Int J Clin Exp Med 2019;12(8):9607-9615
www.ijcem.com /ISSN:1940-5901/IJCEM0077737

Review Article

Endometrial regenerative cells and endometrial cancer stem cells: new insights may provide novel therapeutic targets

Yanping Xu, Naijun Li

Department of Obstetrics and Gynecology, General Hospital Affiliated to Tianjin Medical University, Tianjin 300000, P. R. China

Received April 11, 2018; Accepted December 7, 2018; Epub August 15, 2019; Published August 30, 2019

Abstract: Stem cells are undifferentiated cells that still exist in adult tissues and organs. Stem cells have multi-directional differentiation potential and can be induced into various specialized cell types under specific circumstances *in vitro*. The human endometrium is a highly proliferative tissue that remodels monthly and contains stem cells with self-renewal ability. Menstrual blood-derived stem cells are called endometrial regenerative cells (ERCs) and can be obtained non-invasively. ERCs have been widely applied in tissue engineering via different mechanisms. However, gene mutation in stem cells might lead to cancer stem cells (CSCs), which form a subpopulation of cancer cells with self-renewal ability. CSCs in endometrial carcinoma show resistance to conventional chemotherapy, which is often associated with poor prognosis. Here, the advances in this field are discussed with the aim to provide insights toward novel therapeutics.

Keywords: Endometrial regenerative cells, immunomudulation, ERC-based therapy, endometrial cancer stem cells, micoRNAs

Introduction

The human endometrium is composed of epithelium, endothelium, and stroma and can be divided into a functional layer and a basal layer. The functional layer contains the upper 2/3 of the glands that extend from the surface of both epithelium and stroma; the basal layer contains the lower 1/3 glands, stroma, vasculature, and lymphoid aggregates. The endometrium features a rapid rate of proliferation, differentiation, and shedding of approximately 400 cycles during a woman's reproductive life. While the basal layer is not affected by hormones, the uterine endometrium can thicken from 0.5 mm to 3-5 mm in response to the dynamic cycling process of the functional layer. Clinical observations showed that the endometrium can even regenerate after a very successful resection operation; endometrium regeneration was also found in postmenstrual women who received hormone replacement therapy. It has therefore been postulated that stem cells are present in the endometrium that contribute to the regeneration of the functional layer every month. While endometrial regenerative cells (ERCs) are important in tissue engineering, a subpopulation with stem-cell characteristics has been identified in endometrial carcinoma-endometrial cancer stem cells (ECSCs). ECSCs have been reported to initiate tumor formation in immunocompromised mice and are associated with EC invasiveness and chemotherapeutic resistance. In this review, recent progress in the field of ERCs and potential strategies for targeting ECSCs are discussed.

Existence of endometrial stem cells

Prianishnikov first introduced the hypothesis of the existence of endometrial stem cells in 1978 [1]. Goodell observed a type of hematopoietic stem cells and named them SP cells, where these cells can efflux the DNA dye Hoechst 33342. Most of these cells were in the G0 phase, i.e., in a stationary state. Similar SP cells are representatives of the pluripotency of endometrial stem cells. Chan reported the existence of endometrial epithelial and stromal cells in patients with uterine myomas; furthermore,

these cells could form colonies *in vitro* [2]. Two years later, Chan et al. reported the existence of label-retaining cells in the mice endometrium and further reported that these stem cells are located in "niches". Based on this progress, scholars identified CD146+/PDGFR-β+ mesenchymal stem cells near vessels in both functional layer and basal layer [3]. In summary, three types of stem cells have been identified in the human endometrium: epithelial stem cells, endothelial stem cells, and mesenchymal stem cells. It has been suggested that these cells might originate from bone marrow since bone marrow stem cells generally circulate in numerous organs and tissues. Cervello analyzed the HLA expression in the endometrium in patients who received bone marrow transplantation and reported that none of the HLA antigens matched [4]. There was no mismatched HLA in the control group but still, epithelial cells and mesenchymal cells from donors were found in the endometrium of recipients. Several scholars suggested that endometrial stem cells were the product of embryonic stem cells (ESCs) [5, 6]. Recent studies indicate that stem cells exist in the uterine endometrium *in situ*, namely EnSCs.

Endometrial regenerative cells

Compared to other stem cells, EnSCs offer many advantages. EnSCs proliferate extensively both *in vivo* and *in vitro*, with a doubling time of 19.4 hours, which is twice as fast as the time of bone marrow-derived stem cells [7]. Since clinical treatment is dose-dependent, the application prospect of EnSCs is bright. However, this rapid proliferation tends to cause instability in chromosomes. Animal experiments showed that EnSCs could extend to 40 passages without tumor formation, nor mutation on the chromosome level. The proliferation of EnSCs is regulated by Wnt signaling. It can inhibit EnSC proliferation through intranuclear translocation of β-catenin [8].

