Pathological functions of hypoxia in endometriosis

Kuei-Yang Hsiao[1], Shih-Chieh Lin[1], Meng-Hsing Wu[1,2], Shaw-Jenq Tsai[1]

[1]Department of Physiology, College of Medicine, College of Medicine and Hospital, National Cheng Kung University, Tainan 70101, Taiwan, [2]Department of Obstetrics and Gynecology, College of Medicine and Hospital, National Cheng Kung University, Tainan 70101, Taiwan

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1. ABSTRACT

Endometriosis is one of the most common gynecological diseases that significantly reduce the life quality of affected women. Research results from the past decade clearly demonstrated that aberrant production of estrogen and cyclooxygenase-2-derived prostaglandin E_2 play indispensable roles in the pathogenesis of this disease. However, the etiology of endometriosis remains obscure. Recent evidence reveals a new facet of endometriotic pathogenesis by showing that hypoxia induces the expression of many important downstream genes to regulate the implantation, survival, and maintenance of ectopic endometriotic lesions. These new findings shed lights on future investigations of delineating the etiology of endometriosis and designing new therapeutic strategy for endometriosis.

2. INTRODUCTION

Endometriosis is a common gynecological disorder, characterized by the presence of endometrial tissue outside of the uterine cavity, with a complex, multifactorial etiology. General symptoms of endometriosis include pelvic pain, dysmenorrhea, and infertility, which significantly reduce life quality of affected women. Although the etiology of endometriosis remains largely unknown, retrograde menstruation has been proposed and well-accepted to be a crucial prerequisite for the development (1). This notion is supported by several clinical observations describing that women with vaginal or cervical obstruction have higher risk of developing endometriosis (2-4). Along with these lines of evidence, baboons with ligated cervices tends to develop endometriosis compared to the control group (5). Intriguingly, a more recent survey indicates that endometriosis is found exclusively in species that menstruate (6). However, the theory of retrograde menstruation is insufficient to explain why 90% women of reproductive age have retrograde menstruation but only 10-15% of them develop endometriosis (7). It is clear that retrograded endometrial tissues have to escape from the surveillance of immune system and to establish a network of blood vessel for supporting proliferation in peritoneal cavity. Therefore, for retrograded tissues to successfully survive and implant in the pelvic cavity, the local microenvironment has to play important modulatory roles in the pathogenesis of endometriosis. Two of the local factors, hypoxia and inflammation-derived prostaglandins (PGs) (Figure 1), attract most attention due to the indispensable roles they play during the development of endometriosis.

PGs are increased in the menstrual fluid of women with dysmenorrhea and endometriosis (8), which ind Concentrations of
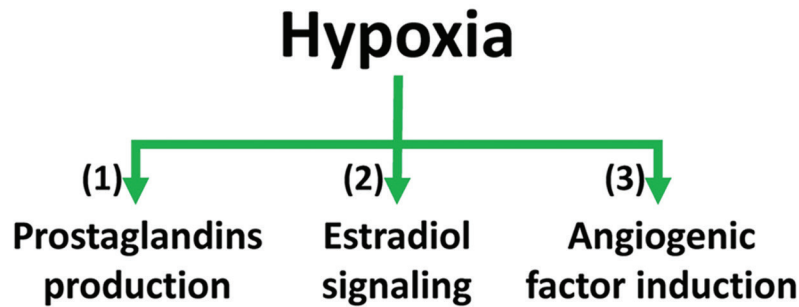
Figure 1. The master role of hypoxia in the endometriosis. Hypoxic stress promotes (1) proinflammatory prostaglandins production, modulates (2) estradiol signaling via regulation of estrogen receptor α and β expression and induces (3) angiogenic factor expression

