Orphan nuclear receptors in angiogenesis and follicular development

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Abstract

Orphan nuclear receptors (ONRs) are a subset of the nuclear receptor family that lacks known endogenous ligands. Among 48 nuclear receptors identified in humans, 25 are classified as ONRs. They function as transcription factors and control the expression of a wide range of genes to regulate metabolism, fertility, immunity, angiogenesis, and many other functions. Angiogenic factors are essential during ovarian follicle development, including follicle growth and ovulation. The correct development of blood vessels contributes to preantral and antral follicular development, selection of the dominant follicle or follicles, follicular atresia, and ovulation. Although progress has been made in understanding the molecular mechanisms that regulate follicular angiogenesis, the role of ONRs as regulators is not clear. Based on their functions in other tissues, the ONRs NR1D1 (REV-ERB β), NR2C2 (TR4), NR2F2 (COUP-TF-II) and NR3B1, 2, and 3 (ERR α , ERR β and ERR γ) may modulate angiogenesis during antral follicle development. We hypothesize that this is achieved by effects on the expression and function of VEGFA, ANGPT1, THBS1, and soluble VEGFR1. Further, angiogenesis during ovulation is expected to be influenced by ONRs. NR5A2 (LRH-1), which is required for ovulation, regulates angiogenic genes in the ovary, including VEGFA and the upstream regulator of angiogenesis, PGE2. These angiogenic molecules may also be regulated by NR5A1 (SF-1). Evidence from outside the reproductive tract suggests that NR2F2 and NR4A1 (NUR77) promote VEGFC and PGF, respectively, and NR4As (NUR77, NOR1) seem to be necessary for the angiogenic effects of VEGFA and PGE2. Together, the data suggest that ONRs are important regulators of follicular angiogenesis.

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Introduction

The nuclear receptors (NRs) are a superfamily of transcription factors and cofactors that regulate cellular function (Bertolin *et al.* 2010, Riggins *et al.* 2010). In humans, 48 NRs have been identified (Benoit *et al.* 2006, Sonoda *et al.* 2008, Meinsohn *et al.* 2019), among which 25 are currently classified as orphan nuclear receptors (ONRs). The ONR genes and their common names are summarized in Table 1. As with other NRs, the ONRs act as transcription factors and cofactors to promote or suppress the transcription of genes. Thus, they control many functions, such as development, metabolism, immunity, steroidogenesis, and angiogenesis (Suntharalingham *et al.* 2015, Garattini *et al.* 2016, Bertacchi *et al.* 2019, Medzikovic *et al.* 2019).

Angiogenesis is indispensable for successful antral follicle development and is believed to play a role in ovulation (Reynolds & Redmer 1998, Duffy *et al.* 2019). During antral follicle development, healthy tertiary follicles and those that are, or will become, dominant have a better developed vasculature than do small antral and atretic follicles (Zeleznik *et al.* 1981, Wulff

et al. 2001). During ovulation, endothelial cells migrate from the theca layer to the inner granulosa layer of the rupturing follicle (Kizuka *et al.* 2012, Trau *et al.* 2015, 2016, Kim *et al.* 2017). Inhibition of angiogenic factors during this period partially or fully blocks ovulation (Kim *et al.* 2014, Bender *et al.* 2018). The principal factors that regulate angiogenesis during follicle development and ovulation are vascular endothelial growth factor-A (VEGFA, also referred to as VEGF), placental growth factor (PGF), VEGFC, VEGFD, prostaglandin-E2 (PGE2), angiopoietin-1 and -2 (ANGPT1, ANGPT2) and thrombospondin-1 (THBS1) (Robinson *et al.* 2009, Rizov *et al.* 2017, Devesa & Caicedo 2019, Duffy *et al.* 2019).

Evidence from studies in nonreproductive tissues indicates that ONRs may regulate one or more of the factors involved in the control of angiogenesis. This has led to the hypothesis that ONRs similarly regulate angiogenesis during follicle growth and ovulation. For instance, NR1D1 (REV-ERB α), NR2C2 (TR4), NR2F2 (COUP-TF-II), NR3B1 (ERR α) and NR5A2 (LRH-1) all regulate VEGFA, PGE2 and THBS1 synthesis (Li *et al.* 2014, Zou *et al.* 2014, Wu *et al.* 2017, Bianco *et al.* 2019, Burgermeister *et al.* 2019, Hu *et al.* 2020). In the

Table 1 Names of 25 orphan nuclear receptor and summary of the effect of these on ovarian function and in the control of expression or activity of ovarian angiogenic factors.

Gene	Common name	Full name	Function on ovary	Effect on the expression of genes that regulate follicular angiogenesis
NR0B1	DAX-1	Dosage-sensitive sex reversal	Not essential but regulates function of NR5A1 and A2 (Murayama et al. 2008)	Inhibits VEGF (Kang et al. 2015)
NR0B2	SHP	Small heterodimer partner	Not essential (Takae et al. 2019) but may regulate function of NR5A1 and A2 (Murayama et al. 2008)	Reduces THBS1 (Smalling et al. 2013)
NR1D1	REV-ERB α	Reverse strand of ERB-alpha	Regulates fertility (deletion causes subfertility) and steroid synthesis (Preitner et al. 2002 , Chen et al. 2012)	Promotes VEGF (Burgermeister et al. 2019); Reduces PGE2 synthesis (Isayama et al. 2015); Reduces THBS1 (Li et al. 2014)
NR1D2	REV-ERB β	Reverse strand of ERB-beta	Mediator of antioxidant effect of melatonin in cumulus cells (Fang et al. 2019)	Affects VEGF, direction of change depends on cell type (Suyama et al. 2016 , Sayed et al. 2019); Promotes PGF (Talia et al. 2016); Regulated by PGE2 (Shin et al. 2014); Reduces PGE2 synthesis (Isayama et al. 2015)
NR1F1	ROR α	Retinoid-related orphan nuclear receptor-alpha		
NR1F2	ROR β	Retinoid-related orphan nuclear receptor-beta	Low to absent in ovary (Bookout et al. 2006)	Promotes VEGF (Talia et al. 2016), PGF (Talia et al. 2016)
NR1F3	ROR γ	Retinoid-related orphan nuclear receptor-gamma	Moderately abundant in the ovary (Bookout et al. 2006)	
NR2A1	HNF4 α	Hepatocyte nuclear factor 4-alpha	Not or very lowly expressed	Promotes VEGF (Hu et al. 2020)
NR2A2	HNF4 γ	Hepatocyte nuclear factor 4-gamma	Not or very lowly expressed	
NR2C1	TR2	Testicular nuclear receptors 2	Not or very lowly expressed	
NR2C2	TR4	Testicular nuclear receptors 4	Female mice lacking NR2C2 (NR2C2 $^{-/-}$) displayed subfertility (Chen et al. 2008)	
NR2E1	TLX	Nuclear receptor tailless	Not or very lowly expressed	May promote or inhibit VEGF (Qin et al. 2010a , Zhu et al. 2016); Inhibits VEGFR1 and sVEGFR1 (Qin et al. 2010a); Increases VEGF-C (Polvani et al. 2014)
NR2E3	PNR	Photoreceptor-specific nuclear receptor	Not or very lowly expressed	
NR2F1	COUP-TFI	Chick ovalbumin upstream promoter-transcription factor-1	Represses gonadotropin receptor expression (Zhang & Dufau 2003)	Promotes VEGF (Zou et al. 2014); Reduces VEGFR2 expression (Likhite et al. 2019), THBS1 (Wu et al. 2017); Reduced by VEGF (Likhite et al. 2019); Regulated by PGE2 (Miao et al. 2010)
NR2F2	COUP-TF-II	Chick ovalbumin upstream promoter-transcription factor-2	Represses FSH expression but seems to promote steroidogenesis (Xing et al. 2002)	
NR2F6	EAR2	V-erb-related gene	Represses gonadotropin receptor expression (Zhang & Dufau 2003)	Promotes VEGF (Zou et al. 2014).
NR3B1	ERR α	Estrogen-related receptor alpha	Regulates steroidogenesis (Ning et al. 2014), PGC number (Mitsunaga et al. 2004)	Promotes VEGF (Zou et al. 2014), ANGPT1 and ANGPT2 expression (Badin et al. 2016)
NR3B2	ERR β	Estrogen-related receptor beta	Regulates steroidogenesis (Ning et al. 2014), PGC number (Mitsunaga et al. 2004)	Regulated by VEGF (Zhou et al. 2016), PGE2 (Land et al. 2015), ANGPT1 (Ismail et al. 2012); Promotes PGF (Li et al. 2019)
NR3B3	ERR γ	Estrogen-related receptor gamma	Regulates steroidogenesis (Ning et al. 2014), PGC number (Mitsunaga et al. 2004)	Regulated by VEGF (Zhou et al. 2016); Reduces THBS2 (McMorrow et al. 2013)
NR4A1	Nur77 TR3 NGFIB	Nerve growth factor-1 β	Regulates steroid synthesis during ovulation (Hughes & Murphy 2021)	Regulated by VEGF (Zhou et al. 2016)
NR4A2	Nurr1 RNR-1 TONOR	Nuclear receptor related-1	Regulates steroid synthesis during ovulation (Hughes & Murphy 2021)	Correlated with VEGF expression (Przygodzka et al. 2016); Promotes PGE2 synthesis (Wang et al. 2019), ANGPT2 expression (Ferraz-de-Souza et al. 2011)
NR4A3	Nor1	Neuron-derived orphan receptor-1	Regulates steroid synthesis during ovulation (Hughes & Murphy 2021)	Promotes VEGF (Bertolin et al. 2014 , Bianco et al. 2019); Promotes expression of PTGS2 (Duggavathi et al. 2008)
NR5A1	SF-1	Steroidogenic factor-1	Important for ovarian steroidogenesis. Deletion from the primordial follicle forward causes infertility (Meinsohn et al. 2019)	
NR5A2	LRH-1	Liver receptor homolog-1	Necessary for ovulation (Duggavathi et al. 2008 , Bertolin et al. 2017)	
NR6A1	GCNF	Germ cell nuclear factor	In the ovary NR6A1 expression is restricted to the oocyte (Zhao et al. 2007)	

