ENDOMETRIOSIS SYMPOSIUM

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Etiopathogenesis of endometriosis
Etiopatogenia de la endometriosis

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Endometriosis is a complex chronic disease characterized by a chronic estrogen-dependent inflammatory process that mainly affects pelvic tissues, including the ovaries, and affects a significant number of women worldwide. Controversy has been and continues to be the common denominator in different aspects related to this disease, including its etiopathogenesis.

It is evident that the pathogenesis of endometriosis is complex and entails multiple factors and processes occurring simultaneously. There are numerous interactions among the immune system, hormones, genes, stem cells, and local cellular populations, all of which contribute to the development of endometriosis and its subsequent progression.

The exact pathogenesis of endometriosis remains unknown. Since J. Sampson proposed the theory of retrograde menstruation as the cause of endometriosis in 1927[1], numerous theories have been studied, but none has been able to explain all aspects of endometriosis.

Theories related to the etiopathogenesis of endometriosis

The exact origin and pathogenesis of endometriosis is unknown. Among the most prominent theories are: the theory of coelomic metaplasia (epithelium covering the abdominal organs); abnormal Müllerian embryonic remnant; lymphatic and vascular metastasis; implantation of endometrial stem cells; and retrograde menstruation.

The journey of endometriotic cells to give rise to different types of endometriosis is highly debated and remains uncertain; thus, new theories have emerged along the way. Peng-Hui Wang et al.[2] present an illustrative summary of the different theories on the origin of endometriosis in a graph with the acronym DIGIT (Fig. 2). These are: the direct implantation theory (D) with retrograde menstruation (an autotransplantation of normal endometrial tissue to an ectopic location); the theory of indirect implantation (I) as a theory of circulatory spread (theory of hematogenous or lymphatic spread, in which endometrial tissue migrates to the circulatory system and extravasates to ectopic sites to grow in a manner similar to cancer); the theory based on genetics (G) as an extrauterine origin (bone marrow as an example) or endometrial origin, stem cells, and genetic-epigenetic interaction theory; and the theory of in situ transformation (TI) as coelomic metaplasia and embryogenic theory with induction of Müllerian rest with persistence of residual embryonic cells from the Wolffian or Müllerian ducts).

However, it should be emphasized that no single theory—or combination of existing theories—fully accounts for the diverse clinical manifestations of endometriosis[3]. Moreover, the promotion of cellular survival, proliferation, lesion formation, and maintenance requires additional factors, such as altered or impaired immune responses, angiogenic stimuli, complex localized hormonal influences, and genetic and epigenetic determinants.

It is most probable that different subtypes of endometriosis arise through distinct pathogenic mechanisms that may diverge or partially overlap. Likewise, the progression of initial endometrial implants remains insufficiently understood, and it is plausible that microenvironmental factors influence whether the disease regresses or advances.

Retrograde menstruation theory

The retrograde menstruation theory, known as Sampson's theory, has been in place since 1925 when it was first described. It holds that as endometrial tissue is shed during menstruation, endometrial fragments containing viable endometrial glands and stroma not only exit through the vagina but also ascend into the fallopian tubes, causing the endometrial cells they contain to regurgitate retrograde into the peritoneal cavity through the permeable fallopian tubes, possibly due to a pressure gradient caused by dyssynergic uterine contractions[4,5]. Once they reach the peritoneal cavity, they attach to the underlying mesothelium and can implant, grow, and invade the various pelvic structures.

Figure 1. Taken from Molecules 2022, 27, 4034. https://doi.org/10.3390/molecules27134034

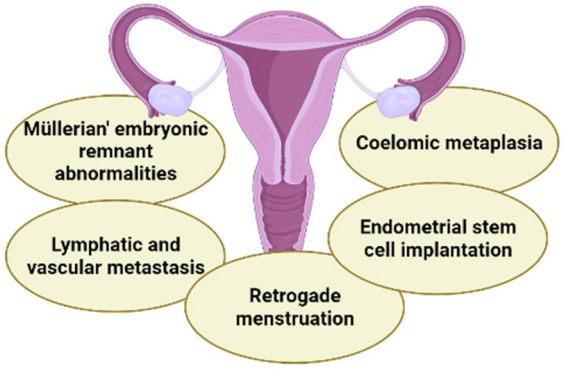
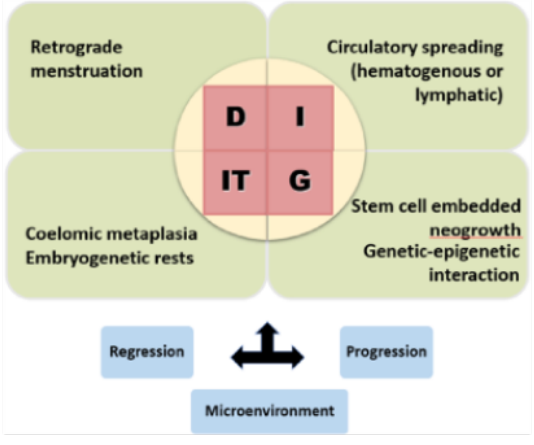


Figure 2. Theories on the origin of endometriosis (DIGIT: direct implantation theory; indirect implantation theory; genetic-epigenetic interaction; in situ transformation). Taken from Peng-Hui Wang et al.[2].



After implantation, the development and growth of the lesion are promoted by angiogenesis[6], which is made possible by the activation of peritoneal macrophages, which produce angiogenic factors such as vascular endothelial growth factor (VEGF)[7].

This hypothesis is supported by epidemiological evidence showing an increased risk of endometriosis associated with greater exposure to menstruation (heavier menstrual bleeding, shorter cycle length, and greater number of menstrual cycles), as well as a higher prevalence in women with Müllerian tract outflow obstruction[8] and asymmetry in the anatomical location of lesions. In fact, the anatomical characteristics of the upper abdomen and the spread of endometrial fragments generated by clockwise peritoneal flow may explain the higher prevalence of lesions on the left side[9].

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The problem with the retrograde menstruation theory is that it could explain ovarian and superficial peritoneal endometriosis, but not deep infiltrative endometriosis or lesions outside the peritoneal cavity[10].

On the other hand, several studies have shown that menstrual reflux during menstruation is physiological in women with patent fallopian tubes, and most of them (76-90%) experience retrograde menstruation without developing endometriosis[11]. Cases of endometriosis in women with retrograde menstruation who develop the disease could be explained by studies

evaluating risk factors for endometriosis such as: short menstrual cycle, longer menstrual flow, and obstruction of uterine flow. These factors increase the amount of menstrual reflux and cells that are regurgitated retrograde[12].

In researching this theory, the baboon model has been used, performing serial diagnostic laparoscopies to assess the amount and composition of menstrual blood in the peritoneal cavity at different stages of the menstrual cycle. The results show a correlation between retrograde menstruation and the development of endometriosis, but researchers admit that this is most likely not the only pathogenic cause of the disease[12].

Understanding how regurgitated cells lead to endometriosis requires understanding gene expression and regulation, and how these functions depend on the presence of cells in ectopic sites. However, the interactions between endometrial cells and the peritoneal surface remain controversial. One study suggested that endometrial epithelial and stromal cells can penetrate intact mesothelium, but at the same time suggested that the adhesion of menstrual fragments only occurs when the underlying mesothelial extracellular matrix is exposed by a previous local injury[13].

In particular, eutopic endometrium is considered to be the origin of most endometriotic lesions[14]. A large number of specific studies have evaluated the differences in gene expression and epigenetic modifications between eutopic and ectopic endometrium involving specific genes or their regulation by microRNA.

The process of implantation of menstrual endometrial cells in the peritoneum involves adhesion, proliferation, and invasion, with different genes related to this process being recognized. Thus, it is frequently reported that genes involved in adhesion, such as ITGB2 and ITGB7, encode integrin β2 and integrin β7, respectively, while genes involved in proliferation, such as PDGFRA, encode the platelet-derived growth factor receptor α, and the PRKCB gene encodes protein kinase C-β. Among the genes involved in invasion are those that encode matrix metalloproteinases and relaxin.