uces excessive myometrium contraction and abnormal uterine arterial vasoconstriction resulting in local hypoxia and menstrual abdominal pain. The retrograded endometrial debris during menstruation is in hypoxic milieu due to lack of hormone and blood supply. In animal study, the growth of hypoxia-pretreated endometriotic implants is increased via the induction of the proliferation and angiogenesis-associated markers, such as vascular endothelial growth factor (VEGF) and hypoxia-inducible factor (HIFs) (9). Hypoxia-inducible factors, a group of transcription factors in response to hypoxic stress, account for the transcriptional modulation of genes in cells under hypoxic stress. Two subunits, α and β, form heterodimeric complex of HIF. Although both are constantly transcribed and translated either under normoxia or hypoxia, they are regulated in a very distinct manner. HIF-1β, also termed aryl hydrocarbon nuclear translocator, is stably expressed under normoxia and hypoxia conditions. In contrast, the α subunit, such as HIF-1α and HIF-2α, undergoes proteolytic degradation through a ubiquitin-mediated, proteasome-dependent pathway in the presence of ambient concentration of oxygen. Under hypoxic condition, HIF α becomes stable and accumulates in the nucleus due to lack of enzymatic activity of prolyl hydroxylases, which prevents HIF α from hydroxylation and thus degradation by 26S proteasome (10).

HIF members express in distinct cell-types and functional layers of human endometrium (11, 12). HIF-1β expresses constantly through the cycle, and reaches its maximal levels in the glandular cells during the proliferative phase. In contrast, HIF-1α expresses mainly in secretory and menstrual phases in the functional layer and protein level reaches the maximal around late secretory phase (11). These findings suggest that HIF may play some important

roles in maintaining normal endometrial functions, especially in cellular and angiogenic gene expression in response to hypoxia at progesterone withdrawal via PG pathway. The first piece of evidence that clearly demonstrates the pathological function of HIF-1α in endometriosis was reported by Wu *et al*., who showed constitutively elevated levels of HIF-1α mRNA and protein in ectopic endometriotic lesions but not paired eutopic endometrial tissues (13). Following this pioneer observation, several papers subsequently reported the function and regulation of HIF-1α during the development of endometriosis (9, 14-18). In this review, we will discuss the most recent findings regarding roles of hypoxia in the pathological processes of endometriosis.

3. HYPOXIA REGULATES ABERRANT CYCLOOXYGENASE (COX)-2 EXPRESSION

PGs belong to a group of long chain fatty acid biosynthesized from arachidonic acid and have been implicated in many physiological and pathological processes such as inflammation, tissue repair, proliferation and angiogenesis (19). In mammals, cells synthesize PGs from arachidonic acid through a cascade of multiple enzymes including phospholipase A2 (PLA_2), prostaglandin G/H synthase (better known as cyclooxygenase, COX), and terminal PG synthase(s). PLA_2 cleaves and releases arachidonic acid from membrane-bound phospholipids. COX then converts arachidonic acid to PGH_2, which is a common PG precursor and will be further converted to other PGs or PG-related metabolites by terminal PG synthase(s). Dysregulation of these particular enzymes have been linked to the development of endometriosis (20-24). COX-2, the enzyme responsible for the rate-limiting step in PGE_2 biosynthesis, was found aberrantly overexpressed
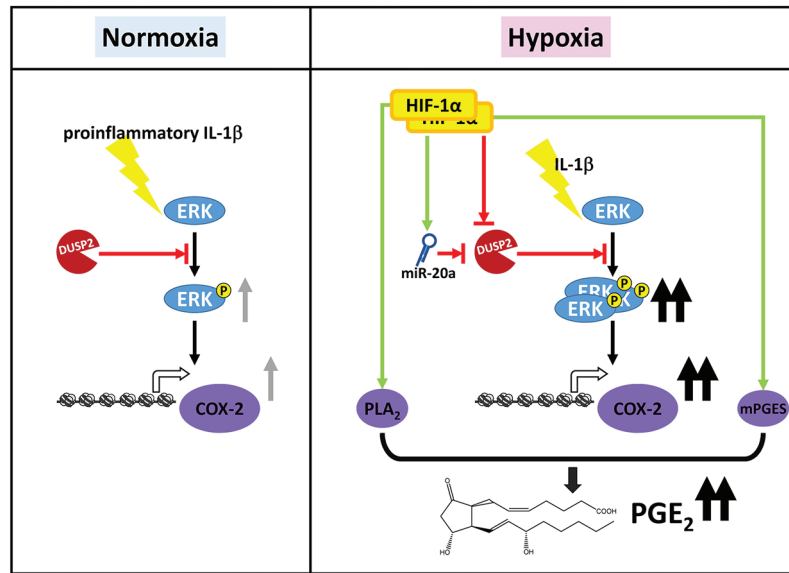
Figure 2. Hypoxia potentiates proinflammatory pathway by modulating DUSP2/ERK molecular module. Under normoxia condition (left panel), IL-1β-induced COX-2 expression is properly regulated by DUSP2 acting on ERK. In contrast, hypoxic stress facilitates the accumulation of HIF-1α (right panel), which either directly represses DUSP2 transcription or indirectly induces miR-20a to target DUSP2 3′-UTR, causing downregulation of DUSP2. Downregulation of DUSP2 unleashes the IL-1β-induced COX-2 expression and further prostaglandin production. Hypoxia also induces expression of PLA2 and mPGES, which work together with COX-2 to produce tremendous amount of PGE$_2$ (purple lines). Both ERK and PGE$_2$ form a positive regulatory loop to stabilize HIF-1α (not shown on the figure). COX-2, cyclooxygenase-2; DUSP2, dual-specificity phosphatase-2; ERK, extracellular signal-regulated kinase; HIF-1, hypoxia-inducible factor-1; interleukin-1β, IL-1β; miR-20a, microRNA-20a; mPGES, microsomal PGE synthase; PLA2, phospholipase A2; PGE2, prostaglandin E2.

