Chapter

Progesterone Resistance and Adult Stem Cells' Genomic and Epigenetic Changes in the Puzzle of Endometriosis

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Abstract

Endometriosis is a chronic inflammatory disease under hormonal/non-hormonal regulation, and microenvironment influences, originating in adult stem cells (mainly of bone marrow/endometrial progenitor mesenchymal type), and their exosomes, with special migratory and adhesion capacities. The postmenstrual repair with regeneration of eutopic and ectopic endometrium has similar genetic and epigenetic changes versus disease-free women. The competition between ectopic and eutopic endometrium for a limited supply of stem cells, and the depletion of normal stem cells flux to the uterus is considered the novel mechanism through which endometriosis interferes with endometrial functions and fertility. The gene expression DNA/RNA or microRNA changes/dysregulation of estrogen and progesterone receptors represent a possible explanation of progesterone resistance or loss of progesterone signalling in ectopic, and eutopic endometrium versus normal. The genes' changes involved in hormonal/non-hormonal pathways control of eutopic/ectopic endometrial cells, and of invaded tissues/organs may explain the disease persistency, progression and severity. Deficient DNA methylation of ERβ, the initial genomic event is followed by pathologic over-expressed ERβ in ectopic stromal cells, and it dictates the decline of PR isoforms, PRB being significantly lower in ectopic and eutopic endometrium. Altered expression of ERα, ERβ, and PRs accompanies the conversion of resident normal endometrial cells to ectopic lesions.

Keywords: endometriosis, progesterone resistance, stem cells, steroid receptors, genomic, epigenetics

1. Introduction

Endometriosis is a chronic inflammatory disease, estrogen-dependent and progesterone-resistant, with a multifactorial etiology, which can appear from intrauterine life [1, 2] and can progress and aggravate as a hidden disease in adolescence [3], being more common during reproductive years, when it is more studied. It is an invasive and metastatic disease, being different from malignancies by missing nuclear atypia [4]. Endometriosis is characterized and diagnosed by

the presence and growth of endometrial-like glands and stroma outside the uterine cavity and musculature, which undergoes cyclic proliferation and breakdown similar to the eutopic endometrium, with peculiar symptoms in most cases, and non-specific also in others. The genetic predisposition, and the epigenetic changes, the systemic, and local environmental factors, and the dysfunctions in endocrine and immune systems, which make possible the new cellular connections induced by exosomes between original tissues and ectopically attached adult stem cells, with bone marrow or endometrial source, are believed to a play significant role in the establishment, maintenance, and progression of endometriosis [5, 6] and its consequences on women's fertility and quality of life. The human endometrium is an angiogenic tissue, with enormous waves of regenerative capacities through cell proliferation, differentiation, and recruitment of inflammatory cells, with episodes of apoptosis and events of breakdown and regeneration without scar, but in ectopic endometrium progression to deeply infiltrative lesions, the scar is present in the form of important fibrosis. The ovarian hormones, estrogens, and progesterone through their receptors—genetic and epigenetic regulated—play an important role in physiology and pathophysiology of eutopic and ectopic endometrium. Excess estradiol and progesterone resistance are documented in eutopic and ectopic endometrium of ill women.

2. Origin and qualities of ectopic endometrium

2.1 Hypotheses and theories on the mechanisms of ectopic endometrium development in different stages

Endometriosis is a multifactors disease, a disease of hypothesis and theories, and many concepts are elaborated in order to elucidate the diagnosis and treatment, to stop the chronic pains and the progression which is like that of a cancer, and the possible malignant transformation in 1% cases [7, 8]. There were explored multiple hypotheses and theories, being reloaded of some old ones, in the conditions of the modern technological possible pathological assessments of eutopic and ectopic endometrium (flow cytometry, immunohistochemistry, genetic analysis), in association with evidences from animal models as mice, rats, baboons, and marmosets [9].

The most referred hypothesis was based on the retrograde deposits of viable endometrial fragments refluxed through the fallopian tubes during the menstruation into the peritoneal cavity, where they attach and invade the peritoneal mesothelium or pelvic organs to establish ectopic growth of endometrial tissue. It is known as J. Samson's theory—or the "transplantation" theory—which is the most widely accepted [10].

The retrograde menstrual blood flow is present in nearly 90% of women [11], but women who develop endometriosis have larger volumes of retrograde menstrual flow than women without disease [12]. The retrograde blood flow is considered to be at the origin of ectopic endometrium in early onset endometriosis (EOE), starting around thelarche/menarche or early adolescence, and EOE may have an origin different from the adult variant, originating from neonatal uterine bleeding [13].

Besides the transportation of endometrial debris from uterine cavity through the fallopian tubes to the peritoneal and organs' surface, the rare condition of the dissemination through regional lymphatic circulation and lymph nodes [14, 15] to extrapelvic, distant organs, with no direct connection to the uterus- thorax, brain, and its structures, is discussed [16]. Since many years have passed, other factors associated with retrograde menstrual blood flow, such as the uterine contractions

during menstruation [17, 18] and/or the involvement of peritoneal fluid [19, 20] as favorable factors for the transportation and spread of retrograde endometrial debris in the peritoneal cavity, are discussed. The retrograde endometrial debris are associated to the adhesive, proliferative, and invasive properties of endometrial cells, mainly of the stromal/mesenchymal ones [21], and to the chemokines (E-cadherin, N-cadherin) elaborated by endometrial cells [22, 23], and in connection to leukocyte actions [24, 25] and to the adhesion properties of the mesothelium are explained the ectopic endometriosis lesions. It is considered that in patients with endometriosis it is a real cross talk between endometrial stromal cells and mesothelial cells, which have a common embryological origin, as it will be discussed later. The new tissue injury and repair (TIAR) concept is comparable [26, 27]: uterine dysperistalsis and hyperperistalsis may induce more trauma, with dislocation of more basal endometrium, and a greater number of stemlike cells present in the retrograde refluxed menstrual blood.

Other two theories are partially connected to one another and to embryologic development. The "coelomic metaplasia" theory—according to the same cell lineage origin of the thoracic, abdominal, and pelvic peritoneum, the Müllerian ducts, and the ovarian germinal epithelium, all being derived from the coelomic wall epithelium of developing embryo, and through metaplasia they generate endometriosis [28]. The second "embryological theory" is very old [29, 30], and it considers the embryonic rests, considering that the presence of cells with the Müllerian origin within the peritoneal cavity are induced to form endometrial tissue when subjected to the appropriate stimuli. von Recklinghausen [29] from Austria was the first who described this disease at the level of the uterus (adenomyomas and cystadenomas) and the tube, and in his opinion their origins were remnants of the Wolffian body. The embryological theory has been recently re-proposed by the scientists from the Italian Foundation of Endometriosis (Rome) (Signorile PG, Baldi A) [8] and the lympho-vascular metastasis or the iatrogenic direct graft implant or the "implantation" theory. Their concept is based on the stem cells as origin of ectopic endometrium.

Hypotheses and theories are actually combined, being considered that endometriosis is the final stage of the combination of some aberrant biological processes, some starting from the intrauterine life, like the "Müllerianosis": the endometrial cells are dislocated outside the uterus during organogenesis, at the moment of mesoderm differentiation from the Müllerian ducts [2, 31]. "Müllerianosis" was revealed by immunohistochemistry in human female fetuses at different gestational ages by the scientists from the Italian Foundation of Endometriosis, from Rome [1, 2, 8]. The Italian scientists have discovered ectopic endometrial cells in five different ectopic sites, outside the uterine cavity, being cited the rectovaginal septum, the proximity of the Douglas pouch, the mesenchymal tissue close to the posterior wall of the uterus, and the rectal tube at the level of muscularis propria and in the wall of the uterus. All these areas are common places of endometriosis in adult women.

Another theory explains that the retrograde menstrual blood flow is possible in women with a genetic predisposition and with an improper innate immune answer, which is conditioned by the exposure to some environmental factors [5]. Recently, the local microenvironment or the peritoneal involvement in the defense against uterine menstrual debris [endometrial cells with plasticity and in terminal differentiation state, plus microvesicles (composed of diverse types of membranes of plasma and endosomal membrane origin) and exosomes released from the endometrial cells] is considered to play a crucial role in the development of endometriosis [6]. The human endometrial exosomes and nanoparticles (~100 nm diameter) released from endometrial cells are mediating the

intercellular connection/communication, and they can transfer small RNAs and mRNA via the extracellular environment to cells at distant sites [32, 33], especially in the stroma as happens in cancer [34], a fact that will be discussed in the next subchapters. The peritoneal clearance through apoptosis of the implanted ectopic endometrial islands from the uterine debris is under genetic, immune system and sexual steroid hormone control. The nature of predisposing individual genetic, biochemical, and hormonal factors or inherent defects of the endometrium, peritoneal cavity, or immune system of patients with endometriosis is unclear [35]. There are controversies if endometriosis is an autoimmune disease due to anti-endometrial antibodies, which were detected in the serum of women with endometriosis and on the increase/decrease/balance in the activity of T-helper1 (Th-1)/T-helper 2 (Th-2) cells in women with endometriosis [36], associated with anti-inflammatory cytokines as IL-4, IL-6, and IL-10, which primarily regulate the intensity and duration of the inflammatory response by suppressing the effects of pro-inflammatory cytokines [interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), and granulocyte-macrophage colony-stimulating factor (GM-CSF), although some have also inflammatory roles [37]. The pro-inflammatory cytokines primarily initiate and amplify the inflammatory response to endometrial debris by signaling the recruit of additional immune cells and pro-inflammatory mediators to the site of endometrial cell adherence. IL-6 is most studied, being with prominent inflammatory and anti-inflammatory functions, which challenge the understanding of its full role in endometriosis. IL-6 is mainly produced by macrophages, and by Th-1 cells and B cells, fibroblasts and endothelial cells may produce IL-6 specially in women with endometriosis, who have higher levels of this cytokine in ectopic and eutopic endometrium and much higher with the severity stage of disease than normal women [38]. All these cytokines and chemokines discovered in endometriosis development are similarly involved in pelvic inflammatory disease and are under genomic and hormonal control through their microRNA receptors, inclusive for progesterone, with well-known anti-inflammatory actions.