Compared to ESCs, EnSCs avoid ethical issues and their low immunogenicity and low tumorigenicity suggest novel diagnosis and therapies in the near future. Bone marrow-derived stem cells express an abundance of factors that are relevant for tumor pathways (TGF-β1, TGF-β2). EnSCs express inflammation factors such as ICAM-1 and IL-8, which indicates that EnSCs may play a role in acute phase of inflammation. Moreover, EnSCs express PDGF-BB and angiopoietin. These factors can aid angiogenesis in tissue repair [9]. These characteristics indicate EnSCs as a suitable source no other existing stem cell model can match for tissue engineering. When suffering from hypoxic or inflammatory conditions, EnSCs have the potential to differentiate into multiple lineages that aid cell-based therapies. It has been recently reported that EnSCs could be extracted from menstrual blood and are then called endometrial regenerative cells (ERCs). In addition to the above-mentioned advantages, ERCs can be obtained in a non-invasive manner and can be efficiently gene modified, which means that they could be genetically manipulated for future gene delivery [10]. ERCs can be induced into induced pluripotent stem cells iPSCs with high efficiency. iPSCs can be achieved via ectopic expression of four transcriptional genes in fibroblasts: OCT4, KLF4, SOX2, and c-MYC. However, iPSCs come at a significant cost and offer low efficiency; furthermore, reprogramming takes as long as four weeks. ERCs could reduce the induction time to 12 days even in the absence of c-MYC [11].

Endothelial progenitors and SDF-1 are important for both the release and homing of stem cells [12]. It has been reported that ERCs express SDF-1 and the chemokine receptor CXCR4, thus contributing to the migration of ERCs in damaged tissue [13]. With regard to surface markers, ERCs express markers of mesenchymal stem cells such as CD9, CD44, CD73, CD90, and CD105, while lacking the mesenchymal stem cell marker STRO-1 [14]. CD31 (endothelial), CD34 (hematopoietic stem cell), and CD45 are negative in ERCs. Interestingly, the ESC marker OCT-4 is positive in ERCs, and it is not influenced by hormones. Musashi-1 is a type of protein that is related to self-renewal and NOTCH was reported to be expressed in ERCs. Both interact with "niches" to participate in ERCs self-renewal and differentiation.

Differentiation potential of ERCs

ERCs can differentiate into osteoblasts, adipose cells, chondrocytes, smooth muscle cells, cardiocytes, hepatic cells, and pancreatic cells. p38 and c-Jun have been suggested to play a role in the normal differentiation of ERCs. As previously mentioned, adult stem cells reside in

a specific location with a specialized microenvironmental structure called "niche". This niche is composed of niche cells and stroma. Good differentiation in *in vitro* experiments requires a specific cell density, cell-cell and cell-matrix contact, the appropriate differentiation factors, and conditioned medium (CM). Therefore, it is important to closely mimic the "niche" microenvironment *in vitro*. However, these factors are difficult to determine [15]. Khanjani compared two protocols for hepatic cell differentiation induced by ERCs, at a high concentration of hepatocyte growth factor (HGF). Mature hepatocyte surface markers (ALB and CK-18) were up-regulated at both protein and mRNA levels. Furthermore, the function of hepatocytes was better when they were induced in serum-free medium [19]. ERCs could also differentiate into decidua-like cells. While the E2+P4 protocol was not effective for decidualizing ERCs, cAMP promoted the expression of decidualization markers (prolactin and insulin like growth factor binding protein-1) [16].

With regard to the differentiation potential compared to other MSCs, Rahimi et al. designed two protocols for cardiomyocyte differentiation. 5-aza+bFGF seemed better at inducing ERCs into cardiomyocytes than 5-aza alone. Under this protocol, ERCs were the better choice for cardiac cell differentiation than BM MSCs [17]. Similarly, when composed to human platelet releasate (HPR), ERCs are equal to BM MSCs in differentiating in osteoblasts [18]. These observations indicate ERCs as an alternative for stem cell-based therapy [19].

