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Review

Luteal angiogenesis and its control

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A B S T R A C T

Angiogenesis, the formation of new blood vessels from preexisting ones, is critical to luteal structure and function. In addition, it is a complex and tightly regulated process. Not only does rapid and extensive angiogenesis occur to provide the corpus luteum with an unusually high blood flow and support its high metabolic rate, but in the absence of pregnancy, the luteal vasculature must rapidly regress to enable the next cycle of ovarian activity. This review describes a number of key endogenous stimulatory and inhibitory factors, which act in a delicate balance to regulate luteal angiogenesis and ultimately luteal function. *In vitro* luteal angiogenesis cultures have demonstrated critical roles for fibroblast growth factor 2 (FGF2) in endothelial cell proliferation and sprouting, although other factors such as vascular endothelial growth factor A (VEGFA) and platelet-derived growth factor were important modulators in the control of luteal angiogenesis. Post-transcriptional regulation by small non-coding microRNAs is also likely to play a central role in the regulation of luteal angiogenesis. Appropriate luteal angiogenesis requires the coordinated activity of numerous factors expressed by several cell types at different times, and this review will also describe the role of perivascular pericytes and the importance of vascular maturation and stability. It is hoped that a better understanding of the critical processes underlying the transition from follicle to corpus luteum and subsequent luteal development will benefit the management of luteal function in the future.

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1. The importance of luteal angiogenesis

The corpus luteum (CL) is a transient endocrine structure that is critical for the establishment and maintenance of pregnancy in mammals. It is formed from the remnants of the ruptured follicle after ovulation and undergoes remarkable growth, differentiation, and remodeling. Often compared to fast growing tumors, the dramatic growth of the CL is reliant on angiogenesis, or the formation of new blood vessels from preexisting vessels from the follicular theca layer [1].

The crucial importance of angiogenesis to luteal structure and function has been demonstrated in a number of species, including domestic ruminants. For example, the experimental blockade of angiogenesis resulted in reduced CL number, limited luteal vasculature, and marked inhibition of steroidogenesis in rats [2]. Similarly, intrafollicular or systemic administration of antiangiogenic factors (e.g., VEGFA trap) to nonhuman primates altered ovulation, reduced endothelial cell (EC) proliferation in the CL, and inhibited progesterone production [3,4]. Furthermore, intraluteal antiangiogenic treatments reduced CL volume and plasma progesterone concentrations and disrupted normal luteal gene expression in the cow [5].

Transgenic mouse models which have targeted angiogenic signals have similarly resulted in both diminished ovarian vasculature and fertility [6]. In addition, poor vascularization has been linked to inadequate luteal function, such as that observed after ovulation induction in women and livestock and in the peripubertal and postpartum periods in domestic animals [7–9].

2. Establishment of the luteal vasculature

Luteal angiogenesis originates from the developing follicle. Early follicles (primordial and primary) have no

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established vascular supply of their own. Rather, blood vessels develop as follicles undergo continued growth, with EC recruitment occurring from the ovarian stromal compartment. Follicular vessels remain within the thecal layer and are excluded from the granulosa cell layer by the basement membrane which divides the two. Following the LH surge, the breakdown of the basement membrane enables blood vessels to invade the granulosa layer as cellular remodeling begins [10]. The continuation of development from ovulatory follicle to CL, therefore, also suggests that appropriate follicular development, including blood vessel formation, may be critical to the success of subsequent luteinization [11]. Indeed, recent evidence showed that follicular vascularity is positively correlated with luteal blood flow and progesterone production [12]. Furthermore, the degree of follicular vascularization has been associated positively with follicular dominance and negatively with atresia [13].

The early events of luteinization are accompanied by marked cell proliferation, with proliferation indices around 40% [14,15]. Critically, most mitotic cells are not steroidogenic luteal cells, but rather they are from the microvasculature [14,15]. Indeed, EC are a prominent cell-type within the CL, occupying around 15% of luteal tissue volume and representing around 50% of all cells at mid-cycle [16]. Such an extensive contribution to the mature luteal tissue ensures that nearly all steroidogenic cells are in immediate contact with at least one capillary [17].