in peritoneal macrophages (23) and in endometriotic stromal cells (24). Aberrant production of PGE$_2$ by macrophages and ectopic stromal cells contributes to numerous pathological processes contributing to the development of endometriosis including steroidogenesis (25-27), cell proliferation (28-31), angiogenesis (15), and immune suppression (32-35). Although elevated proinflammatory cytokines are commonly found in the peritoneal fluid from women with endometriosis (36), it does not fully account for the overexpression of COX-2 in the endometriosis. Instead, we demonstrated that *COX-2* gene is at least 100 times more sensitive to interleukin (IL)-1β treatment in endometriotic stromal cells compared with normal endometrial stromal cells and this increased sensitivity of *COX-2* gene is mediated via extracellular signal-regulated kinase (ERK)-dependent transactivation (24). Since there is no known active mutation of molecules upstream of ERK in endometriosis patients, it is reasonable to suggest that an increase in ERK activity may be mediated by loss-of-function of downstream phosphatases which inactivate ERK. We found dual-specificity phosphatase-2 (DUSP2), a nuclear phosphatase that inactivates ERK, is markedly downregulated in stromal cells of ectopic endometriotic tissues (16).

The bioinformatic analysis revealed that there is a putative hypoxia response element (HRE) in *DUSP2* promoter, suggesting DUSP2 is a potential hypoxia-targeting gene. This notion was supported by the results that hypoxic stress (1% oxygen), hypoxia-mimetic chemicals (desferrioxamine or dimethyloxaloylglycine), and overexpression of HIF-1α downregulate DUSP2. Consistently, HIF-1α knockdown or mutation in HRE of DUSP2 promoter rescues hypoxia-mediated DUSP2 downregulation. DUSP2 downregulation leads to more activated ERKs and p38 mitogen-activated protein kinase (MAPK), and ultimately results in hypersensitivity of COX-2 in response to proinflammatory stimuli (16) (Figure 2, right panel and Figure 3-(2)).

