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Stem Cell as the Novel Pathogenesis of Endometriosis

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1. Introduction

Endometriosis is a common gynecological disease. It is unique to have benign histology but with malignant characteristics. Easy recurrence, multiple organ involvement and malignant transformation potential make endometriosis a complex disease. Multi-factors contribute to the pathophysiology. Recently, endometriosis has been regarded as a stem cell disease (Sasson & Taylor, 2008). Some studies have provided evidence of the possible existence of stem cells in endometrial tissue (Gargett et al., 2004, 2007). We successfully isolated eutopic and ectopic endometrial mesenchymal stem cells (EN-MSCs) derived from one donor to examine the genetic difference analysis that provided a powerful tool for investigating the disease origin (Kao et al., 2011). Our results are consistent with the concept that endometriosis is a stem cell disease. We identified and characterized the MSCs from ectopic and eutopic endometrium by *in vitro* cell characteristics, including serpiginous morphology, surface biomarkers, a lack of gap junctional intercellular communication and the ability of differentiation and transdifferentiation into adipocytes, osteocytes, chondrocytes, neural cell and cardiomyocytes. In an *in vivo* animal study, we found the ability of invasion in eutopic and ectopic MSC.

The origins of endometrium stem cells are still under debate. Bone marrow is one of the origins. Bone marrow MSC circulates to the endometrium and reprograms into the endometrial MSC.

Aims of the chapter are to discuss about the endometrial stem cell identification and characterization and the stem cell theory of endometriosis will be discussed by search from the PubMed publications. The results will update our knowledge of the novel theory --- stem cell as the root of endometriosis.

2. Stem cells as the novel pathophysiology of endometriosis

2.1 Evidence of stem cell in the endometrium

The presence of endometrium stem cells can be identified by the property of clonogenicity, side population cells, stem cell markers, multipotent cells, xeno-transplantation. Expression of pluripotent marker such as Oct-4, and the stem cell factor in ectopic endometrium suggest

that endometriosis has a stem cell origin (Pacchiarottic et al., 2011). There are two types of endometrium mesenchymal stem cells, one derived from the epithelium and the other one from the stromal cells. The locations of these putative stem cells are supposed to be in the basalis of the endometrium (Figure 1). Some stem cell markers, for example, the RNA-binding protein Musashi-1 in colocalization with Notch-1 and telomerase increased in the basalis (Gotte et al., 2008). Recent study showed the endothelial progenitor/stem cells might reside in the endothelial cells (Maruyama et al., 2010). Some report showed the stem cell activity in endometrium through a stem cell niche with numbers of stem cells instead of a single stem cell (Kim et al., 2005). The function of endometrial stem cell/progenitor cell has been demonstrated to repair the damaged uterine surface in mouse model (Kaitu'u-Lino et al., 2010).

2.1.1 Cell cloning studies

The classic adult stem cell property, namely clonogenicity, is defined as a single cell to initiate a colony of cells when cultured at a single cell dilution condition. Both epithelium and stroma cells were reported to show clonogenicity (Gargett et al., 2007). The stromal cells display more clonogenicity than the epithelium cells. Both epithelium and stromal cells can develop large and small colonies. The large colonies were supposed to be initiated by stem cells while the small colonies by more mature transit amplifying cells (Figure 2).

2.1.2 Side population cells

Side population (SP) cells with the expression of ABCG2, which is a plasma membrane transporter, can extrude the DNA binding dye from cells. The cells in the side population are clonogenic and appear to be a universal marker of endometrial stem cell activity. SP cells are detected as a small fraction of cells within the endometrium after incubation with the Hoechst 33342 DNA binding dye. Recent study (Cervell et al., 2011) confirms the SP cells display endometrial stem cell characteristics in molecular markers of undifferentiated cells (Oct-4, GDF3, Nanog, DNMT3beta, GABR3). Phenotype analysis verifies epithelial (CD9+), or stromal (vimentin+) cell origin. The mesenchymal markers (CD90+, CD73+, CD45-) are expressed in SP. All these data imply SP containing the endometrial stem cells.

2.1.3 Stem cell marker and expression of stemness-related genes

Since the lack of universal stem cell-specific markers, adult stem cells are difficult to purify. This is the same in the case of endometrial stem cells. Various markers or combinations of markers have been reported to purify endometrium MSC (Table 1).

