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ESTROGEN AND PROGESTERONE GENE EXPRESSION IN ENDOMETRIOSIS

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Abstract

Endometriosis is a chronic, estrogen-dependent disorder marked by the presence of endometrial-like tissue outside the uterine cavity, which leads to symptoms such as pelvic pain and infertility. This review examines the role of hormonal regulation, particularly estrogen (E2) and progesterone (P4), in the disease's pathogenesis. The imbalance between E2 and P4 signaling is crucial, with elevated E2 levels promoting epithelial proliferation and P4 being vital for stromal decidualization. Disruptions in these hormonal pathways lead to P4 resistance and E2 dominance, which are key factors in endometriosis. The review focuses on genetic variations in hormone-related genes such as ESR1, ESR2, and PGR, and their effects on the disease. Significant alterations in gene expression have been observed, including upregulation of estrogen receptors and downregulation of progesterone receptors in endometriotic tissues. These changes suggest a dysregulated hormonal environment that drives disease progression by enhancing estrogen-driven growth and diminishing progesterone's anti-inflammatory effects. Identifying these mechanisms is essential for developing targeted hormonal therapies and improving treatment strategies.

Keywords: *Endometriosis, Estrogen, Progesterone, Hormonal Regulation, Gene Expression, ESR1, Progesterone Resistance*

Introduction

Endometriosis is a prevalent gynecological condition affecting approximately 10% of women of reproductive age. This disorder is characterized by the presence of endometrial-like tissue outside the uterine cavity, leading to chronic pelvic pain, infertility, and other debilitating symptoms [1]. Despite its high prevalence and significant impact on quality of life, the underlying pathogenesis of endometriosis remains complex and not fully understood [2].

Central to the development of endometriosis is the dysregulation of hormonal signaling, particularly the interplay between estrogen (E2) and progesterone (P4). Estrogen plays a critical role in driving the proliferation of endometrial cells, a process that is normally counterbalanced by progesterone to maintain a stable endometrial environment [3]. However, in endometriosis, this hormonal balance is disrupted. Elevated levels of estrogen promote the growth and survival of ectopic endometrial tissue, while resistance to progesterone impairs its anti-inflammatory and growth-regulating effects. This disruption contributes significantly to the persistence and expansion of endometriotic lesions [3].

Moreover, genetic factors also play a critical role in endometriosis. Variations in hormone-related genes, such as ESR1 (estrogen receptor alpha), ESR2 (estrogen receptor beta), and PGR

(progesterone receptor), have been associated with the disease's susceptibility and progression [1]. Alterations in the expression of these receptors in endometriotic tissues compared to normal endometrial tissues underscore the significance of hormonal dysregulation in the disease's pathophysiology [4]. This review aims to elucidate the intricate relationship between estrogen and progesterone gene expression and endometriosis. By synthesizing the latest research on hormonal signaling and genetic factors, this review seeks to enhance understanding of the disease and identify potential targets for more effective treatment strategies.

Role of Estrogen and Progesterone

Estrogen and progesterone are critical hormones in the regulation of the menstrual cycle and reproductive physiology. Estrogen primarily promotes the proliferation and growth of the endometrial lining during the follicular phase of the menstrual cycle, while progesterone, which surges during the luteal phase, stabilizes the endometrial lining and prepares it for possible implantation [1]. This hormonal interplay is essential for a normal menstrual cycle and reproductive health.

In endometriosis, the hormonal balance was disrupted. Estrogen, through its receptors (ERα and ERβ), drove the proliferation of endometrial-like lesions. High levels of estrogen or increased activity of estrogen receptors led to excessive growth of endometriotic tissue, which contributed to the chronic inflammation and pain associated with the disease. Giudice highlighted that estrogen-induced changes in the expression of growth factors, cytokines, and matrix metalloproteinases (MMPs) further exacerbated the pathological environment in endometriosis [5].

