eISSN 2005-5447
International Journal of Stem Cells Vol. 17, No. 3, 2024 https://doi.org/10.15283/ijsc23091

REVIEW ARTICLE

Human Endometrial Regenerative Cells for Neurological Disorders: Hype or Hope?

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Despite enormous efforts, no effective medication has been found to significantly halt or even slow the progression of neurological diseases, such as acquired (e.g., traumatic brain injury, spinal cord injury, etc.) and chronic (e.g., Parkinson's disease, Alzheimer's disease, etc.) central nervous system disorders. So, researchers are looking for alternative therapeutic modalities to manage the disease's symptoms and stop it from worsening. Concerning disease-modifying capabilities, stem cell therapy has emerged as an expanding domain. Among different types of stem cells, human endometrial regenerative cells have excellent regenerative properties, making them suitable for regenerative medicine. They have the potential for self-renewal and differentiation into three types of stem cells: epithelial stem cells, endothelial side population stem cells, and mesenchymal stem cells (MSCs). ERCs can be isolated from endometrial biopsy and menstrual blood samples. However, there is no comprehensive evidence on the effects of ERCs on neurological disorders. Hence, we initially explore the traits of these specific stem cells in this analysis, followed by an emphasis on their therapeutic potential in treating neurological disorders.

Keywords: Stem cell transplantation, Central nervous system diseases, Endometrium, Regenerative medicine

Introduction

One of the leading causes of disability and death globally is neurological disorders (1). Cerebrovascular disorders, Parkinson's disease (PD), Alzheimer's disease (AD), multiple sclerosis, motor neuron diseases (MNDs), and spinal cord injury (SCI) are common neurological diseases, which contribute the highest burden in disability (2). Current pharmacotherapy, for instance, at the first line for PD symptoms provides reasonable benefits at controlling the symptoms of the condition; however, the efficacy of the long-term use of drugs, despite increasing the dosage or doing brain surgical procedures, reduces with time (3-5). Hence, there is a need for further therapeutic advancements to reduce disease symptoms, slow or halt disease progression, and ultimately reverse the damaging effects on the nervous system.

Numerous studies have shown that stem cell therapy can be considered a potential novel treatment for neurodegenerative diseases based on their self-renewal ability and differentiation capacity into different neural lineage cells

Received: June 15, 2023, Revised: August 28, 2023,
Accepted: October 6, 2023, Published online: January 8, 2024
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(6, 7). Stem cells can reduce neurological disease progression rate and repair the chaotic microenvironment (8). These cells can continuously produce new cells and help repair organ damage depending on the organ features they reside in (8). They are categorized based on their potential differentiation ability into totipotent, pluripotent, multipotent, oligopotent, and unipotent (9). Stem cells can be isolated from embryonic and adult sources (10). Embryonic stem cells (ESCs) are pluripotent and are located in the inner cell layer of a pre-implanted embryo, which differentiate into all germinal layers (8). On the other hand, adult stem cells are found in various tissues like placenta, blood, bone marrow, skin, intestine, and brain (9, 11). Moreover, adult stem cells have the advantage of being sourced from the patient's own body. This enables autologous transplantation, in which the patient receives stem cells that have been expanded or manipulated. Using the patient's own cells reduces the risk of rejection or immunological complications, making autologous transplantation a more feasible treatment option. Additionally, adult stem cells carry a lower risk of tumor formation or uncontrolled growth than ESCs (12, 13). Therefore, prior to clinical practice, several features of stem cells must be pointed out, e.g., tumorigenicity, availability, immunogenicity, and differentiation capacity. Among different types of adult stem cells, human stem cells derived from the endometrium are highly regenerative sources of stem cells with ideal characteristics that make them an appropriate choice in regenerative medicine (14). They are also compatible with the International Society for Cellular Therapies (14).

