Fetal microchimerism and beyond: a new player in regenerative medicine

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Received: December 14, 2022.
Accepted: January 10, 2023.
Early view: January 26, 2023.

https://doi.org/10.3324/haematol.2022.282244

Fetal cells in the maternal circulation have been studied for the last 30 years.[1] They have contributed to developing the non-invasive prenatal diagnosis of congenital disorders in an unborn fetus.[2] In addition, we know that fetal cells, particularly stem cells, can be used in regenerative medicine, and their potential is enormous.[3,4] For example, they can be used to treat a myocardial injury, engraft the haematopoietic system when injected *in utero*, and improve the clinical status in a rat model of necrotizing enterocolitis[3] (Figure 1).

In their article, published in this issue of *Haematologica*; Alkobtawi *et al.*[5] demonstrate that these cells are functional, *in vivo*, and contribute to healing ulcers in a disease setting, such as sickle cell disease (SCD). Fetal microchimeric cells (low levels of fetal cells in the maternal circulation) are potent contributors to maternal wound healing, even postnatally.[5] These fetal cells can differentiate into leukocytes and endothelial cells, thus contributing to the healing of ulcers. This is not surprising since amniotic fluid stem cells can accelerate wound healing by enhancing re-epithelialization and reducing scarring.[5] It has previously been shown, by some of the same authors, that ccl2/ccr2 signaling is responsible for the recruitment of fetal cells in maternal wound healing.[6] Injections of Ccr2 enhance wound healing in pregnant or postpartum mice but not in virgins. This study showed that fetal microchimeric cells could be selectively recruited using Ccr2 injections into maternal injured tissue.[6] The study is critical because it opens the doors for developing potential therapies using fetal stem cells, by *in vivo* recruitment, or postnatally since they can also be easily obtained at delivery by processing the placenta and placental membranes.[7] They can also be stored in a biobank for future use (Figure 1). The study's findings can be expanded to other skin conditions, such as epidermolysis bullosa.[5] In a clinical trial, infusion of allogeneic fetal cord mesenchymal stem cells was found to be safe and had transient clinical benefits in patients with epidermolysis bullosa.[8] It would be interesting to see if fetal cells contribute to the maternal haematopoietic niche and how they can affect ineffective erythropoiesis, a newly highlighted mechanism in SCD.[9] Ineffective erythropoiesis in SCD is accompanied by apoptosis of differentiating erythroblasts between the polychromatic and orthochromatic stages.[9] El Hoss *et al.* have demonstrated that fetal haemoglobin, produced by fetal haemoglobin-containing cells (F-cells), decreases ineffective erythropoiesis[9] by playing an anti-apoptotic role in terminal erythroid differentiation. In the study by Alkobtawi *et al.*, the authors demonstrated that fetal cells display features of hematopoietic progenitor cells by the high expression of genes associated with hematopoietic stem cells, such as Sca1 and Myc.[5] Hence, a future study could assess whether there is any improvement in the levels of ineffective erythropoiesis in SCD patients who are pregnant or just had a baby. This potential therapeutic approach could be added to the various antisickling therapeutic strategies designed to improve bone marrow cellularity and erythropoiesis in SCD patients.[9]

Moreover, the study of Alkobtawi *et al*. emphasizes the crucial need for the biobanking of fetal stem cells and of cord blood stem cells[10] (Figure 1). Some commercial biobanks offer isolation and storage of placental stem cells, but the latter are expensive and are yet to be widely used.[7] Since the mother is tolerant to her semi-allogenic fetus, infusion of expanded fetal stem cells from her baby isolated at delivery should be tolerated with an even more remarkable healing effect.[5] This could be the basis of a phase I clinical trial following the publication by Alkobtawi *et al*. Various ways of targeting the site of ulceration could be addressed. For example, direct injection of these cells around the ulcer or intravenously via a peripheral vein.

Identifying ways of *in-vivo* expansion of fetal micro-chimeric cells, such as Ccr2 injections,[6] by targeting their unique characteristics could be a potential approach to improve their therapeutic potential. It will also be interesting to study the potential of these cells, if they are infused as an allogeneic source of cells, to SCD patients