Immunomodulation of ERCs

MSCs have been reported to have extensive immunomodulation capacity. They are capable of inhibiting MLR and promoting Tregs (regulatory T cell generation) and at same time they inhibit the differentiation of Th1 and Th2 [20]. With regard to the underlying mechanism, the inflammation factor IFN-γ increases in response to tissue impair. Then, chemokines and adhesion molecules are activated, leading to the up-regulation of iNOs. T lymphocytes are inhibited when migrating to stem cells. Murphy [21] suggested a similar conclusion when discussing possible mechanisms of SC-treated limb ischemia: ERCs not only inhibited MLR, but also blocked production of pro-inflammatory factors such as INF-γ and TNF-α. Co-culture of ERCs and PBMCs has been used to test for allogenic reactions. Cells were co-cultured at a ratio of 1:2 for 6 d. ERCs presented a weak stimulatory response in MLR [22]. Nikoo et al. [23] pointed out that ERCs modulated the proliferation of PBMCs in a dose-dependent manner. ERCs showed an inhibitory effect at ratios between 1:1 and 1:2. However, if the ratio ranges between 1:32 and 1:64, ERCs promoted PBMC proliferation. Therefore, when the ERC concentration is low, less cell-cell contact could generate soluble factors, which are required for PBMS proliferation. In contrast, if the concentration is high, intra-cellular interactions could function [24]. ERCs have been suggested to improve stroke and other neurodegenerative diseases via inflammation regulation [25]. First, SDF attracts stem cells to the inflammation site [26], where undifferentiated cells survive longer than differentiated cells [27]. Finally, the host tissue secretes differentiation-stimulating factors, thus avoiding the continuous effect of previously differentiated cells [28]. The survival time of transplanted cells is limited, ensuring the safety of transplanted cells to some extent [29].

ERC-based therapy

Increasing evidence indicates that ERCs hold great potential for cell-free treatment. ERCs can secret MMP3, MMP10, and a number of paracrine factors such as VEGF and FGF [30]. They can protect impaired tissue from further injury. ERCs express VEGF and increase their secretion of TGFβ2, EGF, and NO when exposed in unfavorable conditions. Thus, cytokines may play a role in the treatment of multiple diseases. Moreover, MSCs have been reported to secret cholesterol-rich, phospholipid vesicles, and exosomes. Huang et al. reported that exosomes secreted by MSCs had anti-apoptosis, anti-inflammation, and anti-cardiac functions. Moreover, they contribute to cardiac regeneration and neovascularization. Consequently, exosomes secreted by ERCs enable new insight regarding the treatment of cardiovascular diseases [31]. After transplanting ERCs into a myocardial infarction animal model, Jiang [32] observed an improvement in cardiac function, showing a myocardium volume increase. However, no obvious differentiation of ERCs was seen in the myocardial infarction site. Instead, phosphorylation of survival kinases (AKT) increased as did the expression of Bcl-x1, while

caspase cleavage was inhibited. The entire process showed that ERCs can reduce apoptosis in a paracrine manner. Other functions of ERCs, including the promotion of endogenous progenitor regeneration and the increased density of vasculature, lead to a final increase in myocardial salvage and regeneration. With regard to ERCs, the mechanism is not always identical even for the same disease. ERCs decrease the degree of fibrosis in myocardial infarction and inhibition of TGFβ/Smad-induced endothelial to mesenchymal transition was involved [33].

With regard to diseases of the digestive system, Wu [34] reported that ERCs stimulated β-cell regeneration through endogenous progenitors in a paracrine manner, which ultimately improved hyperglycemia in mice with type-1 diabetes. Ulcerative colitis is a type of inflammatory bowel disease, where ERC treatment achieved pleasant results in UC treatment in animal model. In the studies of LV et al., MPO (a type of activated neutrophil marker) and Mac-1 protein expression were compared using immunohistochemistry between experimental group and control group. MPO and Mac-1 positive cells (macrophage and NK cells) decreased significantly in the ERCs-treated experimental group. IL-4 and IL-10 were up regulated at the mRNA level in the experimental group, while IL-2 and TNF-α were up regulated in the control group. ERCs also impacted the number of immune cells. CD11c+MHC-II+DCs decreased in the experimental group, and it was suggested that ERCs inhibited monocytes from differentiating into DCs, down-regulated the CD3+ CD8+T-cell level, and decreased cytotoxicity in immunomodulation approaches, which was consistent with a previous study [35].

Cancer stem cells in endometrial carcinoma

Cancer stem cells (CSCs) have been reported in tumors such as brain [36], breast [37], prostate [38], ovary [39], lung [40], colon [41], pancreas [42], melanoma [43], and endometrial carcinoma [44]. CSCs are a subpopulation of cancer cells with stem cell properties and are tumorigenic when transplanted into immunocompromised mice [45]. CSCs have unlimited proliferative ability and show resistance to conventional chemotherapy. Endometrial carcinoma (EC) is the most common malignant gynecologic cancer in developed countries [46]. EC can be classified into two types: type I and type II [47]. Type I EC, also known as endometrioid EC, accounts for the majority of cases and often presents a favorable prognosis. Type II non-endometrioid EC however, are often associated with metastasis or deep invasion. Low efficacy is observed when the chemotherapy agents paclitaxel or cisplatin have been applied to type II EC patients [48]. It has been assumed that the poor prognosis of EC might be related to cancer stem cells in EC [49, 50]. Hubbard et al. confirmed that rare cells in EC had colony forming ability and were able to develop additional tumors after serial transplantation for up to five passages [51]. A high proportion of CSCs in cancer has been accepted as an indicator of unfavorable prognosis. CSCs have been considered to originate from normal endometrial stem cells [52]. Genetic alteration such as the depletion of the PTEN (phosphatase and tensin homolog deleted on chromosome 10) gene, has been suggested to play a role in endometrial carcinoma null gland formation. The theory of "stem cell-hit" is generally accepted as the mechanism for CSC origination from somatic stem cells in the normal endometrium [53].