Human endometrial regenerative cells (ERCs) consist of three types of stem cells: epithelial stem cells, endothelial side population (ESP) stem cells, and mesenchymal stem cells (MSCs) (15). ERCs can be obtained from human menstrual blood, known as menstrual blood-derived stem cells (MenSCs), and from the endometrium tissue, known as endometrium-derived stem cells (EnSCs), through biopsy. ERCs have the capacity to differentiate into various lineages, including adipocytes, osteocytes, cardiomyocytes, neurocytes, respiratory epithelial cells, endothelial cells, myocytes, hepatic cells, pancreatic cells, chondrocytes, fibroblasts, smooth muscle cells, neuron-like cells, glial-like cells, germ-like cells, various glandular lineages, and endometrial organoids (16-18). ERCs have been studied in various preclinical studies involving cardiac diseases, reproductive disorders, uterine abnormalities, diabetes, osteoporosis, and liver disease. Additionally, numerous clinical studies have been conducted on Duchene muscular dystrophy, heart failure, and multiple sclerosis (19, 20). The results of these studies are promising for the future of stem cell therapy (21-23).

In one study, intrathecal and intravenous administration of human EnSCs (hEnSCs) in four multiple sclerosis patients with 12 months of follow-up showed safety and efficacy in managing disease progression (19). Furthermore, hEnSCs have immunomodulatory effects by reducing inflammatory T-cells (19, 24). However, there has been limited attention given to the beneficial effects of ERCs in neurological diseases. Therefore, we have written this review to outline the main features of ERCs and highlight their therapeutic potential in addressing neurological disorders.

An Overview of Characteristics of ERCs

Before delving into a more detailed account of the ERCs, some general understanding of endometrium tissue is useful. The endometrium, which consists of the functional (the upper layer) and the basalis (adjacent to the myometrium), undergoes significant cell proliferation during tissue homeostasis and repair capabilities and remains intact during the menstrual period while generating new functional layers (18, 25). Stem cells in the human endometrium have been categorized into three types: epithelial stem/progenitor cells, ESP stem cells, and endometrial MSCs (18). However, a lack of exclusive gene or signaling pathway markers specific to endometrial tissue leads to significant overlap with other somatic stem cell types and even cancer stem cells. Nonetheless, endometrial MSCs can be classified into two categories based on expression pattern, i.e., $CD140b^{+}/CD146^{+}$ endometrial MSCs and sushi domain containing 2 (SUSD2) positive MSCs. These cells are located at the perivascular area. When dig deep on two MSCs, they are different in other markers, e.g., $CD140b^{+}/CD146^{+}$ endometrial MSCs are positive for CD29, CD44, CD73, CD90, and CD105, while negative for CD31, CD34, and CD45. On the other hand, SUSD2 positive-MSCs are positive for CD29, CD44, CD73, CD90, CD105, CD117, CD140b, CD146, STRO-1, and nucleoside triphosphate diphosphohydrolase-2, but they don't express CD31 and CD45 markers. However, it should be noted that some markers are shared between these two types of MSCs. Identifying specific markers and characteristics can help distinguish these cells for their intended applications. Nevertheless, ESP stem cells demonstrate the presence of CD90, CD105, CD73, CD45, CD34, CD31, CD133, STRO-1, and vimentin markers, while lacking CD13, CD105, estrogen receptor alpha, or progesterone receptor. Likewise, epithelial stem/progenitor cells exhibit the expression of N-cadherin, stage-specific embryonic antigen-1, and axin 2 (18, 26, 27).

