The Role of Genetics in Endometriosis: Insights into Pathogenesis and Treatment

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Abstract

Endometriosis is a disease caused by the outgrowth of uterine endometrium-like tissues and it manifests in different patterns under a microscope. The genetic causes of endometriosis are poorly known. This condition shows genetic diversity by causing multiple lesions that change their biochemical activity. This disease is associated with discomfort, adenomyosis, infertility, placentation, and peritoneum inflammation which impact immune and reproductive systems. The inherited genetic and epigenetic variants may demonstrate the alterations in genetics, endometrium, placenta, and immunology that lead to endometriosis development. This book chapter explores the genetic variants that contribute to endometriosis development and their implications for improving diagnostic approaches. Additionally, it focuses on current genome-wide association study findings that have revealed genetic alterations associated with endometriosis along with their underlying biochemical processes and molecular mechanisms. Moreover, this chapter highlights that the diagnostic methods need to incorporate population-specific biomarkers based on the genetic variations found among different ethnic groups. The chapter outlines the future research directions as well as highlights the role of genetics in the improvement of accurate diagnosis and individualized treatments for endometriosis patients.

Keywords: Endometriosis, Genetic, Infertility, Reproduction, Diagnosis

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Introduction

Endometriosis represents the most prevalent cause of severe pelvic pain during the reproductive years of women and links directly to ovulatory and menstrual cycles as well as fluctuating hormone levels (Vercellini et al., 2014). It manifests as ectopic endometrial tissue which contains both endometrium-like epithelium and blood vessels outside the uterus while causing inflammation and fertility problems. A wide range of chronic disorders align with endometriosis including cancer (Liu et al., 2022), autoimmune conditions (Cheng et al., 2022), cardiovascular diseases (Chen et al., 2021), type 2 diabetes (Chen et al., 2021) and nonalcoholic liver disease (Chou et al., 2021). Furthermore, patients with endometriosis are also at a higher risk of infertility, tiredness, multisite discomfort, and other complications. Therefore, endometriosis is considered as a disorder with varying presentation and implications at different life stages (Horne & Missmer, 2022). The actual incidence rates in the public are unknown primarily due to frequent oversight by primary care physicians (Harvey and Warwick, 2010) which is delayed for an average of ten years (Hudelist et al., 2012). Endometriosis significantly impairs women's and their families' quality of life and puts a burden on healthcare systems (Nnoaham et al., 2011). About 10% of women who are of reproductive age suffer from endometriosis. However, it is difficult to ascertain the precise incidence in the general population because it has a subclinical course in some women. It may adversely impact fertility by inducing fibrosis of the fallopian tubes, which can lead to inflammation of the genital tissues, and alter the environment of the uterus. Endometriosis foci have been reported in over 50% of women suffering from infertility (Hodgson et al., 2020).

Multiple factors, including hormones, genome, immunology, epigenetics, and environment are some of the etiological contributors, indicating a multifaceted origin that leads to a highly complex disease not explicable by a particular etiopathogenetic system (Laganà et al., 2019). However, other endometriosis risk factors have recently been investigated, with premature menarche being the most consistently identified, which results in prolonged and severe cycles of menstruation and nulliparity, indicating exacerbated stimulation by ovulation and steroid hormones (Parazzini et al., 2017).

According to the statistics, 7% of women diagnosed with endometriosis have a hereditary disposition in their family line. Conversely, it has been shown that a genetic element accounts for around 50% of the propensity for the condition. Studies have proposed that genes influencing disease susceptibility interact with environmental factors to express other phenotypes, indicating that endometriosis is a highly hereditary feature (Houshdaran et al., 2020; Smolarz et al., 2021).

1. Pathogenesis

The etiology of endometriosis remains unclear. A multitude of models has been suggested to elucidate the initiation of endometriosis and the proliferation of endometriotic tissue inside the uterine cavity and its dissemination to extra pelvic sites. At present, delayed menstrual cycle and models based on stem cell origin are the two main hypotheses that received attention. Other hypotheses include the development of Müllerian rest, the change of the abdominal mesothelioma (referred to as "coelomic metaplasia"), and malignant cancer via the hematogenous or lymphatic dissemination of endometrial cells (Zondervan et al., 2020).

