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RESEARCH WATCH

Seeking the "mother of blood" from human pluripotent stem cells: Are we there yet?

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Abstract Induced pluripotent stem cells (iPSCs) hold great promise for the treatment of human diseases, including the failure of bone marrow. Incremental progress across the past three and half decades has brought us closer to making hematopoietic stem cells from iPSCs clinical solutions. A recent innovative two-step differentiation approach successfully generated transplantable HSCs from iPSC sources. For clinical translation, the long-term safety of these gene-altered HSCs must be determined.

Human pluripotent stem cells (HPSC), either embryonic stem cells (ESC) or somatic-induced pluripotent stem cells (iPSC), hold great promise in generating functional cells of almost every tissue type. In the case of blood cells, the development of engrafting hematopoietic stem cells (HSC) from HPSCs to reconstitute failed bone marrow has been a long-sought goal. Spontaneous red blood cells were first observed more than three decades ago in cultured embryoid body (EB) formed by differentiating mouse embryonic stem cells. Due to difficulty in culturing and expanding HSC in the petri dish along with limited knowledge about the regulatory machinery of embryonic HSC specification, the progress of generating HSCs has been frustratingly slow. From these research efforts, cultures carrying relevant growth factors/morphogens, adherent matrix proteins, and bone marrow stromal cells have been formulated to drive the hematopoietic fate of HPSCs. Under these conditions, hematopoietic cells bearing the protein markers and transcriptome signature similar to bone marrow HSCs have been isolated. However, these putative HSCs were unable to engraft the bone marrow of the experimental animals.[1,2] It was believed that the conventional *in vitro* approach was not sufficient to generate transplantable HSCs from HPSCs. The first proof of principle that HPSC has the potential to generate functional HSCs came from two independent studies published in 2013.[3,4] In those two studies, *in vivo* teratomas were formed by injecting human iPSCs into immunodeficient mice. The formed teratomas were shown to generate hematopoietic niche and bone marrow-homing HSCs. Re-transplantation of these marrow-homing HSCs from teratoma-bearing mice to

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primary recipient mice confirmed their engraftment function. However, both studies lacked meaningful engraftment data in serial (secondary) transplantation experiments, which function as a stringent test for long-term durability of the putative HSCs. In view of clinical application, this xenogeneic approach may prove to be a major obstacle in FDA safety review and GMP scale-up. To overcome this problem, a recent report published by the journal of Nature described a success in generating functional HSCs from Human ESCs and iPSCs by using a two-step differentiation method.[5] In this novel approach, human ESCs and iPSCs were allowed to form EBs in petri dish as a first step in generating "hemogenic endothelium", which was defined by its transcriptome signature and membrane surface markers (CD34+/Flk-1+/CD43−/CD235A−). If allowed to continue, these mesoderm precursors usually give rise to mature blood lineages, but not engrafting HSCs according to multiple published studies. This time around, the investigators cleverly added a second-step of "direct conversion" by which purified hemogenic endothelial cells were retrovirally transduced with 7 master transcription factors (ERG, HOXA5, HOXA9, HOXA10, LCOR, RUNX1, and SPI1) known to impart the self-renewal and engraftment of bone marrow HSCs. These genetically altered cells were subjected to serial primary and secondary transplantation experiments using immunodeficient mice, which further confirmed their function of multilineage blood reconstitution. These results represent an encouraging step closer to efficiently generating bona fide HSCs using HPSC sources without the need of teratoma formation. Nevertheless, clinical translation of these results requires some special considerations. Ectopic expression of hematopoietic transcription factors has been known to cause abnormal hematopoiesis and, in some cases, leukemia in transplanted animals.[2,6] Long term growth behavior of genetically altered HSCs has yet to be carefully scrutinized. At least in the long journey of seeking "the mother of blood" from HPSCs, this study serves as an assuring answer to the question we have been asking all along, "Are we there yet?"

Conflict of interest

The author declares that no conflict of interest exists.

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