation, ovulation and luteinisation. Crucial to the precise regulation of all ovarian functions is the involvement of reproductive hormones; in particular, reproductive steroids and their receptors are the archetypal hormone network. Ligand-activated receptors provide an elegant mechanism for communication between different organs or cell types to control and coordinate the many critical reproductive processes. In the ovary multiple nuclear hormone receptors, including steroid and non-steroid receptors, are activated at specific stages and regulate a com-

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plex network of signalling pathways via their target genes.

## 3.2 Hormonal Control of Dynamic Physiological Change in the Ovary

(a) Folliculogenesis:

The ovarian follicle is composed of an oocyte surrounded by somatic cells – mural granulosa cells, cumulus cells and theca cells. The complex interactions between each of these compartments, often involving steroid hormone signals, are vital for ovarian functions. A typical ovarian follicular cycle is illustrated in Fig. 3.1. Folliculogenesis initiates prior to birth and in the developing ovary, oocytes enter meiosis and germ cell division is arrested early at meiosis I prophase in prenatal development [1]. At, or shortly after birth, meiotically arrested oocytes are assembled into primordial follicles in which they are surrounded by a layer of flat, un-differentiated pre-granulosa cells [2]. Follicle growth and development (folliculogenesis) is sporadically initiated each day in a small number of primordial follicles. During the early stage of follicle development, granulosa cells also display morphological changes, becoming cuboidal and proliferative [3]. During early follicle growth granulosa cells are not steroidogenic, but as the follicle grows, specialised stromal cells called theca cells are recruited from a progenitor pool in the ovarian stroma, then proliferate and differentiate to form the theca layer surrounding the exterior of the follicle. Theca cells express steroidogenic enzymes that are necessary to convert cholesterol to testosterone (T) under the control of luteinising hormone (LH) [4]. This testosterone is secreted and taken up by granulosa cells, which convert it to estrogen (E2) via the P450 Aromatase enzyme encoded by the ***Cyp19a1*** gene, regulated by follicle stimulating hormone (FSH) from the pituitary. This regulation of two independent cell types by two distinct gonadotrophins, known as the two-cell two-gonadotropin theory, provides exquisite control of the regular female hormone cycle driven by the developmental status of the ovarian follicles. E2 produced by growing follicles acts on the pituitary to repress FSH production, while also stimulating GnRH synthesis and release by the hypothalamus, thus promoting the release of LH pulses. As a result, granulosa cells of dominant follicles acquire FSH-independent growth and development, while rising LH levels further stimulate theca cells and begin to also act on granulosa cells, promoting their differentiation to preovulatory stage. During folliculogenesis, granulosa cell specification and the formation of the fluid-filled antral space also lead to the differentiation between cumulus cells, which immediately surround the oocyte and are important in promoting oocyte growth and developmental competence, and mural granulosa cells which are involved in steroid and protein hormone production in response to FSH and LH [5].

(b) Ovulation:

Continued rising E2 from preovulatory follicles causes larger and more frequent pulses of LH release from the pituitary until the pulses merge to become the mid-cycle LH-surge. Preovulatory ovarian follicles respond to the LH surge, resulting in a number of dynamic morphological, molecular and biochemical events in preparation for the release of the mature oocyte into the oviduct and potential fertilisation, embryo development and implantation [6]. A multifaceted interplay between different components of the pre-ovulatory follicle, including oocytes and their surrounding somatic cells, has to be coordinated to achieve ovulation. In oocytes, meiotic resumption occurs leading to the extrusion of the first polar body, which carries half of the genetic material, and the second meiotic arrest at MII stage. At the same time, the surrounding cumulus cell layers produce a specialised extracellular matrix (ECM), causing the cumulus oocyte complex (COC) to expand and increase in volume, as well as gaining additional migratory and invasive properties which are necessary for ovulation [7]. The COC, containing a mature oocyte, is then released into the oviduct from the peri-ovulatory

