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MENSTRUAL BLOOD-DERIVED STEM-CELL IN REGENERATIVE MEDICINE: EMERGING APPLICATION IN WOUND HEALING AND TISSUE ENGINEERING

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Abstract:

The scarcity, donor dependency, and limitations of traditional stem-cell sources have caused great interest in other cell populations for their regenerative potential. Menstrual blood-derived stem/stromal cells (MenSCs) are a viable option, being easily accessible cells of endometrial origin with mesenchymal stromal cell-like properties and multilineage differentiation capabilities. MenSCs participate in cell proliferation, angiogenesis, inflammatory cascades, extracellular matrix remodeling, and tissue repair in different models of injury and disease. Several preclinical studies report the ability of MenSCs to participate in cell proliferation, angiogenesis, inflammatory cascades, extracellular matrix remodeling, and tissue repair in different models of injury and disease. The application of MenSC in tissue engineering, including scaffolds and hydrogels, has shown promise in preliminary studies. However, most reports are based on preclinical findings, and clinical studies are limited and inconsistent. This narrative review discusses MenSC biology and proposed mechanisms of regeneration, including their role in wound healing, tissue engineering and repair, novel approaches, challenges, variations, and inconsistencies regarding their use and explores their future and possible roles in regenerative medicine. It also emphasizes on the opportunities and future directions for research, including the use of MenSCs in combination with scaffolds, hydrogels, cell-free secretome and extracellular vesicle content, 3D bioprinting, and clinical studies following standardized protocols.

Keywords: *Menstrual Blood-Derived Stem Cells, Menstrual Stromal Cells, Regenerative Medicine, Wound Healing, Tissue Engineering, Biomaterials.*

1. Introduction

Regenerative medicine focuses on restoring the structure and function of damaged tissues by applying principles of cell biology, tissue engineering, biomaterials, and molecular therapeutics. However, clinical management of tissue injury remains a formidable challenge, primarily due to the complexity of repair processes. In particular, tissue repair and regeneration require a coordinated response, including control of inflammation, angiogenesis, cell proliferation, extracellular matrix remodeling, and re-epithelialization. Chronic inflammation, insufficient angiogenesis, fibrosis, and defective extracellular matrix deposition are some of the factors associated with impaired tissue repair and regeneration. As a result, researchers are currently focused on cell-based tissue engineering with stem/stromal cells and their derivatives, including various types of cytokines, extracellular vesicles, and engineered materials, to develop novel therapeutic concepts that address tissue repair at multiple levels.

Stromal cells can modulate the immune response by secreting diverse soluble mediators such as immunoregulatory cytokines and extracellular vesicles. Mesenchymal stromal/stem cells (MSCs) have become one of the most intensely studied cell populations for tissue repair and regeneration. The ability of MSCs to migrate into the damaged tissue site and modulate the local microenvironment is considered one of their most important therapeutic attributes. Therefore, MSCs obtained from various tissues, including bone marrow, adipose tissue, and umbilical tissues, have been investigated for their potential to promote tissue repair (1,2).

Bone marrow MSCs require an invasive procedure to obtain, whereas adipose tissue MSCs require liposuction. Furthermore, the number and quality of MSCs can vary significantly depending on the tissue of origin, age, and other factors. MSCs also exhibit significant heterogeneity in cell culture depending on isolation methods, cell expansion conditions, donor variability, etc (3,4). Even for ethical and logistical reasons, alternative sources of MSCs are also of great consideration. One such source is menstrual blood, which can be obtained non-invasively and is isolated from the body on a regular basis.

Mesenchymal stromal/stem cells from menstrual blood (MenSCs) is one of the promising sources of regenerative cells. This cell population was found to possess certain regenerative abilities. MenSCs were identified as a stromal cell subpopulation with unique properties (3). Regarding the actual characteristics of MenSCs, the literature is inconsistent and, in some cases contradictory. First, several terms have been used in different studies to refer to these cells. Researchers have used such synonyms as menstrual blood-derived stem cells and menstrual blood-derived stromal cells. In addition, the term menstrual blood-derived endometrial stem cells has appeared in the literature. Menstrual blood is a mixture of endometrial cells and cells from other tissues, so the former phrase also covers a variety of cell types. Therefore, it would be wrong to consider MenSCs as one specific type of MSCs. Moreover, there are inconsistencies in the literature about MenSCs characterization, which might depend on different isolation methods and nomenclature (4).

