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Hypoxia and the endometrium: An indispensable role for HIF-1α as therapeutic strategies

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ABSTRACT

Hypoxia-inducible factor 1 alpha (HIF-1α) is a major molecular mediator of the hypoxic response. In the endometrium, local hypoxic conditions induced by hormonal fluctuations and endometrial vascular remodeling contribute to the production of HIF-1α, which plays an indispensable role in a series of physiological activities, such as menstruation and metamorphosis. The sensitive regulation of HIF-1α maintains the cellular viability and regenerative capacity of the endometrium against cellular stresses induced by hypoxia and excess reactive oxygen species. In contrast, abnormal HIF-1α levels exacerbate the development of various endometrial pathologies. This knowledge opens important possibilities for the development of promising HIF-1α-centered strategies to ameliorate endometrial disease. Nonetheless, additional efforts are required to elucidate the regulatory network of endometrial HIF-1α and promote the applications of HIF-1α-centered strategies in the human endometrium. Here, we summarize the role of the HIF-1α-mediated pathway in endometrial physiology and pathology, highlight the latest HIF-1α-centered strategies for treating endometrial diseases, and improve endometrial receptivity.

1. Introduction

Since the discovery of local physiological or pathological hypoxia in vivo, the presence of specific nuclear factors associated with hypoxic conditions has been suggested [1]. In 1995, the structure of hypoxia-inducible factor 1 (HIF-1) was identified in mammalian cells and successfully cloned in vitro, providing the first concrete proof for the aforementioned hypothesis [2]. Over four decades, extensive studies have considerably deepened our understanding of the physiological and pathological effects of HIF-1 in hypoxic environments.

HIF-1 is a constitutively expressed heterodimeric protein, consisting of a constant subunit HIF-1β and an oxygen-dependent subunit HIF-1α [3]. Under hypoxic conditions, HIF-1α is upregulated and binds with HIF-1β within the nucleus, inducing the activation of numerous downstream genes by interacting with hypoxia-responsive elements (HREs) [4], including those related to glucose metabolism [5], angiogenesis [6], post-translational modifications (PTMs) [7], and vital cellular activities [8]. Moreover, under hypoxic conditions, the excessive leakage of reactive oxygen species (ROS) from the mitochondria serves as an important trigger for the upregulation of HIF-1α [9]. Owing to the disappearance and remodeling of spiral arteries during the menstrual cycle, the endometrium undergoes frequent occurrences of local hypoxia and cellular oxidative stress (OS). This determines the significance of the precisely controlled patterns of endometrial HIF-1α [10,11].

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Under physiological conditions, fluctuations in HIF-1α levels in response to local hypoxia are necessary for tissue healing during partial repair or physiological regeneration [12]. However, under pathological conditions, elevated or reduced levels of HIF-1α might trigger the ectopic migration of endometrial cells [13], metabolic reprogramming of endometrial cancer cells [14], and degeneration of endometrial cells during senescence [15].

Over the past few decades, there has been an increasing focus on understanding the regulation of HIF-1α in the endometrium and its downstream effects. Substantial evidence indicates that HIF-1α is involved in various endometrial physiological processes, such as menstruation and decidualization. In addition, its role has also been recognized in several endometrial diseases, including endometriosis, endometritis, intrauterine adhesion (IUA), endometrial senescence, and endometrial cancer. However, there is still a lack of a comprehensive review outlining the mechanisms surrounding HIF-1α and its potential impacts on endometrial diseases, along with promising applications for regulating the redox status of the endometrium. Therefore, we aimed to summarize the mechanisms involving HIF-1α in abnormal endometrial redox status under pathological conditions, as well as therapeutic strategies targeting HIF-1α for the treatment of endometrial diseases. Our review begins with a description of the roles of HIF-1α in regulating various physiological events in the endometrium, followed by a systematic discussion of the positive or negative influence of HIF-1α in endometrial diseases. Finally, HIF-1α orientated approaches for maintaining the normal redox status of the endometrium are summarized, followed by a conclusion highlighting the limitations and breakthroughs regarding meeting the future needs of translational and regenerative medicine.

2. Physiological roles of endometrial HIF-1α

Increased HIF-1α production directly regulates downstream target genes in response to hypoxia during the menstrual cycle and endometrial decidualization, participating in endometrial physiological regeneration and the maintenance of redox balance (Fig. 1).

2.1. Endometrial regeneration throughout the menstrual cycle and HIF-1α

The precise regulation of the endometrium by ovarian hormones, results in a monthly periodic shedding and bleeding known as the menstrual cycle. The menstrual cycle is divided into three stages: proliferative, secretive, and menstrual period [16]. The successful transition between the menstrual and proliferative periods is a key factor determining endometrial regeneration, during which HIF-1α plays a crucial role as a regulatory factor for repairing damaged spiral arterioles and achieving endometrial re-epithelialization [17,18].

The presence of hypoxia during endometrial breakdown has been observed in mouse models simulating menstruation, whereas elevated expression of endometrial HIF-1α was observed during the perimenstrual phase (luteo-follicular transition) [19]. However, under hyperoxic conditions, HIF-1α levels in the endometrium reduce, leading to delayed endometrial repair [20]. Based on current knowledge, the activation of the HIF-1 pathway promotes the repair or regeneration of the endometrium through various mechanisms (Table 1). First, HIF-1α plays an essential role in promoting vascularization in the endometrium. The upregulated endometrial HIF-1α further activates the expression of vascular endothelial growth factor (VEGF), interleukin-8 (IL-8), and adrenomedullin, which are crucial components that improve both angiogenesis and lymphangiogenesis via accelerating the proliferation of endothelial cells in the blood and lymphatic vessels [21–24]. Conversely, reduced expression of endometrial HIF-1α and its downstream targets has been associated with heavy menstrual bleeding (HMB), characterized by prolonged bleeding in mouse models [22]. Additionally, the yes-associated protein in the endometrium, a novel molecule regulated via an ROS/HIF-1α-dependent pathway, is essential for maintaining the mechanotransduction signal of extracellular matrix (ECM) stiffness during menstruation. These pathways enhance the integrity and tissue homeostasis of the endometrial ECM and promote angiogenesis [25]. Second, the upregulation of HIF-1α also helps maintain the regenerative ability of endometrial parenchymal cells. According to Zhang et al. [26], HIF-1α can regulate the self-renewal activity of endometrial mesenchymal stem-like cells (eMSCs) via the Notch signaling pathway, which is involved in the dynamic regeneration

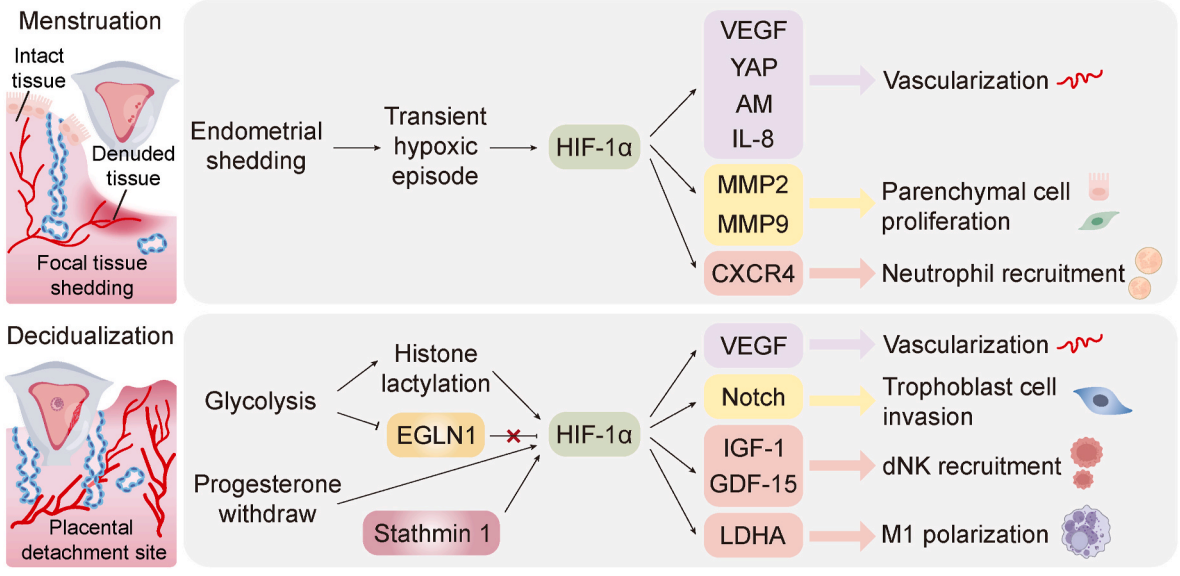

Fig. 1. Endometrial HIF-1α fluctuates during menstruation and decidualization. During menstruation and decidualization, the expression of endometrial HIF-1α is dominated by the stimulation of local hypoxia signals and can also be regulated by essential molecules, such as progesterone, lactate, and Stathmin 1. The upregulation of the HIF-1α and its downstream factors induces the proliferation of endometrial parenchymal cells, angiogenesis, and the recruitment of immune cells, ensuring the endometrium with potent regenerative and differentiative capacities. AM, adrenomedullin; CXCR4, C-X-C motif chemokine receptor 4; dNK, decidual natural killer cell; EGLN1, egl-9 family hypoxia-inducible factor 1; GDF-15, growth differentiation factor 15; HIF-1α, hypoxia-inducible factor 1 alpha; IGF-1, insulin-like growth factor 1; IL-8, interleukin-8; LDHA, lactate dehydrogenase A; MMP2, matrix metalloproteinase 2; VEGF, vascular endothelial growth factor; YAP, yes-associated protein; α-KG, α-ketoglutarate.