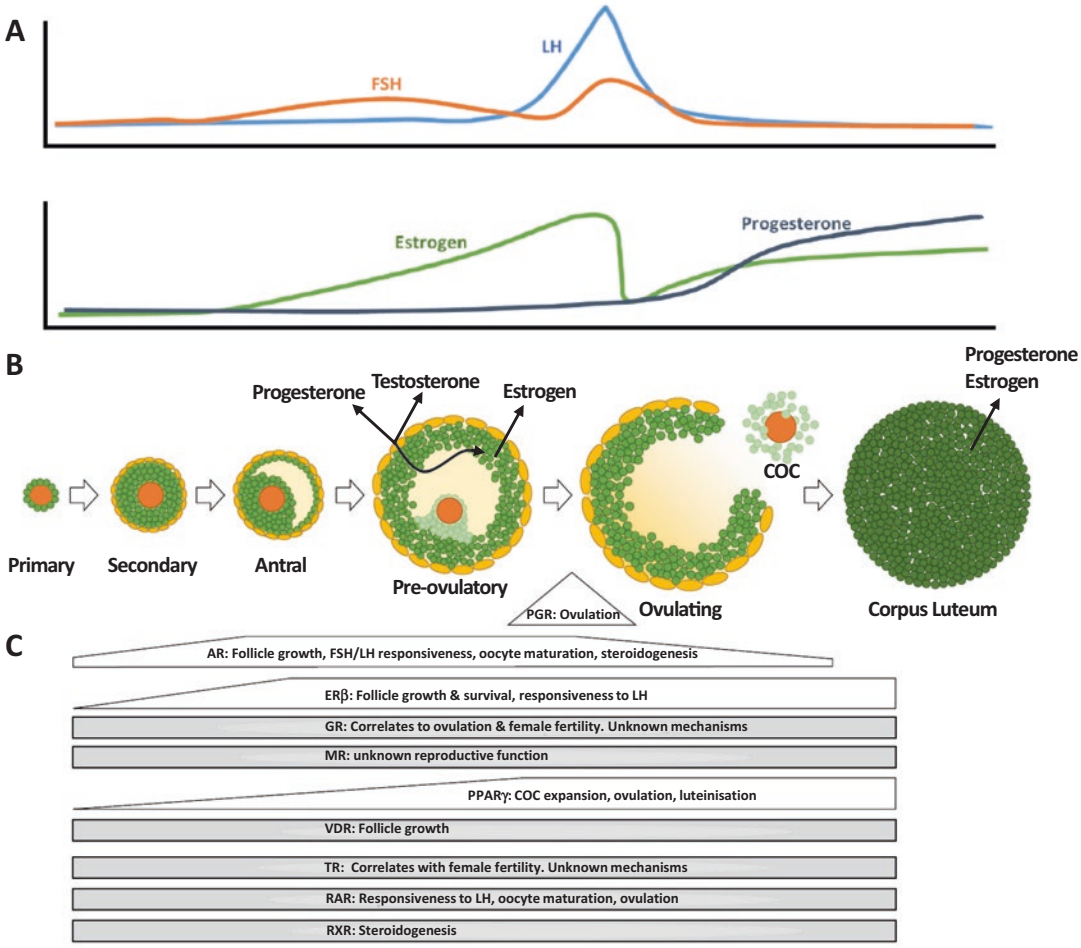


**Fig. 3.1 Follicle development and nuclear receptor action in the ovary**. (**a**) Circulating levels of gonadotropins; follicle stimulating hormone (FSH) and luteinising hormone (LH) and steroids associated with stages of follicle development (folliculogenesis). (**b**) During folliculogenesis, follicles grow and differentiate, form the antrum cavity, granulosa cells (green) diverge into mural granulosa and cumulus cells. Steroidogenic theca cells (yellow) produce progesterone, most of which is converted to testosterone. Testosterone diffuses to the granulosa cell layers, where the aromatase enzyme converts it to estrogen. The rise in circulating estrogen stimulates the hypothalamus and pituitary, prompting the LH surge which triggers release of the mature oocyte from the follicle (ovulation), while residual granulosa cells luteinise, forming the highly steroidogenic corpus luteum which secretes progesterone to support implantation and pregnancy. (**c**) Expression and role of nuclear receptors at different stages of folliculogenesis. Position and size of boxes reflect the temporal expression of each nuclear receptor in granulosa cells. Nuclear receptors that are present in granulosa cells but do not have a well-described temporal expression pattern are greyed

follicle at the follicle apex. For this to occur, the physical cellular barrier of the follicle, composed of multiple layers of ECM as well as granulosa, theca and surface epithelial cells, needs to be thinned and broken down through tissue remodelling. This involves many concurrent processes, including proteolytic degradation of ECM layers, surface epithelial cell apoptosis, immune cell recruitment and theca cell migration [6]. Aside from tissue remodelling, precisely-timed muscle contraction as well as vasocontraction at the apex are also required for the release of the oocyte. The ovulatory surge of LH also induces terminal differentiation of granulosa cells into highly ste-

roidogenic luteal cells, which synthesise cholesterol and convert it to progesterone that acts on the uterus to promote implantation and gestation. Another important part of the tissue remodelling process is the generation of new vasculature around the periovulatory follicle, which is necessary for the formation of the corpus luteum (CL) from the ovulated follicle by providing nutrients and hormones to the developing CL, and providing ready access for highly active hormone secretion from the CL to reach circulation.

## 3.3 Physiological Effects of Nuclear Hormone Receptors on Ovarian Functions

Nuclear hormone receptors are a family of ligand-dependent transcription factors that are usually activated through binding with steroid hormones or other signalling lipid-soluble molecules and directly interact with chromatin. Despite the name, the ligands for many nuclear receptors are as yet unknown and these are thus referred to as 'orphan' nuclear receptors. In addition to genomic actions, many are also known to have non-genomic roles in various contexts [8, 9]. While several orphan receptors have important ovarian roles, in particular SF1 for early ovarian development and LRH1 for folliculogenesis and ovulation, for the purpose of this review, only hormone receptors with well-described ligands and their genomic actions will be considered, with orphan receptors having been reviewed elsewhere [10]. The ligand activated receptors are grouped into two classes:

(a) Steroid receptors (SR), which are steroid hormone-binding transcription factors (NR3 family) including progesterone receptor (PGR), estrogen receptor (ER), androgen receptor (AR), glucocorticoid receptor (GR) and mineralocorticoid receptor (MR).

