International Journal of Pharmacognosy and Pharmaceutical Sciences

ISSN Print: 2706-7009
ISSN Online: 2706-7017
IJPPS 2021; 3(1): 44-48
www.pharmacognosyjournal.net
Received: 11-05-2021
Accepted: 09-06-2021

M Apoorva
Pharm. D, Department of Pharmacy Practice, Jagan's College of Pharmacy, Nellore - Krishnapatnam Port Rd, Brahmadevam, Andhra Pradesh, India

T Anjali
Department of Pharmacy Practice, Jagan's College of Pharmacy, Nellore - Krishnapatnam Port Rd, Brahmadevam, Andhra Pradesh, India

S Suvedha
Department of Pharmacy Practice, Jagan's College of Pharmacy, Nellore - Krishnapatnam Port Rd, Brahmadevam, Andhra Pradesh, India

S Karunavardhan
Department of Pharmacy Practice, Jagan's College of Pharmacy, Nellore - Krishnapatnam Port Rd, Brahmadevam, Andhra Pradesh, India

S Saran Kumar
Department of Pharmacy Practice, Jagan's College of Pharmacy, Nellore - Krishnapatnam Port Rd, Brahmadevam, Andhra Pradesh, India

D Hepcy Kalarani
Department of Pharmacy Practice, Jagan's College of Pharmacy, Nellore - Krishnapatnam Port Rd, Brahmadevam, Andhra Pradesh, India

Corresponding Author:
M Apoorva
Pharm. D, Department of Pharmacy Practice, Jagan's College of Pharmacy, Nellore - Krishnapatnam Port Rd, Brahmadevam, Andhra Pradesh, India

Menstrual blood-use in regenerative medicine

M Apoorva, T Anjali, S Suvedha, S Karunavardhan, S Saran Kumar and D Hepcy Kalarani

DOI: https://dx.doi.org/10.33545/27067009.2021.v3.i1a.87

Abstract
Women producenatural life; but now they will add medically to save lives through the Endometrial Regenerative Cells (ERC) or stem cells reaped from unwanted menstrual fluid, recognized to be the most revoltingstage of woman's life. Menstrual blood, as researchers said that, is found to be the most potent source of stem cells so far.Discovering curative power of stem cells has been a revolutionary breakthrough in the field of surgery and medicine till date, which has actually given many the precious gift of life. The uterine endometrial lining, aannoying source of stem cells, is shed in menstrual process every month. In the rebuilding process that ranges over seven days, billions of cells develop creating almost 5 millimeter-thick lining. These self-renewing cells, also called Endometrial Regenerative Cells, can be developed into other tissues under controlled laboratory conditions and have multipotent markers analogous to stem cells from other sources. The requirement for regenerative therapies incorporating cells that have the ability to engraft and differentiate is vast. Mesenchymal stem cells resulting from bone marrow are presently in clinical trials after demonstrating safety and efficacy in animal models for allogeneic use due to their immunosuppressive proper-ties. Due to their simplicity of collection and isolation, MenSCs would be a great impendingbasis of multipotent cells if they also showed these properties.

Keywords: Endometrial regenerative cells, menstrual blood, MenSCs, regenerative medicine, stem cells

Introduction
Women create life; but now they will contribute medically to save lives through the Endometrial Regenerative Cells (ERC) or stem cells harvested from discarded menstrual fluid, known to be the most disgusting phase of woman's life. Menstrual blood, as researchers say, is found to be the most potent source of stem cells so far. Discovering curative power of stem cells has been a revolutionary breakthrough in the field of surgery and medicine till date, which has actually given many - the precious gift of life.

Endometrial regenerative cell opportunity
The company has developed a novel type of stem cell, the Endometrial Regenerative Cell (ERC) that appears to have the major attributes desirable in an ideal cellular therapy: a) They are derived from non-controversial sources; b) The activity of the cells is not substantially neutralized by the immune system, allowing for use of cells from one standardized source (e.g. universal donor); c) The cells can be administered intravenously since they home to injured or degenerated tissue.Medistem scientists demonstrated that ERC's are capable of transforming into major tissues of the body including heart, lung, liver, brain, and blood vessels. It was published that ERC's also produce large amounts of therapeutic factors, in some situations at higher levels than other types of stemcells. Medistem collaborators have demonstrated that ERC's are potent inducers of new blood vessel formation in animals lacking proper circulation. To date studies have demonstrated that ERC's do not cause adverse effects when administered at therapeutically-relevant doses to animals.Medistem plans to enter clinic trials using ERC's for a condition that will demonstrate proof of concept and safety in a rapid and cost effective way [1-9].

