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Stem cell theory for the pathogenesis of endometriosis

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1. ABSTRACT

Proposed hypothetical causes of endometriosis include retrograde menstruation, lymphatic and vascular metastasis, iatrogenic direct implantation, coelomic metaplasia, embryonic rest, and mesenchymal cell differentiation (induction). Each theory, individually, fails to account for all types of endometriotic lesions, thereby implicating combined and/or type-specific mechanisms. Recent evidence supports the presence of endometrial stem/progenitor cells and their possible involvement in eutopic endometrial regeneration and differentiation. Thus an additional novel mechanism for the origin of endometriotic lesions is that they arise from ectopic endometrial stem/progenitor cells.

2. INTRODUCTION

Endometriosis is defined as the presence of endometrium-like tissues outside of the uterine cavity. It is frequently associated with a variety of symptoms including dysmenorrhea and dyspareunia (1, 2). The common sites for endometriotic implants are the ovaries, pelvic peritoneum, uterine ligaments, and the rectovaginal septum. Endometriosis may also be found rarely on the intestine, bladder, pelvic lymph nodes, cervix, vagina, fallopian tubes, and in distant sites such as the lung, skin, kidney, brain, and spinal column (1-3). The principal microscopic finding is that of glandular components surrounded by endometrial-like stroma (4). Endometriotic lesions, particularly deep infiltrating endometriosis, are also often

accompanied by smooth muscle cell components, presumably arising via smooth muscle metaplasia (5). Angiogenesis and innervation are also observed in endometriotic lesions (6, 7).

Since its identification over 80 years ago, several theories have been proposed to account for the origin and pathogenesis of endometriosis (8-13). Amongst these hypotheses, the retrograde menstruation (implantation) theory has been most widely accepted as it is a very plausible explanation for peritoneal endometriosis (9, 12, 13). Coelomic metaplasia and the embryo rest theories are also well documented (8-13), and may account for the pathogenesis of ovarian endometriomas and rectovaginal endometriosis, respectively (9). However, each theory in itself fails to explain all types of endometriosis. Thus, several combined and/or type-specific mechanisms may be involved in the establishment of endometriotic lesions (8-13).

The human endometrium undergoes cyclical regeneration throughout a woman's reproductive life, which suggests that it contains a population of stem/progenitor cells. Recent evidence supports the presence of endometrial stem/progenitor cells and their possible involvement in eutopic endometrial regeneration and differentiation (14-16). This taken in the context of the implantation theory forms the basis for a novel hypothesis that states that endometrial stem/progenitor cells may be responsible for giving rise to endometriosis when they are ectopically located.

In this review article we first summarize various conventional theories that have been proposed to explain the pathogenesis of endometriosis. We then introduce and discuss a new concept, which we will refer to as the "stem cell theory" in which endometriotic lesion cells originate from endometrial stem/progenitor cells.

3. CONVENTIONAL THEORIES

3.1. Implantation theory

3.1.1. Retrograde menstruation theory

The retrograde menstruation theory or implantation theory, proposed by Sampson more than 80 years ago (17), states that endometriotic lesions may result from the implantation of viable refluxed endometrial tissues on the peritoneal surface and/or pelvic organs via retrograde menstruation through the fallopian tubes (8-13, 18).

This hypothesis has been most widely accepted, in particular, for peritoneal endometriosis (9, 12, 13), as it is biologically plausible and supported by the following observations: 1) menstrual blood and peritoneal fluid contain viable endometrial cells (19, 20), 2) shed endometrial cells are able to implant and proliferate *in vivo* (21, 22), 3) retrograde menstruation is universally (approximately 90%) observed in reproductive-aged women (19), 4) obstructed menstruation is associated with endometriosis (23, 24), and 5) the frequency of endometriotic implants is influenced by an individual's pelvic anatomy (25).

Ovarian endometriomas can also be explained by the implantation theory in which the inversion and invagination of the ovarian cortex implanted with menstrual debris may generate endometriotic lesions within the ovary, which ultimately develop into endometriomas.

Although substantial circumstantial evidence supports this theory, documentation of critical events including initial attachment, secondary proliferation, and invasion of the endometrial implants have not been done on a microscopic level *in vivo* (26-28). It is somewhat surprising that the molecular events joining the relatively common findings of endometriosis and retrograde menstruation remain elusive, and this detracts from an otherwise plausible hypothesis.