The stem cell markers in endometrium are not fully recognized. Some studies have examined the expression of stem cell markers in the endometrium. Oct-4, bcl-2, c-kit (CD117), CD 34, CD45, CD7, CD56 are reported (Mattai C et al., 2006; Cho et al., 2004; Lnych et al., 2007). Forte et al (Forte et al., 2009) studied the expression a panel of stemness related genes in the human endometriotic and endometrial samples. They found genes *UTF1*, *TCL1*, and *ZFP42* showed higher frequency of expression in endometriosis than in endometrium.

The presence of the stem cell markers in the endometrium and endometriotic samples suggest stem cell contributes to the pathogenesis of endometriosis.

2.1.4 Multipotent cells identified in human endometrium

Schwab & Gargett isolated mesenchymal stem-like cells from human endometrium in 2007 (Schwab & Gargett, 2007). They identified the endometrial stromal cells with the capacity of differentiated into cells of adipogenic, myogenic, osteogenic, and chondrogenic cell lineages. In the same year, the other research group (Wolff et al., 2007) also identified the chondrocytes from the human endometrium. These reports demonstrated the multipotent stem cells in the human endometrium. These multipotent endometrial stem/progenitor cells have reported to differentiate into 9 lineages: cardiomyocytic, respiratory epithelial, neurocytic, myocytic, endothelial, pancreatic, hepatic, adipocytic and osteogenic (Meng et al., 2007).

2.1.5 Xenotransplantation

Some studies have demonstrated the formation of endometriotic lesion formation after transplantation of human endometrium into the immunodeficient mice such as severe combined immunodeficiency (SCID) and nude mice. Singly dispersed human endometrial cells were transplanted under the kidney capsules of non-obese diabetic (NOD)/SCID mice. They unveiled the reconstruction of endometrium by showing the formation of chimeric vessels, tortuous endometrial glands, tissue breakdown and bleeding (Masuda et al., PNAS 2007). Our previous investigation revealed the invasion and angiogenesis character after implanting with scaffolds seeded with eutopic or ectopic endometrial MSCs (Kao et al., 2011).

2.2 Source of the endometrium stem cells

Endometrium from the eutopic (inside the uterine cavity) or ectopic (outside of the uterine cavity), from the menstrual blood and bone marrow are the origin of the putative endometrial stem cells.

2.2.1 Isolation and culture of putative eutopic and ectopic endometrial mesenchymal stem cells

Endometrial stem cells can be cultivated from the endometrium epithelium and stroma. We isolated the putative eutopic and ectopic endometrial mesenchymal stem cells from the cases of endometriosis. According to our previous report (Kao et al., 2011), endometrial stromal cells were cultured from the tissue of eutopic and ectopic endometrium (from the endometrioma). At early passage (passage 5), endometrial stromal cells were seeded in triplicate at very low density (200 cells per 100 mm dish) in Dulbecco's modified Eagles's medium-Ham's F12 medium. After 21 days of incubation, large colonies were isolated and trypsinized into single cells. The diluted single cells were seeded in 96-well plates, clonally derived proliferating colonies were individually trypsinized and culture in a 100-mm dish after culture for 14 days. These isolated stem/progenitor cells illustrated the differentiation

into mesoderm (adipogenesis, chondrogenesis, osteogenesis and cardiogenesis) and ectoderm (neurogenesis) (Figure 2).

2.2.2 Menstrual blood plays a role in the endometrial stem cells

Musina et al. isolated endometrium stem cells from the menstrual blood (Musina et al., 2008). The morphology resembled mesenchymal stem cells. The stem cells express CD44, CD90, CD 34, CD45, CD105/Endoglin. Cell differentiation revealed adipocytes, osteoblasts.

2.2.3 Bone marrow contributes to the sources of endometrial stem cells and pathogenesis of endometriosis

Currently, the ultimate source of endometrial stem cells is uncertain. Bone marrow derived stem cells (BMDCs) include hematopoietic stem cells (HSC) and MSC. BMDCs have been reported to be capable of transdifferentiation into hepatocytes, endothelial cells, neurons, cardiomyocyte, skin, gastrointestinal epithelium and endometrium (Taylor et al., 2004; Alison et al., 2000; Mezey et al., 2003; Quanini et al., 2002). Taylor et al. first provided the evidence of BMDCs as the sources of endometrial stem cells (Taylor et al., 2004). After bone marrow transplantation, they detected the endometrial epithelial cells and stromal cells with the donor human leukocyte antigen (HLA) in the recipient's endometrial samples. Another study observed the BMDCs derived from male donor mice engrafted the murine recipient endometrium (Du & Taylor, 2007). Although the transplanted BMDCs present in a small fraction (less than 0.01%), they could differentiate into endometrial cells in the uterus. Some novel theory of BMDCs in endometriosis pathogenesis was recently arisen. Bone marrow-derived circulating endothelial progenitor cells are recruited and incorporated into the vasculature of endometriotic lesions, thus contributing to the development of endometriosis (Matthias et al., 2011). In human studies, the donor BMDCs could transdifferentiate into the endometrial endothelial cells in a bone marrow transplantation recipient (Mints et al., 2008). BMDCs from human male donors were reported to differentiate into endometrial glands in a female transplant recipient (Ikoma et al., 2009). These data provide the evidence BMDCs as possible sources of endometrial stem/progenitor cells and endothelial progenitor cells.