Three different forms of endometriosis are described in the pelvic cavity: peritoneal, ovarian, and deeply infiltrating lesions. The development of endometrial ectopic island on the parietal peritoneal surface or different organs' surfaces is an end point of many molecular mechanisms necessary for the establishment and survival of endometrial implants that may have common origin to the peritoneum. The steps described in endometriotic lesion development are analyzed since many years. After the shedding of viable endometrial cells during menstruation, the retrograde transport of exosomes (vesicles released by the endometrial cells in the terminal state of differentiation and with plasticity) and menstrual cells, with their attachment to the peritoneum and formation of temporary ectopic lesion, under the control of immune system is necessary. The invasion into the mesothelium, survival, and proliferation of the ectopic endometrial cells with endometriotic lesion formation is the final step [5, 6]. In healthy women, the immune system removes the temporary ectopic lesions through apoptosis induction. The released exosomes of ectopic endometrial cells could facilitate immune evasion; enhance proliferation, invasion, and angiogenesis in the lesion, and subsequently progress into a persistent endometriotic lesions. Exosomes could therefore be one important factor to enable a temporary endometriotic lesion to establish a sufficient blood supply in order to grow and survive at the ectopic site, as they act in an autocrine, paracrine, and endocrine manner in intercellular communication. The current knowledge suggests different roles of endometrial fragments outside the uterine cavity: the endometrial stromal cells are involved in the attachment to the

peritoneum, whereas endometrial glandular epithelial cells primarily play a role in the invasion and growth of the lesion. These events are possibly related to a defect in the ability of peritoneal natural killer (NK) cells to eliminate the endometrial fragments regurgitated with menstrual debris by lysis and by the release of soluble non-specific factor(s) which interfere with NK cells from human endometrial stromal cells [39], as well as higher levels of IL-6, which suppress them [40]. The human endometrial mesenchymal stem cells (HMSCs) have another capacity, that of transdifferentiation or metaplasia, which permits them to differentiate in cells without any embryological connection, or to complete differentiated cells, with the change of phenotype [41], a biologic event supposed to be during the dormant phase from fetal life to adolescence [42]in association to some external triggers as transient hypoxia, chronic inflammation.

Endometrial cells are able to exploit the promotion of vasculogenesis and angiogenesis mediated by the inflammatory response that they trigger in cooperation with both immune cells and local tissue, usually the peritoneum. In advanced stages of illness, the ectopic endometrium islands have an enormous development of blood vessels, a high degree of fibrosis, and a degree of neurogenesis. Blood vessel development depends on two processes induced by ectopic endometrial islands—vasculogenesis and angiogenesis—triggered by the endothelial progenitor cells (EPCs) with bone marrow stem cell origin or endometrial progenitor/regenerative/stem cell origin. The high levels of angiogenetic factors as vascular endothelial growth factor (VEGF) and other angiogenic factors including IL-6, IL-8, and TNF-α mediate the process of angiogenesis by activating angiogenic switch of endothelial cells. Lesion local production of estradiol maintains the expression of VEGF and promotes macrophages to produce VEGF and monocyte chemoattractant protein (MCP)-1. Thereby, intercellular communication mediated *via* exosomes could represent a missing link between the different theories on the pathogenesis of endometriosis. Exosomes released by eutopic or ectopic endometrium or shedded endometrial cells could induce metaplasia of cells at ectopic sites ("coelomic metaplasia" and "induction" theories) or aid in tissue remodeling after injury (TIAR concept) (**Figure 1**) [26].

In 2018, a team from Saint Petersburg [43] published a hypothesis on the existence of a special endometriosis development program (EMDP) which switches on in the progenitor/stem cells (SCs) of the endometrium in SCs descended from the Müllerian duct; EMDP suggests that the cells are prone to give rise to endometriosis partly through endometrial-mesenchymal transition, their invasivity into the peritoneum lining, and differentiation and growth into endometriotic lesions. The EMDP was subdivided into three parts: the first one in intrauterine period and the last two in the postnatal life. (1) Transition of mesodermal embryonic cells into cells of the endometrium within Muller duct rudiments, (2) acquisition of endometrial cell abnormalities and cell transition into endometriotic SCs, and (3) invasion of the SCs into the peritoneum lining and their differentiation into endometriotic lesions (**Figure 2**).

2.1.1 The new concept of stem cells for the development of endometriosis

Stem cells are undifferentiated cells with the capacity to remain in this stage for some generations, after cell proliferations. Maintenance of the stem cell population requires cellular self-renewal, i.e., the capacity to generate identical daughter cells. Alternatively, stem cells can undergo asymmetric division, producing an identical daughter cell and a more differentiated daughter, or symmetric division producing two daughter stem cells or two transit-amplifying progenitors. Although neither

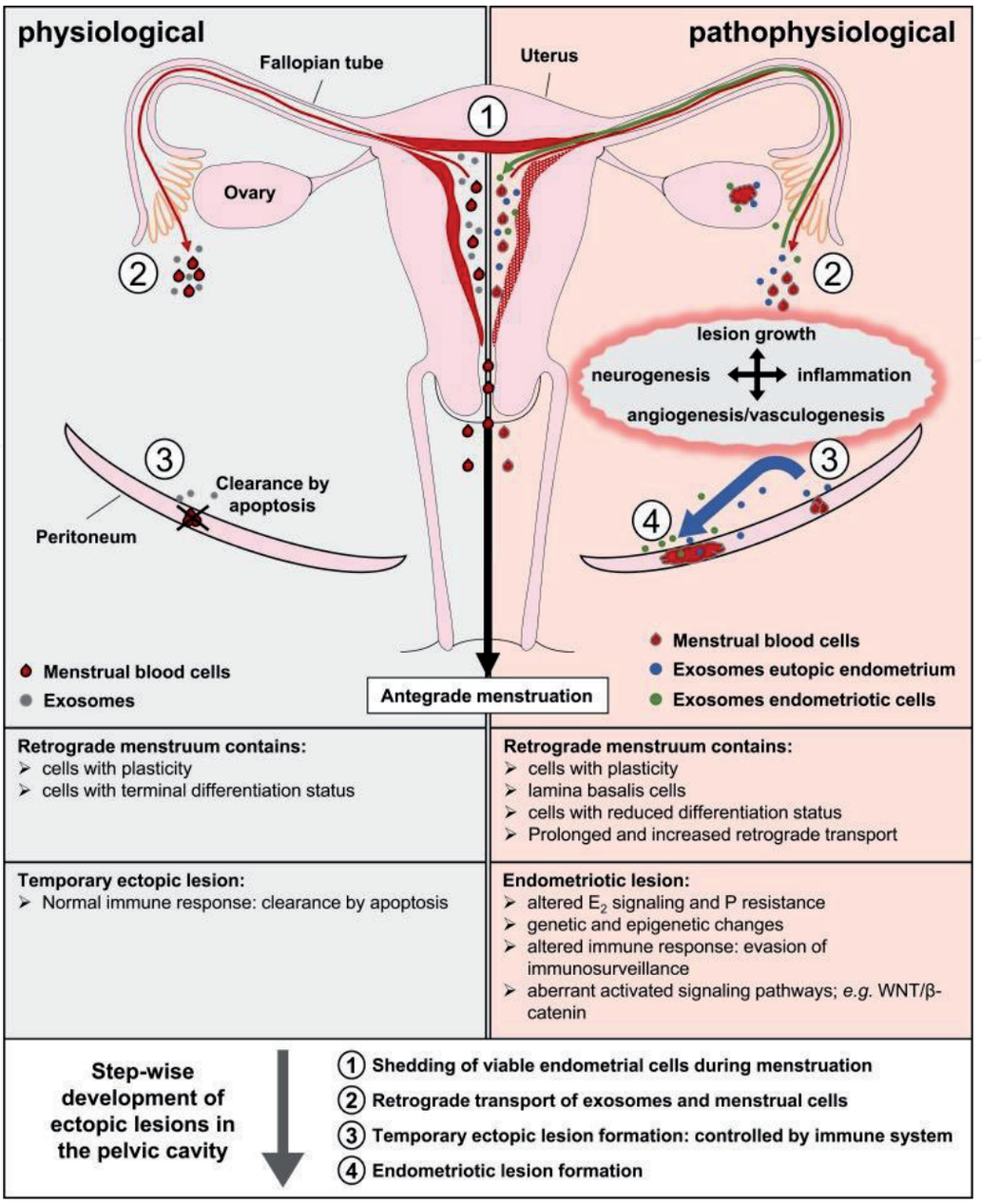

Figure 1.
Molecular and cellular pathways in endometriosis. Adapted from Klemmt et al. [6].

progenitors nor precursors are called stem cells, it is often practically difficult to distinguish adult stem cells from their progenitor/precursor cells. Indeed, for instance, a small subset of hematopoietic progenitor cells have been termed hematopoietic stem cells (HSCs).