It is believed that MenSCs possess certain qualities associated with tissue repair and regeneration. For example, it was found that MenSCs can affect macrophages and regulate the inflammatory response (5). On the other hand, many studies suggest that MenSCs might act mainly through the paracrine mechanism, which supports the idea of their strong anti-inflammatory and regenerative properties. It was found that MenSCs possess a wide range of secretory products that affect different aspects of the wound healing process. These include various pro- and anti-inflammatory cytokines, factors affecting cell migration and proliferation, and extracellular vesicles. The profile of secreted molecules can vary depending on the culture conditions, including hypoxia (6). A similar concept of

MenSCs secretome is being explored for cell-free regenerative medicine approaches (7,8). However, the secretion profile may differ from study to study and depends on donors, culture conditions, and other factors.

The properties described above have provided a solid foundation for considering MenSCs as a valuable tool for tissue engineering. In particular, it was found that transplantation of MenSCs with hyaluronic acid could accelerate the healing process of wounds in a diabetic rat model (9). These promising preclinical results prompted further research into the potential of MenSCs. For example, decellularized tissues together with MenSCs have been explored as a potential regenerative therapy for uterine injuries (10). This approach has also been used in combination with three-dimensional bioprinted scaffolds for spinal cord injury repair (11). This concept can also be beneficial for tissue engineering in general since it combines cell therapies with regenerative biomaterials.

The evidence presented demonstrates that MenSCs possess many valuable characteristics that can be used in tissue engineering and regenerative medicine. However, most of the research so far has been done in vitro or in animal models. Only a few studies have explored the potential of MenSCs in the clinical setting. Moreover, the current literature lacks consistency in defining these cells.

2. Stem cells in regenerative medicine: Background

With regard to regenerative medicine, multipotent stem/stromal cells stand out because, apart from helping in tissue repair, they provide practical avenues for use in therapy. This is because their regenerative properties go beyond their capacity for differentiation and are strongly linked to immunomodulatory and paracrine activities. (1,3). Specifically, endometrial and menstrual blood-derived cell populations are unique in that they provide access to reproductive tissue-related stromal cells and menstrual blood can serve as an invasive and periodically renewable source (3,4).

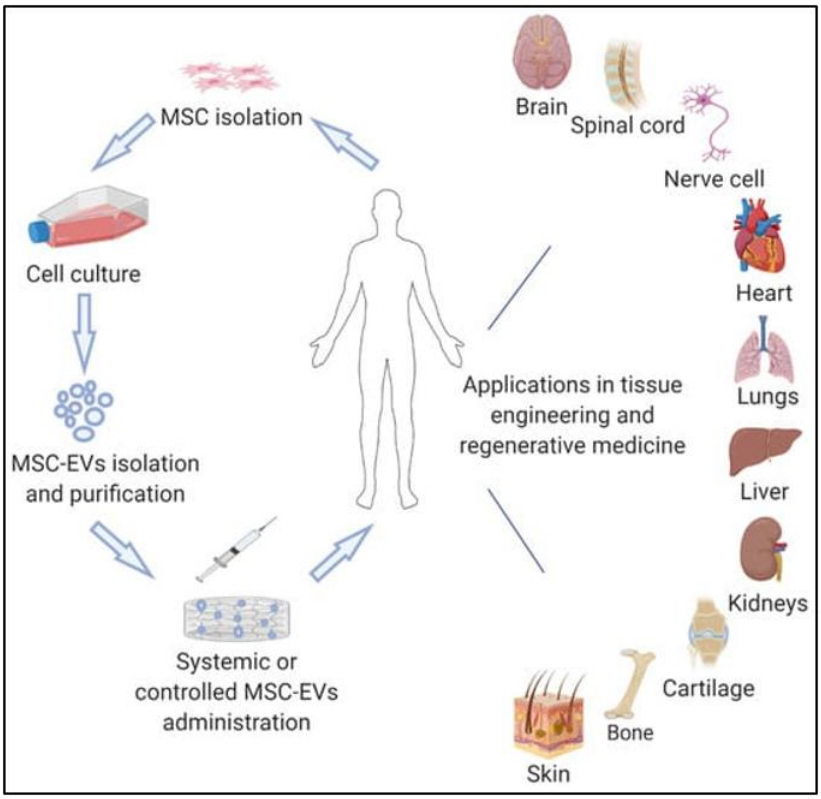

Figure 1: Isolation and potential application of MSC in regenerative medicine (12)

The similarity between the different sources is that MSC-based tissue repair encompasses growth factors and cytokines secretion, inflammation regulation, angiogenesis, extracellular matrix remodeling, and extracellular vesicles secretion among others (1,6). Yet, the variability of cell proliferation, cell yield, secretome, and isolation techniques among other factors from different sources is a crucial barrier to standardization. Such considerations offer the rationale for researching MenSCs as a readily available source as opposed to the assumption that all MSCs have similar regenerative properties.

