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Received 17 May 2024.
Revised 20 May 2024.
Accepted 25 May 2024.
Published Online 01 June 2024

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The Promising Horizon of Menstrual Blood Stem Cell Banking

Abstract— Menstrual Blood-Derived Stem Cells (MenSCs) have emerged as an innovative and promising source of mesenchymal stem cells (MSCs) with substantial potential in regenerative medicine. Their capacity to differentiate into a variety of cell types opens new therapeutic possibilities for previously untreatable conditions. MenSCs are distinct from traditional stem cell sources due to their non-invasive collection methods and recurring availability during menstrual cycles. This review highlights the therapeutic potential of MenSCs and discusses menstrual blood banking, which aligns with global trends and offers a sustainable, ethically sound source of biological material for advanced medical therapies. Clinical applications of MenSCs are actively being explored, demonstrating their versatility and therapeutic value. However, establishing MenSC banking involves several critical considerations, including standardizing collection and isolation procedures, ensuring donor safety, and maintaining stem cell quality. Ethical considerations, particularly within Islamic contexts, are also essential. Successful integration into clinical practice requires overcoming standardization challenges and addressing ethical considerations across diverse cultural contexts.

Keywords**: Menstrual blood-derived stem cells, mesenchymal stem cells, stem cell banking, therapeutics value.**

1 INTRODUCTION

In recent years, there has been an unparalleled interest surge within the scientific community regarding the diverse applications of stem cells derived from menstrual blood, prompting considerable exploration of menstrual blood banking feasibility. These stem cells, known as Menstrual blood-derived stem cells (MenSCs), have showcased multifaceted capabilities that hold the potential to revolutionize treatments across various medical disciplines.

MenSCs, emerging as a novel source of mesenchymal stem cells (MSCs), have demonstrated significant differentiation capacity into a wide spectrum of cell types showing promise, and offering prospects for regenerative therapies capable of tissue repair and potentially addressing previously untreatable ailments (1). The appeal of MenSCs lies in their accessibility, facilitated by a non-invasive collection method, and the recurring opportunities for collection during menstrual cycles, setting them apart from conventional sources of stem cells (2). This trajectory is substantiated by its therapeutic potential for regenerative medicine applications, including skin repair and dermatological conditions (3).

The evolving global perspective on menstrual health underscores the significance of innovative approaches in managing and utilizing menstrual by-products. Menstrual blood banking not only aligns with these evolving trends but also presents a sustainable, ethically sound source of biological material for cutting-edge medical therapies (4, 5, 6). As exploration into the capabilities and applications of MenSCs progresses, the horizon of menstrual blood banking appears promising, heralding a new era of personalized and regenerative medicine. This burgeoning field has the potential to transform approaches to disease treatment and tissue repair, making it an area of research and investment brimming with excitement for the foreseeable future.

MenSCs represent a valuable resource for regenerative medicine due to their unique properties. They offer advantages such as non-invasive collection methods, high proliferation rates, pluripotency, and low immunogenicity. Extensive research has characterized MenSCs, identifying various surface molecules indicative of MSCs, while also noting their negative expression of hematopoietic stem cell markers (1, 7).

MenSCs share phenotypic similarities with bone marrow-derived MSCs, including spindle-shaped morphology, classical three-line differentiation, and surface marker expression. Their robust proliferation and broad differentiation capacity render them suitable for diverse therapeutic applications (Figure 1), ranging from endothelial and cardiomyocytic to neurocytic and osteogenic differentiation.

Moreover, MenSCs exhibit immunomodulatory properties attributed to their exposure to cyclic menstruation and inflammatory signaling. They have been shown to affect both innate and specific immune responses despite disparities between *in vitro* and *in vivo* findings (1, 3).