Table 1
The role of endometrial HIF-1α in the regeneration throughout the menstrual cycle.

Main subjects	Mechanisms	Cooperative pathway	Effects	References
Human endometrial biopsies, ishikawa cell line	Increases the expression of IL-8	Progesterone withdrawal/COX-2/PG	Promoting vascularization	[21]
Human endometrial biopsies, ishikawa cell line	Increases the expression of VEGF	Progesterone withdrawal/COX-2/PG	Promoting vascularization	[23]
Human endometrial biopsies, ishikawa cell line	Increases the expression of adrenomedullin	Progesterone withdrawal/COX-2/PG	Promoting vascularization	[24]
Mouse models	Increases the expression of YAP	The Hippo cascade	Maintaining the mechanotransduction signal	[25]
Human endometrial biopsies, mouse models	Activates the notch signaling pathway	–	Inducing endometrial parenchymal cell generation	[26]
Human endometrial samples, mouse models	Increases the expression of CXCR4	Progesterone withdrawal	Recruiting endometrial neutrophils	[28]

COX-2, cyclo-oxygenase; CXCR4, C-X-C motif chemokine receptor 4; HIF-1α, hypoxia-inducible factor 1 alpha; IL-8, interleukin-8; PG, prostaglandin; VEGF, vascular endothelial growth factor; YAP, yes-associated protein.

of the endometrium. Third, there is a potential relationship between the expression of endometrial HIF-1α and altered frequencies of endometrial immune cells throughout the menstrual cycle. This is based on the viewpoint that both the insufficient expression of HIF-1α and the lack of endometrial immune cells negatively impact endometrial regeneration: the blockage of immune cell accumulation within the endometrium results in a noticeable delay in epithelial shedding and tissue repair [27]. At the molecular level, the elevated expression of HIF-1α regulates the expression of C-X-C motif chemokine receptor 4 and triggers the recruitment of neutrophils during endometrial repair [28].

While existing studies have described the indispensable role of hypoxia and HIF-1α in improving endometrial scar-free repair during menstruation, there are still unknown areas that require further investigation and validation through large-scale pre-clinical and clinical research. First, the question of whether the constant activation of hypoxia-regulated genes in the endometrium is beneficial for endometrial repair remains debatable. Reavey et al. [29] revealed that women with obesity showed high mean values of HIF-1α and its downstream target genes, which may have impaired endometrial repair and increased menstrual blood loss. Moreover, although decreased levels of HIF-1α have been identified in women with HMB, the levels of HIF-1α mRNA failed to show a significant difference, indicating the possibility that other mechanisms are involved in HIF-1α stabilization and PTMs [12]. Additionally, the role of macrophages in the process of endometrial repair is currently recognized [30]. However, it is still unknown whether their accumulation and recruitment in the endometrium are regulated by HIF-1α.

2.2. Endometrial decidualization and HIF-1α

Highly programmed endometrial decidualization is a key event in early pregnancy in mammals, ensuring the maintenance of the pregnancy throughout the entire period [31]. Although existing studies have demonstrated that the redox status and its crucial participants, such as ROS and oxygen-sensitive transcription factors, are related to decidualization, research into specific molecular mechanisms is still in its initial stages [32,33]. HIF-1α is one of the potential candidates participating in these regulatory processes (Table 2).

Decidualization is a progesterone-dependent process characterized by activated endometrial glycolysis and lactate synthesis [34,35]. Both high levels of progesterone and enhanced glycolysis are involved in the regulation of HIF-1α expression. In ovariectomized ewes, the administration of exogenous progesterone mimics the increase in HIF-1α levels observed in pregnant ewes [36]. Mechanistically, the upregulation of HIF-1α in a progesterone-dependent manner involves the interaction between the progesterone receptor and HRE, displaying a partially tissue-specific characteristic [37]. Additionally, endometrial lactate overproduction owing to glycolysis contributes to the histone lactylation of HIF-1α, thereby regulating its expression [38]. This finding builds on the H4K12la/HIF-1α/glycolysis feedback loop and reveals a novel relationship between endometrial metabolic alterations and epigenetic modification during decidualization [38]. Moreover, the upregulation of stathmin 1 in the endometrial epithelium and the underlying endometrial stromal cells (ESCs) is associated with the peak of HIF-1α during embryo implantation and decidualization. However, the underlying mechanisms require further investigation [39].

Regarding the downstream factors of HIF-1α, endometrial HIF-1α determines the expression of matrix metalloproteinase 2 (MMP2) and MMP9 during the formation of the placenta, guiding cell mobility and facilitating the invasion of trophoblast cells into the endometrium [40]. Furthermore, upregulated HIF-1α shows a similar localization of uterine VEGF, suggesting a potential role in VEGF expression and allowing the angiogenesis required for endometrial decidualization during early pregnancy [37]. In contrast, insufficient HIF-1α levels lead to a low

Table 2
The pathways that endometrial HIF-1α involved in the establishment of the maternal-fetal interface.

Physiological process	Main subjects	Mechanisms	Effects	References
Endometrial decidualization	AN3 CA cell line, mouse models	Binds HRE with progesterone and progesterone receptor	Upregulates endometrial HIF-1α	[37]
	Primary human uterine stromal cells, mouse models	Induces the lactylation of histones	Upregulates endometrial HIF-1α	[38]
	Mouse models	Interacts with stathmin 1	Upregulates endometrial HIF-1α	[39]
	HTR8/SVneo cell line, gel-patterned microfluidic system	Increases the expression of MMP2 and MMP9 in a HIF-1α manner	Inducing the invasion of trophoblast cells	[40]
	Human endometrial biopsies	Increases the expression of VEGF in a HIF-1α manner	Promoting vascularization	[41]
Immunosuppression maintenance	Mouse models	Inhibits the ubiquitination of HIF-1α by the α-KG	Enhancing the recruitment of dNK cells	[46]
	Mouse models	Activates the Src/LDHA pathway in a HIF-1α manner	Triggering the M1 polarization of decidual macrophages	[49]

dNK cell, decidual natural killer cell; HIF-1α, hypoxia-inducible factor 1 alpha; HRE, hypoxia-responsive element; LDHA, lactate dehydrogenase A; MMP2, matrix metalloproteinase 2; VEGF, vascular endothelial growth factor; α-KG, α-ketoglutarate.

micro-vessel density in the endometrial tissue, which might partly explain the relationship between reduced endometrial HIF-1α and recurrent implantation failure [41]. A parallel conclusion aroused by impaired HIF-1α contents can be drawn in the case of patients with polycystic ovarian syndrome [42]. In summary, HIF-1α plays a crucial role in determining the process of endometrial decidualization, being precisely involved in ESC differentiation and trophoblast cell invasion.