reciprocal sense, ONRs may be regulated by angiogenic factors themselves, as, for example, the expression and activity of the NR4A family (NUR77/TR3/NGFIB, NURR1/RNR-1/TONOR, and NOR1) are regulated by VEGFA, PGE2 and ANGPT1 (Ismail *et al.* 2012, Land *et al.* 2015, Zhou *et al.* 2016, Li *et al.* 2019). Despite the importance of ONRs in the regulation of angiogenesis and in the control of synthesis and function of ovarian angiogenic factors, the specific roles of these NRs in the ovarian angiogenic context have been not evaluated. However, it is well known that ONRs regulate many aspects of reproduction, including sex steroid synthesis, response to gonadotropins, and ovulation (Xing *et al.* 2002, Chen *et al.* 2008, Meinsohn *et al.* 2019, Hughes & Murphy 2021). Therefore, the objective of the present manuscript is to review the available literature on both follicular angiogenesis and the role of ONRs in the regulation of angiogenesis, to better understand the potential function of these receptors in the ovary.

Orphan nuclear receptor structure and actions

The general structure of NRs (Fig. 1A) consists of a highly variable N-terminal domain, a DNA binding domain (DBD), a hinge region, a conserved ligand-binding domain (LBD), and a variable C-terminal domain (Benoit *et al.* 2006, Sonoda *et al.* 2008, Porter *et al.* 2019, Meinsohn *et al.* 2019). The DBD has two highly conserved zinc-finger motifs unique to NRs. In the N-terminal domain, some NRs may have a ligand-independent N-terminal activation function-1 (AF-1). Additionally, in the C-terminal domain, a ligand-dependent C-terminal activation function-2 can be present (AF-2) (Zhang *et al.* 2011a).

NRs were first identified as transcription factors that are, in general, specifically activated by small hydrophobic molecules, such as steroids, thyroid hormone, retinoic acid, vitamin D, and bile acids (Cave *et al.* 2016, Meinsohn *et al.* 2019). Generally, NRs act as ligand-inducible transcription factors by directly interacting with DNA response elements of target genes. NRs induce transcription as monomers, homodimers, or heterodimers. The effects of NRs on transcription are mediated through the recruitment of coactivators or corepressors. In response to ligand binding, NRs undergo a conformational change that allows the recruitment of multiple coactivators to induce chromatin remodeling and histone acetylation. In some cases, the NR may interact directly with the basic transcriptional machinery of the cell (Aranda & Pascual 2001).

In 1999, the Nuclear Receptor Nomenclature Committee published a unified system of nomenclature for the nuclear receptor superfamily. This system is a phylogeny-based nomenclature in the form of NRxyz. NR stands for NR, x identifies the subfamily, numbered 0 to 6, to which the receptor belongs, y indicates the group within the subfamily designed by a capital letter,

and z numbers the individual genes within subfamily, designed by Arabic numerals (Robinson-Rechavi *et al.* 2003, Novac & Heinzl 2004). The phylogenetic relationship within each subfamily is indicated by the capital letter (y), with more similar receptors indicated by proximal letters (Novac & Heinzl 2004).

Members of the NR superfamily have been further categorized based on the number of characteristics, such as dimerization, DNA binding motif, and ligand selectivity (Mangelsdorf *et al.* 1995, Sonoda *et al.* 2008). Grouping according to the latter criterion results in three classes of NRs: conventional steroid and thyroid hormone receptors, adopted orphan receptors, for which a ligand has been discovered, and ONRs, for which a ligand either has not been identified or appears to be unnecessary for function (Benoit *et al.* 2006, Sonoda *et al.* 2008, Cave *et al.* 2016, Meinsohn *et al.* 2019, Tiwari & Gupta 2021). Although ONRs share the canonical structure of all NRs, each of the 25 ONRs has some particular structural characteristics that define its functions as an activator or repressor of transcription. These structural differences, organized by the phylogenetic family, are summarized Fig. 1B.

Functions and structural variations of ONRs

NR0B1, also known as DAX-1, is a regulator of adrenal development and function and is also necessary for prenatal testicular development and spermatogenesis (reviewed by Lalli & Alonso 2010, Ravel *et al.* 2014, Suntharalingham *et al.* 2015). The closely related NR0B2 or SHP controls various aspects of cell metabolism, including cholesterol metabolism, energy homeostasis, and bile acid metabolism, among other functions (Zhang *et al.* 2001, Chanda *et al.* 2008, Garattini *et al.* 2016 for details). Both of these receptors lack several structural components, including the DBD (Fig. 1), and thus act as coactivators or corepressors, rather than directly regulating transcription (Chanda *et al.* 2008, Zhang *et al.* 2011a, Ehlund & Treuter 2012, Orekhova & Rubtsov 2015 for details).

ONRs of the NR1 family (NR1D1 or REV-ERB α , NR1D2 or REV-ERB β , NR1F1 or ROR α , NR1F2 or ROR β and NR1F3 or ROR γ) are core components of the circadian clock system in mammals (Kojetin & Burris 2014, Welch & Flaveny 2017, Wang *et al.* 2020 for detail). Both NR1D1 and NR1D2 lack the F domain, which is necessary for the activation of ligand-dependent transcriptional activity. This results in the NR1D receptors functioning as repressors of transcription that bind to corepressors, such as NR corepressor 1 (Burris 2008, Solt *et al.* 2011, Kojetin & Burris 2014, Lazar 2016 for detail). Members of the retinoid-related orphan receptor family (the members of NR1 group F) have a similar structure to the retinoic acid receptor family, as their common name suggests. In contrast to the function of the NR1D family, the NR1F receptors activate gene expression in

Figure 1 Schematic representation of the general structure of nuclear receptors (A) and particular structural characteristics of the 25 human orphan nuclear receptors (ONR; B). Yellow represents the A/B or AF-1 domain, beige represents the C or DNA binding domain, gray represents the D or hinge domain, green represents the E or ligand binding domain, and white represents the F or AF-2 domain. The blue section in a few ONRs represents the N-terminal region of the ONR where the domain or domains are not present or have been not yet identified. The red section in NR5A1 and 2 represents the FTZ-F1 or A box domain present only in the NR5A receptors. Differences in sizes of domains in each group of ONRs represent differences in the size of protein (Compiled from Maruyama et al. 1998, Taraviras et al. 2000, Chung & Cooney 2001, Lee et al. 2002, Stein & McDonnell 2006, Zhang et al. 2011a, Ehlund & Treuter 2012, Wang & Cooney 2013, Hermann-Kleiter & Baier 2014, Kojetin & Burris 2014, Lu 2016, Wang & Xiong 2016, Wu & Chen 2018, Meinsohn et al. 2019, Al-khuzaei et al. 2020).

the absence of ligand binding, by recruiting a variety of cofactors (Kojetin & Burris 2014).