Progesterone normally acted to counterbalance estrogen's effects by inducing differentiation and apoptosis in the endometrial lining. However, Bulun et al. reported that, in endometriosis, there was often reduced responsiveness to progesterone, which was thought to result from altered expression or function of progesterone receptors (PR-A and PR-B) within endometriotic lesions [6]. This progesterone resistance prevented the normal regulation of endometrial growth and contributed to the persistence of endometriotic lesions.

The implications of altered gene expression of estrogen and progesterone receptors in endometriosis were significant for the disease's pathophysiology. Burney et al., noted that these hormonal imbalances were central to the progression of endometriosis and also impacted the effectiveness of various treatments. For instance, treatments that modulated estrogen or progesterone activity, such as hormonal contraceptives, progestins, and aromatase inhibitors, were commonly used to manage symptoms. However, their success was often limited by the underlying hormonal dysregulation in endometriosis [7].

Methods

Literature Search Strategy

A comprehensive literature search was conducted to identify relevant studies on estrogen and progesterone gene expression in endometriosis. The search utilized multiple databases, including PubMed, Google Scholar, and Scopus. The search terms included "estrogen gene expression in endometriosis," "progesterone gene expression in endometriosis," "hormonal regulation in endometriosis," and "endometriosis pathophysiology." Studies published up to 2024 were included in the search. A total of 46,500 articles were initially retrieved. After applying inclusion and exclusion criteria, 100 articles were selected for review.

Inclusion and Exclusion Criteria

Inclusion Criteria:

- Peer-reviewed articles
- Clinical studies and experimental research
- Focus on gene expression related to estrogen and progesterone in endometriosis
- Studies that offer insights into the hormonal regulation and molecular mechanisms of endometriosis

Exclusion Criteria:

- Articles published in languages other than English
- Studies not directly addressing gene expression or hormonal regulation
- Review articles, editorials, and opinion pieces

Data Extraction

Data were systematically extracted from the selected studies to ensure a comprehensive analysis. This process involved reviewing the study design, including type and methodology, and noting sample characteristics such as size, demographics, and clinical details relevant to endometriosis. Key findings were summarized, emphasizing the effects of estrogen and progesterone gene expression on endometriosis, variations across studies, and implications for treatment and disease understanding.