3. The response to LH

Ovulation and early luteinization are characterized by complex changes in gene expression, with perhaps hundreds of genes differentially expressed [18–20]. The molecular response to an ovulatory dose of LH is also rapid, with the first changes in gene expression occurring within 30 minutes. Genes associated with ovulation have been implicated in inflammation, steroid and prostanoid pathways, proteolytic disruption of the tissue matrix, and protection against oxidative stress [18]. Others have demonstrated that luteinization is accompanied by a switch from a molecular signature of proliferation and metabolism to one where cell migration and angiogenesis predominate [19].

More recently, the potential importance of post-transcriptional regulation has come to the fore [21]. Small non-coding RNAs such as microRNAs (miRNAs) function primarily as negative regulators of gene expression and are now thought to be key regulators of ovarian function, including the follicular-luteal transition [22]. Mice deficient for the miRNA processing enzyme Dicer displayed luteal insufficiency that was associated with poor angiogenesis and reduced luteal vascular density [23]. In the sheep ovary, a total of 17 miRNAs were identified whose abundance varied significantly between follicular and luteal phases and are potential important regulators of luteinization [24]. This included decreased levels of miR-503 (a known angiogenesis inhibitor) during early luteinization. Interestingly, the theca cell layer was the major site of miRNA expression, with vascular components of the thecal layer expected to be key targets of miRNA regulation, as has been shown in other tissues [25].

4. Control of luteal angiogenesis

4.1. Stimulatory factors

Follicular fluid accumulates angiogenic factors that are likely to provide an initial stimulus to postovulatory angiogenesis [26]. Corpora lutea subsequently produce proangiogenic factors throughout the luteal phase and into pregnancy [27,28], and their actions can result in EC proliferation, migration, and tubule formation *in vitro* and *in vivo*. A significant number of factors are mediators of angiogenesis [29], including vascularization of the CL. Key among these are the heparin-binding factors, namely vascular endothelial growth factor A (VEGFA) and fibroblast growth factor 2 (FGF2).

Vascular endothelial growth factor A is a potent endothelial mitogen, which exists as one of several isoforms [30] as a result of the alternative splicing of a single VEGFA gene. Vascular endothelial growth factor A_{165} is the predominant (human) protein isoform produced by a variety of cells and is so named due to its 165 amino acids, following cleavage of the signal sequence. Molecular species with 121, 189, and 206 amino acids are also described, plus several rare species such as $VEGFA_{145}$ and $VEGFA_{183}$; in the cow, each isoform is one amino acid shorter [31]. All isoforms contain domains that enable receptor binding, and all are biologically active. The various isoforms do exhibit different biochemical properties, however with some predominantly soluble species, such as $VEGFA_{121}$ and $VEGFA_{165}$ and others ($VEGFA_{189}$ and $VEGFA_{206}$), significantly cell or matrix-bound until released after proteolysis of the ECM [30].

The presence of *VEGFA* mRNA and protein has been demonstrated in the ovary of many species [32–36]. In bovine antral follicles, VEGFA was localized to granulosa cells, and cells of the theca layer, and increased with follicular growth and development (Fig. 1; [36]). In the bovine CL, *VEGFA* mRNA was detected throughout the luteal phase and during pregnancy but decreased in the late luteal phase [37], and luteal steroidogenic cells were the major cellular site of VEGFA protein expression (Fig. 1; [37]).

Members of the VEGF family interact with several receptors and co-receptors to exert their actions [30]. Vascular endothelial growth factor A binds to the related receptors VEGFR1 (Flt1) and VEGFR2 (KDR or Flk1), with the mitogenic and angiogenic responses to VEGFA largely mediated via VEGFR2. These tyrosine kinase receptors are expressed on the surface of EC, including those of the ovary [38]. Indeed, VEGFR1 and R2 were expressed by microvascular EC derived from the bovine CL [38]. Others have detected VEGFR2 in bovine luteal cells and smooth muscle cells, as well as EC by immunohistochemistry [39]. VEGFR1 expression did not vary according to luteal stage, whereas VEGFR2 mRNA was most highly expressed in the early [37] to mid [39] CL.

As eluded to earlier, neutralization of VEGF by several routes and in several species, including the cow, caused marked reductions in luteal vascularization and progesterone production [4,5,40]. In addition to its ability to

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