Table 1: Comparison of major MSC sources relevant to regenerative medicine

MSC Source	Collection & Accessibility	Proliferation & Differentiation	Immuno-modulatory & Paracrine Potential	Primary Benefit	Key Limitations
Bone marrow	Invasive aspiration; established source	Moderate; multilineage differentiation	Well established	Extensive characterization; clinical experience	Invasive harvesting; donor age/ variability; limited yield
Adipose tissue	Moderately invasive; relatively abundant	High proliferative capacity; multilineage differentiation	Strong	High cell availability; accessible tissue source	Surgical harvesting; donor/site variability
Umbilical cord / Wharton's jelly	Non-invasive post-delivery collection; accessible when appropriately sourced	High proliferative capacity; broad differentiation potential	Strong immuno-modulatory activity	Young tissue source; non-invasive procurement	Processing/protocol variability; tissue availability depends on collection
Placenta	Non-invasive after delivery; relatively abundant	High proliferative capacity; broad differentiation potential	Strong	Abundant tissue; perinatal source	Regional and isolation hetero-geneity
Endo-metrium	Collection can be invasive; naturally regenerative tissue	High regenerative capacity; mesenchymal differentiation	Immuno-modulatory and paracrine activity	Naturally cyclic regenerative tissue	Collection limitations; cellular hetero-geneity
Menstrual blood (MenSCs)	Non-invasive; periodically renewable	High proliferative potential; mesenchymal differentiation	Prominent immuno modulatory and paracrine activity	Accessible, repeatable collection; no surgical harvesting	Termino-logical heterogeneity; donor/cycle variability; limited clinical evidence

Source: synthesized from (1,2,3,4,6)

3. Menstrual blood-derived stem cell (MenSCs)

3.1 Isolation and expansion

Isolation of MenSC usually starts with the collection of menstrual fluid via menstrual cups or any other method, normally during the first few days of menses. The samples are then transported in ways that reduce the chances of microbial contamination and cell degradation using buffer solutions including antimicrobial and antimycotic mixture. After collection, there is a need to isolate erythrocytes and other unnecessary factors before the stromal cell enrichment process. One technique for achieving this involves density gradient centrifugation using Ficoll media, in which the stromal/nucleated cell layer is isolated with erythrocytes in the bottom layer (3).

After isolation, cells are washed and plated under adherent culture conditions. Removal of non-adherent cells is carried out step-by-step during medium exchanges, leading to enrichment of fibroblast-like stromal cells. Cultured cells are then sub-cultured upon reaching suitable confluency. Nevertheless, this apparently simple procedure is associated with great variability. Variations in the isolation tool, menstrual cycle day, processing time, RBC removal procedure, culture medium, serum content, seeding density, oxygen levels, passage numbers, and donors themselves may affect cell yields and phenotype. For instance, one of the proven methods of MenSC isolation is based on use of menstrual blood obtained during maximum flow and subsequent density gradient centrifugation followed by adherent culture, while the other methods involve RBC lysis prior to culturing (13).