2.2.4 Circulating endothelial progenitor cells (EPCs) contribute to the vascularization of endometriotic lesions

Endometriosis represents an angiogenic disease, rapid vascularization is essential to foster the ectopic endometrium survival and growth. One canonical characteristic of endometriosis is the vascularized endometriotic lesions inside the peritoneal cavity. Recent study (Matthias et al., 2011) indicates for the first time the circulating EPCs from the bone marrow contribute a relative high fraction (about 15%) of the microvascular networks in the engrafting endometriotic lesions in mice model. The recruited EPCs may contribute to the process of vasculogenesis (de novo generation of endothelial cells) (Figure 5). These data provide that the EPCs involve in the integral mechanism in the pathogenesis of endometriosis.

2.3 Endometrial stem cells as the pathogenesis and therapeutic target for endometriosis

2.3.1 Stem cells as a novel pathogenesis of endometriosis

Endometriosis is a multifactorial disease, the pathogenesis includes retrograde of endometrial cells, immunological insufficiency, genetics (Juo et al, 2006; 2009), metaplasia, and environmental hormone disruptor (Huang et al., 2011). Endometrial stem cells were identified in the endometrioma cyst walls (Chan et al., 2011; Kao et al., 2011).

Some hypotheses suggest the theory of stem cell in the pathogenesis of endometriosis (Figueira et al., 2011; Kao et al., 2010). Endometrium stem cells reside in the basalis layer can flux through the tubes and establish endometriotic lesions in the peritoneum. The stimulatory factors consisting of genetic, immunological and inflammatory, angiogenesis factors (Figure 6) promote the growth. An alternative hypothesis explores the extrauterine stem/progenitor cells (for example, from reprogram of bone marrow MSCs and circulating EPCs) function in the pathogenesis of endometriosis.

2.3.2 Therapeutic potential of human endometrial stem cells

Therapeutic potential of human endometrial stem cells has attracted interest of the researchers. Endometrial stem cells were obtained from nine healthy women and were transformed into the dopaminergic nerve cells. These cells were transplanted into the Parkinson-mice model (Wolff et al., 2010) and restored function of brain cells damage by producing dopamine.

The stem cell theory of endometriosis makes the advancement of targeting stem cells as the novel treatment. Stem cells flux and fostered by the peritoneal environment. The stem cells grow into endometriosis with increased survival and proliferative capacity along with environmental factors that contribute to stem cell survival and propagation. The treatment target can focus on the inhibition of stem cell flux and initiation and progression of endometriosis. Recent report (Zhou et al., 2011) cigarette smoke inhibits recruitment of bone marrow derived stem cells to the uterus. This finding is compatible with the epidemiological data of low incidence of endometriosis cases in smokers. Further investigation on the individual components of tobacco may unveil useful treatment in endometriosis. Our recent study reveals interleukin-1 beta can upregulate cyclooxygenase-2 and enhance invasion of human MSC derived from the ectopic endometrium (Kao et al., 2011). These results imply the interleukin-1 beta could be the targeting signalling. Stem cell therapy has been used in the lupus through anti-inflammatory activity (Traynor et al., 2002). Based on the same concept, bone marrow derived mononuclear stem cells has been transplanted in the experimental Wistar rats (Kondo et al., 2011). The expression of the inflammatory cytokines tumor necrosis factor-alpha (TNF-alpha) and vascular endothelial growth factor (VEGF) in the endometriotic implant decreased without reducing the lesion surface area. This provides the evidence that stem cells home the ectopic tissue to reduce the inflammatory process. This conflicts with the stem cell theory, which may indicate when the stem cells derived from the bone marrow, when they engraft the endometrium, they are modified in the gene expression, what will lead to the development of the endometriosis. The modified stem cells play different function as those original stem cells used for therapy. Other targeting of

inhibition in signalling pathways by stem cells and the microenvironment, self- renew pathway blocking, cell recruitment, flux and adhesion prevention will represent novel potential strategies (Taylor et al., 2011).