John Sampson is recognized for formulating the theory that endometriosis originates from eutopic endometrial tissue fragments and cells that are refluxed into the peritoneal cavity through the fallopian tubes during menstruation (Sampson, 1927). Sampson's concept of retrograde menstruation elucidates the physiological and pathological movement of fragments of the endometrium into the peritoneum during the menstrual cycle.

Coelomic metaplasia theory (Fujii, 1991) may elucidate the rare incidents of endometriosis in women not having retrograde menstrual periods or those with dysfunctional fallopian tubes (Suginami 1991), as well as in men receiving high doses of estrogen due to prostatic lymphoma or afflicted with Persistent Müllerian Duct Syndrome (PMDS) (Nerune et al., 2016). Women with Mayer-RokitanskyKüster-Hauser (MRKH) syndrome who acquired endometriosis despite not having a menstrual cycle, which is a sign that endometriosis might occur due to metaplasia (Troncon et al., 2014).

Müllerian rest develops due to the movement of residual cells of the embryonic Müllerian tube, retaining their potential for developing lesions in the endometrium following estrogen stimulation (Signorile and Baldi, 2015). Finally, the benign metastasis idea proposes that endometrial lesions are caused by endometrial cell migration via lymphatics or circulation (Taylor, 2004).

2. Hormonal Factors

Hormones such as estrogen and progesterone signaling are highly synchronized in normal endometrium which results in phase-dependent menstruation. This is crucial for maintaining regular menstruation, pregnancy progression, and implantation of embryos (Marquardt et al., 2019). When stromal cells start decidualizing, progesterone suppresses the effects of estrogen and starts the secretory phase, while estrogen in proliferative phase promotes epithelial growth (Kapoor et al., 2021). Endometriosis development is caused by imbalance of these two hormones—progesterone resistance and excess estrogen as shown in figure 1 (Koukoura et al., 2016).

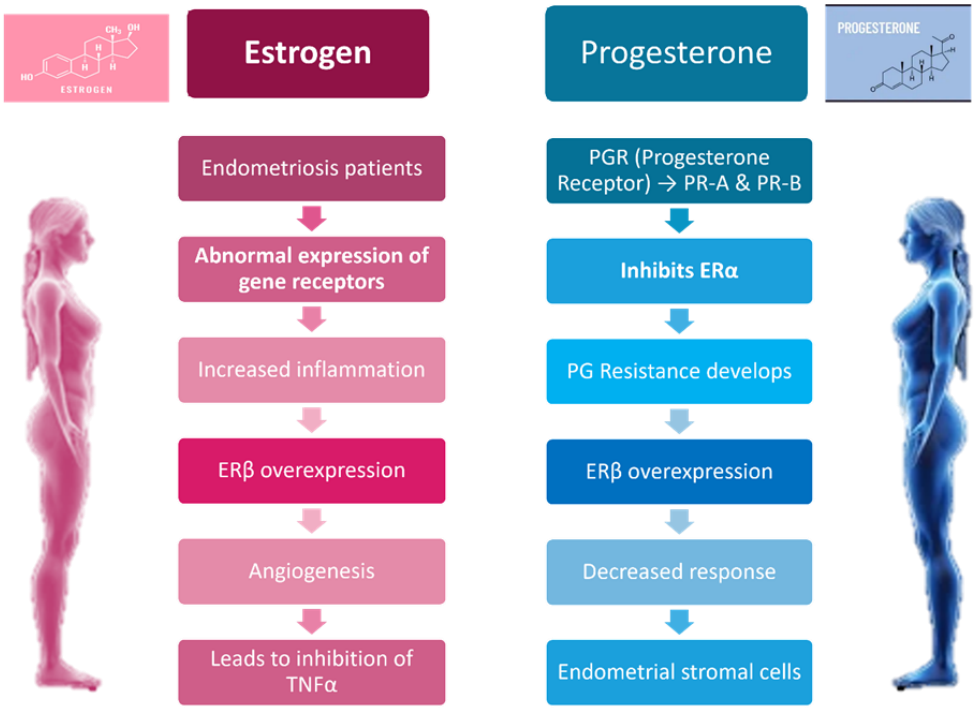

Fig. 1: The role of estrogen and progesterone in the development of endometriosis.