3.1.2. Lymphatic and vascular metastasis theory

This theory proposes that endometriosis may result from the lymphatic and hematogenous dissemination of endometrial cells/tissues (29, 30). It has been advocated to account for the occurrence of endometriosis at distant or unusual sites such as the parenchyma of the lung, lymph nodes, and brain. As in the implantation theory, there are several observations which support this, which include: 1) endometrial tissues are present in the uterine veins of women with adenomyosis (30), and 2) the intravenous injection of endometrial tissue induces pulmonary endometriosis in rabbits (31), and 3) the presence of endometriosis in lymph nodes following lymphadenectomy has been observed in approximately 6% of women (32).

3.1.3. Iatrogenic direct implantation

Endometriosis is rarely observed at surgical scars resulting from many types of procedures including cesarean section, episiotomy, and abdominal laparotomy/laparoscopy (10). The pathogenesis of this type of endometriosis is best explained by the iatrogenic direct implantation theory in which endometrial cells/tissues are deposited into the area of a surgical incision (10). While straightforward, this theory does not exclude the possible contributions of coelomic metaplasia and lymphatic or hematologic dissemination.

3.2. Metaplasia theory

3.2.1. Coelomic metaplasia theory

The premise of this theory, originally proposed by Iwanoff and Meyer, is that yet to be identified cells, which are capable of differentiating into endometrium, may be present among the mesothelial cells lining the ovary and pelvic peritoneum (11, 18). This hypothesis accounts not only for peritoneal endometriosis but also for ovarian endometriomas. Indeed, Nisolle and Donnez argued that endometriomas are caused by metaplasia of the invaginated coelomic epithelium (9). The coelomic metaplasia theory also explains the occurrence of endometriosis in prepubertal (33) and adolescent girls (34), in women who never menstruated (35), and in any location containing mesothelium including the pleural cavity (3).

3.2.2. Embryonic rest theory

In the 1890s, Von Recklinghausen (36) and Russell (37) introduced the embryonic rest theory in which embryonic cell rests of müllerian origin could differentiate into functioning endometrium under a specific stimulus.

In the coelomic metaplasia theory, the origin of endometriosis is basically restricted to the mesothelium, whereas the embryonic rest theory proposes that endometriotic lesions are derived from embryonic cell rests which are not necessarily confined to the mesothelium. Since embryonic cell rests of müllerian origin are present not only in women but also in men, this theory could explain the rare cases of endometriosis reported in men (38, 39). Using this embryonic rest theory Nisolle and Donnez explained the histogenesis of rectovaginal endometriosis, a deep-infiltrating endometriosis of the rectovaginal septum (9). They postulated that rectovaginal endometriosis corresponded to an adenomyotic nodule derived from müllerian rests by a process of metaplasia (9).

3.3. Induction theory

The induction theory proposes that unidentified factors present in the menstrual effluent and/or produced by the menstrual endometrium may induce differentiation of undifferentiated (peritoneal) cells into endometrial-like tissues (10, 11, 13). This theory is partly a prerequisite for the coelomic metaplasia theory in that a specific stimulus is believed to be required for endometrial metaplasia. Several *in vivo* and *in vitro* experiments support the induction theory (40-43); however, the definitive inducing factors and the precise mechanism(s) responsible for endometrial metaplasia and/or differentiation remain to be elucidated.

3.4. Composite theory

None of the previously discussed theories in isolation explains the pathogenesis of all types of endometriosis. Javert proposed combining the theories of implantation, vascular/lymphatic metastasis with the theory of direct extension of endometrial tissue through the myometrium, and termed his explanation the composite theory (44).

In a similar context, Nisolle and Donnez postulated that the pathogenesis of endometriosis may be type specific (9). They proposed that the implantation theory is the most appropriate for peritoneal endometriosis. Coelomic metaplasia of invaginated ovarian epithelial inclusions rather than the implantation/dissemination of refluxed endometrial tissues/cells onto the surface of ovaries could give rise to ovarian endometriomas. Rectovaginal endometriosis is well explained by the embryonic rest theory in which it would result from metaplasia of müllerian remnants present in the rectovaginal septum.