There are also other genes involved in other processes such as immune recognition (with DEFB4A encoding defensin-β4A), the inflammatory response (with TNF and IL1B encoding IL-1β), steroid biosynthesis, biosynthesis response, and angiogenesis (with VEGF encoding vascular endothelial growth factor) and the ANGPT1 and ANGPT2 genes (encoding angiopoietin 1 and 2, respectively), all of which are aberrantly expressed in ectopic endometrium[15]. Although many of these differences represent changes in the ectopic endometrium as a result of its extrauterine location, which would be relevant for understanding the biological characteristics and markers of endometriosis, it is still unclear to what extent the aberrant expression of these genes contributes to its development[16].

Sampson's theory is a widely accepted mechanism, but it does not explain why endometriosis develops in some women but not in others. Most women experience retrograde menstruation, but endometriosis occurs in only 5 to 10% of them. One of two mechanisms could explain why refluxed endometrium successfully implants in the peritoneum: molecular defects, immunological abnormalities, or both[17]. In endometriosis, the eutopic endometrium exhibits multiple subtle but biologically important molecular abnormalities that promote increased production of estrogens, cytokines, prostaglandins, and metalloproteinases.

When eutopic endometrium, a tissue biologically distinct from peritoneum, attaches to mesothelial cells, the magnitude of molecular abnormalities increases dramatically, improving implant survival[18]. A possible second mechanism of implant survival involves a failure of the immune system to eliminate implants from the peritoneal surface[19]. Both mechanisms may contribute to the development of endometriosis.

It is important to note that there are clear molecular differences between endometrial implants and the endometrium, such as the overproduction of estrogen, prostaglandins, and cytokines in endometriotic tissue[20].

Subtle forms of these abnormalities also occur in the endometrium of a woman with endometriosis compared to the endometrium of a woman without the disease (Fig. 3). Furthermore, the gene expression profile of the endometrium of women with endometriosis compared to the endometrium of women free of the disease has

revealed candidate genes related to implantation failure, infertility, and progesterone resistance[22].

In patients with endometriosis, inflammatory and immune responses, angiogenesis, and apoptosis are altered to benefit the survival and replacement of endometriotic tissue[23]. These pathological processes depend in part on estrogen or progesterone, as excessive estrogen and prostaglandin formation and the development of progesterone resistance have become clinically useful points of study, since therapeutic action targeting aromatase in the estrogen biosynthetic pathway, cyclooxygenase-2 (COX-2) in the prostaglandin pathway, or the progesterone receptor reduces pelvic pain, laparoscopically visible endometriosis, or both[24].

Coelomic metaplasia theory

In 1924, Dr. Robert Meyer first suggested that endometriosis could originate from coelomic metaplasia[24]. This theory, which predates Sampson's theory, first proposed the hypothesis that endometriosis could originate from multipotent mesenchymal stem cells derived from coelomic metaplasia. This suggests that the cells lining the abdominal cavity (coelomic cells) can transform into endometrial cells, creating foci of endometriosis outside the uterus.

This theory supports the hypothesis that multipotent mesenchymal stem cells derived from bone marrow or from a niche within the endometrium itself undergo a process of cellular reprogramming, as a result of which these multipotent cells can differentiate into a niche of ectopic endometrial cells[25]. It is believed that they can differentiate into ectopic sites through endocrine disruptors and hormonal or immunological factors in the stromal epithelium, with endocrine disruptors playing an important role in this transformation[26].

This theory may also explain the origin of endometriosis when it occurs in sites external and distant from the pelvic cavity, including abdominal lymph nodes, lungs, brain, and kidneys. This theory includes cases of Müllerian agenesis in which the Müllerian ducts do not develop[27].

This is the most appropriate explanation for cases of patients with Rokitansky-Kuster-Hauser syndrome who lack functional endometrial tissue due to the congenital absence of the uterus and upper vagina[28], where endometriosis cannot be explained by Sampson's implantation theory due to the absence of eutopic endometrium.

The most common form of endometriosis that could be explained by this theory is ovarian endometrioma. The mesothelium, which derives from the coelomic epithelium lining the ovary, has great metaplastic potential and can invaginate into the ovarian cortex. These mesothelial inclusions could transform into endometriosis by metaplasia[29].

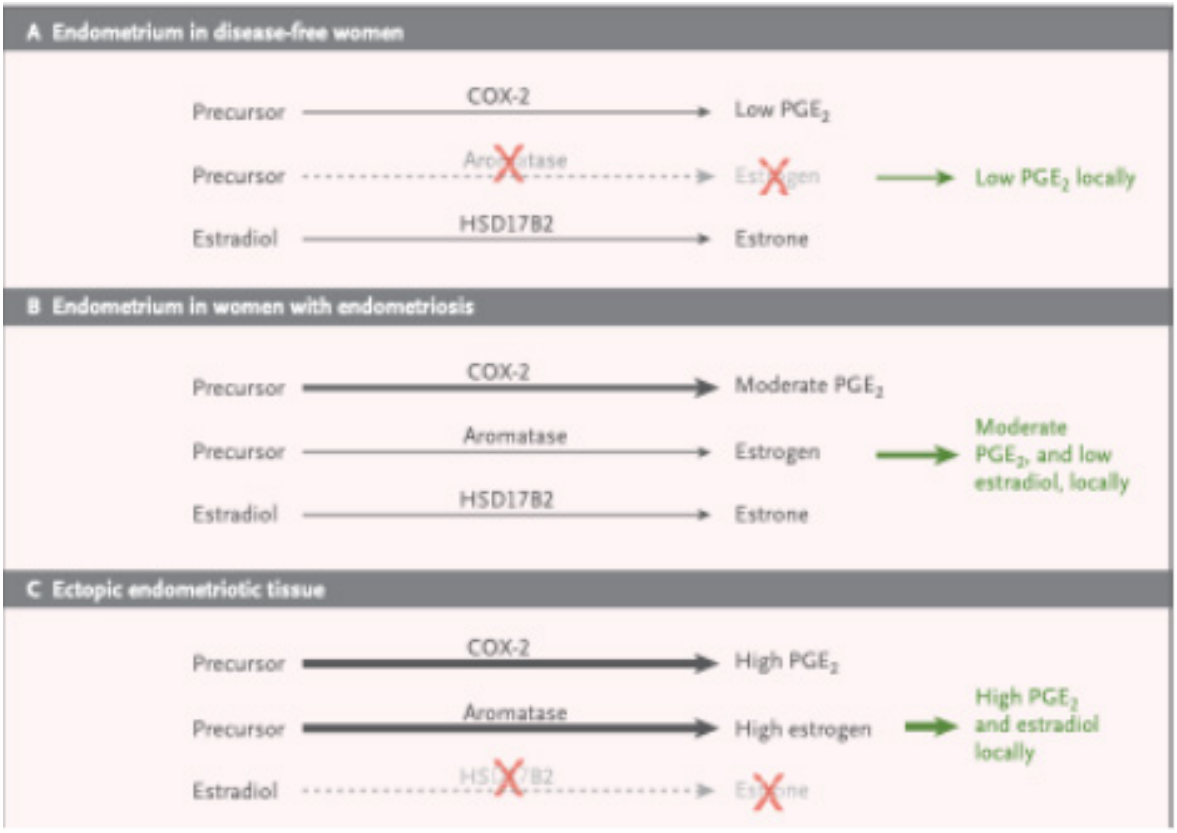
Theory of müllerian embryonic remnant anomalies

During fetal life, Müllerian ducts are primordial embryological structures from which the reproductive system (uterus, fallopian tubes, and the upper two-thirds of the vagina) is formed. These ducts consist of superficial epithelium and mesenchyme, capable of differentiating into endometrial epithelium and stroma[30]. This theory posits that, during organogenesis, Müllerian duct cells undergo a process of disordered differentiation or proliferation[31], causing them to spread to sites outside the expected area of Müllerian duct development[32]. In this way, the residual cells that arise from the embryological migration of the Müllerian duct retain the ability to develop into endometriotic lesions under the influence of estrogen, beginning at puberty or perhaps in response to estrogen[33]. Generally, these cells are located in the posterior pelvic floor and remain inactive until puberty, when the process of endometriotic lesion formation begins with estrogen stimulation.

