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Pathogenesis of Endometriosis and Future Approaches

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ABSTRACT:
Endometriosis is an estrogen-dependent female disease associated with pelvic pain and infertility as a result of abnormal placement of endometrial tissue outside the uterus.Endometriosis, which affects approximately 200 million women worldwide, continues to be an important health problem today due to its uncertainties about its pathogenesis. Since the disease was identified, many different pathogenetic pathways have been considered, such as retrograde menstruation, benign metastasis, immune disorders, hormonal imbalances, involvement of stem cells, and changes in epigenetic regulation. Interaction of the number and amount of menstrual flows with genetic and environmental factors seems to determine the likelihood of development as well as the phenotypic manifestation of the disease However, the true pathogenesis of endometriosis is not fully understood. Therefore, in this review, we outline recent developments that illuminate the main origin and pathogenesis of endometriosis based on current studies and provide new avenues for research that promises to improve early diagnosis and treatment of endometriosis. Although endometriosis is generally thought to be a steroid-sensitive disease, one of the possible causes of the development of endometriosis may be the immune system. A thorough understanding of the histopathogenesis and pathophysiology of endometriosis is essential for the development of new diagnostic and therapeutic approaches to this debilitating condition.

Keywords: Endometriosis, pathogenesis, stem cells, estrogen, progesterone.

I. INTRODUCTION

Endometriosis is defined as the abnormal presence of functional endometrial tissue outside the uterus. In women with endometriosis, the disease occurs with characteristic signs and symptoms, including dysmenorrhea, dyspareunia, chronic pelvic pain,or infertility [1]. It usually occurs in women of reproductive age and decreases after menopause or ovariectomy. Increasing evidence suggests that a combination of genetic, hormonal, immunological, and anatomical factors play a role in the formation and development of ectopic foci of endometriosis [2]. Endometriosis can be classified into three important subtypes according to its histopathology and anatomical locations: superficial endometriosis, deep infiltrating endometriosis (die), and ovarian endometriotic cysts (endometriomas or commonly known chocolate cysts) [3].While superficial endometriosis is usually located on the surface or subserosal region of the peritoneum or internal organs, deep infiltrating endometriosis (die) involves lesions that extend deep into the muscle layer of the intestine, bladder wall,

diaphragm, or other organs. Ovarian endometriosis, on the other hand, is located on the ovary and usually forms a large cystic structure, often called chocolate cysts[4]. Different types of endometriosis are characterized in terms of biological and clinical characteristics. Unlike superficial endometriosis, die causes severe clinical symptoms, including severe pain and gastrointestinal, urological system abnormalities. The situation is more different in ovarian endometriosis. Ovarian endometriotic cysts are usually associated with infertility and have a high risk for cancer development due to endometriosis [1]. The prevalence of endometriosis affects approximately 10% of women of reproductive age and 35-50%of women with pelvic pain and infertility [1,5]. The understanding of the pathogenesis and etiology of endometriosis is still limited despite decades of significant research. Today, there are still questions to be answered. In particular, what is the origin of the different types of endometriosis? Why does die behave like cancer when it is benignAnother question is why do lesions with seemingly normal histology often cause chronic inflammation. A thorough understanding of this mechanism will help develop the necessary treatments [1,6].

Knowing the exact mechanism of the origin and progression of the disease is important in determining appropriate treatment strategies. Therefore, in this review, we discuss how new information aimed at explaining the latest developments about the pathogenesis of endometriosis, diagnosing the disease and reducing symptoms through molecular classification and the development of the disease will guide our future research.