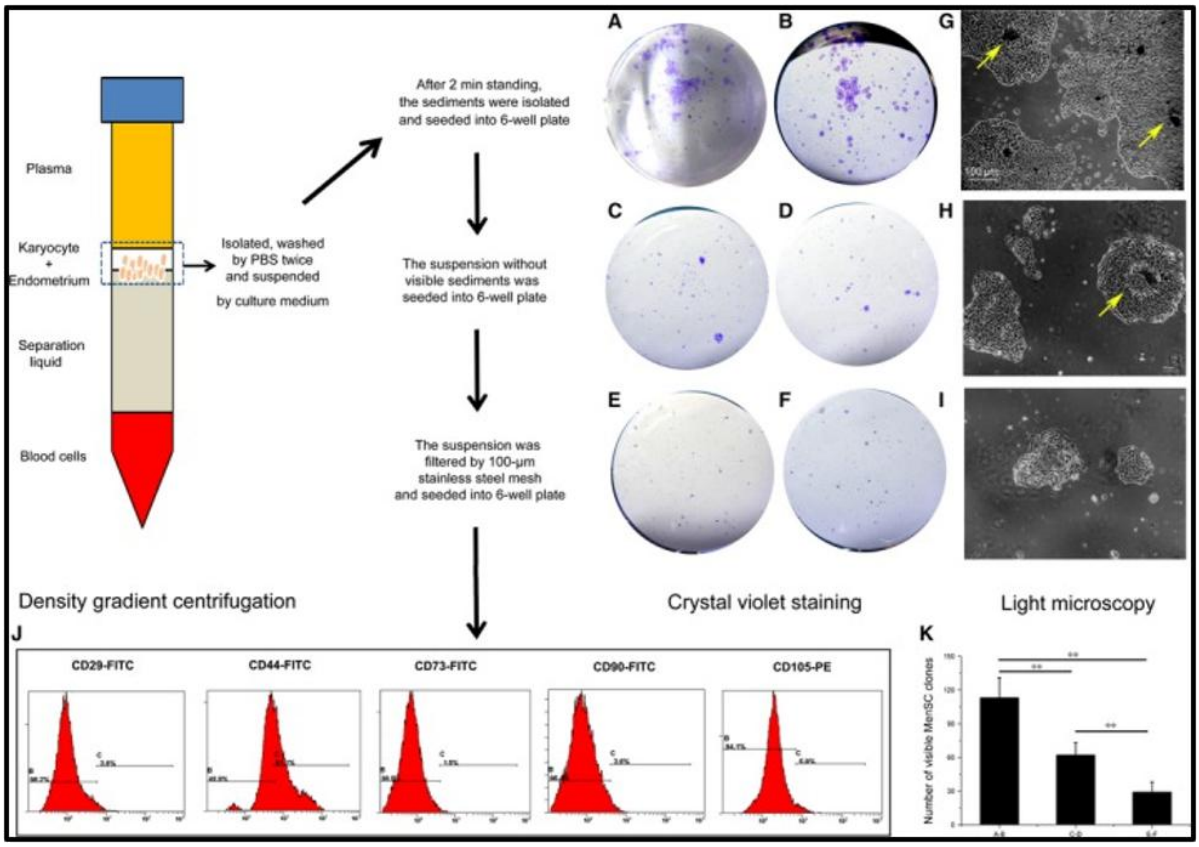

Figure 2: Evidence from localization studies suggests that MenSCs are associated predominantly with shed endometrial tissue present in menstrual blood, rather than with the suspended hematopoietic cell fraction (14)

Menstrual blood collection

↓

Sample processing and RBC removal

(density-gradient separation / RBC lysis)

↓

Stromal-cell enrichment and adherent culture

↓

Expansion and passage

↓

Characterization

• MSC-associated surface markers

• Morphology and viability

• Clonogenicity/proliferation

• Osteogenic/adipogenic/chondrogenic assays

• Secretome and immunomodulatory assays

↓

Therapeutic development

Whole-cell MenSC therapy ↔ MenSC-derived secretome / extracellular vesicles

↓

Regenerative applications

Wound healing | Tissue engineering | Endometrial repair | Cartilage/tissue regeneration

3.2 Phenotypic and functional characteristics

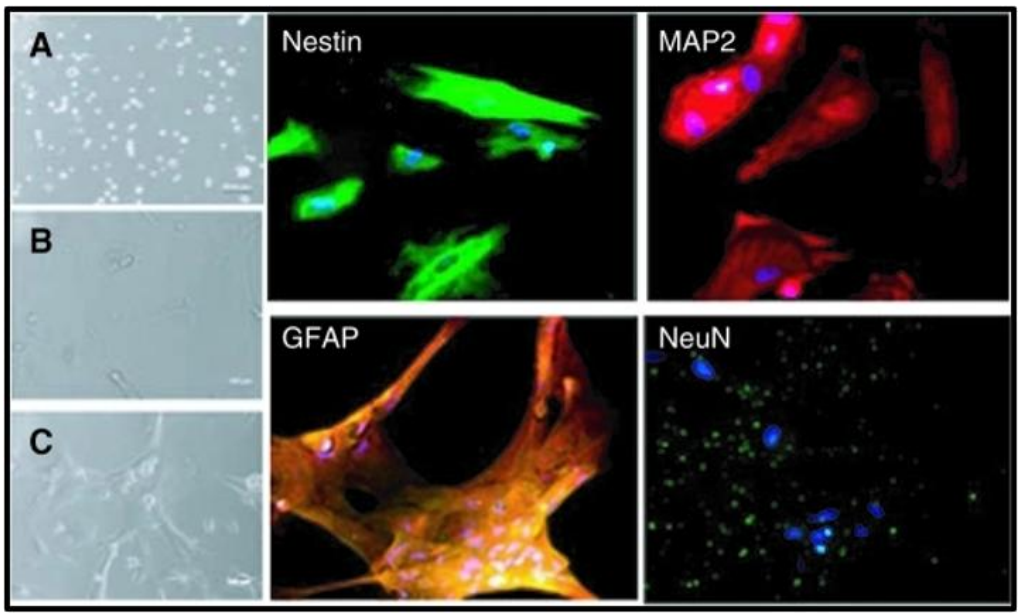

Figure 3: Neural differentiation potential of menstrual blood-derived stem/stromal cells (MenSCs). MenSCs cultured under neural induction conditions exhibit expression of neural-associated markers including Nestin, MAP2, GFAP and NeuN, supporting their reported neurogenic differentiation potential in vitro. (15)

MenSC populations expanded have been shown to have a spindle shape with a fibroblast appearance and the expression of various markers that can be observed on conventional MSC populations. The positive markers identified for MenSC populations include CD29, CD44, CD73, CD90, and CD105 while the negative markers are CD34, CD45, and HLA-DR (3).

