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A COMPREHENSIVE REVIEW ON CLINICAL APPLICATIONS OF MENSTRUAL STEM CELLS

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INTRODUCTION

Mesenchymal foundational microorganisms (MSCs) are heterogeneous subgroup of begetter cells; make them recharge limit and separating potential into different cell like osteoblasts, chondrocytes, and adipocytes[1]. All through the human body cells are being recharged to supplant kicking the bucket cells or recover harmed tissue. Under certain physiological conditions some unspecialized cells might stay lethargic until the cells are required. The two primary kinds of stems cells are sorted grown-up or physical and undeveloped cells. Undeveloped foundational microorganisms are gotten from the inward cell mass of a blastocyst. Then again, grown-up undifferentiated organisms have a controlled conduct, and they are multi-potent when contrasted with the early-stage foundational microorganism's pluripotent capacity [2]. MSC are created from different sources however as of late, MSCs have been found in new sources, like feminine blood and endometrium. There are logical more wellsprings of MSCs standing by to be found, and MSCs might be a decent contender for future exploratory or clinical applications [3].

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Characterization of MSC:

According to International Society for Cell Therapy (ISCT) proposed three criteria for human cells to be considered as MSCs [4].Minimal criteria required for defining multi-potent mesenchymal stromal cells. The International Society for Cellular Therapy position statement as cytotherapy.[5] Plastic-adherence in culture, ability to tri-lineage differentiation in vitro into osteoblasts (bone), adipocytes (fat) and chondroblasts (cartilage) under appropriate culture conditions, Expression of certain surface markers [6], immunophenotype, Proliferation and differentiation, immune modulation properties. [6]

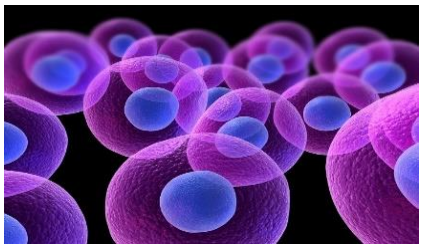

Fig 1: Menstrual Stem Cells Shape and Cell Division 7, [8]

Various sources for generation of mesenchymal stem cells:

MSCs are stromal cells that can self-recharge and exhibit multilineage separation 10 can be disconnected from an assortment of tissues, like umbilical line, bone marrow, fat tissue, dental mash, birth inferred tissue, amniotic liquid and placenta, prepared fringe, blood, synovium and synovial liquid, muscle, skin, endometrium. As of late, numerous MSCs have been gotten from new sources, like feminine blood, endometrium.[9]

Menstrual blood cells as a source for stem cells:

In 2007, Meng with partners isolated a MSC people from ladylike blood (MenSC). The endometrium goes through more than 400 examples of recuperation, detachment, and shedding throughout the whole conceptive season of a woman. Human endometrial lacking cells expect a huge part in this cyclic recuperation and fix. Endometrial undifferentiated life forms (EndoSCs), including epithelial, stromal, and endothelial cells, may add to the discontinuous endometrial recuperation when shed in the female blood, these EndoSCs are consequently insinuated as the ladylike blood-deduced youthful microorganisms (MenSCs).

Production of stem cells from menstrual blood

Various steps are involved in the production of menstrual blood derived stem cells.

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- ★ Collection of menstrual blood cells
- ★ Transportation of menstrual blood cells
- ★ Menstrual blood cell processing
- ★ Cryopreservation of menstrual blood cells
- ★ Concentrated menstrual cell thaw, cell culture, and cell selection

Collection of menstrual blood cells:

The feminine platelets were gathered by means of an obtainment unit arranged by the handling office endorsed under an IRB study for the assortment [10]. A cushioned saline media (DPBS) is utilized all through the cell seclusion measure with (heparin sodium 1,000 USP Units/mL; American Pharmaceutical Partners, Schaumburg, IL). Assortments occurred more than 4 h or less. Feminine blood was gathered on day 1, 2, or 3 during the heaviest progression of the cycle. On a normal 8–10 mL was gathered per test. A normal assortment is ~30 million with somewhere in the range of 0.5% to 40% of follower cells. Just 1 million cells are needed for the principal cell culture to choose the disciple cells with for the most part about 10% of the cells showing adherence. The cells replicates two fold roughly every 24 h.