The stem cells have in vivo the capacity to participate to natural phenomenon as the repair and regeneration of damaged tissues, as is the endometrium during and after menstruation.

Since then, in many populations worldwide, adult stem cells (ASCs)—known as somatic stem cells or tissue-specific stem cells, such as the blood [44], intestines [45], muscles [46], skin [47], nervous system [48–50], heart, liver [51, 52], dental pulp, adipose tissue, synovial membrane, umbilical cord blood, amniotic fluid [53, 54], and the endometrium [55–58], are found.

The human endometrium is an extraordinary model for controlled tissue remodeling. The endometrial tissue renewal at each menstrual cycle during reproductive years (about 7 mm within 1 week in every menstrual cycle, and 500 menstrual cycles during a woman's lifetime) [44], and in postpartum, with conservation of

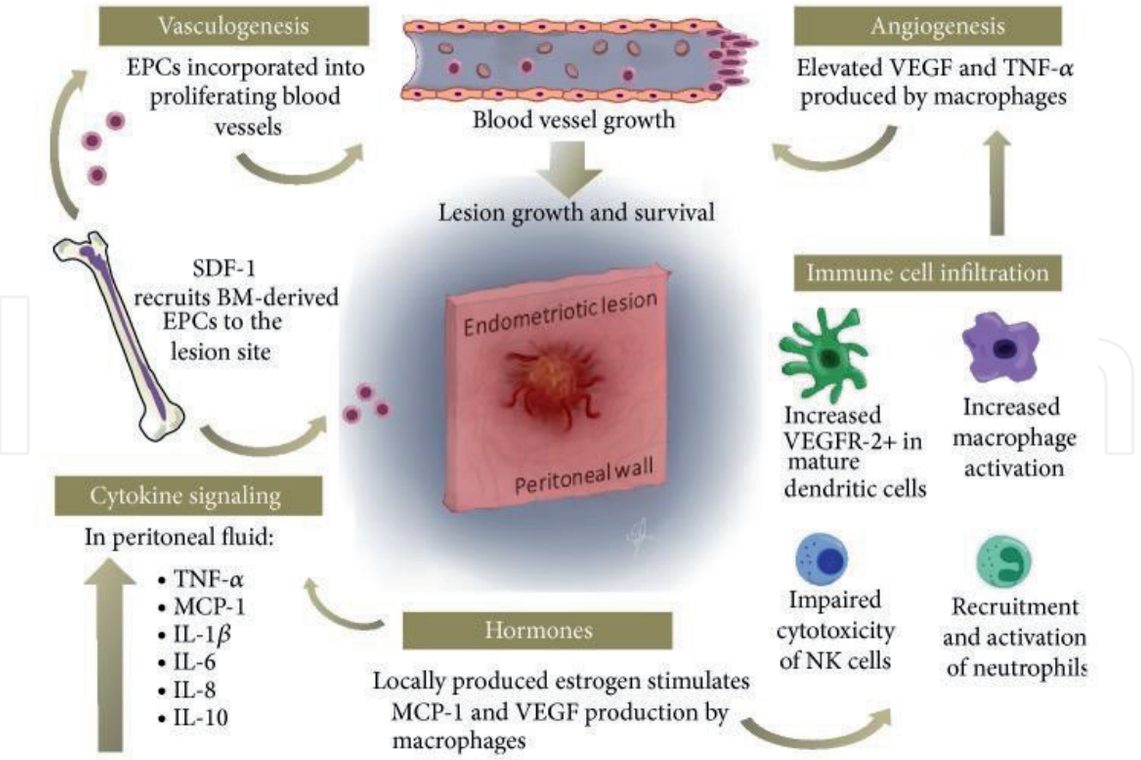

Figure 2.
Neovascularization and ectopic endometrium growth on peritoneal surface. Adopted from Ahn et al. [35]. This is an open-access article distributed under the Creative Commons Attribution Noncommercial License, which permits unrestricted use, distribution, and reproduction in any medium, provided that the original work is properly cited.

this capacity even in postmenopausal years during hormone therapy, is actually explained by the presence of adult stem cells; there are controversies on these cells origin—bone marrow stem cells or endometrial stem cells—epithelial, stromal/mesenchymal, endothelial, niche and side population stem cells [55, 59–61]. There are studies on these types of cells in many research laboratories and medical centers from Australia, Brazil, the USA, Italy, France, Romania, Spain, and the UK, as well as there are controversies if endometrial epithelial cells are derived from the bone marrow [62, 63]. Independent of their origin, the endometrial stem cells are developing the ectopic island of endometriosis from the intrauterine life in female gender [59, 61, 64], and after a dormant period of life, at the menarche they restart their aggressive actions, modulated by sexual steroid hormones.

The concept of endometrial origin of stem cell populations was first proposed by Prianishnikov VA in 1978 [65] due to the highly regenerative nature of the endometrium, and actually the medical communities are waiting to produce novel therapies with these progenitor cells in regenerative medicine, even in infertility from endometriosis [55, 61, 66].

2.2 Adult bone marrow stem cells as the origin of ectopic endometrium

It was postulated that stem cells (SCs) that originated from bone marrow could be attracted in the human endometrium, with generation of endometrial epithelial and stromal cells [61, 67], from the fetal life, but their participation in endometriosis should be proven [68, 69], and mesenchymal bone marrow SCs (bmSCs) in inflammation sites in the peritoneum were found [70]. An Australian team who analyzed the endometrial stem cells for 10 years after their first published paper [61] considers the stem cells originating in the bone marrow to be fibroblasts with

clonogenicity, plastic adherence properties, and multilineage differentiation into bone and marrow lineages in cultures, and they renamed these cells as multipotent mesenchymal stromal cells maintaining the acronym MSCs, for bmMSCs. These cells have comparable properties to stromal endometrial stem subpopulation cells, which will be discussed in the next subchapter.

2.3 Endometrial stem/regenerative/progenitor cells as the origin for ectopic endometrium: the novel concept on HESCs and their progenitor cell capacities

After the preliminary hypothesis and discussion regarding the recovering capacities from the basalis of the primate endometrium, as a bifunctional germinal compartment [65, 71, 72], and the discovery of endometrial regenerative/progenitor/stem cells [55, 56, 73–75], with their presence in the menstrual blood [76–78], a new hypothesis/concept which tries to clarify the underlying pathophysiologic mechanisms of endometriosis, besides the proposed conventional theories explaining the three different aspects of endometriosis, was elaborated. In the concept of Padykula et al. [72] after the menstrual shedding of endometrial functionalis layer, the remaining basal layer was believed to behave as a germinal compartment from which various types of endometrial cells proliferate and differentiate, suggesting that putative endometrial stem cells reside in the basalis. Endometrial stem cells have the characteristics of adult stem cells (ASCs), namely, the clonogenicity and high ability to proliferate, differentiate, and induce rapid angiogenesis, a fact that may contribute to consider their binary qualities in natural functions in the normal endometrium and in endometriosis [5, 79]. Their involvement in endometriosis is from intrauterine life [64], with reactivation after a dormant period in adolescence years in the form of so-called early-onset endometriosis (**Figure 3**) [80].

There are described different types of human endometrial stem cells (HESCs): epithelial—with confirmed location in the basalis of endometrial epithelium, as was postulated [72] stromal/mesenchymal, endothelial, side population—which can differentiate into epithelial and stromal endometrial cells [81], a niche for human epithelial stem cells, and label-retaining cells (LRCs) [82]. All these stem cells can be actually identified with specific markers for immunohistochemistry in endometrial biopsy and/or can be isolated from menstrual blood, being available some devices, as menstrual cups for collection [83]. After repeated examinations of endometrium specimens in all phases of the menstrual cycle, it was concluded that endometrial regenerative cells are located in the basalis, the functionalis being shed at every menstruation, and the basalis which remains intact is the origin of each new cycling endometrium [73]. At 10 years after their first published paper on human and mouse endometrial stem cells, isolated from uterine tissue at hysterectomy, Gargett et al. [61]—from Monash University and Monash Medical Centre (Australia)—are discussing HESC involvement in uterine pathology (endometriosis, adenomyosis, Asherman syndrome, endometrial cancer). The mesenchymal/stromal/endometrial stem cells (eMSCs) or fibroblasts are the most studied. When compared to mesenchymal bone marrow stem cells, there are some differences regarding eMCS abilities to generate a vascularized stroma, with the capacity to differentiate into decidualized stroma when transplanted into an animal at the single-cell level. The eMCSs produced endometrial stroma and incorporated into renal parenchymal blood vessels when xenografted under the kidney capsule of immunocompromised NSG mice [84].