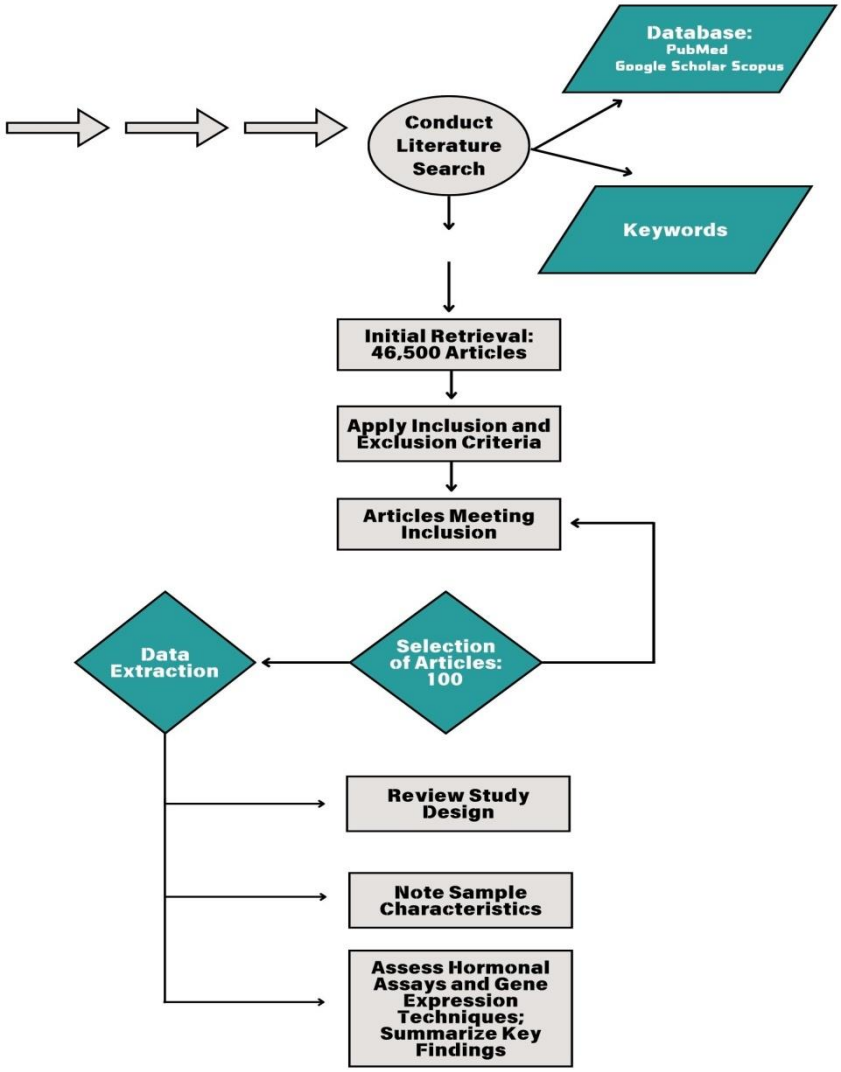

Fig.1: Data Extraction Process for Estrogen and Progesterone Gene Expression in Endometriosis

Estrogen Gene Expression in Endometriosis

Estrogen plays a critical role in the growth, survival, and invasiveness of ectopic endometrial cells, primarily through two nuclear receptors: estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ). The differential expression and function of these receptors in endometriotic tissues significantly contribute to the progression and severity of the disease [8].

Trukhacheva et al., describe estrogen receptors (ERs) as intracellular proteins that mediate the effects of estrogen through the regulation of gene expression. According to their research, there are two main types of ERs, ERα and ERβ, which are encoded by different genes. Despite their structural similarities, these receptors exhibit distinct tissue distributions and functions [9]. Heldring et al., detail the structural composition of ERα, which includes several functional domains, each with a specific role. The A/B domain is responsible for the transcription activation function (AF-1), modulating gene expression independently of ligand binding. The C domain, or DNA-binding domain (DBD), is critical for recognizing and binding to estrogen response elements (EREs) in

DNA. The D domain functions as a hinge region, providing structural flexibility and containing nuclear localization signals. Lastly, the E/F domain encompasses the ligand-binding domain (LBD) and the AF-2 region, both essential for ligand-dependent transcriptional activity and receptor dimerization [10].

Structurally similar to ERα, ERβ shares approximately 60% homology in the LBD and 95% homology in the DBD with ERα. However, differences in the AF-1 region lead to distinct gene regulatory profiles and tissue-specific functions, making ERβ's role unique in certain tissues. These structural differences result in ERβ having a modulatory role in estrogen signaling, often counterbalancing the effects of ERα in various physiological and pathological processes, including endometriosis [11].

1.1 Distribution and Function of ERα and ERβ in Endometriosis

The roles of ERα and ERβ in endometriosis are shaped by their distinct expression patterns in both normal and ectopic endometrial tissues [9]. Understanding the balance between these receptors is crucial, as it largely dictates the biological outcomes of estrogen signaling, which in turn influences both the progression and clinical manifestations of endometriosis.

ERα in Normal Endometrial Tissue

In healthy endometrial tissue, estrogen receptor alpha (ERα) is highly expressed and serves as a primary mediator of estrogen-driven processes during the menstrual cycle. ERα is responsible for facilitating the growth, proliferation, and regeneration of the endometrial lining, preparing it for the possibility of embryo implantation [12]. During the proliferative phase of the menstrual cycle, estrogen levels rise, leading to increased ERα activation. This triggers a cascade of signaling events that promote cell division, vascularization, and other processes necessary for a receptive and functional endometrium [13]. ERα-driven signaling is essential for ensuring that the endometrium can dynamically adapt to fluctuating estrogen levels, enabling the cyclical thickening and shedding associated with normal menstrual cycles. The proper regulation of ERα activity is vital, as any disruption can lead to conditions like endometrial hyperplasia, where excessive proliferation occurs, or infertility, where the endometrium fails to develop adequately [12].