Repetitive proliferation-menstruation cycles of uterus decline stem cells existed in the endometrium (26). It has

been proved that MenSCs exist in deciduous endometrium, which might have a similar nature to EnSCs (27). One study showed the presence of endometrial clonogenic cells and SUSD2+ MSCs in females' menstrual blood, even if they have endometriosis or not (28). These cells can be obtained with a simple uterine biopsy or by collecting human menstrual bleeding from menstrual cups. Therefore, the accessibility of these cells reduces the cost of cell obtaining (29) and can provide an unlimited source for more people with different socioeconomic levels. ERCs availability gives a favorable context for repetitive cell therapies (15, 30). Despite availability, these cells have an excellent potential to differentiate into multi-lineage sources (i.e., mesodermal, endodermal, and ectodermal lineages) (15, 29-32). They can, therefore, be a promising candidate for neuronal regenerative treatments compared to the other sources. Fig. 1 illustrates the various stem cells that can be isolated from the uterus and their characteristics regarding their potential for neural cell differentiation. Besides that, producing more stem cells at low passage (<8) is a central feature of self-renewal capacity that makes them the best candidate for a clinical trial. For MenSCs, a female can provide stem cells for 20,000 patients. Approximately 0.5×105 MenSCs can be derived from 5 ml menstrual blood. It has been shown that one hundred million MenSCs can be harvested at passage 3 (22).

However, MenSCs have a faster proliferation in early passages than late passages. Furthermore, cells derived from younger females have a more proliferative capacity (30). They could grow by a factor of two than bone marrow-derived MSCs (22). These cells become homogenous and make a spindle shape after 3 to 4 passages (32, 33). EnSCs have lower immunogenicity and tumor tropism than other MSCs (15).

Another significant aspect of cell therapy in neurological disorders is neural differentiation. Many complex pathways and molecules participate in neural trans-differentiation and specific neural cell type differentiation (34). Differentiation of hEnSCs into cholinergic neurons was made by nerve growth factor (NGF) and basic fibroblast growth factor (bFGF). It has been indicated that hEnSCs express receptors for NGF like neural stem cells (34). One study assessed oleic acid for improving neurogenesis capacity of hEnSCs (33). The mRNA levels of NF and β-TUBULIN as the neurogenesis markers in hEnSCs treated with oleic acid were significantly increased. Additionally, oleic acid increased the expression of ChAT and NF in hEnSCs, indicating hEnSCs have a great neuronal differentiation capacity (33). As shown in Table 1 (24, 35-43),

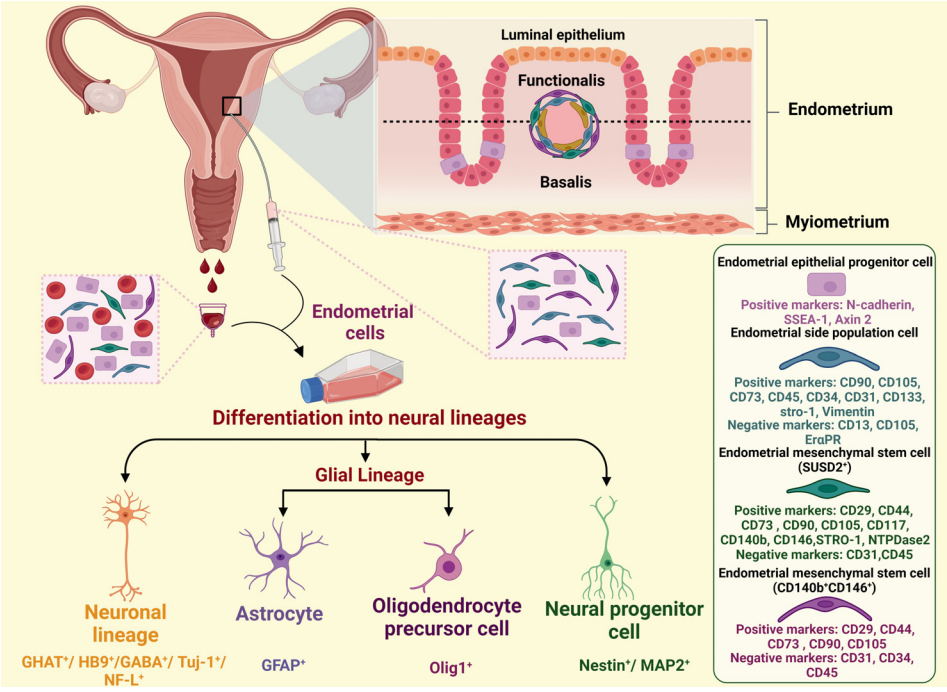

Fig. 1. Schematic diagram of isolation, characterization, and differentiation capacity of human endometrial regenerative cells (ERCs). Human ERCs can be collected from the uterus using an endometrial biopsy device and menstrual silicon cups. ERCs comprise three types of stem cells: epithelial stem cells, endothelial side population stem cells, and mesenchymal stem cells. ERCs have the ability to differentiate into various neural lineages. Created with BioRender.com.