2.3. Endometrial function in maternal-fetal dialogue and HIF-1α

Labor is a complex physiological process that necessitates a well-coordinated interaction between the mother and fetus, where endometrial HIF-1α plays a critical role in modulating the immune function of decidualized tissue (Table 2). Specifically, endometrial HIF-1α significantly contributes to the recruitment of decidual immune cells and the establishment of immunosuppression at the maternal-fetal interface [43, 44]. Decidual natural killer (dNK) cells are the dominant group of immune cells recruited in the decidual tissue. During early pregnancy, dNK

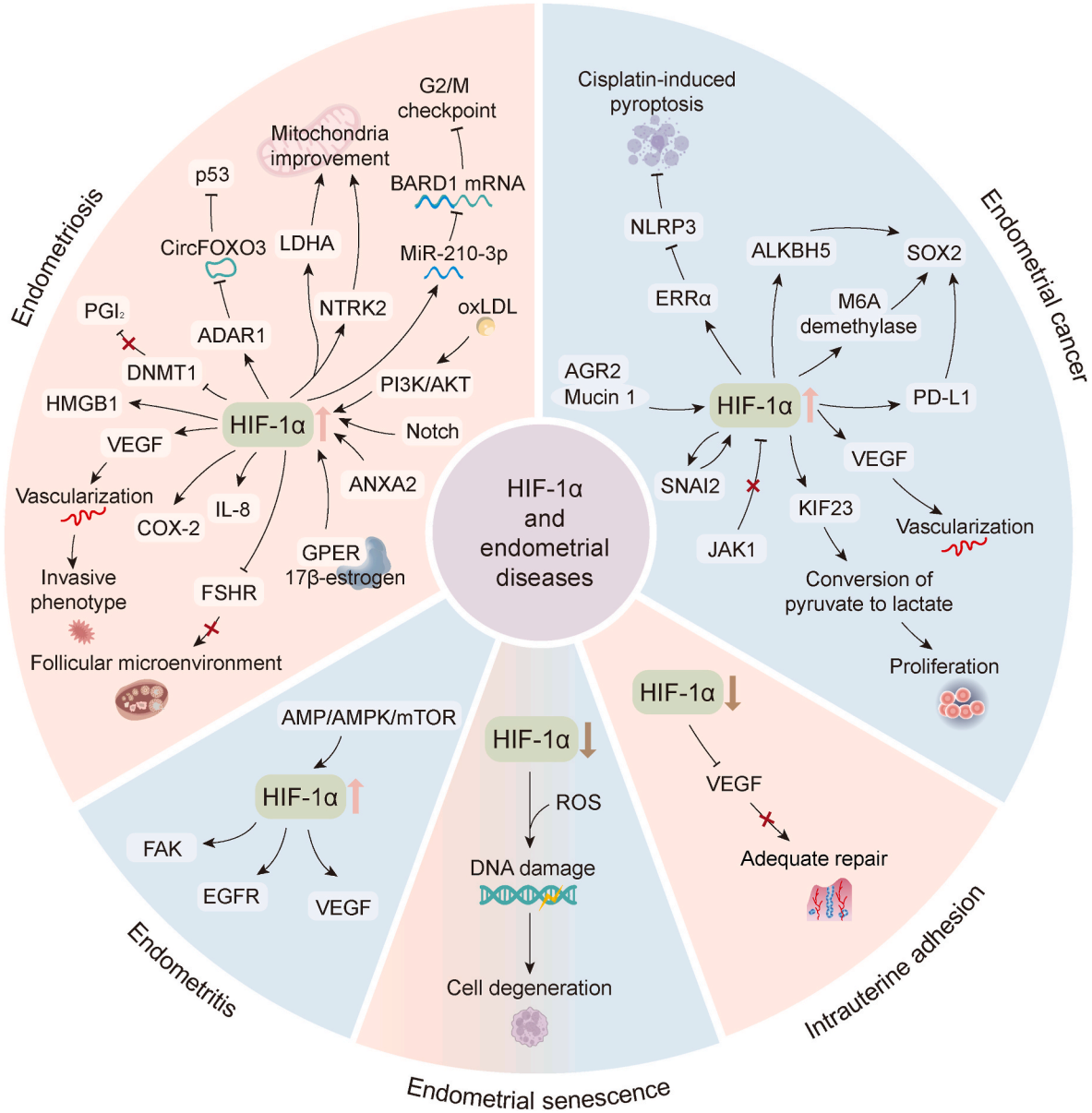

Fig. 2. Essential roles of HIF-1α in the development of endometrial diseases. HIF-1α plays versatile roles in endometrial diseases. The activation of the HIF-1α pathway is potently involved in parenchymal cell proliferation and migration, inflammatory responses, and drug resistance, leading to the development of endometriosis, endometritis, intrauterine adhesion, endometrial senescence, and endometrial cancer. ADAR1, adenosine deaminase 1 acting on RNA; AGR2, anterior gradient 2; AKT, protein kinase B; ALKBH5, AlkB homolog 5; AMP, adenosine 5′-monophosphate; AMPK, Adenosine 5′-monophosphate (AMP)-activated protein kinase; ANXA2, annexin A2; COX2, cyclooxygenase2; DNMT1, DNA methyltransferase 1; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; ERRα, estrogen-related receptor alpha; FAK, focal adhesion kinase; CircFOXO3, circular RNA forkhead box O3; FSHR, follicle-stimulating hormone receptor; GPER, G protein-coupled estrogen receptor; HIF-1α, hypoxia-inducible factor 1 alpha; HMGB1, high mobility group box 1; IL-8, interleukin-8; JAK1, tyrosine-protein kinase 1, KIF23, kinesin family member 23; LDHA, lactate dehydrogenase A; oxLDL, oxidized low-density lipoprotein; MiR, microRNA; mTOR, mammalian target of rapamycin; NLRP3, NOD-like receptor thermal protein domain associated protein 3; NTRK2, neurotrophic receptor tyrosine kinase 2; PD-L1, death ligand 1; PGI_2, prostaglandin I_2; PI3K, phosphatidylinositol 3-kinase; ROS, reactive oxygen species; SNAI2, snail family transcriptional repressor 2; SOX2, SRY-box2; VEGF, vascular endothelial growth factor.

cells are located adjacent to invading trophoblasts, regulating embryo implantation and maternal immune response [45]. In dNK cells, α-ketoglutarate inhibits the egl-9 family hypoxia-inducible factor 1-mediated ubiquitination of HIF-1α, which in turn promotes the transcription of insulin-like growth factor 1 and growth differentiation factor 15, contributing to trophoblast invasion [46]. However, the inactivation of HIF-1α in pregnant mice results in a depletion of dNK and trophoblast cells [47]. Furthermore, as pregnancy progresses, the frequency of M2 macrophages in the decidual tissue increases gradually, synergizing with other decidual immune cells to promote the formation of materno-fetal immune tolerance [48]. Gao et al. [49] proposed that HIF-1α in decidual macrophages triggers the Src/lactate dehydrogenase A (LDHA) pathway, inducing M1 polarization, which may result in an imbalanced decidual M1/M2 macrophage-mediated recurrent pregnancy loss. Thus, given the diverse roles of HIF-1α across different immune cell types, especially the possibility that activated downstream pathways via HIF-1α have no positive effect during decidualization, challenges remain in considering HIF-1α as a controllable factor in clinical applications, such as improving endometrial receptivity.

3. Pathological roles of endometrial HIF-1α

HIF-1α plays an indispensable role in endometrial physiological activities. On the contrary, aberrant levels of the HIF-1α also trigger the pathogenesis and the development of endometrial diseases (Fig. 2).

3.1. Endometriosis and HIF-1α

Endometriosis is a common gynecological disease in women attributed to the implantation of endometrial cells beyond the endometrium, characterized by periodic bleeding of the ectopic endometrial tissue and severe fibrosis of the surroundings [50]. HIF-1α is tightly involved in the progressive angiogenesis and invasive ability of ESCs in endometriosis [51]. The possible pathways that HIF-1α is involved are described in Table 3.

In patients with endometriosis, endometriotic HIF-1α levels are notably upregulated [52]. G protein-coupled estrogen receptor receives stimulation from 17β-estrogen, one of the recognized hormones that can promote the progression of ectopic lesions, enhancing the protein levels of HIF-1α [53]. NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome-mediated pyroptosis activates the Notch signaling pathway involved in the maintenance of endometriotic HIF-1α [54]. Elevated levels of plasma oxidized low-density lipoprotein in women with endometriosis activate the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB, AKT)/HIF-1α signaling pathway in ectopic endometrial epithelial cells involved in HIF-1α stabilization [55].

