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Endometrial Stem Cells and Endometriosis

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1. Introduction

Stem cells (SCs) are undifferentiated cells which are able to remain at this state for several generations following cell proliferations. SCs are also able to take part in natural *in vivo* phenomena such as wound repair after physical damages or tissue regenerations.

On this basis, endometrial stem cells (EnSCs), characterized by higher abilities for proliferation, differentiation, fast angiogenesis during menstruation and immune tolerance for embryo during pregnancy, have been considered as a valuable source of stem cells (Gargett, Chan et al. 2007; Meng, Ichim et al. 2007). Several researches have demonstrated presence of highly pleuripotent mesenchymal stem cells in endometrium by differentiation potency to various cell types such as, insulin producer cells (Li, Chen et al. 2010), osteoblasts (Ai, Mehrabani. 2010) , odontoblasts (Ai, Tabatabaei et al. 2009), neurons (Wolff, Gao et al. 2011) (Ai, Tabatabaei et al. 2009) and Myoblast (Ai, Tabatabaei et al. 2009). These findings may open up new opportunities to use endometrial stem cells in tissue engineering and cell therapy (Ai , Mehrabani. 2009).

Additionally our previous studies demonstrated that EnSCs are able to participate at a phenomenon like angiogenesis in 3-D cultures which is similar to early stages of endometriosis (Esfandiari, Ai et al. 2007; Esfandiari, Khazaei et al. 2007; Esfandiari, Ai et al. 2008) which may propose a novel mechanism in pathogenesis of endometriosis compared to the traditional theory that emphasis on retrograde menstruation as a possible factor. These studies are supported by others who demonstrated recruitment of bone marrow-derived mesenchymal stem cells to the endometrium (Taylor 2004) and these all may point to the role of stem cells at the pathogenesis of endometriosis (Figueira, Abrão et al.; Sasson and Taylor 2008). Therefore, endometrial stem cells could be considered as binary role-player in natural function of endometrium and endometriosis and potentially could be used as a target in endometriosis therapy.

2. Histology of human uterus

The inner layer of uterus (Endometrium) comprises the mucosal lining which is highly regenerative tissue during menstrual cycle. The human endometrium undergoes more than 400 cycles of shedding and regeneration during a woman's reproductive years (McLennan and Rydell 1965). This layer is backed by a thick muscular myometrium which consists of muscular cells. There is no submucosal tissue to separate endometrial glandular tissue from

underlying smooth muscle. The endometrium is composed of single columnar epithelial layer, resting on a layer of connective tissue, the stroma. Tubular glands reach through the endometrial surface to the base of stroma. In a woman of reproductive age, the endometrium itself is structurally and functionally divided into two relatively distinct layers of upper functionalis and lower basalis. The functionalis zone is adjacent to uterine cavity and contains glands and supportive stroma for optimal implantation and growth condition of embryo. Basalis (basal layer), adjacent to myometrium, provides basal region of glands, dense stroma and lymphoid aggregates and from it functional layer develops. During menstrual cycle only the functional layer is regenerated and the basal layer is not affected.

Both endometrium and subendometrial myometrium originate from the Müllerian ducts during embryonic life. However, outer myometrial layer is formed during fetal life and from non- Müllerian origin (Ferenczy and Bergeron 1991).

The cellular components of human endometrium can be primarily divided into two cell types; the epithelial cells (luminal and glandular) and the supporting mesenchymal cells (stromal cells) as well as vascular (endothelial) cells and leukocytes.

3. Endometriosis

It is acknowledged that about 11% of all women population during reproductive age is affected by endometriosis (Buck Louis, Hediger et al. 2011). Endometriosis is a chronic benign gynecological disease which is characterized by the ectopic formation of endometrial stroma and glands mostly seen in pelvic peritoneum. However, it might be seen outside the pelvic peritoneum such as, pelvic viscera(Vercellini, Meschia et al. 1996), rectovaginal septum (Nisolle and Donnez 1997), pleura, abdominal wall, and even sometime in brain (Thibodeau, Prioleau et al. 1987). Briefly, the underlay mechanism is attachment of endometrial cells to the pelvic peritoneum, invasion into the mesothelium, and survival and proliferation of the ectopic endometrial cells. Endometriosis is usually diagnosed after symptoms such as pelvic pain, which might correlate with menstrual cycle, or infertility.

4. Etiology and pathophysiology of endometriosis

The source of endometrial implants is not fully understood. However, there are evidences for competence of some women over others (Di and Guo 2007). The reasons for susceptibility of some patients for development of ectopic lesions are not clear. Comparative microarray analysis of gene expression in patients with ectopic endometrial cells and that of eutopic endometrium has demonstrated an alternative pattern of gene expression in two groups (Taylor, Lundeen et al. 2002; Giudice 2003; Giudice 2006). This is also seen between patient and non-affected women (Gogusev, de Joliniere et al. 1999; Taylor, Lundeen et al. 2002; Giudice 2003; Giudice 2006; Wu, Strawn et al. 2006).