Table 1. Human ERCs in the course of neurological models

	Sample	Type of study	Model	Cell source	Route and no. of injections	No. of cells	Result	Main finding	Reference
1	By curettage from reproductive-aged females undergoing surgery	*In vitro*	MPTP mouse model of PD	Adult hEnSCs	-	-	Exhibited neurogenic morphology, expression of the nestin and dopamine production TH and electrophysiological properties of neurons	hEnSCs differentiated into the dopamine-producing neurons	(35)
		In vivo		Adult hEnSCs	Striatum 4 injections	10^5 cells	Exhibit nestin, and human TH, survive in the location they are transplanted and spontaneously migrate to areas of damage and spontaneously differentiate *in vivo*		
2	Collected by hysterectomy and curettage from eight monkeys	*In vivo*	MPTP monkey model of Parkinson	Monkey EnSCs	Striatum 2 injections into right striatum	4×10^6 cells	Ability to migrate from the striatum and engraft in the substantia nigra. Also show significant migration to the contralateral side	EnSCs can migrate to the foci of cellular injury and differentiate to TH (+) neuron-like cells and protect endogenous dopaminergic neurons	(40)
3	Menstrual blood from healthy females donors	*In vitro*	On MPP+ treated cells	MenSCs-CM	-	-	Significantly reduce ROS generation and significantly reduce the number of cells in late apoptosis stage	MenSCs-CM can protect MPPC-induced cytotoxicity via reducing inflammation, oxidative stress, apoptosis and rescuing mitochondrial membrane potential	(41)
4	Collected with a Diva Cup from healthy females	*In vivo*	APP/PS1 transgenic mouse model of Alzheimer	hMenSCs	Bilaterally into the hippocampus	10^5 cells	Reduced Ab deposition and decreased tau hyperphosphorylation	Decreased tau hyperphosphorylation	(36)

Table 1. Continued

	Sample	Type of study	Model	Cell source	Route and no. of injections	No. of cells	Result	Main finding	Reference
5	Menstrual blood sample	*In vitro*	OGD injury model of stroke	MenSCs	-	-	Cells were Nestin-positive, and readily differentiated into intermediate neuronal and astrocytic phenotype. Also, cells significantly reduced cell death and improved cell survival and elevated levels of trophic factors, such as VEGF, BDNF, and NT3	The present neurostructural and behavioral benefits afforded by transplanted MenSCs	(37)
		In vivo	Rat model of stroke	MenSCs	IC (3 injections, striatum), IV	4×10^5 for IC, 4×10^6 for IV	significantly reduced behavioral abnormalities and increased survival of host cells		
6	Endometrial biopsy	*In vivo*	Mice model of autoimmune encephalomy-elitis	hEnSCs	Intraperitoneally	1×10^6	Suppress neuroinflammation	hEnSCs as a potent immunomodulatory tool for the treatment of autoimmune or neurodegenerative diseases	(24)
7	Uterine tubes and uterus were extracted from C57BL/6 WT and IDO−/−	*In vitro*	Co-culture of murine EnSCs and CD4+ T lymphocytes	Murine EnSCs	-	-	Reduced overall inflammation in the CNS, including mononuclear cells infiltrate, cytokine secretion and microglial activation	Suppressive activity of the unexplored murine EnSCs population, and shows the mechanism depends on IDO-Kynurenines-Aryl hydrocarbon receptor (AhR) axis	(42)
		In vivo Murine model of autoimm-une encephal-omyelitis		Murine EnSCs	Intraperitoneally	1×10^6 cells on days 0 and 10 post-immuniza-tion			
8	Menstrual blood specimens were collected with menstrual cups	*In vivo*	Rat model of hemisected SCI	hMenSCs	Injection into the injured site	1×10^5	Improved the locomotor function, reduced the inflammatorycell infiltrations and vacuolization in the lesion site, increased neuronal markers in the lesion area, enhanced expression and secretion of BDNF, reduced scar formation, and decreased the expression of inflammatory cytokines	MenSCs transplantation promotion of the functional recovery of SCI rats via enhanced expression and secretion of BDNF, reduced scar formation and decreased the expression of inflammatory cytokine	(38)