Critical Limb Ischemia: Approximately 160,000 amputations occur each year due to critical limb ischemia, an advanced form of atherosclerosis. Various types of stem cell

therapies have been demonstrated to exert positive effects on this condition through stimulating production of new blood vessels. Unfortunately, the majority of such therapies are impractical or costly. For example, the administration of a patient's own bone marrow stem cells into the ischemia muscle has been reported to improve pain free walking distance and reduce need for amputation. However bone marrow extraction and processing is a fairly involved procedure that is not currently feasible on a wide-spread basis. The threshold for clinical success using stem cells in CLI is theoretically lower than for other indications since the stem cells are not required to completely differentiate and generate a new organ. For a therapeutic effect the stem cells need only to stimulate the production of new blood vessels, a process called "angiogenesis". In patients with CLI the new blood vessels start providing oxygen and nutrients to the previously ischemic tissue, resulting in healing of ulcers and restoration of leg function.

Approaching Critical Limb Ischemia with ERC-142

Bone marrow transplantation is the only successful stem cell therapy that has saved hundreds of thousands of lives. Arguably its success is attributed to the fact that the bone marrow stem cells were required to do what they were naturally meant to do: make blood. ERC's have a specialized function in the endometrium: to make new blood vessels. With every menstrual cycle the endometrium builds up and then sloughs off. This rapid accumulation of highly vascularized tissue, we believe, is associated with the natural ability of the ERC to generate new blood vessels. Medistem's first clinical use of the ERC in the USA is aimed at using this natural ability of ERC's to make new blood vessels in patients with CLI. Medistem's CLI product is ERC-142, a standardized, "universal donor" cell preparation that is delivered frozen to the doctor's office, and when ready for use is injected into the ischemic muscle of patients with CLI. The planned clinical trials of ERC-142 will assess the ability of this new stem cell population to improve circulation of patients with CLI who have no option but amputation.

Expansion of ERC Angiogenesis Candidates

Therapeutic angiogenesis is considered a "Holy Grail" of biologics. While the ERC-142 program will spearhead clinical development, Medistem plans to concurrently develop other ERC-based products for therapeutic angiogenesis in other conditions. Ischemic heart conditions are believed to affect approximately 1 out of 100 people, being considered a $25 billion/year market in the US alone. Stimulation of angiogenesis by other stem cells has been demonstrated to improve animal models of stroke, liver failure, and wound healing [10-16],

Stemcells-exhibiting life

Stem cells can be termed as undifferentiated cells having distinctive ability to dividemitotically and differentiate into nerve cells, blood cells, muscle cells or any specialized cell when needed.

Limitations of conventional cell sources

Stem cells harvested from the customary sources like embryos or adult tissues, have their own set of limitations. Embryonic stem cells can build any cell type required but has serious ethical and host rejection issues associated with it because the harvesting process destroys the fetus involved. Bone marrow harvesting is an invasive and tedious procedure that yields very small quantity of regenerative cells whose powers are limited as is the case with umbilical cord blood cells, though it has no ethical concerns. Some researchers are trying to use skin cells to derive stem cells, where the procedure takes help of few viruses to embed number of genes. One of these genes is known to be cancerous. Stem cells from these conventional sources have been employed to treat blood-related disorders including leukemia. But ERC will help in devising treatments of numerous diseases such as cardiac disease, diabetes, neurological disorders like spinal cord injury, Parkinson's and Alzheimer's diseases and also, assisting aesthetics-related anti-aging therapies.