However, marker expression only gives limited insights into biological activity. Therefore, functional characterization includes clonogenic analysis, proliferation assay, cell viability, and directed differentiation. Osteogenic and adipogenic differentiation of MenSCs was shown in experiments, while other differentiation potentials, including chondrogenic ones, were observed as well (3). The fact that it is possible to induce lineage-associated marker expression under optimal in vitro conditions does not necessarily mean that the MenSCs regenerate the respective tissues in vivo. Recently, much more attention is paid to the secretory and immunomodulatory potential of MenSCs than to their ability to replace damaged tissues. For instance, secretory potential of MenSCs was shown under hypoxic conditions characteristic of an injured environment (6).

Table 2: Reported phenotypic markers and biological properties of MenSCs

Category	Reported characteristics	Interpretation
Morphology	Spindle-shaped, fibroblast-like adherent cells	Consistent with stromal/MSC-like phenotype
Positive MSC-associated markers	CD29, CD44, CD73, CD90, CD105	Supports mesenchymal stromal-cell identity
Negative/ low markers	CD34, CD45, HLA-DR	Indicates depletion of major hematopoietic/immune populations
Proliferation	High proliferative capacity reported	Supports expansion from relatively small samples
Clonogenicity	Colony-forming populations reported	Indicates proliferative stromal-cell subsets
Differentiation	Osteogenic and adipogenic differentiation; chondrogenic potential reported	Demonstrates mesenchymal differentiation capacity in vitro
Immunomodulation	Modulation of macrophage functional properties	Relevant to inflammatory regulation
Paracrine activity	Bioactive secretome containing soluble and vesicular mediators	Potential mechanism for tissue repair
Hypoxia response	Survival and secretory activity under acute hypoxia	Relevant to injured/wound microenvironments
Extracellular vesicles	MenSC-EVs can influence chondrocyte activity and matrix synthesis in vitro	Supports emerging cell-free regenerative strategies

3.3 Biological properties relevant to biotechnology

MenSCs have several characteristics that make them suitable for regenerative research. Their proliferative capacity permits expansion from relatively small starting samples, although reported growth characteristics vary between donors and protocols. Their clonogenicity and adherent growth support their classification within the

broader stromal-cell framework. Their differentiation potential provides an additional regenerative feature, but the extent and reproducibility of multilineage differentiation remain incompletely established across laboratories. More importantly for tissue repair, MenSCs exhibit substantial immunomodulatory and paracrine activity. Menstrual blood-derived stromal cells can modulate macrophage functional properties, indicating their ability to influence inflammatory microenvironments (5). Their secretome contains soluble mediators and extracellular vesicle-associated factors capable of influencing neighbouring cells. More recently, MenSC-derived extracellular vesicles stimulated chondrocyte activity and cartilage extracellular-matrix synthesis in vitro, providing further evidence that regenerative effects may be mediated through cell-free paracrine mechanisms (8). These findings strengthen the rationale for investigating MenSC-derived secretomes and extracellular vesicles alongside whole-cell therapy.

However, there is not enough evidence for advantage in terms of therapy over the existing MSC sources. In other words, the alleged benefits of MenSCs, especially noninvasive harvesting and high proliferative capacity, have been proven more reliably than enhanced differentiation capacity, increased immunomodulatory capability, or effectiveness of clinical application. Furthermore, the majority of the recent experimental research has taken place either in vitro or in a preclinical setting.

3.4 Sources of heterogeneity and unresolved questions

One of the most serious challenges for the whole field of MenSC is biological and methodological heterogeneity. Donor age, reproductive state, menstrual cycle features, hormonal background, health condition, and donor individual biological heterogeneity may affect the composition of the collected cell population. Collection method and timing will modify the relative numbers of endometrial, blood-derived, epithelial, and immune cells. Culture conditions will exert selective pressure on cells and gradually change their phenotype.

Distinction between MenSCs and isolated endometrial MSCs is also unclear. While the two cell types have similar MSC markers, they cannot be considered the same (6). In addition, the assumption that menstrual blood is a convenient source of cells because it does not require an invasive procedure may cover significant differences in the cell population and regenerative potential (3,4,5). Different sets of markers and different definitions of stemness also complicate comparisons between studies. Thus, the question for the scientific community is not whether MenSCs have regenerative properties; these cells show several features of regenerating tissues in experiments. But whether these properties are reliable, clear, and valuable enough to develop the cell type as a standardized source of regenerating cells is the current question for the researchers to answer.

4. Therapeutic application beyond wound healing

Though wound healing and tissue engineering may be considered the most interesting spheres of application of the menstrual blood-derived stromal/stem cells (MenSCs), there have been some investigations into the use of these properties in several other tissues. It is important to mention, however, that the evidence is not even among different applications. While most investigations have been in vitro or conducted on animals, the human evidence base consists of only reproductive medicine cases. This means that any conclusions about the therapeutic properties of MenSCs should be made depending on the level of evidence.