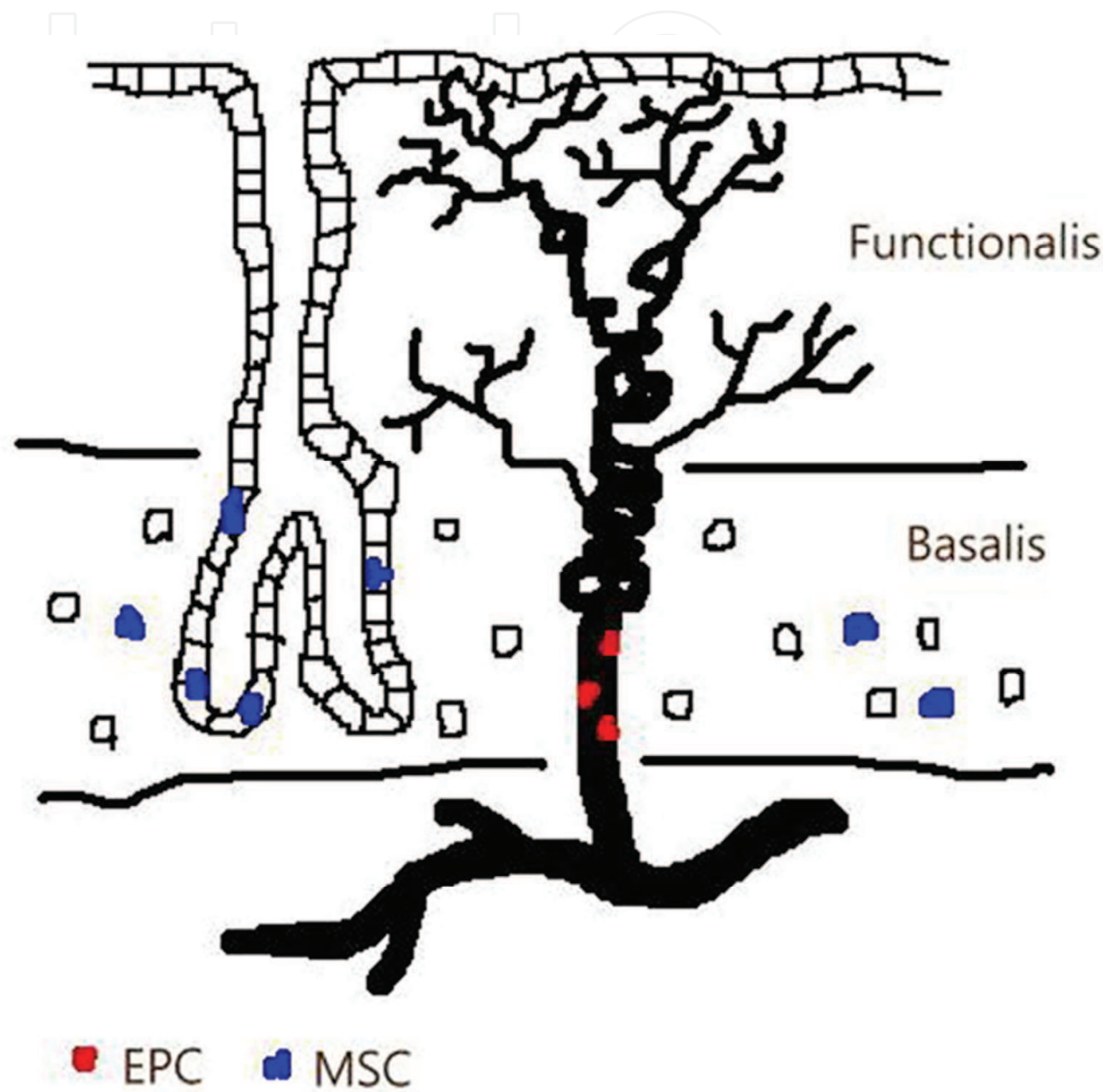


Fig. 1. The location of putative progenitor/stem cells is identified in the basalis of the endometrium. MSC denotes mesenchymal stem cells, and EPC indicates endothelial progenitor cells. (Modified from Maruyama et al., 2010)