(b) Non-steroid receptors, loosely including transcription factors not in the NR3 family that bind and are regulated by ligands that are lipid permeable compounds, such as vitamins, lipid metabolites or retinoids. These include peroxisome proliferator-activated receptor (PPAR), thyroid hormone receptor (TR), vitamin D receptor (VDR), retinoic acid receptor (RAR) and retinoid X receptor (RXR).

(a) Steroid receptors in the ovary:

The steroid hormones are classical regulators of reproductive processes. Highly regulated secretion of hormones and expression of their receptors enable communication and exquisite coordination of the functions of the different reproductive organs in preparation for fertilisation and pregnancy. The ovary is the primary source of estrogen, androgens and progesterone in females and ovaries are themselves responsive to these signals through steroid receptors that are expressed at key developmental stages.

Progesterone (P4) is an essential reproductive hormone critical in the ovary for ovulation, in the uterus for implantation and gestation, as well as in the mammary gland for milk production. In the final stages of ovarian follicle maturation, differentiated granulosa cells of preovulatory follicles respond to the LH surge and begin to express *Cyp11a1,* which encodes the P450 side chain cleavage enzyme that is rate-limiting for P4 production [11]. This results in steadily increasing P4 secretion by the ovarian follicular granulosa cells immediately prior to ovulation, which continues to rise as the follicle luteinises and remains high throughout gestation. P4 mainly functions through the direct binding and activation of its cognate receptor PGR, a nuclear steroid receptor that has profound importance in the regulation and maintenance of normal female reproductive physiology. In different female reproductive tissues, PGR responding to rising P4 secretion from the ovary shows distinct functions that are highly dependent on each tissue context, revealed in studies on PGR knockout (KO) mouse models

[12, 13]. In the pre-ovulatory ovary, PGR is expressed exclusively in granulosa cells and is highly induced in response to the ovulatory LH-surge [14]. PGRKO female mice are infertile due to complete anovulation [12]. Likewise, treatment with PGR antagonist results in ovulation suppression in rodents and humans [15–17], and silencing of ovarian PGR expression results in ovulation disruption in macaques [18]. Luteinisation of follicles is unaffected in PGRKO or PGR-antagonist treated models with the resulting CLs containing entrapped oocytes, indicating that ovulation is specifically dependent on PGR action in the ovary [12]. PGR is a key regulator of a number of ovulatory genes that are involved in tissue remodelling (*Adamts1*), cumulus expansion (*Areg, Ereg*) and also acts upstream to other ovulatory transcription factors (*Pparg, Hif1a*) [19]. PGR includes two main isoforms, PGR-A and PGR-B, both of which are present in most PGR-positive cells. Even though both isoforms are expressed in granulosa cells of pre-ovulatory follicles, PGR-A is credited as the more essential isoform in ovulation, as determined from studies on null mouse models that are specific to each PGR isoform [20, 21]. Female mice that have a mutation which prevents production of functional PGR-A exhibit a specific failure of follicle rupture, but not luteinisation, even after gonadotropin stimulation. However, female mice lacking PGR-B have normal ovulation and fertility. Analysis of total and isoform-specific knockout granulosa transcriptomes indicates that such phenotypic properties are a result of broad differences in gene expression patterns that are driven by PGR-A and not PGR-B, in which PGR-B deletion had very limited impact on gene expression in LH-stimulated ovaries, while PGR-A deletion caused very similar gene expression changes to the total PGRKO [22]. The role of PGR on oocyte development, however, is less clear. Oocytes from total PGRKO mice that are extracted from preovulatory ovaries and subjected to *in vitro* maturation are capable of COC expansion, fertilisation and developing into normal pups [23]. Furthermore, while there is *in vitro* evidence that PGR antagonist treatment has detrimental effects on cumulus expansion in pigs [24], there is no evidence for a role for PGR in human cumulus cells or oocyte maturation.

A direct intraovarian role for estrogen to promote FSH-independent survival, proliferation and differentiation of granulosa cells is well known [25]. In granulosa cells, estrogen receptor β (ERβ) is expressed at all stages of development, from the secondary follicle stage onwards to CL [26, 27]. ERα, however, is not found in granulosa cells but rather in theca and interstitial cells. Correspondingly, it has been shown through a number of mouse models that ERβ is the more important form in ovulation. Knockout of ERβ in female mice results in reduced cumulus expansion, ovulation and corpus luteum formation and hence reduced litter size, which cannot be rescued through gonadotrophin stimulation [28]. A number of FSH-regulated genes, including the LH receptor-encoding gene *Lhcgr* and LH-regulated downstream target genes, show disrupted expression in ERβKO granulosa cells [29]. Thus, in response to E2, ERβ mediates a gene expression profile that is required for granulosa cell differentiation to the fully LH-responsive preovulatory stage. ERβ also has a role in supporting the emergence of dominant follicles and their progression to become preovulatory follicles [30]. This is in contrast to the ERαKO model, in which anovulation can be ameliorated through exogenous gonadotrophin stimulation, indicating that the key role for ERα is in the regulation of gonadotropin release from the pituitary [31]. The involvement of non-classical ERα actions in fertility has also been investigated in separate transgenic mouse models carrying point mutations in the LBD or AF-2 region of ERα respectively, resulting in disrupted ERα ligand binding function and plasma membrane association. Both of these mouse models showed a similar reversible anovulation phenotype due to defects in survival and proliferation of granulosa cells and theca cells. This suggested that ERα can have extranuclear and ligand-independent ovarian functions [32, 33]. Furthermore, theca-specific KO of ERα leads to a less severe reproductive phenotype, where aberrant oestrus cycling pattern results in