All of these conventional theories in isolation or in combination account for the pathogenesis of endometriosis. However, even the well-established retrograde menstruation theory has been questioned because it has not been able to be duplicated experimentally or proven on a microscopic basis (14-16). Indeed, the implantation theory does not address what types of cells/tissues are involved in the establishment of endometriotic lesions. Although the human endometrium is believed to have a unique regeneration potential, it is unlikely that any of the cell types present in the endometrial tissue would give rise to continuously growing endometriotic lesions. The stem cell theory not only identifies a putative endometriosis-initiating cell but also addresses other unresolved/unexplained issues.

4. STEM CELL THEORY

4.1. Adult stem cells and the human endometrium

Adult stem cells (also termed somatic stem cells or tissue-specific stem cells) are found in an undifferentiated state throughout the whole body (15). They are able to self-renew through indefinite and/or asymmetric cell division, under the appropriate physiological microenvironment or “stem cell niche” thereby generating committed cells that go on to maintain their organ of origin. They play a critical role in the replenishment and regeneration of dying cells and damaged tissues, thereby contributing to the structural and functional maintenance of the organs and tissues.

The human uterine endometrium, which mainly consists of glandular epithelium and stroma, exhibits menstruation-associated tissue breakdown and shedding but subsequently displays complete renewal in each monthly menstrual cycle. These dynamic and unique properties support the presence of endometrial stem/progenitor cells that likely reside in the basalis layer and serve as a potential source by which to regenerate the entire endometrium (15).

4.2. Endometrial stem cells and their roles in endometrial physiology

Recently, many groups including ours, through a variety of methods, have identified, isolated, and/or characterized putative endometrial stem/progenitor cells and their relevant cells (45-69), which show plasticity to differentiate into a variety of tissue types. These are listed in Table 1 (16). It seems, however, that each of the methods used produces cells which are distinct from the cells isolated by another method. For instance, several groups including us have employed side population-based method(s) to isolate putative endometrial stem/progenitor cells (45, 53, 56, 66). These endometrial SP cells share some properties; however, they differ with respect to the expression pattern of surface markers, clonal efficiency, preference for culture conditions, and localization in the eutopic normal endometrium (45, 53, 56, 66). Thus, precisely how many types of stem cell exist in the human endometrium, how they differ in phenotype and function, and what hierarchical relationship extends across the various types of these stem cells, remain to be elucidated. Table 1 also summarizes the results of several clinical observations and animal experiments that illustrate the plasticity of adult stem cells, particularly those from the bone marrow in relation to the endometrium in humans (51, 65) and in mice (49, 69). These studies collectively provide

Table 1. Functional identification and differentiation capacities of endometrial stem/progenitor cells. Adapted with permission from reference 16

Stem/progenitor cell type	Possible commitment			References
	Epithelial cells	Stromal cells	Other cells	
Clonogenic human endometrial epithelial cells	+			50
Clonogenic human endometrial stromal cells		+	Adipocytes, osteocytes, smooth muscle cells, chondrocytes	48, 50
Human endometrial $CD146^+PDGF^1$-Rb^+ mesenchymal stem cell-like cells		+	Adipocytes, osteocytes, smooth muscle cells, chondrocytes	63
Human endometrial tissue-reconstituting cells	+	+	Endothelial cells	55
Endometrial stromal cells		+	Chondrocytes, dopaminergic neurons	67, 68
Human ESP cells	+	+	Endothelial cells, smooth muscle cells	45, 53, 56, 66
Bone marrow-derived cells	+	+		49, 51, 65, 69
Menstrual blood cells		+	Cardiomyocytes, myocytes, adipocytes, osteocytes, smooth muscle cells, chondrocytes, neural cells	57, 59- 62
Endothelial progenitor cells (bone marrow-derived)		?	Endothelial cells, perivascular cells	54, 55, 58
Mouse label-retaining cells	+	+	Perivascular cells	46, 47, 52, 64

Abbreviation: [1]PDGF, platelet-derived growth factor

strong evidence that the bone marrow can serve as an exogenous source of endometrial stromal and glandular precursor cells.