Table 1. Continued

	Sample	Type of study	Model	Cell source	Route and no. of injections	No. of cells	Result	Main finding	Reference
9	Human endometrial biopsy	*In vivo*	Mouse model of hippocampal injury	EnSCs-derived extracellular vesicles	Intranasal	Total of 500 mg of EVs (released by 5×10^6 eMSCs) protein per kilogram of animal weight	Prevented histological damage and preserved speed locomotion and displacement changes presumably due to the growth factors contained in those vesicles	Intranasal administration of EnSCs – EVs could improve recovery of hippocampal tissue	(43)
10	Menstrual blood	*In vivo*	Mouse SCI model	hMenSCs	Intrathecal	1×10^5 cell/μl and 2×10^5 cell	MenSCs transplantation Shh–induced MenSCs accelerated neuronal recovery, inhibited the formation ofglial cells and microglial activation atthe injured site, inhibited the expression of inflammatory factors, and improved the inflammatory microenvironment to achieve functional recovery of SCI	MenSCs transplantation improved functional recovery	(39)

The main characteristics of experimental research in the application of endometrial regenerative cells (ERCs) in some neurological models.
PD: Parkinson's disease, hEnSCs: human endometrial derived stem cells, TH: tyrosine hydroxylase, MenSCs: menstrual blood-derived stem cells, MenSCs-CM: conditioned medium of human menstrual blood derived endometrial stem cells, ROS: reactive oxygen species, OGD: oxygen glucose deprivation, VEGF: vascular endothelial growth factor, BDNF: brain-derived neurotrophic factor, NT3: neurotrophin-3, SCI: spinal cord injury, EVs: extracellular vesicles.

hEnSCs differentiation into dopamine-producing neurons is described. It is proved that hEnSCs are promising cell sources for neural tissue engineering (44).

ERCs in the Context of Neurological Disorders

Based on our research in the field of ERCs, we conducted a comprehensive review to examine the effects of these types of stem cells on various neurological disorders. Specifically, we focused on conditions such as PD, AD, MND, as well as acquired brain injuries such as stroke and traumatic brain injury (TBI), by analyzing published articles related to these conditions.

The most common neurodegenerative movement disorder is PD, characterized by the depletion of dopaminergic neurons and the aggregation of misfolded alpha-synuclein, leading to motor and non-motor symptoms (3). Administration of hEnSCs in PD animal models has significantly increased dopamine concentration (35). *In vitro* studies have also demonstrated the ability of hEnSCs to differentiate into dopaminergic neurons that exhibit morphological and molecular characteristics, such as pyramidal cell bodies, axon and dendrite projections, and synapse formation. These cells express nestin and tyrosine hydroxylase, which are neural markers and critical enzymes in dopamine synthesis. Furthermore, hEnSCs show a reasonable survival rate after transplantation and exhibit migration capacity to the damaged region (35).