Transportation of menstrual blood cells:

All the samples which are collected should be shipped to laboratory. These samples should be stored between 40C.The samples were shipped to the laboratory on frozen bricks to assure shipment of cells at a cool temperature.

Menstrual blood cell processing:

The feminine cells gathered in a supported saline funnel shaped assortment tube are exposed to centrifugation at 2,000 rpm for 7 min at ~4°C. The supernatant was utilized for microbiological testing. Pelleted cells are re-suspended for a cell count and practicality. The cells were ready for cryopreservation. Bacteriological examination of the supernatant was performed utilizing the BacT/ALERT framework (Biomerieux, Durham, NC).

Cryopreservation of menstrual blood cells:

Bacteriological analysis of the supernatant was performed using the BacT/ALERT system (Biomerieux,Durham, NC). Most products arrived to the laboratory with some level of

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contamination but after a treatment of an antibiotic cocktail, when the cells were thawed post-processing, the culture was found negative of contaminants. One millilitre of cellular suspension was tested for the total cell count, cell viability, and flow cytometric analysis for specific markers. The entire sample is initially filtered with a 100-µm filter prior to cryopreserving the cells. The cells are cryopreserved in a total volume of 10 mL comprising of 5 mL of cells, 3 mL of the buffered saline (DPBS), 1 mL of the protein HSA (Telacris Bio, Clayton, NC), and 1 mL of the preservative DMSO (99% Stemsol). Cells were cryo-preserved in a controlled rate freezer until it reached −90°C, then the cryovials were transferred to a cryogenic storage unit and stored in the vapour phase of liquid nitrogen at a temperature at or below -150 °C [11].

Concentrated menstrual cells thaw, cell culture and cell selection:

At a temperature of −90°C the cells were moved for long haul stockpiling to a fluid nitrogen fume stockpiling cooler held at roughly −190°C until tests were defrosted for appraisal. To defrost the cells they were taken out from the cooler and defrosted by disturbance in a 37-40 °C dab shower (Lab Armor, Inc., San Antonio, TX). Only preceding total defrost the cells were moved to a wash arrangement comprising of complete media. The cells were washed twice and cultivated in a T-25 tissue culture carafe. The cells were filled in Chang's (Irvine Scientific, Santa Ana, CA) Complete Media. cells were evaluated for time to adherence to carafe, development rate and number of sections. Cells were sub-cultured by utilizing TrypLE Express (Invitrogen, Carlsbad, CA), washed and replated in complete media. The freeze defrosts measure showed an undeniable degree of feasibility after follower cells had been chosen for CD117. Most entries uncovered near 100% suitability as controlled by 7-AAD. CD117 choice was performed by means of Miltenyi framework at post-defrost, with positive chose cells hence extended in culture. The CD117 undifferentiated organisms were isolated from a cell suspension in working cradle utilizing a MS segment and a Mini MACS kit. [12]

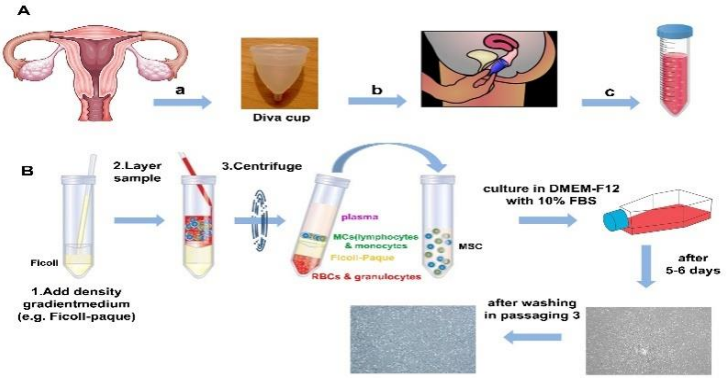

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Fig 2: Concentrated menstrual cells thaw, cell culture and cell selection