We have recently demonstrated that endometrial side population (ESP) cells, which preferentially express a universal stem cell marker, ATP-binding cassette sub-family G member 2 (ABCG2), exhibit the potential for differentiation into glandular, stromal, endothelial and smooth muscle cells (56) (Figure 1). Intriguingly, these SP cells have endothelial progenitor cell (EPC)-like properties (56), and $ABCG2^+$ cells largely corresponding to ESP cells indeed reside preferentially in the vascular wall of endometrial small vessels of both the functional and basal layers (56). We therefore postulate that putative endometrial stem/progenitor cells within the side population may propagate and differentiate into various cell components of the human endometrium through angiogenesis, ultimately contributing to the regeneration of the entire endometrium (15, 56) (Figure 1). Given the localization of ESP cells in the functional layer of the human endometrium (56), the basal layer may not be the only source for renewed endometrium (15). Furthermore, ESP cells have some properties similar to EPCs (56), which originate in the bone marrow (70, 71). These observations are consistent with the above-mentioned paradigm that bone marrow-derived cells contribute to the regeneration of the endometrium.

4.3. Possible role of stem cells in the pathogenesis of endometriosis

When one considers the regeneration and differentiation potentials of endometrial stem/progenitor cells including ESP cells (56) in the context of implantation theory, a reasonable secondary hypothesis is that these putative stem/progenitor cells, which are at least in part originated from bone marrow, can give rise to endometriotic lesions when they are implanted or located at ectopic sites (15, 16, 72) (Figure 2).

Endometrial stem/progenitor cells may be transported to ectopic sites via many routes: retrograde menstruation, lymphatic and vascular dissemination, direct migration and invasion, or a combination. Given the bone-marrow origin of the endometrial stem/progenitor cells (51, 65), it is conceivable that hematogenous dissemination of these cells may be more likely than initially thought. Indeed, bone-marrow-derived cells also populate established endometriotic implants in mice (49, 69) and may be found in endometriosis lesions of hysterectomized mice (49). Thus, the stem cell theory also explains the more unusual cases of endometriosis located at distant sites such as the lung or brain (Figure 2).

As mentioned before, the critical weakness of the retrograde menstruation theory is that, despite the high prevalence of peritoneal endometriosis, it is extremely rare to detect microscopically the initial developmental steps of endometrial implants including the attachment of the endometrial tissue to the peritoneum and its secondary proliferation and invasion (26-28). The stem cell theory with some modification accounts for this. Based on this theory, endometriosis arises from endometrial stem/progenitor cell(s) contained in the implanted endometrial fragments. We propose that endometrial stem/progenitor "cells" rather than endometrial "tissues" implant and give rise to endometriotic lesions; therefore, it may be almost impossible to detect the initial attachment and proliferation events of these cells. If our hypothesis is correct, endometriotic lesions likely become microscopically detectable once the initial events are completed and at that time will be classified as established lesions. In this context, endometrial stem/progenitor cells are both necessary and sufficient for the establishment of endometriosis even if a single or very few cells locate ectopically. In contrast, non-stem/progenitor cells in the endometrium, which are the majority of total endometrial cells, will not give rise to "persistent" endometriosis even when a large number of them exist ectopically.

The functional layer of endometrium is sloughed off at menstruation and is partially refluxed into the peritoneal cavity through the fallopian tubes. Therefore, endometrial stem/progenitor cells should be present in the

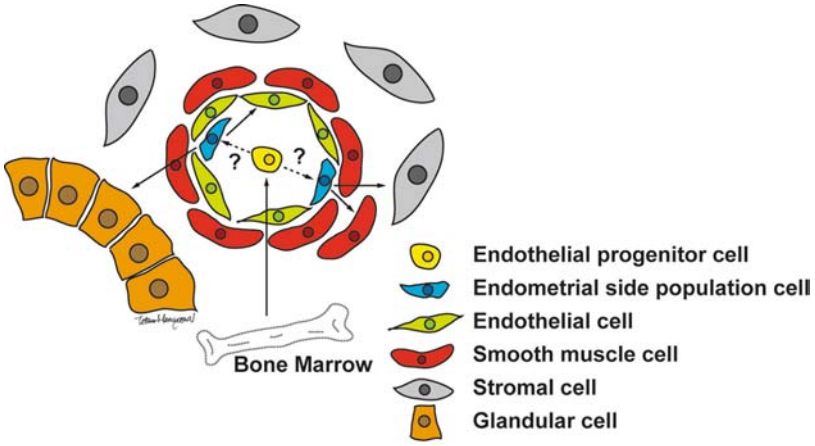

Figure 1. Proposed model for ESP cell-driven endometrial regeneration. Adapted with permission from reference 56.