Although etiology of disease has not been clearly understood, a number of theories have been proposed in correlation with the pathogenesis of endometriosis which includes: genetic and environmental factors, immune system, retrograde menstruation, coelomic metaplasia, embryonic rest theory, lymphovascular metastasis and stem cell-based theory. Clinical manifestation of endometriosis and ectopic formation of endometriotic lesions usually considered as end point result of several aberrant biological process.

5. Stem cell-based theory

5.1 Stem cells

Stem cells are undifferentiated cells which are defined by their functional properties such as; high proliferative potential, substantial self-renewal capacity and ability to differentiate to other organ/tissue-specific cell types. Cellular self- renewal is a capacity that parental stem cells are able to divide into two daughter cells which can happen through symmetrical or asymmetrical division. The symmetrical division produces two identical daughter stem cells or transit amplifying (TA) cells. TA cells undergo repetitive cell division cycles and progressively acquire differentiation marker and lose their self-renewal capacity. Asymmetrical division leads to an identical daughter cell as well as a more differentiated cell.

Although stem cells are potentially capable to proliferation, they remain mostly in a quiescent state until an inductive factor to induce them to proliferation.

Adult stem cells present in all organs and tissues and are responsible for tissue regeneration and repair after damage and trauma encountered during life time.

Rarity and lack of distinguishable morphological features and specific molecular markers of stem cells have hindered their isolation, purification and studies for several years.

Broadly they can be divided into two categories, embryonic and adult stem cells. Stem cells can also be divided into various groups according to their differentiation capacity. For example, the zygote can be considered as a totipotent stem cell, which means it is able to differentiate into all other cell types in embryo and extraembryonic tissue. Other stem cells with decreased levels of potency can be named as; pluripotent, which can differentiate into nearly all cell types (e.g., inner cell mass of the blastocyst), multipotent, which can differentiate into a number of cells that are closely related family of cell (e.g., Hematopoetic stem cells), oligopotent which differentiate into a few cell types (e.g., myeloid or lymphoid stem cells) and unipotent, which differentiate into only one cell type with self-renewal capacity(e.g., muscle stem cell).

Anatomic structure surrounding stem cells which have profound effect on cell function is called niche. Signaling elements and various cellular and molecular interactions inside the niche can determine the fate of cell to stay in undifferentiated state until tissue regeneration or repair to motivate stem cell differentiation.

5.2 Evidences for existence of endometrial stem cells

5.2.1 Indirect evidences

Adult stem cells present throughout whole body and responsible for replenishment and regeneration of damaged tissues and contribute to the structural and functional maintenance of tissues and organs. Human endometrium undergoes periodical process of regeneration during menstrual cycle. The growth rate may vary between 0.5 -7mm in thickness. Menstruation is a phenomenon consisted of various cellular and tissue functions from cell proliferation and differentiation to shedding and regeneration. During each menstrual cycle, the functionalis and a part of basalis layer of endometrium undergo shedding. After shedding, the endometrium regrows under the influence of estrogen.

Regeneration process is comprised of endometrial regrowth, angiogenesis and proliferation of endometrial stromal cells. Shedding and regeneration of the endometrial layer during menstruation and regeneration of functional layer may be considered as an indirect evidence for presence of progenitor/ stem cells. This concept was proposed in 1978 by Prianishnikov (Prianishnikov 1978), and then confirmed by following clinical observations (Wood and Rogers 1993), proliferation experiments and demonstration of gland monoclonality (Tanaka, Kyo et al. 2003; Chan, Schwab et al. 2004; Schwab, Chan et al. 2005). In some other species this process is carried out in the form of endometrial growth and apoptosis rather than menstrual cycle. Therefore, this is conceivable that endometrium consists of an active and regenerative population of cells which are known as endometrial progenitor/stem cells (EnSCs). Since endometrium consists of glands, surface epithelium and supportive stroma, the existence of both epithelial and stromal stem/progenitor cells are plausible.