Recently, in support of this theory, Signorile et al. published their findings from autopsies of female fetuses, where they found the presence of ectopic endometrium in the posterior structures of the pelvic floor: Douglas pouch, rectovaginal septum, rectal tube, and posterior wall of the uterus[34]. These locations are quite common in diagnosed cases of endometriosis.

The embryonic remnant theory is a type of metaplasia theory, which states that the remains of embryonic cells from the Müllerian duct can differentiate into endometriotic lesions. In the coelomic metaplasia theory, the transformation

Figure 3. Normal endometrium and endometriosis
In the normal endometrium (Panel A), COX-2 activity and PGE2 production are low. Estrogen is not produced due to the absence of aromatase. During the luteal phase, the enzyme 17β-hydroxysteroid dehydrogenase 2 (HSD17B2) catalyzes the conversion of estradiol to estrone, which is less estrogenic. In the endometrium of women with endometriosis (Panel B), there is a subtle increase in COX-2 activity and detectable aromatase activity. In ectopic endometriotic tissue (Panel C), there are high levels of COX-2 and aromatase. Increased PGE_2 in endometriotic implants may cause chronic pelvic pain. Estradiol levels should be high, as aromatase produces excess estradiol and it is not metabolized due to deficient HSD17B2 activity. Taken from Bulum et al.[21].



occurs only in the mesothelium, but there is no such restriction in the embryonic remnant theory[31].

Theory of lymphatic and vascular metastasis

In 1927, Sampson suggested an additional pathogenic mechanism to the theory of retrograde menstruation: the theory of metastatic endometriosis. This theory proposes that endometrial cells and tissue fragments can spread through the lymphatic vessels that drain the uterus during menstruation and be transported from the uterine cavity through the blood or lymphatic vessels to colonize distant ectopic sites, such as the lung, diaphragm, abdominal wall, or brain. This hypothesis better describes the rare incidence of extrapelvic endometriosis in women and is supported by evidence of endometrial cell emboli in the lymph nodes[35].

Currently, there are some reports of endometriosis in lymph nodes, confirmed by histopathological examination showing the presence of endometrial glandular and stromal cells in the lymph node[36].

It has been discovered that there is a deregulation of the expression of lymphangiogenic growth factors and their receptors in the eutopic endometrium of women diagnosed with endometriosis. The main promoters of lymphangiogenesis in the endometrium are VEGF-C and VEGF-D, which are positively regulated by proinflammatory cytokines such as interleukin 1 β (IL-1 β), tumor necrosis factor α (TNFα), IL-7, and CD74[37]. In addition, the density of lymphatic microvessels in the eutopic endometrium of patients also increases. Therefore, these changes together could facilitate the entry of endometrial tissue into the lymphatic circulation[38]. However, it is still unclear how this dysregulation actually affects the development of endometriosis.

Theory of endometrial stem cell implantation

Stem cells are multipotent cells with high replicative potential that have an unlimited capacity to renew themselves and produce more differentiated daughter cells[39].

In recent years, numerous studies have focused on the impact of stem cells on endometriosis. These studies show that there are diverse populations of somatic stem cells in the endometrium, including epithelial, mesenchymal, and mixed populations[40]. The main functions of these cells are tissue remodeling, regeneration, and homeostasis.

This theory has gained considerable importance in recent years. It has two main variants based on tissue derived from stem cells, which are believed to originate from the uterine endometrium or bone marrow[41]. Regardless of the origin of the stem cells, hormones and other factors in the tissue microenvironment contribute to the adhesion, invasion, inflammation, angiogenesis, and evasion of immune surveillance necessary for the establishment of endometrial implants[42].

The basis of this theory lies in the dissemination of these cells through different mechanisms, such as retrograde menstruation, lymphatic and vascular dissemination, direct migration, or a combination of all of these, to the implantation site. At this site, influenced by various factors that are not yet fully understood, these multipotent cells begin their proliferation process, often dependent on hormonal cycles, especially estrogen[43]. Therefore, the difference in this theory lies in the fact that it not only fits the model of retrograde menstruation but also explains the pathogenesis of deep infiltrating endometriosis and extra-abdominal endometriosis[44].

The migration of endometrial stem cells remains hypothetical. The first mechanism would be that endometrial stem cells are found in menstrual blood and can reach the peritoneal cavity through the fallopian tubes[34]. The second mechanism is abnormal cell migration during the organogenesis of the female reproductive tract. The last mechanism is the ability of endometrial stem cells to passively enter the angiolymphatic space during menstruation and circulate through the bloodstream[45].

This theory is important because it may explain the pathogenesis of the three subtypes of endometriosis and their ectopic location outside the abdominal cavity. After the migration phase, the stem cells adhere and begin to form endometrial lesions. The potential of stem cells to form lesions was demonstrated by Cervelló et al. by implanting endometrial cells under the renal capsule in immunocompromised mice, resulting in endometriosis[46].

Theory of bone marrow-derived stem cells

This variant of the stem cell theory is based on another source of stem cells: bone marrow. These cells can be incorporated into the endometrium to regenerate tissue[40].

The theory is based on the following: bone marrow stem cells, which circulate through the blood vessels, settle in soft tissue instead of heading to the endometrium, while a small number of cells are recruited to the eutopic endometrium. Recent studies suggest that the CXCL12/CXCR4 axis is involved in the recruitment of bone marrow-derived stem cells, so a malfunction of this axis may cause the incorrect placement of stem cells[45].

The advantage of the bone marrow-derived stem cell theory is its ability to explain extrapelvic endometriosis without the concept of "benign metastasis."

Genetic and epigenetic changes

Endometriosis is a multifactorial disease, where the interaction of genetic and epigenetic factors plays a crucial role in its development.

The first studies related to genetics in patients diagnosed with confirmed endometriosis appeared in the 1980s[47]. Over the years, various studies have demonstrated the relationship between heredity and endometriosis through family aggregation studies, which refer to the presence of specific characteristics found in a given family that cannot be attributed to coincidental events. When a mother has endometriosis, the probability of her daughters developing the disease is 8%, and when a sister has it, the

probability is 6%. In the control population, the risk of daughters developing the disease is less than or equal to 1% in both situations[48]. In addition, a positive family history of endometriosis is associated with a higher probability of severe manifestations of the disease[49].

A series of cumulative genetic-epigenetic events may occur prior to the establishment of endometriosis, as cell division and/or replication errors, which have a low incidence but always occur, but always occur, may be increased by cellular genomic instability, a genetic background vulnerable to the development of endometriosis, and altered epigenetic processes involving changes in gene expression arising from changes in chromosomes but not involving alternation in the DNA sequence mediated by DNA methylation (cytosine residues) and histone modification (methylation or acetylation of specific histones in chromatin), significantly influenced by a disruptive interaction between many factors, such as age, sex, diet, gut microbiome, environmental, microenvironmental, immunological, hormonal factors, and oxidative stress, as well as toxins.

The identification of genetic variants that influence the likelihood of developing endometriosis may be a crucial factor in the pathogenesis of the disease[50]. In view of this, Genome-Wide Association Studies (GWAS) have identified various genetic variations (Single Nucleotide Polymorphisms (SNPs)) in patients with endometriosis. The genes identified include:

- VETZ: Involved in cell growth, migration, and adhesion.
- CDKN2B-AS1: Controls specific tumor suppressors; its inactivation has been correlated with the development of endometriosis and endometrial cancer.
- WNT-4: Essential in the development of the female reproductive system and the formation of the Müllerian duct.
- GREB1: Involved in estrogen regulation.
- ID4: Found in co-suppressor genes related to human ovarian tumors.