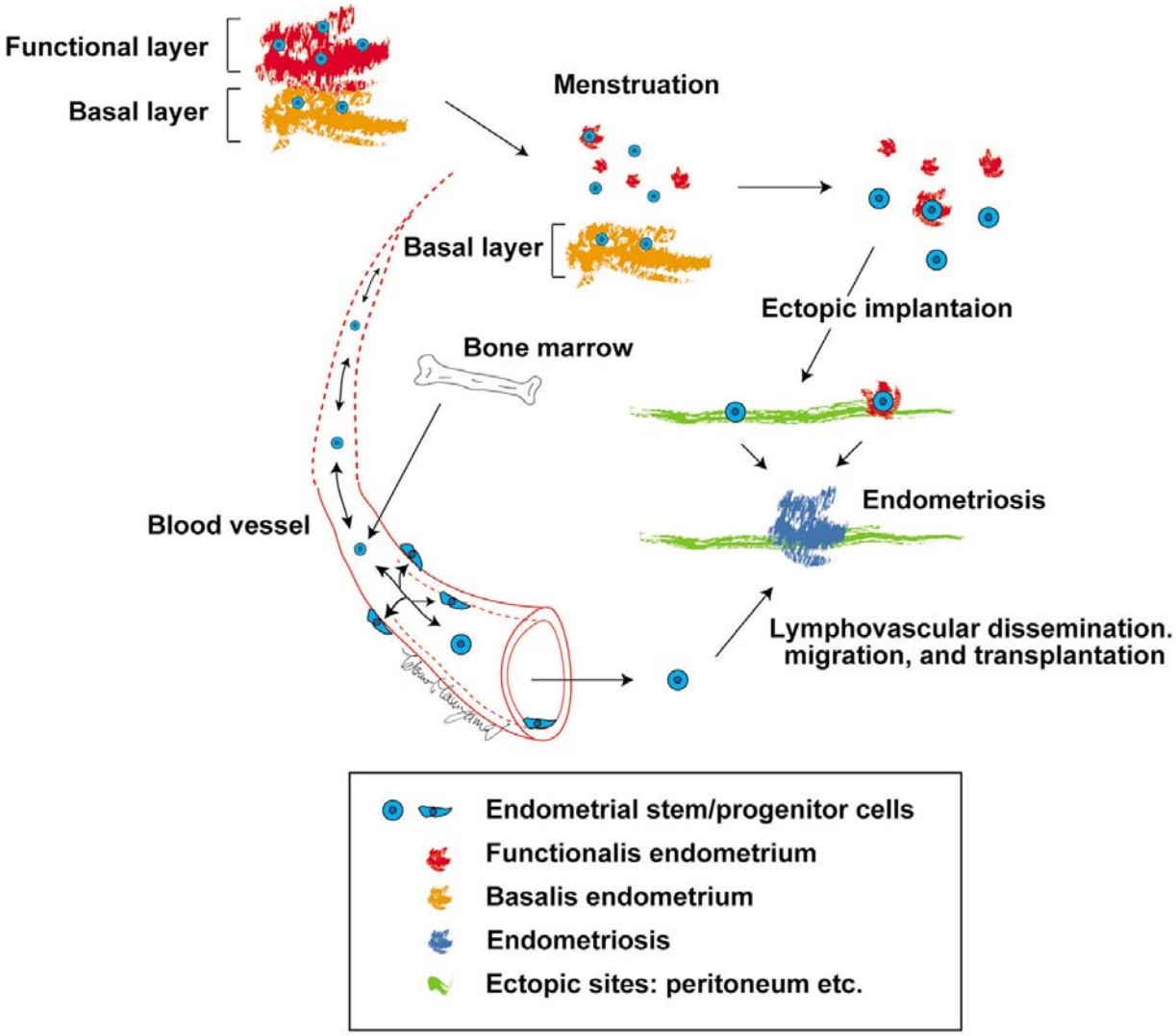

Figure 2. Proposed model for the ectopic location of putative endometrial stem/progenitor cells including ESP cells and the subsequent establishment of endometriotic lesion. Adapted with permission from reference 15.

functional layer if the stem theory is correct. Although these cells are believed to localize to the basal layer (73, 74), our data have shown that ABCG2+ cells, largely corresponding to ESP cells, one of the putative endometrial stem/progenitor cells, are also present in the functional layer (56).