Human endometrial mesenchymal stem cells (HMSCs) were identified with specific markers used for their enrichment [CD146(+)PDGFRβ(+) (platelet-derived

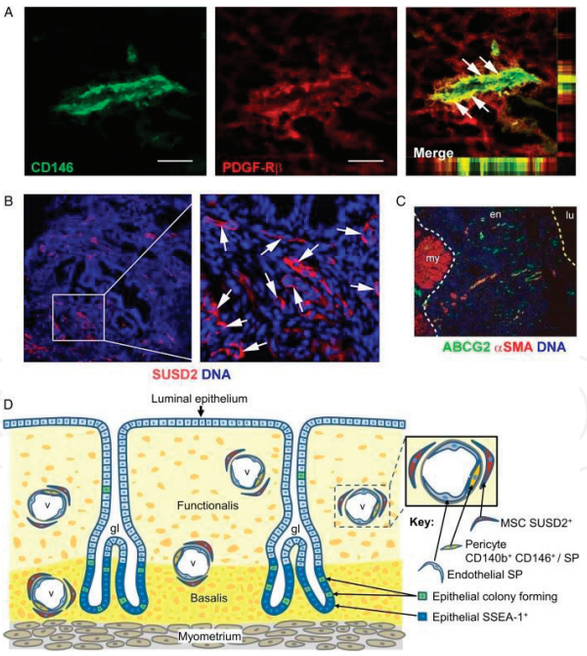

Figure 3.
Localization of human endometrial mesenchymal stem cells. (A–C) Immunofluorescence images of human endometrium showing perivascular identity of human eMSCs. (A) Co-localization (white arrows) of CD146 and platelet-derived growth factor receptor beta (PDGF-Rβ) in pericytes of venules and possibly capillaries in the functionalis stroma. (B) Perivascular SUSD2 expression (white arrows). (C) ATP-binding cassette, subfamily G member 2 (ABCG2) and αSMA co-staining showing perivascular and endothelial identity of SP cells. The white dotted lines indicate the junction between the endometrium (en) and myometrium (my) and yellow dotted line indicates the luminal surface (lu) of the uterine epithelium. (D) Schematic showing location of stem/progenitor cells identified in the human endometrium. Epithelial progenitor cells are postulated to be a subpopulation of cells located in the basalis, in the base of the glands, by SSEA-1 marker. Sushi domain containing-2+ (SUSD2+) eMSCs are perivascular cells. eMSC co-expressing CD146 and PDGFRβ/CD140b are most likely pericytes, as they are located adjacent to endothelial cells in vessels (v) in both the basalis and the functionalis. SP cells are a heterogeneous population comprising CD31+ endothelial cells and CD140b+CD146+ pericytes. Scale bar in (A) = 50 μm. (A) Adopted from Gargett et al. [61]. This is an open-access article distributed under the terms of the Creative Commons Attribution Noncommercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits noncommercial reuse, distribution, and reproduction in any medium, provided that the original work is properly cited. For commercial reuse, please contact journals.permissions@oup.com.

growth factor receptor β) and SUSD2(+) (sushi domain containing-2), and they were distinguished from stromal fibroblasts. HMSCs were located perivascular, and like the pericyte, they were identified in endometrial basalis and functionalis vessels [78]. These Australian researchers presented the similarities and differences between eMSCs and endometrial stromal fibroblasts and the identity of bone marrow-derived cells involved in endometrial function.

It is a novel concept regarding the migratory and invasive abilities of HESCs and their progenitor cells, being increasingly recognized their contribution to the intense tissue remodeling associated with embryo implantation, trophoblast invasion, endometrial regeneration, and endometriosis/adenomyosis progress [85]. Numerous reports indicate that endometriosis and adenomyosis are associated with increased basal and stimulated invasiveness of HESCs and their progenitor cells, suggesting a link between a heightened menstrual repair response and the formation of ectopic implants. The abilities of migration and invasiveness of HESCs are controlled by a complex array of hormones—estradiol and progesterone, growth factors, chemokines, and inflammatory mediators—and involve signaling through Rho GTPases, phosphatidylinositol-3-kinase, and mitogen-activated protein kinase pathways, studied in laboratories from Western Europe (Germany, The Netherlands, Italy), first in early pregnancy and later in endometrial pathology [86, 87].

The clonogenic qualities of epithelial and mainly of stromal/mesenchymal stem cells, in association with the migratory and invasive qualities of the last ones from the eutopic endometrium of women with endometriosis, may explain the development of endometriosis. It can be discussed if stem/progenitor cells which develop the implants of endometriosis are abnormal by the increase of their capabilities to stabilize and implant in ectopic islands, through the lack of the tumor suppressor molecule E-cadherin [22], or if normal stem/progenitor cells are implanting on abnormal peritoneum [88].

In other studies, the answers to these issues were to discuss a combination of the genetic predisposition or the special immunohistochemical pattern of mesenchymal or stromal stem cells from the retrograde menstrual blood flow, with high expression of CD9, CD10, and CD29– [89], and/or with DNA/RNA changes, and/or with an improper immune response possible at exposure at some environmental factors [5].

2.4 Comparison of eutopic and ectopic endometrium with normal cycling endometrium

Normal endometrium is containing large quantities of distinct stromal cells with abundant PRs, which influence epithelial cell proliferation and differentiation and protect against carcinogenic transformation. In endometriosis, eutopic and ectopic tissues do not respond sufficiently to progesterone, being considered to be progesterone-resistant, a fact that contributes to proliferation and survival of ectopic endometrium. The ectopic endometrium is similar to eutopic endometrium but with some peculiarities. The restoration of eutopic endometrium after each menstruation is without scar, a fact that is not present in ectopic endometrium, which undergoes cyclic proliferation and breakdown similar to the endometrium, but with a fibrotic progressive scar. On the other hand, between the two endometrial areas are very strong connections, considered to be bidirectional, and a competition between ectopic and eutopic endometria for a limited supply of stem cells, with different origins, that contribute to restoration/repair of eutopic endometrium after menstruation or other pathological conditions, and the depletion of normal stem cells flux to the uterus is a novel mechanism by which endometriosis interferes with endometrial function and fertility [90].

The phenotype, proliferative, and differentiation in vitro capacities of stromal cells from ectopic lesion from peritoneum, ovarian and deeply infiltrating endometriosis in comparison to the same structures of normal women, were analyzed using the contrast microscopy, immunocytochemistry, and functional bioassays [21]. The doubling time of stromal cells from the deeply infiltrating lesions is lower than that of endometrial stromal cells, and the levels of prolactin and insulin-like growth factor-binding protein-1 (synthesized by the stromal cells) are reduced in supernatants from stromal cells derived from the three types of lesions and from the endometrium of ill women. The conclusion of the British doctors was that endometriotic cell lines and endometrial cells from women with endometriosis are losing the capacity of differentiation, which can explain the cells' capacities for proliferation and survival in the ectopic environment.

When treating the complications of endometriosis, it is recommended to evaluate not only the effect on the endometriotic lesion itself, but it is also essential to consider the effect on normal uterine endometrium in the categories of reproductive age population, including stem cell recruitment as an essential means of uterine repair [90].

The molecular analyses of eutopic and ectopic endometrium versus endometrium of disease-free women are bringing us some news for endometrial pathologies—endometriosis and endometrioid endometrial cancer. The activation of AKT

pathway in endometriosis is reported in a relatively small number of studies. The study of p(Ser473)-AKT in ectopic and eutopic tissue in different stages of the menstrual cycle depicted a higher level of the AKT in endometriotic tissues [91], mainly from ovarian endometriomas, a fact confirmed by other studies, which have revealed in examined endometrioma tissues an association of lower levels of PTEN in epithelial cells of both endometrial types [92–94].

3. Progesterone resistance in endometriosis

3.1 Short history of progesterone resistance/pseudocorpus luteum insufficiency

Progesterone resistance (PR) was first described and nominated as pseudocorpus luteum insufficiency [95], being considered as a local defect of progesterone (P4) action on endometrial stroma. The patient with this disorder was an infertile woman with normality regarding menstrual cycle, duration of luteal phase, and plasma immunoreactive LH and P4 concentrations but with an immature endometrium histologically. These clinicians were the first who assessed the progesterone receptors in the endometrium, as it was recognized 5 years later by Chrousos et al. [96]. PR is discussed together with other hormones' resistances, and it is a clinical consequence of many gynecological disorders regarding the ovaries—PCOS, the endometrium—abnormal uterine bleeding associated with endometrial hyperplasia, the eutopic endometrium in endometriosis, the decidual causes of infertility or recurrent pregnancy loss, or the myometrium—for miscarriage and preterm birth, when it is lost the uterine quiescence. The fetal endometrium remains progesterone-resistant, except when fetal distress causes decidualization and menstruation at birth [80], or the "neonatal menstruation," which is a biomarker reflecting a stage of endometrium development that may subsequently have an impact on the reproductive life of the adolescent and the young adult.