The nine ONRs that belong to the NR subfamily 2 are implicated in the regulation of several physiological processes, including hepatic function, metabolism, development, testicular function, neuronal and cardiovascular development, and retinal function (Tan et al. 2013, Lu 2016, Lin et al. 2017, Sobhan & Funa 2017, Bertacchi et al. 2019). NR2A1 (HNF4 α) has a unique N-terminal dimerization domain, which is necessary for homo- and heterodimerization (Ryffel 2001, Lu 2016). NR2A1 and NR2A2 (HNF4 γ) are similar in structure (Taraviras et al. 2000, Sasaki et al. 2018). NR2C1 (TR2) was one of the first NRs identified in humans (Chang & Kokontis 1988, Chang et al. 1989). Later, NR2C2 was cloned from human and rat hypothalamus, prostate, and testis (Chang et al. 1994). The protein sequence of NR2C2 has 83% homology with NR2C1 in the DBD and 57% in the LBD (Liu et al. 2014). NR2E1 (TLX) constitutively represses gene transcription (Benod et al. 2014, Sobhan & Funa 2017) and has some unique structural characteristics. In this receptor, the AF-2 domain is present, but the AF-1 domain is not (Benod et al. 2016, Wang & Xiong 2016, Sobhan & Funa 2017 for details). NR2E3 (PNR) has the canonical structure of NRs and contains the AF-1 domain, allowing it to act as a repressor or activator of transcription (Schorderet & Escher 2009, Tan et al. 2013). Both NR2F1 (COUP-TFI) and NR2F2 possess the classical NR domains and may activate or repress the transcription of genes (Tang et al. 2015, Yang et al. 2017, Bertacchi et al. 2019 for detail). The closely related NR2F6 (EAR2) is structurally similar but primarily acts to repress transcription (Raccurt et al. 2005, Hermann-Kleiter & Baier 2014).

NR3B1 (ERR α), NR3B2 (ERR β) and NR3B3 (ERR γ) are the estrogen-related receptors. They are implicated in regulation of energy metabolism, stem cell biology, and development (Huss et al. 2015, Divekar et al. 2016). As their common name indicates, these ONRs are structurally similar to ER α and ER β , but with relatively low homology, and are not activated by estrogens (Horard & Vanacker 2003). In fact, these receptors are constitutively activated, due to a structure that favors exposure of the AF-2 domain (Misawa & Inoue 2015).

The functions of NR4A1 (NUR77/TR3/NGFIB), NR4A2 (NURR1/RNR-1/TORON) and NR4A3 (NOR1) include regulation of cellular proliferation and apoptosis, angiogenesis, inflammation, metabolism, heart function, and cancer (Kurakula et al. 2014, Herring et al. 2019, Medzikovic et al. 2019). The protein structure of the NR4A members includes each of the classical NR domains, but the LBD of NR4A1 and NR4A2 has no ligand-binding pocket and therefore lacks the ability to interact with ligands (Wang et al. 2003, Flaig et al. 2005, Pawlak et al. 2015).

NR5A1 (SF-1) and NR5A2 (LRH-1) regulate cholesterol homeostasis, steroidogenesis, cell proliferation, and

stem cell pluripotency. During embryonic and fetal development, NR5A2 controls development beyond gastrulation, whereas NR5A1 is necessary for the genesis of the adrenal gland, sexual differentiation, and Leydig cell function (Bertolin *et al.* 2010, Meinsohn *et al.* 2019). The two NR5As share several important structural characteristics. The N-terminal domain of both these receptors lacks AF-1. Thus, these receptors can be phosphorylated in this region to bind to cofactors, which modify their transcriptional activity (Młynarczyk & Rękawiecki 2010). Moreover, members of the NR5A subfamily contain an additional 30-amino acid C-terminal extension, designated FTZ-F1 or A box. This permits these ONRs to function as monomers (Meinsohn *et al.* 2019).

As noted previously, ONRs control a wide variety of functions, such as development, metabolism, immunity, steroidogenesis, and angiogenesis. Nonetheless, information on the role of these receptors in the regulation of ovarian angiogenesis is currently somewhat limited. Our goal in this review is to delineate the potential functions of ONRs in this process based on evidence for their roles in angiogenesis in the ovary and in non-reproductive tissues.

Angiogenesis during follicle growth and ovulation

Preovulatory follicles

Follicular development is initiated when quiescent primordial follicles are activated to join the growing pool of follicles. The supply of nutrients and oxygen to follicles from these earliest stages, including primordial and primary follicles, depends on the vasculature in the ovarian stroma (Fraser & Wulff 2001). As the primary follicle develops to its next stage, that of the secondary follicle, the differentiation of stromal cells into theca cells results in the addition of cellular layers to the follicle and allows it to develop its own extra-follicular vasculature, essential for follicular growth from this point onward (Robinson *et al.* 2009). The vascular network of the follicle is confined to the theca layer by the basement membrane that separates the theca and granulosa layers. Thus, the granulosa cell layer remains avascular until ovulation (Fraser & Wulff 2001, Tamanini & De Ambrogi 2004, Fraser 2006).

The establishment of a vascular network in the theca layer is an essential event in the development of preantral follicles. In the sow and marmoset, vascularity appears in the theca layer from secondary follicles and increases gradually during antral follicle development (Wulff *et al.* 2001, Martelli *et al.* 2009). In the sow, this results in a high correlation between the vascular area of healthy preantral follicles and the proliferation indices of granulosa and theca cells (Martelli *et al.* 2009). The prevailing view is that dynamic angiogenesis is essential for the attainment of follicle dominance and thus survival (Reynolds & Redmer 1998, Plendl 2000). In the rhesus

monkey, the percentage of the theca layer occupied by blood vessels in the dominant follicles is greater than that in smaller antral follicles (Zeleznik *et al.* 1981). As a result of their increased vascularity, dominant follicles are believed to be exposed to more gonadotropins from circulation than are nondominant antral follicles (McNatty *et al.* 1981). In follicles that do not persist to later stages of development, reduction of endothelial cell proliferation in the theca layer is associated with atresia (Greenwald 1989). Several reports have confirmed this finding in a number of species, including cattle and pigs (Mattioli *et al.* 2001, Jiang *et al.* 2003). In the marmoset, the vasculature of atretic tertiary follicles is less extensive compared with the vasculature of healthy late secondary or healthy tertiary follicles (Wulff *et al.* 2001). Thus, it has been suggested that the decrease in vascularization is a cause or a consequence of atresia, perhaps because dying follicles fail to produce the factors needed to support vasculature.

Ovulation

Follicular vasculature is a dynamic aspect of the ovulatory process, with vascular changes contributing to follicular rupture and luteinization. The importance of angiogenesis and vascular changes during ovulation has been recently reviewed (Duffy *et al.* 2019). After induction of ovulation with human chorionic gonadotropin (hCG), endothelial cells are restricted to the theca layer for a period of 12 h in both humans and cynomolgus macaques. However, as ovulation approaches, between 18 and 36 h after the ovulatory signal, endothelial cells invade into the granulosa cell layer (Trau *et al.* 2015, 2016, Kim *et al.* 2017). There is evidence that blocking some angiogenic factors partially or fully blocks ovulation in monkeys (Kim *et al.* 2014, Bender *et al.* 2018). A similar phenomenon was observed in mice (Kizuka *et al.* 2012). In contrast, in sows, a distinct increase in angiogenesis was observed during the periovulatory period but without invasion of vasculature into the granulosa layer (Martelli *et al.* 2009). Together, this evidence suggests that the LH surge induces angiogenic changes required for ovulation.