Some of these loci are strongly associated with advanced cases of endometriosis (stages III and IV according to ASRM), suggesting a correlation between SNPs and the development of moderate to severe disease[51].

Somatic Mutations: The relationship between endometriosis and the risk of ovarian cancer has prompted the analysis of somatic mutations. Exome sequencing has found that 79% of lesions (ovarian endometriomas and/or deep infiltrating endometriosis - DIE) have mutations, and 26% of these are found in the ARID1A, PIK3CA, KRAS, and PPP2R1A genes. It is important to note that PIK3CA and KRAS are genes that are frequently mutated in ovarian cancer. These findings may partially explain the aggressive nature of DPE lesions compared to superficial lesions and suggest a critical role for these mutations in the implantation and establishment of endometriotic lesions[52].

Epigenetic changes

Epigenetic modifications are reversible changes in a cell's DNA or histones that regulate gene expression without altering the DNA sequence. They are influenced by a complex interaction between age, sex, diet, gut microbiome, environmental, microenvironmental, immunological, and hormonal factors, oxidative stress, and toxins. Two of the most characterized epigenetic modifications are DNA methylation (cytosine residues) and histone modification (methylation or acetylation of specific histones in chromatin)[51].

Numerous pieces of evidence show that endometriosis is an epigenetic disease, as follows:

Hypermethylation of the HOXA10 gene:

The HOXA10 gene promoter is hypermethylated in the endometrium of women with endometriosis compared to healthy women without the disease. This gene is expressed in the eutopic endometrium and increases dramatically during the secretory phase of the menstrual cycle, which corresponds to the time of implantation and increased circulating progesterone.

Hypermethylation is generally associated with gene silencing, causing changes in transcription and reduced expression. The reduction of

HOXA10 in women with endometriosis is related to defects in uterine receptivity, which could explain the low fertility rate of these women[53]. In addition, hypermethylation of the HOXA10 gene results in reduced expression of E-cadherin, an intercellular adhesion molecule, which promotes the breakdown of intercellular junctions and the process of cell invasion[47].

Hypermethylation of the progesterone receptor-B (PR-B) promoter:

This leads to a reduction in PR-B expression, a scenario that contributes to progesterone resistance, a key feature of endometriosis[54].

Hypomethylation of specific genes:

On the other hand, some genes may be hypomethylated, resulting in increased expression. The main genes or promoter regions where hypomethylation occurs are the estrogen receptor-β (ER-β), steroidogenic factor-1 (SF-1), and aromatase. SF-1 is a transcription factor that activates several genes for estrogen biosynthesis, which in turn is not detected in eutopic endometrial stromal cells because the SF-1 promoter is generally hypermethylated in endometrial cells. Hypomethylation of the SF-1 promoter at ectopic sites explains its overexpression and the consequent increase in estrogen. The same is true for the aromatase gene and the ER-β promoter, where overexpression in ectopic endometrial cells also leads to an increase in estrogen and its receptor, respectively[55].

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Histone Acetylation:

Another relevant epigenetic modification is the methylation or acetylation of specific histones in chromatin. Enzymes called histone deacetylases are responsible for the modulation and acetylation of these enzymes.

In endometriosis, HDAC1 and HDAC2 activity is increased. This leads to hypoacetylation of cyclins, which induces cell cycle and proliferation[56].

DNA METHYLTRANSFERASE ENZYMES (DNMTs):

These enzymes are responsible for DNA methylation. Normally, the expression of DNMTs in the endometrium is regulated by estrogen and progesterone and varies according to the phase of the cycle. In patients with endometriosis, hypermethylation of local cell DNA occurs due to increased expression of the DNA methyltransferases DNMT1, DNMT3A, and DNMT3B, which are crucial for endometrial decidualization[57].

- MicroRNAs (miRNAs): These are short non-coding RNA molecules that regulate post-transcriptional mRNA translation by repressing and degrading mRNA. In endometriosis, an abnormal spectrum of microRNAs is observed that influence the expression of relevant target mRNAs[58]. A wide spectrum of microRNAs is involved in different stages of endometriosis. These include:

  - miRNA-135a/b: Regulates HOXA10, is overexpressed in endometriosis, and causes resistance to progesterone.

  - miR-199: Is downregulated, which prevents the suppression of COX-2 and leads to the synthesis of proinflammatory prostaglandins such as IL-8.

  - miRNA-96b: Downregulated, resulting in increased proliferation of endometrial lesions.

- miR-126: Overexpressed, increases VEGF and FGF signaling in endothelial cells, promoting neoangiogenesis and the development of mature vasculature.

- miRNA-223: Has been found to be decreased in eutopic and ectopic endometrial stromal cells. Its upregulation could suppress the proliferation, invasion, and migration of these cells, and even reverse the epithelial-mesenchymal transition, making it a potential therapeutic target[59]

- miRNA-21: Promotes the growth, proliferation, and angiogenesis of ectopic stromal cells.

• Other miRNAs such as miR-26b-5p and miR-215-5p (downregulated) and miR-6795-3p (overexpressed) have been correlated with disease severity and are involved in signaling pathways such as MAPK and PI3K-Akt, which regulate inflammation, cell growth, differentiation, proliferation, and angiogenesis, and are also potential therapeutic targets.

Genetic-epigenetic, hormonal, and immunological interactions

Genetic and epigenetic factors do not act in isolation. Endometriosis is the result of dysregulated interactions involving genetics, epigenetics, immunoregulation, hormones, and environmental factors. For example, progesterone resistance, a key feature of endometriosis, is influenced by hypermethylation of the progesterone receptor. The elevated estrogen environment, in turn, can induce the translocation of NF-κB (Nuclear Factor kappa B) to the nucleus and activate peritoneal macrophages, leading to an increase in proinflammatory cytokines. Deregulation of interactions between genetic and epigenetic factors is fundamental to the onset of endometriosis, especially after a series of cumulative incidents that exceed the cell's capacity to adapt.

Hormonal imbalance

Progesterone and estrogen signaling in a healthy endometrium is highly coordinated and depends on the phase of the menstrual cycle, which is important for maintaining a normal menstrual cycle, embryo implantation, and pregnancy development. Estrogen induces epithelial proliferation during the proliferative phase, while progesterone inhibits the action of estrogen and initiates the secretory phase, when stromal cells begin decidualization (60). Dysregulation of these two hormones (progesterone resistance and estrogen dominance) leads to the development of endometriosis (Fig. 4).

Estrogens

Endometriosis is often considered an estrogen-dependent disease

The reason for this assertion is that endometriosis mainly affects women of reproductive age, but it can also occur in postmenopausal women if they have high estrogen levels or undergo estrogen replacement therapy[61].

The main functions of estrogen in a healthy endometrium include: stimulation of epithelial proliferation and induction of leukemia inhibitory factor (LIF), a cytokine of the IL-6 family, which is important for successful embryo implantation and decidualization of the endometrium.

In endometriosis, studies report high levels of estradiol in menstrual bleeding and abnormal expression of enzymes involved in estrogen metabolism, which can lead to higher estrogen concentrations and inactivation of estrogen synthesis.

There are two types of estrogen receptors in the endometrium, ERα and ERβ, encoded by different β genes: ESR1 and ESR2, respectively[61]. Normally, they work together, but in patients with endometriosis, receptor expression is altered: the ERα:ERβ ratio is significantly reduced due to high levels of ERβ. The main problem caused by abnormal ERα expression is increased synthesis of inflammatory cytokines, prostaglandins, and tumor-promoting and angiogenic factors[20,29]. On the other hand, ERβ overexpression inhibits TNFα-induced apoptosis and also promotes inflammation[62]. The synthesized prostaglandins induce inflammation and prevent cell apoptosis; tumor-promoting and angiogenic factors favor the progression of endometrial lesions, and the inhibition of apoptosis promotes cell proliferation and lesion growth[63]. In addition, estrogen can stimulate the growth of peripheral nerve fibers by positively regulating nerve growth factors (NGF) that cause nociceptive pain[63].