Regenerative medicine redefined

The uterine endometrial lining, a rich source of stem cells, is shed in menstrual process every month. In the rebuilding process that ranges over seven days, billions of cells develop creating almost 5 millimeter-thick lining. These self-renewing cells, also called Endometrial Regenerative Cells, can be developed into other tissues under controlled laboratory conditions. These cells possess multipotent markers similar to stem cells from other sources. These Endometrial stem cells were first discovered by an Australian researcher Caroline Gargett from Monash University. She was enthralled to find that a sanitary waste could be so resourceful, citing her findings as "very interesting and very significant". She found the cells exhibiting characteristics similar to adult stem cells.

Advantages of endometrial regenerative cells

Stem cells from menstrual blood are easier to collect through a harmless procedure. An inexpensive source, it is not painful to the donor women and can be collected for about 35 years of a woman's menstruating age. However, younger women yield better quality of endometrial progenitor cells. Moreover, it takes care of ethical concerns as linked to the embryonic source and there is no fear of tissue rejection too. With multitude of benefits associated with these newly discovered stem cells, potential treatments could be devised for several medical conditions. The ERC's can be processed and preserved effortlessly for future implementation. Researchers say that these cells have a higher reproduction rate, doubling every 19.4 hours, compared to the elemental cells from other sources. Compared to bone marrow, menstrual blood yields almost 30 times more stem cells. These "pluri-potent" cells can develop into cardiac, hepatic, pleural, respiratory epithelial, adipocytic, osteogenic, pancreatic, and neurocytic cells, i.e. roughly nine cell categories, so far the highest known for any stem cell source. This implies that many medical conditions that have no cure till date, may find a new therapy though this regenerative medium. Host rejection is not a trouble with the ERC's because they possess an immune system defining suppressing effect, enabling many patients other than the donor to accept curative therapies [17-25].

Banking the ERC

Florida-based Cryo-Cell International, known to be the biggest cord blood bank, also claims to have found stem cells in menstrual fluid. Chief scientist at Cryo-Cell, Julie

Allickson described the cells as "highly proliferative which can differentiate into at least five separate lineages and express stem cell markers.""C'Elle" - Cryo-Cell's menstrual blood-banking initiative takes care of sample-collection, processing and storing cells. Giving life a definite hope With thorough advancements going on, medical fraternity is sure that the future of regenerative medicine has arrived. While more in-depth researches are required to establish medical employment of endometrial stem cells, the new finding is definitely a momentous achievement in the field of stem cell transplant. Menstruation is really not bad at all - ERC brings along a promising step in the realm of regenerative medicine and surgery, to give life.

The question then becomes whether there is a source of multipotent stromal stem cells that can be safely obtained, in a renewable fashion, and maintain potency to differentiate. Recently, stromal cells were identified in endometrial tissue. [26, 27]However, obtaining the cells directly would be a very invasive procedure. The endometrial lining of the uterus has a remarkable capacity for regeneration. During each menstrual cycle there is vast growth of tissue and blood vessels, which is shed at the end of the cycle. The shed blood and tissue contain a heterogeneous population of cells including some with regenerative capacity [28]. The uterine stromal cells have similar multipotent markers commonly found in bone marrow mesenchymal stem cells and May actually originate in part from bone marrow [29-31]. Important markers for determining multipotency are Oct-4 and SSEA-4, which are found to be expressed in many multipotent and pluripotent stem cells including ESCs, along with the cell surface marker c-kit (CD117) [32-34]. In order to evaluate the practicality of obtaining multipotent stem cells from the uterus, in a safe and reproducible manner, we analyzed the shed menstrual blood and tissue to identify stromal cells (MenSCs). We present here a population of MenSCs that express the multipotent markers Oct-4, SSEA-4, and c-kit, along with their ability to be directionally differentiated *in vitro* into multiple cell lineages derived from mesoderm and ectoderm and the ability to be easily expanded. Work done so far in the area of menstrual stem cells various research groups throughout the world are now exploring this new source of stem cells. In 2007, Bio Communicable Research Institute, Wichita, USA, reported about the Endometrial Regenerative cells as a Novel Stem cell Population. Last year “Cryo International” company has discovered the fact that menstrual blood can be used to isolate stem cells. In the same year, Keio University scientist tried to use them for generating heart tissues. DrAmitN. Patel and others from Pittsburgh have found out about the pluripotency and self-renewal capability of MenSC. Recently life cell international, Chennai, India have come up with a plan to launch the first menstrual stem cell bank in India.