Regulation of angiogenesis during follicle development and ovulation and the role of ONRs

The factors that regulate angiogenesis during follicle development and ovulation have been reviewed elsewhere (Robinson *et al.* 2009, Rizov *et al.* 2017, Devesa & Caicedo 2019, Duffy *et al.* 2019). In these reviews and in the reports of others, the consensus view is that the principal players in follicular and ovulatory angiogenesis are VEGFA, PGF, VEGFC, VEGFD, PGE2, ANGPT1, ANGPT2, and THBS1.

VEGFA system

VEGFA is a member of a protein family that also includes VEGFB, VEGFC, VEGFD and PGF (Apte *et al.* 2019). Among these, VEGFA is the most studied, both in the ovary and in other tissues. The importance of VEGFA in the regulation of physiological and pathological angiogenesis has been widely discussed (see recent review by Apte *et al.* 2019 for detail). Several isoforms produced by alternative splicing of immature VEGFA mRNA have been identified in humans and other mammals (Fig. 2). The isoforms are denoted as VEGFxxx where xxx represents the length of the protein in the number of amino acids. In addition to these isoforms of varying sizes, alternative splicing of the proximal or distal region of exon 8 yields two groups of isoforms of equal size. If splicing occurs at the proximal splice site of exon 8, it will produce isoforms designated as VEGFxxxa or simply VEGFxxx, but if splicing is at the distal splice site of exon 8, the VEGFxxxb isoforms are produced (Harper & Bates 2008, Nowak *et al.* 2008).

The biological effects of VEGFA isoforms are mediated by two tyrosine kinase receptors, namely VEGFR1 (FLT-1) and VEGFR2 (FLK1 or KDR). These two receptors seem to regulate partially distinct subsets of downstream effects. Effects of VEGFxxx isoforms on proliferation, survival, vascular permeability, and cellular migration are mediated by VEGFR2, whereas effects of VEGFxxx through VEGFR1 are limited to the stimulation of vascular permeability and cellular migration (Rosales-Torres & Guzmán-Sánchez 2011, Shibuya 2015). Additionally, alternative splicing of the immature mRNA of these membrane receptors results in two different soluble receptors, namely soluble VEGFR1 and soluble VEGFR2 (Stevens & Oltean 2019). These soluble receptors lack the transmembrane and intracellular domains, but their ligand-binding domain is preserved (Stevens & Oltean 2019). This suggests that the soluble VEGFA receptors negatively regulate the biological effects of VEGFxxx. Together, these isoforms have been designated as the VEGFA system.

VEGFA system in follicular growth and development

Bovine granulosa cells express total VEGFA mRNA more abundantly than do theca cells (Ortega-Serrano *et al.* 2016), and mRNA coding for VEGF120 and VEGF164 isoforms is increased in bovine granulosa cells of healthy ovarian follicles compared to granulosa cells of atretic follicles (Zamora-Gutiérrez *et al.* 2019). Similarly, in cows, there is a linear increase in the VEGFA mRNA expression and VEGFA protein concentration in follicular fluid concomitant with the increase in estradiol concentration and follicle size (Berisha *et al.* 2000, 2016a). In nonhuman primates, inhibition of

Figure 2 VEGFA isoforms generated by alternative-splicing of immature VEGFA mRNA. In addition to the variation in sizes (number of amino acids), alternative splicing of the proximal or distal region of exon 8 yields two groups of isoforms of equal size but antagonistic in function. If splicing occurs at the proximal splice site of exon 8, it will produce isoforms designated as VEGFxxxa or simply VEGFxxx (angiogenic isoforms), but if splicing is at the distal-site of exon 8, the VEGFxxxb isoforms (antiangiogenic isoforms) are produced (modified from Harper & Bates 2008).

VEGFA action in the follicle reduces preantral and antral follicular growth by reducing angiogenesis (Wulff *et al.* 2002, Taylor *et al.* 2007). Additionally, injection of a transcriptionally active fragment of the VEGFA gene into the ovarian medulla in prepubertal miniature pigs, together with eCG treatment, increases ovarian weight and the number of large follicles, when compared to ovaries treated with eCG alone (Shimizu *et al.* 2003). Together, these results suggest that VEGFA is involved in the angiogenic process that is necessary for the selection of the preovulatory follicle or follicles.

VEGFA isoforms also control angiogenesis during ovulation. In cynomolgus macaques, mRNA abundance of VEGF165 and VEGF121 in preovulatory follicles, as well as the follicular fluid concentrations of VEGFA protein, increase at 12 h after hCG treatment, after which the mRNA decreases and the protein content ceases to change (Bender *et al.* 2018). As with follicular development, inhibition of VEGFA during the ovulation period compromises ovulation (Bender *et al.* 2019).

Antiangiogenic VEGFA forms

The VEGFA system has antiangiogenic members. While VEGFxxx are angiogenic isoforms that promote proliferation, migration, and survival of endothelial cells, VEGFxxxb isoforms have only a weak angiogenic effect and are considered antiangiogenic (Guzmán *et al.* 2015). VEGF165b binds to either VEGFR1 or VEGFR2 and reduces tyrosine phosphorylation of these receptors (Nowak *et al.* 2008), leading to a reduction of downstream effects. In diabetic retinopathy, a lower ratio of VEGF165b to total VEGFA is associated with increased angiogenesis during disease progression (Jiang *et al.* 2020). Similarly, when human umbilical vein endothelial cells (HUVEC) are treated with either

VEGF121b or VEGF165b, they proliferate less robustly than cells treated with VEGF165a do. In summary, the data indicate that a greater abundance of the VEGFxxx isoforms is a mechanism that inhibits angiogenesis.

In the ovary, overexpression of VEGF165b led to reduced fertility and increased follicular atresia in mice (Qiu *et al.* 2012). However, the VEGF120b isoform is more abundant in healthy bovine follicles than in atretic follicles (Zamora-Gutiérrez *et al.* 2019), suggesting that individual VEGFxxx isoforms have varying ovarian effects.

VEGFR1 and soluble VEGFA receptors also are antiangiogenic factors. VEGFR1 is less likely to be phosphorylated in response to VEGFA binding as compared to VEGFR2 (Waltenberger *et al.* 1994). This results in attenuated VEGFA-mediated angiogenesis (Boonyaparakob *et al.* 2003). Cancer therapy studies have shown that an increase in the expression of soluble VEGFR1 (Owen *et al.* 2012) or soluble VEGFR2 (Schmitz *et al.* 2006, Szentirmai *et al.* 2008) reduces tumor cell proliferation and increases apoptosis (Szentirmai *et al.* 2008), which is associated with a reduction in tumor angiogenesis. In human breast cancer, the expression of soluble VEGFR1 improves the disease prognosis, because the soluble form reduces tumor growth and vascularization (Toi *et al.* 2002).

In the context of bovine ovarian function, a reduction in the expression of soluble VEGFR1 and soluble VEGFR2 may facilitate VEGF action to increase angiogenesis during follicle selection (Ortega-Serrano *et al.* 2016). In addition, mRNA for soluble VEGFR2 was found in greater abundance in atretic bovine follicles compared to healthy follicles (Zamora-Gutiérrez *et al.* 2019). Additionally, antral follicle growth is characterized by a reduction in the oxygen levels within the follicle in several species, including human and cow (Lim *et al.* 2021), and it is well known that hypoxia is necessary for normal granulosa cell function (Zeebaree *et al.* 2018). Recently, a reduction in the mRNA of soluble VEGFR1 and soluble VEGFR2 in bovine granulosa cells cultured under hypoxic conditions has been demonstrated (Hernández-Morales *et al.* 2021), suggesting that hypoxia may promote angiogenesis by reducing the abundance of soluble VEGFRs.