PR is discussed as the decreased sensitivity and responsiveness of the target tissue to bioavailable P4 [96]. In the medical literature, PR is limited to endometriosis, but more and more papers do not agree to this [97]. At the first glance, the terms "estrogen dependence" and "progesterone resistance" appear to describe opposite sides of the same coin. Actually, there are emerging evidences suggesting that PR in endometriosis is not just a consequence of perturbed progesterone signal transduction caused by chronic inflammation, but it is associated with epigenetic chromatin changes that determine the intrinsic responsiveness of endometrial cells to differentiation cues [98]. The concept of "progesterone resistance," and its clinical relevance, is far from being well established and it is in need for redefinition [98].

3.2 Estrogen and progesterone action in eutopic and ectopic endometrium

The uterus is one of the most important organs with different cell types differently influenced by sexual steroid hormones, and the relative balance of progesterone and estrogen steroidal activity governs the function of normal endometrium throughout the menstrual cycle. The growth-promoting effects of estrogen during the proliferative phase of the cycle are countered by progesterone antiproliferative actions at the postovulatory onset of the secretory phase, with decidualizing the endometrial stroma later in the secretory phase. The steroid hormones linked to specific nuclear receptors which are able to bind to the promoter of target genes and then regulate proliferation and/or differentiation processes, in order to prepare the stroma/decidua for embryo's implantation [99].

Endometriosis is appreciated as an ultimate hormonal disease, owing much to its estrogen dependency and aberrations in estrogen production and metabolism and progesterone resistance. Several lines of evidence have linked endometriosis with excessive estradiol (E2) signaling in the ectopic tissues [100]. The high ectopic endometrium levels of E2 are associated with its local biosynthesis through the presence of very well-known enzymes (17β-hydroxysteroid dehydrogenase-1 and aromatase) [101, 102] and with the activation of estrogen receptors and stimulation of mitotic activity and inflammatory response. The proliferative, pro-inflammatory, and antiapoptotic effects of E2 appear to be exacerbated in women with endometriosis; physiological E2 concentrations are able to induce an enhanced inflammatory response mediated by local chemokine production and to reinforce the mechanisms of cell survival mediated by extracellular signal-regulated kinases and Bcl-2 [103]. Progesterone controls endometrial proliferation and differentiation, which are important cellular events in uterine function—normal menstruation, embryo implantation, and protection against the development of estrogen-driven endometrial cancer. The postovulatory surge in P4 triggers a highly coordinated and sequential response as arrest of estrogen-dependent epithelial cell proliferation, followed by the secretory transformation of the glands, recruitment of various bone marrow-derived immune cells, and angiogenesis [104]. P4 acts on stromal cells of the normal endometrium and is inducing the secretion of paracrine factor(s), which are inducing the expression of the enzyme 17β-hydroxysteroid dehydrogenase type 2 (17β-HSD-2) which metabolizes the biologically active estrogen E_2 to estrone (E_1), in the neighboring epithelial cells, and the epithelial cell proliferation is arrested.

Since then it is known that progesterone reduces natural killer (NK) cell activity [105], increases suppressor cell levels [106], inhibits cytotoxic T-cell activity [107], induces the production of lymphocyte-blocking proteins [108], and modifies the cytokine response from the Th-1 to the pre-pregnancy Th-2 pattern [109]. All these cytokines are involved actually in the defense to the ectopic retrograde endometrial debris, exosomes, and endometrial stromal stem cells.

Recently in the USA, in Michigan State University—in the Departments of Comparative Biosciences, of Animal Science, and of Molecular & Integrative Physiology, the effects of progesterone to alleviate endometriosis, induced in the peritoneal cavities of immunocompetent female mouse and maintained with exogenous estrogen, if the administration is before the induced endometriotic lesions are discussed (**Table 1**) [110].

P4 is regulating multiple events on reproductive tissues, the responses to P4 are vastly different in normal and ill target tissues and cells, the mechanisms responsible for this striking contrast in progesterone's effects in normal versus diseased tissues are largely unknown, and one plausible explanation being the specific microenvironment within target tissues—including locally secreted factors, expressed receptors, and paracrine and autocrine communication—determines the overall effect of P4.

- P4 restricts expansion of the ectopic lesions by inhibiting endometrial cell proliferation and neovascularization
- P4 suppresses E_2-dependent inflammatory responses in the ectopic lesions
- P4 maintains ER-α-/PR-mediated signaling; their loss in the ectopic lesions leads to resistance to P4 therapy if the treatment is postinduction of lesion

Table 1.
Progesterone alleviates endometriosis, induced in the peritoneal cavities of female immunocompetent mouse and maintained with estrogen (after Li et al. [110]).

3.3 Estrogens' and progesterone receptors in eutopic and ectopic endometrium

The ovarian hormones, estrogen and progesterone, modulate uterine events in a spatiotemporal manner, from the midsecretory phase, and prepare the endometrium to become receptive to the blastocyst signals, and decidualized stromal cells are seen from the late secretory phase of the menstrual cycle.

Being an estrogen-dependent illness, aberrant levels of estrogen receptors (ER-α and ER-β, with their genes *ESR1* and *ESR2*) are observed in women with endometriosis. Both ERs play essential roles in the establishment and development of ectopic lesions [111], and ample evidence indicates that ER-β is excessively expressed in the ectopic lesions, when compared with normal endometrium [112], being described a positive ratio of miRNA *ESR2* to *ESR1 in endometriomas in comparison to endometriotic implants and eutopic endometrium* [113]. The studies on knockout mouse have shown that the attachment of ectopic endometrium, the sizes, and the proliferation with endometriosis progression are associated with the presence of *ESR2 and absence of ESR1* [114].

P4 and its receptors PR-A and PR-B have an important role in endometriosis. The eutopic endometrium of ill women has an attenuate answer to P4; the PR isoform B is not expressed in their endometrium, being only the isoform PR-A, because progesterone-responsive genes are not deleted in eutopic endometrium of ill women in comparison with normal women in the early secretory phase of the cycle, a fact that suggests that these women have a progesterone-resistant phenotype [114, 115].

Recent studies have confirmed isoform PR-A predominance in endometriotic ill women and have shown its presence in all menstrual cycle phases [116], as it is similar to the condition of endometrioid endometrial cancer, with overexpression of PR-A isoform. Another aspect is the higher level of PR-A in ovarian endometriosis comparative to peritoneal form [116].

Gargett et al. [61] are discussing the endometrial gland estrogen receptors [ER-α (ESR1) and ER-β (ESR2)] and their genes *ESR1* and *ESR2* and PR. Using special markers as stage-specific embryonic antigen 1 (SSEA-1 or CD15) to localize the endometrial epithelial stem/progenitor cells in the basalis of endometrial glands of cycling women, the SSEA-1^+ endometrial epithelial cells in culture had greater telomerase activity, and longer telomeres, and were more quiescent with lower proliferation rates than SSEA-1^- epithelial cells and features of progenitor cell populations [117]. It was revealed that in polarized epithelium, SSEA-1+ cells expressed lower levels of ER-α (ESR1) and PR when compared with the SSEA-1− cells [117], suggesting a less differentiated cell phenotype and reliance on growth factors released from ESR1-expressing niche cells to mediate estrogen-induced proliferative signals. In contrast, earlier studies [118] have shown that ESR1 is detected in basalis glands of the normal endometrium throughout the menstrual cycle, whereas functionalis expression is restricted to the proliferative stage, a fact that suggested to the Australian researchers that human endometrial epithelial progenitor cells are a subset of the SSEA-1+ population that may reside in the functionalis abutting the basalis.

3.4 Progesterone resistance in endometriosis: mechanisms of progesterone resistance in endometriosis

Endometriosis is a chronic inflammatory estrogen-dependent and progesterone-resistant disease, because of missing or blunted progesterone-induced

molecular changes or inadequate response to progesterone of both the eutopic and ectopic endometrial cells and tissue [119, 120], facts that are present all duration of the menstrual cycle. Several mechanisms were described, being discussed whether progesterone resistance is innate, acquired, or present in eutopic and ectopic tissue. Many concepts try to cover the disorder, with clinical relevance; the mechanisms of progesterone responsiveness converge to the reduction of the nuclear PRs, steroid receptor coactivators, or downstream or degradation of other molecular effectors (TGFβ, Dickkopf-1, retinoic acid, c-*myc*, etc.). The lack of the PR-B isoform is associated with very low levels of PR-A isoform; and in the conditions of stromal cell defect, P4 does not induce epithelial 17β-HSD-2 expression, and this is the cause of continuing epithelial mitosis, by the failure of E2 metabolism to E1, mainly in women with moderate/severe disease, compared with the normal ones [119].

The altered ratio between PR isoforms is associated with an altered complex network of interactions with signaling pathways, downstream effectors, transcription factors, coregulators, chromatin-remodeling factors, and DNA [120]. Studies have shown the role of non-genomic overactive pathways of transcription factors as AKT pathways [with three isoforms (Akt1, Akt2, Akt3) differently involved in endometriosis initiation and progression and endometrial cancer] and MAPK pathway (only in the stromal cells) [121]. Rapid activation of AKT by estradiol and progestins promotes survival of endometriotic stromal cells, by downregulation of PRs, with proliferation and migration of endometrial stromal cells [122]. Experiments on xenograft mice have proven a decreased cell viability and increased apoptosis to cells in culture after AKT inhibitor administration [92, 123]. The overactive AKT pathway is associated with the inflammatory and hormonal nature of endometriosis [81, 123]. Overactive AKT from endometriotic stromal cells attenuates also decidualization through its downstream target FOXO1 [124].