High levels of HIF-1α in endometriotic lesions subsequently upregulate the transcription of a series of genes involved in the pathological process. First, HIF-1α aids in the survival of endometriotic cells under OS conditions [56]. MicroRNA-21–3p (MiR-210–3p), a dominant HIF-1α-responsive miRNA, targets the 3′ untranslated region of BARD1 mRNA, blocking the G2/M cell cycle checkpoint depending on the BARD1 complex, leading to uncontrolled proliferation [56]. Moreover, addressing the imbalanced oxidative state in ectopic tissues leads to reduced HIF-1α expression, while the expression of BARD1 is concurrently upregulated, ultimately mitigating the progression of endometriosis [56]. In addition, the transcription of LDHA and neurotrophic receptor tyrosine kinase 2 in endometriosis is activated by HIF-1α, improving the mitochondrial function of pathological cells and protecting them from apoptosis [57,58]. Similarly, HIF-1α regulates cell autophagy via the activation of the adenosine deaminase 1 acting on RNA, thereby participating in the pathogenesis of endometriosis [59]. Second, activated HIF-1α leads to the invasion of ectopic lesions. The expression of genes related to classic epithelial-mesenchymal transition alterations in human endometrial epithelial cells is upregulated in response to hypoxia and HIF-1α, suggesting a prerequisite for the pathogenesis of endometriosis [13,60]. HIF-1α also upregulates prostacyclin synthase levels via the inhibition of DNA methyltransferase 1, which promotes the synthesis of PGI_2, enhancing the adhesion of endometriotic cells [61]. In contrast, in HIF-1α$^{-/-}$ mouse models with endometriosis, the decreased expression of transforming growth factor β and integrins in endometrial cells indicates an alternative role for the HIF-1α pathway in regulating ESC invasion [13]. Meanwhile, as one of the promoting factors of VEGF and MMP overexpression, HIF-1α leads to the generation of neovascular networks and induces remote metastasis of ectopic endometrial lesions toward neonatal blood vessels [62]. Third, elevated HIF-1α can stimulate the expression of IL-8 and

Table 3
The pathways that endometrial HIF-1α are involved in endometriosis.

Main subjects	Upstream regulators of HIF-1α	Downstream regulators of HIF-1α	Biological processes	References
Human endometriosis samples	17β-estrogen/G protein-coupled estrogen receptor	VEGF, MMP9	Promotes vascularization	[53]
Human endometriosis samples	NLRP3 inflammasome-mediated pyroptosis/motch1	VEGF	Promotes vascularization	[54]
Human endometriosis samples	OxLDL/PI3K/AKT	VEGF	Promotes vascularization	[55]
Human endometriosis samples, ishikawa cell line, mouse models	Hypoxia	MicroRNA-21–3p/BARD1 complex	Uncontrolled proliferation	[56]
Human endometriosis samples, THESC cell line, ishikawa cell line	Hypoxia	LDHA	Improves mitochondrial function	[57]
Human endometriosis samples, mouse models	Hypoxia	NTRK2	Improves mitochondrial function	[58]
HESC cell line	Hypoxia	ADAR1	Inhibits autophagy	[59]
HESC cell line	Hypoxia	DNMT1, PGI_2	Enhances the adhesion of endometriotic cells, inhibits the activity of NK cells	[61]
Human endometriosis samples	Hypoxia	IL-8, cyclooxygenase-2	Contributes to the inflammatory response	[63]
Mouse models	Hypoxia	HMGB1	Contributes to the inflammatory response	[64]
Human endometriosis samples, KGN cell line, mouse models	Iron, ROS	FSHR	Oocyte deficiency	[74]
Human endometriosis samples, ishikawa cell line, mouse models	Estrogen/annexin A2	VEGF	Promotes vascularization and romotes invasive phenotype	[77]

ADAR1, adenosine deaminase 1 acting on RNA; AKT, protein kinase B; DNMT1, DNA methyltransferase 1; FSHR, follicle-stimulating hormone receptor; HMGB1, high mobility group box1; HIF-1α, hypoxia-inducible factor 1 alpha; IL-8, interleukin-8; LDHA, lactate dehydrogenase A; MMP9, matrix metalloproteinase 9; NK cell, natural killer cell; NLRP3, NOD-like receptor thermal protein domain associated protein 3; NTRK2, neurotrophic receptor tyrosine kinase 2; oxLDL, oxidized low-density lipoprotein; PGI_2, prostaglandin I_2; PI3K, phosphatidylinositol 3-kinase; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor.

cyclooxygenase2 contributing to the inflammatory response observed during the development of endometriosis, and may partially be responsible for the classic clinical symptoms of endometriosis, such as chronic pelvic pain [63]. The accumulation of high mobility group box1 in mouse endometriotic cells is linked to increased inflammatory responses, which is also associated with hypoxia and the overexpression of HIF-1α [64]. Moreover, the possibility of hypoxia-mediated responses participating in other molecular mechanisms has been suggested, including the potential crosstalk among hypoxia-responsive unfolded proteins and non-coding mRNAs, which may play an essential role [65,66]. For example, increased levels of HIF-1α inhibit the cyclization of circFOXO3, subsequently downregulating p53 and affecting autophagy [59]. The hypoxia-induced unfolded protein response may also regulate HIF-1α levels through protein degradation, although this hypothesis requires further investigation in the endometrium [67].

Notably, considering the diversity of implantation sites for ectopic endometrial lesions, the activation of HIF-1α signaling pathways in various tissues can exert pathological effects through different mechanisms. Ovarian endometriosis is the most common subtype of endometriosis, leading to a decrease in the quality and quantity of oocytes and infertility [68]. Previous studies identified the upregulation of HIF-1α and its downstream proangiogenetic factors in ovarian endometriotic tissues, especially the outer capsule of ovarian endometriosis [69]. Interestingly, miR-210, a factor expressed in ectopic lesions that induces autophagy and enhances endometriotic cell survival, exhibits a similar expression pattern to HIF-1α [70]. Knockdown of HIF-1α and the administration of specific autophagy inhibitors reduce the migration and invasion of endometriotic cells [71,72]. These findings suggest hypotheses that increased endometriotic HIF-1α could activate autophagy in ovarian endometriosis and promote disease progression. In addition, excessive accumulation of iron and ROS owing to leakage from ovarian endometriotic cysts exerts a negative effect on the expression of the follicle-stimulating hormone receptor in granular cells in a HIF-1α dependent manner, generating an impaired follicular microenvironment, thereby attributing to oocyte deficiency [73,74]. These findings offer new insights into the role of HIF-1α in creating an impaired follicular microenvironment and oocyte deficiency through iron or ROS accumulation, establishing a novel link between HIF-1α and altered steroid hormone regulation under oxidative conditions [74]. Adenomyosis refers to the invasion of endometrial tissues into the myometrium, accompanied by prolonged menstruation and dysmenorrhea [75]. The expression of HIF-1α decreases in adenomyosis lesions, which is the primary reason for insufficient endometrial repair and HMB [76]. However, Zhou et al. [77] reported that the overactivation of the HIF-1α pathway is a critical pathological factor in adenomyosis. According to their research, the expression of endometrial HIF-1α can be regulated by annexin A2, a response regulator to estrogen. This regulation leads to the activation of VEGF and promotes the angiogenic capacity and invasive phenotype of endometrial cells in adenomyotic lesions [77]. These conflicting findings highlight the need for further research to resolve these discrepancies. However, in the case of deep infiltrating endometriosis (DIE), Powell et al. [78] revealed that HIF-1α mRNA failed to exert an additional impact on the progression of DIE, compared with superficial endometriotic lesions. This can be partly explained by the formation of a mature microvascular network in the lesions of DIE and the absence of hypoxic conditions [79].

3.2. Endometritis and HIF-1α

Endometritis is a reproductive system inflammatory disease involved in complex pathogenesis. Common triggers include bacterial infections, pregnancy complications, and postpartum complications [80]. In patients with chronic endometritis, an increase in peri-implantation endometrial HIF-1α has been observed, which is a crucial trigger for the upregulation of VEGF, resulting in excessive endometrial vascularization and infertility [81]. The activation of the HIF-1 pathway also upregulates epidermal growth factor receptor and focal adhesion kinase, resulting in endometrial epithelial cells adhering to trophoblast cells and a retained placenta, triggering an inflammatory response [82]. In addition, in animal models with endometritis depending on the administration of lipopolysaccharide, Jiang et al. [83] suggested a molecular mechanism involved in upregulating HIF-1α levels. Research has also identified that the reduction in phosphorylated activation of adenosine 5′-monophosphate (AMP)-activated protein kinase (*p*-AMPK) and the activation of the mammalian target of rapamycin (mTOR) are crucial factors that induce the expression of endometrial HIF-1α and cause inflammation. Conversely, restoring these pathways leads to anti-inflammatory responses and improvements in reproductive capacity [83].

