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One of the key circuits in regulating genes involved in producing blood stem cells is deciphered

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Researchers from the group on stem cells and cancer at IMIM (Hospital del Mar Medical Research Institute) have deciphered one of the gene regulation circuits which would make it possible to generate hematopoietic blood cells, i.e. blood tissue stem cells. This finding is essential to generate these cells in a laboratory in the future, a therapy that could benefit patients with leukaemia or other diseases who need a transplant and who, in many cases, do not have a compatible donor.

In the process of generating stem cells, many molecule signals intervene which, through a regulating circuit are induced at a certain moment and remain active during a specific time until they switch off so these cells can differentiate. Anna Bigas, the coordinator of the research group on stem cells and cancer at IMIM explains: "We discovered that the Notch protein, which is involved in the development of most tissues, is responsible for activating the gene GATA2 which is necessary to generate hematopoietic stem cells; at the same time, it induces the reproduction of its own repressor, HES-1". The team lead by Bigas has also shown that this regulating circuit allows the limited production of GATA2, and this is essential for the production of hematopoietic stem cells.

The study was developed over 4 years and consisted in performing a large number of experiments with the collaboration of groups from Japan, Holland and the USA. On the one hand, researchers identified the

mechanism regulating the gene GATA2 in hematopoietic stem cells of a mouse embryo and, on the other hand, they identified DNA sequences regulating this gene; i.e. the sequences of gene GATA2 where the Notch protein and the repressor HES-1 bind. After generating several mutations in these sequences, researchers saw that if the Notch protein does not bind to GATA 2, the gene is not activated, whereas if it's the repressor HES-1 that doesn't bind to it, then there is an over-production of the protein GATA 2. Researchers also proved that embryos where HES-1 has been eliminated may not generate functional hematopoietic stem cells due to excessive production of GATA 2.

One of the difficulties encountered by the researchers when carrying out this study is that, from a methodological approach, some of the required techniques were not possible to carry out at IMIM's laboratories, and for this reason collaboration was established with the group lead by Prof. Masayuki Yamamoto at the Tohoku University School of Medicine in Sendai, Japan. The first signatory of the paper, Dr. Jordi Grau, travelled to Sendai for four months but, due to the earthquake in 2011, it was impossible to conclude the task. It was thanks to the collaborations established with the group lead by Prof. Elaine Dzierzak at the Erasmus University in Rotterdam that it was finally possible to continue with the project.

The process of generating stem cells specifically from tissue in a laboratory is being studied in many laboratories around the world, but this has not yet been achieved. This shows that we need further research into the mechanisms used be the embryo to generate these cells and which regulating genes are involved in this process. "We discovered a basic circuit but there are still many more to discover. Our end objective is to validate our results with cells coming from mouse embryonic stem cells and then being able to use this knowledge to generate human hematopoietic stem cells in a laboratory for therapeutic purposes. These cells could then be used for patients needing a hematologic transplant

and do not have a compatible donor" concludes Dr. Bigas.

More information: "Hes repressors are essential regulators of Hematopoietic Stem Cell Development downstream of Notch signaling". Jordi Guiu, Ritsuko Shimizu, Teresa D'Altri, Stuart T. Fraser &, Jun Hatakeyama, Emery H.Bresnick, Ryoichiro Kageyama, Elaine Dzierzak, Masayuki Yamamoto, Lluis Espinosa and Anna Bigas. *Journal of Experimental Medicine*. jem.rupress.org/content/210/1/71.full.pdf+html

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