5.3 Evidence from cell cloning studies

The first reports for the existence of EnSCs on human endometrium came from clonogenic studies which identified epithelial and stromal stem cells (Tanaka, Kyo et al. 2003). By study carried out later on purified single cell suspensions obtained from hysterectomy tissue, 0.22±0.07% of endometrial epithelial cells and 1.25±0.18% of stromal cells formed individual colonies within 15 days (Chan, Schwab et al. 2004). Although both were clonogenic, the stromal stem cells were significantly more clonogenic than epithelial stem cells, and small and large colonies were observed in two types. The number of large colonies was lower than the smaller (0.09% of epithelial cells and 0.02% of stromal cells) and it may be hypothesized that they belong to stem cells population which are rare among other more mature transit amplifying cells. These colonies displayed significantly greater self-renewal capacity compared with the small and loose colonies. This observation lead to the hypothesis that larger colonies belong to endometrial stem/progenitor cells, and the smaller belong to transit amplifying (TA) cells with greater extent of differentiation.

The presence of clonogenic stromal and epithelial cells are also reported in inactive, noncycling endometrium (Schwab, Chan et al. 2005). This study showed similar frequency of clonogenicity for epithelial and stromal cells in different phases of the menstrual cycle or in inactive endometrium. These data further point to the presence of endometrial stem/progenitor cells within basalis layer in higher number than the functionalis layer.

5.4 Side population cells

Side population (SP) cells are a small fraction of cells within tissues with dye-effluxing properties. They are detected by flowcytometric analysis of pre-incubated cells with DNA-binding dye, Hoechst 33342. This is due to the expression of ABCG2, a plasma membrane transporter. SP cells have been identified from various adult tissues, demonstrating that this phenotype may represent a common feature of adult stem cells. SP cells were identified in short-term culture of two fractions filtered from human endometrial cell suspension (Kato, Yoshimoto et al. 2007). Upper fraction comprised mainly of epithelial ($CD9^+$) cells and the lower fraction contained both epithelial and stromal ($CD13^+$) cells. Further differentiation studies on Matrigel demonstrated the capacity of epithelial side population to differentiate into gland-like structures expressing CD9 and E-cadherin. On the side, cell differentiation

study of lower fraction showed the capacity to differentiate into $CD13^+$ stromal-like clusters. Additionally, to test whether endometrial SP cells reconstitute the endometrial tissue with stromal and glandular structure, they were xenotransplanted into NOG mice (Maruyama 2010). These studies not only demonstrated the presence of endometrial stem/progenitor cells, they have also provided an experimental animal model for endometriosis which is valuable in endometriosis studies.

5.5 Evidence from mouse

Mouse could be used as an experimental model for endometriosis and endometrial stem cell studies. However, the structure and physiology of mouse endometrium is not exactly similar to that of human. The mouse lacks an endometrial basalies layer, and the endometrium does not shed during menstruation but rather it is reabsorbed after the cycle. In spite of these dissimilarities, the murine estrous cycle has characteristics similar to those of human menstrual cycle and then mouse uterus can provide data on the molecular and cellular information for the pathogenesis of endometriosis and normal activity of endometrium tissue.

On this basis, several studies have been conducted to demonstrate the presence of endometrial stem cells in mouse endometrium (Cervello, Martinez-Conejero et al. 2006; Chan and Gargett 2006). For example, label-retaining cells (LRCs) have been shown in the mouse uterus. Label retaining is a technique to identify a stem cell population *in vivo* on the basis of quiescent state of stem/progenitor cells. The cells in this state are able to retain DNA strand incorporated stains such as, 5-bromo-2´-deoxyuridine (BrdU) for a longer period than the active dividing cells. A study conducted by Chan and Gargett showed that 3% of mouse endometrial epithelium after a 56-day chase period and 6% of endometrial stromal cells after an 84-day chase period are LRCs. Also, in another study Cevello et al demonstrated that 9% of stromal cells after 49 days were LRCs and this decreased to 1.7% after 112-day chase period. However, no epithelial LRCs were identified even after 21 days (Cervello, Martinez-Conejero et al. 2006). Presence of LRCs have also been demonstrated in myometrium (Szotek, Chang et al. 2007).

5.6 Endometrial regenerative cells (ERCs) from menstrual blood

Endometrial stem/progenitor cells have also been obtained from menstrual blood. These cells can be maintained in culture for more than 68 doubling and during this time they are able to retain their markers such as CD9, CD29, CD41a, CD44, CD59, CD73, CD90 and CD105 without karyotypic abnormalities (Musina, Belyavski et al. 2008). Proliferative rate of these cells are also significantly more than mesenchymal stem cells from the source of umbilical cord.

Endometrial regenerative cells (EnRCs) from menstrual blood are different from endometrial stem cells at expression of STRO-1. These cells are also negative for hematopoetic markers such as, CD34, CD45, CD133, but express embryonic stem cell marker, Oct4.

Ease of collection could be considered as an important characteristic of EnRCs which make them more attractive. Karyotypic stability of EnRCs suggests a large scale expansion capability.

