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Review

Hypoxia-inducible factor-1 alpha signaling: Regulation of vascular endothelial growth factor-dependent angiogenesis during ovarian corpus luteum development in mammals

Zhenghong Zhang[1,2], Qianping Luo[1], Yong Cheng[2] and Zhengchao Wang[1]*

[1]Provincial Key Laboratory for Developmental Biology and Neurosciences, College of Life Sciences, Fujian Normal University, Fuzhou, 350007, People's Republic of China. [2]Provincial Research Center for Animal Transgenesis and Biopharming, College of Veterinary Medicine, Yangzhou University, Yangzhou 225009, People's Republic of China.

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The corpus luteum (CL) is a temporary endocrine structure in mammals, which is the site of intense capillary network (angiogenesis). The angiogenesis is a process of vascular growth that is mainly limited to the reproductive system in healthy adult animals, which enables the hormone-producing cells to obtain the oxygen, nutrients and also precursors necessary to synthesize and release different hormones essential for the maintenance of ovarian functions. Vascular endothelial growth factor (VEGF) is thought to play a paramount role in the regulation of normal and abnormal angiogenesis in the ovary, especially in the newly formed CL. Recent studies have also indicated that hypoxia is important for establishing the vascular system during the CL development, which induces hypoxia-inducible factor (HIF)-1α expression in luteal cells (LCs). Therefore, the molecular regulation of luteal VEGF expression during CL development becomes more important to be explored. Based on our recent research findings, the present review will clarify the role of HIF-1α signaling in VEGF-dependent angiogenesis during CL development. Investigations of the angiogenic mechanisms may lead to new strategies in treatment for fertility control and for some types of ovarian dysfunction, such as polycystic ovarian syndrome (PCOS), ovarian hyperstimulation syndrome (OHSS) and ovarian neoplasia.

Key words: Phosphatidylinositol 3-kinase (PI3K), mammalian target of rapamycin (mTOR), hypoxia-inducible factor (HIF)-1α, vascular endothelial growth factor (VEGF), prolyl-hydroxylase (PHD), corpus luteum.

INTRODUCTION

The corpus luteum (CL) is a temporary endocrine structure in mammals, which plays an important role in the female reproductive cycle and is formed temporarily from a ruptured and ovulated follicle with rapid angiogenesis (Young et al., 2000; Wulff et al., 2001; Fraser et al., 2005; Fraser and Duncan, 2005; Nishimura and Okuda, 2010). The ruptured follicle just after ovulation is thought to be under hypoxia conditions because of bleeding and an immature vasculature (Amselgruber et al., 1999). Recent studies have indicated that hypoxia is important for establishing the vascular system during the CL development (Nishimura and Okuda, 2010), which induces hypoxia-inducible factor-1α (HIF-1α) expression in luteal cells (LCs) (Semenza, 2000b; Molitoris et al., 2009; Miyazawa et al., 2010). Where vascular endothelial factor growth

*Corresponding author. E-mail: zcwang@fjnu.edu.cn. Tel: 86-591-2286-8203. Fax: 86-591-2286-8199.

(VEGF) is regulated by hypoxia, there is an up-regulation of specific transcription factors, notably HIF-1α (Semenza, 2000a, b; Critchley et al., 2006). However, the physical role of HIF-1α in this process of CL development is still in poorly understanding.