ERβ in Normal Endometrial Tissue

Estrogen receptor beta (ERβ), in contrast, is expressed at significantly lower levels in normal endometrial tissue and plays a more modulatory role. While ERα drives cell proliferation, ERβ acts as a counterbalance, promoting cellular differentiation and tempering excessive growth. This

receptor's function is integral to maintaining the delicate equilibrium required for optimal endometrial health [11]. By modulating the proliferative effects of ERα, ERβ helps prevent abnormal cellular growth, thereby reducing the risk of hyperplasia and other related pathologies. ERβ's protective role is further underscored by its ability to inhibit pro-inflammatory pathways and reduce the expression of growth factors and cytokines that could otherwise lead to unchecked tissue expansion [9]. This fine-tuned interplay between ERα and ERβ ensures that the endometrium remains functional and responsive without tipping toward pathological states [10].

ERα and ERβ in Endometriotic Lesions

In the context of endometriosis, the expression patterns of ERα and ERβ become dysregulated, driving the development and persistence of the disease. Endometriotic lesions are characterized by a marked overexpression of ERα, leading to an exaggerated sensitivity to estrogen. This heightened ERα activity fuels the abnormal proliferation and invasiveness of ectopic endometrial tissue, allowing it to survive and thrive in environments outside the uterus, such as the ovaries, fallopian tubes, or pelvic lining [9]. The overactivation of ERα also exacerbates inflammatory responses, which are closely linked to the pain and discomfort experienced by many individuals with endometriosis. The increased ERα signaling in these lesions creates a positive feedback loop, where estrogen continuously promotes the expansion and maintenance of endometriotic tissue, thereby worsening the disease's progression [14].

On the other hand, ERβ is often expressed at higher levels in certain endometriotic lesions compared to normal endometrial tissue. The elevated presence of ERβ could theoretically serve as a compensatory mechanism, attempting to counteract the excessive ERα-driven proliferation. ERβ's role in inhibiting inflammation and promoting cellular differentiation suggests that it might help mitigate some of the aggressive characteristics of endometriosis [15]. However, in many cases, the compensatory effect of ERβ is insufficient to restore balance. The overall expression and functional dominance of ERα overshadow ERβ's modulatory effects, leading to a net increase in estrogen-driven proliferation, survival, and invasiveness of endometriotic cells. This imbalance between ERα and ERβ is a key factor in the persistence and exacerbation of endometriosis, contributing to the chronic nature of the condition and its resistance to conventional treatments [9].

The differential expression and roles of ERα and ERβ in endometriosis have significant implications for both diagnosis and treatment. Given the overexpression of ERα in endometriotic lesions, targeting this receptor could be a viable therapeutic approach. Selective estrogen receptor modulators (SERMs) and aromatase inhibitors, which reduce local estrogen production, are being

explored as treatment options to mitigate the disease's progression. Additionally, therapies aimed at enhancing ERβ's protective effects or restoring the balance between ERα and ERβ may offer new avenues for managing endometriosis. Understanding the molecular mechanisms underlying the dysregulation of these receptors could lead to more effective, targeted treatments that address the root causes of the condition rather than just alleviating its symptoms [6].

1.2 Molecular Pathways Influenced by Estrogen in Endometriosis

Estrogen's impact on endometriosis extends far beyond its direct effects on the expression of estrogen receptors. It drives multiple molecular pathways that contribute significantly to the pathophysiology of the disease [6]. Estrogen, through its receptors, influences a wide range of cellular processes including cell proliferation, inflammation, angiogenesis, and tissue remodelling [12]. Han et al., emphasized that understanding the molecular pathways regulated by estrogen was crucial for elucidating how endometriotic lesions established, grew, and persisted. In this context, they identified three major pathways: the regulation of growth factors, modulation of cytokines and inflammatory markers, and the influence on matrix metalloproteinases (MMPs) [15]. Simoncini et al., further elucidated that the mechanisms by which estrogen affected these pathways were intricate and involved both genomic and non-genomic actions [16].