3.3. Intrauterine adhesion and HIF-1α

IUA, or Asherman syndrome, is characterized by intrauterine fibrosis resulting from a failure in the scar-free repair of the endometrium [84]. The physiologic transient hypoxia during menstruation causes elevated levels of HIF-1α, which is a critical determinant of endometrial repair and regeneration. Therefore, the insufficient levels of endometrial HIF-1α are considered to contribute partly to the pathogenesis of IUA [85]. According to the current animal or pre-clinical experiments, stable transcription of HIF-1α helps to promote the expression of VEGF, contributing to angiogenesis and the improvement of endometrial function in patients with IUA [86]. However, there is currently a lack of evidence to disclose molecular mechanisms for the decrease in HIF-1α expression in IUA, highlighting the need for further studies to investigate potential downstream signals in response to this decrease.

3.4. Endometrial senescence and HIF-1α

During endometrial senescence, the degeneration of ESCs and eMSCs caused by OS or redox imbalance is an important factor [87]. Both ROS accumulation and natural antioxidant deficiency are crucial factors that lead to the functional deficiency of these cells [88]. Relatively, the elevated HIF-1α levels may rescue cell viability and exert a protective effect on defending cell senescence [89,90]. The protective effect of HIF-1α is possibly attributed to the prevention of stress-induced senescence and the inhibition of DNA damage caused by H_2O_2 [15]. HIF-1α may also play a potential role in alleviating endometrial pathological progression through its ability to reduce the levels of intracellular ROS derived from mitochondria [91]. However, most of the knowledge about the role of the HIF-1α pathway in endometrial aging comes from earlier studies and new attention is required to update our understanding of this field.

3.5. Endometrial cancer and HIF-1α

Endometrial cancer is a common gynecologic malignant tumor worldwide, and its incidence and mortality are gradually increasing [92]. The rapid proliferation of parenchymal cells and the immature development of blood vessels in the microenvironment give rise to local hypoxia. Subsequently, activated HIF-1α and OS-related inflammatory responses exert direct and indirect effects on the endometrial cells and micro-environment, leading to uncontrolled proliferation and carcinogenesis [93]. In endometrial cancer, a noticeable upregulation of HIF-1α mRNA and protein is detected in pathological specimens from patients and is closely related to disease severity, which is classified by lymph vessel stromal invasion, postoperative International Federation of Gynecology and Obstetrics staging, and lymph node metastasis [94]. The various roles of HIF-1α in the progression of endometrial cancer are summarized in Table 4.

For a start, the HIF-1α pathway can be activated by various mechanisms in endometrial cancer cells. Activated anterior gradient 2 (AGR2) interacts with mucin 1 and induces the expression of HIF-1α, amplifying

Table 4
The pathways that endometrial HIF-1α are involved in endometrial cancer.

Subjects	Upstream regulators of HIF-1α	Downstream regulators of HIF-1α	Biological processes	References
Human endometriosis samples, endometrial carcinoma cell line, mouse models	AGR2/mucin 1	Glycolysis related genes	Promotes proliferation, migration and invasion	[95]
Human endometriosis samples	SNAI2	MicroRNA-221	Triggers epithelial-to-mesenchymal transition	[96]
Human endometriosis samples, endometrial carcinoma cell line	Downregulation of JAK1	BNIP3, CA9, Caveolin 1, PDK3, PGK1, and PLAT	Promotes proliferation, migration and invasion	[97]
Endometrial carcinoma cell line	Betulin	VEGF	Promotes vascularization	[98]
Human endometriosis samples, endometrial carcinoma cell line, mouse models	KIF23	Glycolysis related genes	Promotes proliferation	[101]
Endometrial carcinoma cell line, mouse models	Hypoxia	PD-L1, m6A demethylases, and ALKBH5	Maintains stem-like cell properties	[102,103]
Human endometriosis samples, endometrial carcinoma cell line, mouse models	ERRα	NLRP3 inflammasome-mediated pyroptosis	Contributes to the resistance of cisplatin-induced pyroptosis	[105]

AGR2, anterior gradient 2; ALKBH5, AlkB homolog 5; BNIP3, BCL2 interacting protein 3; CA9, carbonic anhydrase 9; ERRα, estrogen-related receptor alpha; HIF-1α, hypoxia-inducible factor 1 alpha; JAK1, tyrosine-protein kinase; KIF23, Kinesin family member 23; NLRP3, NOD-like receptor thermal protein domain associated protein 3; PDK3, pyruvate dehydrogenase kinase 3; PD-L1, Programmed cell death ligand 1; PGK1, phosphoglycerate kinase 1; PLAT, tissue-type plasminogen activator; SNAI2, snail family transcriptional repressor 2; VEGF, vascular endothelial growth factor.

the roles of AGR2 in promoting tumor cell proliferation, invasion, and metastasis [95]. Additionally, the positive loop between snail family transcriptional repressor 2 and HIF-1α promotes the dedifferentiation of tumor cells and contributes to endometrial cancer progression [96]. Loss-of-function, or the downregulation of tyrosine-protein kinase 1 (JAK1) in endometrial cancer, participates in the activation of HIF-1/2α and contributes to endometrial cancer cell development. However, the overexpression of JAK1 leads to the inhibition of HIF pathways under hypoxia [97]. A previous study observed that betulin, a risk factor for endometrial cancer, strongly induced HIF-1α expression and subsequent VEGF expression, playing a pro-survival role in the pathogenesis and progression of endometrial cancer [98]. Moreover, HIF-1α plays a vital role in tumor cell induction and progression. First, activated HIF-1α allows tumor cells to efficiently use energy in the hostile microenvironment, facilitating their survival [99]. In early endometrial cancer or endometrial hyperplasia, the upregulation of HIF-1α can lead to the overexpression of VEGF, leading to the appearance of neovascularization, providing an important process of nutrient acquisition [100]. Conversely, the administration of eicosapentaenoic acid, a predominant omega-3 polyunsaturated fatty acid known for enhancing antioxidant enzyme activities, negatively modulates the HIF-1α/VEGF signaling pathway, countering endometrial hyperplasia [100]. Additionally, kinesin family member 23, a novel target in endometrial cancer, responds to HIF-1α by promoting the conversion of pyruvate to lactate, thereby developing the "Warburg effect" and enhancing cancer cell proliferation [101]. Second, the activation of HIF-1α helps maintain cancer stem-like cell properties. In eCSCs, elevated HIF-1α levels lead to the excessive transcription of programmed cell death ligand 1, m6A demethylases, and AlkB homolog 5, promoting the expression of SRY-box2 and the restoration of the stem-like state [102,103]. Recently, Cao et al. [104] performed a quantitative proteomic analysis to predict the role of the HIF-1α pathway in maintaining the tumorigenicity of SCs, indicating the potential involvement of hexokinase 2, which still needs to be investigated in future studies. Furthermore, HIF-1α levels have been assessed as a key reason for drug resistance. Triggered by HIF-1α, overexpressed estrogen-related receptor α inhibits the formation of the inflammasome, contributing to the resistance of cisplatin-induced pyroptosis in an NLRP3-dependent manner [105]. Furthermore, patients with endometrial cancer accompanied by a higher baseline of HIF-1α expression exhibit a defective therapeutic response to pre-surgical metformin; however, the underlying mechanisms remain under research [106]. Still, there are controversial studies suggesting a possible protective effect of elevated HIF-1α on the survival rate of patients with endometrial cancer, given that the overexpression or inhibition of protein degradation of HIF-1α accelerated the apoptosis of tumor cells in endometrial cancer [107]. These contradictory results have critical implications for further investigation.

Taken together, HIF-1α plays an indispensable role in regulating the malignancy of endometrial cancer. Upregulated HIF-1α is involved in tumor cell dedifferentiation, proliferation, and metastasis, along with the appearance of resistance to clinical therapies. Notably, whether excessive HIF-1α triggers the activated cellular apoptosis in endometrial cancer needs further investigation. Therefore, appropriately regulating HIF-1α levels in endometrial tumor cells to reduce disease burden is still a key research topic that requires further study.

4. HIF-1α-oriented therapeutic strategies in endometrial diseases

The imbalanced redox status during hypoxia is closely connected to the pathogenesis and progression of several endometrial diseases, with aberrant activation or inhibition of the HIF-1α pathway being a significant contributing factor. Most HIF-1α-centered redox strategies have well-defined targets and can specifically intervene in both upregulated and downregulated signaling pathways through clear mechanisms of action, facilitating stable and reliable therapeutic effects. In the following sub-sections, we summarized the studies focusing on treating endometrial diseases via interference with HIF-1α (Fig. 3, Table 5).

