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MINI REVIEW

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Epigenetic regulation of the pathological process in endometriosis

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Abstract

Background: Endometriosis is one of the most common gynecological diseases that greatly compromises the quality of life in affected individuals. A growing body of evidence shows that the remodeling of retrograde endometrial tissues to the ectopic endometriotic lesions involves multiple epigenetic alterations, such as DNA methylation, histone modification, and microRNA expression.

Methods: This article retrospectively reviewed the studies that were related to the epigenetic regulatory factors that contribute to the development and maintenance of endometriosis. A literature search was performed in order to collect scientific articles that were written in English by using the key words of "endometriosis," "epigenetics," "DNA methylation," "histone modification," and "microRNA."

Results: Epigenetic modifications, including DNA methylation, histone modification, and microRNA expression, are involved in the pathogenesis of endometriosis. These epigenetic players are regulated or tuned by microenvironmental cues, such as locally produced estradiol, proinflammatory cytokines, and hypoxic stress, and reciprocally regulate the process or response to those stimuli.

Conclusion: Understanding the molecular mechanisms that underlie these epigenetic regulatory processes would shed light on the etiology and/or progression of endometriosis and facilitate the development of novel therapeutic strategies.

KEYWORDS

DNA methylation, endometriosis, epigenetics, histone modification, microRNA

1 | INTRODUCTION

Endometriosis, defined as the presence of endometrial glandular and stromal tissues, is one of the most common gynecological diseases, with a 10%-15% prevalence rate in women of reproductive age. The combination of retrograded menses and the immunosuppression hypothesis is the most accepted theory of the pathogenesis of endometriosis. Although the ectopic lesions were established from eutopic tissues, mounting evidence indicated that the characteristics of each are very distinct, suggesting that epigenetic regulation could be involved in the alteration of these phenotypes.

Epigenetic mechanisms have been recognized as important players in the development of a broad range of human diseases, including cancerous, neurologic, endocrine, and immune diseases. The alteration of chromatin conformation constitutes the basis of epigenetic regulation because the pattern of gene expression changes without changing the genomic sequence. Chromatin conformation can be altered by DNA methylation and post-translational modifications of histones. The change of chromatin conformation alters the accessibility of DNA to its modulator, which can be either a transcription activator or repressor, and thus the subsequent outcome of an open chromatin would be highly context-dependent. In this mini-review, the roles or implications

of different epigenetic elements, including DNA methylation, histone modification, and microRNA (miRNA) expression, will be discussed.

2 | ALTERATION OF DNA METHYLATION IN ENDOMETRIOSIS

It has been known that the alteration of DNA methylation plays an important role and has great impacts on the chromatin remodeling and transcription networks. The major form of DNA methylation in mammalian cells is 5-methyl cytosine, which is catalyzed by a group of DNA methyltransferases (DNMTs), consisting of DNMT1, DNMT3a, and DNMT3b. DNA methyltransferase1 takes hemi-methylated DNA as a substrate, which is responsible for cell cycle-coupled DNA methylation that transmits the epigenetic marks from passage to passage. In contrast, DNMT3a and 3b are de novo methyltransferases that use unmethylated DNA as a substrate. Although both hypomethylated and hypermethylated DNA for specific genes have been reported in endometriotic epithelial and stromal cells (see below for details), the authors' recent study revealed that the genome of endometriotic stromal cells is globally hypomethylated due to the downregulation of DNMT1.[1]

It has been comprehensively discussed that DNA methylation plays an important role during the pathogenesis of endometriosis.[2] Thus, in this review, the focus is on how it might be regulated and interact with other epigenetic elements. Hypoxia and inflammation, two critical driving forces for the development of endometriosis,[3,4] modulate the expression of DNMTs distinctly and can act together to cause aberrant DNA methylation patterns[1,5,6] (Figure 1). Two recent reports found that global methylation decreases in ectopic stromal cells,[1,6] which is mainly caused by hypoxia-mediated DNMT1 downregulation (Figure 1, left). In contrast to the suppressive effect of hypoxia on DNMT1, a blockage of the prostaglandin E_2 (PGE_2) pathway has no effect on the level of DNMT1 but suppresses DNMT3a expression[5] (Figure 1, right), implying that the level of DNMT3a might be maintained or stimulated by an inflammation pathway.