ONRs regulate VEGFA system members

The regulation of the expression and function of the VEGFA system members depends on several factors, including hormones, growth factors, and oxygen availability. There is evidence from studies of angiogenesis in organs other than the ovary to suggest that ONRs may regulate proteins of the VEGFA system and thus control angiogenesis (Table 1). These ONRs include NR0B1, NR1D1, NR1F1, NR1F3, NR2C2, NR2F2 and all members of the NR3A and NR4A and NR5A subfamilies.

Nr0b1

Deletion of NR0B1 in the testis causes disordered neovascularization and an increase in the concentration of VEGFA protein in the testis (Kang *et al.* 2015), suggesting that NR0B1 may reduce the synthesis of VEGFA to inhibit excess vasculature development. The expression of NR0B1 has also been reported in human (Sato *et al.* 2003, Nakamura *et al.* 2009), mouse (Salmon *et al.* 2005) and rat (Saxena *et al.* 2007) granulosa cells, as well as in bovine theca cells (Murayama *et al.* 2008). The main function of NR0B1 in the ovary is to reduce steroid synthesis by inhibiting the ability of NR5A1 and NR5A2 to induce transcription of important steroidogenic genes, including StAR and CYP17A1 (Tajima *et al.* 2003, Saxena *et al.* 2007, Murayama *et al.* 2008, Shimizu *et al.* 2009, Bertolin *et al.* 2010). Nevertheless, no evidence yet exists to implicate this ONR in the regulation of ovarian vasculature, and females lacking NR0B1 are fertile (Yu *et al.* 1998). This suggests that its absence does not sufficiently impair angiogenesis in the ovaries of these individuals.

ONR1 family members

NR1D1 also regulates VEGFA expression. In colorectal cancer cells, NR1D1 binds to an NR1F1-responsive element (RORE) in the VEGFA gene promoter, resulting in increased VEGFA synthesis (Burgermeister *et al.* 2019). NR1D1 is expressed in human (Jiang *et al.* 2020) and rat (Chen *et al.* 2013) granulosa cells. Murine females lacking NR1D1 are subfertile, with fewer fertile matings and smaller litters relative to their WT counterparts (Chomez *et al.* 2000, Preitner *et al.* 2002). In rat granulosa cells, NR1D1 is regulated by FSH (Chen *et al.* 2012). The use of a pharmacological agonist to enhance the activity of this ONR promotes the expression of StAR (Chen *et al.* 2012). This evidence indicates that inadequate steroid hormone synthesis contributes to the phenotype of subfertility observed in females lacking NR1D1. Moreover, if this ONR also regulates VEGFA in the ovary, the subfertility could also potentially be associated with deficient angiogenesis. These concepts remain to be investigated.

NR1F1 and NR1F3 regulate angiogenesis via the VEGFA system in several contexts, including retinopathy (Sun *et al.* 2017), ischemia (Besnard *et al.* 2001), cancer (Xiao *et al.* 2015), tissue repair (Ling *et al.* 2017), and testicular development (Sayed *et al.* 2019). Insufficient expression or inhibition of NR1F1 or NR1F3 reduces VEGFA expression and angiogenesis under conditions of reduced oxygen concentration (Sun *et al.* 2015, Suyama *et al.* 2016) and this varies with cell type (Talia *et al.* 2016). In contrast, deficient expression of NR1F1 is associated with increased VEGFA synthesis in murine testes (Sayed *et al.* 2019). There is a similar low level of NR1F1 expression in the murine hindlimb ischemia model,

in which there is a high rate of angiogenesis without an accompanying change in protein concentration of VEGFA (Besnard *et al.* 2001). In colon cancer cells, pharmacological activation of NR1F1 reduces VEGFA mRNA expression (Xiao *et al.* 2015). This suggests that the effect of the NR1F family, and perhaps NR1F1 in particular, on angiogenesis is highly dependent upon cell type.

NR1F1 is expressed in cumulus cells of the rat and sheep ovary (Coelho *et al.* 2015, Fang *et al.* 2019). In ovine cumulus cells in culture, melatonin treatment reduces oxidative stress via induction of NR1F1 (Fang *et al.* 2019). Effects of NR1F1 on ovarian angiogenesis or regulation of VEGFA in the ovary have yet to be reported.

Subfamily ONR2

ONRs of subfamily 2, most notably NR2C2 and NR2F2, are involved in regulating angiogenesis via the VEGFA system. In prostate cancer cells, inhibition of NR2C2 reduced the mRNA for both HIF1a and VEGFA, whereas overexpression of this ONR increased the abundance of both (Hu *et al.* 2020). Female mice with germline deletion of NR2C2 displayed subfertility, irregular estrous cycles, impaired response to superovulation, and increased follicular atresia. (Chen *et al.* 2008). This is due, in large part, to the ability of NR2C2 to regulate FSH and LH receptors in granulosa cells (Zhang & Dufau 2001). These gonadotropin receptors are upstream to key steroidogenic enzymes, such as StAR and CYP11A1, which are also dysregulated in mice lacking NR2C2 (Chen *et al.* 2008). The evidence that NR2C2 is a regulator of HIF1a and VEGFA (Hu *et al.* 2020) suggests that inadequate ovarian vascular development could explain, in part, the phenotype of increased follicular atresia in NR2C2 knockout mice. Further investigation is needed to delineate this relationship.

NR2F2 is essential for angiogenesis and cardiovascular development. This has been illustrated by the death of NR2F2-null embryos due to defects in these processes during early embryonic development (Pereira *et al.* 1999). Although the results of some of these studies are conflicting, the importance of NR2F2 as a regulator of angiogenesis through regulation of VEGFA expression has been verified (Zhou *et al.* 2000, Lin *et al.* 2011, Xu *et al.* 2015). In marrow-derived mesenchymal stem cells, astrocytes, and prostate adenocarcinoma, NR2F2 seems to positively regulate VEGFA (Li *et al.* 2013, Zhu *et al.* 2016, Lilis *et al.* 2018). In contrast, conditional deletion of NR2F2 in pancreatic islet tumors resulted in an increase in the mRNA for VEGFA (Qin *et al.* 2010a). When Polvani *et al.* (2014) silenced NR2F2, there was no discernable change in VEGFA mRNA. These conflicting results might be explained by the observation that NR2F2 binds to different regions of the promoter of VEGFA to regulate its transcription in different types of human cancer cells (Erdos & Bálint 2019).

NR2F2 may also regulate other members of the VEGFA system. Conditional deletion of NR2F2 is associated with a reduction in tumor angiogenesis and malignancy, seemingly through an increase in VEGFR1 and soluble VEGFR1 (Qin *et al.* 2010b). This suggests that NR2F2 may regulate not only VEGFA ligands but also VEGFA receptors, to favor a proangiogenic environment in the tissues.

NR2F1 and NR2F2 are expressed in murine (Xing *et al.* 2002, Petit *et al.* 2007) and bovine (Wehrenberg *et al.* 1992, Murayama *et al.* 2008) theca and granulosa cells, as well as in human follicles (Sato *et al.* 2003). All three NR2F receptors, NR2F1, NR2F2, and NR2F6, reduce gonadotropin receptor expression (Zhang & Dufau 2001, 2003). Despite this negative effect on gonadotropin receptor expression, there seems to be a role for NR2F2 in promoting the expression of steroidogenic genes. Heterozygote females lacking one allele of NR2F2 (NR2F2^{+/-}) have reduced ovarian mRNA expression of NR2F2 and reduced mRNA expression of CYP11A1, HSD3B1 and StAR, relative to WT mice. Additionally, the corpora lutea of NR2F2^{+/-} females have vascular defects (Takamoto *et al.* 2005). This suggests a potential role for NR2F2 in the regulation of luteal angiogenesis. Given that some of the findings regarding the role of NR2F2 in both VEGFA expression and ovarian function are contradictory, further investigation is required to determine the effects of NR2F2 in the regulation of VEGFA in the ovary.