MicroRNAs (miRNAs) are small noncoding RNA modulating the target gene expression through cleavage or translational repression. The regulatory function of miRNAs has been implicated in hypoxia, inflammation, tissue repair, cell proliferation, apoptosis, extracellular matrix remodeling, and angiogenesis in endometriosis (37). It has been reported that expression of miR-20a is relatively higher in ectopic lesions compared to that in eutopic endometrial tissues (15, 38). By using bioinformatic
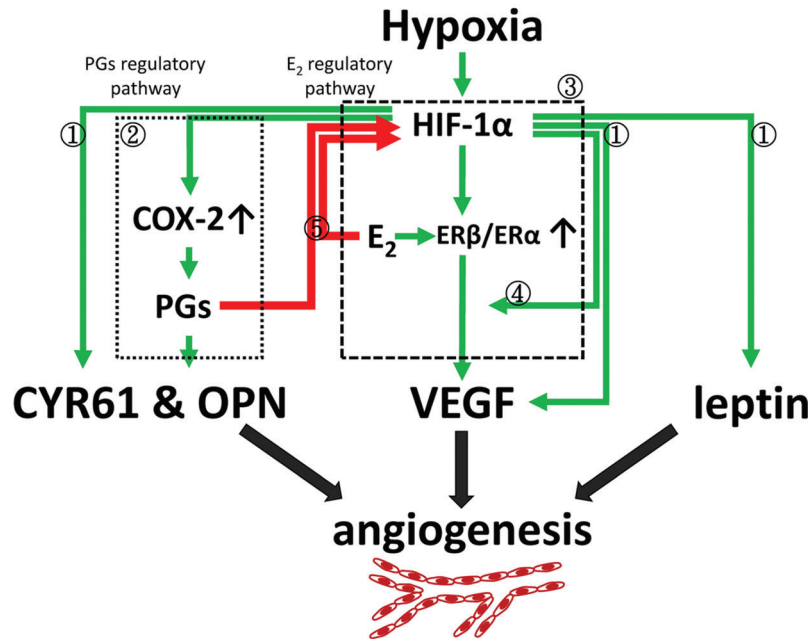
Figure 3. Hypoxia induces multiple angiogenic pathways. Hypoxia directly triggers CYR61, VEGF and leptin expression (1), while indirectly promotes both CYR61 and OPN expression through the impact on COX-2/PGs pathway ((2), dot frame). Hypoxia increases the ratio of ERβ/ERα favoring the expression of VEGF ((3), dash frame) and also promotes estradiol-induced VEGF expression (4). Both prostaglandins and estrogen stabilize HIF-1α to form a positive feedback loop ((5), red lines), enhancing the effect of hypoxia on angiogenesis. COX-2, cyclooxygenase-2; CYR61, cysteine-rich protein 61; HIF-1, hypoxia-inducible factor-1; ER, estrogen receptor; OPN, osteopontin; PG, prostaglandin; VEGF, vascular endothelial growth factor.

and molecular biology approaches, we identified that promoter of miR-20a harbors a functional HRE, a cis-DNA segment where HIF binds to. Further study demonstrated that expression of miR-20a is induced by hypoxia (1% oxygen). Interestingly, one of the targets of miR-20a is DUSP2. Along with this line of evidence, introducing mutation to miR-20a targeting site in DUSP2 3′-UTR rescues hypoxia-mediated DUSP2 downregulation. Forced expression of miR-20a represses DUSP2 expression, which further promoting ERK phosphorylation and resulting overexpression of downstream ERK-regulated genes, such as COX-2, angiogenic and mitogenic factors, in endometriotic stromal cells (15) (Figure 2, right panel). Taken together, these lines of evidence strongly support that hypoxia is a critical factor that potentiates COX-2 gene sensitivity in ectopic endometriotic stromal cells.

4. HYPOXIA TUNES ESTROGEN-MEDIATED SIGNALING FAVORING THE DEVELOPMENT OF ENDOMETRIOSIS

The establishment and development of endometriosis highly depend on estrogen. First, the identification of endometriosis typically appears after menarche and endometriotic lesions usually regress in women with menopause or ovariectomy (39). Second, Dizerega *et al*. demonstrated that only implanted endometrial tissues in castrated monkeys receiving capsules with estrogen or progesterone successfully established endometriotic lesions (40). Two isoforms of nuclear estrogen receptor (ERα and ERβ) and one G protein-coupled estrogen receptor (GPR30) mediate most of regulatory functions of estrogen in an isoform-specific manner (41, 42). All of three isoforms are implicated in the development and maintenance of endometriosis. In a mouse uterine fragments-implanted model, fragments from either ERα- or ERβ-knockout donor mice developed less and smaller endometriotic-like lesions compared to tissues from wild-type donors (43) whereas a mouse model of endometriosis-induced by implantation of human endometrium demonstrated that treatment with ERβ-selective agonist induces the regression of endometriotic-like lesions (44). In orchestration with the roles of ERα and ERβ, treatment with a GPR30-selective ligand also promotes proliferation of eutopic endometrial stromal cells (45), supporting the important role of estrogen in the pathogenesis of endometriosis.