more pronounced fertility decline in older female mice, further indicating that ERα has only a minor role in the theca, and is most important in regulating gonadotropin release to mediate reproduction [34]. In breast cells and in the endometrium, ER has been shown to be immediately upstream of PGR expression through direct binding of ER to response elements within the PGR promoter [35]. Such sites are dispensable for PGR expression in granulosa cells [36]. Rather, the effect of ERβ on PGR expression in this context is more likely indirect, through the mediation of LH receptor expression, which is required for LH-induced PGR induction as shown through transcriptomic analysis of ERβKO vs WT granulosa cells [29, 37]. A similar pathway is likely the mechanism by which ERβ regulates other ovulatory transcription factors, including RUNX1 and RUNX2. Rather than having a direct role in ovulation, transcription analysis of ERβ KO vs WT in pre-ovulatory follicles indicates that ERβ is required for growth and development of follicles, in particular steroidogenesis and the PKA-cAMP signalling pathway that is responsive to FSH.

Androgen receptor (AR) is a nuclear hormone receptor closely related to PGR, with very similar protein structure and DNA binding sequence specificity [38]. In the ovary, AR is expressed in the oocyte, cumulus, granulosa and theca cells at most stages throughout folliculogenesis [39]. Androgens, the key ligands of AR, are synthesised in the ovarian theca cells which express the rate limiting steroidogenic enzyme *Cyp17a1* under the control of LH [40]. Treatment with the AR ligand T or the non-aromatisable AR ligand dihydrotestosterone (DHT) promotes follicle growth *in vitro* [41, 42]. T is also required for *Fshr* and *Lhcgr* expression and hence for the induction of PGR in cultured granulosa cells [43]. *In vivo* treatment with non-aromatisable ligand DHT also stimulates the expression of LH-responsive ovulatory genes, indicating this is a direct effect of androgen, not its conversion (via aromarisation) to E2 [40]. Global KO of AR in mice results in overall poorer female fertility, with a reduction in antral follicle count, impaired oocyte maturation and reduced expression of steroidogenesis genes [44]. When AR is knocked out specifically in granulosa cells, defective folliculogenesis is again observed as well as disruption in steroidogenesis and the estrus cycle [45, 46]. However, in young mice ovulation can be rescued with exogenous gonadotropin, suggesting that AR also has non-ovarian reproductive functions. Knockout of AR in other ovarian cell types, including the oocyte and theca cells, has no effect on female fertility [45, 47], indicating that only AR action in granulosa cells is compulsory for female reproduction. Another key physiological focus on androgen action in the ovary is in the aetiology of polycystic ovary syndrome (PCOS), which is linked to elevated androgen exposure during development and affects androgen levels, metabolism, insulin sensitivity, fat deposition, risk of cardiovascular disease and many other diseases in adults. In the ovary, elevated T levels cause arrested follicle growth at the antral stage, leading to an accumulation of immature cystic follicle structures – which gave the condition its name – and resulting in failure to ovulate, hence sub-fertility [48]. Ablation of AR in neuronal cells can ameliorate many of the features of PCOS, indicating that the effects of androgen excess are multifactorial and includes effects on the central nervous system [49]. Thus the balance of AR signalling appears to be important for fertility regulation, with either too low or too high stimulation being detrimental [50].

Corticosteroid receptors include glucocorticoid receptor (GR) and mineralocorticoid receptor (MR), which are activated by the adrenal hormones cortisol and aldosterone. GR is expressed in oocytes and granulosa cells [51] and is shown in macaques to be LH-induced [52]. Due to the lethal effect of GR knockout in mouse, little is known about the role of GR in the context of reproduction. The recent generation of a viable GRKO model in zebrafish has begun to indicate a role of GR in female fertility, as GRKO female fish display reduced ovulation and fertilisation rate [53]. However, it is unknown whether this is

a specific consequence of ovarian GR ablation or whether it is due to systemic lack of GR. MR is reported to have different expression patterns in the ovary depending on the species [52, 54], however its roles remain unknown.

In summary, the ovary is the primary source of female reproductive hormones, while specialised spatio-temporal expression of corresponding SR are also mediated through hormonally controlled mechanisms. As a consequence, ovarian functions are tightly governed by steroid hormones and corresponding SR, resulting in the highly-coordinated regulation of folliculogenesis, ovulation, oocyte maturation and luteinisation. While the roles of of ERβ, PGR and AR in female fertility have been described extensively, the roles of GR and MR remain largely unexplored.

