New cell line is capable of giving rise to red blood cells outside the body

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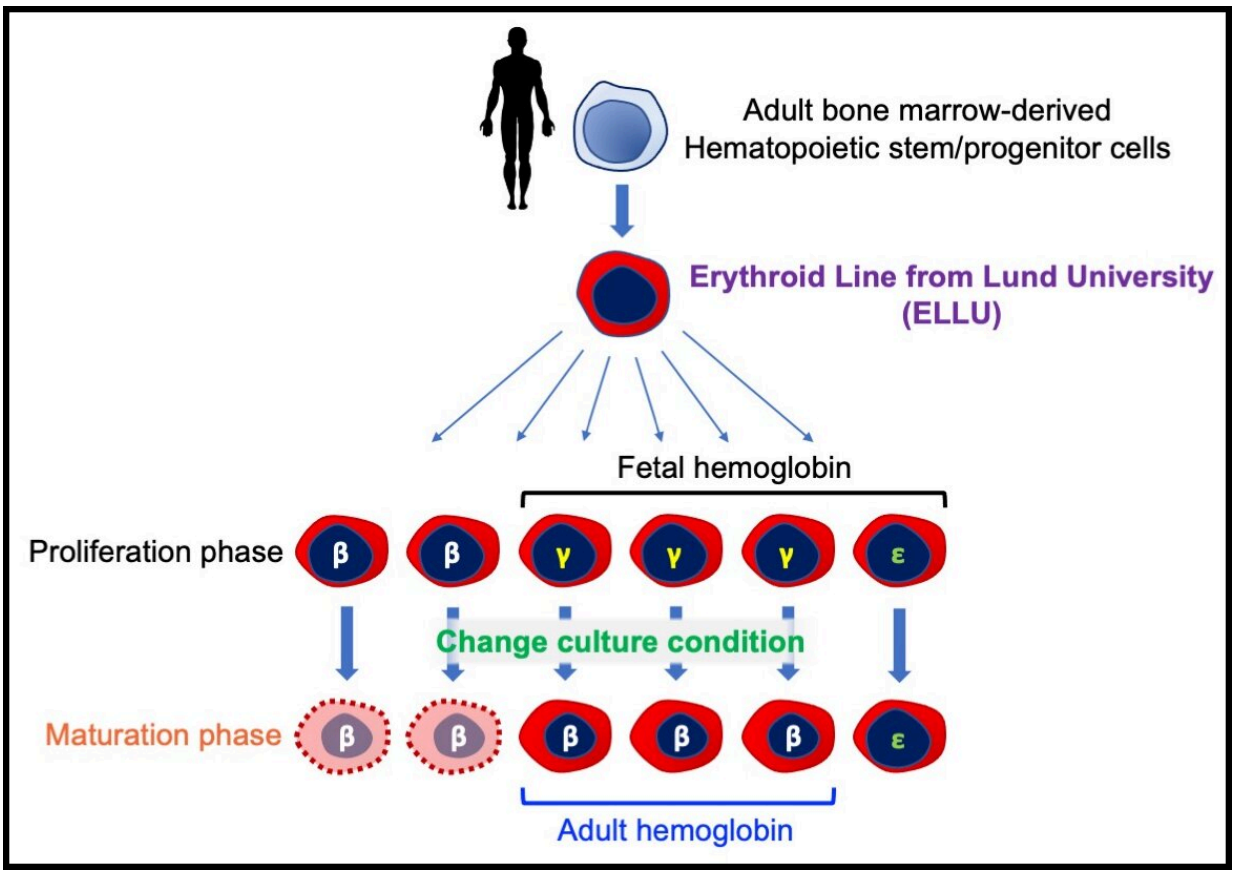


