Menstrual Blood Stem Cells — Promising Future?

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Rose is waiting outside her doctor’s office. She had already walked back and forth five times in the long iodoform-smelling hospital corridor when the doctor summoned her in.

She has liver fibrosis, a disease where the liver tissue responds to wound or injury by secreting an excess of molecules that provide the physical and biochemical structure to cells. This causes the tissue to harden leading to morbidity and liver failure. Her treatment option is liver transplant, which would involve finding the elusive right donor and surviving on drugs that would suppress her immune system. Stem cell therapy is an alternate strategy she can adopt. Apart from replenishing damaged cells and tissues, stem cells also have another trick up their sleeve. They can modulate our immune system by releasing molecules that regulate our immune response.

Bone marrow is currently the most common source of mesenchymal stem cells. However to extract it, Rose will have to undergo a painful and invasive operation where a special needle will be placed in the marrow cavity of the hip bone, and two or three punctures in the bone will be made in order to aspirate stem cells and blood. She may have soreness and persistent pain for a week or more after the extraction. Also, not all studies show positive results with the use of bone marrow stem cells. So, she wants to seek out alternative sources of mesenchymal stem cells. This is where menstrual stem cells — stem cells discovered in the menstrual blood — step in.

Menstrual blood has always been in the news for all the wrong reasons: it is considered impure and even talking about it is taboo across several religions and cultures. It has been pronounced invisible and non-existent in a patriarchal world, unless it surfaces — shamefully and mistakenly — as spots, patches, and smears on women’s clothing.

Ironically, this ‘bad blood’ was shown to have an unexpected life-giving resource by researchers in 2007 — stem cells. Xiaolong Meng and his colleagues at Bio-Communications Research Institute, Wichita, USA collected menstrual blood in a urine cup from a healthy menstruating woman. When they isolated and grew the cells from it, they found that these cells had an incredible rate of doubling — every 19.2 hours. This was 2–3 times faster than the normal cells. They also came upon a remarkable trait — it expressed OCT-4, a protein frequently used to identify and mark embryonic stem cells. Had they stumbled upon a new and unheard-of source of stem cells?
These studies were just the beginning. Just three months after the published report of stem cells in menstrual blood and endometrium, Amit Patel and his colleagues at the University of Pittsburgh, US published another study where they not only tested the cloning potential of these cells from the menstrual blood, but also coaxed them in to bone, neuron, heart, and fat cells.

Are Menstrual Stem Cells Better

Collection of menstrual stem cells is as convenient as collecting menstrual blood from the first few days of the menstrual cycle in a medical-grade silicon cup. The cup is kept in place for three hours, and then the blood transferring to a tube with buffer and antibiotics. From this collection, stem cells can be isolated as these cells have higher density than the other cells.

How often can it be collected? An average woman bleeds once a month, 400-500 times in her total lifetime. But with all its ease of access and collection, are these cells as potent as bone-marrow stem cells - the current reigning choice of stem cells for therapeutics?

Alcayaga-Miranda and her colleagues in the Laboratory of Nano-Regenerative Medicine, Universidad de Los Andes, Santiago, Chile tested just that. They compared how well these cells compare to the extensively studied and applied bone marrow stem cells. They compared several properties between the two types of stem cells – self-renewal capacity, how many different cell types can they be coaxed into (differential potential), and their migration capacity.

Self-renewal was measured by assessing by how well it can multiply (or proliferate). Stem cells often gravitate towards injury or wound to assist in replenishing the pool of dead/injured cells in the tissue. This behavior can be quantified via a simple experiment where a petri dish plated with cells is scratched with the tip of a pipette, and the number of cells that migrate back in to the scratch area is measured.

Alcayaga-Miranda found that stem cells isolated from menstrual blood had 3.5 times better self-renewal capacity, and they also performed better on the migration capacity assay than bone marrow stem cells. Both bone marrow and menstrual stem cells could be induced to form liver, bone, cartilage cells with equal potential.

“Menstrual blood stem cells and eMSCs are derived from a tissue that is regenerating every month – they are primed to proliferate and regenerate tissue as a primary function, in contrast to bone marrow stem cells,” states Dr. Gargett. Thus, on all counts, menstrual stem cells seem to be on par with the bone marrow derived stem cells: they can be easily collected and have equal potency as bone-marrow stem cells.

There is another crucial limitation of a method where only a single sample can be collected at a time, as in the case of bone marrow. With each division cycle, the stem cells have reduced potency to multiply and form different cell types. Thus, with time, collected stem cells have reduced potential to have therapeutic effects. This is where a periodic sample collection, as in menstrual blood, can maintain the high therapeutic action of stem cells.

So why haven’t researchers started exploring the wonders of these stem cells in diseases and injuries? Well, they have.
What were your clues to start looking for the presence of endometrial stem/progenitor cells in human endometrium?

Caroline Gargett: My PhD was in the field of Haematology, studying leukemic lymphocytes. But when my PhD supervisor moved to Sydney, I commenced at Monash University Department of Obstetrics and Gynaecology as a postdoctoral scientist. I learnt from my supervisor how most (two thirds) the endometrium is shed at menstruation and that there is a basal layer that remains. From this a new functional layer of endometrium grows each menstrual cycle. With my haemopoietic stem cell knowledge, it was very easy to consider that endometrial stem/progenitor cells would be present in the basal non-shed layer of human endometrium and that they would contribute to monthly endometrial regeneration. In fact I was surprised that this hadn’t really been considered before (apart from one scientist 10-15 years earlier, but had not known how to demonstrate this and then moved out of science soon after). I developed this concept to understand why some women get endometriosis while others do not.

Would you say that endometrial stem cells are on par with bmMSCs as a therapeutic agent?