(b) Non-steroid nuclear receptors:

Several families of nuclear receptors that are structurally related to the steroid receptor family but are regulated by ligands linked to cell homeostasis and metabolism, such as lipid derivatives, fatty acids or vitamins, are also expressed in the ovary. These ligand-receptor interactions play important paracrine roles in regulation of folliculogenesis and ovulation.

The peroxisome proliferator activated receptor (PPAR) family, consisting of PPARα, PPARδ and PPARγ, has fatty acids and prostaglandins as its activating ligands. PPARα and PPARδ are present in theca and stromal cells [55], while PPARγ is expressed in mouse granulosa cells at most stages of follicular development [55] and is induced through a PGR-dependent mechanism after the ovulatory LH-surge [56]. Consequentially, PPARγ has been shown to be critical for ovarian functions. A granulosa-specific PPARγ KO mouse model has dramatically impaired ovulation as well as reduced CL formation and progesterone production [56]. Evidence suggests there are species differences in the role of PPARγ during ovulation, since the expression of PPARγ mRNA has been shown to be reduced after ovulation induction in macaque [57] and rat granulosa cells [55]. While the pattern of regulation in human is yet to be demonstrated, pharmacological activators of PPARγ have been shown to improve ovulation in women with PCOS [58]. In mice, treatment in the periovulatory stage with agonists of PPARγ have also been shown to improve the developmental competence of oocytes impacted by metabolic disturbance [59]. PPARα and PPARδ have not been found to participate in the regulation of reproduction in genetic ablation models, with PPARα KO mice being fertile [60] and PPARδ KO being embryonically lethal [61]. A number of PGR-regulated genes are now recognised to be downstream of PPARγ during ovulation in mice, including *Edn2* and *Il6*, which are important in smooth muscle contraction and cumulus expansion [56]. PPARα and PPARγ are also present in ovarian macrophages, where expression of the inflammatory mediator *Nos2* is regulated by PPAR agonist [59].

The nuclear receptor for vitamin D (VDR) is expressed in granulosa cells [62] and associated with follicle growth and granulosa cell proliferation [63]. The ablation of VDR in mice thus results in female infertility due to impaired folliculogenesis [64]. In some reports, this reproductive phenotype can be ameliorated through a calcium-supplemented diet, however other data contradict this suggestion [63]. In a pathology context, vitamin D signalling has also been linked to PCOS, and vitamin D supplement has been shown to be beneficial in PCOS patients in improving glucose and lipid metabolism, testosterone level, insulin resistance and ovarian follicle development [65–69].

The thyroid hormone receptor (TR) family consists of isoforms TRα and TRβ, both of which are expressed in oocytes, granulosa cells and theca cells at different stages of follicle development [70]. For TRα, an alternative splicing isoform (TRα-2) is more important for female reproduction, as shown through impaired fertility in TRα-2 KO female mice [71]. Mice that have

either TRα-1 (the canonical TRα isoform) or TRβ ablated are reported to have normal fertility [72, 73], however double KO of both transcription factors results in reduced fertility rate [74], alluding to the existence of a shared mechanism of TRα-1 and TRβ in regulating female reproduction which until now has remained unexplored. Additionally, a recent report has suggested a correlation between TRα in human granulosa cells and fertility, in which TRα-2 mRNA level is higher in infertile women and TRα expression is negatively correlated to *Has2* and *Ptgs2* [75].

The three subtypes of retinoic acid receptor (RAR) – RARα/RARβ/RARγ – are expressed in the ovary, specifically in granulosa cells and oocytes [76], and the role of RA in folliculogenesis and granulosa cell functions has been indicated in a number of studies. In granulosa cells, treatment with RA promotes the expression of LHR through inducing *Lhcgr* promoter demethylation in a granulosa cell-specific manner [77]. Mice given a vitamin A-deficient diet or treated with an inhibitor of alcohol dehydrogenase (required for RA conversion) show reduced ovulation and oocyte maturation rate [78]. Using a lacZ reporter mouse model, it has been shown that RA acts through the activation of RAR, but this did not differentiate between different RAR isoforms. Conversely, triple KO of all three RAR in granulosa cells does not affect fertility [79], thus necessitating further studies into the mechanism through which RA regulates ovarian functions. Another nuclear receptor with little known reproductive function is RXR. Activated by a number of retinoid molecules, there has been little to no research on the involvement of the three RXR proteins (RXRα, RXRβ, RXRγ) in ovarian functions, although RXRβ and RXRγ KO mice reportedly reproduce normally [80]. In granulosa cells, PPARγ and RXR have been shown to regulate the ovary specific promoter of *Cyp19a1*, thus modulating E2 production [81].

Together with steroid hormones, non-steroid ligands and their nuclear receptors play diverse roles in follicle development and ovulation, as summarised in Fig. 3.2. However, in contrast to SR which have been the focus of reproduction biology for many years, details on the importance and mechanism of non-steroid receptors in female fertility are largely absent from the literature, apart from more recent works on the PPAR family.