Undoubtedly, VEGF plays an important role in the regulation of normal and abnormal angiogenesis in the ovary (Neulen et al., 1995; Lee et al., 1997; Fraser et al., 2005; Fraser and Duncan, 2005; Shimizu et al., 2007; Shimizu and Miyamoto, 2007; van den Driesche et al., 2008; Khandrika et al., 2009), especially in the newly formed CL (Redmer and Reynolds, 1996; Fraser and Wulff, 2001, 2003; Tamanini and De Ambrogi, 2004). Hypoxia is a potent stimulus for VEGF expression (Koos, 1995; Lee et al., 1997), given that ovulation causes a decline of local oxygen concentration, producing a hypoxic environment, thus may be the main stimulator for VEGF production in the developing CL (Nishimura et al., 2006; Nishimura and Okuda, 2010). However, gonadotropins have a clear role in the regulation of follicular growth and angiogenesis, because gonadotropin releasing hormone (GnRH) antagonist treatment in the luteal phase of marmoset results in luteolysis and associated vascular regression (Young et al., 2000). Therefore, it is likely that VEGF expression is also regulated by gonadotropins during mammalian CL formation in the ovary. Indeed, human chorionic gonadotrophin (hCG) stimulates VEGF synthesis in human luteinized granulosa cells (Koos, 1995; Neulen et al., 1995; Christenson and Stouffer, 1997; Laitinen et al., 1997; Lee et al., 1997; Fraser et al., 2005; Fraser and Duncan, 2005). In addition, luteal vascularization and the development of ovarian hyperstimulation syndrome (OHSS) are absolutely dependent on luteinizing hormone (LH)/hCG stimulation (Neulen et al., 1995; Nastri et al., 2010). Furthermore, in a fully formed and highly vascularized CL, exogenous hCG also up-regu-lates VEGF expression (Wulff et al., 2001; Shimizu et al., 2007; Shimizu and Miyamoto, 2007). Together, VEGF may be regulated by HIF-1α under both hypoxic and normoxic conditions, as HIF-1α can regulate VEGF mRNA expression under gonadotrophin-stimulated conditions (Zhang et al., 2001b). Therefore, the present review will focus on the mechanisms of how HIF-1α regulates VEGF expression and of how HIF-1α is regulated in order to clarify the contribution of HIF-1α signaling to VEGF-dependent angiogenesis during ovarian CL formation.

Together, HIF-1α signaling may play a vital role in VEGF-dependent angiogenesis during ovarian CL development. Moreover, luteal angiogenesis can be used as a target for investigation of the physiological role of individual angiogenic factors, which will shed light on the phenomenon of luteal insufficiency and have clinical relevance in manipulating luteal functions. Besides these, the observations made on inhibition of VEGF should form a platform for deciphering the role of other putative angiogenic regulators.

VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) IN LUTEAL CELLS (LCS) DURING CORPUS LUTEUM (CL) DEVELOPMENT

VEGF, also known as vascular permeability factor (VPF), is a major specific stimulator of endothelial cell proliferation, which acts through two tyrosine kinase receptors, VEGFR-1 and VEGFR-2 (Shimizu et al., 2007; Shimizu and Miyamoto, 2007; Zhang et al., 2010). In primates, VEGF protein is localized in the hormone-producing cells of the CL, being highest in the granulosa-derived cells (Ravindranath et al., 1992; Christenson and Stouffer, 1997; Lee et al., 1997; Endo et al., 2001; Kaczmarek et al., 2005; Tesone et al., 2005; Tropea et al., 2006; Shimizu et al., 2007; Shimizu and Miyamoto, 2007). VEGF plays a fundamental role in the physiological angiogenesis and the vascularization of the follicular luteinizing granulosa layer during CL formation (Christenson and Stouffer, 1997; Kaczmarek et al., 2005; Shimizu et al., 2007; Shimizu and Miyamoto, 2007). Because inhibition of VEGF in vivo during the luteal phase will prevent luteal angiogenesis and subsequent progesterone secretion (Wulff et al., 2001; Fraser et al., 2005; Fraser and Duncan, 2005; Fraser et al., 2006; Duncan et al., 2008), while the excess VEGF generation during the vascularization of multiple follicles is also thought to cause OHSS (Neulen et al., 1995; Nastri et al., 2010). Furthermore, if VEGF is inhibited, the CL will have a rudimentary vascular bed with poor functions (Fraser and Lunn, 2000; Duncan et al., 2008). VEGF is also required for the ongoing function and the vasculature maintenance of the mature CL (Fraser et al., 2005; Fraser and Duncan, 2005; Fraser et al., 2006). Indeed, it has been reported that hypoxia, rather than gonadotropins, is the main regulator of VEGF secretion in primary cultures of luteal cells (Tesone et al., 2005; Tropea et al., 2006). However, the mechanism by which VEGF expression increased in these ovarian cells is poorly understood. Therefore the mechanism of HIF-1α involved in VEGF transcriptional regulation during physiological angiogenesis in the ovary need to be further investigated.

ROLE OF HYPOXIA-INDUCIBLE FACTOR (HIF)-1α IN VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) TRANSCRIPTION

Contribution of hypoxia-inducible factor (HIF)-1α to transcriptional regulation of vascular endothelial growth factor (VEGF)

HIF-1, a helix-loop-helix transcriptional factor, which

consists of HIF-1α and HIF-1β, has been cloned and characterized as a transcriptional activator of many oxygen-sensitive genes, such as erythropoietin, heme oxygenases, transferrin, and several glycolytic enzymes (Wang and Semenza, 1993a, b; Wang et al., 1995; Wang and Semenza, 1995). It has been indicated that HIF-1α is an inducible protein by a decrease of O_2 concentration in tissue or cells. HIF-1α is not inducible, but it can be bound to HIF-1α to form a dimer to activate the transcription of many genes containing cis hypoxia-response element (HRE) in their promoter or enhancer regions (Kazi et al., 2005; Kazi and Koos, 2007; Molitoris et al., 2009).