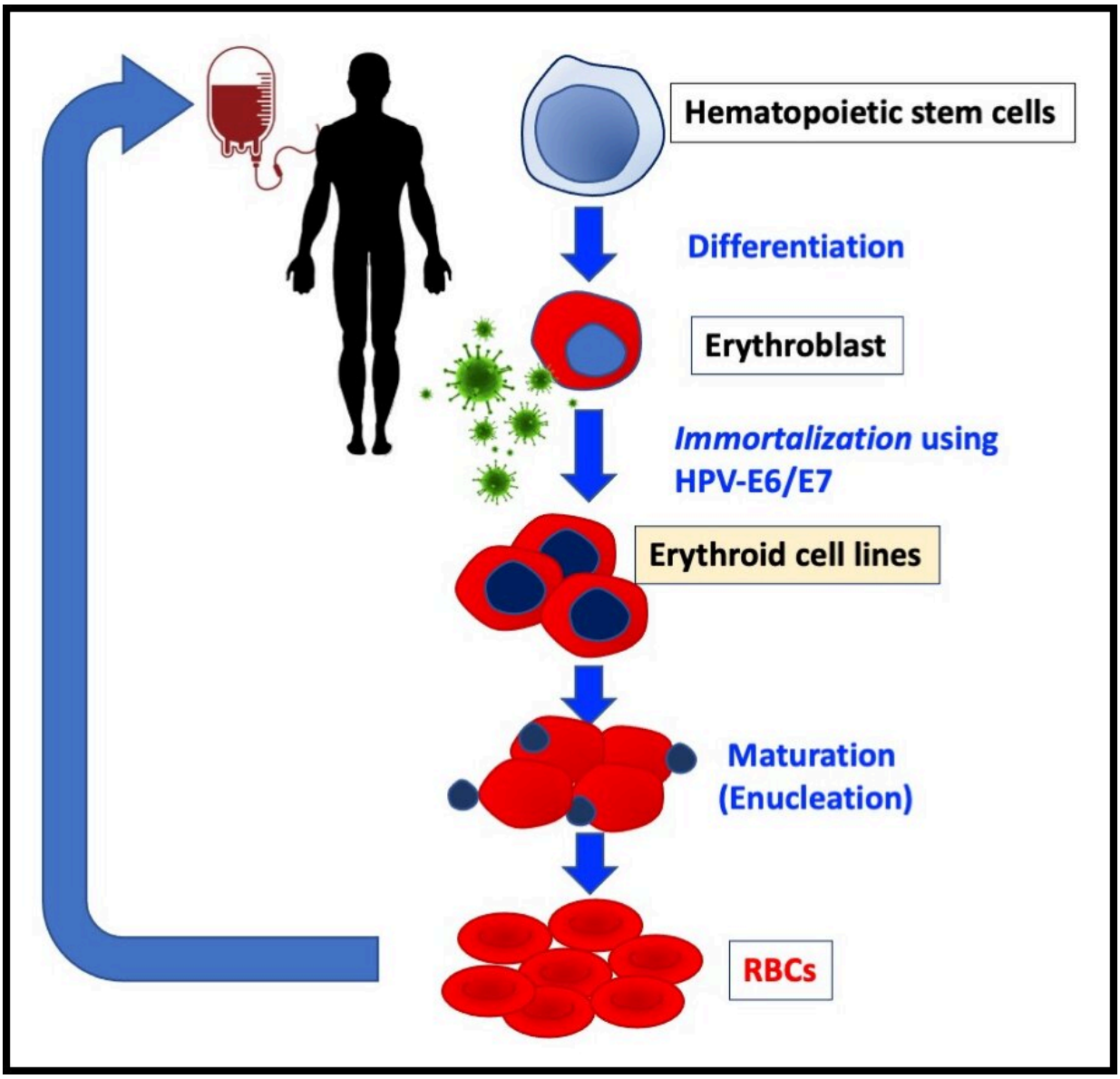
Despite ELLU clones originating from a single adult donor, they have different hemoglobin patterns. Clones expressing adult type hemoglobin started dying upon differentiation while clones with fetal hemoglobin gradually started expressing adult globin and generated more stable cells. Credit: Kumamoto University

Recently developed cell line is a potential source for generating endless amounts of red blood cells outside the body.

A collaborative research team from Kumamoto University (Japan), the Japanese Red Cross Society and Lund University (Sweden), has established a new cell line from human adult bone marrow that can grow infinitely and differentiate toward red blood cells (RBCs). This cell line has the potential to contribute to future transfusion therapies.