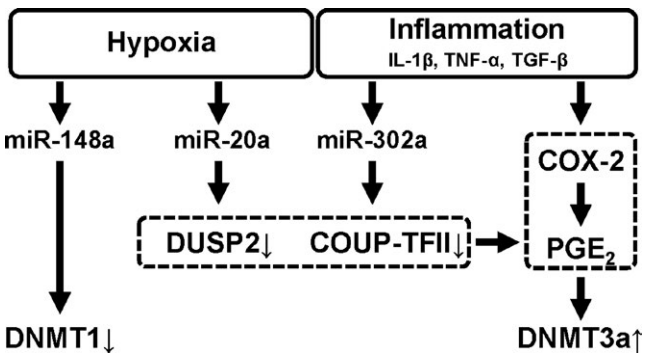

FIGURE 1 Hypoxia and inflammation regulate DNA methylation through microRNAs (miRs). These two major microenvironmental cues promote epigenetic remodeling. Hypoxia causes global hypomethylation through miR-148a-mediated DNA methyltransferase (DNMT)1 downregulation (left). Inflammatory stimulation induces DNMT3a expression and loci-specific hypermethylation (right). Hypoxia-induced miR-20a and inflammatory cytokine-induced miR-302a suppress dual specificity phosphatase (DUSP)2 and chicken ovalbumin upstream promoter (COUP)-transcription factor (TF)II, respectively, to potentiate an inflammatory response and to contribute to the modulation of DNA methylation. COX, cyclo-oxygenase; E_2, estradiol; IL, interleukin; PGE_2, prostaglandin E_2; TGF, transforming growth factor; TNF, tumor necrosis factor

The development and maintenance of endometriosis highly depend on the estrogen pathway. The expression of steroidogenic acute regulatory protein (StAR) and aromatase (CYP19), two proteins that control the key steps of 17β-estradiol biosynthesis, was shown to be elevated in the ectopic tissues and isolated primary stromal cells.[7,8] During the last two decades, studies have shown that hypoxia and inflammation play a central role in the regulation of this steroidogenic pathway during the development of endometriosis (Figure 2). It has been shown that *StAR* and *CYP19* harbor less methylated caffeoyl phenylethanoid glycoside islands in their promoter and/or intronic regions,[9-11] contributing to their aberrant expression in ectopic lesions. In addition, the promoter and/or intronic regions of several aberrantly expressed nuclear receptors that mediate the effect of steroid hormones or modulate the steroidogenic activity, such as estrogen receptor (ER)β[12] and steroidogenic factor (SF)-1,[13,14] also were hypomethylated, highlighting the central role of epigenetic dysregulation on the pathway of steroid hormones. In contrast, the inactivation of 17β-estradiol also is regulated by DNA methylation. The gene body of 17β-hydroxysteroid dehydrogenase type II, the enzyme that converts 17β-estradiol to the less potent form, estrone, is hypermethylated and is inactivated in ectopic stromal cells (Figure 2).[15] Not only so, even the promoter of progesterone receptor isoform B, a functional nuclear receptor that induces 17β-hydroxysteroid dehydrogenase type II expression, is also hypermethylated in endometriotic cells,[16] a phenomenon that is probably mediated by tumor necrosis factor (TNF) α.[17] As a result, the conversion of the potent 17β-estradiol to the less potent estrone is suppressed. These data indicate that DNA methylation is coordinately regulated to facilitate the production or to enhance the activity of 17β-estradiol in endometriosis.

In parallel to 17β-estradiol biosynthesis, PGE_2 production that is mediated by the elevated expression of cyclo-oxygenase (COX)-2 also plays critical roles in the development of endometriosis.[18] It has been reported that the promoter of COX-2 is hypomethylated[9] and contributes to aberrant COX-2 induction in ectopic stromal cells, which in turn enhances the positive feedback to PGE_2-mediated 17β-estradiol production[19] and DNMT3a elevation.

3 | ALTERATION OF THE HISTONE CODE IN ENDOMETRIOSIS

3.1 | Histone acetylation

Histones, the key components of the nucleosome, pack the lengthy genomic DNA molecules into compact forms in the nuclei. The core histones share a conserved tripartic structure, consisting of the amino-terminal tail, a globular domain, and a carboxyl-terminal tail.