II. THE ORİGİN OF ENDOMETRİOSİS

The normal-looking ectopic endometrium, located outside the uterus and surviving, is one of the most intriguing features of endometriosis. There are a number of theories that explain the origin of endometriosis and how tissue spreads through the abdominal cavity [3,7]. The pathogenic hypothesis, supported by the most robust evidence, is retrograde menstruation, and more recently, the contribution of extrauterine stem cells is also being considered. However, other theories such as hematogenous or lymphatic spread, solomic metaplasia, and Müllerian rest induction have also been proposed [1,3,4]. The theory of retrograde menstrual bleeding is known as the Sampson theory and has been valid since it was first described in 1925. The main idea of this theory is that menstrual blood containing endometrial cells returns to the peritoneal cavity through open fallopian tubes and settles in places where implantation of these cells can take place [8,9]. But despite this theory, there is no single theory that explains the different clinical pictures and pathological features of endometriosis. In addition, there is no single theory explaining the presence of endometriosis in the thoracic cavity, which is rarely seen in women with Mayer-Rokitansky-Küster-Hauser syndrome and in men in rare cases. In addition, it is possible that superficial endometriosis, deep infiltrating endometriosis (die) and ovarian endometriotic cysts can develop through different mechanisms. This leads to various theories [1].

III. RETROGRADE MENSTRUATION THEORY

Sampson's theory of retrograde menstruation has been widely accepted. During menstruation, the viable endometrial parts move along the fallopian tubes, possibly under a pressure effect caused by dissynergic uterine contractions. When they reach the peritoneal cavity, endometrial parts can settle, grow and spread into pelvic structures [10,6]. Retrograde theory is the theory that best explains the superficial endometriosis found in the mucosa and subserous parts of the fallopian tubes, internal organs and peritoneal wall, as well as in ovarian endometriotic cysts. For the development of superficial endometriosis, retrograde menstrual tissue fragments also need molecular markers to adhere primarily to the serosal surface. Immediately after the ischemic tissue binds to the surface and continues to survive, angiogenesis takes place so that it can develop and progress [11]. Early menarche and prolonged menstrual flow are biologically affected by changes at the molecular level that will support cell implantation and growth in ectopic regions step by step (Figure 1), [7]. It has also been suggested that an enlarged corpus luteum rupture during menstruation allows the endometrium to reach the ovarian tissue during retrograde menstruation. After the closure of the remaining parts of the ruptured and shed corpus luteum, the remaining endometrial tissues provide nutrition for this region to form ovarian endometriosis foci. With the blood support of local estrogen stimulation in the endometrium, these foci grow and prepare the easily recognizable endometriotic cyst scenario in masses on the ovary [11]. The problem of retrograde menstruation

theory is that it is insufficient to explain lesions other than deep infiltrating endometriosis or peritoneal cavity [1,12].

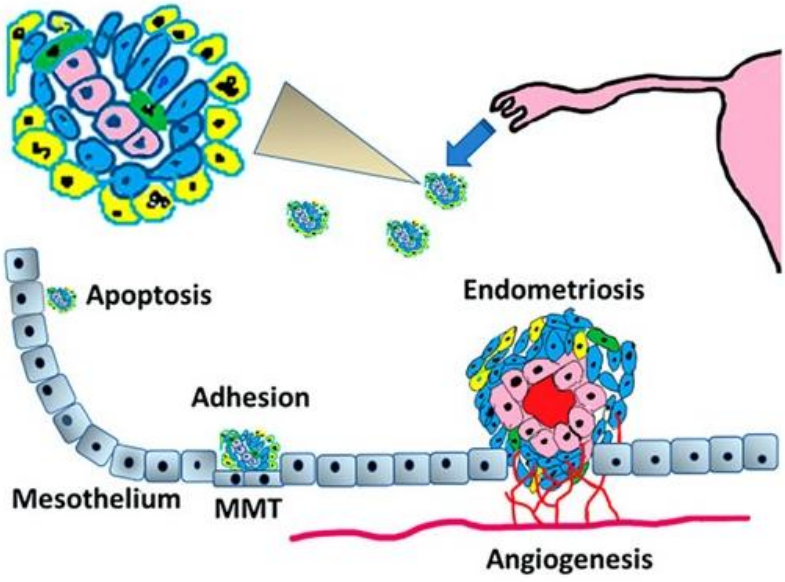

Figure 1. Schematic drawing depicting the development of endometriosis from retrograde menstrual bleeding. Endometrial tissue fragments from the fallopian tube usually consist of epithelial (pink) and stromal cells (blue) surrounded by several stem cells (green) and inflammatory cells (yellow). Meanwhile, apoptosis occurs and angiogenesis results in the persistence and progression of lesions under the influence of hormones [13].