5.7 Endometrial cancer stem cells

Presence of specific type of stem cells called cancer stem cells have been pointed at recent years (Bomken, Fišer et al. 2010). Cancer stem cell refers to a subset of tumour cells which are able to self-renew and generate the diverse cells in tumour cell mass. In fact, many features of carcinoma can be explained by the stem cell concept, including clonal origin and heterogeneity of tumors, the mesenchymal influence on cancer behavior, the local formation of precancerous lesions and the plasticity of tumor cells (Miller, Lavker et al. 2005).

A gold standard to evaluate the presence of cancer stem cells is to check their tumorogenicity on immunocompromised mice following serial transplantation. It is now postulated that cancer stem cells are responsible for cancer return after current cancer therapies e.g., radio- or chemotherapy. Recently, presence of endometrial cancer stem cells among endometrial carcinoma cells has been reported (Hubbard, Friel et al. 2009).

5.8 Signalling pathways involved in EnSCs' biology

Evidences from early studies of human EnSCs revealed the influences of three growth factors on clonogenisity of both epithelial and stromal cells. These are platelet-derived growth factor-BB (PDGF-BB), transforming growth factor-α (TGF-α) and epithelial growth factor (EGF). Basic fibroblast growth factor (b-FGF) was also able to induce clonogenicity on stromal stem cells but was not effective on epithelial cells. This could point to the difference of two cell types in expression of cognate receptor and this may propose two relatively distinct niches for them.

Also in serum-free culture condition, epithelial cells are relying on fibroblast feeder layer for clonogenicity. This may emphasis on the importance of epithelial-stromal interactions.

5.9 Endometrial stem cell markers

No specific marker has been identified for endometrial progenitor stem cells. This may hinder the isolation of EnSCs from surrounding cells utilizing the techniques such as FACS and MACS. Instead, a technique called label-retaining cell (LRC) have been successfully utilized to identify progenitor/stem cells among others in vivo.

Oct-4 is a transcription factor which is crucial for the maintenance of cell pluripotency and is known to be expressed in embryonic stem cells, germ cells, whole embryos at various stages of development and adult stem cells. It is also reported in almost half of the endometrial samples (Matthai, Horvat et al. 2006). Expression of Oct4 mRNA has been detected in all endometrial samples of 89 women in follicular or luteal phase of menstrual cycle (Bentz, Kenning et al. 2010).

Expression of other general stem cell markers such as bcl-2, c-kit (CD117) and CD34 have also been reported on endometrial stem cells (Cho, Park et al. 2004). Haematopoietic stem cell markers (CD34 and CD45) that co-express CD7 and CD56 have also been identified in human endometrial cell suspension that may belong to lymphoid progenitors.

Expression and localization of Musashi-1, a RNA-binding protein, have been evaluated in endometrial, endometriotic and endometrial carcinoma tissue specimens (Götte, Wolf et al. 2008). Musashi-1 is an epithelial progenitor cell marker. It is expressed on endometrial glandular and stromal cells and in proliferative endometrium. The proportion of Musashi-1-

positive cells in the basalis layer significantly increase in the stroma (1.5 fold) and in endometrial glands (three fold) compared to functionalis. Musashi-1 is also expressed in high levels in endometriosis and endometrial carcinoma (Götte, Wolf et al. 2008).

5.10 Differentiation ability of endometrial stem cells

Differentiation potency of endometrial stem cells has been demonstrated in several studies, suggesting their potency to be used as a useful source in cell therapy and tissue engineering. Kato et al used two markers of CD9 and CD13 to show that side population cells can differentiate into endometrial epithelial and stromal cells respectively(Kato, Yoshimoto et al. 2007).

Additionally, endometrial stromal cells have the potency to differentiate into chondrocytes when cultured in a defined chondrocyte medium. Also, large putative stromal stem/progenitor cell colonies consist of multipotency by differentiation into mesenchymal lineages-adipocytes, smooth muscle cells, chondrocytes and osteoblasts when cultured in an appropriate differentiation medium. By contrast, the small, loose colonies failed to demonstrate similar differentiation capacity that may suggest these cells are derived from TA cells.

Endometrial regenerative cells from menstrual blood are also able to differentiate to various cell lineages such as, insulin producer cells (Li, Chen et al. 2010), osteoblast (Ai, Mehrabani. 2010) , odontoblasts (Ai, Tabatabaei et al. 2009), and neurons (Wolff, Gao et al. 2011 and Ai, Esfandiari et al. 2009a).

EnSCs have been recently used to replace dopaminergic neurons in a murine model of Parkinson's disease (Wolff, Gao et al. 2011). Cardiogenic potential of EnSCs have also been high-lighted by several studies (Hida, Nishiyama et al. 2008).