4.1. *Interfering HIF-1α gene transcription*

Although no existing agents have been developed to selectively inhibit HIF-1α gene transcription, several natural or artificial agents have been used to downregulate the levels of HIF-1α mRNA translation through non-selective actions. For example, irinotecan, topotecan, and camptothecin, known as topoisomerase 1 inhibitors, are reported to have potent abilities to suppress HIF-1α mRNA expression via binding with the human HIF-1α gene locus [108,109]. Topotecan has been used in clinical trials to treat endometrial cancer in combination with other antitumor drugs [110,111]. In addition, melatonin, a natural hormone from the pineal gland involved in antioxidative responses, can inhibit HIF-1α gene transcription [112]. In endometrial cancer, the administration of melatonin helps to reverse the activation of the HIF-1α/VEGF pathway and suppress the viability of tumor cells [113]. The decrease in HIF-1α levels can serve as potential markers for evaluating the treatment effectiveness of melatonin, offering insights into the mechanisms of melatonin treatment that are involved in the improvement of various endometrial diseases. Moreover, nuclear factor erythroid 2-related factor 2 (NRF2), a critical transcription factor response to OS, is reported to bind with an antioxidant response element upstream of the HIF-1α gene

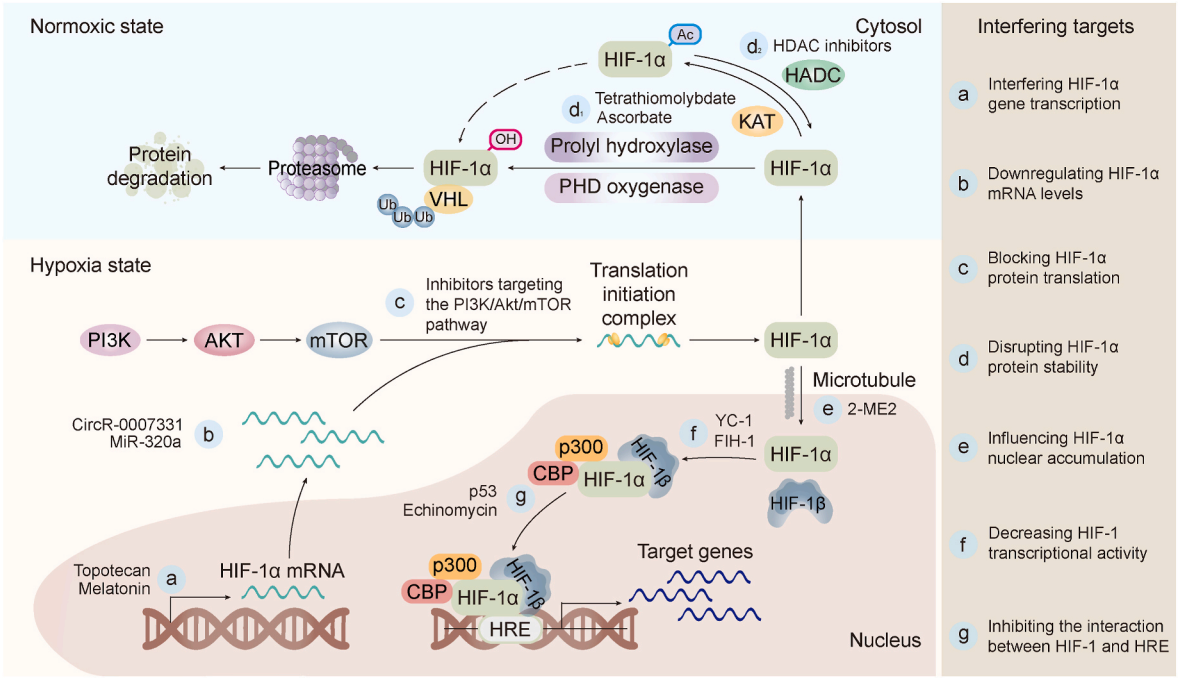

Fig. 3. The HIF-1α pathway and potential interfering targets treating endometrial diseases. Interfering targets: a. Interfering HIF-1α gene transcription; b. Downregulating HIF-1α mRNA levels; c. Blocking HIF-1α protein translation; d. Disrupting HIF-1α protein stability; e. Influencing HIF-1α nuclear accumulation; f. Decreasing HIF-1 transcriptional activity; g. Inhibiting the interaction between HIF-1 and HRE. AKT, protein kinase B; ARE, antioxidant response element; CBP, cyclic-AMP response binding protein; CircR, Circular RNA; FIH-1, factor inhibiting HIF-1; HDAC, histone deacetylase; HIF-1α, hypoxia-inducible factor 1 alpha; HRE, hypoxia-responsive element; HSP, heat shock protein; KAT, lysine acetyltransferase; MiR, microRNA; mTOR, mammalian target of rapamycin; NRF2, nuclear factor erythroid 2-related factor 2; PHD, prolyl hydroxylase domain; PI3K, phosphatidylinositol 3-kinase; VHL, von Hippel-Lindau; 2-ME2, 2-Methoxyestradiol.

Table 5
Drugs or interventions targeted the HIF-1α pathway in the treatment of endometrial diseases.

Drugs/Interventions	Disease	Subjects	Mechanisms	Effects	References
Topotecan, everolimus	Endometrial cancer	Human (NCT00703807)	Interfering HIF-1α gene transcription	Dose-limiting toxicity due to myelosuppression	[109]
Topotecan, selinexor	Endometrial cancer	Human (NCT02419495)	Interfering HIF-1α gene transcription	Preliminary tumor efficacy	[110]
Melatonin	Endometrial cancer	Human umbilical vein endothelial cells	Interfering HIF-1α gene transcription	Reverses the activation of the HIF-1α/VEGF pathway	[112]
Circ-0007331 knockdown, miR-200c-3p	Endometriosis	Primary cells from clinical samples of ovarian chocolate cysts	Downregulating HIF-1α mRNA levels	Decreases cell proliferation and invasion	[116]
MiR-320a	Endometrial cancer	Primary cells from clinical samples of endometrial cancer	Downregulating HIF-1α mRNA levels	Decreases cell proliferation, inhibits the expression of VEGF	[117]
Stop smoking	Abnormal decidualization	Primary cells from clinical samples of the endometrium	Promoting HIF-1α protein hydroxylation	Decreases ROS	[128]
Tetrathiomolybdate	Endometrial cancer	ECC-1 and IGROV-1 cell lines	Promoting HIF-1α protein hydroxylation	Targets HIF-1α through a PHD-dependent manner	[129]
Ascorbate	Endometrial cancer	Primary cells from clinical samples of the endometrium	Promoting HIF-1α protein hydroxylation	Reverses the activation of the HIF-1α/VEGF pathway	[130]
Romidepsin	Endometrial cancer	11z cell lines	Promoting HIF-1α protein acetylation	Inhibits HDAC and the HIF-1α/VEGF pathway	[132]
Entinostat	Endometrial cancer	Human (NCT03018249)	Promoting HIF-1α protein acetylation	Poor effects	[133]
2-Methoxyestradiol	Endometriosis	Mouse	Influencing HIF-1α nuclear accumulation	Inhibits the growth of endometriotic lesions	[140]
YC-1, FIH-1	Endometrial cancer	HHUA cell lines	Inhibiting HIF-1 transcriptional activity	Cancer cell senescence	[146]
Echinomycin	Endometriosis	Primary cells from clinical samples of ovarian chocolate cysts	Interfering the interaction between HIF-1 and HRE	Reverses the activation of the HIF-1α/VEGF pathway	[148]

FIH-1, factor inhibiting HIF-1; HDAC, histone deacetylase; HIF-1, hypoxia-inducible factor 1; HRE, hypoxia-responsive element; PHD, prolyl hydroxylase domain; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor.

and upregulates its expression in breast and bladder tumors [114]. This discovery establishes a direct regulatory link between two crucial oxygen-responsive transcription factors, connecting the HIF-1α pathway with redox status and offering novel therapeutic insights for treating diseases. Although no similar results have been reported in studies targeting endometrial cancer, the upregulation of NRF2 and HIF-1α has been recognized during its development [115]. Exploring whether the inhibition of NRF2 also downregulates the transcription of HIF-1α during the progression of endometrial cancer is a promising research direction.