Genomic Mechanisms

Estrogen exerts its effects genomically by interacting with estrogen receptors (ERs), predominantly ERα and ERβ. The classical genomic pathway begins with estrogen binding to ERs in the cytoplasm, prompting receptor dimerization. The estrogen-receptor complex then translocates to the nucleus, where it binds to estrogen response elements (EREs) in the promoter regions of target genes. This interaction recruits coactivators and transcriptional machinery, leading to gene activation [10]. Bulun et al., demonstrated that estrogen upregulated genes like Bcl-2, an anti-apoptotic protein that prevented cell death, and VEGF (vascular endothelial growth factor), which was essential for angiogenesis. This pathway supported the growth and survival of endometriotic lesions by enhancing cellular proliferation and tissue vascularization [6]. Heldring et al., further explained that, in addition to the classical genomic pathway, estrogen influenced gene expression through non-classical genomic mechanisms. They found that ERs interacted with other transcription factors such as AP-1 and SP-1, extending estrogen's regulatory reach to genes lacking EREs in their promoters. This non-classical pathway allowed estrogen to impact a broader range of genes involved in endometriosis, including those related to cell invasion and tissue remodelling [10].

Non-Genomic Mechanisms

Estrogen's non-genomic effects involve rapid signaling through membrane-bound estrogen receptors [17]. Upon estrogen binding, these receptors activate second messengers like cyclic AMP (cAMP) and phosphatidylinositol-3-kinase (PI3K). The activation of downstream kinases such as Akt and extracellular signal-regulated kinases (ERK) then modulates cellular processes including proliferation, survival, and migration [18]. This rapid signaling contributes to the invasive characteristics of endometriotic cells by enhancing their ability to grow and spread within the pelvic cavity [17].

These non-genomic pathways complement estrogen's genomic actions by enabling quick cellular responses that support endometriotic lesion development [18]. By affecting key signaling pathways, estrogen enhances the ability of endometriotic cells to invade surrounding tissues and persist in the ectopic locations where they reside [17].

Regulation of Growth Factors

Estrogen significantly influences the progression of endometriosis by promoting the expression of growth factors such as vascular endothelial growth factor (VEGF) and insulin-like growth factor 1 (IGF-1) [19]. These factors are critical for angiogenesis and cellular proliferation within endometriotic tissues [20]. VEGF, in particular, is a key angiogenic factor that estrogen upregulates by binding to estrogen receptors, activating downstream signaling cascades that enhance VEGF transcription [21]. The resultant VEGF binds to its receptors on endothelial cells, promoting their proliferation and migration, thus forming new blood vessels. These newly formed vessels supply endometriotic tissues with nutrients and oxygen, facilitating their growth and persistence [20].

VEGF also increases vascular permeability, leading to the accumulation of inflammatory cells and fluid within the pelvic cavity [22]. This exacerbates the inflammatory environment typical of endometriosis, creating a self-sustaining cycle of growth and invasion supported by a rich blood supply [19]. Targeting VEGF and its receptors has emerged as a potential therapeutic approach. Anti-VEGF agents like bevacizumab aim to inhibit this pathway, potentially reducing lesion growth by cutting off their blood supply [23]. However, challenges such as balancing efficacy with side effects need to be addressed before these therapies can be widely applied [22].

Estrogen and Matrix Metalloproteinases (MMPs)

Estrogen also influences the expression of matrix metalloproteinases (MMPs), enzymes that degrade extracellular matrix (ECM) components. MMPs, including MMP-2 and MMP-9, are crucial for tissue remodeling and the invasive behavior of endometriotic cells [24]. Estrogen regulates MMP expression through genomic and non-genomic pathways [25]. Genomically, estrogen binds to ERs, activating transcription factors that enhance MMP gene expression. Non-genomically,

estrogen activates signaling pathways such as the mitogen-activated protein kinase (MAPK) pathway, leading to the post-translational activation of MMPs [17].