Safety studies: The safety study assessed cell infusion in Harlan Sprague Dawley Mice and Dunkin Hartley Albino Guinea Pigs. The study participants received an intra peritoneal injection of the cells or the negative control material. The participants were observed for a seven-day period. After one week the participants were assessed for weight, survival and specific response to the cells. Under the conditions of the study the presence of extraneous toxic contaminants was not detected, and all animals remained healthy, without reactions and no weight loss. [13]

Clinical applications of MenSCs:

MenSCs have been extensively utilized in preclinical investigations, and large numbers of which have shown successfully restorative capacities in anticipation and control of different sicknesses, including liver infection, diabetes, stroke, Duchenne strong dystrophy, ovarian-related illness, myocardial dead tissue, Asherman condition, Alzheimer's infection, intense lung injury, cutaneous injury, endometriosis, and neurodegenerative diseases. [14]

Tissue Regeneration Therapy

MenSCs has already been recognized in several kinds of diseases in pre-clinical research, about their therapeutic potential which is essential for future clinical applications in tissue repair and regenerative medicine. Like BM-MSCs, Men SCs also have several excellent properties which, includes the ability to drift into injury sites, differentiation into different cell lineages, secretion of soluble factors, and regulation of immune responses. Therefore, more research needs to be explored before MenSC becomes a common use in clinical application and treatment in the tissue regeneration. [15]

Liver Disease

Fulminant hepatic failure (FHF) has high mortality rate which occurs due to rapid necrosis of liver cells. Experimental studies determines that MenSC-derived exosomes,

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(MenSC -EX) which mediate cellular signaling pathways both in vivo and in vitro possessed therapeutic potential by inhibiting hepatocyte apoptosis in D-galactosamine (D-Gal) and lipopolysaccharide(LPS) induced FHF in mice, and the further studies states that the levels of TNF-α, IL-6, and IL-1β were reduced by co-culture with AML12 hepatocytes (a normal mouse hepatocyte cell line) in vitro. The study suggests that MenSC-ex can improve liver function by increase the rate of survival in FHF model mice. MenSC are also potential in treating chronic liver diseases by targeting the pancreatic mediators.[16]

Diabetes

Type 1 diabetes mellitus (T1DM), known as a kind of autoimmune diabetes, is a multi-factorial disease by the deficiency of secreting insulin in islet β cells to influence the normal organism metabolism, ultimately leading to elevated blood glucose levels and a severe decline in insulin secretion. From the experimental studies MenSC provides facilitate β-cell regeneration and enhances the number of β-cells by increasing the expression of neurogenin 3, forkhead box A2, pancreatic and duodenal home box1 these activates the endogenous progenitor cell differentiate post MenSC transplantation in T1DM mice. Clarifying the precise mechanism involved in MenSC-induced β-cell regeneration will facilitate the future use of MenSCs to treat diabetes.

Ischemic stroke

Ischemic stroke occurs during the identification of rapid physical and mental fluctuations, and it leads to a series of fundamental impairments. Borlongan et al. demonstrated that improved ischemic stroke in an oxygen glucose deprivation (OGD) by in vitro studies in rat model by MenSC. In the rat model of ischemic stroke, the behavioral and histological disorders were improved by intracerebral or intravenous transplantations. By increasing vascular endothelial growth factors (VEGF), brain-derived neurotrophic factors (BDNF) and neurotrophin 3 (NT-3), the MenSC reduce the cell death of OGD-exposed rat primary neurons. In treating the ischemic stroke neuro structural and behavioural benefits by transplanted MenSCs are used as a source of cell therapy.[17]

Duchenne muscular dystrophy

Duchenne muscular dystrophy (DMD) is a life-threading x-linked muscle degeneration

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disease. It is due to genetic mutations which results in the increase in the inflammatory response. Muscle degeneration and repair of skeletal muscle abnormalities by enhancing the muscle like proteins in immune compromised DMD mice model is demonstrated by the Umezawa's and this team. MenSC also have the greater potential of differentiation of muscle cells as has transformation of muscular dystrophic cells into anti-atrophic cells through trans-differentiation both in vitro and in vivo.