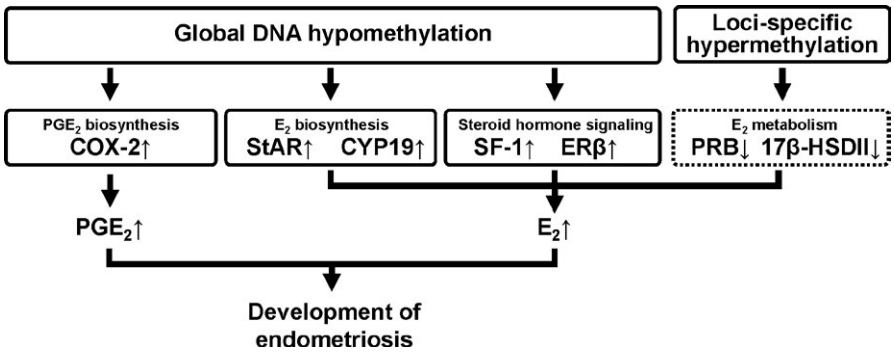

FIGURE 2 DNA methylation contributes to inflammation and the acquisition of steroidogenic capacity and enhances estradiol (E_2) signaling. Global DNA hypomethylation contributes to the upregulation of the genes that are involved in prostaglandin E_2 (PGE_2) biosynthesis and E_2 biosynthesis and signaling, while loci-specific hypermethylation suppresses the genes that are related to E_2 inactivation. COX, cyclo-oxygenase; CYP, cytochrome P450; ER, estrogen receptor; HSD, hydroxysteroid dehydrogenase; PRB, progesterone receptor isoform B; SF, steroidogenic factor; StAR, steroidogenic acute regulatory protein

The majority of post-translational modification takes place on the amino-terminal tail of histones extruding from the nucleosome, which regulates various molecular processes, such as chromatin remodeling, transcription, splicing, and DNA damage.

Histone acetylation, one of the earliest discovered modifications, promotes transcriptional activation through the disruption of electric charges between the DNA and histone tail and/or acetyl-lysine reading proteins. Two categories of proteins, histone acetyltransferases and histone deacetylases (HDACs), counteract each other to modulate the levels of histone acetylation. It has been reported that the levels of HDAC1 and/or HDAC2, two of the most abundant HDACs in human cells, were deregulated in endometriotic stromal cells. While one study reported that both HDAC1 and HDAC2 were upregulated in endometriotic stromal cells,[20] two other studies reported the upregulation of HDAC1 and HDAC2.[21,22] Nevertheless, the expression of HDAC1 and HDAC2 were induced by the steroid hormones, 17β-estradiol and progesterone,[20] a notion that is consistent with the central role of steroid hormones in the development of endometriosis (Figure 3). Accompanying the aberrant expression of HDACs, the global levels of histone H3 and H4 acetylation decreased in the endometriotic stromal cells.[21,23] Of special note, while both of these studies found decreased levels of histone H3 acetylation, one reported no difference in histone H4 acetylation. This discrepancy could partly result from the distinct antibodies that are used for detecting acetylation sites (not specified in all studies). In addition, it has been known that the application of antibodies to explore the combinational modifications of histone is constrained by the nature of multiple adjacent modifications,[24,25] which can vary the results from laboratory to laboratory. Intriguingly, although inactive genes (e.g. *ERα*, *CCAAT-enhancer-binding protein* [*C/EBP*]α, *CDH1*, *p21*, and *homeobox A10*) in ectopic endometriotic lesions have lower levels of histone H3 and/or H4 acetylation in their promoters, aberrantly expressed genes (eg, *SF-1*) have a high level of histone acetylation in their promoters,[23,26] suggesting that the level or distribution of acetylation is not solely regulated by HDACs, but also by other acetyltransferases in a gene-specific manner. For example, the histone acetyltransferases, such as steroid receptor coactivator-1, p300, and cyclic adenosine monophosphate response element binding protein, have been reported to regulate the function of the estrogen receptor, PGE_2-induced 17β-estradiol synthesis, and the development of endometriotic lesions (Figure 3).[19,27,28]

