Stem cell research

How stem cells form the placenta

Researchers at Helmholtz Zentrum München have been studying how pluripotent stem cells develop into placental cells, or trophoblasts. Four transcription factors appear to play a special role in this process, as the scientists report in 'PNAS'.

Trophoblasts are cells that form the outer layer of a blastocyst*, which attaches itself to the wall of the uterus. In humans, trophoblasts are formed between five and twelve days after fertilization. Enzymes then degrade the mucus that lines the uterus and enable the blastocyst to embed itself. In the next stage, the placenta is formed from embryonic and maternal tissues.

The aim of the research team led by Dr. Micha Drukker, who heads the Human Pluripotent Stem Cell Group at the Institute of Stem Cell Research at Helmholtz Zentrum München, was to discover how pluripotent stem cells transform into trophoblasts, which develop into the placenta.

"We were able to show that the potent morphogen BMP4 is responsible for activating a small network of four transcription factors, which we named the trophectoderm four, or TEtra," explains study leader Dr. Drukker. "These factors initiate all further steps."

Extensive genetics and epigenetics data of trophoblast development

For the purpose of this study, the team around the lead authors Dr. Dmitry Shaposhnikov and Christian Krendl, produced extensive maps and examined both the transcriptome and epigenome (CpG methylation, H3K4me3 and H3K27me3) of progenitor and placental cells that were derived from human pluripotent stem cells. In the process, they discovered the role of the four above-mentioned TEtra transcription factors: TFAP2A, TFAP2C, GATA2 and GATA3.

"At the onset of trophoblast differentiation, the TEtra factors occupy multiple sites in epigenetically inactive placental genes and activate them," Dr. Drukker notes. "At the same time, they terminate the stem cell characteristics, by down-regulating Oct4 factor expression." Conversely, when the researchers knocked down the GATA3 transcription factor in an experimental model, development of the trophectoderm was interrupted.

The authors of the study believe their findings will open up new avenues in the understanding of placental development and pregnancy-related complications. Furthermore, the data provide a genome-wide analysis of active and inactive chromatin during trophoblast development of human pluripotent stem cells.

With regards to placental progenitor cells, the scientists see no immediate therapeutic applications. However, understanding their development is of importance generating other clinically relevant cell types from pluripotent stem cells, including neurons or pancreas cells.

Further information

* The blastocyst is a stage in the development of mammalian embryos and occurs about four days after fertilization. This stage is preceded by the morula.

Background:
The study was conducted in close cooperation with the working groups led by Prof. Fabian Theis and Dr. Nikola Müller from the Institute of Computational Biology as well as with partners at the LMU in Munich (Prof. Wolfgang Enard) and in Oregon (Prof. Shawn L. Chavez).

Lead author Christian Krendl was a graduate student at the Helmholtz Graduate School of Environmental Health (HELENA) and has since received his doctorate.

Original publication:
Krendl, C. & Shaposhnikov, D. et al. (2017): GATA2/3-TFAP2A/C transcription factor network couples human pluripotent stem cell differentiation to trophectoderm with repression of pluripotency. Proceedings of the National Academy of Sciences, DOI: 10.1073/pnas.1708341114

The Helmholtz Zentrum München, the German Research Center for Environmental Health, pursues the goal of developing personalized medical approaches for the prevention and therapy of major common diseases such as diabetes and lung diseases. To achieve this, it investigates the interaction of genetics, environmental factors and lifestyle. The Helmholtz Zentrum München is headquartered in Neuherberg in the north of Munich and has about 2,300 staff members. It is a member of the Helmholtz Association, a community of 18 scientific-technical and medical-biological research centers with a total of about 37,000 staff members. www.helmholtz-muenchen.de/en

The Institute of Stem Cell Research (ISF) investigates the basic molecular and cellular mechanisms of stem cell maintenance and differentiation. From that, the ISF then develops approaches in order to replace defect cell types, either by activating resting stem cells or by re-programming other existing cell types to repair themselves. The aim of these approaches is to stimulate the regrowth of damaged, pathologically changed or destroyed tissue. www.helmholtz-muenchen.de/en/isf

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