Increased MMP activity facilitates the breakdown of ECM, allowing endometriotic cells to invade surrounding tissues. This enhanced invasiveness contributes to the spread of endometriosis and the formation of lesions in various pelvic locations. MMPs also help establish niches conducive to endometriotic cell survival and proliferation, complicating the disease's management [24]. Therapeutic strategies targeting MMPs are under investigation. MMP inhibitors aim to reduce lesion invasiveness and slow disease progression. Despite their efficacy in preclinical models, challenges such as specificity and systemic side effects have limited their clinical application [25]. Ongoing research seeks to develop more selective MMP inhibitors to improve treatment outcomes for endometriosis.

Table 1: Gene Expression changes in Endometriosis

Gene	**Expression Change**	**Reference**
Estrogen Receptors (ESR1, ESR2)	Upregulated	[27]
Progesterone Receptor (PGR)	Downregulated	[28]
Matrix Metalloproteinases (MMPs)	Upregulated	[29]
Tissue Inhibitors of Metalloproteinases (TIMPs)	Downregulated	[30]
Cyclooxygenase-2 (COX-2)	Upregulated	[31]
Interleukin-6 (IL-6)	Upregulated	[32]
Transforming Growth Factor-β (TGF-β)	Upregulated	[23]
Vascular Endothelial Growth Factor (VEGF)	Upregulated	[33]
Nerve Growth Factor (NGF)	Upregulated	[34]
Cyclin D1	Upregulated	[35, 36]
Glycodelin	Downregulated	[37]

Progesterone Receptor Gene Expression in Endometriosis

Progesterone is crucial for regulating normal endometrial physiology, including tissue remodeling, decidualization, and maintaining immune homeostasis [38]. However, in endometriosis, the response to progesterone is notably impaired due to changes in progesterone receptor (PR) gene expression (Chen et al., 2020) [3]. The progesterone receptor (PR) is encoded by the PGR gene and exists in two main isoforms: PR-A and PR-B [39]. The balance between these isoforms is essential for normal endometrial function, but this balance is often disrupted in endometriosis [40].

In endometriotic lesions, studies have consistently found a significant downregulation of the PR-B isoform, which is critical for mediating progesterone's anti-inflammatory and anti-proliferative effects [41]. PR-B is considered the more active isoform for full transcriptional activity and normal tissue response to progesterone [42]. The reduced expression of PR-B impairs the receptor's ability to mediate the beneficial actions of progesterone, leading to a state of progesterone resistance [43]. This downregulation is one of the primary molecular features driving the persistence of endometriotic tissue [41]. For example, a study by Bulun et al., reported that PR-B expression is notably decreased in endometriotic tissue compared to healthy endometrium [6]. This reduction contributes to the diminished response to progesterone treatment commonly seen in endometriosis patients [3]. The decreased PR-B expression is often associated with epigenetic alterations such as hypermethylation of the PGR gene promoter, which silences PR-B transcription [44].

While PR-B expression is reduced, PR-A expression is often upregulated or maintained at similar levels in endometriotic lesions [41]. PR-A functions as a dominant-negative regulator of PR-B, meaning that when PR-A is overexpressed relative to PR-B, it inhibits the normal function of PR-B. This imbalance between the isoforms leads to a reduced sensitivity to progesterone and contributes to the pathogenesis of endometriosis [42]. A study by Attia et al., demonstrated that PR-A is predominantly expressed in endometriotic tissues, with an elevated PR-A ratio [45]. This altered ratio shifts the tissue's response from normal anti-inflammatory and anti-proliferative signaling toward a more pathological state, promoting lesion growth and invasion. The overexpression of PR-A hinders the normal regulatory functions of PR-B, compounding the effects of progesterone resistance [42].

The differential expression of PR-A and PR-B in endometriosis is largely attributed to epigenetic changes [3]. Methylation of the PGR gene promoter specifically affects the PR-B isoform, leading to its silencing [44]. These epigenetic modifications are more pronounced in endometriotic lesions compared to the normal endometrium, driving the observed imbalance in PR isoform expression [3]. In addition to promoter methylation, histone modifications and altered expression of microRNAs have been implicated in the regulation of PGR gene expression. These epigenetic changes further enhance PR-A expression while suppressing PR-B, reinforcing the progesterone-resistant phenotype of endometriotic tissue [41].