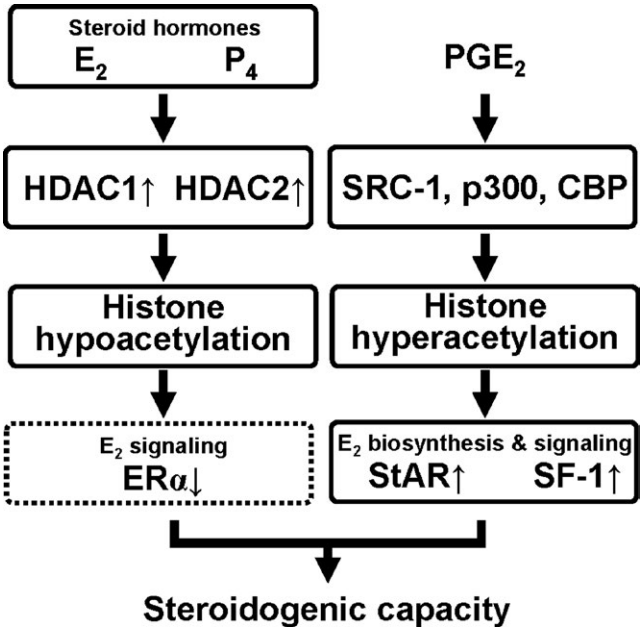

FIGURE 3 Histone acetylation contributes to an acquired steroidogenic capacity. Estradiol (E_2) and progesterone (P_4) together induce the expression of histone deacetylase (HDAC)1 and HDAC2, which further cause the downregulation of estrogen receptor (ER) α. Histone acetyltransferases, such as steroid receptor coactivator (SRC)-1, p300, and cyclic adenosine monophosphate response element binding protein (CBP), are required for the actively expressed genes, steroidogenic factor (SF)-1 and steroidogenic acute regulatory protein (StAR) in endometriotic cells. PGE_2, prostaglandin E_2

3.2 | Histone deacetylase inhibitor for endometriosis treatment

The critical role of histone acetylation in the transactivation of key genes in endometriosis makes it an attractive therapeutic target.

Treatment with HDAC inhibitors in vitro (immortalized human endometrial stromal and epithelial cells) and in vivo (rat model of endometriosis) caused cell cycle arrest, apoptosis, and thus reduced the lesion size in vivo.[29,30] Other works that focused on the reactivation of the genes that suppress the development of endometriosis, such as *C/EBPα* and *death receptor 6*, also are reported.[26,31] Of particular note, although modulating histone acetylation might ameliorate endometriosis, one should bear in mind that other molecular events also are controlled by the means of acetylation. For example, the application of HDAC inhibitors to cause histone hyperacetylation inhibits the mitosis and DNA damage responses.[32-35] Thus, how to maximize the therapeutic impact and minimize cytotoxicity should be thoroughly investigated before HDAC inhibitors can be used to treat endometriosis.

4 | DYSREGULATION OF MICRORNA EXPRESSION IN ENDOMETRIOSIS

MicroRNAs belong to a group of single-stranded, non-coding RNAs with an average size of 22 nucleotides. They play important regulatory roles in gene expression through pairing with messengerRNA (mRNA) to modulate RNA splicing, degradation, and translation.[36] The genome-wide analysis of the miRNA expression profile demonstrated that dysregulated miRNAs play critical roles during the development of endometriosis through modulating the cell cycle progression, apoptosis, steroidogenic pathway, hormone signaling, inflammation, and response to hypoxia.[37,38] MicroRNAs that target the mediators of inflammation (COX-2, interleukin [IL]-6, and IL-6 receptors), inducer of apoptosis (B-cell lymphoma-2), cycle regulator (cyclin D1), and angiogenic factors (vascular endothelial growth factor, IL-8) are typically downregulated in the endometrium and/or endometriotic tissues of women with endometriosis, supporting the multifaceted role of miRNAs during the pathogenesis of endometriosis.

4.1 | MicroRNAs regulate the steroidogenic pathway

It has been reported that miRNAs modulate the signaling pathway of steroid hormones, which plays a central role in the pathogenesis of endometriosis. The expression levels of miR-23a and miR-23b are aberrantly suppressed in the endometrium of women with endometriosis, compared to those of women without endometriosis. Furthermore, the levels of miR-23a and b are much lower in the ectopic endometriotic lesions.[39] Typically, a high level of miR-23a and b in the normal endometrium inhibits the expression of SF-1 and thus keeps the normal endometrium in low steroidogenic activity. However, in the endometrium of women with endometriosis, the suppressed level of miR-23a and b allows for the elevated expression of SF-1 and further promotes the expression of StAR and CYP19, suggesting that miR-23a and b play an important role in the acquisition of the steroidogenic capacity of the endometriotic tissues (Figure 4). Although a hypomethylated promoter was reported for SF-1 in endometriosis, a hypermethylated promoter of miR-23a and b was one of the mechanisms responsible for its downregulation in gynecological cancers.[40]

4.2 | MicroRNA-mediated hyperactivated inflammatory responses

In addition to the steroidogenic pathway, miRNAs also modulate inflammation. The effect of PGE_2 was prolonged by hypoxia-induced miR-20a that targets dual specificity phosphatase (DUSP)2, which is a repressor of extracellular signal-regulated kinase (ERK)-1 and -2 signaling downstream of PGE_2. The miR-20a-mediated hypoxia-inhibited DUSP2 prolongs the phosphorylation of ERK-1 and -2, which further augments the PGE_2 signaling and thus potentiates PGE_2-induced gene expression[41] (Figures 1 and 4). In contrast, the biosynthesis of PGE_2 also is stimulated through a miRNA-mediated positive feedback loop.[42] Chicken ovalbumin upstream promoter (COUP)-transcription factor (TF)II, which binds the COX-2 promoter region and elevates the expression of COX-2 in the eutopic endometrium, is suppressed by inflammatory stimuli from the peritoneal fluid. Treatment with IL-1β, TNFα, or transforming growth factor β suppresses the expression of COUP-TFII through miR-302a binding to its 3′-untranslated region (UTR). In a similar manner to DUSP2, the downregulated repressive transcription factor, COUP-TFII, augments the inflammatory cytokine-induced COX-2 expression, which forms a positive feedback loop for the inflammatory stimulation (Figures 1 and 4).