3.1. Estrogen

Endometriosis is frequently characterized as an "estrogen-dependent" ailment. This is because endometriosis primarily affects women who are of reproductive age, however, it may also develop in postmenopausal women if they have high levels of estrogen or are on estrogen treatment (Jiang et al., 2016). In a healthy endometrium, estrogen promotes epithelial proliferation and produces leukemia inhibitory factor (LIF), a cytokine from the IL-6 family essential for the effective implantation of embryos and endometrial decidualization (Marquardt et al., 2019).

The two estrogen receptors ERα and ERβ are encoded by two specific genes, including ESR1 and ESR2 (Koukoura et al., 2016). Endometriosis patients demonstrate an abnormal expression pattern of ERα and ERβ receptors that leads to reduced ERα/ERβ ratios and increased levels of ERβ (Figure 1) (Kim et al., 2013). Aberrant ERα expression results in increased production of prostaglandins together with inflammatory mediators, tumor-promoting, and angiogenic substances (Kapoor et al., 2021). The overexpression of ERβ increases inflammatory activity while reducing TNFα-induced apoptotic activity (Jiang et al., 2021).

3.2. Progesterone

The activation of the receptor ERα leads to progesterone receptor (PGR) synthesis. PR-A and PR-B are the two variants of PGR, and their expression rises throughout proliferation and lowers after ovulation (Figure 1). The expression of ERα is inhibited by expressed PGR, which forms a feedback mechanism. Endometriosis causes progesterone resistance due to a reduced ratio of ERα: ERβ along with elevated levels of estrogen, with insignificant PR-B and significantly decreased PR-A levels compared to healthy endometrium (Kim et al. 2013). Endometrial stromal cells with progesterone resistance exhibit lower reactivity to progesterone (Saunders and Horne, 2021).

Furthermore, PGR mutation induces infertility in mice by reducing or eliminating ovulation, causing uterine hyperplasia, preventing endometrial decidualization, and limiting mammary gland development (Marquardt et al., 2019). Consequently, to address the deficiency of progesterone, progestin treatment is a viable alternative for hormonal treatment of endometriosis. This treatment alleviates pelvic discomfort associated with endometriosis and eradicates laparoscopically observable endometrial lesions (Kim et al., 2013).

3. Role of Genetics

Endometriosis is a multifaceted condition influenced by both hereditary and environmental factors that contribute to its risk. Heritability of endometriosis is considered to be around 50%, according to extensive twin analysis (Saha et al., 2015). Several studies on potential genes have been undertaken to explore ideas about the genetic basis of endometriosis; however, these studies have mostly provided non-replicable results (Rahmioglu et al., 2015; Borghese et al., 2017), a phenomenon often seen in the field of complex diseases. Multiple factors contribute to this, including the credibility of the biological hypothesis examined, the limited testing of a few DNA variations within a select group of genes in a pathway, and complications caused by heterogeneous cases and insufficient research sample sizes (Houshdaran et al., 2020).The first effort to use genome-wide, hypothesis-free methods to comprehend the genetic causes of endometriosis was carried out between 1995 and 2005 using cooperative family-based linkage studies (Zondervan et al., 2007). In families with multiple women who are endometriosis-affected, these investigations examined the presence of significant gene effects. Significant linkage was found on 10q26 and 7p13-15, which carry genes including CYP2C19, INHBA, SFRP4, and HOXA10 and are likely to have variations that increase the risk of endometriosis (Borghese et al., 2017).