Several categories can be identified when examining the mechanisms of action for ERCs in PD. These stem cells have shown the ability to inhibit inflammatory pathways, reducing the expression of inflammatory markers, such as COX-2, interleukin (IL)-1β, IL-6, inducible nitric oxide synthase (iNOS), and tumor necrosis factor α (TNFα). Additionally, MenSCs secrete neurotrophic agents such as NGF, brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT3), and NT4/5, which can reduce apoptosis in PD models. MenSCs also express members of the GDNF family of ligands, including ARTN, GDNF, NTN, and PSPN, as well as other dopaminergic neurotrophic factors that enhance the survival of dopaminergic neurons. Furthermore, MenSCs can restore mitochondrial membrane potential, which is often disrupted in PD pathogenesis (3, 27).

In AD, the main pathology is believed to be an imbalance between oxidant and antioxidant processes because of the deposition of amyloid-beta peptides and the activation of microglia (36). This imbalance leads to progressive neuronal loss, resulting in the clinical manifestations of AD. Administering MenSCs has been shown to convert microglia activity to a non-inflammatory state by reducing pro-inflammatory cytokines like IL-1β and TNFα, while increasing anti-inflammatory markers such as IL-4, YM1, Arg1, Fizz1, and CD206 in the hippocampus and cortex of AD models. This conversion of microglia leads to the production of insulin-degrading enzyme and neprilysin, which degrades amyloid-beta plaques. Another mechanism involves the inhibition of the β-secretase enzyme (36). MenSCs also inhibit glycogen synthase kinase-3b after transplantation, reducing tau hyperphosphorylation, a characteristic feature of AD (36). Amyotrophic lateral sclerosis (ALS), the most common neurodegenerative disease in the middle ages, is classified as a MND characterized by the degeneration of motor neurons in the central nervous system. Unfortunately, this condition leads to death within 3 to 5 years (45). While there is currently no systematic study explicitly exploring the effects of hEnSCs and MenSCs on ALS models, a review of the existing literature suggests that hEnSCs may hold promise as a potential treatment for ALS.

For instance, a comparative study demonstrated that hEnSCs exhibited a higher capacity for differentiation into motor neurons than human bone marrow stem cells (46). Additionally, *in vitro* studies have shown that hEnSCs express several motor neuron markers, such as ISL-1, CHAT, β-tubulin III, NF-H, HB9, pax6, Islet-1, TUJ-1, NES, NEFH, and SYP (46-49). In ALS, it is imperative to utilize stem cells that can form synaptic connections with muscle cells. In an experimental study, hEnSCs grafted inside a conduit made of poly ε-caprolactone (PCL)/Collagen/nanobioglass (NBG) not only demonstrated successful growth and connection with damaged nerve regions but also exhibited improved synapse formation with muscle cells (50).

To fully understand the potential of ERCs in ALS models, further investigation is needed to evaluate their effects on maintaining axonal integrity, besides their neuroprotective properties and ability to differentiate into motor neurons. Table 2 summarizes the potential differentiation of hEnSCs and MenSCs into motor neurons. The last category that we reviewed was acquired brain injuries including stroke and TBI, which have high mortality rates and long-lasting disability. The pathological changes are categorized into primary and secondary injuries. Solid evidence demonstrates that a variety of cellular and molecular alterations play vital roles in connecting primary injury to the secondary injury, e.g., inflammatory pathways

Table 2. The differentiation capacity of hEnSCs into motor neuron

Cell type	Scaffold	Cell number	Markers	Duration of differentiation (day)	% Cell expression marker	Mechanism	Beneficial result	Main finding	Reference
hEnSCs	Tissue culture polystyrene (TCP) and poly ε-caprolactone (PCL) nanofibrous scaffold	5×10^4 cells	ISL-1, CHAT, islet-1, Pax6, NF-H, Hb9, and β-tubulin III	15	40～90	Significant upregulation of motor neuron markers	Exhibiting neural morphology and interconnection of cells	Improved motor neuron differentiation	(46)
hEnSCs	Biodegradable PLGA nanofiber scaffolds	5×10^4 cells	ISL-1, CHAT, β-tubulin III NF-H HB9, pax6	15	40～89	Increased gene expression of markers	Exhibiting neural morphology and interconnection of cells	Improved motor neuron differentiation	(48)
hEnSCs	Electro spun Biocomposite Polycaprolactone/Collagen scaffolds	5×10^4 cells	NF-H, TUJ-1, Chat, Islet-1, and HB9	15	60～80	Inhibition of the PI3K/Akt pathway Neural marker expression	Exhibiting neural morphology characteristics	Improved motor neuron differentiation	(47)
hEnSCs	Epothilone B (EpoB)	2×10^5 cells	ISL-1, CHAT, and HB9 NES NEFH SYP, and β-tubulin III proteins	15	More than 90	Upregulation of motor neuron markers	Improved axonal length and neuronal alignment	Improved motor neuron differentiation	(49)