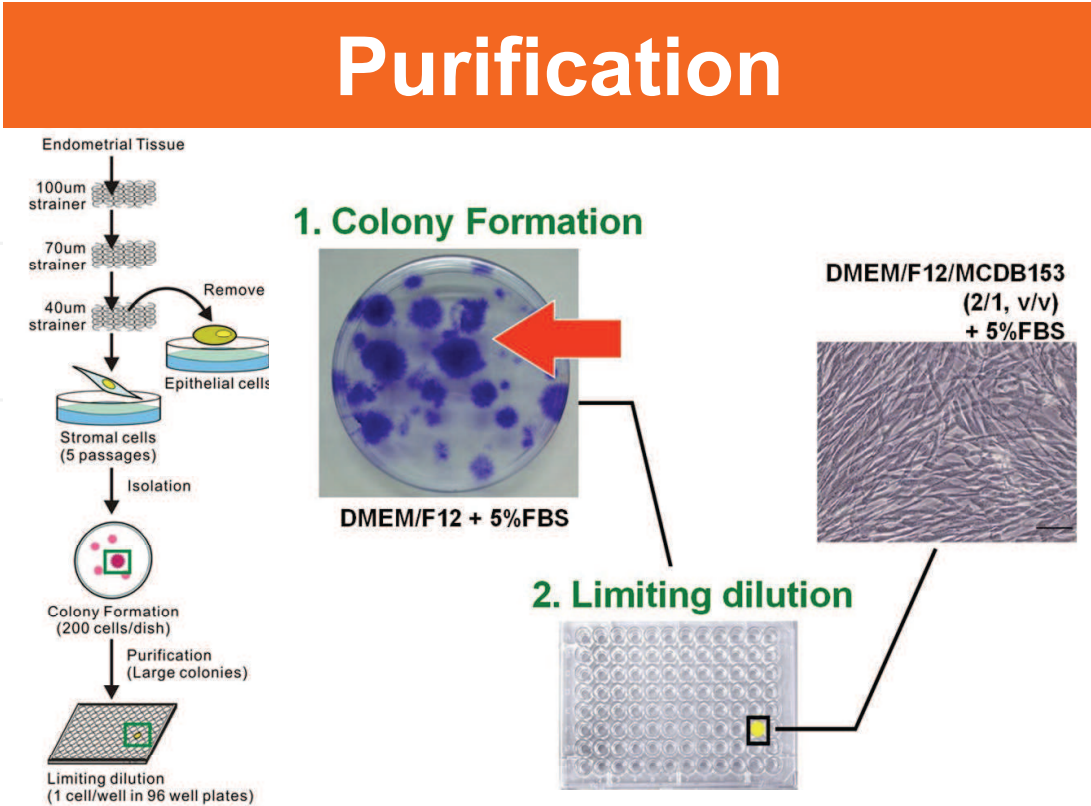


Fig. 2. Purification of stem cells from endometrial stromal cells. Large and small colonies develop after single cell limiting dilution. The large colonies are cultivated for stem cells identification.