Given the importance of hypoxia-induced adaptation in the gene expression, hypoxia in the ovary may importantly activate the expression of VEGF during mammalian CL formation. Therefore the mechanism of HIF-1α mediating the transcriptional activation of VEGF in LCs during CL development was investigated through determining the effects of hypoxia and changes of HIF-1α levels by pharmacological and molecular interventions on VEGF mRNA expression (Zhang et al., 2011a). The findings clearly demonstrated that VEGF mRNA expression increased significantly under hypoxia, which is consistent with previous reports (Huang et al., 1998; Nishimura et al., 2006; Nishimura and Okuda, 2010). Furthermore, hypoxia-induced increase of HIF-1α implied that transcriptional regulation of VEGF may be mediated through activation of HIF-1α, because this hypoxia-induced upregulation of VEGF mRNA was blocked by HIF-1α inhibition with ferrous ammonium sulfate (FAS) in LCs (Zhang et al., 2011a), suggesting this transcription factor is probably involved in the transcriptional activation of VEGF. To further understand the role of HIF-1α in the activation of VEGF transcription, the inducers of HIF-1α, desferrioxamine (DFX) and cobalt chloride ($CoCl_2$), were used to address whether HIF-1α induction stimulates VEGF mRNA expression. Interestingly, both of these HIF-1α inducers markedly increased HIF-1α mRNA and protein levels and resulted in the upregulation of VEGF mRNA. In contrast, inhibition of HIF-1α production by an iron donor FAS, substantially blocked the hypoxia-induced increase in HIF-1α and VEGF mRNA in LCs. These results indicated that VEGF can be also activated by pharmacologically increased HIF-1α levels in LCs.

Many studies have indicated that HIF-1α is regulated at the post-mRNA level and that ubiquitin-proteasome is a primary protease system responsible for the degradation of HIF-1α, but HIF-1α mRNA was also found to increase in response to hypoxia in vivo in mice or rats (Huang et al., 1998; Kallio et al., 1999; Kim et al., 2009). Further examinations of ubiquitin-proteasome importantly contributing to intracellular HIF-1α levels and thereby to the transcriptional activation of downstream genes were investigated. Therefore HIF-1α degradation inhibitor MG-132 to block the protease pathway was used (Huang et al., 1998; Zhang et al., 2011a) and the effect on VEGF mRNA was then examined (Huang et al., 1998; Zhang et al., 2011a). VEGF transcripts were found to increase markedly when LCs were pretreated with MG-132, even under normoxic conditions (Zhang et al., 2011a; Zhang et al., 2011b). Because MG-132 primarily acted to block the degradation of HIF-1α protein, HIF-1α mRNA levels were not altered dramatically by this protease inhibition. This increase in VEGF mRNA levels associated with the increase in HIF-1α protein suggested that transcriptional regulation of VEGF gene primarily requires a structural or functional integrity of HIF-1α protein in LCs.

Role of hypoxia-inducible factor (HIF)-1α decoy in transcriptional regulation of vascular endothelial growth factor (VEGF)

In addition to pharmacological interventions, a molecular decoy approach to determine the role of HIF-1α in the transcriptional regulation of VEGF gene was also used (Zhang et al., 2011a). The findings demonstrated that HIF-1 activity in LCs transfected with a cis-element oligodeoxynucleotide (dsODN) containing an HIF-1 binding site, *5′-CGTG-3′* decreased significantly and VEGF mRNA level increased to a much lesser extent under hypoxia in transfected cells than those in control cells, because this anti-gene therapy strategy can decoy and thereby block the binding of transcription factors to their binding sites in promoter or enhancer regions by introducing a synthesized dsODN containing a binding cis element (Morishita et al., 1998). All of these provide the direct evidence that using dsODN transfection to spe-cifically decoy HIF-1α and block HIF-1 binding, increased mRNA expression of VEGF in response to hypoxia was attenuated, which further supports HIF-1 mediates the transcriptional activation of the VEGF gene. This hypoxia-induced transcriptional activation may be one of the important mechanisms mediating increased expression of VEGF during CL formation in the mammalian ovary (Figure 1).