Markers to identify endometrial cancer stem cells (ECSCs)

CD133 has been widely accepted as a cancer stem cell marker in several solid tumors. A previous study has demonstrated CD133 as a potential marker for ECSCs [54, 55]. CD133+ cells were found to generate both CD133+ cells and CD133- cells, suggesting that they had self-renewal ability. ABCG2 is a multi-drug resistance gene that was up regulated in CD133+ cells compared to CD133- cells [56]. CD133+ cells also showed increased invasiveness, which is likely caused by high levels of MT-MMT expression [57]. Overall the survival rate was significantly lower in strong CD133+ expression patients compared to a lower expression group. The proportion of CD133+ cells could be a dependent prognostic factor for EC and this finding may help with the determination of molecular targets for ECSCs [58]. SP cells have been isolated in various tumors and have been reported to exhibit stem cell-like characteristics. SP cells isolated from EC could form invasive tumors with both tumor cells and stromal-like cells [59]. Furthermore, these SP cells demonstrated good potential to differentiate into mesenchymal cell lineages, according to a study that reported the differen-

tiation of SP cells into cells that expressed α-SMA in Matrigel [60].

Role of microRNAs in ECSCs

B-lymphoma mouse Moloney leukemia virus insertion region 1 (BMI-1) is a self-renewal gene that was recently found to be overexpressed in EC. Aberrant BMI-1 expression was seen in CSCs. BMI-1 has been reported to induce EMT in EC. EC cell invasion could be reduced by silencing BMI-1 expression. This knockdown of BMI-1 inhibited clonal growth and cell proliferation. MicroRNAs are non-coding RNAs that can bind to the 3' untranslated region (UTR) of the target mRNA, which finally leads to RNA degradation or protein expression repression. In the research of Dong et al., miR-194 directly targeted BMI-1 and induced mesenchymal to epithelial transition (MET), thus reducing the cell invasiveness in EC [61].

Gao [62] compared miRNA-134 expression between human endometrial cancer stem cells (huECSCs) and human endometrial cancer cells (HuECCs) and reported a significant difference. miR-134 suppressed HuECSC proliferation and migration by reducing protein O-glucosyltransferase (PLGLUT1) and notch pathway proteins. Additionally, miR-134 prevented HuECSCs from forming sphere clones, which reduced the multi-drug resistance of HuECSCs. Overexpression of miR-134 suppressed the formation of xenograft tumors by exerting an effect on the G2/M phase, which led to cell cycle arrest.

miR-101 is downregulated in poorly-differentiated endometrial cancer cell lines. Reexpression of miR-101 induced senescence and apoptosis in aggressive endometrial cancer cells. Similar to miR-134, the ectopic overexpression of miR-101 inhibited EMT-induced cancer cell invasiveness and improved the chemosensitivity to paclitaxel by abrogating the sphere-forming capacity in EC. EZH2, MCL-1, and FOS were direct targets of miR-101. miR-101 levels were lower in EC while elevated EZH2, MCL-1 and FOS were observed in EC, which could be responsible for the CSC-like phenotype and invasiveness in EC cells [63]. Their inverse expression levels in EC tissue suggest new strategies in EC therapeutics.

Increasing evidence suggests that activation of the PI3K/AKT pathway is related to the EMT/CSC phenotype [64]. As previously described, the PTEN-PI3K-AKT-mTOR axis promoted EMT in EC by upregulating EMT inducers. This signaling pathway was vital for CSC properties. miRNAs that downregulate PI3K/AKT related genes could be applied as a potential approach in EC treatment.

