Journey from stem cell to blood cell revealed

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Researchers have discovered previously undetected steps in the process by which stem cells become blood cells, a process called haematopoiesis. An international collaboration, including Winthrop Professor Wendy Erber, has established that a highly complex series of events determine the fate of closely related populations of blood progenitor cells.

Professor Erber, a co-author of the study, is Head of The University of Western Australia's School of Pathology and Laboratory Medicine.

The study, which is part of the large international BLUEPRINT research project to understand blood disorders, identified thousands of differences in gene expression between blood cell types. These differences result from many specific events that are crucial for normal blood development. Errors in this process can lead to blood disorders including leukaemia. The research was published today in *Science*.

For the first time a comprehensive catalogue of transcription factors and other proteins that regulate this sophisticated process has been generated. This research has discovered the extent to which the RNA is cut and pasted together in different ways during haematopoiesis leading to specific forms of proteins for each of these stages. Until this study, haematopoiesis was relatively well understood at the level of DNA. What was not known was how the genetic information in DNA was then transcribed to generate RNA, leading to protein formation.

"We have identified thousands of novel places where the RNA is processed in an alternative way," said Willem Ouwehand, Professor of

Experimental Haematology at the University of Cambridge and the Wellcome Trust Sanger Institute. The critical importance of the alternative splicing of RNA in blood cell development was illustrated by studying the role of two different forms of the same transcription factor in the formation of megakaryocytes, the progenitor cell for blood platelets.

Professor Erber said: "Such events changed the amount, structure and behaviour of proteins derived from a single gene. Alternative proteins could drive stem cells towards becoming different mature blood cells."

The hematopoietic stem cells and other cells needed for this study had not previously been studied in great detail because they are extremely rare in the bone marrow of adults, Professor Erber said. "In this study we were able to purify the cells from umbilical cord blood donations, where the concentration of these progenitor cells is surprisingly high."

The results of this study have significant applications for patients with blood disorders. Scientists can begin to design diagnostics and new therapies for blood disorders including leukaemia. They will be of great value in future studies in stem cell transplantation therapy, regenerative medicine and discovering the genetic basis of rare inherited haematological and immunological disorders.

"This work was only possible with a large international research team with a diverse range of skills. It is exciting as a researcher at UWA to participate in an international collaboration leading to such a ground-breaking discovery," Professor Erber said.

More information: "Transcriptional diversity during lineage commitment of human blood progenitors," *Science* 26 September 2014: Vol. 345 no. 6204 1251033 DOI: 10.1126/science.1251033

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