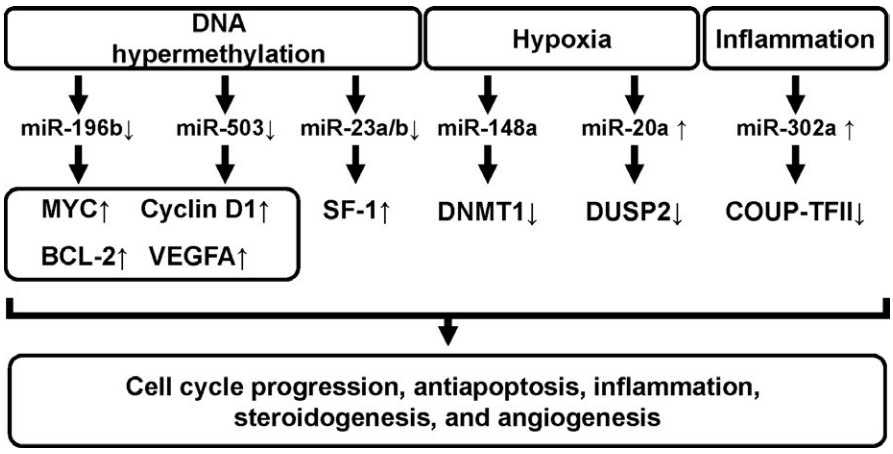

FIGURE 4 MicroRNAs (miRs) that are involved in the development of endometriosis. DNA hypermethylation-suppressed miRNAs and hypoxia- and inflammation-induced miRNAs work coordinately to regulate multiple cellular processes and to promote the development of endometriosis. Bcl, B-cell lymphoma; COUP, chicken ovalbumin upstream promoter; DNMT, DNA methyltransferase; DUSP, dual specificity phosphatase; SF, steroidogenic factor; TF, transcription factor; VEGFA, vascular endothelial growth factor A

4.3 | MicroRNA-mediated hypoxic response

As mentioned previously, the global DNA hypomethylation in the ectopic tissues is triggered by microenvironmental hypoxic stress.[1] MicroRNA-148a, the key player mediating this global passive demethylation, is aberrantly elevated in the ectopic stromal cells. The administration of exogenous oligo-mimicking miR-148a suppresses the expression of DNMT1, while treatment with the miRNA inhibitor to miR-148a rescues the hypoxia-inhibited DNMT1 expression. Under hypoxia, miR-148a and argonaute 2, an essential component of the RNA-induced silencing complex, coordinate with adenylate–uridylate-rich element RNA-binding protein 1 to bind to 3′-UTR of DNMT1 to cause the degradation of its mRNA. The decreased DNMT1 level in the endometriotic stromal cells causes the passive demethylation of numerous genes through multiple cell cycle progression. The downregulated DNMT1 and global hypomethylation might further trigger the DNMT3a- and 3b-mediated locus-specific hypermethylation. Two recent studies reported that the locus-specific hypermethylation-mediated miR-196b and miR-503 suppression derepresses the genes that are related to the inhibition of cell proliferation, induction of apoptosis, and angiogenesis, thus promoting the pathogenesis of endometriosis.[38,43] These observations suggest the regulatory complexity and feasibility between epigenetics and small non-coding RNAs (Figure 4).

5 | CONCLUSION

It has been demonstrated that estrogen signaling, hypoxia, and inflammation are three interlinked driving forces in the development of endometriosis, while epigenetic components play a central role in coordinating these three factors. Through the understanding of epigenetic modulations in retrograde endometrial tissues, a more comprehensive picture about how ectopic lesions are transformed and remodeled to a distinct steroidogenic tissue could be shown. By dissecting the interactions among the microenvironmental factors (ie, hypoxia and inflammation) and epigenetic regulation (ie, DNA methylation, histone modification, and miRNA expression), it might be possible to develop novel remedies that target the epigenetic effectors for the better treatment of endometriosis.

DISCLOSURES

Conflict of interest: The authors declare no conflict of interest. *Human and Animal Rights*: This article does not contain any study with human or animal participants that has been performed by any of the authors.

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