4.2. Downregulating HIF-1α mRNA levels

The downregulation of HIF-1α mRNA makes the HIF-1α pathway unable to respond to hypoxia or OS, which suppresses the activation of the HIF-1α pathway under various pathological conditions in the endometrium from the start, aiming to offset the negative effects of hypoxia or excessive ROS to the greatest extent possible. Dong et al. [116] confirmed that circRNA 0007331 and miR-200c-3p are key non-coding RNAs regulating HIF-1α mRNA levels by searching for modified miRNA expression patterns in the pathological tissues of endometriosis. They reported a noticeable reduction in HIF-1α mRNA and protein expression by restoring the levels of these two non-coding RNAs, during which the invasive phenotype of ectopic endometrial cells was inhibited [116]. Regarding endometrial cancer, miR-320a identified and purified from extracellular vesicles derived from cancer-associated fibroblasts has been found to bind directly to and regulate the mRNA of HIF-1α [117]. The administration of miR-320a lowers HIF-1α and VEGF expression in tumor cells and inhibits their proliferation [117].

4.3. Blocking HIF-1α protein translation

The PI3K/AKT/mTOR pathway is one of the most widely investigated pathways regarding affecting protein synthesis [118]. The activation of mTOR regulates the protein synthesis of HIF-1α by inducing the phosphorylation of dominant molecules involved in the translation initiation complex, such as 4E-BP1 [119], eIF-4E [120], and p70s6k [121]. Many studies have suggested that the suppression of PI3K/AKT/mTOR downregulates the levels of HIF-1α protein, leading to the inhibition of endometrial disease development and progression, including endometriosis [122], endometrial cancer [123,124], and endometritis [83]. In brief, under pathological conditions, the regulation of the mTOR/HIF-1a axis affects essential cell activities such as angiogenesis, apoptosis, autophagy, and metabolic alterations can be adjusted. Exogenous interference targeting the mTOR pathway may be a potent treatment strategy for various endometrial diseases.

4.4. Disrupting HIF-1α protein stability

PTMs are crucial factors regulating the stability of the HIF-1α protein and the activities of HIF-1α pathways [125]. In the endometrium, the degradation of the HIF-1α protein under normoxic conditions is closely related to hydroxylation and acetylation. Pro 402 and Pro 564 within the oxygen-dependent degradation domain of HIF-1α protein can be hydroxylated by prolyl hydroxylase domain oxygenases, followed by the formation of recognition signals for E3 ubiquitin ligase von Hippel-Lindau, inducing a process of protein degradation via the ubiquitin-proteasome system [126]. The prolyl hydroxylase, containing oxygen and 2-oxoglutarate as its substrates, also triggers the prolyl hydroxylation of HIF-1α, maintaining low levels of HIF-1α under normoxic states [127]. Kida et al. [128] reported that the destructive effect of smoking on the endometrium could be attributed to the inhibition of the HIF-1α prolyl hydroxylation enzyme, resulting in constant activation of the HIF-1α pathway even under normoxic conditions, subsequently inducing cellular stress and inflammatory responses. In contrast, the therapeutic effect of tetrathiomolybdate and ascorbate on endometrial cancer is attributed to the elevation of the activity of HIF-prolyl hydroxylase, leading to a noticeable decrease in endometrial HIF-1α expression and an inhibition of angiogenesis [129,130]. Moreover, the acetylation and deacetylation of the HIF-1α protein at the sites of lysine are also important factors affecting its stability. In this process, acetylation is mainly controlled by members of the lysine acetyltransferase (KAT) families, while deacetylation is mainly regulated by the histone deacetylase (HDAC) families, including I, IIa, IIb, and III subgroups. Protein deacetylation induced by I and IIa members of HDAC upregulates the protein levels of HIF-1α, while acetylation of HIF-1α and deacetylation catalyzed by other HDAC subgroups and KAT reduce the HIF content [131]. Therefore, the application of inhibitors of I and IIa members of HDAC is an important means of improving pathological responses induced by hypoxia. To date, several studies have reported the therapeutic effects of HDAC inhibitors on endometrial diseases, including endometriosis and endometrial cancer [132,133]. However, existing pieces of evidence have reported downregulatory patterns of members of I and IIa subgroups on HIF-1α proteins. HDAC1 promotes deacetylation at K709, leading to protein ubiquitination [134]. The negative effects of HDAC4 and HDAC5 on HIF-1α activity have also been reported; however, the mechanisms involved require further studies [134,135]. Therefore, additional experimental studies are needed to elucidate the intricate regulation of HIF-1α acetylation and deacetylation in the hypoxia response, advancing the identification of molecular drugs that effectively regulate HIF-1α levels in endometrial diseases. Furthermore, the phosphorylation, methylation, SUMOylation, and other uncharacterized PTMs of HIF-1α protein in other tissues or organs are receiving increasing attention [136]. These PTMs of the HIF-1α protein are reported to be involved in the processes of protein stabilization, nuclear accumulation, heterodimerization, and acetylation of HIF-1α, functioning as crucial factors regulating the HIF pathway [136]. However, these regulatory mechanisms of the HIF-1α protein remain largely unexplored in research on the endometrium, presenting a potential target for the treatment of endometrial diseases.

4.5. Influencing HIF-1α nuclear accumulation

Microtubule function plays an essential role in promoting the nuclear accumulation of HIF-1α, which is a prerequisite for the dimerization of HIF-1α and HIF-1β [137]. Both aberrant microtubule-stabilizing and microtubule-destabilizing alter nuclear frequencies of HIF-1α and the activation of its downstream pathways [8,137]. 2-Methoxyestradiol, a metabolic product of estrogen in vivo, is a typical inhibitor of microtubule protein assembly, leading to the depolymerization of microtubules [138]. The administration of 2-methoxyestradiol inhibits the nuclear translocation of HIF-1α and HIF-2α and downregulates the expression of their proteins [139]. In endometriosis, systemic treatment with 2-methoxyestradiol blocks the HIF-1α pathway and inhibits the upregulation of angiogenetic factors, inhibiting the growth of endometriotic lesions in a dose-dependent manner [140]. Although there is still a lack of evidence to prove the therapeutic effect of 2-methoxyestradiol on other endometrial pathological conditions via regulation targeting HIF-1α nuclear translocation, this represents a promising research field, making it a potential candidate for endometrial disease improvement.

4.6. Decreasing HIF-1 transcriptional activity

Following the formation of a heterodimer with HIF-1β, HIF-1 recruits other transcriptional coactivators, including p300 and its paralogue, cyclic-AMP response element binding protein binding protein (CBP), to trigger the transcription of target genes [141]. The COOH-terminal transactivation domain (CAD) of HIF-1α is responsible for the tight combination of p300/CBP, and inhibiting this interaction decreases HIF-1 transcriptional activity significantly [142]. Drugs that interfere with the binding of p300 to CBP inhibit HIF-1α activation during hypoxia and imbalanced OS. YC-1, originally developed as an antiplatelet aggregation agent in 1994, has emerged in recent years for its ability to dissociate the connection of CAD/p300, exerting potent anticancer activities [143,144]. Similarly, factor inhibiting HIF-1 (FIH-1), an asparaginyl hydroxylase, hinders the binding of HIF-1α with transcriptional coactivators via the hydroxylation of CAD [145]. In the case of endometrial cancer, the transfection of YC-1 and FIH-1 into tumor cells negatively regulates the HIF-1α pathway and activates tumor cell senescence, preventing tumor growth [146]. Therefore, it seems feasible to use specific inhibitors on the transcriptional activity of HIF-1 as a

treatment for endometrial diseases.

4.7. Inhibiting the interaction between HIF-1 and HRE

Specific interactions between HIF-1 and the sequence 5′-(A/G)CGTG-3′ within HREs are responsible for the major effects of the HIF-1α pathway, which is a crucial link in the development of various diseases [147]. Studies on the endometrium have demonstrated the therapeutic effects of the inhibition between HIF-1 and HREs on endometriosis, from which risk profiles for the HIF-1 inhibitor, echinomycin, have been described [148]. In addition, p53 has been recently reported to serve as a chaperon to stabilize its binding at HIF-1α downstream hypoxia-responsive elements, which may be a novel target for treating diseases related to HIF-1α activation [149]. However, further research is needed to determine whether this viewpoint applies to the endometrium.

5. Challenges and future perspectives in the clinical application

The local hypoxic environment is an important factor in maintaining the normal physiological state of the endometrium, in which the regular fluctuations of endometrial HIF-1α play an indispensable role. Currently, interventions targeting the various links in which HIF-1α plays its transcriptional role show the potent contribution in treating endometrial diseases. However, it is noticeable that there are still many challenges that need to be paid more attention to when applying them to a large scale in clinical practice.