4.1. GWAS

Genetic variants associated with various diseases are identified by a genome-wide association study (GWAS). GWAS played an important role in the identification of genetic loci involved in the development of endometriosis (Rahmioglu et al., 2014).

4.2. Novel Genetic loci

Various genetic loci involved in endometriosis have been reported in recent studies. During meta-analysis, five loci such as ESR1, CYP19A1, HSD17B1, VEGF, and GnRH were identified which are linked to genes that regulate the production of steroid hormones (Sapkota et al., 2017). A better understanding of these genetic loci can help researchers identify diagnostic markers for endometriosis.

4.3. Gene expression and pathways

Genes found in these specific regions significantly contribute to biological activities linked to endometriosis. Research shows that endometriosis linkage exists between WNT4 and VEZT as these genes function within cell adhesion pathways and hormone regulation pathways. A potential diagnosis of endometriosis may be identified by the dysfunction of these genes (Albertsen et al., 2013).

5. Genetic Pathways and Mechanisms in Endometriosis

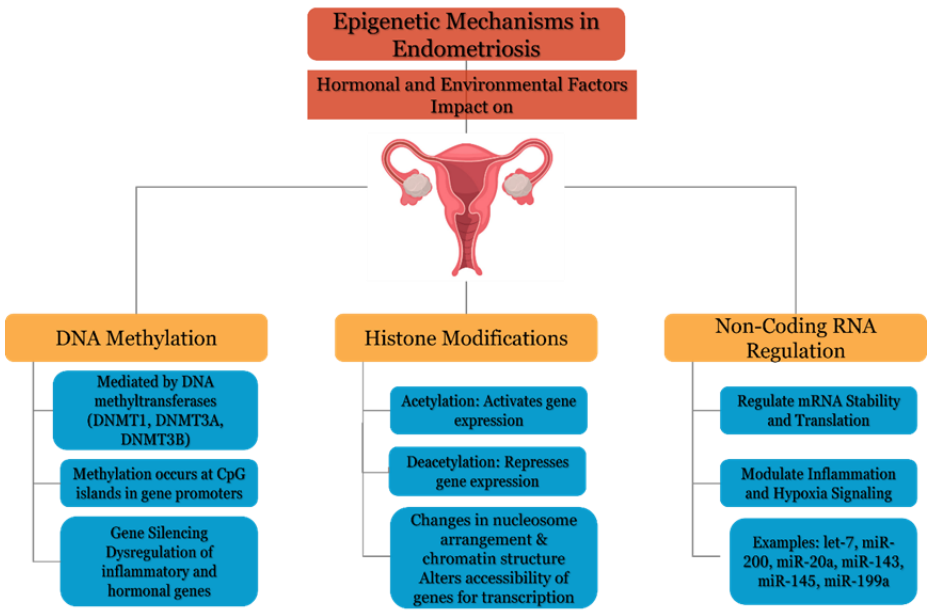

Fig. 2: The genetic mechanism and pathways of endometriosis

5.1. Epigenetics in Endometriosis

Every human cell, although having the same genome, displays considerable morphological and functional variations, resulting in the development of different tissues and organs that perform different functions. The process of pathogenesis for complex human disorders depends on epigenetic mechanisms (Figure 2). The investigation into the patho-mechanism of endometriosis, particularly regarding its consequences such as pain and infertility has highlighted the significance of epigenetic inheritance linked to epigenetic alterations. Environmental factors significantly affect the epigenome, resulting in the emergence of disease. The epigenome, hormonal and immunological state, directly affects each other, leading to the pathogenesis of endometriosis (Bulun et al., 2019).

Non-coding RNA (ncRNA) including miRNA and siRNA play an important role in epigenetic processes, along with DNA methylation and histone alterations (Bulun et al., 2019). All genes and intergenic areas of DNA, which are encased with proteins into chromatin, undergo modification by epigenomic processes. The modification of chromatin structure underlies epigenetic control (Hsiao et al., 2017). Epigenetic processes influence transcript stability, DNA conformation, nucleosome arrangement, chromatin density, nuclear architecture, and ultimately the determination of gene expression or silencing (Martin and Fry, 2018).