Other practical therapeutics targeting ECSCs

Significant progress in specific approaches targeting ECSCs has been achieved. Scholars have confirmed that the stem cell marker Musashi-1 was upregulated in endometrial carcinoma. Decreased Notch-1 expression was observed following knockdown of Musashi-1, while p21WAF1/CIP1 was up-regulated in Ishikawa endometrial carcinoma cells [65]. p21WAF1/CIP1 upregulation induces both apoptosis and cell cycle arrest in various cell lines [66]. The Notch pathway is related to self-renewal in CSCs. γ-secretase could inhibit the release of Notch intracellular domain, which would be effective in treating CSCs [67]. Histone Deacetylases (HDACs) participate in the inhibition of several tumor suppressor genes and re-expression of these genes could be induced via treatment of sodium butyrate (NaB), a HDAC inhibitor. NaB was observed to induce cell death via different mechanisms including the enhancement of DNA damage response (DDR) signals and elevated p21 expression levels. Colony formation was also suppressed in RK12V-SP cells [68]. TGF-β is an upstream inducer of EMT. EMT is generally related to metastasis and invasiveness of EC. TβRI-KI, a TGF-β type I receptor kinase inhibitor, effectively inhibited EMT and the sphere forming capacity of EC. Salinomycin is an antibacterial drug, with effectivity in killing breast cancer stem cells [69]. Kusunoki et al. reported that EMT-associated genes were upregulated in Hec1-SP cells. Salinomycin inhibited EMT-induced migration of Hec1-SP cells by suppressing the expression of fibronectin. Moreover, salinomycin downregulated Wnt target genes and induced apoptosis in Hec1-SP cells [70]. While CSC targeting agents have yielded satisfying outcomes, more detailed research should be conducted pre-clinically to prevent off-target effects.

In conclusion, ERCs are attracting increasing attention. ERCs are regarded as the "off the shelf" solution in many fields. However, ERCs also have limitations in some aspects. Certain types of diseases happen among high-risk groups such as males or postmenstrual women in epidemiology. This constitutes obstacles for

autologous ERC transplantation. However, even animal experiments for different diseases result in satisfactory outcomes. Clinical trials are only in the early phase and a limited number of diseases has been tested. Further studies are required to further clarify the issue. The existence of ECSCs offers new suggestions with regard to the chemotherapeutic resistance and poor prognosis in EC. Combination of conventional therapy with CSC-targeting agents has great potential in EC treatment. However, due to different ratios of CSCs in patients and CSC evolution within a patient, particular attention should be paid to achieving a better outcome with less side effects.

Acknowledgements

The present study was supported by grants from the National Natural Science Fund of China (81171032, 81100807), the Natural Science Foundation of Liaoning, China (20-1102264), the Research Project of Liaoning Department of Education (L2014316) and National Natural Science Foudation of China (81701410).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Naijun Li, Department of Obstetrics and Gynecology, General Hospital Affiliated to Tianjin Medical University, No. 154 Anshan Road, Heping District, Tianjin 300000, P. R. China. Tel: +86 18222764910; E-mail: 1357305-223@qq.com

References

[1] Prianishnikov VA. On the concept of stem cell and a model of functional-morphological structure of the endometrium. Contraception 1978; 18: 213-23.

[2] Chan RW, Schwab KE and Gargett CE. Clonogenicity of human endometrial epithelial and stromal cells. Biol Reprod 2004; 70: 1738-1750.

[3] Spitzer TL, Rojas A, Zelenko Z, Aghajanova L, Erikson DW, Barragan F, Meyer M, Tamaresis JS, Hamilton AE, Irwin JC, Giudice LC. Perivascular human endometrial mesenchymal stem cells express pathways relevant to self-renewal, lineage specification, and functional phenotype. Biol Reprod 2012; 86: 58.

[4] Cervelló I, Gil-Sanchis C, Mas A, Faus A, Sanz J, Moscardó F, Higueras G, Sanz MA, Pellicer A, Simón C. Bone marrow-derived cells from male donors do not contribute to the endometrial side population of the recipient. PLoS One 2012; 7: e30260.

[5] Baksh D, Song L, Tuan RS. Adult mesenchymal stem cells: characterization, differentiation, and application in cell and gene therapy. J Cell Mol Med 2004; 8: 301-316.

[6] Snyder EY and Loring JF. A role for stem cell biology in the physiological and pathological aspects of aging. J Am Geriatr Soc 2005; 53: 287-291.

[7] Meng X, Ichim TE and Zhong J. Endometrial regenerative cells: a novel stem cell population. J Transl Med 2007; 5: 57.

[8] Kazemnejad S, Khanmohammadi M, Zarnani AH, Nikokar I and Saghari S. Role of Wnt signaling on proliferation of menstrual blood derived stem cells. J Stem Cells Reg Med 2013; 19: 14-18.

[9] Gargett CE and Ye L. Endometrial reconstruction from stem cells. Fertil Steril 2012; 98: 11-20.

[10] Rossignoli F, Caselli A and Grisendi G. Isolation, characterization, and transduction of endometrial decidual tissue multipotent mesenchymal sromal/stem cells from menstrual blood. Biomed Res Int 2013; 2013: 901821.

[11] Rodrigues D, Asensi KD and Vairo L. Human menstrual blood-derived mesenchymal cells as a sourse of rapid and efficient nuclear reprogramming. Cell Transplant 2012; 21: 2215-2224.