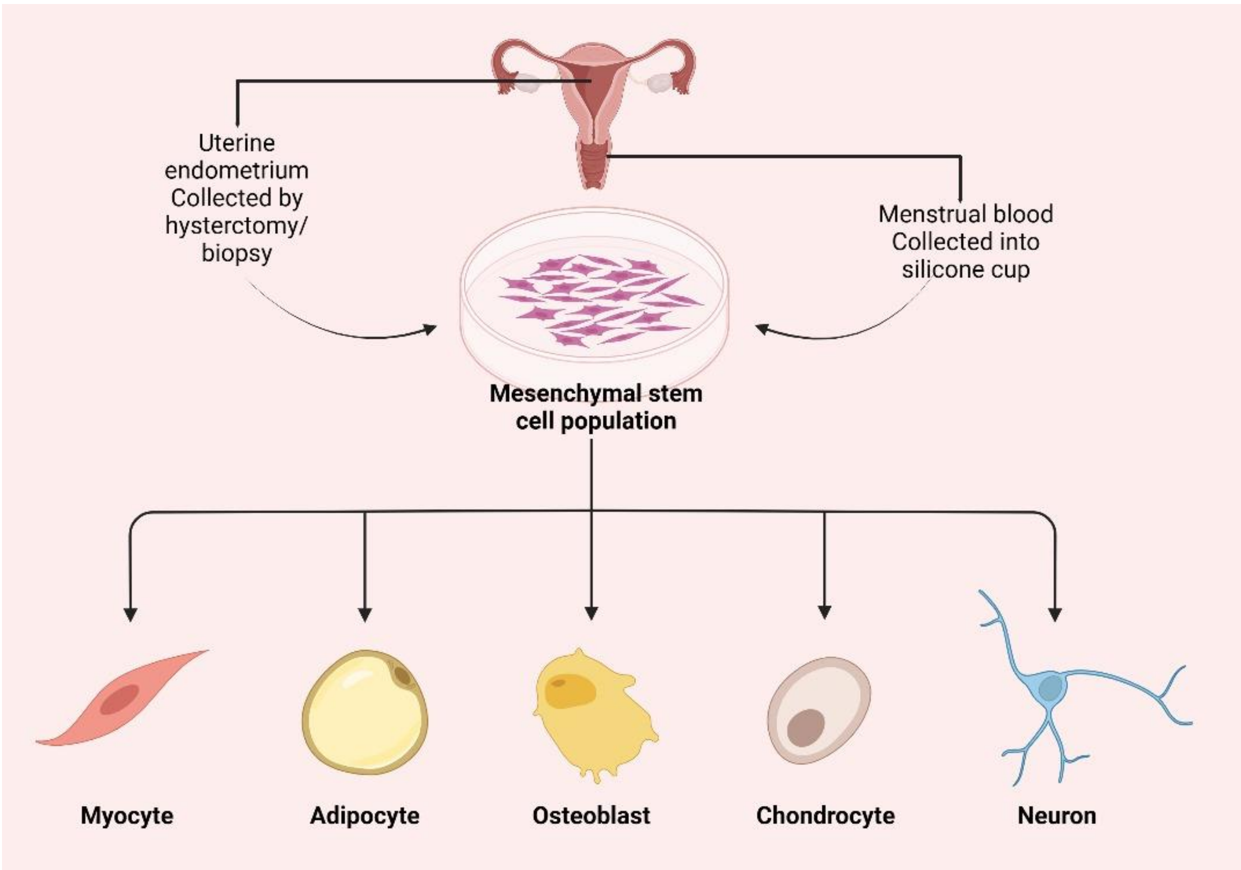

Figure 1: Isolation and culturing strategies of Menstrual Blood-Derived Stem Cells (MenSCs) and their potential to differentiate into various cell types and tissues.

Recent attention has focused on the paracrine effects of MenSCs, particularly through the secretion of extracellular vesicles (EVs) like exosomes. These EVs carry bioactive molecules, including proteins and microRNAs, which contribute to tissue repair and regeneration. *In vivo* studies have underscored the reparative properties of MenSCs, primarily attributed to their paracrine effects rather than their ability to directly differentiate and integrate into tissues. EVs are lipid-bound particles released by cells into the extracellular space, manifesting primarily as exosomes, microvesicles, and apoptotic bodies. These vesicles serve as carriers for bioactive molecules such as proteins, lipids, and nucleic acids, facilitating intercellular communication by transporting their cargo to recipient cells. Integral to various cellular processes including immune responses and coagulation, EVs also participate in the conveyance of DNA and RNA, thereby influencing cellular functions and signaling pathways. In essence, extracellular vesicles play indispensable roles as mediators of cell-cell communication, exhibiting diverse functions across both physiological and pathological conditions (8).