Progesterone

Progesterone receptor (PGR) expression is induced by the action of estrogens through their ERα receptor. PGR has two isoforms: PR-A and PR-B, whose expression increases during the proliferative phase and decreases after ovulation[62]. Expressed PGR inhibits ERα expression, establishing a feedback system.

In endometriosis, due to the low ERα:ERβ ratio and high estrogen levels, resistance to progesterone develops: PR-B is undetectable and PR-A levels are significantly lower than in the endometrium of healthy women. Resistance to progesterone manifests as a lower response of endometrial stromal cells to progesterone[64].

Immune dysregulation

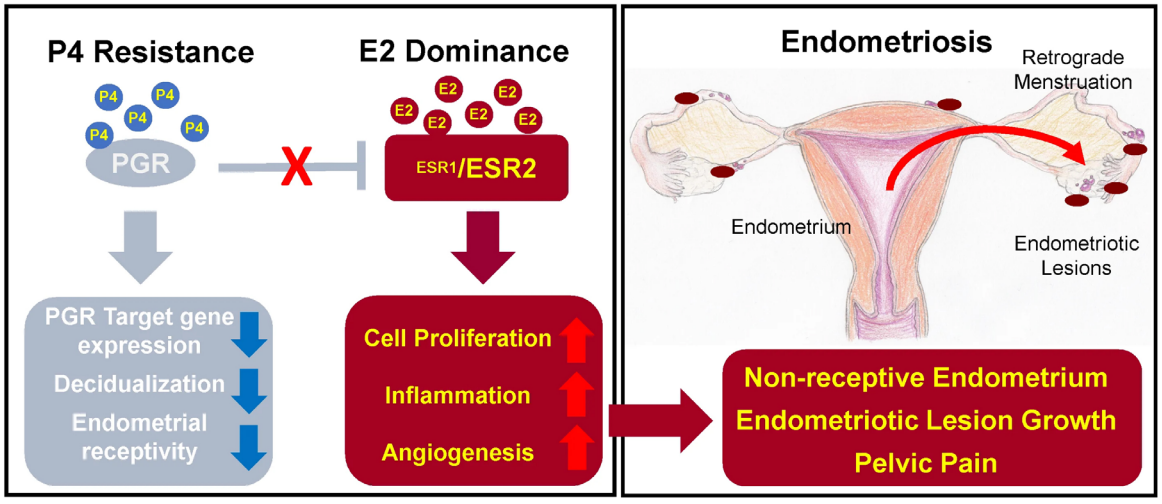
Inflammation, caused by immune dysregulation, is one of the main mechanisms involved in endometriosis. This dysregulation is one of the main pro-inflammatory pathways that block the functions of cells involved in diseases where cell proliferation and infiltration occur. The immune cells involved in pro-inflammatory pathways block the functions of apoptotic mechanisms and potentially the formation and development of harmful cells that attach to sites distant from endometrial lesions[65]. The immune cells involved in the formation and further development of endometrial lesions are: macrophages, neutrophils, NK cells, dendritic cells, and T cells (Fig. 5).

Macrophages

Macrophages detect and phagocytose pathogens and foreign cells, act as antigen-presenting cells to activate T cells, and participate in the tissue regeneration of healthy endometrium[67]. Normally, macrophages represent approximately 10% of the total immune cell population in the proliferative phase of the endometrium. Their number varies according to the phase of the menstrual cycle, regulated by estradiol and progesterone. During menstruation, their number increases significantly to phagocytose and thus eliminate apoptotic cells and cell debris during endometrial desquamation.

In endometriosis, the number of macrophages increases in the eutopic endometrium and peritoneal fluid in all phases of the menstrual cycle and without cyclical changes[68]. Conversely, phagocytic function decreases due to lower expression of CD3, CD36, and annexin A2[69]. This causes incomplete endometrial shedding and the presence and survival of shed tissue in the peritoneal cavity[68]. Peritoneal macrophages release proinflammatory cytokines TNFα, IL-6, IL-8, and IL-1β, which recruit neutrophils, causing inflammation and promoting the development of endometrial lesions[70]. Macrophages also produce VEGF, which promotes angiogenesis in endometriosis. On the other hand, some studies have found a predominance of the M2 macrophage subtype in endometriotic lesions and the peritoneal cavity[71]. In addition, this subtype

Figure 4. Effects of progesterone and estrogen dysregulation on the endometrium. Taken from Marquardt, R.M. et al.[60].



promotes the growth of nerve fibers, so the predominance of this macrophage subtype could be related to the intense pain experienced by women with endometriosis[66,67].

Neutrophils

Neutrophils participate in endometrial repair and the regulation of cyclic vascular proliferation in healthy endometrium. Neutrophil counts in peritoneal fluid are increased in women with endometriosis. This could be attributed to the local increase in the concentration of chemoattractants secreted by epithelial cells, such as IL-8, epithelial neutrophil activating peptide 8 (ENA-78), and human neutrophil peptides 1-3 (HNP1-3), which attract neutrophils to the peritoneal cavity[71].

One study found that depletion of neutrophils with anti-Gr-1 antibodies in the early stage of endometriosis significantly reduced the number of endometrial lesions[72]. In contrast, this antibody had no effect in advanced disease, suggesting that neutrophils are not involved in the progression of endometriosis, but only in its induction. However, neutrophils express cytokines, for example, VEGF, IL-8, and C-X-C chemokine motif ligand 10 (CXCL10), which cause disease progression[72].

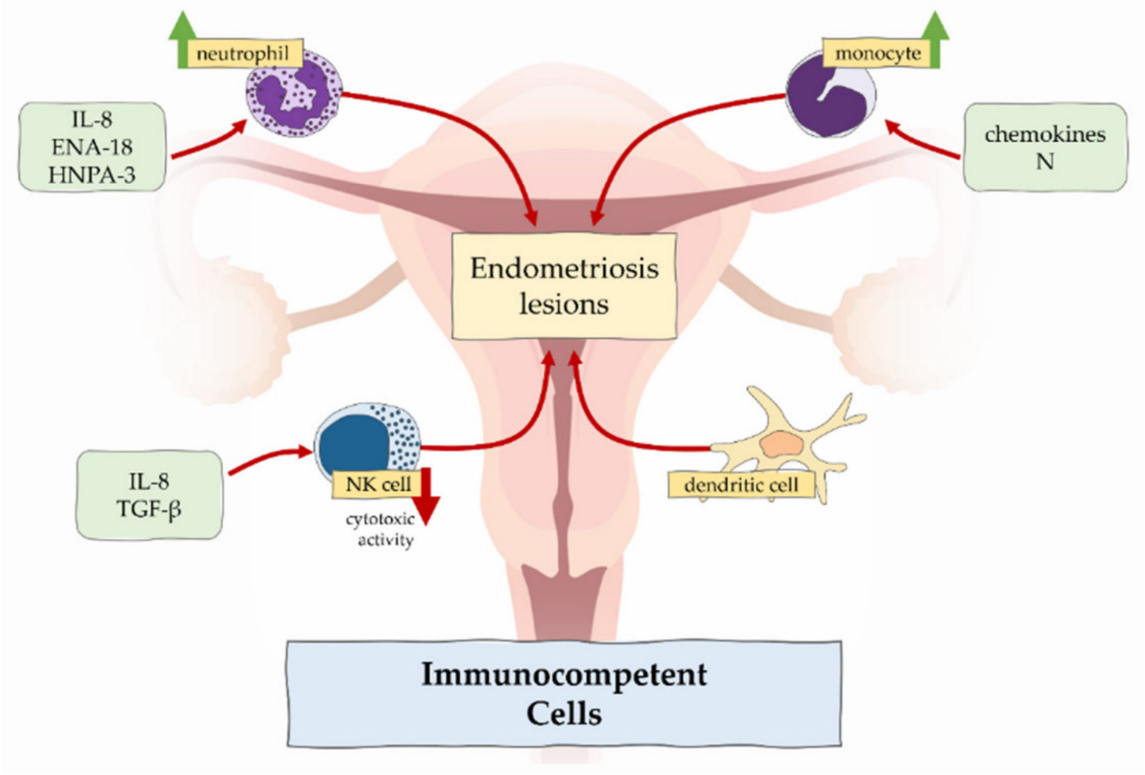
NK cells

The function of natural killer (NK) cells in the immune system is to produce cytokines that control tumor immunity and microbial infections. In the case of endometriosis, their cytotoxic function is suppressed by IL-6, IL-15, and transforming growth factor β (TGFβ)[63]. Therefore, endometrial cells that enter the peritoneal cavity tend to remain there. However, the number of NK cells does not differ between women with and without endometriosis.