Aberrant expression of ERα, ERβ, and GPR30 have been reported in women with endometriosis. ERα downregulation and/or ERβ upregulation are found in endometriotic tissue, causing the higher ratio of ERβ/ERα (46-52) whereas GPR30 overexpresses in endometriotic tissues (53, 54). Although multiple lines of evidence demonstrate a higher ratio of ERβ/ERα in endometriotic tissues (46-52), the underlying mechanism of which still remains unclear. A study from Xue *et al*. showed hypermethylated ERα promoter and hypomethylated ERβ in endometriotic tissue, suggesting that epigenetic dysregulation such as DNA methylation is involved (51). However, another study found no difference in DNA methylation patterns in ERα and ERβ promoter regions between endometriotic and endometrial tissues (55). This discrepancy may result from the diversity of different population and methods for detecting methylation. Further investigations in DNA methylation are warranted to resolve this discrepancy. In contrast to the controversy of DNA methylation, hypoxia has been shown to regulate the expression of ERβ, ERα, and GPR30. Treatment of eutopic endometrial stromal cells with hypoxia induces ERβ but inhibits ERα expression leading to a marked increase in ERβ/ERα ratio. The suppressive effect on ERα and the induction of ERβ by hypoxia (1% oxygen) is regulated at the transcriptional level in a HIF-1α dependent manner (52). In addition to the regulation of ERs by hypoxia, GPR30 is also upregulated by hypoxia in a HIF-1α-dependent fashion, and mediates the anti-apoptotic effect of estrogen in hypoxia-induced apoptosis (56). The interplay between hypoxia and estrogen could be further complicated since estrogen induces nuclear accumulation of HIF-1α (Figure 3-(5)) and this effect can be repressed by an anti-estrogen antagonist (57). Taken together, the direct positive regulation of HIF-1α on ERβ expression and *vice versa* the estrogen on HIF-1α accumulation may favor the establishment of endometriotic lesions (Figure 3-(3)).

5. HYPOXIA FACILITATES THE LEPTIN SIGNALING IN THE PATHOGENESIS OF ENDOMETRIOSIS

Leptin is originally identified as an endocrine hormone, which is primarily secreted by adipocytes, acts on hypothalamus to regulate energy homeostasis. A growing body of evidence indicates leptin and its receptors widely expressed in various tissues such as stomach, muscle, placenta, ovary, and uterus and also act in paracrine and autocrine fashions (58-63). In addition to the regulatory roles in maintaining energy homeostasis, functions of leptin also involve in cell proliferation, angiogenesis, and immune response.

It has been demonstrated that level of leptin was elevated either in serum or peritoneal fluid from women with endometriosis (64, 65). Furthermore, leptin receptor was expressed in both endometriotic stromal and epithelial cells (66, 67), suggesting the paracrine and autocrine effects of leptin in endometriosis. Either in primary endometriotic lesion-derived cells or immortalized endometriotic cells, leptin stimulates both stromal and epithelial cells proliferation in an ERK/JNK dependent manner (66, 67). In a murine model, blocking the signaling of leptin by administration of leptin antagonist reduces levels of mitotic and angiogenic markers and causes less vascularized lesions, supporting that leptin and its receptor contribute to the pathogenesis of endometriosis by promoting cell proliferation and angiogenesis (68).

Although it has been shown that leptin itself is involved in a positive regulatory loop in which leptin stimulates leptin expression (66), the initiated signal stimulating leptin expression in endometriotic stromal cells was not revealed until recently. Two functional HREs were found in human leptin promoter and first intron (13). Promoter activity of leptin was abolished in the HRE-mutated reporter constructs, supporting the key role of hypoxia in leptin induction. Most importantly, normal endometrial stromal cells do not express leptin, which can be induced when culturing in hypoxic condition (1% oxygen). Hypoxia-mimetic treatment recapitulates elevated leptin expression in endometriotic stromal cells in a HIF-1α dependent fashion. Taken together, these findings demonstrate that aberrant expression of leptin in endometriotic lesions is induced by hypoxia (Figure 3-(1)).