Despite their promise, challenges remain in standardizing MenSC isolation and characterization, including donor variability and procedural differences. Addressing these challenges will be crucial in fully realizing the therapeutic potential of MenSCs in regenerative medicine. Our group has shown that MenSCs have a promising therapeutic potential in various disease models, including type 1 diabetes (T1D) (9) and Parkinson's disease (PD) (10). In T1D mouse models, MenSC transplantation improved symptoms and exerted protective effects on main organs, likely through angiogenesis, antiapoptotic effects, and immunomodulation suggesting MenSCs as promising seeding cells for clinical diabetic treatment. Similarly, in PD models, our group has demonstrated that MenSC-conditioned medium (CM) has protective effects against cytotoxicity induced by MPP+, a neurotoxin (10). Our study has shown that MenSCs released multiple neurotrophic factors, potentially contributing to the therapeutic function of MenSC-CM in treating PD highlighting MenSCs potential in neurodegenerative disease therapy. A study demonstrated that MenSCs provide protection to co-cultured primary neurons subjected to experimental *in vitro* stroke. More importantly, transplanting these stem cells, either directly into the brain or peripherally, ameliorated stroke-induced behavioral and histological deficits (11). These significant effects make MenSCs a promising option for early cell therapy in stroke treatment.

It has also been reported that autologous MenSCs can aid in the recovery of damaged endometrium and improve infertility in patients with refractory intrauterine adhesion (7). MenSCs treatment significantly promoted angiogenesis in the injured endometrium by enhancing the proliferation and anti-apoptotic capacity of endometrial cells, likely through the activation of the PI3K/Akt signaling pathway. Additionally, MenSCs treatment significantly improved pregnancy rates and increased the number of embryos in pregnant mice (12).

In a clinical case study involving a COVID-19 patient with severe pulmonary injury caused by an inflammatory response, glucocorticoid, antiviral, and antibiotic therapies were withdrawn due to side effects, and MenSC therapy was proposed as an alternative (13). These properties of MenSCs indicate their ability to regulate the inflammatory response, thereby reducing the severe cytokine storm associated with COVID-19 and restoring the normal function of immune cells and tissues, which in turn improves breathing patterns. Their homing potential allows MenSCs to enhance the repair capabilities of immune and other cells, facilitating the reconstruction of damaged tissues through receptor-mediated interactions (13).

Furthermore, MenSC-EVs showed efficacy comparable to MenSC transplantation in protecting against acute lung injury (ALI) in a mice model. In the mice model of ALI, our group has demonstrated that the therapeutic potency of MenSC-EVs was attributed to their functional miRNA content, particularly miR-671-5p targeting AAK1, suggesting a potential strategy for pulmonary inflammatory disorders (14). However, the increasing trend of utilizing stem cell secretomes in place of transplantation raises concerns, as it may lead to interventions without sufficient supporting data, posing risks to patients and credibility challenges in the field.

To facilitate the clinical application of MenSCs, considerations must include factors from production to evaluation, such as cell dosage, delivery route, and efficacy assessment. Optimal storage conditions, like nonfreezing low temperature with human serum albumin supplementation, can maintain MenSC viability and support their extensive clinical application (15). Additionally, ensuring MenSC quality is crucial, particularly in patients with autoimmune diseases, where abnormalities in MSC function may exist. Cryopreservation of MenSCs from younger, healthy donors may optimize therapeutic outcomes, especially for those at high risk of disease. However, further experimental studies and clinical trials are needed to validate MenSC cryopreservation protocols and their efficacy in treating various conditions.

Establishing Menstrual Blood Stem Cell Banking for Clinical Use: Considerations and Challenges

Establishing menstrual blood stem cell banking for clinical applications presents several considerations and challenges that necessitate careful examination of various factors, including collection procedures, stem cell heterogeneity, safety measures, donor age, stem cell quality, and quality control protocols. Addressing these challenges is vital to fully harnessing the therapeutic potential of MenSC-based therapies and facilitating their widespread clinical application. Optimizing collection procedures is essential to ensure the reliability and consistency of MenSCs obtained for banking. Standardized protocols for menstrual blood collection, processing, and isolation of MenSCs are crucial to minimize variability between samples and ensure reproducibility. MenSCs exhibit inherent heterogeneity influenced by various factors such as donor characteristics, hormonal status, and environmental conditions. Understanding and characterizing this heterogeneity is essential for establishing banking protocols that accommodate variability in MenSC properties and functions.

