Endometrium-derived menstrual stem cells as a potential source of adult stem cells for organoid development.

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Stem cells are critical in a lot of medical applications these days because of their high proliferative capacity and self-renewal characteristics. There are many sources for adult stem cells such as the embryo and bone marrow. However the stem cell acquisition from bone marrow is not only invasive but also painful while embryonic stem cell acquisition has ethical issues. In order to circumvent such hurdles the endometrium-derived menstrual stem cells (MnSc) were chosen as a potential source of adult stem cells for organoid development. MnScs can be obtained from volunteers in a non-invasive method and have been previously shown to have differentiation capabilities although not as efficiently as the embryonic stem cells. In this study, the MnScs will be used to develop organoids that have a plethora of medical applications.

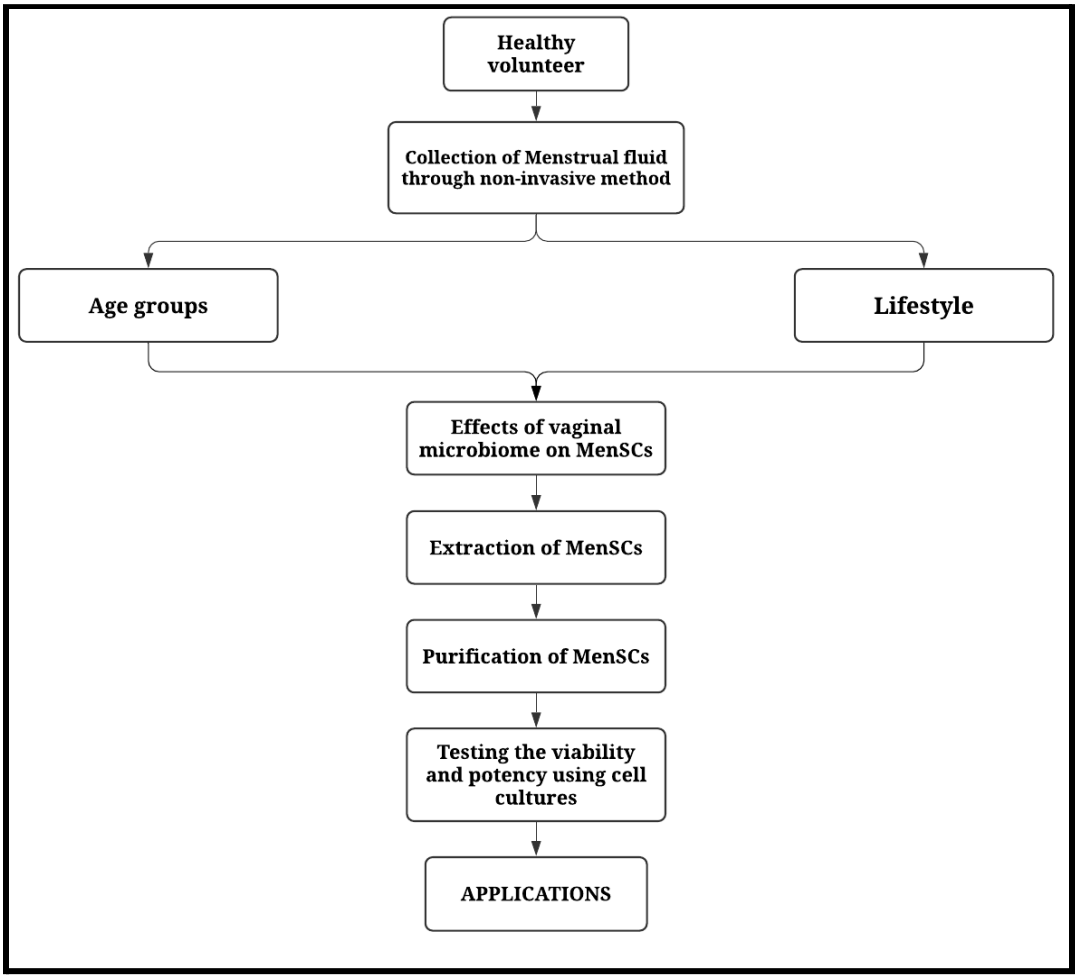

Figure 1. Flowchart representing the proposed methodology for collection, extraction, purification and differentiation of MnScs.

Among the types of stem cells discovered till date the embryonic stem cells (ESc) have the highest potency. During embryonic development they differentiate to form other cells in the body. Using EScs can help to treat a wide range of disorders such as diabetes, heart malfunctions, etc. (1-3) and also to study genetic disorders by designing proper organoid models *in vitro*. However the usage of EScs is restricted due to ethical issues because human embryos are needed to extract EScs. Induced pluripotent stem cells (iPSc) are normal somatic human cells which are induced to become pluripotent. The iPScs are widely studied to understand their pluripotent characteristics as an alternative to the EScs. Whether one prefers to use the EScs or iPScs, they are prone to the host immune responses and may get rejected (4). Additionally, these cells might be genetically unstable if not stored properly suggesting that there is still a lot more research to be done before fully approving them for regular medical usage in order to avoid any unforeseen malfunctions.

Stem cells that are differentiated to give rise to cells of specific lineage are called multipotent stem cells. These multipotent stem cells present in our body are indicated as adult stem cells. They are mostly involved in regenerating damaged tissue and maintaining homeostasis by replacing the dying cells (5). The best sources for these stem cells include bone marrow and other sources like placenta, umbilical cord, lung, adipose tissue, etc. (5). However, acquisition from bone marrow is invasive and is thus generally not preferred. Extraction of stem cells from other sources is also restricted, such as storage of umbilical cord is not available and allowed at all places. On the other hand, the treatment using stem cells from these sources is not affordable for many people.

Recently it has been found that the mesenchymal stem cells are also present in menstrual fluid (6). Compared to the other sources the endometrium-derived menstrual stem cells (MnScs) have less ethical concerns because they can be non-invasively extracted. They are tested positive for embryonic stem cell marker octamer binding transcription factor 4 (OCT-4), major histocompatibility complex 1 (MHC 1), and MSC surface markers like CD29, CD73, CD90. *In vitro* analysis of MnScs revealed that they are highly proliferative and genetically stable (7, 8). A study on their therapeutic effects revealed that they are capable of differentiation and immunomodulation via interaction with different immune cells (9). However, this research so far is not enough to make use of them when compared to the research done on the applications of stem cells from other sources. As the main focus of our project, menstrual fluid will be collected from healthy volunteers through a non-invasive method. Collection of menstrual fluid samples will be based on these two variables (lifestyle and age) followed by analysis of vaginal microbiome effects on MnScs. When endometrium ruptures blood along with ruptured tissue passes through vagina and hence vaginal secretions also are a part of menstrual fluid. Vaginal microbiome is composed of various microorganisms. Our approach also integrates studies on effects of the vaginal microbiome on MnScs. These analyses on the samples collected will be followed by extraction of stem cells, purification and testing for viability. We hypothesize that this approach can help us to get a clear understanding of their potency for organoid development.

Currently, we are in the process of analyzing the feasibility of using MnScs for the development of organoids that have multiple medical applications. The ongoing and upcoming research on MnScs will be published in the future issues of TCABSE-J.

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Conflict of interest: The strategic communication presented here is an ongoing project currently at TCABS-E, Rajahmun--dry, India. The authors invite collaborations without any conflict of interest.