First, successfully adjusting HIF-1α levels at various levels to alleviate pathological alterations in the endometrium depends on a detailed illustration of the mechanisms of endometrial HIF-1α regulation. The HIF-1α pathway is activated in various tissues or organs of the body in response to local hypoxia or ROS signals with many molecular mechanisms involved [150,151]. However, compared with other tissues, there is still a significant gap in the regulatory patterns of endometrial HIF-1α, such as the phosphorylation of HIF-1α protein, which is potentially one of the key reasons limiting the application of HIF-1α-centered strategies in treating endometrial diseases. Additional efforts should be invested to determine how HIF-1α regulates both physiological characteristics and pathological properties in the endometrium, which is a solid foundation for expanding the application of HIF-1α-centered strategies in endometrial diseases. Second, in addition to the HIF-1α-oriented intervention mentioned above that has been elucidated for the involvement in HIF-1α transcription, translation, and transcriptional activity in the treatment of endometrial diseases, there are still many promising regulators of HIF-1α whose underlying mechanisms have not been fully identified. Certain Chinese herbal medicine ingredients have shown promise in significantly reducing the area of endometriotic lesions, largely by inhibiting HIF-1α, which has been validated in both mouse models and in vitro studies using endometriotic tissues. However, the detailed mechanism of interaction related to these molecules remains to be studied [152–156]. Notably, downregulating the HIF-1α pathway in certain cells can effectively protect the physiological changes of the normal endometrium, such as the immune effect of dNK during decidualization, which depends on the stabilization of HIF-1α proteins [46]. However, in decidual macrophages, excessive activation of the HIF-1α pathway may lead to M2 macrophage-mediated recurrent pregnancy loss [49]. Therefore, it is necessary to develop highly specific HIF-1α regulatory molecules to improve the application of HIF-1α-centered strategies. Furthermore, several molecules that are reported to participate in the regulation of the HIF-1α pathway, such as receptor tyrosine kinase inhibitors, mTOR inhibitors, enzymes involved in protein PTMs, and melatonin, may also have effects on other crucial cellular activities. This may be one of the potential sources of side effects associated with the use of these drugs in treating endometrial diseases. Employing well-designed carriers of these drugs can offer a method to address this challenge and achieve targeted regulation.

Furthermore, it is crucial to fully elucidate the potential activation modes and downstream targets of endometrial HIF-1α, as this holds significant promise for treating endometrial diseases. On the one hand, identifying the aberrant increase or decrease of endometrial HIF-1α levels under various pathological conditions can pinpoint definitive interference targets to further explore therapeutic strategies. Numerous studies have observed increased HIF-1α levels and the upregulation of its downstream targets in endometrial tissues with a proliferative phenotype under both physiological and pathological conditions. Specifically, the HIF-1α pathway ensures that endometrial tissue can regulate angiogenesis, proliferation, and the recruitment of immune cells. Not only the elevated expression of endometrial HIF-1α plays a crucial role in denuded tissue growth during the menstrual cycle and the establishment of the maternal-fetal interface through decidualization, but also endows pathological tissues of endometriosis, endometritis, and endometrial cancer with “proliferative” traits, contributing an invasive phenotype. Conversely, the inactivation of the endometrial HIF-1α pathway has been observed in various endometrial pathologies that fail to achieve proper repair or regeneration, including IUA, endometrial senescence, and impaired endometrial decidualization. Therefore, modulating the HIF-1α pathway at different levels of gene expression regulation to restore normal endometrial HIF-1α levels is considered a fundamental approach in HIF-1α-centered strategies. Additionally, increasing evidence indicates that aberrant levels of endometrial HIF-1α play a critical role in oxidative stress. Restoring HIF-1α levels by correcting the abnormal redox balance in endometrial diseases seems to help enhance therapeutic options. For instance, the use of typical antioxidant drugs to reduce excessive ROS has been reported to correct impaired HIF-1α levels in endometriotic lesions, endometrial senescence, and endometrial hyperplasia, subsequently alleviating the progression of these pathologies [15,56,100,157]. Since current research on endometrial HIF-1α regulation primarily focuses on endometriosis, endometrial cancer, and abnormal decidualization, further studies are needed to demonstrate the benefits of HIF-1α-centered treatments for various endometrial pathologies. On the other hand, a deeper understanding of the periodic activation patterns of the HIF-1α pathway in the endometrium identifies HIF-1α and its *cis*-acting elements as a natural switch that physiological events can modulate. For instance, the HRE sequence can be localized upstream of target genes when designing exosome liposome hybrid carriers, serving as an on/off regulatory switch in a HIF-1α-dependent manner, leading to an improvement in the endometrial microenvironment [158]. Given recent advances in the successful construction of various hydrogel carriers, we believe that regulating the expression of target genes based on the activation modes of endometrial HIF-1α represents a promising research avenue that merits further exploration.

Additionally, we summarize the current understanding of the potential roles of other HIF family proteins, including HIF-1β, HIF-2α, and HIF-3, in the endometrium. HIF-1β is a constitutively expressed cytoplasmic protein, whose expression is minimally influenced by hypoxic conditions during the menstrual cycle [159]. Interestingly, its elevation during the proliferative phase is potentially regulated by the aryl hydrocarbon receptor pathway, although the underlying molecular mechanisms are still being investigated [160]. HIF-2α, a functional homolog of HIF-1α and an alternative dimerization partner for HIF-1β, has not been extensively studied in the endometrium [161]. Some studies have reported an upregulation in HIF-2α expression in endometriosis, contributing to aberrant epigenetic modifications and an invasive phenotype [162,163]. However, the upregulation of HIF-2α in normal endometria and endometrial cancer is minimal [36,164]. Instead, evidence suggests that HIF-2α has a significant expression in the placenta and myometrium, indicating its importance in other uterine regions under hypoxic or stress conditions [165,166]. The study of HIF-3 in the endometrium faces similar challenges, with only a few studies addressing changes in endometrial HIF-3 levels and its relatively low presence in most endometrial cell types [36]. Therefore, we emphasize

that appropriate alterations in endometrial HIF-1α levels induced by hypoxia and the activation of its downstream targets are crucial for endometrial physiology, making HIF-1α-centered strategies for treating endometrial diseases indispensable in clinical applications.

Collectively, we conclude that HIF-1α-centered strategies targeting endometrial diseases are promising research fields; however, long-term scientific research is still required before the wide-spread clinical application of these therapeutic approaches for improving endometrial pathologies. We believe that a continuously deepened understanding of HIF-1α regulatory patterns in the endometrium will overcome these problems and provide a solid foundation for treating endometrial diseases.

6. Conclusions

In conclusion, we comprehensively reviewed the crucial role of the HIF-1α pathway in the physiological characteristics and pathological progression of the endometrium and highlighted the potential of applying HIF-1α-centered strategies to treat endometrial diseases in clinical settings. To date, it has been a long exploration aiming at the periodic fluctuations and aberrant activation or suppression of the endometrial HIF-1α. The existing intervention methods regulate the content of endometrial HIF-1α at various levels, including transcription, post-transcription, translation, and post-translation levels, making the HIF-1α-centered network more abundant. This significant progress contributes to a profound understanding of the HIF-1α-centered strategies for endometrial diseases, such as endometriosis, endometritis, IUA, endometrial senescence, and endometrial cancer. However, as summarized above, there are numerous gaps for scholars to fill in these areas to achieve the translation of these HIF-1α strategies into clinical practice. We believe that further study in this field will advance the treatment of endometrial diseases.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Abbreviation

AKT	protein kinase B
CAD	COOH-terminal transactivation domain
CBP	cyclic-AMP response binding protein binding protein
DIE	deep infiltrating endometriosis
dNK cell	decidual natural killer cell
ECM	extracellular matrix
eMSC	endometrial mesenchymal stem-like cell
EMT	epithelial-mesenchymal transition
ESC	endometrial stromal cell
FIH-1	factor inhibiting HIF-1
HDAC	histone deacetylase
HIF-1	hypoxia-inducible factor 1
HMB	heavy menstrual bleeding
HRE	hypoxia-responsive element
IL-8	interleukin-8
IUA	intrauterine adhesion
JAK1	tyrosine-protein kinase 1
KAT	lysine acetyltransferase
LDHA	lactate dehydrogenase A
MMP2	matrix metalloproteinase 2
mTOR	mammalian target of rapamycin
NLRP3	NOD-like receptor thermal protein domain associated protein 3
NRF2	nuclear factor erythroid 2-related factor 2
OS	oxidative stress
PI3K	phosphatidylinositol 3-kinase
ROS	reactive oxygen species
PTM	post-translational modifications
VEGF	vascular endothelial growth factor
α-KG	α-ketoglutarate

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