Benign transformation tendency of malignant tumour cells for intrauterine transplantation

Fang Ma

To the Editor:

Troeger et al. [1] have reported that similar early homing of allogeneic and xenogeneic stem cells and reasonable early engraftment of allogeneic murine foetal liver cells (17.1% donor cells in peripheral blood 4 weeks after intrauterine transplantation [IUT]), whereas xenogeneic HSC are rapidly diminished due to non-self-renewal and low differentiation capacities in the host's microenvironment.

IUT, as a promising treatment for foetal defects, is concerned with the rapid growth and immature immune system of the foetus, which may provide an opportunity for engraftment expansion of foreign tissues chiefly including some stem cells [2] such as haematopoietic stem cells (HSCs), embryo stem cells (ESCs) and MSCs. Nevertheless, there are potential hurdles to be overcome in IUT of stem cells, the first being the risk of uncontrolled proliferation and malignant transformation [3].

Striking parallels can be found between stem cells and cancer cells: similar signalling pathways may regulate self-renewal in stem cells and cancer cells, and cancer cells may include cancer stem cells – rare cells with indefinite potential for self-renewal which drive tumorigenesis [4]. However, cancer stem cells may display some similarity and distinctive features compared with HSCs, ESCs and MSCs. To explore what happens when malignant tumour cells introduced into the mouse embryo environment at D14-D16 by IUT, Astigiano et al. [5] and our primary research demonstrated that the malignant cells, including some embryonic cancer (EC) cells, H_{22} and S_{180} cells (the H_{22} cell line was originated from hepatoma, the S_{180} cell line from sarcoma) were not capable of causing tumours, remained latent and could be tracked down in tissues during adulthood as benign cells as is the fate of normal stem cells. Further, the malignant tumour cells for IUT showed a differentiation trend to benign cells, fluorescence analysis revealing that expression of protein kinase C (PKC) was markedly reduced in the H_{22} cells transplanted into the mouse foetal abdominal cavity by IUT after injection at 24h, 48h, and 72h of GFP-expressing H_{22} cells and laser confocal microscopy analysis in our research.

Recent investigation of malignant tumour cells for IUT has shown that there is benign transformation of the malignant phenotype of tumour cells, including proliferation and differentiation. This suggests we may be able to allay concerns about the risk of uncontrolled proliferation and malignant transformation of stem cells through IUT. At the same time it has provided us with new clues, i.e. firstly there were similar and contrary fates as between benign stem cells and malignant stem cells; secondly it indicates that the embryonic environment retains a certain ability to "normalise" tumour cells during post-implantation development as well.

Overall, further study of benign and malignant stem cells for IUT may provide insightful information about the obstacles facing IUT, lay the foundations for further understanding of IUT and suggest a new approach to benign transformation of malignant tumour cells.

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Authors' reply

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In-utero transplantation of adult progenitor cells (e.g. haematopoietic or mesenchymal stem cells) is probably not associated with uncontrolled proliferation or malignant transformation, as is an issue after transplantation of embryonic stem cells into adult recipients [1]. Also, tumour formation at the injection site has been observed after in-utero transplantation of embryonic stem cells [2]. Fang Ma reports the opposite, a transformation of embryonic malignant tumour cells into benign cells after in-utero transplantation, and speculates that the specific foetal milieu causes this development. This preliminary observation needs further research on the distinct gene expression pattern in these cells over time.

However, even if the foetus was protected against malignant tumour formation by its specific environment, the adult host mother is not. It is known that foetal cells cross the placenta throughout gestation, persist for decades and may cause autoimmune-like conditions [3, 4]. Obviously not only mature cells but also stem cells traffic into vari-

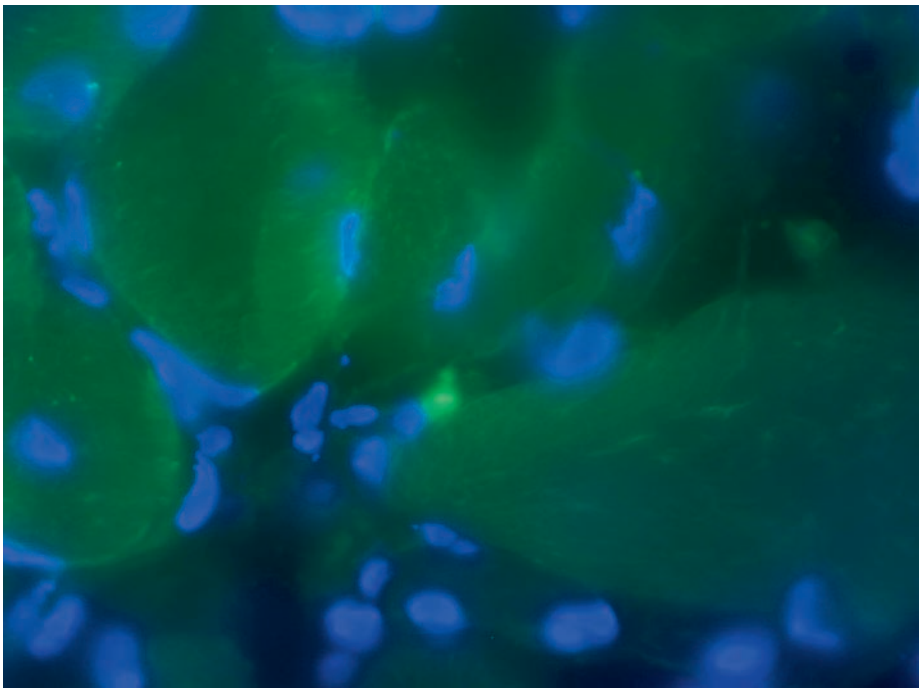

Figure 1

Cryostat section of the maternal scar and muscle tissue of the abdominal wall one week after delivery of pubs who received eGFP+ MSC by in-utero transplantation. Nuclei are stained using DAPI (blue dye). One cell is eGFP positive (green).

ous tissues of the mother, being mainly trapped by the lungs [5].

Interestingly, these cells are abundant in maternal injury sites after in-utero transplantation. We have transplanted GFP+ murine foetal liver-derived MSC in-utero into C57BL6 foetuses at gestation day 13.5. Briefly, pregnant mice were anaesthetised using an isoflurane, the uterus was exposed by performing a lower abdominal midline incision and 105 MSC in 5 µl PBS were injected into the abdominal cavity of the mouse foetuses using a pulled glass capillary. The abdominal wound was closed in two layers. About half of the transplanted pups were delivered. One week after delivery pups and mother mice were sacrificed and organs including scar tissue of the abdominal wall were analysed by fluorescence microscopy. We detected GFP+ single cells at the laparotomy scar of the host mother (see figure 1). This observation is in agreement with other authors who mated GFP+ male mice with wild-type female mice and observed a relevant traffic of foetal GFP+ cells into a chemical, but not surgical, liver injury site [6]. In contrast to these experiences in pregnant mice, adult surgical wound models revealed that injected GFP+ bone marrow-derived stem cells were found in surgical skin wounds, which is in accordance with our findings [7].

It may be speculated that embryonic stem cells would, accordingly, traffic into the mother after in-utero transplantation. Whether these cells have implications for the mother's health status remains unclear. However, on the basis of experience in adults tumour formation in the host mother is a serious issue and needs further attention before embryonic stem cells are used for in-utero stem cell transplantation to treat foetal diseases.

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