The ONRs of subfamily 3

NR3B1 and NR3B3, but not NR3B2, regulate angiogenesis by controlling the expression of VEGFA system members. This evidence mostly comes from studies in human endothelial cells and cancer. In several lines of human endothelial cells, inhibition of NR3B1 with an inverse agonist or via gene silencing reduces angiogenic proliferation, migration, and tube-like structure formation (Zhang *et al.* 2015, Li *et al.* 2016, Matsushima *et al.* 2016, Wu *et al.* 2017). In human endometrial and ovarian cancer cell lines, the use of an inverse agonist of NR3B1 or NR3B1 siRNA reduces tumor weight, the proliferation of tumor cells and tumor microvascular density (Luo *et al.* 2009, Zhang *et al.* 2015, Matsushima *et al.* 2016, Kokabu *et al.* 2019). The mechanisms by which inhibition of NR3B1 reduces angiogenesis in both endothelial and cancer cells include a reduction in mRNA and protein concentrations of VEGFA (Luo *et al.* 2009, Zhang *et al.* 2015, Li *et al.* 2016, Matsushima *et al.* 2016, Wu *et al.* 2017) and a reduction in the kinase activity of VEGFR1 (Li *et al.* 2016). Although the majority of the evidence suggests a proangiogenic role for NR3B1, in one study, the deletion of NR3B1 in HUVEC resulted in an increase in VEGFR2, accompanied by a reduction in cellular proliferation, along with an increase in migration and

tube-like formation (Likhite *et al.* 2019). The increase observed in the expression of VEGFR2 could explain the increase in migration and tube-like formation observed in this study, since this receptor is the principal regulator of the biological effects of VEGFA.

It is well documented that hypoxia, through the HIF system, is the major regulator of VEGFA expression (Tamura *et al.* 2019). In human cancer cells, there is an electrostatic interaction between NR3Bs and the functional heterodimer HIF1 α /HIF1 β , but not with either monomer (HIF1 α or HIF1 β) alone (Ao *et al.* 2008). Interestingly, pharmacological inhibition of NR3Bs in human cancer cells blocks the increase in VEGFA expression induced by hypoxia (Ao *et al.* 2008). In contrast in prostate cancer cells, NR3B1 may bind to HIF1 α alone to promote the expression of VEGFA under hypoxic conditions (Zou *et al.* 2014). Although it seems clear that NR3B1 acts as a cofactor to HIF1 α to regulate transcription of VEGFA, there is another line of evidence showing that this ONR binds to a coactivator of another nuclear receptor, PGC-1 α (peroxisome-proliferator-activated receptor-c coactivator-1 α), to promote VEGFA expression via an HIF1 α -independent pathway (Arany *et al.* 2008). In primary embryonic fibroblasts, overexpression of PGC-1 α induced VEGFA expression in cells from WT mice but not those from NR3B1^{-/-} mice (Arany *et al.* 2008). In agreement with these results, induction of VEGFA expression with the flavonoid baicalin in human glioblastoma cells is inhibited by silencing of NR3B1, PGC-1 α , or both (Zhang *et al.* 2011b). Arany *et al.* (2008) suggested that the first intron of the VEGFA gene has conserved NR3B1-binding sites that are additionally coactivated by PGC-1 α thereby eliciting robust induction of VEGFA transcription.

As with NR3B1, the role of NR3B3 in the regulation of vascular development has been documented. In diabetic db/db mice, which have a deletion in the leptin receptor gene, loss of muscular vasculature is prevented by overexpression of NR3B3 in skeletal muscle (Badin *et al.* 2016). In this model, NR3B3 overexpression increases mRNA of total VEGFA (Fan *et al.* 2018a,b) and VEGFA isoforms 121, 165 and 180, (Badin *et al.* 2016). Likewise, inhibition of NR3B3 reduces angiogenesis stimulated by IL-6 *in vivo*, and silencing of this ONR also reduces VEGFA protein concentrations in chondrocytes treated with the interleukin IL-6 (Zhao *et al.* 2019). NR3B3 binds to the estrogen receptor response element (ERRE; AGGTCA) in the VEGFA promoter of the rat, indicating that this site may mediate NR3B3-induced VEGFA transcription (Zhao *et al.* 2019).

Despite the clear evidence that ONRs of subfamily 3 regulate VEGFA expression and angiogenesis, these ONRs seem not to be vital to ovarian function, although just a few reports are available in this regard. The presence and abundance of NR3B2 and NR3B3 mRNA

and protein have been quantified in sow cumulus granulosa cells *in vitro* (Kempisty *et al.* 2015). In human granulosa cells, mRNA coding for NR3B3 has also been reported (Amar *et al.* 2020). Female mice lacking NR3B1 (NR3B1^{-/-}) have no detectable ovarian abnormalities and are fertile (Luo *et al.* 2003). In another study, germline deletion of NR3B2 in the embryonic gonad resulted in a reduction in the number of germ cells in both adult males and females (Mitsunaga *et al.* 2004). Additionally, adult females lacking this receptor did not become pregnant, in spite of apparently phenotypically normal oocytes in their ovaries (Mitsunaga *et al.* 2004). Thus, it seems that ONRs of subfamily 3 are important for the regulation of VEGFA expression, but it is not yet known whether these effects are obligatory at the level of the ovary.

The ONR4 family

The importance of the NR4A subfamily as transcription factors involved in the control of angiogenesis is well documented (Mohan *et al.* 2012, Peng *et al.* 2019, Ye *et al.* 2019). The effects may be reciprocal, as several lines of evidence from *in vitro* and *in vivo* angiogenic models show that VEGFA and other angiogenic factors increase mRNA and protein concentrations of NR4A1, NR4A2, and NR4A3 (Liu *et al.* 2003, Rius *et al.* 2006, Zeng *et al.* 2006, Martorell *et al.* 2009, Zhao *et al.* 2011, 2014, Qin *et al.* 2013, Zhou *et al.* 2016). To date, direct or reciprocal angiogenic effects have not yet been evaluated at the ovarian level. Loss of NR4A1 and NR4A3 inhibits proliferation and migration in HUVEC, even in the presence of VEGFA (Rius *et al.* 2006, Zhao *et al.* 2011, Chen *et al.* 2020). These results suggest that the effect of NR4A1 on angiogenesis results from an impaired ability of cells to respond to VEGFA, even when VEGFA is present in the system. HUVEC cells transfected to overexpress NR4A1 have a proliferation rate that is similar to non-transfected cells that have been treated with VEGF165 added to the culture media, and both proliferate at a greater rate than controls (Zeng *et al.* 2006). Moreover, VEGFA treatment has no additional effect on proliferation in transfected cells that are already overexpressing NR4A1 (Zeng *et al.* 2006).

The germline deletion of NR4A1 does not disrupt reproductive function (Lee *et al.* 1995, Cheng *et al.* 1997), whereas global knockout of NR4A2 or NR4A3 results in the death of offspring prior to or immediately after birth (Zetterström *et al.* 1997, Ponnio *et al.* 2002, DeYoung *et al.* 2003). Additionally, ONRs of the NR4A subfamily have been implicated in ovulation (Carletti & Christenson 2009) and steroidogenesis (Wu *et al.* 2015). Other studies have demonstrated the involvement of these ONRs in the actions of fibroblast growth factors on bovine granulosa cell function (Jiang *et al.* 2011, 2013, Jiang & Price 2012, Han *et al.* 2017) and as

immediate-early genes in response to the LH surge (Hughes & Murphy 2021). The rapid induction of NR4A1 and NR4A2 causes the ovarian shift from estradiol to progesterone synthesis in response to the ovulatory signal, via suppression of CYP19A1 (Wu *et al.* 2005). Additionally, NR4A1 appears to modulate the effects of gonadotropins on antral follicle development (Segers *et al.* 2012) and inhibin synthesis and secretion (He *et al.* 2013). This receptor also negatively regulates the excessive follicular growth in hyperandrogenism models (Xue *et al.* 2012). Deletion of NR4A1 in mice reduces mRNA of both androgen receptor and kit ligand, two important molecules involved in follicular growth and follicle activation, respectively (Dai *et al.* 2012). The importance of NR4A1, 2, and 3 in angiogenesis, particularly their regulation of the angiogenic function of VEGFA, and their evident role in ovulation lead to the hypothesis that these receptors are involved in regulating angiogenesis during ovulation.