6. HYPOXIA INDUCES NEO-VASCULARIZATION IN ECTOPIC ENDOMETRIOTIC TISSUES

One of the greatest challenges to the retrograde endometrial tissues in peritoneal cavity is to establish an available vessel network for exchanges of oxygen, nutrients, and metabolites. To overcome this constrain of limited oxygen level, the cells have to acquire the ability to recruit and to modulate the assembly of endothelial cells, smooth muscle cells into pre-existing vessels, namely angiogenesis.

Hypoxia has been known as a master regulator of angiogenesis. In normal endometrium, hypoxia treatment induces expressions of several VEGF isoforms in both epithelial and stromal cells (69), suggesting that hypoxia and VEGF may also modulate angiogenesis in endometriosis. In support with this notion, levels of VEGF in the peritoneal fluids collected from women with endometriosis are actually higher than those in control group (70, 71). A more recent study demonstrates that suppression of HIF-1α-downstream VEGF expression and therefore blockade of angiogenesis reduces the size of endometriotic lesions in a mouse model (14). Of note, the estrogen-induced VEGF expression is also facilitated by HIF-1α (Figure 3-(4)). Although *VEGF* promoter has no consensus estrogen response element, estrogen triggers PI3K/Akt-dependent pathway to stabilize HIF-1α (Figure 3-(5)). Both HIF-1α and ERα are recruited to VEGF promoter upon estrogen treatment and further induce VEGF expression (72, 73).

In addition to VEGF, other hypoxia-induced angiogenic factors are also implicated in the development of endometriosis. First of all, the abovementioned leptin is a potent angiogenic factor (74-76). In a murine model, blockage of leptin signaling either by treatment of leptin antagonist or by implantation of endometrial tissues derived from leptin receptor knockout mice results in reduced vascular lesions and less VEGF expression. Of note, although blockage of leptin signaling causes lower VEGF expression, the restoration of VEGF level by intraperitoneal injection does not rescue the development of vascular lesions, indicating that individual angiogenic factors may have distinct and non-dispensable roles in the process of vascular remodeling (68).

Secondly, a group of angiogenic factors, including cysteine-rich protein 61 gene (CYR61) and osteopontin, were identified to be upregulated by hypoxia (15, 77). CYR61, belonging to CCN protein family, was originally found to express at sites where neovascularization occurs and a ligand to $\alpha_v\beta_3$ integrin, which is involved in angiogenesis (78, 79). Later studies demonstrate that CYR61 promotes neovascularization in the model of rat cornea (80) and cyr61-deficiency in mice is embryonic lethal due to severe vascular defects during placental development (81). CYR61 is aberrantly expressed in endometriotic tissues (15, 82, 83), indicating its potential angiogenic roles in the pathogenesis of endometriosis. Elevated CYR61 expression

is recapitulated by hypoxia treatment in eutopic stromal cells via a HIF-1/2α-dependent DUSP2 downregulation-mediated mechanism (15). Similar to CYR61, osteopontin is another potent angiogenic factor that has been shown in both *in vitro* and *in vivo* models (84, 85). Higher osteopontin level is found in women with endometriosis (86) and this elevated expression of osteopontin is induced by hypoxia in a HIF-dependent manner (15) (Figure 3-(1)). Taken together, the microenvironmental hypoxia triggers multiple distinct but yet compensatory pathways to ensure the proper development of vessel networks at the sites where endometrial tissues reside.