## 3.4 Signalling Mechanism of Nuclear Receptors in the Ovary

(a) Steroid receptor genome interactions in the ovary

As discussed, most steroid ligands are produced in the ovary, hence local concentrations of steroids are elevated at certain stages of the reproductive cycle, with their receptors being expressed under the control of reproductive hormones including steroids and gonadotropins. Upon activation by ligand binding, steroid receptors dimerise and, if cytoplasmic, translocate from the cytoplasm to the nucleus [82]. As in all target tissues, SR in the ovary mainly exert their effects through directly binding DNA at specific hormone nuclear receptor response element sequences (HRE), leading to the transcriptional induction or repression of specific genes. The canonical response elements bound by PGR, AR, GR and MR are minor variations on a highly similar core motif (5′-GnACAnnnTGTnC-3′), whereas ER utilises a different motif (ERE, 5′-AGGTCAnnnTGACCT-3′). Further characterisation of specific binding motif preference found that sequences flanking the core HRE motif are important for GR and AR specific interaction [83, 84], but this has not been elaborated for PGR. These motifs are present in the regulatory regions (promoter or enhancer) of many target genes and bound by specific activated receptors to regulate transcription. The influence of SR is not only restricted to genes with full consensus HRE, as SR are also recruited to regions with HRE half-sites [85–87], or can be tethered to chromatin through interaction with other DNA-binding transcription factors [88, 89].

Growing evidence that SR can interact with target chromatin sites through tethering at non-canonical motifs adds complexity to the mechanisms of the transcriptional regulation by SR. In

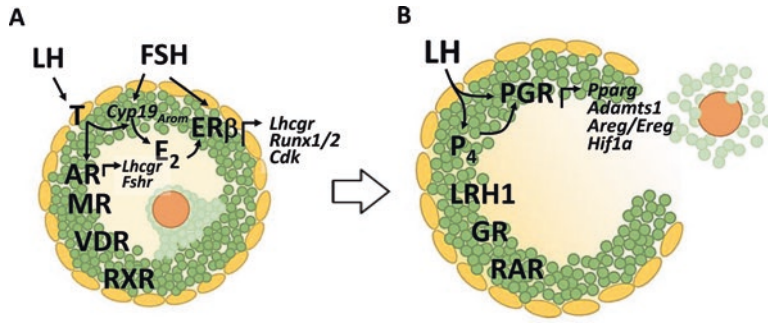


**Fig. 3.2 Hormone regulation of gene expression during folliculogenesis and ovulation.** (**a**) During folliculogenesis gonadotrophins LH and FSH promote production of testosterone (T) and its conversion by Cyp19a1 (aromatase) to estradiol (E2) in theca and granulosa cells respectively. Testosterone and E2 in turn act through their nuclear receptors, androgen receptor (AR) and estrogen receptor beta (ERβ), promoting expression of FSH and LH receptors (*Fshr, Lhcgr*), cell proliferation genes such as cyclin dependent kinases (*Cdk*), and others. Mineralocorticoid receptor (MR), vitamin D receptor (VDR) and Retinoid X receptor (RXR) also contribute to control of folliculogenesis. (**b**) The ovulation activating LH-surge induces high expression of progesterone receptor (PGR) which stimulates a cascade of ovulation genes including peroxisome proliferating receptor gamma (*Pparg*), A disintegrin and metalloproteinase-1 (*Adamts1*), Amphiregulin and Epiregulin (*Areg, Ereg*) and Hypoxia induced factor-1 alpha (*Hif1a*). The orphan receptor LRH1, as well as glucocorticoid receptor (GR) and retinoic acid receptor (RAR) are also important regulators of ovulatory gene expression

such cases, the cooperation between SR and other DNA-binding transcription factors in a context-specific manner is crucial, as is the role for each transcription factor in the recruitment of the transcriptional machinery. Despite the importance of steroid hormones and their receptors in female fertility, the unique molecular mechanisms that distinguish their ovarian functions from other hormone-responsive organs remain largely unexplored. Recently, the unique roles of PGR in different female reproductive tissues have been identified at the cistromic and transcriptomic levels. PGR displays specific preferences for DNA binding in each tissue, which results in tissue-specific gene regulation patterns. A study comparing PGR cistromes between T47D breast cancer cell line versus primary leiomyoma found less than 15% overlap in PGR-binding sites [90]. Similarly, less than 10% of PGR binding sites were found to be shared between progesterone-responsive granulosa cells and uterine tissue, which leads to the regulation of distinct sets of genes in different female reproductive tissues with little overlap [14]. Further exploration into the chromatin binding patterns of PGR in each context discovered a strong preference for proximal promoter regions (within 3 kb of transcription start sites) in granulosa cells but not in the uterus. Additionally, a predilection for interaction with distinct non-canonical motifs was also indicated in granulosa cells, suggesting direct interaction of PGR with AP1 and RUNX transcription factors in an ovarian-specific context [14]. Apart from regulating gene expression through promoter binding, PGR also shows the potential to mediate enhancer action through binding non-promoter regions. For example, in granulosa cells PGR binds a number of chromatin sites within *Zbtb16* intronic bodies, including sites previously shown to have enhancer action that promotes the expression of *Zbtb16* [91]. PGR chromatin binding is highly associated with chromatin accessibility, as demonstrated through ATAC-seq and H3K27ac ChIP-seq of mouse peri-ovulatory granulosa cells [14, 22]. Importantly, PGR shows an active role in driving chromatin accessibility and does not only take advantage of pre-accessible chromatin sites, suggesting PGR-chromatin binding is not dependent on a pioneer factor [22]. Although several studies have focused on AR and GR chromatin binding [92–94], none has been performed in the context of the ovary. Given the stark differences in SR action in different tissue contexts, investigation

into the ovarian cistromic action of these SR will be required to fully understand their importance in ovarian functions.