Unlike superficial endometriosis, die is usually located deeper in the structure of the organs in the muscle layers of the gastrointestinal tract, bladder, and ureter. From here, it is included that stem cell-like cells form foci similar to cancer metastasis about the pathology of die. If die occurs with retrograde menstruation, it should be assumed that the menstrual endometrium, which includes epithelial and stromal cells, can enter the angiolymphatic circulation without any interruption and has the ability to invade the common veins and exit the veins to be located within the muscle layers [1].

IV. METASTASIS THEORY

Although endometriosis in the pelvic organs can be explained by the theory of retrograde menstruation, it cannot explain the implantation of endoemtriosis outside the peritoneal or pelvic cavities. The theory of vascular spread suggests that endometrial cells may be involved in the vascular system or lymphatic system of the uterus during menstruation and may be transported from there to other regions [14]. This condition, just like tumor cells, may begin to grow in variable regions in appropriate tissue environments, which may explain the presence of endometriosis in extrapelvic regions such as lymph nodes, lung, liver, and brain [13]. It is possible that some lymphovascular traffic of endometrial cells contributes to the pathogenesis of endometriosis; however, the incidence of endometriosis in distant organs is rare, so the spread of the disease is unlikely to occur through this mechanism.

V. ENDOMETRİAL STEM CELL THEORY

The theory of endometriosis related to stem cells has been the most popular theory recently. The two main versions of the theory are based on the tissue origin of the root hubs, which are thought to originate from the uterine endometrium or bone marrow [15]. Stem cells are undifferentiated cells capable of self-renewal and producing offspring cells. In the normal endometrium, there are epithelial-derived, mesenchymal, and various multipotent endometrial stem cell populations [15,16]. Although retrograde menstruation directs menstrual debris out of the uterus, it may be the differentiation of mesenchymal stem cells within this reflux that causes endometriosis to develop. The strength of endometrial stem cell theory is that it not only adapts to the retrograde

menstrual pattern, but also explains the pathogenesis of DIE and endometriosis outside the abdominal cavity. Because stem cells of endometrial origin can passively enter the angiolymphatic cavity during menstruation and spread in this process [1]. These stem cells in the endometrium are known to be responsible for the epithelial regeneration of the functional layer during the proliferative phase in response to estrogen, but the mesenchymal stem cells are localized in the perivascular region of the basal and functional layers and are responsible for the formation of the functional stroma [17]. Another mechanism for the migration of stem cells to ectopic regions is associated with abnormal expression of WNT and Hox genes during organogenesis of the female reproductive system, which triggers abnormal migration of cells [18].After the migration phase, stem cells adhere and begin to form endometrial lesions. The stem cell potential in lesion formation was proven by Cervelló et al. in 2011. In this experiment, it was reported that endometrial stem cells and multipotent population cells developed endometriosis by implanting immunosuppressed NOD-SCID mice under the kidney capsule [19]. In fact, this theory is an important finding for endometriosis because it can explain the pathogenesis and ectopic implantation of all three subtypes of endometriosis outside the abdominal cavity [1,4].