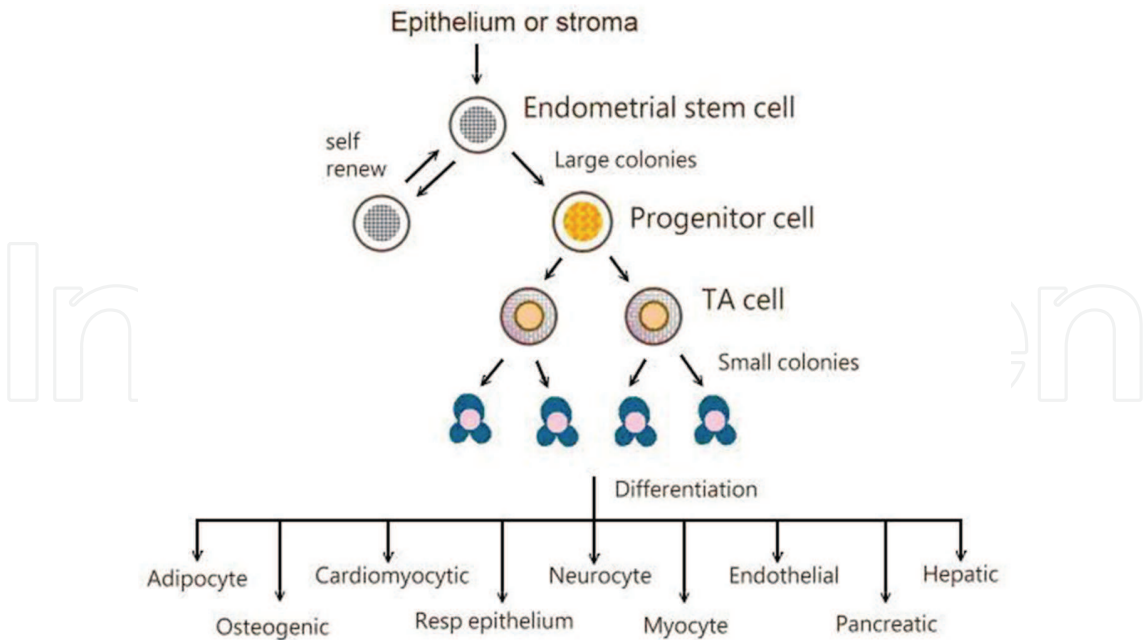


Fig. 3. Isolation and differentiation of endometrial stem/progenitor cells. Endometrial stem/progenitor cells can be isolated from endometrial epithelium and stromal cells. These cells can differentiated into 9 lineages, including adipocyte, myocyte, respiratory epithelium, neurocyte, osteogenic, cardiomyocytic, endothelial, pancreatic and hepatic cells.

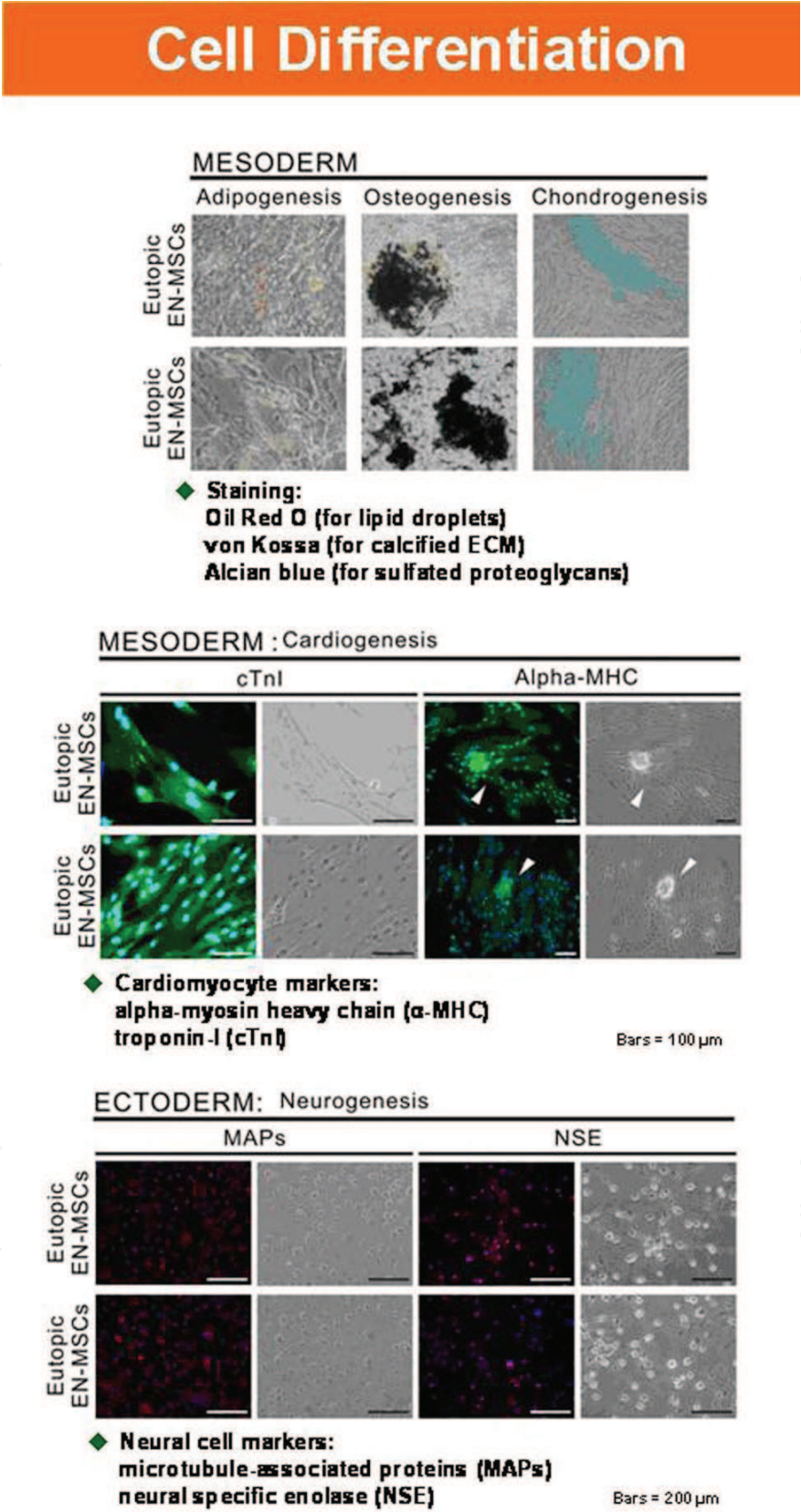


Fig. 4. Mesenchymal stem cells derived from eutopic and ectopic endometrial stromal cells differentiate into mesoderm and ectoderm lineages.