Endometrial stem/progenitor cells comprise only a small fraction of all endometrial cells. For instance, ESP cells occupy only approximately 2% of the endometrial cell population (56). Thus, the chance of endometrial/stem progenitor cells implanting ectopically and giving rise to endometriotic lesions is very low. Furthermore, in general, stem/progenitor cells function only in the presence of an appropriate stem cell niche. Thus, it is plausible that the coincidence of the initial implantation event and the presence of a suitable stem cell niche may be extremely rare, which may partly account for the discrepancy between the incidence of endometriosis and the frequent occurrence of retrograde menstruation.

The clonality of an endometriotic lesion is pertinent to its origin and natural history. Several studies have demonstrated that ovarian endometriomas are monoclonal in origin (75-77), supporting the single-cell derivation of endometrial ovarian cysts. Conversely, peritoneal endometriotic lesions are polyclonal (78, 79). Importantly, however, individual glands of endometriotic lesions are monoclonal (78). These observations indicate that single and/or multiple precursor cells may give rise to a single peritoneal endometriotic lesion, the glands of which individually arise from a single stem/progenitor cell (78). Recent studies suggest that certain stem cell markers are expressed preferentially in endometriotic lesions (80-82). These findings collectively support the stem cell theory. Stem cell theory does not contradict the metaplasia theory which states that presently unidentified precursor cells in the mesothelium and/or müllerian duct remnants are capable of differentiation into endometrial cells under some specific stimulus (9-13). If the stem cell theory is widely interpreted, these putative precursor cells can be regarded as endometrial stem/progenitor cells.

Sasson and Taylor originally proposed a possible role for as-yet-unidentified endometrial stem cells in the pathogenesis of endometriosis (72). The recent data of our group and others (45, 56) further strengthens this concept of a “stem cell theory” by identifying the ESP cell as not only being the most likely candidate for the endometrial stem/progenitor cell. Additionally, these observations suggest that the ESP also contains the endometriosis-initiating (EMI) cell. Considering the pathogenesis of endometriosis, EMI cells should have the following properties. First, since the functional layer shed during menstruation, the retrograde menstruation theory (implantation theory) requires the presence of EMI cells in the functional layer. Second, attachment, migration and angiogenesis are essential for the implantation and survival of EMI cells at ectopic site(s). EMI cells, therefore, should have migratory potential and angiogenic capability. Third, to give rise to endometriotic lesion(s) containing glandular structures, EMI cells should demonstrate pluripotency. Our recent data have revealed that ESP cells satisfy most of the criteria of EMI cells in that ESP cells are present in the functional layer and have migratory, angiogeneic and stem cell-like properties (56). In addition to lending further credence to the stem cell theory of endometriosis, our ESP cell observations also provide additional support to the retrograde menstruation theory. Thus, our current review offers novel data and provides a new insight into the pathogenesis of endometriosis (72).

5. SUMMARY AND PERSPECTIVE

More than 100 years have passed since the first theory explaining endometriosis was proposed. To date, the implantation and metaplasia theories have been widely accepted, and they are not mutually exclusive. Each theory alone, however, fails to completely explain the pathogenesis of all types of endometriosis. In keeping with the emerging paradigm of stem cell biology in the female reproductive tract (14-16, 45-69, 83, 84), a stem cell theory has been recently proposed to account for the establishment of endometriotic lesions. Evidence in support of the stem theory is growing; however, no direct evidence for the role of endometrial stem/progenitor cells in the pathogenesis of endometriosis has been reported to date. Although many groups, including ours, have identified, isolated, and characterized putative endometrial stem/progenitor cells, no consensus exists regarding which of these distinct populations represents the endometrial stem/progenitor cell fraction. Once an endometrial stem cell is defined, it will be possible for the stem cell theory of endometriosis to progress beyond the level of a simple hypothesis.

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Abbreviations: ABCG2: ATP-binding cassette sub-family G member 2; EPC: endothelial progenitor cell; ESP: endometrial side population

Key Words: Endometriosis, Endometrium, Stem, Progenitor Cells, Pathogenesis, Implantation, Metaplasia, Bone Marrow, Regeneration, Endothelial Progenitor Cells, Endothelial Cells, Review

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