Cells discarded from womb lining during a woman's period are new type of stem cell

DrXiaolong Meng of the Bio-Communications Research Institute in Wichita, Kansas, led the research team consisting of scientists from the University of Alberta, University of Western Ontario and Medistem Laboratories. The team identified a new type of stem cell that can be reproducibly isolated from menstrual blood collected from healthy female subjects. "We have many problems with our current methods of stem cell therapy, like those taken from bone marrow," commented DrMeng, "They may be rejected by the recipient and/or have limited potential to generate new tissue. Now we've found a possible new way to overcome these difficulties by using cells from menstrual blood."

The growth of new blood vessels from pre-existing blood vessels is an essential part of the uterine or womb phase of the menstrual cycle. Cells collected from the menstrual blood of women include types which can be cultured in the laboratory, which replicate almost 70 times in a very rapid time span. This replication rate is far faster than cells which are currently used, taken from umbilical cord blood and bone marrow. The cells are so unique in their ability to develop into at least 9 different cells including heart, liver and lung, that researchers called the cells Endometrial Regenerative Cells (ERC). Not only do ERC replicate at a phenomenal rate of almost every 20 hours, but they produce unique growth factors at a rate of almost 100,000 greater than cells from umbilical cord blood.

A mere 5ml of menstrual blood collected from a healthy woman provided enough cells which after two weeks of culture provided beating heart cells. The results of this breakthrough research indicate that these cells could be cultured at a large scale, thereby providing an alternative to the current methods of using bone marrow and umbilical cord blood, which itself poses threats of rejection.

Menstruation yield adult stem cells

Menstruation may have a fringe benefit as a source of adult stem cells. Scientist report that menstrualblood contains adult stemcells that can develop into nine different types of cells:

- Heart cells
- Lung cells
- Nerve cells
- Muscle cells
- Pancreatic cells
- Liver cells
- Fat cells
- Bone cells

Cell procurement and processing

An endometrial/menstrual cell sample was procured by using a Divacup (Kitchener, ON) during the first few days of a menstrual cycle. The cells were harvested with the informed consent of the donor as approved by an institutional review board. The cells were transferred in phosphate-buffered saline (PBS) with penicillin/strepto-mycin and heparin. The sample was shipped at 4 °C until it reached the processing laboratory within 24–48 h after procurement. The sample was centrifuged and supernatant was evaluated for bacteria. The cells were then cultured.

Growth, multipotent marker expression and characterization of MenSCs

MenSCs rapidly expand at a doubling rate of 24–3 6 h; starting with 50,000 cells we obtained 48,000,000 by day 26and they maintained diploid cells with-out chromosomal aberrations as determined by karyotype analysis at passage. Moreover, RTPCR data demonstrated that MenSCs expressed the multipotent marker Oct-4 at passage 12, but not SOX-2 or Nanog. Flow cytometric analysis illustrated that MenSCs were positive for stromal cell and/or mes-enchymal stem cell markers such as CD44, CD 105, CD166,

CD90, CD49f, MHC I, CD29, and CD9 while negative for CD38, CD133, CD45, CD34, MHC II, and LIN, and mildly positive for CXCR4 related to stem cellhoming. In addition, flow cytometric analysis confirmed that MenSCs highly expressed the pluripotent marker SSEA-4 and c-kit+ (CD117). Also, SSEA-4 and c-kit+ were colocalized on isolated clones from MenSCs. Cultured MenSCs appeared to have stromal cell morphology. Stromal stem cells have been shown to have great potential for future use in clinical translation of regenerative therapies. [35-37]We have presented a population of stromal cells isolated from human menstrual blood (MenSCs). The MenSCs are characterized at both the cellular and molecular level, along with the ability to easily expand and differentiate. This study demon-strates that MenSCs are a unique cell population that can be safely isolated and provide an expandable source of stem cells from child-bearing aged women. The expression of multipotent markers Oct-4, SSEA-4, and c - kit (CD1 17) in the MenSCs is not common in most other adult stem cells. We have isolated clones with positive c-kit and SSEA-4 colocalization. This unique population of MenSCs is different than one recently de-scribed by Cui *et al*., which demonstrated skeletal muscle differentiation where they found menstrual blood cells expressing the following flow profile: positive CD13, CD29, CD44, CD54, CD55, CD59, CD73, CD90, CD105, MHC-I and negative CD14, CD31, CD34, CD45, CD50, c-kit, CD133, MHC-II. Cells have the multipotent markers mentioned above, which are absent in the cells identified and used by Cui *et al*. [38]