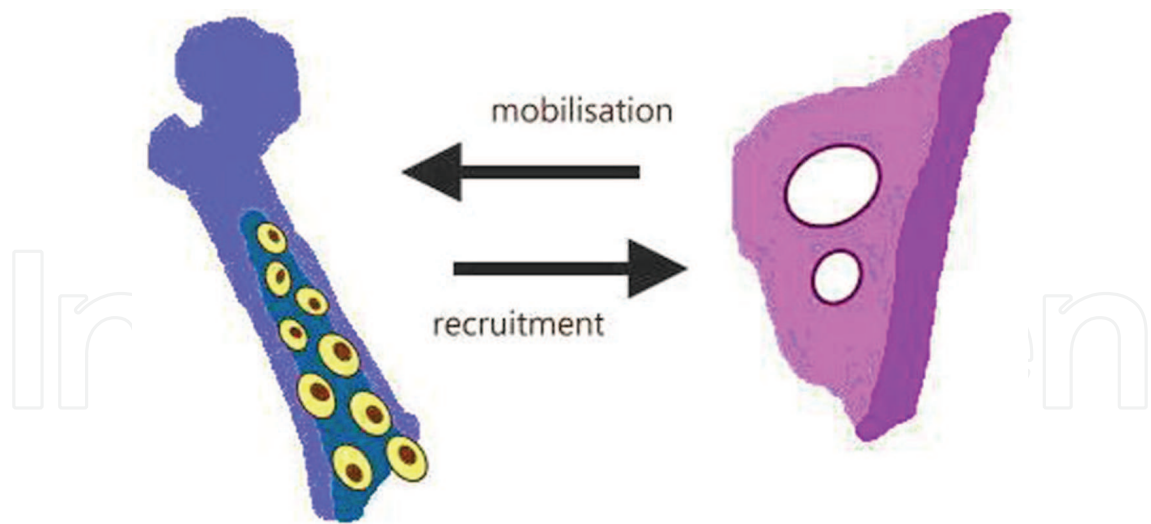
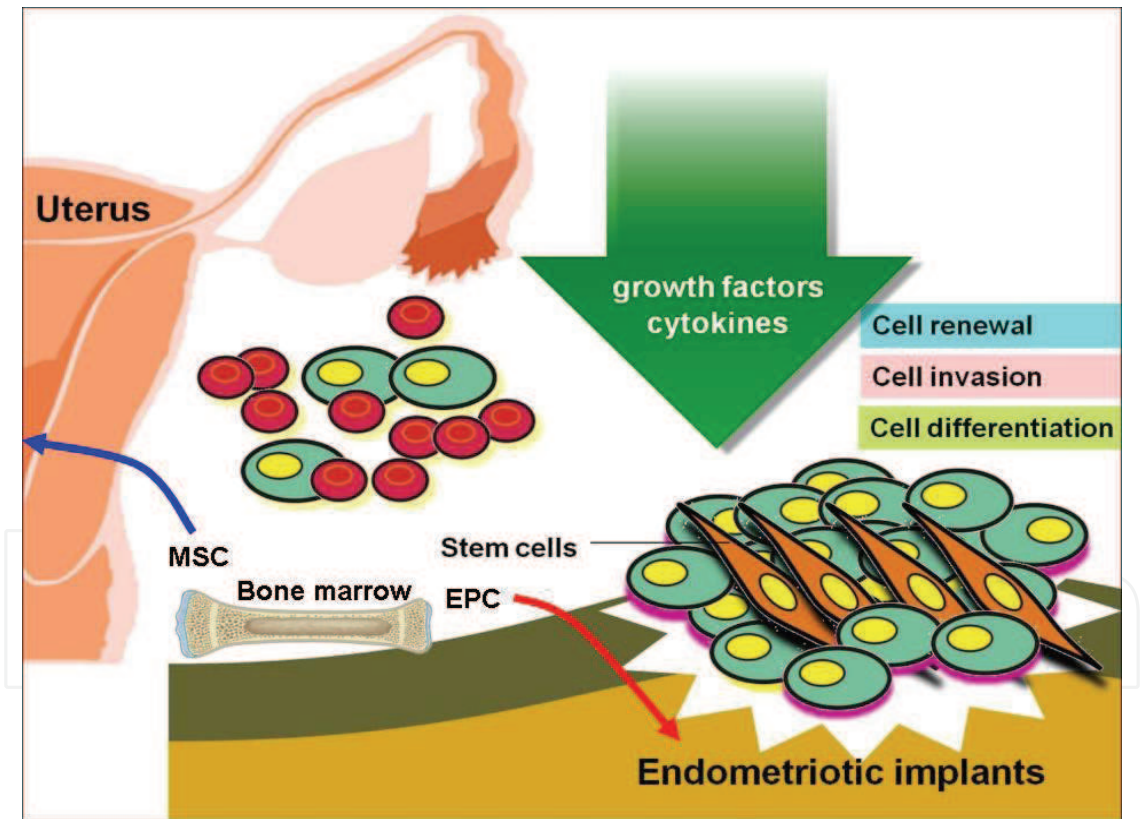