7. INTERACTION BETWEEN HYPOXIA AND PGS

Both hypoxia and PGs play crucial roles in the normal endometrium physiology. Endometrium, the believed origin of endometriotic tissue, exhibits many of the classic hallmarks of inflammation upon menstruation. One of the most important hallmarks is to produce substantial proinflammatory cytokines, such as PGs. It was demonstrated that withdrawal of ovarian steroids induces COX-2 expression and subsequently increases production of PGs including PGE_2 and $PGF_{2\alpha}$ in human endometrial stromal cells (87). An episode of $PGF_{2\alpha}$-mediated transient hypoxia is then induced by vasoconstriction when $PGF_{2\alpha}$ acts on spiral arterioles of endometrium. In parallel to $PGF_{2\alpha}$, PGE_2 stabilizes HIF-1α via the E-series prostanoid receptor 2 (EP2) pathway in a model of endometrial epithelial cells (11). Together both hypoxia and PGs ($PGF_{2\alpha}$ and PGE_2 particularly) induce factors mediating cyclic repair of endometrium such as VEGF, IL-8, and CYR61 (88-90).

As the capacity in response to hypoxia and producing PGs in endometrium, retrograded endometrial tissues inherit these traits. In a similar but distinct scenario, retrograded endometrial tissues are facilitated to develop to endometriotic lesion by reciprocal interaction between hypoxia and dysregulated immune response. Both elevated levels of $PGF_{2\alpha}$ and PGE_2 have been found in peritoneal fluid from women with endometriosis (23, 91). Intriguingly, overexpression or elevated activity of phospholipase(s) and terminal PG synthase(s) is found in endometriotic lesions and macrophages (20-22, 92) (Figure 2, right panel). In a mouse implantation model, both endometrial fragments from microsomal PGE synthase-1 knockout (mPGES-1-KO) donor to wild type recipient and endometrial fragment from wild type

donor to mPGES-1-KO recipient show reduced size of endometriotic lesion compared to wild type to wild type transplantation (93), supporting the idea that terminal PG synthase is crucial to the development of endometriosis. Regarding the regulation of PLA_2 and PGES, several lines of evidence have indicated that hypoxia is a key inducer (94-97) and thus it is reasonable to rationalize that hypoxic environment causes the elevated levels of PGs in peritoneal cavity (Figure 2, right panel).

More intriguingly, hypoxia and PGs act independently or collectively in modulating the development of endometriosis. Overexpression of pro-angiogenic factor CYR61 in eutopic endometria and ectopic endometriotic lesions of women with endometriosis is regulated by both hypoxia and PGs (82, 83, 89) (Figure 3-(1) and (2)). There are also studies in models other than endometriosis indicating that PGs stabilize or activate HIF-1α. In a study of colorectal cancer, elevated PGE_2 enhances HIF-1α transcriptional activity through a MAPK-dependent pathway, which ultimately induces VEGF production and promotes colorectal tumor cell survival and angiogenesis (98). Similar to PGE_2, $PGF_{2\alpha}$ is also capable to activate HIF-1α under normoxic condition in a model of adipogenesis (99). Therefore, hypoxia and PGs alone or in synergy dysregulated gene expression that plays important roles in the development and persistence of endometriotic lesions.

8. CLOSING REMARKS

In the last decades, more and more biochemical, cellular and molecular differences between eutopic endometrial and ectopic endometriotic tissues have been discovered. It is no doubt that hypoxic stress is one of the most critical driving forces behind these differences. Hypoxic stress leads to the aberrant expression of COX-2 and thus PGs over-production, which causes a positive feedback loop of COX-2 expression and HIF-1α stabilization. Hypoxia also promotes cell proliferation through modulation of ER expression, leptin signaling, and indirectly the PGE_2 pathway. Last but not the least; hypoxia induces angiogenic factors such as VEGF, leptin, CYR61, and osteopontin to facilitate the establishment of valid vessel networks. These hypoxia-regulated gene networks regulate key pathological processes of endometriosis. Unraveling the mechanisms of gene-gene and gene-environment interactions may provide valuable information to design selective inhibitors against these novel targets downstream of

hypoxia as effective therapeutic regimens to prevent or control the development of endometriosis.

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Send correspondence to: Shaw-Jenq Tsai, Department of Physiology, College of Medicine, National Cheng Kung University, 1 University Road, Tainan 70101, Taiwan, Tel: 886-6-2353535, Fax: 886-6-2362780, E-mail: seantsai@mail.ncku.edu.tw