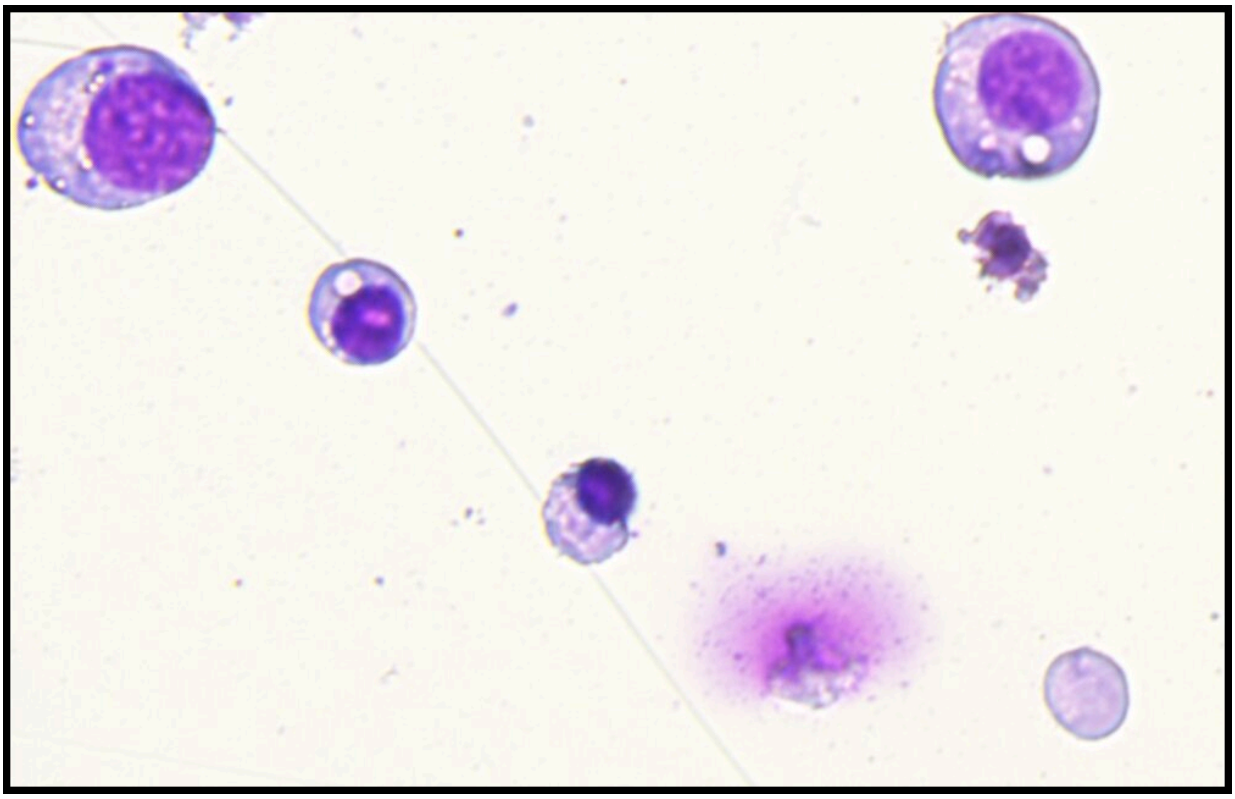
Transfusion is an essential clinical treatment for treating dozens, if not hundreds, of maladies and medical procedures ranging from anemia to surgical operations. Currently, the transfusion system relies heavily on blood donated from volunteers. However, the number of donors is inadequate and has been decreasing yearly even though the requirements for transfusions constantly remains high. In particular, less common blood types are always at a risk of shortage. Furthermore, contamination of donated blood (by viral infection or other factors) further reduces availability.

To solve these burdens, producing RBCs outside of the body has been considered an alternative to increase the blood supply available for transfusion. Industrially produced RBCs are clean, and their production can be controlled to stably provide desired blood types. It is important to note that RBCs are the most abundant type of cell (>80% of all cells) in the body. Thus, sources that are able to continuously provide enormous amounts of RBCs are required. Immortalized cell lines that can limitlessly proliferate and generate RBCs are therefore expected to become significant alternatives to compensate a serious blood supply shortage for therapies that require transfusion.



Hematopoietic stem cells isolated from various sources such as bone marrow and umbilical cord blood are differentiated to erythroblasts, immature red blood cells that still hold a nucleus. These cells are then transduced with virus expressing HPV-E6/E7 to be immortalized. Established cell lines can be easily maintained and expanded infinitely. At a desired time, those cells are placed into a different culture condition to mature toward RBCs, which are then used for transfusion. Credit: Kumamoto University

It is here where the research team headed by Prof. Miharada from Kumamoto University succeeded in establishing a new RBC generating cell line. Their creation, which they named Erythroid Line from Lund University (ELLU), was developed from isolated human bone marrow cells ($CD34^+$ hematopoietic stem and progenitor cells) and can grow infinitely and differentiate into RBCs. The researchers previously established cell lines using erythroid cells differentiated from human umbilical cord blood $CD34^+$ cells and human induced pluripotent stem (iPS) cells, both of which contain fetal (γ) globin. However, cells having adult (β) globin are more desired for use in transfusion therapies.



Maturation of an immortalized human erythroid cell line, ELLU, toward an enucleated reticulocyte. ELLU was established by ectopic expression of HPV-E6/E7 genes, and it wasn't necessary to turn-off expression of those genes but rather change the culture conditions to trigger the differentiation toward mature

cells. In this image, a number of ELLU cells at various stages of differentiation can be seen. Credit: Ms. Svetlana Soboleva

Previously, human papillomavirus (HPV) E6/E7 genes are frequently used to immortalize cells. It has been believed that turning off the HPV-E6/E7 is essential when the cells begin differentiation to RBCs. However, Prof. Miharada's team demonstrated that ELLU cells can differentiate without such a complicated system. Interestingly, ELLU cells showed considerable variation in their hemoglobin expression, with some clones expressing adult globin adult (β) globin while others mainly containing fetal (γ) globin, despite the fact that all of the cells were derived from adult bone marrow. They also unexpectedly found that clones expressing adult type hemoglobin started dying upon differentiation. In contrast however, clones with fetal hemoglobin gradually started expressing adult globin and generated more stable cells.

"We believe that our findings will contribute to simplifying the methods used to establish immortalized cell lines, and allow us to select clones that have the maximum potential for producing RBCs," Prof. Miharada stated.

More information: Svetlana Soboleva et al, Establishment of an immortalized human erythroid cell line sustaining differentiation potential without inducible gene expression system, *Human Cell* (2021). DOI: 10.1007/s13577-021-00652-7

Provided by Kumamoto University

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