4.1 Endometrial regeneration and intrauterine adhesions

Menstrual stem cell repair of endometrial tissue can be viewed as one of the most convincing biological applications of MenSCs as these cells come from tissue subject to constant injury, shedding and renewal. The issue

of using MenSCs in intrauterine transplantation as a possible way to repair the injured endometrial tissue has been addressed. One of the investigations has considered intrauterine transplantation of menstrual blood-derived cells from infertile patients for the endometrium repair (16).

More recent experimental studies have further explored MenSCs in relation to endometrial regeneration. For instance, the use of a menstruation-derived stem-cell-based strategy for the repair of thin endometrium and restoration of fertility has been reported (16). These studies show that MenSCs might affect endometrial tissue repair by means of paracrine stimulation of stromal and epithelial cells, modulation of inflammation, angiogenesis and extracellular matrix remodelling. However, differences in the protocols used make comparisons between different studies difficult. Endometrial regeneration thus emerges as one of the most promising fields of MenSC application; however, this therapy has still not become clinical practice.

4.2 Cartilage and musculoskeletal regeneration

The EVs secreted by the MenSCs had their effect on the chondrocytes in inducing the production of cartilage matrix proteins in vitro (8). This study serves as additional support to the hypothesis that paracrine signaling molecules secreted by MenSCs could control the chondrogenic activity without cell engraftment. The limitation of this study is that it is only an in vitro experiment.

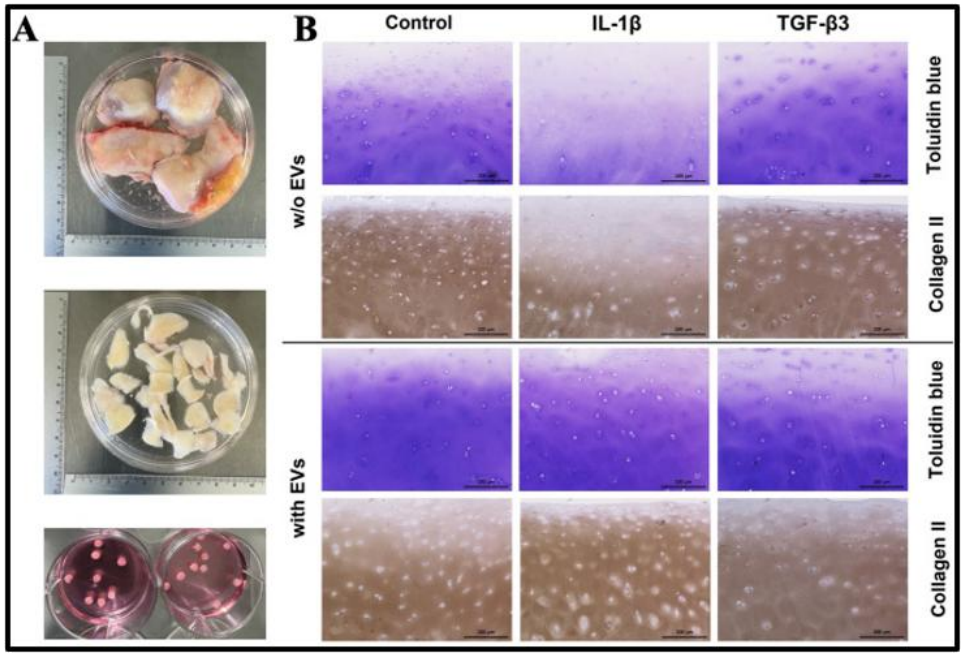

Figure 4. Immunohistochemical/histological sample analysis of cartilage explants, cultured with/without IL-1β (10 ng/mL), TGF-β3 (10 ng/mL) for 7 days and MenSC-EVs for 3 days (8)

Tissue engineering approaches utilizing MenSCs have also been studied, wherein the use of three-dimensional biomaterials is involved. Human MenSCs together with 3D-bioprinted composite scaffolds for spinal cord injury (11). This study is based on the broad concept that MenSCs could serve as the biological component in an engineered microenvironment rather than a freely floating cell suspension.

4.3 Neurological injury

The use of MenSCs in the neurological domain is justified not only by the ability of these cells to replace tissue but also by other evidence. It has been shown that MenSCs derived from menstrual blood decreased

neuroinflammation via M1/M2 macrophage polarization in cellular and rat models of Parkinson's disease (17). This fact is important since it underlines the role of immunomodulatory effects as a possible mechanism for MenSC action. MenSCs do not need to differentiate into neurons to have some influence on the inflammatory environment around the lesioned/ damaged neurons.