5.11 Endometrial regeneration and angiogenesis

Endometrium is well known for its profound angiogenic potency which may point to the presence of a highly regenerative back-up layer (Esfandiari, Ai et al. 2007; Esfandiari, Khazaei et al. 2007; Esfandiari, Ai et al. 2008 and Ai, Esfandiari et al 2009a and 2009b). Angiogenesis plays a pivotal role in endometrium regeneration during menstrual cycle. It is also involved in establishment and development of endometriosis lesions (Donnez, Smoes et al. 1998; Fujishita, Hasuo et al. 2000).

5.12 Sources of endometrial stem/progenitor cells

5.12.1 Fetal stem cells

It is thought that some embryonic cells in the intermediate mesoderm undergo mesenchymal to epithelial transitions to form the coelomic epithelium that later invaginates to make the paramesonphric or Murrelian ducts (Kobayashi and Behringer 2003). Müllerian ducts comprise of surface epithelium and underlying urogenital ridge mesenchyme which are the source of endometrium and myometrium. A few epithelial and mesenchymal cells are thought to remain in the adult endometrium and contribute to tissue regeneration during menstrual cycle. This small population of stem cells might be subdivided into epithelial and stromal or even more committed sub-lineages or might exist in the form of ultimate uterine stem cells with a capacity to replace all endometrial and myometrial cells.

5.13 Bone marrow-derived stem cells as a possible source of endometrial progenitor/stem cells

Interestingly, regenerative turnover in endometrium is equivalent to that in bone marrow (Fuchs and Segre 2000). Bone marrow is commonly known as a source of hematopoetic and non-hematopoetic stem cells. Hematopoetic stem cells are mainly involved in the homeostasis of cellular part of blood. However, non-hematopoetic stem cells can differentiate into various cell types, e.g., endothelial cells, hepatocytes, neurons, skin, cardiomyocyte, gastrointestinal epithelium (Alison, Poulsom et al. 2000; Mezey, Key et al. 2003; Taylor 2004), suggesting their possible contribution to the maintenance of multiple tissues.

Apart from fetal source of stem cells resideing in adult endometrium which is speculated to account for the endometrium replacement after each menstrual cycle, new observations support the role of bone marrow-derived stem cells at endometrial regeneration.

Migration and presence of donor-derived bone marrow cell to/in endometrium and generation of experimental endometriosis have been reported after murine bone marrow transplantation (Taylor 2004; Du and Taylor 2007). Also, presence of chimerism in the endometrial glands and stroma of four women who received single-antigen HLA-mismatched bone marrow transplants can point to the contribution of bone marrow stem cells to the repopulation of the endometrium (Taylor 2004). Bone marrow-derived cells are indistinguishable from endogenous endometrial cells and express glandular and stromal differentiation markers.

Whether bone marrow-derived stem cells are involved in the normal function and regeneration of endometrium or pathogenesis of endometriosis is not clear. However, this theory is appropriately able to explain ectopic endometriosis.

5.14 Stem cell-based theory of endometriosis

Today, a combination theory is more acceptable for the pathogenesis of endometriosis. Evidences for existence of pluripotent endometrial stem cells, and contribution of bone marrow as an alternative source of EnSCs as well as the direct correlation of endometriosis and menstrual retrograde have convinced researchers to propose that stem/progenitor cells are present in the blood that reach the peritoneal cavity (Figueira, Abrão et al. 2011). Endometrial stem cells shed through fallopian tube during menstruation might be responsible for endometriotic implants. Also, this theory could account for the distant ectopic implants, as circulatory stem cells are able to reach peritoneal cavity as well as distant tissues and organs such as brain.

Several experiments have demonstrated that endometrium-derived cells are capable of establishing endometriotic implants (Te Linde and Scott 1950; Ridley and Edwards 1958; D'Hooghe, Bambra et al. 1995). Xenografts of human endometrial tissue or dissociated endometrial cells have been used in immunocompromised mouse to investigate pathogenesis of endometriosis (Grümmer 2006; Masuda, Maruyama et al. 2007). This model provides an appropriate in vivo system to test the possible role of EnSCs in endometriosis. This is further supported by the demonstration of clonogenic cells in a long-term culture derived from a sample of endometriosis tissue (Tanaka, Nakajima et al. 2003).