T lymphocytes

One of the important factors that maintains the development of endometriosis is the imbalance between type 1 T lymphocytes (Th1) and type 2 T lymphocytes (Th2). These two types of lymphocytes have different functions in the immune system: Th1 lymphocytes produce cytokines

Figure 5. Immunocompetent cells in endometriosis. Changes in immunocompetent cells in endometriosis. Taken from Abramiuk, M. et al. The role of the immune system in the development of endometriosis.[66].



and promote cellular response, while Th2 lymphocytes influence B lymphocyte differentiation and suppress cellular and humoral response[73]. In endometriosis, Th2 lymphocytes represent the main population of T lymphocytes, so potentially harmful cells go unnoticed. In addition, the immune response of CD4+ Th1 lymphocytes in the peritoneal fluid is suppressed due to increased expression of IL-10 and IL-12.

On the other hand, the peripheral concentration of cytotoxic T lymphocytes (CD8+) and activated T lymphocytes (HLA-DR) in healthy women increases during the luteal phase compared to the follicular phase of the menstrual cycle, but similar fluctuations in cytotoxic and activated T lymphocytes are not observed in patients with endometriosis[74].

Recently, the association between regulatory T lymphocytes (Treg cells) and endometriosis has been described. The main function of regulatory T cells is to modulate the immune system. In patients with endometriosis, an increase in the number of Tregs is observed in the peritoneal fluid and a decrease in the peripheral blood. These changes can lead to the development of autoimmune reactions and suppress the local cellular immune response.

Dendritic Cells

Dendritic cells also play an important role in the immune system. They are responsible for presenting antigens to T lymphocytes and therefore participate in the immune response in mucosal surfaces. There are two types of cells, plasmacytoid and myeloid. Plasmacytoid cells participate in virus recognition and produce interferons, while myeloid cells participate in T-cell activation and are the most relevant cells for endometriosis. In healthy individuals, the number of dendritic cells increases to eliminate endometrial debris during menstruation. In women with endometriosis, the density of myeloid dendritic cells in the endometrium is significantly reduced. In the peritoneal cavity, the number of dendritic cells increases, which can promote neuroangiogenesis, causing and increasing the sensation of pain[75].

Conclusion

The etiology of endometriosis is a complex puzzle, and no single theory can explain all of its diverse clinical presentations and pathological characteristics.

Hypotheses have varied over time. The first hypothesis, in the 19th century, was that endometriosis lesions were metaplastic changes, where one differentiated cell was transformed into another differentiated cell. Subsequently, metaplasia of embryological remnants was described for specific types of endometriosis. Today, metaplasia is understood as epigenetic changes that transform a differentiated cell, a stem cell, or a bone marrow cell into another differentiated cell. Depending on the type of epigenetic changes, metaplasia can be reversible or irreversible.

In 1925, Sampson described the hypothesis of retrograde menstruation and implantation. This theory became popular because endometrial cells are viable with the potential for implantation on the peritoneal and ovarian surfaces. However, when it was discovered that retrograde menstruation occurred in almost all women, but that not all women developed the disease, it became difficult to support this hypothesis.

Sampson's theory is incompatible with the biological variability and clonal aspect of endometriosis lesions. Each lesion, whether typical, ovarian cystic, or deep, is a clonal tumor that originates from a single cell, and if a woman has 10 different lesions, these are 10 different clones. This explains why the lesions are different, heterogeneous, with some having no aromatase activity and others having strong aromatase activity or resistance to progestogens.

Since the implantation theory cannot explain many other observations of endometriosis, the “genetic-epigenetic” (GE) theory (76) has emerged, which posits that the onset of a new endometriosis clone is triggered by a set of GE incidents. Women are born with specific GE characteristics, which explains the hereditary aspect, susceptibility to developing endometriosis, and many associated factors, such as infertility and endometrial and plasma changes.

During life, additional GE incidents may occur during cell division, especially in the endometrium, which is the fastest-growing tissue. Endometriosis only begins when the cumulative set of inherited and acquired GE incidents exceeds a threshold. This explains why each lesion has a different set of GE incidents and why lesions or clones are heterogeneous. Therefore, endometriosis is not a single disease, but a mixture of sever-

al diseases with typical, cystic, and deep endometriosis as the main forms of clinical presentation.

Therefore, growing evidence about genetic and epigenetic factors provides a deeper understanding of the mechanisms underlying the initiation and progression of the disease.

The identification of associated single nucleotide polymorphisms (SNPs), somatic mutations in endometriotic lesions, and complex networks of DNA methylation, histone acetylation, and miRNA dysregulation reveal that endometriosis is not simply a disease of ectopic implants, but a condition rooted in molecular alterations that impact cell proliferation, immune response, hormonal sensitivity, and invasive capacity. This knowledge is crucial as it opens new avenues for the development of new diagnostic and therapeutic strategies, targeting the molecular roots of the disease.

Endometriosis, viewed from the perspective of genetics and epigenetics, is comparable to a complex computer program: it is not just an error in a line of code (a single gene), but an intricate network of adjustments in the configuration (epigenetics) with multiple failures, which combined, fundamentally alter the functioning of the system, leading to the manifestations of the disease. Understanding these "programming errors" is the key to better understanding the disease, "reprogramming" the pathology, and rethinking treatments to restore patients' health.