However, there are still no clinical studies. Parkinson's disease is a complicated disease including mechanisms such as neuronal loss, neuroinflammation, protein metabolism changes, and neuronal circuit disruption. The modulation of macrophage/microglia polarization can hardly be considered the complete mechanism of MenSC action. Long-term results and safety issues are still unclear.

4.4 Pulmonary injury and fibrosis

Pulmonary damage represents yet another case in which the MenSC effects seem to be achieved via anti-inflammatory and cytoprotective mechanisms. Human menstrual blood-derived stem cells weaken bleomycin-induced pulmonary fibrosis in a mice model (18). Reported effects were due to their anti-apoptotic and anti-inflammatory effects, which suggests that MenSCs can change the pathological tissue microenvironment rather than regenerate damaged pulmonary cells.

This research adds valuable in vivo information but is limited to a chemical model of fibrosis only. The applicability of its results to heterogeneous human fibrotic pulmonary conditions cannot be assured. Furthermore, various cell doses, modes of administration, stability, and production aspects might significantly impact the treatment results. Therefore, although promising, the pulmonary applications of MenSCs are still preclinical.

5. MenSCS IN Personalized and precision regenerative medicine

Precision medicine involves designing a prevention strategy or treatment approach on the basis of biological characteristics of a patient instead of designing a general intervention for all patients. With regard to regenerative medicine, precision medicine can involve selecting a cell source, a cell product, a biomaterial, a dose or delivery mode based on the biological characteristics of a particular patient. Menstrual blood stromal/stem cells (MenSCs) are likely to be very appealing in this context as they can be extracted from a single individual on repeated occasions and possess high levels of proliferation capacity, immunomodulation and paracrine activity. But the idea that MenSCs are already a precision regenerative medicine therapy is largely conceptual since there is no broad evidence available.

5.1 Autologous versus allogeneic approaches

MenSCs present a promising option for autologous therapy in that cells may be easily isolated from the very patient who is going to receive them and then expanded and stored for future use. The use of an autologous approach is expected to minimize the risk of immune compatibility issues. Such an approach would be especially applicable for reproductive purposes, when menstrual-derived cells will target the endometrial environment of the same patient. The feasibility of intrauterine delivery of menstrual-derived cells to patients with endometrial damage or intrauterine adhesions was confirmed experimentally (19,20). Nevertheless, autologous use of menstrual-derived cells cannot always ensure superior and standardized product. The patient-derived cells may be affected by his/her age, reproductive condition, health conditions, medications, or other biological factors. On the other hand, the cells derived from the screened donors will provide ready-to-use product with greater production scalability due to their immunomodulatory properties. Therefore, the question whether to use autologous personalized products or allogeneic standardized products still needs to be resolved.

5.2 Donor and menstrual cycle variability

MenSC biology is prone to donor-related variability. The menstrual cycle features, the hormonal profile, the age, the state of health, and other donor-related variables might have an effect on the number of isolated cells and their physiological condition. Moreover, menstrual blood is a biological substance with heterogeneity, and the differences in its collection and preparation might alter the composition of the isolated cells (3,4). Such issues become critical in the case of precision medicine as the personalization implies measuring the biological parameter for selecting a treatment.

It should also be noted that the age-related and disease-induced alterations might impair the processes of cell growth, secretion, immunomodulation, and differentiation. Therefore, the application of a patient's own MenSCs cannot guarantee their ideal regenerative potential.

5.3 Donor screenings, cell banking and potency testing

A clinically relevant personalized MenSC system would need stringent donor screening, including infectious disease testing, patient history, reproductive and menstrual history, and standardized sampling protocols. For autologous use, menstrual samples might conceivably be obtained, expanded, characterized, and cryopreserved to develop a personalized cell bank for use in treatment in the future.

However, banking alone is not sufficient to make it personalized. Potency testing that can predict the therapeutic efficacy is a must. Traditional surface marker analysis can define the MSC-like characteristics, but offers little in terms of functional potency. MenSC characterization must therefore include proliferative capability, immunomodulation, secretome content, extracellular vesicles, and functional tests of disease-specific relevance (3,6). Potency assays need to be standardized.

5.4 Molecular profiling and omics-based personalization

There is an even more advanced way to develop precise MenSC-based treatment. Using transcriptomics, donor-specific transcriptional signatures of proliferation, angiogenesis, inflammation, extracellular matrix remodeling, or immunomodulation can be identified. In addition, single-cell analysis might distinguish heterogeneous subpopulations within menstrual samples and find out if certain states of cells are linked with their greater regenerative potential.

In the same way, secretome profiling might help to identify donor-specific patterns of cytokines, growth factors, and extracellular-vesicle content. This point is especially important since regeneration induced by MenSCs may rely mainly on the paracrine effect rather than on engraftment of the cells. For instance, hypoxia can affect secretion of MenSCs, indicating that cellular microenvironment changes the therapeutic product (6). Recent research on MenSC-derived secretome and extracellular vesicles highlights the need to study cell-free therapies which might be more controlled (7,8).