The monoclonality of some endometrial lesions (Jimbo, Hitomi et al. 1997; Tamura, Fukaya et al. 1998; Wu, Basir et al. 2003) is consistent with the concept that endometriosis could have a stem cell origin. Furthermore, polyclonal endometriotic lesions may point to repeated seeding of the lesions with cells from other sources such as bone marrow or from establishment of different fragments of shed endometrium containing several stem cells. Although stem cell-based pathogenesis of endometriosis is not fully established the previous studies have demonstrated the role of unfractionated endometrial stem cells to ectopic endometrial growth (Sasson and Taylor 2008). Endometriosis was also generated experimentally by ectopic wild-type endometrial implantation in the peritoneal cavity of hysterectomized LacZ transgenic mice (Du and Taylor 2007). LacZ-expressing stem cells of extrauterine origin were incorporated into the endometriosis implants. These cells were able to differentiate into epithelial and stromal cells at a frequency of 0.04% and 0.1%, respectively (Du and Taylor 2007).

In a study carried out by Leyendecker et al. expression pattern of estrogen receptor, two isoforms of progesterone receptor and P450 aromatase were compared on normal endometrium and ectopic endometriotic implants (Leyendecker, Herbertz et al. 2002). The expression pattern of the endometriotic implants was identical to that of basalis layer of eutopic endometrium and was out of phase with the functionalis layer. This study also demonstrated that more basalis layer was shed in women with endometriosis compared to the normal women. As basalis layer contain endometrial stem/progenitor cells and it is shed in larger extent in endometriosis that is in accordance with the larger volume of retrograde menstrual flow, this may suggest that endometriosis implants results from the retrograde menstruation of endometrial stem/progenitor cells.

Additionally, it has been postulated that some forms of endometriosis may arise from remnants of fetal müllerian cells which have characteristics of stem cells such as multipotency and self-renewal.

Thus, stem cell-based pathogenesis of endometriosis could be suggested and this theory could account for the observations that support the cellular origin of ectopic implants.

6. References

Ai, J. and D. Mehrabani (2010). "The Potential of Human Endometrial Stem Cells for Osteoblast Differentiation." Iranian Red Crescent Medical Journal 12(5): 585-587.

Ai, J., F. S. Tabatabaei, et al. (2009). "Human endometrial adult stem cells may differentiate into odontoblast cells." Hypothesis 7(1).

Alison, M. R., R. Poulsom, et al. (2000). "Cell differentiation: hepatocytes from non-hepatic adult stem cells." Nature 406: 257.

Bentz, E. K., M. Kenning, et al. (2010). "OCT-4 expression in follicular and luteal phase endometrium: a pilot study." Reproductive Biology and Endocrinology 8(1): 38-45.

Bomken, S., K. Fišer, et al. (2010). "Understanding the cancer stem cell." British journal of cancer 103:439-445.

Buck Louis, G. M., M. L. Hediger, et al. (2011). "Incidence of endometriosis by study population and diagnostic method: the ENDO study." Fertility and sterility. 96(2): 360-365

Cervello, I., J. A. Martinez-Conejero, et al. (2006). "Identification, characterization and co-localization of label-retaining cell population in mouse endometrium with typical undifferentiated markers." Human Reproduction 22(1): 45-51.

Chan, R. W. S. and C. E. Gargett (2006). "Identification of Label Retaining Cells in Mouse Endometrium." Stem Cells 24(6): 1529-1538.

Chan, R. W. S., K. E. Schwab, et al. (2004). "Clonogenicity of human endometrial epithelial and stromal cells." Biology of reproduction 70(6): 1738-1750.

Cho, N. H., Y. K. Park, et al. (2004). "Lifetime expression of stem cell markers in the uterine endometrium." Fertility and sterility 81(2): 403-407.

D'Hooghe, T. M., C. S. Bambra, et al. (1995). "Intrapelvic injection of menstrual endometrium causes endometriosis in baboons (Papio cynocephalus and Papio anubis)* 1." American journal of obstetrics and gynecology 173(1): 125-134.

Di, W. and S. W. Guo (2007). "The search for genetic variants predisposing women to endometriosis." Current Opinion in Obstetrics and Gynecology 19(4): 395-401.

Donnez, J., P. Smoes, et al. (1998). "Vascular endothelial growth factor (VEGF) in endometriosis." Human Reproduction 13(6): 1686-1690.

Du, H. and H. S. Taylor (2007). "Contribution of Bone Marrow Derived Stem Cells to Endometrium and Endometriosis." Stem Cells 25(8): 2082-2086.

Esfandiari, N., J. Ai, et al. (2007). "Expression of Glycodelin and Cyclooxygenase 2 in Human Endometrial Tissue Following Three dimensional Culture." American Journal of Reproductive Immunology 57(1): 49-54.

Esfandiari, N., M. Khazaei, et al. (2007). "Effect of a statin on an in vitro model of endometriosis." Fertility and sterility 87(2): 257-262.

Ferenczy, A. and C. Bergeron (1991). "Histology of the human endometrium: from birth to senescence." Annals of the New York Academy of Sciences 622(1): 6-27.