Caroline Gargett: They may be even better than bmMSCs. We have started some comparative studies (still unpublished) and we show endometrial MSCs (eMSCs) are more proliferative and clonogenic. But we believe eMSCs have great potential clinically because they are derived from a tissue in non-invasive manner by biopsy, which does not require an anaesthetic or from menstrual blood; derived from a tissue that is regenerating every month; easy to isolate from endometrial tissue; and easy to culture in serum-containing and serum-free medium.

Endometrial stem cells have been coaxed into a variety of cell types, including adipocytes, osteocytes, chondrocytes, and even neuronal lineages. Where do you think lies its maximum therapeutic potential?

Caroline Gargett: I believe that bmMSC are superior in therapeutic potential for generating adipocytes, osteocytes and chondrocytes as these are the lineages these cells normally make and there is likely some genetic memory of origin retained by these cells.

There are also enough women’s reproductive health issues that would benefit from an eMSC cell-based therapy. One of the major ones is a condition called Asherman’s syndrome, where the endometrium has been replaced with scar tissue. These women cannot get pregnant or carry their own baby. Surrogacy is the only option. I believe they could be treated with endometrial stem/progenitor cells.

It is also possible that endogenous eMSC could be activated in some way for women suffering from thin endometrium – ie endometrium that does not grow thick enough for an embryo to implant. Also in older women who use donor eggs as their ovaries are no longer functional – the endometrium in these women can be thinner as well.

We are exploiting the regenerative and reparative capacity of eMSCs to treat a very common disorder, pelvic organ prolapse (POP. This would be a huge market in comparison to the above women’s reproductive health needs.
Can Menstrual Stem Cells Treat Diseases?

Mice ferreted around restlessly in their dark cages in the Institute of Cell and Development, Zhejiang Institute, China. They had been injected with CCl₄ twice a week for the past four weeks, which has induced liver fibrosis in them – the same disease from which Rose suffers. Lu Chen and his co-workers used these mice as a model system to study liver fibrosis.

They injected saline (control group) or menstrual stem cells in the tail-vein of these mice suffering from liver fibrosis. They euthanized these mice one or two weeks after transplantation and harvested their livers to study it. Two weeks after transplantation, the levels of extracellular proteins – whose excess causes liver fibrosis – was significantly reduced in mice with menstrual stem cells compared with mice injected with buffer. Liver function, analysed by the levels of liver enzymes, also improved in mice injected with menstrual stem cells.

One of the hallmarks to repair injury using stem cells involves their migration to the specific sites of damage or wound. To test if menstrual stem cells could also perform this feat, Chen and colleagues transplanted menstrual stem cells with a fluorescent protein to track them in normal mice and in mice with fibrotic livers. Indeed, they found that the fluorescent cells (i.e. menstrual stem cells) were present more in fibrotic livers compared with normal livers. Thus, menstrual stem cells can selectively migrate to regions of damage or injury and regenerate or repair the tissues.

Treating Humans?

47-year-old Theresa was diagnosed with multiple sclerosis in 2000. After suffering from extreme pain in the left arm and right leg, fatigue, and impaired mobility from the medication, she looked for non-conventional modes of treatment and stumbled upon menstrual stem cells in 2006. She presented herself to The Second Xiangya Hospital, Central South University, Changsha, PR China in 2007.

The doctors explained the experimental nature of the strategy and injected her intravenously with 3 million menstrual stem cells on days 1, 3, and 4. She did not experience any adverse effects at the time of stem cell administration. One year later she came back for a follow-up examination and additional stem cell treatment. Physical exam, chest X-ray, complete blood count, serum biochemistry was done – none of them showed any abnormalities. Till the last reported study, she did not suffer from any notable adverse events.

Several reproductive health issues in women would benefit from an endometrial or menstrual blood stem cell-based therapy. One such condition is Asherman’s syndrome, where the endometrium is replaced with scar tissue. These women cannot get pregnant or carry their own baby. Surrogacy is the only option.

According to Dr. Gargett, such conditions “could be treated with endometrial stem/progenitor cells in decellularised endometrial scaffolds for regenerating sufficient endometrial tissue for implanting an embryo. This work is still in conceptual stage for several groups.”

This could also be employed in women suffering from thin endometrium – i.e. endometrium that does not grow thick enough for an embryo to implant. Dr. Gargett’s Lab has recently used eMSCs to treat pelvic organ prolapse (POP), a very common disorder where vaginal tissues herniate as a result of childbirth injury and intensify due to ageing. This condition affects 25% of all women.

However, menstrual/endometrial stem cells have still not attained the mainstream stem cell therapy status. “A primary limitation of these studies has been that the ‘stem cells’ were derived from cultured menstrual blood without any purification step for selecting the clonogenic population. Thus, the cultures are a mix of stem cells (in the minority) and fibroblasts or stromal cells, which reduces their potential. Also, only women have eMSCs and menstrual blood stem cells, but they could be used allogeneically – in genetically similar (sibling or a parent) or an unrelated individual.

Pre-clinical trials and preliminary studies have indicated that these stem cells are safe to administer allogeneically. Another limitation is the lack of knowledge about endometrium and eMSCs in the mainstream adult stem cell biology field, states Dr. Gargett.

While there is a long way for these stem cells to become a conventional stem cell therapy, hundreds of thousands of people like Rose are undergoing painful, invasive, and debilitating bone marrow harvest and organ transplants every year for therapeutic purposes. They are plagued by stressful search of finding the right donor at the right time, and battling with medications and draining post-surgery trauma.

For such people, these studies may indicate light at the end of the tunnel where the menstrual blood can be a practical, accessible, non-invasive, and painless way of obtaining stem cell therapy.