Table 2: Comparison of Progesterone Receptor Isoforms PRA and PRB

Feature	**PRA (Progesterone Receptor A)**	**PRB (Progesterone Receptor B)**
Source Gene	PGR gene	PGR gene
N-terminal Region	Different from PRB due to alternative promoter usage	Different from PRA due to alternative promoter usage
DNA-Binding Domain (DBD)	Central domain responsible for binding progesterone response elements	Central domain responsible for binding progesterone response elements
Ligand-Binding Domain (LBD)	Located in C-terminal region, binds progesterone	Located in C-terminal region, binds progesterone
Transactivation Domains	AF-1: Predominantly found in PRA, functions independently of ligand binding	AF-2: Essential for PRB activity, requires ligand binding
Function	Acts as a repressor of PRB activity, inhibits other steroid receptors	Mediates the full spectrum of progesterone effects, promotes normal endometrial differentiation and tissue remodeling
Transcriptional Activity	Largely independent of progesterone binding, dominant-negative regulator when overexpressed	Essential for anti-inflammatory and anti-proliferative responses, promotes tissue remodeling

Progesterone Resistance in Endometriosis: Molecular Mechanisms

Progesterone resistance is a defining feature of endometriosis and is closely linked to the altered expression and function of progesterone receptor (PR) isoforms [6]. Several mechanisms contribute to this resistance, leading to impaired progesterone signalling [41]. Epigenetic modifications, such as DNA methylation, play a crucial role in regulating PR expression [3]. In endometriosis, hypermethylation of the PGR gene promoter, particularly affecting PRB, results in its reduced expression [44]. This imbalance skews the PRA ratio, favoring PRA dominance [45]. Since PRA functions as a repressor of PRB, this shift exacerbates progesterone resistance, impairing the normal anti-proliferative and differentiative actions of progesterone [42].

The transcriptional activity of PRB requires interaction with co-activators, such as steroid receptor co-activators (SRCs), to regulate gene expression [43]. In endometriosis, these interactions are disrupted, leading to diminished PRB activity. Elevated levels of co-repressors further inhibit PRB's function, contributing to the persistence of the disease [41]. Additionally, PRB is instrumental in mediating progesterone's anti-inflammatory effects. Under normal conditions, PRB signaling downregulates pro-inflammatory cytokines and promotes immune tolerance. However, in endometriosis, reduced PRB expression diminishes these protective effects, creating a pro-inflammatory environment. Elevated levels of cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) foster conditions that support the survival and growth of ectopic lesions [3].

Furthermore, the interaction between PRs and other transcription factors, such as FOXO1, is essential for progesterone-driven gene expression [3]. In endometriosis, these interactions are compromised, preventing the transcription of genes involved in apoptosis and cell cycle regulation. As a result, endometriotic cells evade normal growth control mechanisms, promoting lesion survival and expansion [43].

Conclusion

This review underscores the pivotal role of estrogen and progesterone gene expression in the pathogenesis of endometriosis. The dysregulation of hormonal signaling, particularly the imbalance between estrogen and progesterone, significantly contributes to the persistence and progression of endometriotic lesions. Elevated estrogen levels and altered estrogen receptor expression drive the proliferation and survival of ectopic endometrial tissue, while progesterone resistance impairs its regulatory functions. The differential expression of estrogen receptors (ERα and ERβ) and progesterone receptors (PR-A and PR-B) in endometriotic tissues highlights the complex interplay between these hormones and their impact on disease progression. Understanding these molecular mechanisms is crucial for developing targeted therapies that address the underlying hormonal imbalances in endometriosis. Investigating selective estrogen receptor modulators (SERMs) and progesterone receptor modulators that can precisely correct these hormonal imbalances may offer new avenues for effective treatment.

Conflict of interest

The authors declare that they have no conflict of interest.

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