Figueira, P. G. M., M. S. Abrão, et al. "Stem cells in endometrium and their role in the pathogenesis of endometriosis." Annals of the New York Academy of Sciences 1221(1): 10-17.

Figueira, P. G. M., M. S. Abrão, et al. (2011). "Stem cells in endometrium and their role in the pathogenesis of endometriosis." Annals of the New York Academy of Sciences 1221(1): 10-17.

Fuchs, E. and J. A. Segre (2000). "Stem cells: a new lease on life." Cell (Cambridge) 100(1): 143-155.

Fujishita, A., A. Hasuo, et al. (2000). "Immunohistochemical study of angiogenic factors in endometrium and endometriosis." Gynecologic and obstetric investigation 48(1): 36-44.

Gargett, C. E., R. W. S. Chan, et al. (2007). "Endometrial stem cells." Current Opinion in Obstetrics and Gynecology 19(4): 377-383.

Giudice, L. C. (2003). Genomics' role in understanding the pathogenesis of endometriosis, 21(2): 119-124.

Giudice, L. C. (2006). "Application of functional genomics to primate endometrium: insights into biological processes." Reprod Biol Endocrinol 4(suppl 1): S4.

Gogusev, J., J. B. de Joliniere, et al. (1999). "Detection of DNA copy number changes in human endometriosis by comparative genomic hybridization." Human genetics 105(5): 444-451.

Götte, M., M. Wolf, et al. (2008). "Increased expression of the adult stem cell marker Musashi 1 in endometriosis and endometrial carcinoma." The Journal of Pathology 215(3): 317-329.

Grümmer, R. (2006). "Animal models in endometriosis research." Human reproduction update 12(5): 641-649.

Hida, N., N. Nishiyama, et al. (2008). "Novel Cardiac Precursor Like Cells from Human Menstrual Blood Derived Mesenchymal Cells." Stem Cells 26(7): 1695-1704.

Hubbard, S. A., A. M. Friel, et al. (2009). "Evidence for cancer stem cells in human endometrial carcinoma." Cancer research 69(21): 8241-8248.

Jimbo, H., Y. Hitomi, et al. (1997). "Evidence for monoclonal expansion of epithelial cells in ovarian endometrial cysts." The American Journal of Pathology 150(4): 1173-1178.

Kato, K., M. Yoshimoto, et al. (2007). "Characterization of side-population cells in human normal endometrium." Human Reproduction 22(5): 1214-1223.

Kobayashi, A. and R. R. Behringer (2003). "Developmental genetics of the female reproductive tract in mammals." Nature Reviews Genetics 4(12): 969-980.

Leyendecker, G., M. Herbertz, et al. (2002). "Endometriosis results from the dislocation of basal endometrium." Human Reproduction 17(10): 2725-2736.

Li, H. Y., Y. J. Chen, et al. "Induction of Insulin-Producing Cells Derived from Endometrial Mesenchymal Stem-like Cells." Journal of Pharmacology and Experimental Therapeutics 335(3): 817-829.

Maruyama, T. (2010). "Stem/progenitor cells and the regeneration potentials in the human uterus." Reproductive Medicine and Biology 9(1): 9-16.

Masuda, H., T. Maruyama, et al. (2007). "Noninvasive and real-time assessment of reconstructed functional human endometrium in NOD/SCID/ cnull immunodeficient mice." Proceedings of the National Academy of Sciences 104(6): 1925-1930.

Matthai, C., R. Horvat, et al. (2006). "Oct-4 expression in human endometrium." Molecular human reproduction 12(1): 7-10.

McLennan, C. E. and A. L. F. H. Rydell (1965). "Extent of endometrial shedding during normal menstruation." Obstetrics & Gynecology 26(5): 605-621.

Meng, X., T. E. Ichim, et al. (2007). "Endometrial regenerative cells: a novel stem cell population." Journal of Translational Medicine 5(1): 57-67.

Mezey, É., S. Key, et al. (2003). "Transplanted bone marrow generates new neurons in human brains." Proceedings of the National Academy of Sciences of the United States of America 100(3): 1364-1369.

Miller, S. J., R. M. Lavker, et al. (2005). "Interpreting epithelial cancer biology in the context of stem cells: tumor properties and therapeutic implications." Biochimica et Biophysica Acta (BBA)-Reviews on Cancer 1756(1): 25-52.

Musina, R. A., A. V. Belyavski, et al. (2008). "Endometrial mesenchymal stem cells isolated from the menstrual blood." Bulletin of experimental biology and medicine 145(4): 539-543.

Nazemian, Z., A. Jolly, et al. (2008). "Angiogenesis following three-dimensional culture of isolated human endometrial stromal cells." International Journal of Fertility and Sterility 2(1): 19-22.