However, at the moment, omics profiling is only a research approach, not an established method for choosing MenSC-based therapies. Any transcriptional signature does not have any practical application unless it helps to predict the response to therapy, its efficacy, and safety.

5.5 Patient-specific biomaterials and individualized delivery

Precision regenerative medicine could go beyond selection of cells to engineering of the therapeutic microenvironment. For example, MenSCs could be used in combination with hydrogels, decellularized matrices, or bioprinted structures tailored to their specific biochemical and physical characteristics for a certain tissue. The

concept of tissue-engineering strategies using MenSCs has already been demonstrated experimentally with utilization of decellularized uterine matrices and three-dimensional bioprinted composite scaffolds (10,11). Although such strategies offer the possibility for individualization of biomaterials, they still remain mostly experimental.

Likewise, individualization of treatment based on disease severity could be achieved through individualized cell dose, mode of delivery, treatment schedule, and carrier.

6. Emerging and speculative applications

Evidence therefore can be classified into three categories. Demonstration of personalized applications is not wide: autologous transplantation of menstrual cells has been studied on human uterine disorders, showing evidence that patient-specific MenSC application is possible (19,20). Future research will involve donor-specific potencies, MenSC cell banks, secretome/EV profiles, molecular characterization, and combination with patient-specific biomaterials. In recent times, there has been an in vitro progress in the activities of chondrocytes and formation of extracellular matrix of cartilage for repairing of the cartilage that is considered very promising (8). It will be possible in the future to use MenSC in treating epidermal cells damaged due to UV, burn and chemically induced injuries (21). The study done on the anti-tumour effect of MenSC has shown decrease in the volume and weight of various types of cancer including hepatocellular carcinoma, prostate carcinoma, and squamous carcinoma which may have paracrine interaction with MenSC (22).

Patient/donor
↓
Menstrual blood collection
↓
MenSC isolation and expansion
↓
Phenotypic + molecular characterization
(surface markers | transcriptomics/single-cell analysis | secretome/EV profiling)
↓
Potency and safety assessment
↓
Personalized therapeutic product selection
(whole cells | secretome | EVs)
↓
Patient-/tissue-specific biomaterial and delivery selection
↓
Individualized dose and administration strategy
↓
Treatment
↓
Clinical and molecular monitoring
↓
Therapy adjustment / repeat treatment

7. Conclusion

Mesenchymal stem/stromal cells isolated from menstrual blood (MenSCs) represent a promising candidate for regenerative medicine due to their unique attributes such as non-invasive and periodical availability, proliferation capacity, mesenchymal stromal features, and potent immunomodulatory and paracrine properties. In various preclinical models, MenSCs and their progeny have proven their capacity to modulate tissue repair processes associated with inflammatory modulation, angiogenesis, cell proliferation, extracellular matrix remodeling, and specific tissue regeneration. Moreover, the use of MenSCs as components of hydrogel, decellularized matrix, three-dimensional bioprinted materials, and other biomaterial constructs increases their potential in tissue engineering. New data on MenSC secretome and extracellular vesicles imply that regenerative effects can be obtained independently from prolonged cell engraftment.

However, current evidence should be carefully interpreted. It is premature to consider MenSCs as a homogeneous and intrinsically better alternative to existing sources of MSCs. Moreover, even though there are encouraging results regarding applications for endometrium, musculoskeletal system, nervous system, lungs, and wound healing, most of the data obtained up until now remains preclinical; clinical trials are still rare and heterogeneous. The next step of the research on MenSCs should focus on standardization and translational validation, not just increasing the number of reported applications. Standardized manufacturing processes, stratification of donors, quantitative potency testing, mechanism of action investigation, biodistribution, safety, long-term assessment, and appropriately designed controlled clinical trials will be critical to prove reproducible efficacy of this therapy. On the other hand, the use of MenSCs together with extracellular vesicles, secretome, advanced biomaterials, 3D bioprinting technology, and omics-based characterization can lead to creation of more efficient and precise approaches. But again, it should be done within the framework of comparison to existing sources of MSCs and relevant clinical controls.

Ultimately, the value of MenSCs in regenerative medicine will come down to whether or not their biological properties, which have been shown in experimental research studies, are translatable to clinical success. As it stands now, MenSCs should be considered an interesting, but experimental, form of regenerative cell therapy. The journey from their current status to becoming something that is clinically viable will involve several factors such as robust biological characterization, reproducible manufacturing, accurate potency assessment, scientific understanding, and good clinical research. Through all of these steps, MenSCs, along with their cell-free analogues, may become a valuable part of future regenerative and precision-medicine platforms.

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