VI. BONE MARROW-RELATED STEM CELL THEORY

Stem cell theory plays an important role in determining the source of endometriosis. This theory suggests that outside of endometrial cells, it originates from a different source of stem cells, such as bone marrow. Research shows that these stem cells can contribute to the formation of endometriosis lesions by entering the endometrial tissue and interacting with various factors there [18]. Various cell populations such as mesenchymal, hematopoietic and endothelial progenitor cells are known to play a role in endometrial regeneration, and these cells have been suggested to contribute to the physiological regeneration of the endometrium [20]. According to this theory, bone marrow stem cells circulating through blood vessels settle in soft tissues instead of the endometrium, while a reduced number of cells are collected in the eutopic endometrium [17]. Recent studies have shown that the CXCL12/CXCR4 axis plays a role in the uptake of Several bone marrow-derived stem cell populations (BMDSC) into both eutopic and ectopic endometrial tissue. In processes such as cancer,CXCL12/CXCR4 activation has been shown to function through endothelial cells by increasing metalloproteinase expression, promoting angiogenesis, and facilitating tumor progression and metastasis [21,22]. CXCR4 is a chemokine receptor expressed on its surface and is found in stem cells, and CXCL12 is its ligand [23,24]. An in vitro study showed that physiological estradiol (E2) and CXCL12 and CXCR4 expression by mouse bone marrow stem cells increased, while progesterone (P4) by human endometrial stromal cells increased the expression of these genes[25].BMDSCs are considered the main source of stem cells that lead to endometriosis outside the peritoneal cavity and may be the source of rare cases of endometriosis in men [26]. A recent study in mice revealed that mesenchymal stem cells from peritoneal endometriosis contribute to vascularization in lesions and have the ability to spread to the lungs. These stem cells can differentiate into cells expressing alveolar cell markers in the lungs, suggesting their multifaceted potential [27]. Compared to the eutopic endometrium, endometriosis-induced cells have been found to express higher levels of cytokeratin, Wnt, and proteins involved in epithelial-mesenchymal transition [28].

VII. THE ROLE OF HORMONES

In a healthy endometrium, progesterone and estrogen signals move in a coordinated manner and depend on the phases of the menstrual cycle.This is critical for the successful development of menstrual cycle embryo implantation and pregnancy[29].While estrogen promotes epithelial proliferation during the proliferative phase, progesterone inhibits the action of estrogen and initiates the secretory phase when stromal cells begin decidualization [6]. The imbalance of these two hormones plays a central role in the development and maintenance of endometriosis (Figure 2.)

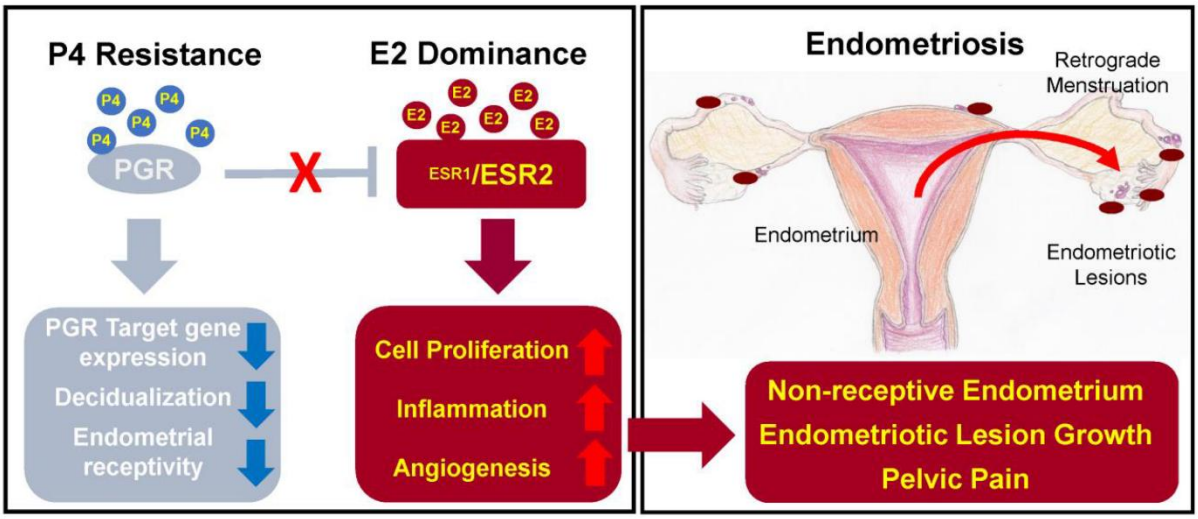

Figure 2. Progesterone and estrogen dysregulation and its effects on the endometrium. [6,29].

Ovarian steroid hormones are thought to regulate the growth of ectopic lesions similar to eutopic endometrium. In this context, both eutopic and ectopic endometrial tissue may gain sensitivity to estrogen and the development of endometriosis may accelerate [13].