Differentiation capabilities into motor neuron is a promising function of human endometrium-derived stem cells (hEnSCs) for the treatment of motor related disorders.

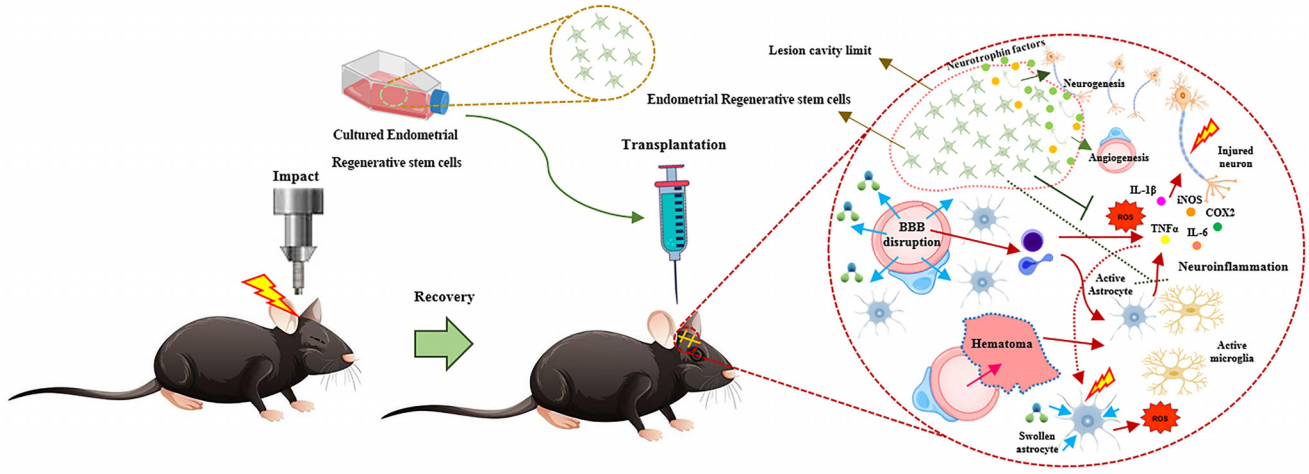

Fig. 2. Mechanisms of probable therapeutic effects of human endometrial regenerative cells (hERCs) in a traumatic brain injury model. hERCs can alleviate detrimental effects of brain injury through several important pathways; 1. Increasing the expression of neurotrophic factors, such as nerve growth factor, brain-derived neurotrophic factor, and neurotrophin-3 for triggering the neurogenesis; 2. Improving the volume of lesion cavity; 3. Decreasing the expression levels of proinflammatory cytokines in the brain tissue and prevention of neuroinflammation; 4. Reducing the expression of proapoptotic genes, such as *Bad* and *Bax*; 5. Increasing nerve regeneration and improving the axonal remyelination; 6. Decreasing the leukocytes infiltration following inflammatory condition; 7. Suppressing the main inflammatory cytokines and reactive oxygen species (ROS); 8. Restoring the reactive glial cells and controlling vasogenic and cytotoxic edema with reduction of proinflammatory cytokines and ROS; 9. Inducing the formation of micro vessels. BBB: blood-brain barrier, IL-1β: interleukin 1 beta, IL-6: interleukin 6, TNFα: tumor necrosis factor α, COX2: cyclooxygenase 2, iNOS: inducible nitric oxide synthase.