[12] Elsheikh E, Sylven C, Erizon BG, Palmblad J and Mints M. Cyclic variability of stromal cell-derived factor-1 and endothelial progenitor cells during the menstrual cycle. Int J Mol Med 2011; 27: 221-226.

[13] Patel AN and Silva F. Menstrual blood stromal cells: the potential for regenerative medicine. Regen Med 2008; 3: 443-444.

[14] Gargett CE, Schwab KE, Zillwood RM, Nguyen HP and Wu D. Isolation and culture of epithelial progenitors and mesenchymal stem cells from human endometrium. Biol Reprod 2009; 80: 1136-1145.

[15] Lin J, Xiang D, Zhang JL, Allickson J and Xiang C. Plasticity of human menstrual blood stem cells derived from the endometrium. J Zhejiang Univ Sci B 2011; 12: 372-380.

[16] Sugaward K, Hamatani T and Yamada M. Derivation of human decidua-like cells from ammion and menstrual blood. Sci Rep 2014; 4: 4599.

[17] Rahimi M, Zarnani AH, Mohseni-Kouchesfehani H, Soltanghoraei H, Akhondi MM and Kazemnejad S. Comparative evaluation of cardiac markers in differentiated cells from menstrual blood and bone marrow-derived stem cells in vitro. Mol Biotechnol 2014; 56: 1151-1162.

[18] Darzi S, Zarnani AH and Jeddi-Tehrani M. Osteogenic differentiation of stem cells derived from menstrual blood VS bone marrow in the presence of human platelet releasate. Tissue Eng Part A 2012; 18: 1720-1728.
[19] Khanjani S, Khanmohammadi M and Zarnani AH. Comparative evaluation of differentiation potential of menstrual blood VS bone marrow-derived stem cells into hepatocyte-like cells. PLoS One 2014; 9: e86075.
[20] Prevosto C, Zancolli M, Canevali P, Zocchi MR, Poggi A. Generation of CD4+ or CD8+ regulatory T cells upon mesenchymal stem cell-lymphocyte interaction. Haematologica 2007; 92: 881-888.
[21] Murphy MP, Wang H and Patel AN. Allogeneic endometrial regenerative cells: an "off the shelf solution" for critical limb ischemia? J Trans Med 2008; 6: 45.
[22] Verdi J, Tan A, Shoae-Hassani A and Seifalian AM. Endometrial stem cells in regenerative medicine. J Bio Eng 2014; 8: 20.
[23] Nikoo S, Ebtekar M, Jeddi-Tehranai M, Shervin A, Bozorgmehr M, Kazemnejad S and Zarnani AH. Effect of menstrual blood-derived stromal stem cells on proliferative capacity of peripheral blood mononuclear cells in allogeneic mixed lymphocyte reaction. J Obstet Gynaecol Res 2012; 38: 804-809.
[24] Najar M, Rouas R and Raicevic G. Mesenchymal stromal cells promote or suppress the proliferation of t lymphocytes from cord blood and peripheral blood: the importance of low cell ratio and role of IL-6. Cytotherapy 2009; 11: 570-583.
[25] Rodrigues O, Carolina M, Voltarelli J, Allickson JG, Kuzmin-Nichols N, Garbuzova-Davis S and Borlongan CV. Recent progress in cell therapy for basal ganglia disorders with emphasis on menstrual blood transplantation in stroke. Neurosci Biobehav Rev 2012; 36: 177-190.
[26] Park DH, Musso J 3rd, Klasko SK, Cruz E, Borlongan CV and Sanberg PR. Inflamation and stem cell migration to the injured brain in higher organisms. Stem Cells Dev 2009; 18: 693-701.