References

1. Sampson, J. A. Peritoneal endometriosis due to the menstrual dissemination of endometrial tissue into the peritoneal cavity. Am. J. Obstet. Gynecol. 14, 422–469 (1927).
2. Peng-Hui Wang, Szu-Ting Yan, Wen-Hsun Chang, Fa-Kung Lee, Wen-Ling Lee. Endometriosis: Part I. Basic concept. Taiwanese Journal of Obstetrics & Gynecology 61 (2022) 927- 934
3. Signorile PG, Viceconte R, Baldi A. New insights in pathogenesis of endometriosis. Front Med 2022; 9:879015.
4. Yovich, J.L.; Rowlands, P.K.; Lingham, S.; Sillender, M.; Srinivasan, S. Pathogenesis of endometriosis: Look no further than John Sampson. Reprod. Biomed. Online 2020, 40, 7–11. [CrossRef] [PubMed]
5. Sampson, J.A. The development of the implantation theory for the origin of peritoneal endometriosis. Am. J. Obstet. Gynecol.1940, 40, 549–557.
6. Nisolle, M.; Donnez, J. Peritoneal endometriosis, ovarian endometriosis, and adenomyotic nodules of the rectovaginal septum are three different entities. Fertil. Steril. 1997, 68, 585–596.
7. Izumi, G.; Koga, K.; Takamura, M.; Makabe, T.; Satake, E.; Takeuchi, A.; Taguchi, A.; Urata, Y.; Fujii, T.; Osuga, Y. Involvement of immune cells in the pathogenesis of endometriosis. J. Obstet. Gynaecol. Res. 2018, 44, 191–198.
8. Missmer, S. A. et al. Reproductive history and endometriosis among premenopausal women. Obstet. Gynecol. 104, 965–974 (2004).
9. Vercellini, P. et al. Asymmetry in distribution of diaphragmatic endometriotic lesions: evidence in favour of the menstrual reflux theory. Hum. Reprod. 22, 2359–2367 (2007).
10. Wang, Y.; Nicholes, K.; Shih, I.M. The origin and pathogenesis of endometriosis. Annu. Rev. Pathol. 2020, 15, 71–95.
11. D'Hooghe, T.M.; Debrock, S. Endometriosis, retrograde menstruation and peritoneal inflammation in women and in baboons. Hum. Reprod. Update 2002, 8, 84–88.
12. Signorile, P.G.; Viceconte, R.; Baldi, A. New insights in pathogenesis of endometriosis. Front. Med. 2022, 9, 879015.
13. Witz, C. A., Cho, S., Centonze, V. E., Montoya-Rodriguez, I. A. & Schenken, R. S. Time series analysis of transmesothelial invasion by endometrial stromal and epithelial cells using three-dimensional confocal microscopy. Fertil. Steril. 79(Suppl. 1), 770–778 (2003).
14. Reis, F. M., Petraglia, F. & Taylor, R. N. Endometriosis: hormone regulation and clinical consequences of chemotaxis and apoptosis. Hum. Reprod. Update 19, 406–418 (2013).
15. Sanchez, A. M. et al. The endometriotic tissue lining the internal surface of endometrioma: hormonal, genetic, epigenetic status, and gene expression profile. Reprod. Sci. 22, 391–401 (2015).
16. Borghese, B., Zondervan, K. T., Abrao, M. S., Chapron, C. & Vaiman, D. Recent insights on the genetics and epigenetics of endometriosis. Clin. Genet. 91, 254–264 (2016).
17. Lucidi RS, Witz CA, Chrisco M, Binkley PA, Shain SA, Schenken RS. A novel in vitro model of the early endometriotic lesion demonstrates that attachment of endometrial cells to mesothelial cells is dependent on the source of endometrial cells. Fertil Steril 2005; 84:16
18. Nair A, Nair H, Lucidi R, et al. Modeling the early endometriotic lesion: mesothelium-endometrial cell co-culture increases endometrial invasion and alters mesothelial and endometrial gene transcription. Fertil Steril 2007; 90:1487-95.
19. Dmowski WP, Gebel HM, Rawlins RG. Immunologic aspects of endometriosis. Obstet Gynecol Clin North Am 1989; 16:93-103.
20. Noble LS, Takayama K, Zeitoun KM, et al. Prostaglandin E 2 stimulates aromatase expression in endometriosis-derived stromal cells. J Clin Endocrinol Metab 1997; 82:600-6.
21. Bulun SE, Lin Z, Imir G, et al. Regulation of aromatase expression in estrogenresponsive breast and uterine disease: from bench to treatment. Pharmacol Rev 2005; 57:359-83.
22. Kao LC, Germeyer A, Tulac S, et al. Expression profiling of endometrium from women with endometriosis reveals candidate genes for disease-based implantation failure and infertility. Endocrinology 2003; 144:2870-81.
23. Dmowski WP, Gebel HM, Rawlins RG. Immunologic aspects of endometriosis. Obstet Gynecol Clin North Am 1989; 16:93-103.
24. Zondervan, K.T.; Becker, C.M.; Koga, K.; Missmer, S.A.; Taylor, R.N.; Viganò, P. Endometriosis. Nat. Rev. Dis. Primers 2018, 4, 1–25. [CrossRef]

25. Konrad, L.; Dietze, R.; Kudipudi, P.K.; Horné, F.; Meinhold-Heerlein, I. Endometriosis in Mrkh Cases as A Proof for The Coelomic Metaplasia Hypothesis? Reproduction 2019, 158, R41–R47. [CrossRef]

26. Rolla, E. Endometriosis: Advances and Controversies in Classification, Pathogenesis, Diagnosis, and Treatment. F1000Research 2019, 8, 529

27. Mandai, M.; Osuga, Y.; Hirata, T.; Enomoto, T.; Nakai, H.; Honda, R.; Taniguchi, F.; Katabuchi, H. Cancers Associated with Extraovarian Endometriosis at Less Common/Rare Sites: A Nationwide Survey in Japan. J. Obstet. Gynaecol. Res. 2020, 46, 917–923.

28. Cho, M.K.; Kim, C.H.; Oh, S.T. Endometriosis in a patient with Rokitansky-Kuster-Hauser syndrome. J. Obstet. Gynaecol. Res. 2009, 35, 994–996.

29. Nisolle, M.; Donnez, J. Peritoneal endometriosis, ovarian endometriosis, and adenomyotic nodules of the rectovaginal septum are three different entities. Fertil. Steril. 1997, 68, 585–596.

30. García-Solares, J.; Donnez, J.; Donnez, O.; Dolmans, M. Pathogenesis of Uterine Adenomyosis: ¿Invagination or Metaplasia? Fertil.Steril. 2018, 109, 371–379.

31. Gordts, S.; Koninckx, P.; Brosens, I. Pathogenesis of Deep Endometriosis. Fertil. Steril. 2017, 108, 872–885.

32. Laganà, A.S.; Garzon, S.; Götte, M.; Viganò, P.; Franchi, M.; Ghezzi, F.; Martin, D.C. The Pathogenesis of Endometriosis: Molecular and Cell Biology Insights. Int. J. Mol. Sci. 2019, 20, 5615.

33. Burney, R.O.; Giudice, L.C. Pathogenesis and Pathophysiology of Endometriosis. Fertil. Steril. 2012, 98, 511–519.

34. Signorile, P.G.; Viceconte, R.; Baldi, A. New insights in pathogenesis of endometriosis. Front. Med. 2022, 9, 879015.

35. Mechsner, S.; Weichbrodt, M.; Riedlinger, W.; Bartley, J.; Kaufmann, A.; Schneider, A.; Kohler, C. Estrogen and Progestogen Receptor Positive Endometriotic Lesions and Disseminated Cells in Pelvic Sentinel Lymph Nodes of Patients with Deep Infiltrating Rectovaginal Endometriosis: A Pilot Study. Hum. Reprod. 2008, 23, 2202–2209.

36. Jerman, L.F.; Hey-Cunningham, A.J. The role of the lymphatic system in endometriosis: A comprehensive review of the literature. Biol. Reprod. 2015, 64, 1–10.

37. Takehara, M.; Ueda, M.; Yamashita, Y.; Terai, Y.; Hung, Y.C.; Ueki, M. Vascular endothelial growth factor A and C gene expression in endometriosis. Hum. Pathol. 2004, 35, 1369–1375.

38. Keichel, S.; Barcena de Arellano, M.L.; Reichelt, U.; Riedlinger, W.F.; Schneider, A.; Köhler, C.; Mechsner, S. Lymphangiogenesis in deep infiltrating endometriosis. Hum. Reprod. 2011, 26, 2713–2720.

39. Figueira, P.G.; Abrão, M.S.; Krikun, G.; Taylor, H.S. Stem cells in endometrium and their role in the pathogenesis of endometriosis. Ann. N. Y. Acad Sci. 2011, 1221, 10–17

40. Djokovic, D.; Calhaz-Jorge, C. Somatic stem cells and their dysfunction in endometriosis. Front. Surg. 2014, 1, 51.

41. Sasson, I.E.; Taylor, H.S. Stem Cells and The Pathogenesis of Endometriosis. Ann. N. Y. Acad. Sci. 2008, 1127, 106–115.

42. Cousins, F.L.; Dorien, F.O.; Gargett, C.E. Endometrial Stem/Progenitor Cells and Their Role in The Pathogenesis of Endometriosis. Best Pract. Res. Clin. Obstet. Gynaecol. 2018, 50, 27–38.

43. Maruyama, T.; Yoshimura, Y. Stem Cell Theory for The Pathogenesis of Endometriosis. Front. Biosci. 2012, 4, 2754–2763.

44. Liu, Y.; Zhang, Z.; Yang, F.; Wang, H.; Liang, S.; Wang, H.; Yang, J.; Lin, J. The Role of Endometrial Stem Cells in The Pathogenesis of Endometriosis and Their Application to Its Early Diagnosis. Biol. Reprod. 2020, 102, 1153–1159.