ERβ plays a critical role in granulosa cell specification and function [29]. However, the activation of gene expression by ERβ in granulosa cells is dependent on the presence of FOXL2, another granulosa cell specification factor [95, 96]. This guidance of chromatin binding by cell-specific co-factors could explain the mechanism for unique transcriptional activity of ERβ in granulosa cells, however to date there has been no systematic comparison of ERβ and FOXL2 binding sites. Similarly, FOXL2 has also been implicated in AR action in granulosa cells [95]. The exact mechanism for such involvement remains unknown, however in prostate and mammary gland the related transcription factor FOXA2 has been shown to play a vital pioneer function for ER and AR [97].

(b) Steroid receptor isoforms:

Many SR are expressed in various different isoforms as a result of diverse translation initiation sites or alternative transcript splicing from a single gene. The two main PGR isoforms, A and B, generated from different translational start codons, have long been the focus of attention due to their discrete roles in different reproductive tissues. The longer PGR-B isoform includes the additional activation function-3 (AF-3) transactivation sequence in the N-terminal region, which mediates different co-regulator interactions [98]. This results in a higher transactivation capacity for PGR-B compared to PGR-A, and specific transcriptomes governed by each isoform. Not only does each PGR isoform exhibit discrete tissue-specific functions, the interplay between the isoforms can be highly complex and is precisely regulated in a spatiotemporal pattern and tissue-specific manner. In the ovary, both PGR-A and PGR-B are present and induced in response to the LH surge, with PGR-A being slightly predominant [20]. In the context of cancer, the balance of PGR-A:PGR-B ratio is important for cellular responses and the elevation of tumour development [99]. Interestingly, elevated PGR-A abundance can cause trans-repression of not only PGR-B but also other SR including GR and ER, without affecting their expression level [100]. Attempts have been made to elucidate the nature of such trans-repressive function, however the exact nature of the inhibitory process, such as the involvement of other co-repressors or the effect on PGR-B stability, is still poorly understood. In the uterus, this auto-inhibitory function plays an important role during parturition, in which uterine progesterone withdrawal induces PGR-A trans-repression of PGR-B function, leading to an upregulation in contraction and inflammation genes and consequently to the onset of labour [101, 102]. Whether such a mechanism also influences PGR action in granulosa cells remains unknown.

AR, GR and MR can also be translated in multiple isoforms, with the two main isoforms of AR and MR generated through separate translation start sites. For AR, it has been shown in the human ovary that the abundance of the full-length AR-B outweighs that of the slightly more truncated AR-A [103]. Like PGR, AR-A and AR-B are also shown to be functionally diverse [104]. Less is known about MR isoforms and isoform-specific expression pattern in the ovary; however it has been shown that MR-A possesses stronger transactivation action than MR-B [105]. The main isoforms of GR are GRα and GRβ, generated through alternative splicing events, and within each isoform multiple variants can arise based on different translation start sites. GRβ can act as a dominant negative inhibitor of GRα at glucocorticoid-responsive target genes [106]. The composition and dynamics of GR in the ovary and whether different GR isoforms are involved in the mediation of GR action in the ovary remains a mystery. The ERα and ERβ isoforms are expressed from separate genes and are less commonly found in the same cell types. In the ovary in particular, *Esr*2, which encodes ERβ, plays the predominant role in granulosa cells mediating folliculogenesis, while *Esr*1 encoding ERα is more predominantly expressed in theca cells [26, 27], thus it is less likely that the two isoforms are directly functionally linked in the ovarian context.

(c) Steroid receptor protein interactions:

A wide range of coactivators and corepressors has been associated with SR in various biological contexts. A classic coactivator family is the aptly named SR coactivators (SRC), whose members, especially the earliest known coactivators SRC-1, SRC-2 and SRC-3, were identified through their ability to bind SR upon ligand activation and mediate SR transcriptional activation [107, 108]. This ability to promote SR transactivation is explained by the histone acetyltransferase activity of SRC [109]; furthermore, SRC can also interact with other histone modifiers, thus promoting additional chromosomal modifications in preparation for transcription. One key example is CBP/p300, which can act in synergy with SRC-1 to promote PGR and ER activation of gene expression *in vitro* [110]. Recent work on the synergy of the ER/SRC/CBP interaction has further elucidated the relationship between different components of the nuclear receptor-related transcription complex, in which SRC-3 proteins act as linkage between ER and CBP/p300 that in turn acetylates nearby histones and facilitates chromatin accessibility and gene transcription [111]. The expression of SRC1–3 as well as SRA and the corepressors NCOR and SMRT has been demonstrated in the ovary as well as in granulosa tumor cells [112]. However, to date there is insufficient study on the expression and actions of the SRC family during ovarian folliculogenesis, thus this aspect of steroid action remains not fully understood.