Nisolle, M. and J. Donnez (1997). "Peritoneal endometriosis, ovarian endometriosis, and adenomyotic nodules of the rectovaginal septum are three different entities." Fertility and sterility 68(4): 585-596.

Prianishnikov, V. A. (1978). "On the concept of stem cell and a model of functional-morphological structure of the endometrium." Contraception 18(3): 213-223.

Ridley, J. H. and I. K. Edwards (1958). "Experimental endometriosis in the human." American journal of obstetrics and gynecology 76(4): 783.

Sasson, I. E. and H. S. Taylor (2008). "Stem cells and the pathogenesis of endometriosis." Annals of the New York Academy of Sciences 1127(1): 106-115.

Schwab, K. E., R. W. S. Chan, et al. (2005). "Putative stem cell activity of human endometrial epithelial and stromal cells during the menstrual cycle." Fertility and sterility 84: 1124-1130.

Szotek, P. P., H. L. Chang, et al. (2007). "Adult Mouse Myometrial Label Retaining Cells Divide in Response to Gonadotropin Stimulation." Stem Cells 25(5): 1317-1325.

Tamura, M., T. Fukaya, et al. (1998). "Analysis of clonality in human endometriotic cysts based on evaluation of X chromosome inactivation in archival formalin-fixed, paraffin-embedded tissue." Laboratory investigation 78(2): 213-218.

Tanaka, M., S. Kyo, et al. (2003). "Evidence of the monoclonal composition of human endometrial epithelial glands and mosaic pattern of clonal distribution in luminal epithelium." American Journal of Pathology 163(1): 295-301.

Tanaka, T., S. Nakajima, et al. (2003). "Cellular heterogeneity in long-term surviving cells isolated from eutopic endometrial, ovarian endometrioma and adenomyosis tissues." Oncology reports 10(5): 1155-1160.

Taylor, H. S. (2004). "Endometrial cells derived from donor stem cells in bone marrow transplant recipients." JAMA: the journal of the American Medical Association 292(1): 81-85.

Taylor, R. N., S. G. Lundeen, et al. (2002). "Emerging role of genomics in endometriosis research* 1." Fertility and sterility 78(4): 694-698.

Te Linde, R. W. and R. B. Scott (1950). "Experimental endometriosis." American journal of obstetrics and gynecology 60(5): 1147-1173.

Thibodeau, L. L., G. R. Prioleau, et al. (1987). "Cerebral endometriosis." Journal of neurosurgery 66(4): 609-610.

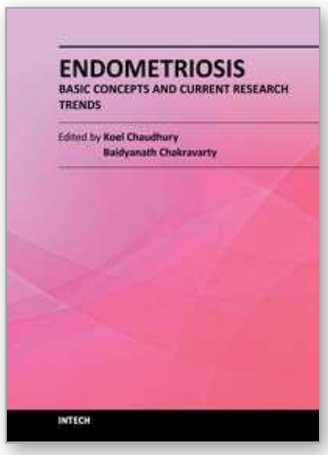
Vercellini, P., M. Meschia, et al. (1996). "Bladder detrusor endometriosis: clinical and pathogenetic implications." The Journal of urology 155(1): 84-86.

Wolff, E. F., X. B. Gao, et al. (2011). "Endometrial stem cell transplantation restores dopamine production in a Parkinson's disease model." Journal of Cellular and Molecular Medicine 15(4): 747-755.

Wood, C. and P. Rogers (1993). "A pregnancy after planned partial endometrial resection." Australian and New Zealand journal of obstetrics and gynaecology 33(3): 316-318.

Wu, Y., Z. Basir, et al. (2003). "Resolution of clonal origins for endometriotic lesions using laser capture microdissection and the human androgen receptor (HUMARA) assay* 1." Fertility and sterility 79: 710-717.

Wu, Y., E. Strawn, et al. (2006). "Genomic alterations in ectopic and eutopic endometria of women with endometriosis." Gynecologic and obstetric investigation 62(3): 148-159.



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This book provides an insight into the emerging trends in pathogenesis, diagnosis and management of endometriosis. Key features of the book include overviews of endometriosis; endometrial angiogenesis, stem cells involvement, immunological and hormonal aspects related to the disease pathogenesis; recent research reports on infertility, endometrial receptivity, ovarian cancer and altered gene expression associated with endometriosis; various predictive markers, and imaging modalities including MRI and ultrasound for efficient diagnosis; as well as current non-hormonal and hormonal treatment strategies This book is expected to be a valuable resource for clinicians, scientists and students who would like to have an improved understanding of endometriosis and also appreciate recent research trends associated with this disease.

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