Furthermore, reproductive hormones like hCG and LH may also take part in the regulation of VEGF expression in the mammalian ovary. For example, VEGF mRNA expression in human luteinized granulosa cells has been shown to be dose and time dependently enhanced by hCG in vitro (Neulen et al., 1995; Nastri et al., 2010). Chronic or acute exposure to hCG directly stimulates VEGF production and secretion by monkey (Christenson and Stouffer, 1997) and human luteinized granulosa cells (Neulen et al., 1995; Laitinen et al., 1997; Lee et al., 1997; Wulff et al., 2001; Nastri et al., 2010). The administration of a GnRH antagonist decreased VEGF mRNA expression in the monkey corpus luteum (Ravindranath et al., 1992). In addition, luteal vascularization and the

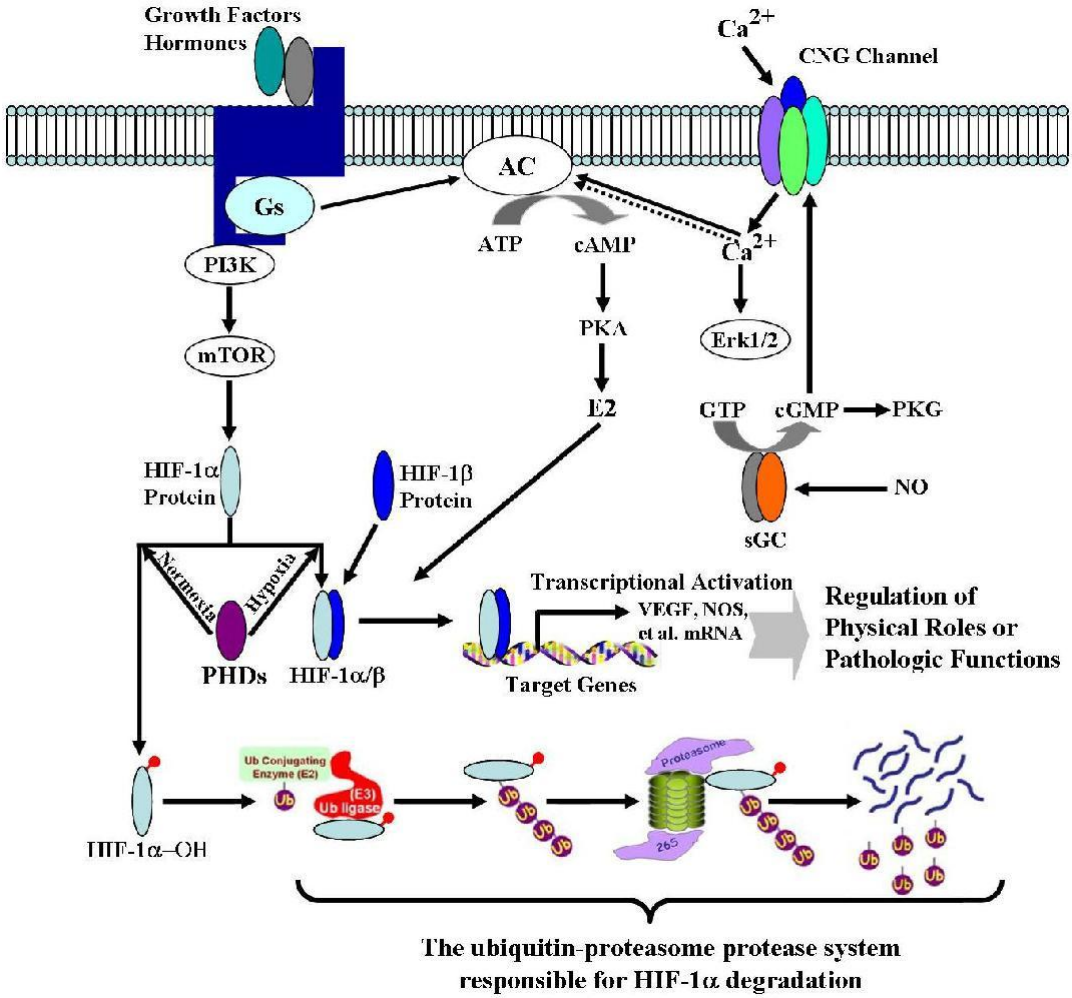

Figure 1. Main putative signaling pathway in ovarian luteal cells. HIF-1α sits at a very important location in the whole signaling network, and directly many target genes expression, which will regulate the physical and pathological functions (Wang et al., 2007; 2010; 2011; Wang and Shi, 2007; Pang et al., 2011; Zhang et al., 2011a; b). In the hypoxia conditions, the outside-stimulating factors, such as growth factors and hormones, regulate HIF-1α protein synthesis by the signaling pathway of PI3K/mTOR and PKA/E2. Then HIF-1α combines with HIF-1α to form an heterodimer HIF-1, which can bind to the hypoxia response element (HRE) of VEGF gene, and then activate the transcription of VEGF to regulate ovarian physiology. In normal oxygen conditions, the PHD hydroxylate two proline residues Pro402 and Pro564 of HIF-1α, eventually leading to the rapid degradation of HIF-1α by the ubiquitin-proteasome pathway, which makes HIF-1α in a dynamic equilibrium state. Some abbreviation in the figure as follows: Gs, stimulating adenylate cyclase G protein; AC, adenylate cyclase; PI3K, phosphatidylinositol 3-kinase; PKB, Protein Kinase B (c-Akt); HIF-1, hypoxia-inducible factor-1; PKA, Protein Kinase A; E2, estrogen; sGC, soluble guanylyl cyclase; cGMP, cyclic guanine monophosphate; PKG, Protein Kinase G; CNG channel, cyclic nucleotide-gated ion channel; PHD, HIF prolyl-hydoxylase.

angiogenesis during CL development. However how to regulate HIF-1α signaling during mammalian CL formation is still poorly understood. Therefore, the crosstalk between hypoxia and reproductive hormones in regulating VEGF expression during this process was investigated, which may act through HIF-1α signaling in a phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) or HIF prolyl-hydoxylase (PHD) manner (Figure 1) (Pang et al., 2011; Zhang et al., 2011b).