3.5 Progesterone receptors in eutopic and ectopic endometrium

Progesterone action has been primarily ascribed to the well-characterized classical signaling pathway involving ligand binding, activation of nuclear progesterone receptors (PRs), and subsequent activation of genes containing progesterone response elements (PREs). Immunohistochemistry identifies during the mid to late luteal phase of menstrual cycle five progesterone nuclear receptors or classic PRs (PR-A, PR-B) and the truncated isoforms (PR-C, PR-M, and PR-S; the PR-C is generated by the initiation of translation from further downstream, not recognized usually), and the two types of cell surface-associated proteins [membrane progesterone receptors (mPRs) and the progesterone membrane receptor component (PGMRC)]. PR-A and PR-B belong to a family of ligand-activated transcription factors and share common structural and functional elements (i.e., regulatory region). The P4 genomic mechanism of action is exerted through specific progesterone response elements (PREs) within the promoter region of target genes to regulate transcription of the genes. These PRs induce classic regulation of gene expression while also transducing signaling cascades that originate at the cell membrane and ultimately activate transcription factors. As for estrogens the genomic and non-genomic mechanisms of P4 are coupled, and the nuclear PRs are upregulated by E2 in endometrial cells, implicating crucial progenitor cells, as preferential targets of P4.

A functional feedback interaction between the P4 and estrogen hormonal systems is crucial for normal endometrial differentiation/decidualization—a key

step toward the establishment of pregnancy, and for balancing the often-opposing actions of the progesterone/PR and estrogen/ER systems [125].

Recently, a new paradigm of the direct effect of P4 on the cells' chromatin, with chromatin remodeling and gene regulation in stem/progenitor cells, is discussed. The interaction of nuclear receptors and other transcription factors with the chromatin is considered to be a highly dynamic process, characterized by rapid cycles, measured in seconds of transient association and dissociation with the chromatin [126]. The classic description was a static one, considering a slow process during hours and sometimes days and during which PRs are activated, then bind to the promoter of target genes, recruit coregulators, and assemble them in a multimeric complex that has the right enzymatic activity to modify the local chromatin structure, which in turn will lead to changes in the transcriptional machinery, efficacy of RNA synthesis, translation, and, ultimately, protein levels. The "non-genomic" mechanisms explain the rapid activation of cytoplasmic kinase signaling that can result in both transcription-independent and transcription-dependent effects. These "non-genomic" actions can be partially explained by membrane transport *via* nuclear receptor. The mPRs (molecular mass of approximately 40 kDa) had thought to be composed of three subtypes, mPR-α, mPR-β, and mPR-γ, which belong to the seven-transmembrane domain adiponectin Q receptor (PAQR) family, plus two new discovered subtypes (mPRδ and mPRε). Progesterone receptor membrane component-1 (PGRMC-1) and PGRMC-2, with a single-transmembrane domain protein, are mediating the rapid non-genomic effects of E2 and P4, such as the activation of MAPK signaling and intracellular Ca^{2+} increase [127, 128]. mPRβ activates also MAPK cascade, without GPCR signaling, and progesterone-stimulated mPRβ activation did not exhibit the elevation of [Ca^{2+}] [129]. In comparison to the mPRs, the single-transmembrane protein Pgrmc1 (molecular mass 25–28 kDa) and the related Pgrmc2 are a part of a multi-protein complex that binds to P4, to other steroids, and to pharmaceutical compounds [127].

Actually, the novel techniques allow genome-wide mapping of binding nuclear receptors to DNA and real-time monitoring of transcription. *PR* expression in uterine cells is stimulated by estrogens *via* ER-α, and consequently progesterone responsiveness is dependent on the presence of an estrogenic drive [130]; low levels of estrogen are required for progesterone responsiveness throughout the luteal phase, and, conversely, ER-α expression in uterine cells is inhibited by progesterone *via* PRs [131]. It is known that continuous exposure of the endometrium to progesterone downregulates PR expression in the endometrial epithelium [132], the PR being detected only in stroma and myometrium throughout most of gestation in the ovine uterus [133].

Endometrial biopsies from luteal phase (days 15 ± 31) of normal, fertile subjects detected a steady decrease in expression of stromal cell PRs (both isoforms A and B) immunostaining from a mid-cycle maximum and a more rapid decrease in expression of PR in epithelial cell, particularly between days 22 and 24, from the mid-cycle maximum also [134, 135].

The human nuclear PRs are encoded by a single gene located on chromosome 11 (11q22–11q23). Expression of *PR* is controlled by two promoters to produce two major mRNA transcripts that encode two proteins: the full-length *PR-B* (116 kDa) controlled by the distal *PR-B* promoter region and initiated from the first AUG translational start codon and *PR-A* (94 kDa) controlled by the proximal PR-A promoter region and initiated from the second AUG (492 bases upstream) translational start codon. It is now generally accepted that response to P4 is determined by the combined actions of PR-A and PR-B, which upon ligand binding form

homodimers or heterodimers that have distinct transcriptional activities at specific sets of gene promoters.

The PR initiates paracrine signaling within the uterine microenvironment during the preimplantation period and of extrauterine microenvironment in cases of ectopic endometrium. P4 facilitates the subsequent downstream expression of PR targets within the epithelium and stroma. The potential molecular pathways which are involved in the pathological mechanisms and in endometriosis were assessed and determined: c-Jun, CREB-binding protein, protein kinase B (AKT), and cyclin D1 (CCND1) signaling [136].

The dysregulation of the PR isoforms has been shown to occur in women with endometriosis, demonstrating the integral requirement for proper balance of these isoforms in hormone-responsive tissues [114].

PRs are differentially expressed in the endometrial structures—glands and stroma, and during menstrual cycle. The transformation of endometrial stromal fibroblasts (ESC) into specialized secretory cells (decidualization) is fundamental for the establishment of a receptive endometrial microenvironment which can support and maintain pregnancy.

PR-A is exerting a negative control on PR-B-mediated transcription and the mediated transcription of the ER and glucocorticoid receptors [137], a fact that may underlie, at least in part, the mechanism by which progesterone functionally antagonizes the effects of estrogen. PR-A and PR-B can interact as dimers with DNA progesterone-responsive element and with signaling proteins of the Src/Ras/Erk pathway outside the nucleus [138].

De novo motif analysis indicated that, although the two isoforms bind to the same DNA sequence motif, they are both common and unique neighboring motifs where other transcription factors, such as FOSL1/FOSL2, JUN, C/EBPβ, and STAT3, bind to and dictate the transcriptional activities of these isoforms. Chromatin immunoprecipitation sequencing in combination with gene expression profiling revealed that PR-B controls a substantially larger cistrome and transcriptome than PR-A during human endometrial stem cell differentiation (**Figure 4**).

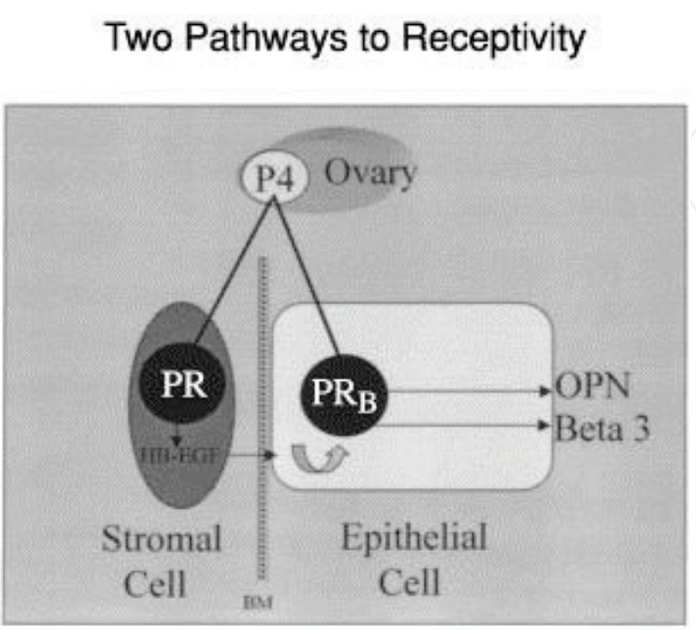

Figure 4.
Progesterone action on the epithelial and stromal cells of the endometrium to prepare it for embryo receptivity. Progesterone has both a direct influence on endometrial epithelium via PR-B, and an indirect influence via the endometrial stromal cells. Adapted from Groll and Lessey [196].

4. Genomic and epigenetic changes of adult stem cells in ectopic and eutopic endometrium: heredity in endometriosis

Women suffering from endometriosis were observed since then to have peculiarities including genetic predisposition, aberrant immunological response, and altered peritoneal environment that make them susceptible to attachment and growth of ectopic endometrial cells, with their exosomes, and that the ectopic endometriotic lesions are histologically similar to their putative eutopic precursors, yet significant biochemical differences exist between these two tissues. The findings provide a framework for causality and mechanisms underlying attenuate progesterone response in endometriosis, especially in the deeply infiltrating groups, but there are still unclear or controverted aspects in the genetics and consequences of progesterone resistance in endometriosis [139].