45. Wang, Y.; Nicholes, K.; Shih, I.M. The origin and pathogenesis of endometriosis. Annu. Rev. Pathol. 2020, 15, 71–95. Wang, Y.; Nicholes, K.; Shih, I.M. The origin and pathogenesis of endometriosis. Annu. Rev. Pathol. 2020, 15, 71–95. Wang, Y.; Nicholes, K.; Shih, I.M. The origin and pathogenesis of endometriosis. Annu. Rev. Pathol. 2020, 15, 71–95.

46. Cervelló, I.; Mas, A.; Gil-Sanchis, C.; Peris, L.; Faus, A.; Saunders, P.T.; Critchley, H.O.; Simón, C. Reconstruction of endometrium from human endometrial side population cell lines. PLoS ONE 2011, 6, e21221

47. Daraï, E.; Ploteau, S.; Ballester, M.; Bendifallah, S. Endométriose: Physiopathologie, Facteurs Génétiques Et Diagnostic Clinique. Presse Med. 2017, 46, 1156–1165.

48. Simpson, J.L.; Bischoff, F.Z.; Kamat, A.; Buster, J.E.; Carson, S.A. Genetics of Endometriosis. Obstet. Gynecol. Clin. N. Am. 2003, 30, 21–40.

49. Deiana, D.; Gessa, S.; Anardu, M.; Daniilidis, A.; Nappi, L.; D'alterio, M.N.; Pontis, A.; Angioni, S. Genetics of Endometriosis: A Comprehensive Review. Gynecol. Endocrinol. 2019, 35, 553–558.

50. Zondervan, K.T.; Becker, C.M.; Koga, K.; Missmer, S.A.; Taylor, R.N.; Viganò, P. Endometriosis. Nat. Rev. Dis. Primers 2018, 4, 1–25.

51. Bulun, S.E.; Yilmar, B.D.; Sison, C.; Miyazaki, K.; Bernardi, L.; Liu, S.; Kohlmeier, A.; Yin, P.; Milad, M.; Wei, J. Endometriosis. Endocr. Rev. 2019, 40, 1048–1079.

52. Suda, K.; Nakaoka, H.; Yoshihara, K.; Ishiguro, T.; Adachi, S.; Kase, H.; Motoyama, T.; Inoue, I.; Enomoto, T. Different mutation profiles between epithelium and stroma in endometriosis and normal endometrium. Hum. Reprod. 2019, 34, 1899–1905.

53. Signorile, P.G.; Severino, A.; Santoro, M.; Spyrou, M.; Viceconte, R.; Baldi, A. Methylation Analysis of Hoxa10 Regulatory Elements in Patients with Endometriosis. BMC Res. Notes 2018, 11, 722.

54. Wu, Y.; Strawn, E.; Basir, Z.; Halverson, G.; Guo, S. Promoter Hypermethylation of Progesterone Receptor Isoform B (Pr-B) In Endometriosis. Epigenetics 2006, 1, 106–111.

55. Guo, S. Epigenetics of Endometriosis. Mol. Hum. Reprod. 2009, 15, 587–607.

56. Laganà, A.S.; Garzon, S.; Götte, M.; Viganò, P.; Franchi, M.; Ghezzi, F.; Martin, D.C. The pathogenesis of endometriosis: Molecular and cell biology insights. Int. J. Mol. Sci. 2019, 20, 5615.

57. Asghari, S.; Valizadeh, A.; Aghebati-Maleki, L.; Nouri, M.; Yousefi, M. Endometriosis: Perspective, lights, and shadows of etiology. Biomed. Pharmacother. 2018, 106, 163–174.

58. Teague, E.M.; Print, C.G.; Hull, M.L. The role of microRNAs in endometriosis and associated reproductive conditions. Hum Reprod. Update 2010, 16, 142–165.

59. Xue, Y.; Lin, X.; Shi, T.; Tian, Y. MiRNA-223 expression in patient-derived eutopic and ectopic endometrial stromal cells and its effect on epithelial-to-mesenchymal transition in endometriosis. Clinics 2022, 77, 100112.

60. Marquardt, R.M.; Kim, T.H.; Shin, J.H.; Jeong, J.W. Progesterone and estrogen signaling in the endometrium: What goes wrong in endometriosis? Int. J. Mol. Sci. 2019, 20, 3822.

61. Koukoura, O.; Sifakis, S.; Spandidos, D.A. DNA methylation in endometriosis (Review). Mol. Med. Rep. 2016, 13, 2939–2948.

62. Kim, J.J.; Kurita, T.; Bulun, S.E. Progesterone action in endometrial cancer, endometriosis, uterine fibroids, and breast cancer. Endocr. Rev. 2013, 34, 130–162.

63. iang, I.; Yong, P.J.; Allaire, C.; Bedaiwy, M.A. Intricate connections between the microbiota and endometriosis. Int. J. Mol. Sci. 2021, 22, 5644.

64. Saunders, P.T.K.; Horne, A.W. Endometriosis: Etiology, pathobiology, and therapeutic prospects. Cell 2021, 184, 2807–2824.

65. Kapoor, R.; Stratopoulou, C.A.; Dolmans, M.M. Pathogenesis of endometriosis: New insights into prospective therapies. Int. J. Mol. Sci. 2021, 22, 11700.

66. Abramiuk, M.; Grywalska, E.; Małkowska, P.; Sierawska, O.; Hrynkiewicz, R.; Nied´zwiedzka-Rystwej, P. The role of the immune system in the development of endometriosis. Cells 2022, 11, 2028.

67. Vallvé-Juanico, J.; Houshdaran, S.; Giudice, L.C. The endometrial immune environment of women with endometriosis. Hum. Reprod. Update 2019, 25, 565–592.

68. Berbic, M.; Schulke, L.; Markham, R.; Tokushige, N.; Russell, P.; Fraser, I.S. Macrophage expression in endometrium of women with and without endometriosis. Hum. Reprod. 2009, 24, 325–332.

69. Wu, M.H.; Chuang, P.C.; Lin, Y.J.; Tsai, S.J. Suppression of annexin A2 by prostaglandin E 2 impairs phagocytic ability of peritoneal macrophages in women with endometriosis. Hum. Reprod. 2013, 28, 1045–1053.

70. Smolarz, B.; Szyłło, K.; Romanowicz, H. Endometriosis: Epidemiology, classification, pathogenesis, treatment and genetics (Review of literature). Int. J. Mol. Sci. 2021, 22, 10554.

71. Izumi, G.; Koga, K.; Takamura, M.; Makabe, T.; Satake, E.; Takeuchi, A.; Taguchi, A.; Urata, Y.; Fujii, T.; Osuga, Y. Involvement of immune cells in the pathogenesis of endometriosis. J. Obstet. Gynaecol. Res. 2018, 44, 191–198.

72. Takamura, M.; Koga, K.; Izumi, G.; Urata, Y.; Nagai, M.; Hasegawa, A.; Harada, M.; Hirata, T.; Hirota, Y.; Wada-Hiraike, O.; et al. Neutrophil depletion reduces endometriotic lesion formation in mice. Am. J. Reprod. Immunol. 2016, 76, 193–198.

73. Slabe, N.; Meden-Vrtovec, H.; Verdenik, I.; Kosir-Pogacnik, R.; Ihan, A. Cytotoxic T-cells in peripheral blood in women with endometriosis. Geburtshilfe. Frauenheilkd. 2013, 73, 1042–1048.

74. Rizner, T.L. Estrogen metabolism and action in endometriosis. Mol. Cell. Endocrinol. 2009, 307, 8–18.

75. Maridas, D.E.; Hey-Cunningham, A.J.; Ng, C.H.M.; Markham, R.; Fraser, I.S.; Berbic, M. Peripheral and endometrial dendritic cell populations during the normal cycle and in the presence of endometriosis. J. Endometr. Pelvic Pain Disord. 2014, 6, 67–119.

76. Koninckx PR, Ussia A, Adamyan L, Wattiez A, Gomel V, Martin DC. Pathogenesis of Endometriosis: The Genetic/Epigenetic Theory. Fertil Steril (2019) 111:327–39.