VIII. ESTROGEN HORMONE

Endometriosis has been called an estrogen-dependent disease from the past to the present. The reason for this is that the disease often affects women in the reproductive period. However, postmenopausal women receiving estrogen therapy also have the disease [30].Although serum estrogen levels in patients with endometriosis are not significantly different from those in healthy women, it is a fact that estrogen-mediated changes play a role in the etiology of endometriosis. Estrogen dominance is due to local estrogen synthesis and increased estrogen receptors. The hormone estrogen is considered an important biological driver of chronic inflammation and supports endometriotic cell survival as well as lesion progression [31]. Endometriosis studies have reported abnormal expression of high levels of estradiol (estrogen steroid hormone) and enzymes involved in estrogen metabolism in menstrual blood. There are two estrogen receptors encoded by different genes:ESR1 (ERα) and ESR2 (ERβ)[29,32]. ERα and ERβ normally work together, but the expression of receptors varies in patients with endometriosis; the ERα: ERβ ratio is significantly reduced due to high levels of ERβ. Among the reasons for this change, promoter methylation may be a cause of the increased ERβ/ERα ratio in endometriotic cells. Furthermore, the main problem caused by abnormal expression of ERα is also associated with increased synthesis of inflammatory cytokines, prostaglandins, tumor promoting and angiogenic factors [33,34]. Estrogens play an important role in the adhesion of endometriotic tissue to the peritoneum, the survival of the lesion, the production of inflammatory substances (metalloproteinases, cytokines or prostaglandins and growth factors), and angiogenesis [35].

Excessive ERβ expression leads to inhibition of apoptosis caused by TNF-α, while also promoting inflammation [30]. Erβs, on the other hand, activate the pathways that increase the survival of lesions, reshape the pelvic peritoneal tissue and produce inflammatory substances that cause pain by stimulating nociceptors in pelvic tissues, and can stimulate the growth of peripheral nerve fibers by regulating nerve growth factors (NGF) [6,30].

IX. PROGESTERONE HORMONE

The expression of the progesterone receptor (PGR) is induced by ERα through the estrogen action. PGR has two isoforms: PR-A and PR-B; the expression of these isoforms increases during the proliferative phase and decreases after ovulation.In endometriosis, the fact that the progesterone signal is typically irregular and the endometrial tissue cannot respond appropriately to progesterone exposure is a symptom of progesterone

resistance [36]. In endometriosis, progesterone resistance develops as a result of low ERα: ERβ ratio and high estrogen levels: PR-B levels are undetectable and PR-A levels are significantly lower than the endometrium of healthy individuals.Progestin therapy to compensate for progesterone deficiency is one of the hormonal treatment options for endometriosis. With this treatment, pelvic pain due to endometriosis can be reduced and endometrial lesions that can be seen laparoscopically can be eliminated [36]. Studies on progesterone and progesterone receptors have shown that defective methylation of endometriotic stromal cells leads to suppression of PRs. Thus, a lack of receptors leads to progesterone resistance, which increases the resting state of endometriotic lesions and the survival rate of chronic inflammation [13]. Due to the important effect of estrogen and progesterone on the development of endometriosis, it is primarily aimed to ensure the balance of these hormones in treatment. Therefore, the treatment options used include combined oral contraceptives, progestins, gonadotropin-releasing hormone agonists, danazol, and aromatase inhibitors.

X. IMMUNE IRREGULARITY

Inflammation, cell proliferation and infiltration caused by immune dysregulation are one of the main mechanisms involved in diseases. In endometriosis, proinflammatory pathways inhibit the functions of apoptotic mechanisms and may cause potentially harmful cells to adhere to distant sites [37]. Macrophages, neutrophils, NK cells, dendritic cells and T cells from immune cells are the most effective cells in the formation and development of endometrial lesions [38]. In order to change this immune dysregulation and prevent endoemtriosis, it is recommended to change the cellular immune system in endometriosis, so that immune cells do not recognize and attack endometriotic deposits and can create a new supportive and sufficient microenvironment.

