Embryo blood cells are stem cell–independent

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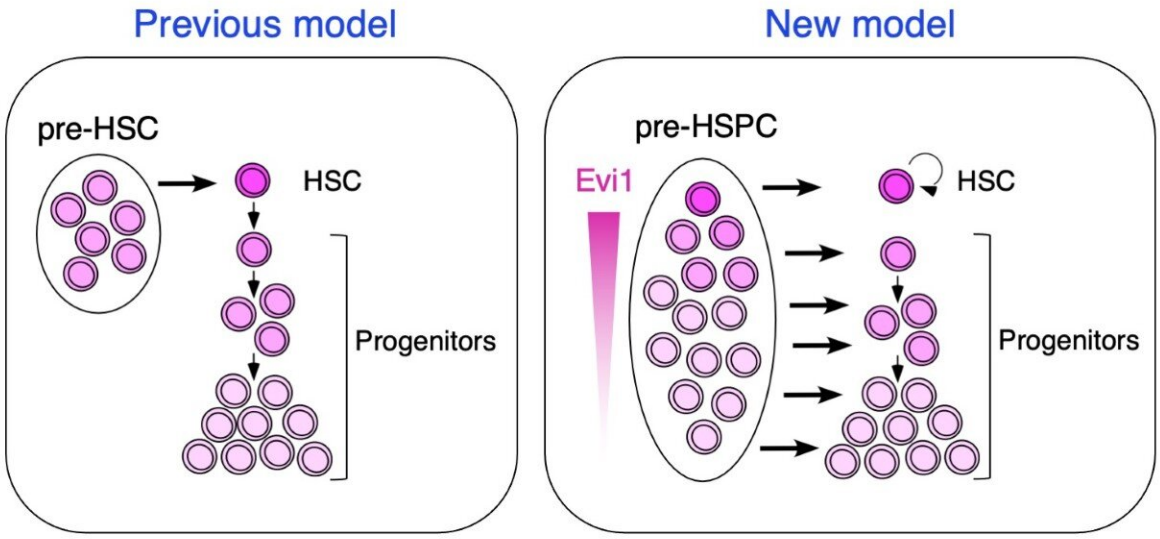

(Left) In the standard model, hematopoietic progenitors are generated from HSCs. (Right) In the proposed model, HSCs and progenitors are generated independently from pre-hematopoietic stem and progenitor cell (pre-HSPC) populations. Credit: Dr. Tomomasa Yokomizo

The fetal liver is the major hematopoietic organ during the embryonic stage. It is generally believed that hematopoietic hierarchy in the fetal liver is established through the differentiation of fetal hematopoietic stem cells (HSCs). This view assumes that the relationship between HSCs and descendant progenitors is conserved from embryo to adult.

Using lineage tracing and HSC-depleted mutant mice, a research collaboration based in Kumamoto University, Japan found that the majority of hematopoietic progenitors are generated directly from precursor cells and not from HSCs. Moreover, lineage tracing also revealed that fetal HSCs minimally contribute to the production of progenitors before birth. The researchers believe these findings suggest that most blood cells in the embryo are HSC-independent and prompt a reconsideration of the role of stem cells in embryo body formation. Their study was published in *Nature*.

Regarding hematopoietic system formation, the researchers also tackled a long-standing question of the origin of HSCs. Previous transplantation experiments combined with ex vivo cultures have proposed that HSCs are mainly generated from the intra-embryonic aorta-gonad-mesonephros (AGM) region. However, this finding has been debated because of a lack of clear molecular and in vivo evidence. Now, the researchers have shown for the first time that the transcription factor Evi1 is specifically expressed in intra-embryonic arteries and is both required and sufficient for HSC generation.

So far, a method has not been established to specifically produce HSCs from iPS/ES cells. Therefore, a clear understanding of HSCs and the formation of the hematopoietic system in the embryo is needed to facilitate further advances in regenerative medicine. The findings presented in this work provide important evidence for improving culture systems to obtain clinically relevant HSCs.

"We know why hematopoietic stem cells are difficult to produce," said Dr. Yokomizo. "Our work here shows that Evi1 expression could be a good indicator of their induction in vitro."

HSCs are important in the fight against a number of blood and immune disorders. Dr. Yokomizo and his team are ultimately trying to make it

much easier to create HSCs in the lab for use in transplantation. Currently, they are looking into how HSCs are produced before birth.

More information: Tomomasa Yokomizo et al, Independent origins of fetal liver haematopoietic stem and progenitor cells, *Nature* (2022). DOI: 10.1038/s41586-022-05203-0

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