Identification of a protein complex that helps maintain the separation of embryonic and extraembryonic lineages

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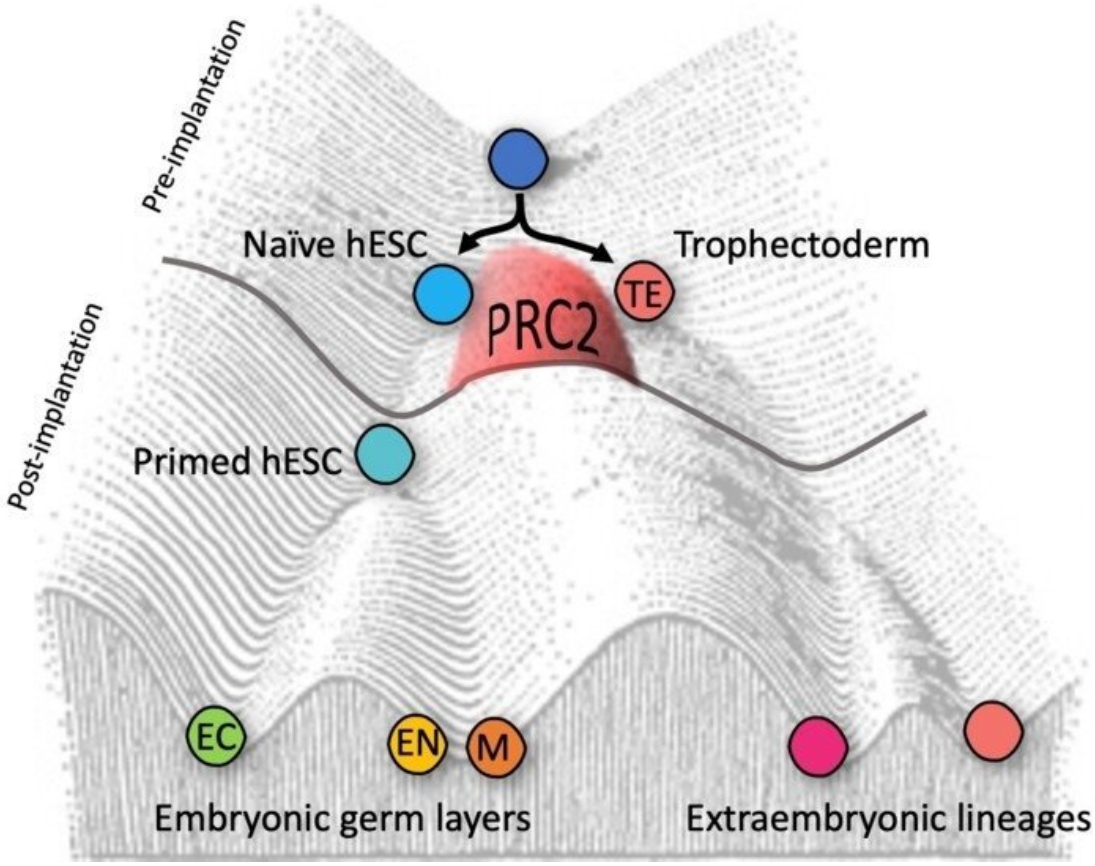

Waddington's epigenetic landscape. Credit: Simon Elsässer

Researchers from Karolinska Institutet identify an epigenetic regulator controlling the very first cell type specification in the human embryo. The study is published in *Nature Cell Biology*.

In the course of early embryonic development, pluripotent stem cells first give rise to three lineages or "germ layers," which then generate all cell types, tissues and organs of the human body, e.g. skin, gut, heart, muscles, bones, brain.

"It is thought that epigenetic information—encoded 'on top' of the genetic information—is passed on together with the genetic information through each cell division, ensuring that each individual cell remembers its specialized task in building the complex human organism," says Associate Professor Simon Elsässer, at the Department of Medical Biochemistry and Biophysics, and senior author of the study.

Extraembryonic tissue

But if generating a complex human organism doesn't seem a complicated enough task, the fertilized egg also gives rise to so-called extraembryonic tissue that serves as a support structure during the pregnancy without being part of the human body: a thin layer of cells—the trophoblast—surrounds the embryonic cells and later, upon implantation into the uterus wall, forms the placenta.

Hence, the very first decision in development is made between embryonic and extraembryonic cell fate. It is well-known that the two lineages strictly follow their own, separate developmental programs and never mix again, but the molecular mechanism of how this is achieved remains elusive.

Lineage commitment

Researchers at KI have now identified a protein complex that helps maintain the separation of embryonic and extraembryonic lineages. The aim of the work was to elucidate how distinct cell types are established during early human development. Such insights could be gleaned by studying surplus embryos donated by couples undergoing fertility treatment. However, modern cellular models for embryonic development circumvent the need for this limited resource.

"Human embryonic stem cells can be derived from the early embryo and are thought to represent the embryonic cells shortly following implantation. These cells can be propagated indefinitely, and can also be reverted to an earlier embryonic state, called the naïve state, which precedes implantation," says Assistant Professor Fredrik Lanner at the Department of Clinical Science, Intervention and Technology who has a long track record in studying human development and human embryonic stem cell models.

For this study, the two researchers decided to join forces and characterize the epigenetic landscape present in naïve human embryonic stem cells, to explore how cell identity is defined and distinguished from the extraembryonic lineages that arise at the same time in the preimplantation embryo. Ph.D. students from both laboratories, Banushree Kumar and Nerges Winblad, led the experimental work for the study involving a number of state-of-the-art methods including quantitative ChIP-seq and single-cell transcriptomics. Computational biologist Carmen Navarro completed the team of lead authors.

Maintaining cell identity

Intriguingly, a specific modification to the histone H3 protein, known to keep genes in an "off"-state, marked key trophectoderm regulators in naïve embryonic stem cells. Inactivating the responsible enzyme, Polycomb Repressor Complex 2 (PRC2), the team found that the cells

generated extraembryonic cell types.

While the role of PRC2 as an epigenetic repressor is well studied, it has previously been thought to spring into action only after implantation of the blastocyst, to regulate development of the three germ layers. Indeed, when the team inactivated PRC2 in primed embryonic stem cells, which resemble more the post-implantation stage, they did not observe any induction of extraembryonic lineages. Using single-cell transcriptomics, the team was able to trace the precise trajectory that allows naïve but not primed pluripotent cells to adopt extraembryonic cell fates.

Waddington's landscape

The team concluded that PRC2 functions as an epigenetic barrier which maintains embryonic lineage and prevents aberrant activation of trophectoderm genes. "Our findings are very much in line with Conrad Waddington's ideas in the 1950s, that cells navigate through an 'epigenetic landscape' which guides cells to follow predetermined differentiation routes, and perturbation of the underlying landscape can make cells to take the wrong turn," says Banushree Kumar.

The results of the study add to our understanding of human development and early pregnancy and provide an avenue to study disease conditions, such as preeclampsia, in cellular models.

More information: Banushree Kumar et al, Polycomb repressive complex 2 shields naïve human pluripotent cells from trophectoderm differentiation, *Nature Cell Biology* (2022). DOI: 10.1038/s41556-022-00916-w

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