Also, the MenSCs appear to have similar characteristics as the human endometrial stem cells identified by Cho *et al*. [39] with c-kit (CD117), Matthai *et al*. [40] with Oct-4, clonally expanded by Gargett *et al*. [41], and the mouse endometrial stem cells identified by Cervello *et al*. with both c-kit+ (CD1 17) and Oct-4. Thus, it could be interpreted that MenSCs are the shed version of endometrial stem cells that can be easily harvested in a noninvasive manner. The expression of multipotent markers is indicative of cells that have the capacity to differentiate into cell types derived from multiple germ layers. The transcription factor Oct-4 and SSEA-4 both are markers expressed by human embry-onic stem cells [42], which are also highly expressed in our MenSCs, and may explain the rapid cell expansion. It may also explain the ability to be direction-ally differentiated into several cell types. The differentiated cell types demonstrate plasticity of the MenSCs by the fact that cells have not only phenotypic cell surface markers by flow cytometry and immunocytochemistry but also mRNA expression. These data demonstrate that MenSCs are expandable and express multipotent stem cell markers. The need for regenerative therapies incorporating cells that have the ability to engraft and differentiate is vast. However, the ideal cell would also have the ability to be used in an allogeneic manner. Mesenchymal stem cells derived from bone marrow are currently in clinical trialsafter demonstrating safety and efficacy in animal modelsfor allogeneic use due to their immunosuppressive proper-ties [43-49]. Due to their ease of collection and isolation, MenSCs would be a great potential source of multipotent cells if they also exhibited these properties.

Conclusion

The need for regenerative therapies incorporating cells that have the ability to engraft and differentiate is vast. However, the ideal cell would also have the ability to be used in an allogeneic manner. Mesenchymal stem cells derived from bone marrow are currently in clinical trialsafter demonstrating safety and efficacy in animal modelsfor allogeneic use due to their immunosuppressive proper-ties. Due to their ease of collection and isolation, MenSCs would be a great potential source of multipotent cells if they also exhibited these properties.