PI3K/mTOR involved in hypoxia-inducible factor (HIF)-1α and vascular endothelial growth factor (VEGF) expression

HIF-1α activates the transcription of VEGF, which is required

for angiogenesis; therefore it is possible that hCG may also mediate angiogenesis via the induction of HIF-1α and VEGF. In addition to a detailed exploration of the downstream mechanism of HIF-1α, recent studies have clarified the upstream process modulated by major signaling pathways including PI3K/mTOR and mitogen-activated protein kinase (MAPK) pathways (Richard et al., 1999; Zhong et al., 2000; Jiang et al., 2001; Yaba et al., 2008; Alam et al., 2009; Khandrika et al., 2009; Miyazawa et al., 2009, 2010), which leads to an increased translation of HIF-1α mRNA into the protein (Zhong et al., 2000; Jiang et al., 2001; Alam et al., 2009). Therefore the mechanism of hCG-induced HIF-1α and VEGF expression was further explored, and different specific inhibitors were also used to examine whether the PI3K/mTOR and/or MAPK pathways are involved in hCG-induced HIF-1α and VEGF expression in LCs (Zhang et al., 2011b). The findings indicated that PI3K inhibitor wortmannin inhibited hCG-induced HIF-1α and VEGF expression, whereas the MAPK inhibitor PD98059 did not alter HIF-1α and VEGF expression induced by hCG (Zhang et al., 2011b). The report also indicated that the mTOR inhibitor rapamycin inhibited hCG-induced HIF-1α and VEGF expression. Together, these suggest that the PI3K/mTOR signaling pathway is required for HIF-1α and VEGF expression induced by hCG, whereas the MAPK pathway is not required in LCs *in vitro*. These findings are consistent with previous reports (Franke et al., 1995; Brunn et al., 1996; Franke et al., 1997; Zhong et al., 2000; Jiang et al., 2001; Yaba et al., 2008; Alam et al., 2009; Miyazawa et al., 2009:, 2010), such as induction of HIF-1α by heregulin can be blocked by PI3K inhibitors LY294002 and wortmannin, or by mTOR inhibitor rapamycin (Franke et al., 1995; Brunn et al., 1996; Franke et al., 1997). However, previous reports have also shown that HIF-1α can be induced via the MAPK pathways, including extracellular regulated kinase (ERK) (p42 and p44) in the Chinese hamaster fibroblast cells and p38 MAP kinases in prostate cancer (Richard et al., 1999; Khandrika et al., 2009). This finding is also consistent with the study of Richard et al. (1999), suggesting that the role of MAP kinase in regulating HIF-1α may be stimulus- and cell type-specific (Richard et al., 1999). Therefore, the induction of HIF-1α and VEGF expression via activation of the PI3K/mTOR signaling pathway could be an important mechanism to further understand hCG/LH-mediated angiogenesis in mammalian developing CL (Figure 1).