4.1 Genomic regulation in endometriosis

The genetic aspects in endometriosis must be referred to the complex pathogenomic architecture and multiple interactions of the genetic qualities of the migratory and adhesive mesenchymal/stromal cells, to the qualities of the tissues/organs where the ectopic endometrial cells arrive, and to other factors involved in the development of the disease, as the complex combinations of functional protein modules, and alteration of different metabolic pathways by sexual steroid hormones, their receptors and co-regulators, and immune systems. The genes of endometrial stem cells, such as *OCT4*, *SOX2*, *SOX15*, *NOTCH1*, and *TWIST1*, which can be deregulated in endometriosis, leading to altered SC behavior of migration and adhesivity in ectopic location, which is associated with miRNA of angiogenic factors [42]. The transcriptome analysis of eutopic and ectopic endometrium shows genetic peculiarities in women with endometriosis versus disease-free women [140–142], with relevant dysregulation of the proliferative-to-secretory transition in the endometrium in cases with endometriosis, PR gene polymorphism, and epigenetic alterations in stem cell populations, and their resulting exosomes in endometriosis, including imbalance of miRNA expression of PRs, histone and DNA modifications, and chromosomal aberrations, are some possible answers to the unclear pathophysiologic aspects and to some clinical relevance complications—as chronic severe pelvic pain, dyspareunia, infertility, miscarriages, recurrent pregnancy loss, preterm birth, and progression to malignancy, specially of the ovary, which were assessed by recent, large international collaborative studies [143, 144]. There are questions about the relationships between eutopic and ectopic endometria, regarding the trigger of progesterone-attenuated response and infertility [145]. It is unknown if the defective endometrium gives rise to a predisposition toward endometriosis and infertility or, alternatively, if endometriosis causes the altered endometrial receptivity, in cases with failure of ART. In experiments on mice, the methylation of *Hoxa 10* and *Hoxa 11* (known as a potential mechanism responsible for altered gene expression) decreased the endometrial receptivity in the endometriosis group.

The eutopic endometrium of ill women has an attenuate response to P4 because estrogen-responsive genes are nor suppressed in their stromal cells comparative to normal women in early secretory phase of menstrual cycle, a fact that suggests a resistant phenotype to progesterone [111, 114, 115].

4.2 Heredity in endometriosis

Since the 1990s, there is increasing evidence of a germline predisposition to endometriosis. A familial clustering of endometriosis in humans [146] and rhesus

monkeys [147] as well as increased prevalence among first-degree relatives of women with all disease severities compared to the general population [148] has been reported. The age at onset of symptoms is similar in affected, non-twin sisters [149], and there is concordance in monozygotic twins [147]. The complex gynecologic disorder of endometriosis was since then recognized as showing heritable tendencies, with recurrent risks of 5–7% for first-degree relatives [150]. Familial and epidemiologic studies support that this disease is a genetic disorder of polygenic/multifactorial inheritance, being determined the number and locations of causative genes. Using microarray for real-time PCR validation for the genome-wide linkage analysis, in a study of 1176 families with affected sibling pairs versus disease-free women, Treloar et al. [151] identified a region of significant linkage to endometriosis on chromosome 10q26, and four genes [a disintegrin and metalloproteinase domain 12 (ADAM12; 10q26.3; 2.29 ESE), arginyltransferase 1 (ATE1; 10q26.13; 1.61 PE, 1.57 ESE), and fibronectin type III and ankyrin repeat domains 1 (FANK1; 10q26.2; −1.85 ESE)] which have statistical significant changes, but the gene CYP26A1 had a fold change in the real-time PCR analysis that did not reach statistical significance. After the publication of this study, there are debates on the familial aggregation [152, 153].

4.3 Progesterone receptor polymorphism

Endometriosis is considered a polygenic disorder [154] requiring alterations in multiple biological pathways for the establishment and proliferation of ectopic endometrial cells, a fact documented in a meta-analysis of European and Japanese cohorts [155]. The human progesterone receptor gene is located on chromosomes 11q22–11q23 [156].

Multiple genes are expressed differentially in the eutopic endometrium of ill patients vs. disease-free women; and the most studied gene expression, the HOX gene, was proven to be altered in stromal stem cells from the ectopic endometrium [157]. To date, many deregulated genes have been identified in endometriotic cells with a wide variety of functions, including apoptosis, vascularization, cell cycle regulation, DNA repair, encoding detoxification enzymes, immune system regulation, and cell adhesion. PR polymorphism is controverted in literature [152]; some authors consider to have little or no relevance in endometriosis development. The multinational study [144] of a total of 45,923 cis-eQTLs for 417 unique genes and 2968 trans-eQTLs affecting 82 unique genes showed dynamic changes in expression of individual genes along the cycle, which include alteration in both mean expression and transcriptional silencing. The genetic polymorphisms predispose women to endometriosis [158], a fact that was not sustained by the results of three meta-analyses on association of endometriosis and some genetic polymorphisms coding for dioxin detoxification enzymes, sex steroid biosynthesis, and their receptors [159–161], even though meta-analyses is known to have upward biases in risk estimates. A quite old review on this topic found "a strikingly large amount of conflicting results" and concluded that "polymorphisms may have a limited value in assessing possible development of endometriosis" [152].

The endometrial specimens in different phases of the menstrual cycle, mainly in the secretory phase, were analyzed and there was demonstrated a signature of enhanced cellular survival, persistent expression of genes involved in DNA synthesis, and cellular mitosis in the setting of endometriosis, were analyzed, and, on another hand, the genes for susceptibility of attenuated progesterone response when in endometriosis from the families *FOXO1A*, *MIG6*, and *CYP26A1* (151), *HOX* [142], *WNT* [68], and 12 single nucleotide polymorphisms at 10 independent genetic loci associated with endometriosis have also been identified were identified [162].

Comparative gene expression analysis of progesterone-regulated genes in secretory-phase endometrium confirmed the observation of attenuated progesterone

response, which is the main issue of this chapter. The genetic polymorphism of PRs was studied also on *PROGINS* receptor gene [163], recently on the PROGINS allele [143], and on *+331G/A* genes (especially for comparison between superficial and deeply infiltrating endometrioses [86]). The +331C/T has been shown to influence the transcription of PR-B relative to PR-A with the T allele favoring PR-B [137, 164]. PR-B acts as a classic hormone receptor, mediating the effects of progesterone, whereas PR-A acts as a repressor of PR-B, and as a result, the presence of the +331T allele is hypothesized to lead to increase the effect of P4.

In the recent published multinational and multicenter collaborative study focused on the genotypes for the +331C/T SNP (associated with low risk of endometriosis, because of increased synthesis of PR-B) and PROGINS allele (equivocal from other analyses) in cases with a history of endometriosis [144]. The occurrence of endometriosis was reduced in women carrying one or more copies of the +331T allele, whereas there was no association between the PROGINS allele and endometriosis (**Table 2**). The conclusion regarding PRs was that the +331T allele drives to a reduced PR-A to PR-B ratio, and if the observed association with endometriosis is confirmed, it would suggest that this ratio is important for endometriosis; more than this the authors' conclusion was that a reduced risk is biologically plausible since endometriosis is responsive to progesterone.

4.4 Progesterone target genes

In the last 15–20 years, the relationship between PR-A and PR B is more and more understood. The exclusive expression of PR-B in the luminal epithelium may act as a reservoir of PR-A heterodimerizing partners, or PR-B may homodimerize and regulate epithelial target genes. The expression ratio of the PR isoforms within the uterine compartments could potentially regulate the gene expression profile; it was observed in ill women. The expression of progesterone target genes is blunted, and decidualization is inadequate [115]. The prototype progesterone-responsive gene, glycodelin, was discovered to be strikingly downregulated in the endometrium of women with endometriosis compared with disease-free women [165], and recently glycodelin is the third biomarker for early diagnosis of endometriosis, besides zinc-α and brain-derived neurotrophic factor (BDNF).

Other earlier studies were considering the additional effect of environmental factors as dioxin to genes [166] or the interaction between multiple genes and/or the interaction between genes to other factors to produce the disease phenotype [167].

The location of endometrial stem cells outside the uterus may be another explanation of their different actions in ectopic and eutopic endometrium in ill women in comparison to disease-free women [78].

Single nucleotide polymorphism (SNP)	Cases with endometriosis (n)	Cases without endometriosis (n)	OR (95% CI)	p-Value	p^{het}
+331 C/T (rs10895068)	345	5369	0.65 (0.43, 0.98)	0.042	0.46
PROGINS C/A (rs1042838)	343	5339	0.94 (0.76, 1.16)	0.56	0.24

OR = odds ratio, compares heterozygotes and rare homozygotes to common homozygotes for +331C/T, per copy of the allele carried for PROGINS, stratified on study site and age group; p-value for heterogeneity across study sites.

Table 2.
Association between the two PRs SNPs and endometriosis in the multinational study population (adapted from Fung et al. [144]).