5.2. DNA Methylation in Endometriosis

The widely recognized epigenetic alteration that causes human genome inactivation is DNA methylation as shown in figure 2. To suppress gene expression, methyl groups are incorporated into CpG (cytosine-preceding guanosine) regions found in the promoters of genes. The targeted modification of genes is known as DNA methylation (Koukoura et al., 2016). Research shows endometriosis leads to modified methylation patterns across 40,000 CpG islands (Grimstad et al., 2017). Research performed on women with endometriosis has generated ambiguous results that point toward atypical expression patterns of DNA methyltransferases (DNMTs) occurring in endometriotic tissue compared to normal endometrium. During the secretory phase of the endometrium, DNMT expression levels decrease in endometriotic cells (Dyson et al., 2015). Ectopic endometria demonstrated elevated DNMT1, DNMT3A, and DNMT3B expression compared to normal control tissue (Wu et al., 2007).

5.3. Role of non-coding RNAs

Non-coding RNAs (ncRNAs) function as gene expression controllers in the post-transcriptional stage instead of epigenetic mechanisms. Small-sized 22-nucleotide-containing, non-coding RNA molecules are classified as micro RNAs (MiRNAs). They function as key regulatory agents by raising or lowering transcriptional and proteomic activities during the process of RNA breakage or through mRNA translation repression according to Catalanotto et al. (2016). Mashayekhi et al. (2019) reported let-7, miR-200, miR-20a, miR-143, 145, and miR199a as the main miRNAs involved in endometriosis. Research demonstrates that miRNAs function as both regulatory and targeting agents of epigenetic processes through their signaling processes that lead to hypoxia and inflammation.

6. Diagnosis

Endometriosis symptoms, including pelvic discomfort and/or infertility, are commonly linked to other ailments, which delay the diagnosis (Horne and Saunders, 2019; Zondervan et al., 2020). The nature and intensity of the symptoms indicate the risk of endometriosis. Approximately 50% of the larger deep lesions may be detected by clinical examination (Koninckx et al., 2021). The preferred technique for identifying deep endometriosis and detecting cystic ovarian endometriosis is imaging. However, imaging and clinical examination are unable to exclude superficial and microscopic lesions. Consequently, the decision to perform a laparoscopy due to suspected endometriosis is a clinical choice, as a woman with severe pain or infertility has a 50% chance of developing typical endometriosis and an increased chance of having inconspicuous lesions (Kvaskoff et al., 2015).

Although a 95% sensitivity found in 100 women has credibility limits of 85-97%, the accuracy and credibility limits of imaging are hardly considered. When a diagnostic test's prevalence is low, its predictive value decreases. Simple calculations show that test results with 99% sensitivity and specificity will culminate in 50% false positives for a disease that occurs in 1% of cases. A 1% error in 10,000 women without the condition results in 100 false positives, while 99 women with the disease will get an accurate diagnosis (Koninckx et al., 2021).

6.1. Non-Invasive Diagnostics

The rapid development of non-invasive diagnostic methods for endometriosis has been facilitated by next-generation sequencing (NGS) approaches. Endometriosis-related genetic and epigenetic changes may be detected by liquid biopsies, which analyze circulating cell-free DNA or RNA. A less intrusive and more patient-friendly alternative to conventional diagnostic techniques such as laparoscopy is NGS-based screening of fluid biopsy samples (Ferrero, 2019).

6.2. Transcriptomic Analysis

Transcriptomic analysis of endometriosis has significantly improved due to NGS technology. RNA sequencing (RNA-seq) allows researchers to measure and analyze gene expression levels in both endometrial tissue and endometriotic lesions. This technique reveals gene and biological pathway deregulation that contributes to endometriosis development. RNA-seq helps researchers detect unique genes that express differently which lead to new diagnostic biomarker discoveries and improves understanding of endometriosis molecular pathology (Kang et al., 2022).