Fig. 5. Endothelial progenitor cells are mobilized and recruited to the endometriotic lesions, subsequently vasculogenesis (de novo generation of endothelial cells) occurs (modified from Laschke et al., 2011).



MSC indicates mesenchymal stem cell.
EPC means endothelial progenitor cell.

Fig. 6. The possible theory of endometrial stem/progenitor cells in the pathogenesis of endometriosis. The endometrial stem cells reflux to the peritoneum, and the microenvironmental factors such as growth factors, cytokines etc., stimulate the stem cells function (cell renew, invasion and cell differentiation). Bone marrow derived MSC and EPC may also contribute to the pathogenesis as described in the text.

Biomarker	Relevance/function	Expression
Oct-4	Stem cell	Positive
hTERT	Telomerase reverse transcriptase	Positive
CD9	MSC/angiogenesis	Positive
CD29	MSC/adhesion molecule	Positive
CD41a	MSC/fibrinogen receptor	Positive
CD44	MSC/hyaluronic acid receptor	Positive
CD73	MSC/migration	Positive
CD90	MSC/marker of T cells, hematopoietic and MSC	Positive
CD105	MSC	Positive
CD49f	MSC	Positive
Musashi-1	Endometrial stem cell	Positive
CD34	Hematopoietic stem cell	Negative
CD45	Leukocyte cell	Negative
SSEA-4	Embryonic stem cell	Negative
Nanog	Embryonic stem cell	Negative

MSC: mesenchymal stem cell
Modified from Meng et al., 2007

Table 1. Biomarkers of endometrial mesenchymal stem cells.

3. Conclusion

Since the retrograde implantation theory developed in the 1920s by Sympton, the etiology of endometriosis involves a complex interplay of genetic, immunologic, inflammatory and environmental factors. Nevertheless, endometriosis remains an enigmatic disease to cause pelvic pain and infertility. The characteristics of recurrence and wide spray make the disease malignant-like. Stem cell theory opens the latest advanced avenue for etiology of endometriosis. Increasing studies illustrate the presence of endometrial stem/progenitor cells, either from the residing cells in the endometrium or reprogram of bone marrow MSC. EPC from the bone marrow can contribute to the de novo angiogenesis. The EPC enhances endometriosis formation. Endometriosis is a recurrent disease, thus making the treatment costly and psychologically debilitating. Novel treatment modalities include selective ER modulators, tissue factor (the initiator of the hemostatic cascade) targets, statins and angiogenic blockers, immunoconjugate molecule and stem cells. Administration of endometrial stem cells to the disease model could suppress the immunological reaction, and was supposed to have potential in the treatment. Other therapy modalities to target the stem cells flux, adhesion and signalling control pathway are novel treatment strategies.

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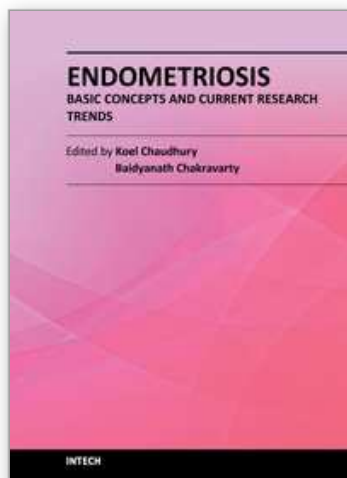
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This book provides an insight into the emerging trends in pathogenesis, diagnosis and management of endometriosis. Key features of the book include overviews of endometriosis; endometrial angiogenesis, stem cells involvement, immunological and hormonal 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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