Aside from recruiting chromatin remodellers and components of the basal transcription complex, SR can also interact with members of other DNA-binding transcription factor families, which can enable tethering to non-canonical motifs or cooperative mechanisms that lead to the targeting of an expanded range of genes without the HRE motif. In the ovary, the identification of specific PGR binding partners at PGR-bound chromatin sites in individual PGR-regulated genes led to the suggestion that PGR interacts with SP1 related transcription factors [88]. Further genome-wide assays identified enrichment of AP1 and RUNX motifs at PGR bound sites [14]. Such studies have indicated a specific suite of transcription factors that are likely to be involved in PGR regulation of ovarian function. This PGR-RUNX interaction has to date only been identified in granulosa cells, suggesting that this may be a tissue-specific mechanism of hormone action. PGR colocalisation with both RUNX1 and RUNX2 in response to ovulatory cues was demonstrated through proximity ligation assay and comparative ChIP-seq analysis showed that PGR and RUNX1 chromatin binding regions closely overlapped, sharing a high number of mutual chromatin binding sites as well as downstream target genes. These findings illustrate physical and functional interactions of PGR and RUNX1/2. At the same time, PGR was also shown to interact with members of the JUN/FOS and NR5A families, members of which are also expressed in ovarian granulosa cells and play a role in ovulation. Whether all of these proteins assemble into one mutual transcription complex or whether each exhibits unique interacting dynamics with PGR remains to be explored.

Together, these findings on the interactions of SR indicate that the precise co-expression pattern of the different SR members, as well as other transcription factor families, can influence the hormone response, providing a potential mechanism for cell-specific regulatory action. As SR members can share binding partner repertoires, in granulosa cells where PGR, AR, ERβ and GR are known to be co-expressed, deciphering the individual and mutual interactomes of these SR will be complex.

(d) Interaction with non-protein co-regulators:

SR action can also be modulated by RNA components, which are often overlooked due to their low abundance. The classic RNA regulator of SR is *Sra1,* a long non-coding RNA (lncRNA) that forms a physical interaction with and promotes SR transactivation [113, 114]. Curiously, *Sra1* can also exhibit SR regulatory function in the form of an encoded protein, named SRAP [115]. The *Sra1* lncRNA seems to generically bind SRs and non-steroid nuclear receptors and can mediate their interaction with other protein co-regula-

tors [116], while the mechanism for SRAP action remains unknown [117]. While the roles of *Sra1* and SRAP are mainly examined in the context of tumorigenesis [118, 119], transgenic mice with overexpressed *Sra1* are subfertile and the presence of *Sra1* and its protein counterpart has been linked to reproductive disorders that affect the ovary and uterus [120–122]. The spatial and temporal patterns of *Sra1* expression during folliculogenesis and ovulation have not been explored in depth, however our unpublished data shows an induction in *Sra* transcription and associated interaction with PGR post-LH surge. Another lncRNA that has been attributed to SR regulation is *Gas5*. The genomic structure of *Gas5* is complex and generates various isoforms due to alternative splicing and intronic retention [123]. Furthermore, small nucleolar RNA (snoRNA) encoded in the *Gas5* introns are also functional regulators of protein methylation, in particular, the methylation of ribosomal subunits that regulates their stability and translational activity [124]. Unlike *Sra1* where a functional protein has been identified, so far there has been no protein product found for *Gas5*. Originally linked to cellular response to stress conditions, *Gas5* also plays prominent roles in the modulation of SR activity. This has been particularly demonstrated for GR, but *Gas5* also interacts with all members of the NR3C steroid receptor family [125, 126]. In this context, *Gas5* secondary RNA structure mimics the HRE chromatin folding structure and acts as a decoy, forming a physical interaction with the DNA binding domain of GR and competing with target DNA for GR occupancy, and inhibits GR transactivation functions. Evidence has shown that *Gas5* in cumulus cells is associated with pregnancy outcomes [127] and other studies have indicated the presence of *Gas5* in oocytes and granulosa cells [128], as well as an association with stem cell renewal and pluripotency [129]. Both lncRNA and other short ncRNA including miRNA have been shown to play various roles in ovarian functions, such as oocyte development and ovulation [130].

## 3.5 Conclusions

Nuclear receptors have long been linked to the physiology of female reproductive cycles and fertility success, indeed steroid receptor regulation of reproductive processes are among the earliest known hormone actions. These steroid hormones and their receptors have unique as well as shared roles within the ovary, suggesting that there are interrelationships between nuclear receptors in regulating transcription networks that are important for various aspects of ovarian functions, specifically in guiding the progress of folliculogenesis, ovulation and luteinisation. Given that nuclear receptor action is highly dependent on tissue context, it is also likely that nuclear receptor ovarian functions are a result of a unique combination of transcription modulators as well as specific interactions between each hormone receptor and their co-regulators or other transcription factors. Evidence is emerging from investigations into these ovarian interactomes as well as non-protein cofactor partners that supports the formation of ovary-specific transcriptional complexes. The identification and characterisation of the complex regulatory network that governs various aspects of ovarian function is crucial in our understanding of female fertility. This is especially important in the development of infertility treatment as well as novel targets for female contraceptives.

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