Critical limb ischemia

Critical limb ischemia (CLI) is condition in which final stage limb damage occurs due sever haemorrhage causing a series of physiological and pathological abnormalities which leads to limb pain or insufficient nutrition to limbs. Murphy et al. Demonstrated that administration of MenSCc in mouse model to improve CLI by producing high levels of growth factors, IL-4, hypoxia inducible factor-1alpha (HIF-1α), and matrix metallo proteinases (such as MMP3 and MMP10) with a paracrinerole; inhibiting the inflammatory response and blocking the pro-inflammatory signalling pathway and producing a large amount of endothelial progenitor cells to mediate cell differentiation. Studies state that MenSCs provides guideline for the better treatment outcomes through clinical trials.[18]

Ovarian-related disease

Ovarian cancer is the fatal disease with indistinct symptoms and lack of reliable screening methods. Women under the age of 40 years mostly suffer with the premature ovarian failure (POF) and infertility problems. In the POF mouse model estrogen cycle and infertility problems are resorted by the administration of MenSCs had demonstrated by the Lai et al. Wang et al. demonstrated the improvement of ovarian microenvironment by reducing the cell apoptosis and interstitial fibrosis. MenSC provides the effective treatment in the POF condition by repairing the injured ovarian, resorting the function of ovaries, stimulating the ovarian regeneration. Tumor transplant animal model experimental study by Lai and group found that MenSCs also potential in treating the epithelial ovarian cancer (EOC). [19]

Myocardial infarction

Myocardial infarction (MI) is a type of coronary artery disease (CAD), it is defined as the necrosis of the cardiomyocytes due to excessive ischemic condition. It is a long-term disease in which the patient may suffer from severe hemodynamic deterioration sometime even

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leads to death. Hida et al. confirmed that in nude rat model the transplanted MenSCs restores the damaged cardiac function. Jiang et al. further demonstrated that MenSC reduced apoptosis, promoted cell proliferation, and recruited c-kit^{+} cells in an immunological MI model rat. The inhibition of endothelial cells to mesenchymal transition (EMT), which helped to reduce the total number of cardiac fibroblasts and tissue fibrosis progression was demonstrated by Wang's team.

Asherman syndrome

Asherman condition (AS) is characterized as the total or fractional destruction of the uterine depression with grips, bringing about amenorrhea or other feminine deviations, repetitive pregnancy misfortune, and barrenness. In the 3year non-control forthcoming review with 7 Asherman condition ladies after MenSCs transplantation, the outcomes expresses that 5 ladies showed the huge expansion in the 7 mm. 4 of them were exposed to frozen incipient organism move (FET) and one patient created as an unconstrained pregnancy. This review recommends that autologous MenSC transplantation is a potential choice for the treatment of Asherman condition in ladies. [20]

Alzheimer's disease (progressive memory loss)

Alzheimer's disease, caused by amyloid-beta (Aβ) production, is progressive memory loss and cognitive dys-function, and its neuro pathological features are induced by the hyper phosphorylated tauproteins,which are composed of extracellular Aβ plaque deposits and intra-cellular neuro fibrillary tangles (NTFs). Research studies states that transplantation of MenSC in mouse model has improve the spartial learning and memory ability of AD in mouse. MenSC furthermore improved amyloid plaques in vivo studies and reduced tau hyper phosphorylation. It is also observed that intracranial transplantation of MenSCs notably enhances the expression of Aβ-degrading enzymes and reduces the level of pro-inflammatory cytokines to change the microglia-associated phenotype. The result states that MenSCs can degenerate Aβ and acts as anti-inflammatory effect for improving AD in vivo studies.[21]

Acute lung injury

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Acute lung injury (ALI) and its more severe form, acute respiratory distress syndrome, are defined as severe complications with systemic inflammatory responses in the air spaces and lung parenchyma. It can cause by many factors such as tidal volume, mechanical ventilation, or hypoxia condition factors in turn causes the inflammatory reaction if these inflammatory reactions prolonged then the patient suffer from shortness of breath or even death. Experimental studies showed that MenSCs promoted the repair of injured lung by inhibiting the inflammatory response in LPS-induced in mice. In addition, MenSCs improves pulmonary microvascular permeability, reduced histo-pathological injury and down regulated the MenSCs may be a feasible way around the problems of hepatocyte transplantation in severe liver disease. The results suggest that MenSC-based treatment may become an attractive strategy for improving in regenerative medicine.[22]