[27] Le Belle JE, Caldwell MA and Svendsen CN. Improving the survival of human CNS precursor-derived neurons after transplantation. J Neurosci Res 2004; 76: 174-183.
[28] Fujiwara Y, Tanaka N, Ishida O, Fujimoto Y, Murakami T, Kajihara H, Yasunaga Y and Ochi M. Intravenously injected neural progenitor cells of transgenic rats can migrate to the injured spinal cord and differentiate into neurons, astrocytes and oligodendrocytes. Neurosci Lett 2004; 366: 287-291.
[29] Jablonska A, Kozloeska H, Markiewicz I, Domanska-Janik K and Lukomska B. Transplantation of neural stem cells derived from human cord blood to the brain of adult and neonatal rats. Acta Neurobiol Exp 2010; 70: 337-350.
[30] Meng X, Ichim TE and Rogers A. Endometrial regenerative cells: a novel stem cell population. J Trans Med 2007; 5: 57.
[31] Huang L, Ma W, Ma Y, Feng D, Chen H and Cai B. Exosomes in mesenchymal stem cells, a new therapeutic strtegy for cardiovascular diseases? Int J Biol Sci 2015; 11: 238-245.
[32] Jiang Z, Hu XY and Yu H. Human endometrial stem cells confer enhanced myocardial salvage and regeneration by paracrine mechanisms. J Cell Mol Med 2013; 17: 1247-1260.
[33] Zhang ZC, Wang JA, Xu YC, Jiang Z, Wu R, Wang L, Chen P, Hu X and Yu H. Menstrual blood derived mesenchymal cells ameliorate cardiac fibrosis via inhibition of endothelial to mesenchymal transition in myocardial infarction. Int J Cardiol 2013; 168: 1711-1714.
[34] Wu X, Luo Y, Chen J, Pan R, Xiang B, Du X, Xiang L, Shao J and Xiang C. Transplantation of human menstrual blood progenitor cells improves hyperglycemia by promoting endogenous progenitor differentiation in type 1 diabetic mice. Stem Cells Dev 2013; 23: 1245-1256.
[35] Lv YC, Xu XL, Zhang B, Zhou G, Li H, Du C, Han H and Wang H. Endometrial regenerative cells as a novel cell therapy attenuate experimental colitis in mice. J Tran Med 2014; 12: 344.
[36] Bao S, Wu Q, McLendon RE, Hao Y, Shi Q and Hjelmeland AB. Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. Nature 2006; 444: 756-760.
[37] Ai-Hajj M, Wicha MS, Benito-Hernandez A, Morrison SJ and Clarke MF. Prospective identification of tumorigenic breast cancer cells. Proc Natl Acad Sci USA 2003; 100: 3983-3988.
[38] Gu G, Yuan J, Wills M and Kasper S. Prostate cancer cells with stem cells characteristics reconstitute the original human tumor in vivo. Cancer Res 2007; 67: 4807-4815.
[39] Visvader JE and Linderman GJ. Cancer stem cells in solid tumours: accumulating evidence and unsolved questions. Nat Rev Cancer 2008; 8: 755-768.
[40] Eramo A, Lotti F, Sette G, Pilozzi E, Biffoni M, Di Virgilio A, Conticello C, Ruco L, Peschle C, De Maria R. Identification and expansion of the tumorigenic lung cancer stem cell population. Cell Death Differ 2008; 15: 504-514.
[41] Ricci-Vitiani L, Lombardi DG, Pilozzi E, Biffoni M, Todaro M and Peschle C. Identification and expansion of human colon-initiating cells. Nature 2007; 445: 106-110.
[42] Hermann PC, Huber SL and Herrler T. Distinct populations of cancer stem cells determine tu-