HYPOXIA-INDUCIBLE FACTOR (HIF) PROLYL-HYDROXYLASES (PHDS) RESPONSIBLE FOR HYPOXIA-INDUCIBLE FACTOR (HIF)-1α HOMEOSTASIS

PHDs are the major enzymes to promote the degradation of HIF-1α (Bruick and McKnight, 2001; Ivan et al., 2001; Jaakkola et al., 2001; Wang et al., 2010; Pang et al., 2011). PHDs catalyze site-specific proline hydroxylation of HIF-1α, and prolyl-hydroxylated HIF-1α is recognized and targeted for degradation by the ubiquitin-proteasome pathway. Three isoforms of HIF prolyl-hydroxylase, inclu-ding prolyl hydroxylase domain-containing proteins 1, 2, and 3 (PHD1, 2, and 3), have been identified (Bruick and McKnight, 2001; Epstein et al., 2001; Ivan et al., 2001; Jaakkola et al., 2001; Wang et al., 2010). Therefore the expression level of these three isoforms was firstly investigated and PHD2, the most abundantly expressed in LCs was found. PHD2 participates in the functional regulation through regulating HIF-1α level (Chan and Giaccia, 2010; Wang et al., 2010) and the importance of PHD2 in angiogenesis was also clarified (Chan and Giaccia, 2010). Many previous experiments have already indicated VEGF-dependent CL angiogenesis mediated by HIF-1α (Ravindranath et al., 1992; Neulen et al., 1995; Christenson and Stouffer, 1997; Lee et al., 1997; Wulff et al., 2001; Kaczmarek et al., 2005; Nastri et al., 2010; Nishimura and Okuda, 2010; Zhang et al., 2011a), which regulates the expression of many genes whose protein products play critical roles in developmental and physiological processes (Zhong et al., 2000; Wulff et al., 2001; Nishimura et al., 2006; Yaba et al., 2008; Miyazawa et al., 2009, 2010; Nishimura and Okuda, 2010). In addition to a detailed exploration of the downstream mechanism of HIF-1α, recent studies have clarified the upstream process modulated by PHDs, which regulates HIF-1α degradation by the ubiquitin-proteasome pathway. In particular, PHD2 has been drawing considerable attention because PHD2 is considered to be the key oxygen sensor of all identified PHD enzymes (Chan and Giaccia, 2010; Wang et al., 2010), as knockdown of PHD2 results in elevated HIF protein and several recent studies have highlighted the importance of PHD2 in tumourigenesis (Chan and Giaccia, 2010).

Given the important role of PHD2 in the regulation of HIF-1α levels, the effect of hCG on the expression of HIF-1α was examined (Zhang et al., 2011b), and the role of PHD2, the primary isoform of PHDs, in hCG-induced activation of HIF-1α was determined by transfecting of PHD2 transgenes into LCs (Pang et al., 2011). The changes of VEGF mRNA level in each group were also revealed (Pang et al., 2011). Finally, these foundings demonstrated that PHD2 was the mediator of cellular HIF-1α and its target gene VEGF in LCs, which may be an important mechanisms regulating VEGF-dependent angiogenesis via HIF-1α signaling during mammalian CL development (Figure 1).

CONCLUSION

Considerable progress has been made on describing the

cellular and molecular events associated with angiogenesis. HIF-1α signaling pathway plays an important role in VEGF-dependent angiogenesis during CL development (Shimizu et al., 2007; Shimizu and Miyamoto, 2007; Gutman et al., 2008; Huang et al., 2008; van den Driesche et al., 2008; Miyazawa et al., 2009, 2010). The interaction between PI3K/mTOR and PHD signaling pathways regulating VEGF expression via HIF-1α may be one of the important mechanisms during mammalian CL formation in the ovary. Furthermore, antagonism of HIF-1α signaling affords an opportunity for the development of novel treatments for fertility control and for some types of ovarian dysfunction (Miyazawa et al., 2009; Chan and Giaccia, 2010; Miyazawa et al., 2010), particularly those conditions characterized by pathological angiogenesis and excessive vascular permeability, such as polycystic ovarian syndrome (PCOS), OHSS and ovarian neoplasia.

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