Cutaneous wound

Cutaneous wound improvement is done by biological progress to restore the damaged tissue, along with cell differentiation and proliferation, and variety of cell apoptosis thereby producing multiple layers of connective tissue. The repaired skin is usually cured in the form of a scar, and the main purposes of the cutaneous regeneration are to understand how to induce skin to reconstruct damaged parts without forming scars. In a mouse excisional wound model experiment , the MenSCs improve the wound healing by enhances the new blood vessel formation is demonstrated by the Cuenca et al. MenSCs also produces some cytokines , platelet-derived growth factors and elastin are participate in wound repa[ir].[23]

Endometriosis

Endometriosis is a typical gynaecological problem de-fined as endometrial organs and interstitial development outside the uterus. Nikoo et al. discovered that MenSCs assumed a vital part by looking at the capacity in morphology, CD marker articulation, cell expansion, intrusion, advertisement hesion, and some immuno-modulatory atoms between ladies with endometriosis (E-MenSCs) and non-endometriosis (NE-MenSCs). These finding proposes that MenSC plays a basic part in further developing endometriosis. [24]

Respiratory system

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Xiang et al. by using the mouse model in a disease condition known as acute lung injury determine the possible benefits of MenSCs in respiratory diseases. The MenSCs was administrated intravenously to the mice and only after four hours of injection the MenSCs were identified in the lungs. The results of the studies showed the notable repaired in the lung impairment by improving the pulmonary micro vascular permeability, down regulating inflammation, inhibition of apoptosis and reconstruction of the alveolar-capillary membrane function after administration of MenSCs.

Musculoskeletal system

Umezawa' steam trans differentiated MenSCs into myoblasts/myocyte in vitro studies and in in-vivo studies by implantation of primary cultured MenSCs restored sarcolemma expression of dystrophin in dystrophied muscle of DMD mice. The cellular fusion with myoblast was another mechanism of recovery or reacquisition of dystrophin-expressing cells in addition to myogenic differentiation of MenSCs. Ichim et al. reported that the treatment with MenSCs increases the muscle strength, decreased frequency of respiratory infections and reacquisition of general mobility in the patient suffering with Duchenne muscular dystrophy.

Digestive system

Lu et al. demonstrate the restoration of hepatic function by MenSCs. In colitis mouse model , anti-inflammatory modulation in liver injury .Therapeutic benefits of the MenSCs in the liver repair is demonstrated by the Xiang's groups. In a colitis mouse model, MenSCs in liver injury acts as anti-inflammatory agent when the MenSCs admistrated in 3 times consecutively. Wc et al. intravenously injected human MenSCs into streptozotocin-induced diabetic mice and found ame-liorated diabetic symptoms of the treated mice with expanded life span, reversed histological changes of islets, and better glycemic control.

Nervous system

MenSCs gives adequate cell substitution to stroke fix. Borlongan et al. announced a significant neuro protective job of MenSCs in hypoxic injury. Han group infused MenSCs intra tumorally or intravenously into a forceful glioma rodent model and yielded critical cancer restraint, demonstrated by de-wrinkled the angiogenesis and CD133+ cell number, a

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mark of growth cells dwelling in hypoxic specialty. MenSCs are an amazing vehicle for conveying qualities or medications to trigger cancer site-explicit apoptosis

Cardiovascular system

Hida et al. had cultured human MenSCs check their potention in treating myocardial infrarction (MI) of rats. Jiang et al. examined the benefits of MenSCs transplantation by administration MenSCs in an immunocompetent rat model.The results stated that increased myocardium volume, promoted endogenous cardiac regeneration, decrease apoptosis and increased vascular density by the administration. Ichim et al. in acase report reveals the evidence of transplantation of MenSC in a congestive heart failure patient. [25]

References

1. Prianishnikov VA. The concept of stem cell and a model of stem cell and a model of functional-morphological structure of the endometrium. Contraception.1978; 18:213–223.

2. Bianco P. Mesenchymal stem cells. Annu Rev Cell Dev Biol. 2014; 30:677–704.

3. Becker AJ, Culloch EA, Till JE. Cytological demonstration of the clonal nature of spleen colonies derived from transplanted mouse marrow cells. Nature. 1963; 197:452–4.