References

1. Cervello I, Martinez-Conejero JA, Horcajadas JA, Pellicer A, Simon C. Identification, characterization and co-localization of label-retaining cell population in mouse endometrium with typical undifferentiated markers. Hum. Reprod. 2007;22:45–51.
2. Chan RW, Schwab KE, Gargett CE. Clonogenicity of human endometrial epithelial and stromal cells. Biol. Reprod. 2004;70:1738–1750.
3. Cho NH, Park YK, Kim YT, Yang H, Kim SK. Lifetime expression of stem cell markers in the uterine endometrium. Fertil. Steril. 2004;81:403–407.
4. Cogle CR, Yachnis AT, Laywell ED, Zander DS, Wingard DR, Steindler DA. Bone marrow transdifferentiation in brain after transplantation: A retrospective study. Lancet. 2004;363:1432–1437.
5. Cui CH, Uyama T, Miyado K, Terai M, Kyo S, Kiyono T. Menstrual blood-derived cells confer human dystrophin expression in the murine model of Duchenne muscular dystrophy via cell fusion and myogenic transdifferentiation. Mol. Biol. Cell. 2007;18:1586–1594.
6. De Coppi P, Bartsch G, Siddiqui MM, Xu T, Santos CC, Perin L. Isolation of amniotic stem cell lines with potential for therapy. Nat. Biotech. 2007;25:100–106.
7. Delo DM, De Coppi P, Bartsch Jr. G, Atala A. Amniotic fluid and placental stem cells. Methods Enzymol. 2006;419:426–438.
8. Gang EJ, Bosnakovski D, Figueiredo CA, Visser JW, Perlingeiro RC. SSEA-4 identifies mesenchymal stem cells from bone marrow. Blood. 2007;109:1743–1751.
9. Gargett CE. Identification and characterization of human endometrial stem/progenitor cells. Aust. NZ J. Obstet. Gynaecol. 2006;46:250–253.
10. Greco SJ, Liu K, Rameshwar P. Functional similarities among genes regulated by OCT4 in human mesenchymal and embryonic stem cells. Stem Cells. 2007;25:3143–3154.
11. Henderson JK, Draper JS, Baillie HS, Fishel S, Thomson JA, Moore H. Preimplantation human embryos and embryonic stem cells show comparable expression of stage-specific embryonic antigens. Stem Cells. 2002;20:329–337.
12. Kearns M, Lala PK. Bone marrow origin of decidual cell precursors in the pseudopregnant mouse uterus. J. Exp. Med. 1982;155:1537–1554.
13. Le Blanc K. Immunomodulatory effects of fetal and adult mesenchymal stem cells. Cytotherapy. 2003;5:484–489.
14. Ludwig TE, Levenstein ME, Jones JM, Berggren WT, Mitchen ER, Frane JL. Derivation of human embryonic stem cells in defined conditions. Nat. Biotechnol. 2006;24:185–187.
15. Mattai C, Horvat R, Noe M, Nagele F, Radjabi A, Van Trotsenburg M. Oct-4 expression in human endometrium. Mol. Hum. Reprod. 2006;12:7–10.
16. Minguell JJ, Erices A, Conget P. Mesenchymal stem cells. Exp. Biol. Med. 2001;226:507–520.
17. Nandoe Tewarie RD, Hurtado A, Levi AD, Grotenhuis JA, Oudega M. Bone marrow stromal cells for repair of