and oxidative stress are the key players in expanding the pathological changes in relation to secondary injury. Moreover, the presence of cavity lesions resulting from mechanical trauma, such as TBI and SCI, poses a significant obstacle to treatment. Regarding this concept, stem cells with high bystander effects can be a best therapeutic option. Particularly, promising results were observed after transplantation of MenSCs by secreting neurotrophic factors, such as vascular endothelial growth factor (VEGF), BDNF, and NT3 (37). Furthermore, promising findings have been observed in the reduction of cavity lesions using MenSCs in a spinal cord hemi-section model. Cellular assessments revealed increased axonal regeneration and decreased expression of chondroitin sulfate proteoglycans in the MenSCs group compared to the control group. Additionally, MenSCs transplantation was found to inhibit the expression of TNFα and IL-1β (38). Notably, in an SCI model, the rate of motor function recovery was found to correlate with the differentiation of oligodendrocyte progenitor cells in the MenSCs group (51). Furthermore, MenSCs transplantation enhanced motor function recovery in SCI animals and stimulated the immune response and defense. Transcriptome sequencing and analysis revealed the close association of SCI with immune system processes. The transplantation of MenSCs was closely linked to pathways involved in the differentiation of Th1, Th2, and Th17 cells. Additionally, MenSCs regulated the differentiation and activation of Th2 and M2 macrophages, produced anti-inflammatory factors, and attenuated the inflammatory response at the injury site, thereby promoting SCI function recovery. In the MenSCs transplantation group, the expression of iNOS and CD206 in microglia decreased, indicating reduced inflammation. Moreover, MenSCs improved the balance between M1 and M2 microglia within the highly inflammatory microenvironment (39).

Additionally, positive outcomes can be achieved when combining hEnSCs with different scaffolds. In the case of differentiating hEnSCs seeded on PCL/gelatin scaffolds, enhanced neuronal regeneration, increased motor function, and axonal remyelination were observed in an SCI model (52). Furthermore, hEnSCs seeded on PCL demonstrated a reduction in the secondary response to injury and an improvement in motor function (53). The potential therapeutic effects of hEnSCs and MenSCs in acquired brain injuries are summarized in Fig. 2. Considering these findings, these cells can be considered suitable candidates for stem cell therapy in the context of acquired brain injuries.

Conclusion

Accessibility and high survival rates after transplanta-

tion are key characteristics for the clinical use of stem cells. Thus, the search for readily available stem cells with excellent survival and differentiation capabilities becomes crucial in translating stem cell applications to benefit patients. In this context, we investigated the potential of ERCs as promising candidates for treating neurological disorders. We reviewed the current evidence and discussed the beneficial effects of ERCs in this area. ERCs have shown the ability to alleviate pathological changes by inhibiting inflammatory and apoptotic pathways. Moreover, they secrete various neuroprotective agents that promote remyelination, axonal growth, and improve synaptic integrity and extracellular remodeling. Considering the available data, it is essential for future research to carefully examine the potential effects of ERCs, including evaluating their safety and efficacy at the clinical level.

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Funding

None.

Acknowledgments

We would like to thank the Clinical Research Development Unit, Imam Reza Hospital, Mashhad University of Medical Sciences, for their assistance in this manuscript.

Potential Conflict of Interest

There is no potential conflict of interest to declare.

Data Availability Statement

All data analyzed during this study are included in this published article.

Authors' Contribution

Conceptualization: SSN. Data curation: SSN, JM. Investigation: JM, EN, RAA. Methodology: SSN, JM. Project administration: SSN. Resources: JM. Software: AS. Supervision: SSN. Validation: SSN. Visualization: AS. Writing – original draft: JM, EN, SSN. Writing – review and editing: SSN, JM.

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