Furthermore, ensuring the safety of MenSCs for clinical use entails rigorous screening of donors to prevent the transmission of infectious diseases. Implementation of standardized testing procedures and adherence to regulatory guidelines are imperative to mitigate potential risks associated with disease transmission. The age of MenSC donors can impact the quality and regenerative potential of harvested cells. Strategies to address age-related changes in MenSC properties, such as optimizing isolation techniques and culture conditions, are essential for maintaining stem cell quality and efficacy in therapeutic applications. Implementing robust quality control measures throughout the banking process is essential to guarantee the safety, purity, and potency of MenSCs for patient use. Comprehensive quality assessments, including cell viability, phenotypic characterization, and functional assays, are necessary to ensure the integrity of stored MenSCs. While a standardized protocol for MenSC banking is currently unavailable, the guidelines for such banking operations should adhere to the Malaysian National Standards for Cord Blood Banking and Transplantation, with the exception of blood collection procedures. Nevertheless, for the characterization process, adherence to the international standard for MSC characterization set forth by the International Consortium of the International Society for Cell Therapy is imperative.

The literature on stem cell ethics in Malaysia highlights valid concerns that necessitate proactive theological discourse to inform decisions regarding various aspects of stem cell technology, including research methodologies, regulation, policy development, and legislation. There are two main sources of stem cells: adult stem cells and embryonic stem cells. The Islamic perspective on the use of stem cells is closely tied to their source and purpose. Consequently, there are differing fatwas regarding the permissibility of obtaining adult versus embryonic stem cells. Islamic contemporary scholars unanimously agree on the necessity of using adult stem cells for research and therapeutic purposes in patients requiring treatment for various diseases. However, they hold divergent views on the permissibility of obtaining embryonic stem cells. Different views also arise depending on whether embryonic stem cells are derived from aborted embryos or those fertilized *in vitro*. This disagreement stems from contrasting interpretations among scholars of the four Islamic schools of thought regarding the legal status of a miscarriage fetus before 40 days of completion. The debate hinges on the concept of ensoulment, which, according to the Hadith of Prophet Mohammed (PBUH), occurs 120 days after conception. Until ensoulment, the human embryo is not considered a person.

To understand the Islamic perspective on the use of (MenSCs) for therapeutic purposes, we must first consider the broader Islamic view on menstrual blood. In Islam, menstrual blood is regarded as impure, and women during menstruation are prohibited from performing prayers and fasting. This raises the question: how does Islam view MenSCs, given their origin in menstrual blood? Despite being derived from an impure source, MenSCs undergo a purification process to isolate the stem cells for therapeutic use.

In Islam, sources deemed "shubhah" (doubtful) or impure can be used in cases of "dharurat" (necessity), especially for medical reasons where they can save lives. The critical question is whether MenSCs are indispensable for therapeutic purposes, or if other stem cell sources, such as cord blood, dental pulp, and adipose-derived stem cells, can suffice. These alternatives are readily available and can be banked for future personalized treatments, thus potentially mitigating the need to rely on MenSCs.

Therefore, while MenSCs offer significant therapeutic potential, the availability of other stem cell sources provides viable options, particularly for those who adhere to Islamic guidelines. For Muslims, this means considering the religious implications of MenSC use and exploring alternative sources that align with their beliefs.

However, for individuals not bound by Islamic regulations, MenSCs present a feasible option for stem cell banking. This is particularly beneficial for those unable to bank cord blood or who are beyond childbearing age, offering a method to secure stem cells for future medical needs. Thus, MenSCs represent a valuable option in clinical medicine, especially for those seeking alternative sources of stem cells for therapeutic purposes.

2 CONCLUSION

In conclusion, the burgeoning interest in MenSCs underscores their potential to revolutionize regenerative medicine. Their unique properties, including non-invasive collection methods, high proliferation rates, and broad differentiation capacity, position them as a promising alternative to traditional stem cell sources. MenSCs show significant therapeutic promise across various medical disciplines, not limited to skin repair, neurodegenerative diseases, and autoimmune conditions. As research and clinical applications advance, the establishment of standardized protocols for menstrual blood banking and addressing ethical considerations, especially within diverse cultural contexts, will be critical. The integration of MenSCs into clinical practice holds the potential to transform treatment approaches and enhance personalized medicine, making it an exciting field of research and development for the foreseeable future.

ACKNOWLEDGEMENT

The author extends their gratitude to Universiti Sains Malaysia for supporting the Breast Cancer Translational Research Program (BCTRP@IPPT) through the Top-down Research University Grant Scheme, under the grant code 1001/CIPPT/8070033.

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