XI. MACROPHAGES

Macrophages are versatile cells that can present appropriate immune responses to different tissue injuries, not only functionally but also depending on their phenotype. It also participates in tissue regeneration of the healthy endometrium by acting as antigen-presenting cells to activate T cells [37,39]. In the normal endometrium, macrophages represent about 10% of the total number of immune cells in the proliferative period. However, this number varies according to the dominance of estrodiol and progesterone during the menstrual cycle. During the menstrual phase, their number increases significantly to make phagocytosis. Because this process is necessary for the elimination of apoptotic cells and other cell residues during endometrial shedding [40]. In endometriosis, regardless of the phases of the menstrual cycle and without cyclic changes, an increase in the number of macrophages occurs in the eutopic endometrium and peritoneal fluid [38,41]. Although there was an increase in the number of macrophages, phagocyte function decreased due to decreased expression of CD3, CD36 and Annexin A2 [42]. Peritoneal macraphages, on the other hand, secrete TNF-α, IL-6, IL-8 and IL-1β, which are proinflammatory cytokines that collect neutrophils, trigger inflammation and support the development of endometrial lesions. It is also known that macrophages produce Vascular Endothelial Growth Factor (VEGF), which supports angiogenesis in endometriosis [43].

XII. BAND NEUTROPHILS

Neutrophils play a role in repairing the endometrium of a healthy woman and controlling proliferation during the cycle. Neutrophils have been shown to increase in number in peritoneal fluid in patients with endometriosis. Neutrophils have also been shown to express cytokines such as VEGF, IL-8, CXC chemokine motif ligand 10 (CXCL10), which cause disease progression [41].

XIII. NK CELLS

Natural killer (NK) cells make up about 15% of all lymphocytes in circulation and are natural lymphoid cells that have the ability to kill malignant or infected cells without prior sensitization.
In relation to endometriosis, cytotoxic functions are suppressed by IL-6, IL-15 and transforming growth factor β (TGF-β). Therefore, there may be a tendency for endometrial cells entering the peritoneal cavity to remain there. However, the amount of NK cells does not differ in women with and without endometriosis [44]. It has been shown that NK cell activity is significantly reduced in serum or endometrial stroma cultures in patients with

endometriosis. However, they stated that the cause of this effect is not related to estradiol, progesterone or prostaglandin E2 level in the menstrual cycle, but may be caused by apoptosis [45].

XIV. T CELLS

T lymphocytes are often classified as cytotoxic T cells or helper T cells. Cytotoxic T cells have the ability to destroy a specific target through the cytotoxic mechanism, while helper T cells receive signals from antigen-presenting cells and activate to enhance further immune response. Recently, the auxiliary T-cell classification has been made in the form of Th1, Th2, Th17, and regulatory T-cells. In studies on endometriosis, this proposition has been accepted [46]. An important factor driving the development of endometriosis is the imbalance between Th1 and Th2 T lymphocytes. These two species have different functions in the immune system: Th1 lymphocytes support cellular responses by producing cytokines, while Th2 lymphocytes suppress cellular and humoral responses by affecting the differentiation of B lymphocytes [43]. In endometriosis, Th2 lymphocytes represent the main population of T cells, leading to potentially harmful cells remaining unnoticed. On the other hand, the immune response of CD4+ Th1 lymphocytes in the peritoneal fluid is suppressed due to increased expression of IL-10 and IL-12 [33]. Recently, studies have been conducted to demonstrate the relationship between regulatory T cells (Treg cells) and endometriosis. The main function of regulatory T cells is the modulation of the immune system, maintenance of tolerance to self-antigens, and prevention of autoimmune diseases. In patients with endometriosis, an increase in peritoneal fluid Treg cells but a decrease in peripheral blood is observed. These changes can lead to the development of autoimmune reactions and suppress the local cellular immune response [33].

XV. THE THEORY OF SULOMIC METAPLASIA

In 1924, Robert Meyer proposed the theory of solomic metaplasia. The female reproductive system begins with the development of two Müllerian canals derived from cellular cells of mesodermal origin [47]. According to this theory, the original cellomic membrane undergoes metaplasia and forms the endometrial stroma and glands. It is considered the most valid theory explaining endometriosis cases in men receiving high doses of estrogen for the treatment of prostate carcinoma and patients with Rokitansky-Kuster-Hauser syndrome without functional endometrial tissue due to congenital aplasia of the uterus and upper part [6,12]. This theory is also used to explain the most common ovarian endometrioma. It is suggested that the mesothelium originating from the cellomic epithelium surrounding the ovary has a large metaplasic potential and can spread to the ovarian cortex. It has been stated that these mesothelial inclusions can turn into endometriosis through metaplasia. However, it remains unclear what growth factors are effective here [6, 48].