SF-1 and LRH-1

NR5A1 and NR5A2 have also been implicated in the regulation of VEGFA and in angiogenesis. Lalli *et al.* (2013) suggested that NR5A1 regulates angiogenesis during adrenal gland development, as well as in adrenocortical tumors. Interestingly, during maternal recognition of pregnancy in the sow, luteal expression of both NR5A1 and of VEGFA increases, accompanied by a reduction in HIF1a (Przygodzka *et al.* 2016). It has been well-documented that NR5A1 is important for ovarian steroidogenesis (Meinsohn *et al.* 2019), so this ONR may regulate angiogenesis through its effects on steroid synthesis (Karizbodagh *et al.* 2017, Trenti *et al.* 2018). However, the extent to which this occurs is yet to be determined.

NR5A2 regulates angiogenesis in tumors. Overexpression of NR5A2 in pancreatic cells increases cell proliferation, tumor growth, and angiogenesis (Lin *et al.* 2014a,b). NR5A2 is also a regulator of angiogenesis in the ovary. Gene ontology analysis from a recent RNAseq study showed that NR5A2 regulates multiple pathways during the ovulation process, including angiogenesis and cellular migration (Bianco *et al.* 2019). These authors showed that at least 80 genes related to blood vessel development are regulated by loss of NR5A2, of which 14, including VEGFA, increase in granulosa cells after the LH surge in control mice but fail to change when NR5A2 is depleted in granulosa cells (Bianco *et al.* 2019). Similarly, conditional deletion of NR5A2 in granulosa cells of antral follicles (with Cyp19A1-cre) reduces the mRNA of VEGFA at 12, 18 and 24 h after LH surge (Bertolin *et al.* 2014). These data suggest that NR5A2 is an essential regulator of angiogenesis that occurs in response to the ovulatory LH signal.

Other members of the VEGF family

The role of the VEGF family members PGF, VEGFC and VEGFD in angiogenesis has been explored in several tissues, including the ovary, under both physiological and pathological conditions (Vrachnis *et al.* 2013, Nejabat *et al.* 2017, Melincovici *et al.* 2018, Wei & Zhao 2020). In cynomolgus macaques, PGF mRNA expression and protein concentration in follicular fluid are greater at 36 h after hCG treatment compared to pretreatment and 12 h after hCG (Bender *et al.* 2018). Interestingly, injection of ovulatory follicles with antibodies directed against PGF-reduced angiogenesis of these follicles and compromised ovulation (Bender *et al.* 2018). This suggests that PGF is necessary for vascular changes during ovulation. VEGFC and VEGFD are principally implicated in lymphangiogenesis (Melincovici *et al.* 2018), but they have been also shown to regulate vascular changes during ovulation. In adult female cynomolgus monkeys, the LH surge did not affect mRNA expression of VEGFC or D in granulosa cells (Kim *et al.* 2017). In contrast, in the mouse, LH surge increased the mRNA expression of VEGFC and D in granulosa cells (Brown *et al.* 2010). With respect to protein expression, Kim *et al.* (2017) showed an increase in VEGFC and D concentration at 24 h after hCG treatment. These results suggest that either a transcriptional or posttranscriptional effect of LH on these molecules exists, depending on the species. Both VEGFC and D promote migration of monkey ovarian microvascular endothelial cells *in vitro*, but only VEGFD promotes proliferation (Kim *et al.* 2017).

Some ONRs may regulate these members of the VEGF family. Inhibition of NR1F3 alone or both NR1F1 and NR1F3 reduced PGF mRNA and protein in oxygen-induced retinopathy models (Talia *et al.* 2016). A reduction in tumor angiogenesis and malignancy due to silencing of NR2F2 is associated with the reduction in mRNA expression of VEGFC (Polvani *et al.* 2014). PGF may also regulate the expression of ONRs. In human trophoblast cells, NR4A1 increased PGF mRNA and protein abundance (Li *et al.* 2019). Nevertheless, no reciprocal effect has been confirmed; and, in HUVEC, PGF treatment affected neither NR4A1 mRNA nor NR4A1 protein (Zeng *et al.* 2006).

Interactions between ONRs and PGE2 in angiogenic events

The prostaglandin, PGE2, modulates angiogenesis in tumor growth (Hashemi Goradel *et al.* 2019), and because PGE2 is necessary for ovulation (Lim *et al.* 1997, Davis *et al.* 1999, Hizaki *et al.* 1999), its role in the regulation of ovulatory angiogenesis has recently drawn attention (Duffy *et al.* 2019). Inhibition of PGE2 synthesis resulted in inhibition of LH-stimulated angiogenesis (Trau *et al.* 2015) and blocked ovulation (Kim *et al.* 2014). In non-human primates, endothelial cells express PGE2

receptors, and the increase in PGE2 synthesis after the LH surge is accompanied by an increase in angiogenesis (Trau *et al.* 2015). This suggests a direct effect of PGE2 on ovarian endothelial cells. *In vitro*, PGE2 stimulates endothelial cell migration in a similar way to VEGFA but does not alter endothelial cell proliferation or survival (Trau *et al.* 2015, 2016). Thus, it is likely that PGE2 promotes endothelial cell migration from theca layer to the granulosa compartment during ovulation.

Three ONRs, NR1D1, NR5A1, and NR5A2 are associated with PGE2 synthesis. In rat endometrial stromal cells, NR1D1 binds to a RORE in the promoter of prostaglandin G/H synthase 2 (PTGS2 or COX2) to inhibit its transcription, and thus reduces PGE2 synthesis (Isayama *et al.* 2015). In preadipocytes, silencing of NR5A1 reduces the secretion of PGE2, whereas overexpression increases it (Wang *et al.* 2019). In mouse granulosa cells, conditional deletion of NR5A2 in granulosa cells by Amhr-Cre recombinase reduces PTGS2 mRNA at 4 and 12 h after ovulatory signal (Duggavathi *et al.* 2008).

In the reciprocal sense, PGE2 is also a regulator of several ONRs. It has been shown that PGE2 activates NR1F1 in colorectal cancer cells via PKC α -dependent phosphorylation (Shin *et al.* 2014). PGE2 regulates the transcription and activity of NR3B1 to regulate steroidogenesis in prostate stromal cells (Miao *et al.* 2010, Ning *et al.* 2014). In the culture of hematopoietic stem cells or dental cementoblast cells, PGE2 treatment increased mRNA for NR4A1 (Moldovan *et al.* 2009, Land *et al.* 2015).

Overall, these results suggest that, among the ONRs, NR5A2 is necessary for PGE2 synthesis and, given its additional role in the regulation of VEGFA, it is reasonable to hypothesize that NR5A2 could also be necessary for the angiogenesis that accompanies ovulation. In addition, NR1D1 and NR5A1 also may promote PGE2 synthesis and function to mediate angiogenesis during ovulation, in addition to direct effects on VEGFA system members.

Angiopoietin and ONR interactions

Angiopoietins are essential for angiogenesis. In addition to their role in controlling the proliferation and survival of endothelial cells, they regulate the remodeling and maturation of blood vessels (Fagiani & Christofori 2013, Gillen *et al.* 2019). Their regulation is complex as ANGPT1 is the natural agonist of the TIE2 receptor, whereas ANGPT2 is an antagonist of the same receptor (Isidori *et al.* 2016). In the bovine follicle, there is no change in the mRNA expression of ANGPT1 with an increase in follicular size and estradiol concentration, but there is a reduction in the mRNA expression of ANGPT2 (Hayashi *et al.* 2004). During ovulation in cows and rhesus monkeys, the mRNA for ANGPT1 gradually increases, while the mRNA coding for ANGPT2 does not change (Hazzard *et al.* 1999, Shimizu *et al.* 2007). In these studies, the ratio of ANGPT2 to ANGPT1 declined linearly from the beginning of the

ovulatory signal to follicle rupture. In rats, the pattern of mRNA expression of angiopoietins differs from that in cows and macaques. In this species, mRNA abundance of ANGPT1 did not change between 0 and 24 h after hCG treatment, whereas ANGPT2 increased at 6 and 12 h after hCG, as compared with 0 h, after which it declined (Miyabayashi *et al.* 2005). It is important to note that even though these authors do not report the ratio of ANGPT2/ANGPT1, their data indicate that this ratio declined between 6 and 24 h after hCG, consistent with observations in cows. Together, these data indicate that the abundance of ANGPT2 relative to ANGPT1 is a likely modulator of angiogenic potential in the ovary as in other tissues (Yu & Ye 2020). Indeed, an increase in the ratio of ANGPT2 to ANGPT1 is associated with the onset of blood vessel regression and atresia in antral follicles (Hayashi *et al.* 2003), whereas a reduction in this ratio seems to be necessary for angiogenesis during ovulation (Miyabayashi *et al.* 2005, Shimizu *et al.* 2007).