7. Therapeutic Implications

NSAIDs and progestins together with estroprogestins represent first-line therapeutic approaches for controlling endometriosis-related pain (Barra et al., 2018).

7.1.1. NSAIDs

The main benefits of NSAIDs include treating primary menstrual cramps and managing dysmenorrhea and other chronic inflammatory conditions (Marjoribanks et al., 2015). NSAIDs function as both pain relievers and anti-inflammatory agents therefore physicians use them to treat endometriosis. During a double-blind randomized controlled trial (RCT) researchers distributed 24 patients with moderate-to-very-severe dysmenorrhea due to endometriosis treatment between a placebo group and naproxen (275 mg four times daily) administration. Patients who took naproxen experienced a higher frequency of moderate to excellent pain relief results than patients who took the placebo medication. Research showed that 83% of women experienced total or substantial pain relief while taking naproxen compared to 41% who received the placebo (Ferrero et al., 2015).

7.1.2. Estroprogestins

Administration of estroprogestins by oral or vaginal ring or transdermal patch at present provides relief from endometriosis-related pain as well as dysmenorrhea while providing contraceptive protection, sustained safety, and menstrual cycle management (Dunselman et al., 2014). For the treatment of endometriosis-related pain, a double-blind, placebo-controlled, multicenter RCT examined the effectiveness of periodic COC [ethinylestradiol, (EE) 0.035 mg and norethindrone acetate, (NETA)] at a low dose (1 mg) in 51 women and placebo in 49 women. The COC group had less severe dysmenorrhea at the four-month follow-up than the placebo group; however, neither COC nor a placebo substantially reduced the severity of non-menstrual pelvic discomfort (Harada et al., 2008).

7.1.3. Progestins

Progestins represent the drugs applied as monotherapy to cure endometriosis in female patients. The various forms of progestin drug delivery currently available include oral tablets followed by intramuscular injections and surgical implants and intrauterine devices that release medication (Barra et al., 2018). Low doses of these chemicals decrease FSH and LH production in females by modifying gonadotropin-releasing hormone (GnRH) release patterns. During normal endometrial development the suppressed ovarian steroidogenesis together with reduced serum steroid levels generates anovulution, produces decidualized and acyclic tissues (Brown et al., 2012). Progestins represent the drugs applied as monotherapy to cure endometriosis in female patients. The various forms of progestins drug delivery currently available include oral tablets followed by intramuscular injections, surgical implants, and intrauterine devices that release medication (Barra et al., 2018). Low doses of these chemicals decrease FSH and LH production in females by modifying gonadotropin-releasing hormone (GnRH) release patterns. During normal endometrial cycling decidualization and acyclicity are reported due to the suppression of ovarian steroidogenesis causing anovulation and decreased serum ovarian steroid hormones (Brown et al., 2012).

7.2. Second-line Therapies

A thorough diagnosis is necessary before administering second-line therapies to women if first-line therapies are ineffective in alleviating their pain symptoms (Ferrero et al., 2015).

7.2.1. Gonadotropin Releasing Hormone Agonists

GnRH-a injectable depot solutions are examples of second-line treatments. These are decapeptides that vary from natural GnRH by having one or more amino acids substituted. These medications inhibit the synthesis of estrogen in the ovaries by downregulating pituitary GnRH receptors, which inhibits the release and synthesis of gonadotropins. Hypestrogenism and concomitant amenorrhea cause endometriotic implants to regress. Furthermore, new peritoneal seedlings are prevented by secondary amenorrhea (Bedaiwy et al., 2017).