4. Dah Ching D, Woei CS, Shinn Z. Mesenchymal stem cells Cell transplantation. 2011; 20 (1), 5-14.

5. M Dominici 1 , K Le Blanc, I Mueller, I Slaper-Cortenbach, Fc Marini, Ds Krause, Rj Deans, A Keating, Dj Prockop, Em Horwitz. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. 2006;8(4):315-7.

6. Williams AR, Hare JM. Mesenchymal stem cells: biology, pathophysiology, translational findings, and therapeutic implications for cardiac disease. *Circ Res*. 2011; 109(8):923-940.

7. https://images.app.goo.gl/5dCqi7CqY5G2RqK27.

8. https://images.app.goo.gl/wg83SSVaRKV6WvYu9.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

9. Lindenmair A, Hatlapatka T, Kollwig G, et al. Mesenchymal stem or stromal cells from amnion and umbilical cord tissue and their potential for clinical applications. Cells. 2012; 1(4):1061-1088.

10. Yang H, Zhou B, Prinz M, Siegel D. Proteomic analysis of menstrual blood. Mol Cell Proteomics. 2012; 11(10):1024-1035.

11. Borlongan CV, Kaneko Y, Maki M. Menstrual blood cells display stem cell-like phenotypic markers and exert neuroprotection following transplantation in experimental stroke. *Stem Cells Dev*. 2010;19(4):439-452.

12. Murray KA, Gibson MI. Post-Thaw Culture and Measurement of Total Cell Recovery Is Crucial in the Evaluation of New Macromolecular Cryoprotectants. Biomacromolecules. 2020; 21(7):2864-2873.

13. Allickson JG, Sanchez A, Yefimenko N, Borlongan CV, Sanberg PR. Recent Studies Assessing the Proliferative Capability of a Novel Adult Stem Cell Identified in Menstrual Blood. Open Stem Cell *J*. 2011; 3(2011):4-10.

14. Chen L, Zhang C, Chen L, et al. Human Menstrual Blood-Derived Stem Cells Ameliorate Liver Fibrosis in Mice by Targeting Hepatic Stellate Cells via Paracrine Mediators. *Stem Cells Transl Med*. 2017; 6(1):272-284.

15. Chen L, Qu J. & Xiang C. The multi-functional roles of menstrual blood-derived stem cells in regenerative medicine. Stem Cell Res Ther. 2019; 10**,** 1.

16. Chen L, Qu J, Mei Q, et al. Small extracellular vesicles from menstrual blood-derived mesenchymal stem cells (MenSCs) as a novel therapeutic impetus in regenerative medicine. Stem Cell Res Ther. 2021; 12(1):433.

17. Woodruff TM, Thundyil J, Tang SC, Sobey CG, Taylor SM, Arumugam TV. Pathophysiology, treatment, and animal and cellular models of human ischemic stroke. Mol Neurodegener. 2011; 6(1):11.

18. Uccioli L, Meloni M, Izzo V, Giurato L, Merolla S, Gandini R. Critical limb ischemia: current challenges and future prospects. *Vasc Health Risk Manag*. 2018; 14:63-74.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 04, 2021

19. Komorowska B. Autoimmune premature ovarian failure. *Prz Menopauzalny*. 2016;15(4):210-214.

20. https://www.ncbi.nlm.nih.gov/books/NBK448088/

21. Matute-Bello G, Frevert CW, Martin TR. Animal models of acute lung injury. *Am J Physiol Lung Cell Mol Physiol*. 2008; 295(3):L379-L399.

22. Murphy MP, LeVine H 3rd. Alzheimer's disease and the amyloid-beta peptide. *J Alzheimers Dis*. 2010; 19(1):311-323.

23. Eming SA, Martin P, Tomic-Canic M. Wound repair and regeneration: mechanisms, signaling, and translation. Sci Transl Med. 2014; 6(265):265sr6.

24. https://www.ncbi.nlm.nih.gov/books/NBK536055

25. Lijun C, Jingjing Q, Charlie X. The multi-functional roles of menstrual blood-derived stem cells in regenerative medicine. Stem Cell Research & Therapy. 2019; 10:1.