NR3B3 and NR5A1 are the only ONRs that have been reported to regulate angiopoietins. In diabetic db/db mice, loss of muscle vasculature is prevented by overexpression of NR3B3 in skeletal muscle. In this model, NR3B3 overexpression increases ANGPT1 and ANGPT2 (Badin *et al.* 2016). With respect to NR5A1, Ferraz-de-Souza *et al.* (2011) identified a 1.1-kb SF-1-binding region in the ANGPT2 promoter and confirmed that NR5A1 activates transcription of this gene in human adrenocortical tumor cells. As with the VEGF family, angiopoietins are regulators of NR4A1 mRNA and protein concentrations in HUVEC, but this effect is weak compared with that of VEGFA (Ismail *et al.* 2012).

THBS1 and follicular growth and ovulation

THBS1 was the first antiangiogenic protein identified (Good *et al.* 1990). THBS1 inhibits endothelial cell migration, proliferation, and survival. This molecule also induces endothelial cell apoptosis and counteracts the activity of angiogenic factors, including VEGFA (Lawler & Lawler 2012). The role of THBS1 in ovarian angiogenesis has been reviewed recently (Farberov *et al.* 2019). Mice lacking the THBS1 receptor, CD36, develop many antral follicles, but they are unable to ovulate (Osz *et al.* 2014). In bovine ovarian follicles, the mRNA expression of THBS1 in granulosa cells (Berisha *et al.* 2016b) and the protein concentration of THBS1 in follicular fluid and granulosa cells declines linearly with the increase in follicular diameter, and is negatively correlated with the concentration of VEGFA (Greenaway *et al.* 2005). In marmoset monkeys, the mRNA and protein of THBS1 are significantly increased in atretic tertiary follicles (Thomas *et al.* 2008), which have fewer blood vessels than do their healthy counterparts. Similarly, in *ex vivo* culture, addition of THBS1 to culture media of rat follicles dramatically reduces angiogenesis and increases follicular atresia (Garside *et al.* 2010).

Although the mechanism by which THBS1 reduces angiogenesis has not been elucidated, Greenaway *et al.* (2007) suggested that THBS1 binds to VEGFA to prevent VEGF-mediated angiogenesis.

THBS1 has further been implicated in angiogenesis during ovulation. Deletion of CD36 in mice increases vascularization of antral follicles, but they are unable to ovulate and luteinize, which corroborates the concept of an antiangiogenic effect of THBS1 (Osz *et al.* 2014). Despite this evidence, it has recently been shown that THBS1 has the opposite effect on angiogenesis during ovulation. In cynomolgus macaques, THBS1 mRNA and protein concentrations in granulosa cells of preovulatory follicles increased after the LH surge, reaching the peak just before the expected time of ovulation (Bender *et al.* 2019). Moreover, *in vitro* experiments using monkey ovarian microvascular endothelial cells showed that THBS1 promotes angiogenesis. In addition, an intrafollicular injection of an antibody against THBS1 prior to hCG treatment reduced angiogenesis and compromised ovulation (Bender *et al.* 2019).

THBS1 has several domains that act as angiogenic or antiangiogenic factors. The binding of THBS1 to its receptor, CD36, occurs through type I repeats and blocks angiogenesis. THBS1 binds to another cognate receptor, low density lipoprotein receptor-related protein-1 (LRP1), via N-terminal domain, thereby inducing angiogenesis (Huang *et al.* 2017). The N-terminus is the major heparin-binding site of THBS1. During the cellular matrix degradation that is characteristic of ovulation, metalloproteinases degrade heparin and release the N-terminus of THBS1 (Huang *et al.* 2017), potentially explaining the angiogenic effects of THBS1 during this process. Additionally, differential expression of THBS1 receptors across follicle status and ovulation could explain the contrasting effects of this molecule in different stages of ovarian angiogenesis.

THBS1 and ONRs

Based on existing evidence, it appears that NR0B2 regulates THBS1 mRNA, but does not regulate VEGFA, PGF, PGE2 or angiopoietins. In the murine liver, deletion of NR0B2 increases the mRNA coding for THBS1 leading to hepatic pathology (Smalling *et al.* 2013). Evidence for the role of NR0B2 in ovarian function is limited. Only one recent study reports that NR0B2 is expressed in murine granulosa cells. In these cells, expression was in response to activation of farnesoid-X receptor (Takae *et al.* 2019).

Other ONRs that regulate thrombospondins are NR1D1, NR3B1, and NR4A2. NR1D1 mediates the effects of carbon monoxide on rat aortic endothelial cell migration, by reducing the expression of THBS1 and thus increasing cellular migration (Li *et al.* 2014). The mechanism by which inhibition of NR3B1 reduces angiogenesis in both endothelial and cancer cells is through THBS1 (Wu *et al.* 2017). Finally, in primary

Figure 3 Changes in angiogenesis during antral follicle development (A) and ovulation (B), as well the relationships between orphan nuclear receptors (ONRs) and ovarian angiogenic factors. Putative vascular elements within the theca and granulosa compartments of the follicle are in red. ONRs that regulate or are regulated by specified angiogenic factors are connected by same color of font and arrows. Differences in font size for the ovarian angiogenic factors represent the relative strength and quantity of evidence that supports the role of each factor in each stage of follicular development, with larger font indicating stronger evidence. Arrows with dashed lines represent evidence that is not clear or is contradictory, while solid arrows indicate clear causal relationships.

human fibroblast-like synoviocytes, elevated NR4A2 expression reduces mRNA expression of THBS1 and depletion of NR4A2 increases it. Together with the increase in THBS1, there is a reduction in VEGFA mRNA expression and the ratio of THBS1 to VEGFA increases dramatically, suggesting that deletion of NR4A2 causes an antiangiogenic endocrine milieu in this context (McMorrow *et al.* 2013).

Conclusion

The findings reviewed herein indicate that angiogenesis is indispensable for development of antral follicles and also for ovulation. During antral follicular growth, there

is an increase in VEGFA (mainly VEGFA angiogenic isoforms) together with a reduction in the ANGPT2/ANGPT1 ratio, THBS1, and soluble VEGF receptors. Together, these changes are expected to promote angiogenesis and development of antral follicles. Integrating our understanding of ONRs that control angiogenesis by regulating ovarian angiogenic factors (Table 1) in tissues other than the ovary with the role of ONRs in follicular growth, the following hypothesis is suggested (Fig. 3). During antral follicle growth NR1D1, NR2C2, NR2F2 and NR3B1 promote VEGFA expression, and reduce THBS1 (NR1D1, NR3B1) and soluble VEGFR1 (NR2F2) to facilitate angiogenesis during this period (Fig. 3A). In contrast, during ovulation (Fig. 3B), angiogenesis is promoted by an increase in VEGFA, VEGFC, PGF, PGE2 and probably also THBS1, accompanied by a reduction in ANGPT2/ANGPT1 ratio. Throughout this period, in addition to the ONRs that are believed to regulate angiogenesis of antral follicles, other ONRs may also play significant roles. These include the NR5As, which promote VEGFA expression and PGE2 synthesis, and NR2F2 and NR4A1, which could upregulate VEGFC and PGF respectively. In addition, the transcription and activity of the NR4As in the ovary could also be regulated by VEGFA, PGE2 and ANGPT1, suggesting that angiogenic factors regulate ONRs and their downstream effects. Together, this suggests that NR2F2, NR3B1, NR4As and NR5As are important for ovulatory angiogenesis (Fig. 3B). In summary, we suggest, based upon this literature review of ONR-regulated angiogenesis throughout the body, that these ONRs play multiple roles in angiogenesis during follicular growth and ovulation.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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