7.2.2. Danazol

Danazol is a synthetic steroid derivative of ethisterone, which has anti-gonadotropic, hypestrogenic, and hyperandrogenic properties. It helps reduce endometriosis symptoms by causing endometrial shrinkage and ectopic endometriotic implants. The medicine was widely used for the management of endometriosis in the 1970s and 1980s; however, its use is associated with adverse effects such as weight gain, skin problems hirsutism, and other androgenic reactions. Furthermore, the availability of GnRH-a led to a decrease in danazol usage (Nawaz et al., 2022). A double-blind, placebo-controlled randomized controlled trial evaluated the clinical effectiveness and tolerability of danazol and MPA in treating mild to severe endometriosis (Wong and Tang, 2004).

8. Future Directions and Emerging Trends in Genetic Research

Genetic research in endometriosis is progressively advancing, with new patterns shaping future diagnosis approaches. The future diagnostic methodologies in endometriosis could be significantly influenced by prominent emergent trends in genetic research such as multi-omics approaches (Higashiura et al., 2012).

8.1. Polygenic Risk Scores (PRS)

The risk evaluation system starts with individual scores built from multiple genetic variations targeting specific diseases. Scientists develop endometriosis PRS models through sequential analysis of genetic variations contributing to disease risk development (Ferrero, 2019). These evaluations based on genetic scores can identify endometriosis sensitivity levels in individuals while generating precise risk assessments. PRS serves two functions by allowing these assessments for disease severity and treatment response to help create specialized treatment plans. The utilization of PRS demonstrates its potential to identify differences between various endometriosis types therefore making diagnostics more precise (Santoro et al., 2020).

8.2. Multi-Omics Approaches

Understanding disease mechanisms requires multi-omics methods that link genetic information from genomics, transcriptomics, epigenomics, proteomics, and metabolomics data. Research studies into endometriosis using multi-omics approaches reveal extensive molecular changes that facilitate the discovery of biomarkers and new treatment methods (Pisarska et al., 2019). These multi-omics technologies can improve the sensitivity and accuracy of endometriosis detection through novel diagnostic biomarkers (Goulielmos et al., 2020). CRISPR-Cas9: technique has revolutionized genomic research to perform precise targeted genetic modifications within living organisms (Devi et al. 2024). Research using CRISPR technology for specific deletions and mutations in endometrial cancer cells to investigate cancer-causing genes (Zhang et al., 2020). The study by Devi et al. (2024) demonstrated that CRISPR technology can be used to disrupt cancer-causing genes while also restoring tumor-suppressing genes in cell-based biological models which generates targeted therapy possibilities and functional insights into cancer gene functions. New variations of CRISPR technology such as CRISPR-Cas12 and CRISPR-Cas13 have increased both genome editing tools and RNA targeting distributions which enhances the scope of cancer research (Zhang et al., 2020).
Single-cell genomics: has been widely known as an analytical method for studying tumor cellular diversity with remarkable accuracy (Zhang et al., 2020). Researchers identify cancer cell populations leading to treatment resistance and disease relapses through precise analysis of tumor cell genomics and transcriptomes (Papalexi & Satija, 2018). Spatial transcriptomics uses a mapping gene expression technique to preserve lost spatial information in tissue context during conventional bulk sequencing (Chen et al., 2024).

Conclusion

The revolutionary role of genetic advancements in the diagnosis and treatment of endometriosis is highlighted in this chapter. Endometriosis is a widespread and complex disorder that can cause significant distress and result in chronic pelvic pain, infertility, and damage to the organs. Endometriosis is now recognized as a systemic illness rather than one primarily affecting the pelvis. It disrupts liver and adipose tissue metabolism, promotes systemic inflammation, and changes gene expression in the brain, resulting in pain sensitization and mood disturbances. Early detection and diagnosis are critical to providing prompt medical treatment. The variability of endometriosis complicates its research, diagnosis, treatment, and management. Genetic markers, risk prediction models, and multi-dimensional methodologies potentially transform this sector through earlier identification, accurate assessments, and individualized management approaches. Future research needs to validate, replicate, and integrate advanced genetic methods into standard clinical practice to improve the therapeutic application of genetic insights in the diagnosis and treatment of endometriosis.

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