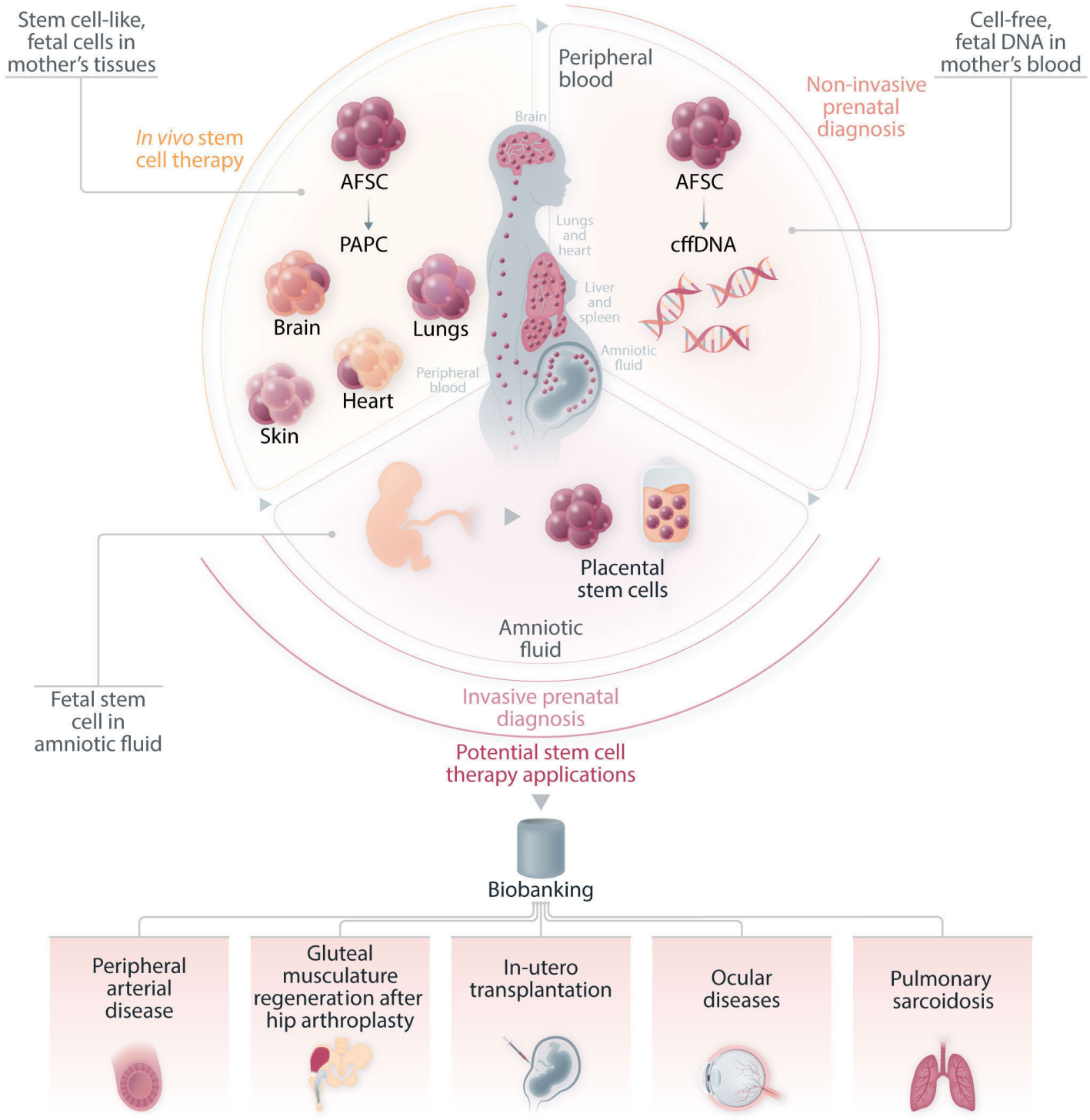

Figure 1. Illustration of fetal microchimerism in the maternal circulation. Fetal cells in the maternal circulation might be a form of amniotic fluid stem cells (AFSC), which can give origin to pregnancy-associated progenitor cells (PAPC). These cells can engraft maternal tissues, which is the reason for the wound healing seen in the study by Alkobtawi *et al.*[5] The cell-free fetal DNA (cffDNA) used in non-invasive prenatal diagnosis results from the apoptotic disposal of AFSC or PAPC. Fetal stem cells could be harvested at birth and banked for potential therapeutic pathways. Figure adapted from Rosner *et al.*[10] and Antoniadou *et al.*[7]

with severe leg ulcers, having been HLA-matched first. In addition, fetal cells collected at birth could be used to treat the fathers of the infants, since they are also semi-allogeneic to their offspring.

Fetal stem cells are superior to their adult counterparts because they have better pluripotency, greater proliferation capacity, lower senescence levels and longer telomeres. They can be used for the treatment of many diseases.[4] These cells can easily be recruited *in vivo* by injecting Ccr2 at the site of interest and non-invasively collected at birth and biobanked.[4,5] Further studies should explore the contribution of fetal microchimeric cells to the hematopoietic system in SCD, their effect on ineffective erythropoiesis, how they can be recruited efficiently *in vivo* and their biobanking potential. By recruiting fetal cells already in the maternal circulation, the study by Alkobtawi *et al.*[5] gives hope for further expansion of the therapeutic options for the various co-morbidities in SCD and improvement of the quality of life of SCD patients.

Disclosures

No conflicts of interest to disclose.

Contributions

PS and SEH drafted, edited and approved the manuscript.

Funding

PS is supported by an NIHR Clinical Lectureship (CL-2018-17-002), an Academy of Medical Sciences Starter Grant for Clinical Lecturers (SGL023\1023) and grants from the Fetal Medicine Foundation. SEH has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement number 101024970.

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