mor growth and metastatic activity in human pancreatic cancer. Cell Stem Cell 2007; 1: 313-323.
[43] Monzani E, Facchetti F and Galmozzi E. Melanoma contains CD133 and ABCG2 positive cells with enhanced tumorigenic potential. Eur J Cancer 2007; 43: 935-946.
[44] Mirantes C, Espinosa I, Ferrer I, Dolcet X, Prat J and Matias-Guiu X. Epithelial-to-mesenchymal transition and stem cells in enndometrial cancer. Hum Pathol 2013; 44: 1973-81.
[45] Cervello I, Mirantes C, Santamaria X, Dolcet X, Matias-Guiu X and Simon C. Stem cells in human endometrium and endometrial carcinoma. Int J Gynecol Pathol 2011; 30: 317-327.
[46] Cervelló I, Mas A, Gil-Sanchis C, Simón C. Somatic stem cells in the human endometrium. Semin Reprod Med 2013; 31: 69-76.
[47] Wallace AE, Gibson DA, Saunders PT and Jabbour HN. Inflammatory events in endometrial adenocarcinoma. J Endocrinol 2010; 206: 141-157.
[48] Ma S, Lee TK, Zheng BJ, Chan KW and Guan XY. CD133+ HCC cancer stem cells confer chemoresistance by preferential expression of the Akt/PKB survival pathway. Oncogene 2008; 27: 1749-1758.
[49] Ginestier C. ALDH1 is a marker of normal and malignant human mammary stem cells and a predictor of poor clinical outcome. Cell Stem Cell 2007; 1: 555-567.
[50] Silva IA. Aldehyde dehydrogenase in combination with CD133 defines angiogenic ovarian cancer stem cells that portend poor patient survival. Cancer Res 2011; 71: 3991-4001.
[51] Hubbard SA, Friel AM, Kumar B, Zhang L, Rueda BR and Gargett C. Evidence for cancer stem cells in human endometrial carcinoma. Cancer Res 2009; 69: 8241-8.
[52] Phesse TJ and Clarke AR. Normal stem cells in cancer prone epithelial tissues. Br J Cancer 2009; 100: 221-7.
[53] Baker N. Crypt stem cells as the cells-of-origin of intestinal cancer. Nature 2009; 457: 608-11.
[54] Nakamura M, Kyo S, Zhang B, Zhang X, Mizumoto Y and Takakura M. Prognostic impact of CD133 expression as a tumor initiating marker in endometrial cancer. Hum Pathol 2010; 41: 1516-29.
[55] Rutella S, Bonanno G, Procoli A, Mariotti A, Corallo M, Prisco MG, Eramo A, Napoletano C, Gallo D, Perillo A, Nuti M, Pierelli L, Testa U, Scambia G, Ferrandina G. Cells with characteristics of cancer stem/progenitor cells express the CD133 antigen in human endometrial tumors. Clin Cancer Res 2009; 15: 4299-4311.
[56] Nakamura M, Zhang XZ, Zhang XZ, Mizumoto Y, Maida Y, Bono Y, Takakura M and Kyo S. Molecular characterization of CD133+ cancer stem-like cells in endometrial cancer. Int J Oncol 2014; 44: 669-677.
[57] Kohga K, Tatsumi T and Takehara T. Expression of CD133 confers malignant potential by regulating metalloproteinases in human hepatocellular carcinoma. J Hepatol 2010; 52: 872-879.
[58] Maeda S, Shinchi H and Kurahara H. CD133 expression is correlated with lymph node metastasis and vascular endothelial growth factor-C expression in pancreatic cancer. Br J Cancer 2008; 98: 1389-1397.
[59] Kato K, Takao T, Kuboyama A, Tanaka Y, Ohgami T and Yamaguchi S. Endometrial cancer side population cells show prominent migration and have a potential to differentiate into the mesenchymal cell lineage. Am J Pathol 2010; 176: 381-92.
[60] Kato K. Endometrial cancer stem cells: a new target for cancer therapy. Anticancer Res 2012; 32: 2283-93.
[61] Dong PX, Kaneuchi M, Watari H, Hamada J, Sudo S, Ju JF and Sakuragi N. MicroRNA-194 inhibits epithelial to mesenchymal transition of endometrial cancer cells by targeting oncogene BMI-1. Mol Cancer 2011; 10: 99.
[62] Gao YT, Liu T and Huang YY. MicroRNA-134 suppresses endometrial cancer stem cells by targeting POGLUT1 and Notch pathway proteins. FEBS Lett 2015; 589: 207-214.
[63] Konno Y, Dong P, Xiong Y, Suzuki F, Lu J, Cai M, Watari H, Mitamura T, Hosaka M, Hanley SJ, Kudo M, Sakuragi N. MicroRNA-101 targets EZH2, MCL-1 and FOS to suppress proliferation, invasion and stem cell-like phenotype of aggressive endometrial cancer cells. Oncotarget 2014; 5: 6049-62.
[64] Dong PX, Konna Y, Watari H, Hosaka M, Noguchi M and Sakuragi N. The impact of microRNA-mediated PI3K/AKT signaling on epithelial-mesenchymal transition and cancer stemness in endometrial cancer. J Trans Med 2014; 12: 231.
[65] Götte M, Greve B, Kelsch R, Müller-Uthoff H, Weiss K, Kharabi Masouleh B, Sibrowski W, Kiesel L, Buchweitz O. The adult stem cell marker Musashi-1 modulates endometrial carcinoma cell cycle progression and apoptosis via Notch-1 and p21WAF1/CIP1. Int J Cancer 2011; 129: 2042-9.
[66] Jain MV, Jangamreddy JR, Grabarek J, Schweizer F, Klonisch T, Cieslar-Pobuda A and Los MJ. Nuclear localised Akt enhances breast cancer stem-like cells through counter-regulation of p21(waf1/cip1) and p27(kip1). Cell Cycle 2015; 14: 2109-2120.
[67] Alison MR, Lim SM, Nicholson LJ. Cancer stem cells: problems for therapy? J Pathol 2011; 223: 147-61.

[68] Kato K, Kuhara A, Yoneda T, Inoue T, Takao T, Ohgami T, Dan L, Kuboyama A, Kusunoki S, Takeda S and Wake N. Sodium butyrate inhibits the self-renewal capacity of endometrial tumor side-population cells by inducing a DNA damage response. Mol Cancer Ther 2011; 10: 1430-9.

[69] Bandyopadhyay A, Wang L, Agyin J, Tang Y, Lin S, Yeh IT, De K and Sun LZ. Doxorubicin in combination with a small TGFbeta inhibitor: a potential novel therapy for metastatic breast cancer in mouse models. PLoS One 2010; 5: e10365.

[70] Kusunoki S, Kato K, Tabu K, Inagaki T, Okabe H, Kaneda H, Suga S, Terao Y, Taga T, Takeda S. The inhibitory effect of salinomycin on the proliferation, migration and invasion of human endometrial cancer stem-like cells. Gynecol Oncol 2013; 129: 598-605.