the spinal cord: Towards clinical application. Cell Transplant. 2006;15:563–577.
18. Patel AN, Geffner L, Vina RF, Saslavsky J, Urschel Jr., HC, Kormos R. Surgical treatment for congestive heart failure with autologous adult stem cell transplantation: A prospective randomized study. J Thorac. Cardiovasc. Surg. 2005;130:1631–1638.
19. Schwab KE, Chan RW, Gargett CE. Putative stem cell activity of human endometrial epithelial and stromal cells during the menstrual cycle. Fertil. Steril. 2005;84:1124-1130.
20. Schwab KE, Gargett CE. Co-expression of two perivascular cell markers isolates mesenchymal stem-like cells from human endometrium. Hum. Reprod. 2007;22:2903–2911.
21. Taylor HS. Endometrial cells derived from donor stem cells in bone marrow transplant recipients. JAMA. 2004;29281–85.
22. Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS. Embryonic stem cell lines derived from human blastocysts. Science. 1998;282:1145–1147.
23. Toma C, Pittenger MF, Cahill KS, Byrne BJ, Kessler PD. Human mesenchymal stem cells differentiate to a cardiomyocyte phenotype in the adult murine heart. Circulation. 2002;105:93–98.
24. Vilquin JT, Rosset P. Mesenchymal stem cells in bone and cartilage repair: Current status. Regen. Med. 2006;1:589-604.
25. Yao S, Chen S, Clark J, Hao E, Beattie GM, Hayek A. Long-term self-renewal and directed differentiation of human embryonic stem cells in chemically defined conditions. Proc. Natl. Acad. Sci. USA. 2006;103:6907–6912.
26. Cho NH, Park YK, Kim YT, Yang H, Kim SK. Lifetime expression of stem cell markers in the uterine endometrium. Fertil. Steril. 2004;81:403–407.
27. Schwab KE, Chan RW, Gargett CE. Putative stem cell activity of human endometrial epithelial and stromal cells during the menstrual cycle. Fertil. Steril. 2005;84:1124-1130.
28. Cui CH, Uyama T, Miyado K, Terai M, Kyo S, Kiyono T. Menstrual blood-derived cells confer human dystrophin expression in the murine model of Duchenne muscular dystrophy via cell fusion and myogenic transdifferentiation. Mol. Biol. Cell. 2007;18:1586–1594.
29. Kearns M, Lala PK. Bone marrow origin of decidual cell precursors in the pseudopregnant mouse uterus. J. Exp. Med. 1982;155:1537–1554.
30. Schwab KE, Gargett CE. Co-expression of two perivascular cell markers isolates mesenchymal stem-like cells from human endometrium. Hum. Reprod. 2007;22:2903–2911.
31. Taylor HS. Endometrial cells derived from donor stem cells in bone marrow transplant recipients. JAMA. 2004;292:81–85.
32. Gargett CE. Identification and characterization of human endometrial stem/progenitor cells. Aust. NZ J. Obstet. Gynaecol. 2006;46:250–253.
33. Greco SJ, Liu K, Rameshwar P. Functional similarities among genes regulated by OCT4 in human mesenchymal and embryonic stem cells. Stem Cells. 2007;25:3143–3154.
34. Yao S, Chen S, Clark J, Hao E, Beattie GM, Hayek A. Long-term self-renewal and directed differentiation of human embryonic stem cells in chemically defined conditions. Proc. Natl. Acad. Sci. USA. 2006;103:6907–6912.
35. Toma C, Pittenger MF, Cahill KS, Byrne BJ, Kessler PD. Human mesenchymal stem cells differentiate to a cardiomyocyte phenotype in the adult murine heart. Circulation. 2002;105:93-98.
36. Vilquin JT, Rosset P. Mesenchymal stem cells in bone and cartilage repair: Current status. Regen. Med. 2006;1:589-604.
37. Zurita M, Vaquero J. Functional recovery in chronic paraplegia after bone marrow stromal cells transplantation. Neuroreport. 2004;15:1105–1108.
38. Cui CH, Uyama T, Miyado K, Terai M, Kyo S, Kiyono T. Menstrual blood-derived cells confer human dystrophin expression in the murine model of Duchenne muscular dystrophy via cell fusion and myogenic transdifferentiation. Mol. Biol. Cell. 2007;18:1586–1594.
39. Cho NH, Park YK, Kim YT, Yang H, Kim SK. Lifetime expression of stem cell markers in the uterine endometrium. Fertil. Steril. 2004;81:403–407.
40. Mattai C, Horvat R, Noe M, Nagele F, Radjabi A. Oct-4 expression in human endometrium. Mol. Hum. Reprod. 2006;12:7–10.
41. Gargett CE. Identification and characterization of human endometrial stem/progenitor cells. Aust. NZ J. Obstet. Gynaecol. 2006;46:250–253.
42. Henderson JK, Draper JS, Baillie HS, Fishel S, Thomson JA, Moore H. Preimplantation human embryos and embryonic stem cells show comparable expression of stage-specific embryonic antigens. Stem Cells. 2002;20:329–337.
43. Le Blanc K. Immunomodulatory effects of fetal and adult mesenchymal stem cells. Cytotherapy. 2003;5:484-489.
44. Ludwig TE, Levenstein ME, Jones JM, Berggren WT, Mitchen ER, Frane JL. Derivation of human embryonic stem cells in defined conditions. Nat. Biotechnol. 2006;24:185–187.
45. Mattai C, Horvat R, Noe M, Nagele F, Radjabi A, Van Trotsenburg M. Oct-4 expression in human endometrium. Mol. Hum. Reprod. 2006;12:7–10.
46. Minguell JJ, Erices A, Conget P. Mesenchymal stem cells. Exp. Biol. Med. 2001;226:507–520.
47. NandoeTewarie RD, Hurtado A, Levi AD, Grotenhuis JA, Oudega M. Bone marrow stromal cells for repair of the spinal cord: Towards clinical application. Cell Transplant. 2006;15:563–577.
48. Patel AN, Geffner L, Vina RF, Saslavsky J, Urschel Jr., HC, Kormos R. Surgical treatment for congestive heart failure with autologous adult stem cell transplantation: A prospective randomized study. J. Thorac. Cardiovasc. Surg. 2005;130:1631–1638.
49. Schwab KE, Chan RW, Gargett CE. Putative stem cell activity of human endometrial epithelial and stromal cells during the menstrual cycle. Fertil. Steril. 2005;84:1124-1130.