4.5 MicroRNA (miRNA) dysregulation of steroid hormone receptor expression in endometriosis

The receptors of sexual steroid hormones (ERs, PRs) are involved in endometriosis, and correlated to them is the exploration of the correlation between microRNA (miRNA) and ER/PR in eutopic and ectopic endometrium. There are recently discovered stranded noncoding RNAs (ncRNAs) [168]. MicroRNAs (miRNAs) are single-stranded noncoding RNA molecules with approximately 22 nucleotides in length, and they control posttranscriptional gene regulation, which were proposed to contribute to human reproductive physiology; their abnormal expression was involved in the pathogenesis of many diseases of female reproductive tract, including endometriosis. While the majority of the literature supports the notion that miRNAs inhibit translation, there is some evidence that miRNAs can actually enhance translation in certain biological scenarios.

miRNAs are postulated to play a role in normal biological processes, to be critical regulators of cellular development and physiology, while their mis-expression has been associated with numerous diseases [169]. A recently published paper [170] at the Department of Molecular and Integrative Physiology, at the University of Kansas Medical Center (USA) tries to determine if the "mis-expressed" endometriotic tissue is a cause (driver of the disease) or a result of endometriosis (passenger).

More than 10 years ago, there are comparative microanalyses of genetic expressions—the miRNAs in women with ectopic endometrial cells and eutopic endometrium—that have proven an alternative pattern in the two groups [171–173], as well as the differences of ill women versus disease-free women [172–175]. miRNA regarding ER shows a ratio of 100:1 in *ESR2* (RE-β) to *ESR1* (RE-α) in endometriomas vs. superficial endometriotic lesions and eutopic endometrium [112, 113].

Different miRNAs are identified by microarray with real-time reverse transcription-polymerase chain reaction (real-time RT-PCR), and they were done in paired eutopic/ectopic endometrium from the same patients. In the published papers, there are identified upregulated (over expressed) and downregulated (underexpressed) miRNA expressions in eutopic and different ectopic lesion locations (peritoneal, ovarian), and some are "mis-expressed." Using the Ingenuity Pathway Analysis (IPA) software, potential molecular pathways were assessed and determined to involve c-Jun, CREB-binding protein, protein kinase B (AKT), and cyclin D1 (CCND1) signaling, all of which have previously been associated with endometriosis pathogenesis [136]. According to the involvement in endometriosis, the molecules directly involved in endometriosis (cytokines, enzymes, growth factors, kinases, ion channels, ligand-dependent nuclear receptors, peptidases, phosphatases) are assessed.

There are differences between authors; there were conflicting reports on whether or not miRNA expression was influenced by the stage of the menstrual cycle (proliferative [136] or secretory [176]), the type of endometrial cell (miRNA of endometrial stromal cells was for the first time assessed by Hawkins et al. [177]), the type of miRNA, and the level in eutopic and ectopic tissue [miRNA from *miR-29* family (was evaluated using primary human endometrial stromal cells in vitro)], which had different levels—(high for [136] and [176] and decreased for [178], who compared it to disease-free women). The role of *miR-29c* in endometrial cell proliferation, invasion, and apoptosis in vitro was examined. *miR-29c* suppressed endometrial cell proliferation and invasion, promoting cell apoptosis. The conclusion was that *miR-29c* exhibits inhibitory action on endometrial cell proliferation and invasion by inhibiting the expression of *c-Jun*. Another studied miRNA—the stromal cell *miR-183*, was examined in response to ovarian steroids (17β-estradiol and P4), and inflammatory cytokines (TNF-α) were concluded from this study that repressed levels of *miR-183* may modulate the growth and invasive potential of

endometriotic endometrial stromal cells contributing to the development and progression of endometriosis [179]. The microarray to identify differentially expressed miRNAs between endometriotic lesion tissues from women with stage III/IV disease compared with eutopic endometrium from women without endometriosis has shown that lesion tissue expressed significantly higher levels of expression of seven miRNAs and significantly lower levels of expression of ten miRNAs [180]; some miRNAs were predictors of angiogenesis in endometriotic lesions. Expression of VEGFA was significantly upregulated, whereas EGFR2, PTEN, and CXCR4 were markedly downregulated in lesion tissue compared with the endometrium from women without endometriosis. The authors concluded that the differentially expressed miRNAs could modulate VEGFA, EGFR2, PTEN, and/or CXCR4 expression and contribute to the pathogenesis of endometriosis. Their conclusion is quite similar to other researchers from Spain [181]: the expression levels of miRNAs related to angiogenesis (the pro-angiogenic factors (VEGF-A) and the angiogenesis inhibitor thrombospondin-1 (TSP-I) are different in eutopic endometrium from that observed in ovarian endometrioma, rectovaginal nodule. Ovarian endometriomas exhibited significantly lower levels of pro-angiogenic VEGF-A mRNA and protein and higher levels of *miR-125a* and *miR-222* than the corresponding eutopic endometrium. In contrast, levels of the angiogenesis inhibitor were significantly higher in endometriomas, and this was associated with reduced levels of *miR-17-5p*.

According to the results of the last mentioned study [170], it was considered that from the initial generation of miRNA profiles, investigations were focused on specific miRNAs and putative targets, which can become relevant to the pathophysiology of endometriosis and may aid in determining whether these miRNAs function as drivers of the disease.

miR-126 was proposed to be analyzed as a regulator of angiogenesis, growth, adhesion, and invasion in ectopic endometriotic lesions versus eutopic endometrium of disease-free women, and the results of this parameter are discordant—higher in earlier studies [136], and reduced in the more recent one, the level of reduction being parallel to the severity of endometrioma [182].

4.6 Epigenetics in endometriosis: methylation pattern of sexual steroid hormone receptors

There is accumulating evidence that various epigenetic aberrations exist in endometriosis. In the last 10 years, evidence from reviewed and retrieved studies has emerged that endometriosis may be an epigenetic disease [153], epigenetics appearing to have a better explanatory power than genetics, and to be a common denominator for hormonal and immunological aberrations in the puzzle of endometriosis. Genomic imprinting; DNA methylation; histone modifications with different nominations (acetylation/ histone phosphorylation/histone ubiquitylation/ histone sumoylation); microRNAs [183] and recently discovered, stranded, noncoding RNAs (ncRNAs) [168]; transcription factor network; and chromatin remodeling are known to regulate transcription of target genes. Genomic imprinting is an epigenetic phenomenon known to regulate DNA methylation of either maternal or paternal alleles [184], and the male and female germ lines guide the allele-specific DNA methylation marking and histone modification onto specific gene regions of parental alleles [185]. The epigenome, the collection of DNA methylation, and the histone modifications can be influenced by environmental factors. Exposure to xenobiotics, chronic inflammation, and transient hypoxia are associated with DNA hypomethylation of stromal endometrial stem cells through the destabilization of *DNMT1* mRNA; *DNMT1*, *DNMT3A*, and *DNMT3B* are overexpressed in the epithelial component of endometriotic implants as compared to normal controls or in the

eutopic endometrium of women with endometriosis [186], but fetal programming postulates that chronic adult-onset diseases with an epigenetic component originate in utero when the early embryo is exposed to factors that permanently shape its epigenetic mark, a fact presented in the previous subchapter.

Aberrant DNA methylation represents a possible mechanism, linking gene expression alterations observed in endometriosis with hormonal and environmental factors. Methylation is one of the most important epigenetic functions that implies the addition of methyl group at the DNA dinucleotides in the position 5 of the cytosine of the "promoter" zone and induces silencing of the gene under DNA methyltransferase action [68, 187].

Endometriotic lesions have altered methylation patterns of ER-β, and the ER may mediate regulation of one another [188]. The authors consider that aberrant DNA hypomethylation of ER may favor the progression to cancer of old ectopic endometrial lesions.

DNA methylation makes possible the process "epithelial to mesenchymal transition" (EMT), in which the epithelial cells lose polarized organization of the cytoskeleton and cell-to-cell contacts, acquiring the high motility of mesenchymal cells. It is supposed that two stimulating signals, hypoxia and estrogen, can activate the EMT process in endometriosis through different pathways. The pathways involve many cellular factors such as TGF-β and Wnt, ultimately leading to cell proliferation and migration, and the changes of epithelial cells are thought to be prerequisites for the original establishment of ectopic endometriosis lesions [189].

The reasons for non-response to progestins in endometriosis are not entirely clear, studies point the possible epigenetic silencing of the PR gene, without knowledge of causes for the epigenetic silencing of PRs. DNA methylation of the ER and PR promoter has been demonstrated in endometriosis; inflammation and oxidative stress can be involved in epigenetic changes in DNA and chromatin remodeling proteins [190–192]. ER-β promoter is hypomethylated in endometriotic cells, which accounts for its overexpression [193]. The promoter of PR-B hypermethylation is concomitant to reduction of PR-B, a fact explaining progesterone resistance in endometriosis [11, 114].

Ectopic endometrial stromal cells are hypomethylated, and are different from normal endometrial stromal cells which are hypermethylated [194].

The hypermethylation of *HOXA 10* promoter reduces HOXA 10 expression in induced endometriosis of stromal endometrial cells of mice [195].

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