XVI. GENETIC AND EPIGENETIC FACTORS

It is known that the risk of endometriosis increases in the family history of patients affected by endometriosis. However, the exact causes have not yet been identified. Despite the genetic similarity between eutopic and ectopic endometrial tissues, many studies indicate that they differ at the epigenetic level and have different miRNA profiles [5]. In their study investigating epigenetic abnormalities in endometriosis, Bulun et al. showed that there are many molecular abnormalities in endometriosis cases, including activation of the eutopic endometrium, activation of the mouse breast tumor virus integration site family (WNT), and activation of biosynthetic steps resulting in increased production of estrogen, cytokines, prostaglandins, and metalloproteinases [49, 50]. As a result of the meta-analysis of genome-wide studies, at least five genomic regions statistically associated with endometriosis were identified.Inaddition, in a study using exome sequencing of deep endometriotic lesions, somatic mutations were reported in 79% of lesions [51, 52]. Especially in 26% of these lesions, mutations were found in known cancer driver genes such as ARID1A, PIK3CA, KRAS and PPP2R1A [51]. In line with the results obtained from these studies, it is interesting that these mutations were found only in endometrial epithelial cells. When these findings are compared with superficial peritoneal lesions, it seems to explain the aggressive behavior of die. Further studies are needed to better understand the role of these gene changes in deep endometriotic lesions.

As can be understood from this, the pathogenesis of endometriosis is complex and involves many factors and processes, and each factor has a complex interaction with each other. Considering all these reasons, it is very clear from the discussions that the pathogenesis of endometriosis is multifactorial and that a single theory cannot explain all aspects of endometriosis.

XVII. CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

Although endometriosis is a difficult disease to diagnose and treat, it is usually benign. A multidisciplinary approach to endometriosis research is necessary to improve the current situation. One of the most important features of endometriosis is that it is an estrogen-dependent inflammatory disease. Ectopic localization of normal endometrial tissue may occur as a result of overreaction during endometrial regeneration in the uterus. Endometrial progenitor and stem cells increase in circulation in the proliferative phase of endometrial regeneration. These cells may have a high survival capacity in the extrauterine region, which means that they may contribute to endometriosis as well as their ability to regenerate the endometrium. In addition, the normal endometrium provides local immune control and inflammatory network to clear these ectopic lesions. Therefore, the struggle between endometriosis and local inflammation may determine the fate of the development of fibrotic or active endometriosis. What is more interesting is that recent advances in molecular genetic analysis in the development of endometriosis indicate that the model for the formation of die lesions is convincing, but that new revisions are still needed. Despite recent advances, some key problems with endometriosis are still pending resolution. As is known, it is the uncertainty about how endometriosis develops. The evidence is that a single model is inconsistent and that different models probably need to be integrated for other types of endometriosis. There will be a more descriptive identification of cells, stem cells or epithelial progenitor cells responsible for the regeneration of the endometrium and epithelial cells of lesions with endometriosis. Thus, the biomarkers required for the treatment of endometriosis can also be determined. Another important step is to map the cell profile and important signaling pathways that play a role in endometriosis, such as NF-κB and COX-2. Immune profiling is needed to evaluate cell populations and their distribution in individual endometriotic lesions. Molecular pathology studies are needed to determine whether different types of endometriosis (i.e. superficial, die, endometriotic cysts) are characterized by different inflammatory environments or whether different immune checkpoints have functions. Especially in terms of epigenetic studies, the relationship between the severity, response to treatment and correlation of molecular genetic changes for gene mutations should be investigated and this point can be classified.

Finally, further studies are needed to evaluate the safety and efficacy of target-based therapies aimed at maximizing therapeutic effects and minimizing systemic side effects. It promises to shed light on women's reproductive health by solving this mysterious but common disease and to improve the quality of life of women with endometriosis.

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