Advances in research on the most general type of stem cells

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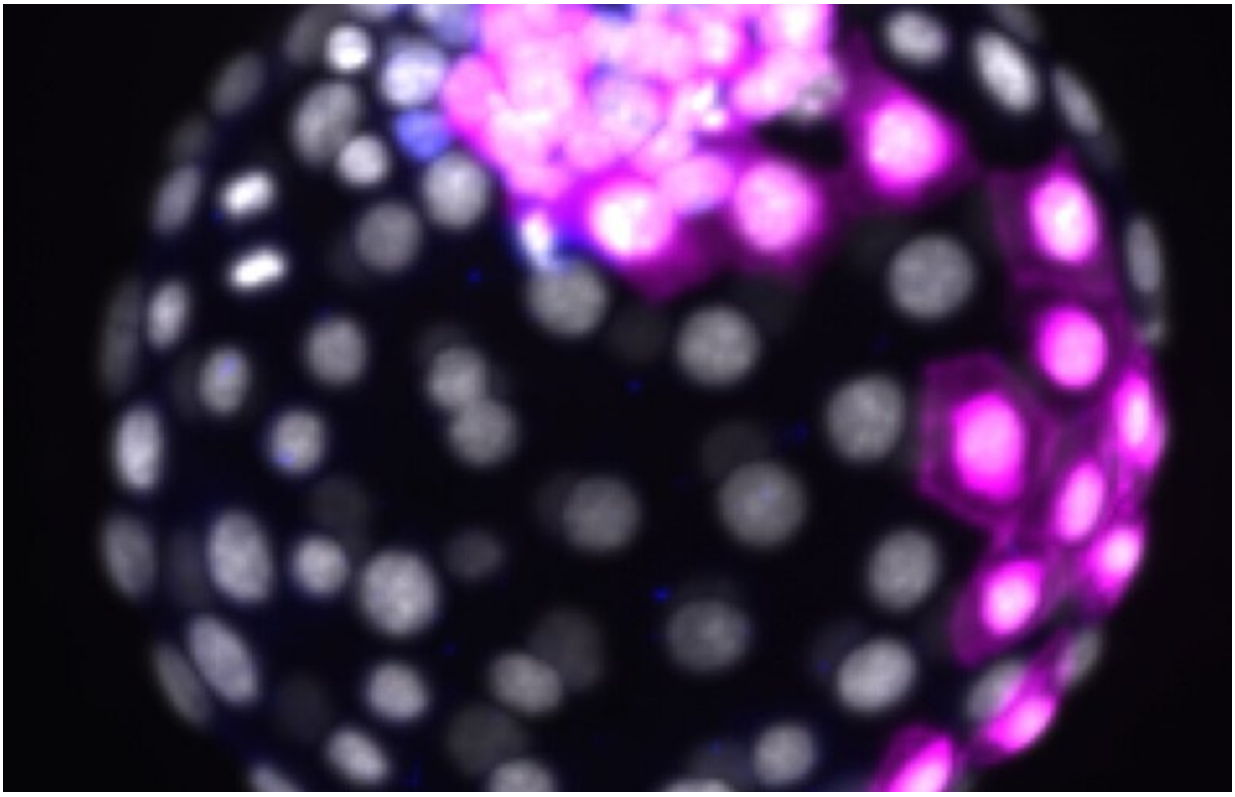

Mouse embryo following injection of truly totipotent morula cells labeled in magenta. Morula cells are found shortly after an egg is fertilized. Credit: Eszter Posfai

Stem cell research is the prerequisite for regenerative medicine, which with the help of the body's cells recreates and heals important organs.

Now, researchers at Karolinska Institutet, SickKids in Canada and KU Leuven in Belgium have found a method for defining the most general type of stem cells, that can develop into all cell types in the body. The study of totipotent stem cells in mice has been published in *Nature Cell Biology*.

"There is a lot of interest in pushing the boundaries of stem cell potential in order to capture the totipotent state so we needed criteria to assess whether a stem cell line has actually achieved this goal," says Dr. Janet Rossant, chief of research emeritus and senior scientist in the Developmental & Stem Cell Biology program at SickKids.

Replicating mouse stem cells in a totipotent state within a laboratory has been a long-sought goal of stem cell biologists around the world. If successfully created, such a stem cell line could have profound impact on the field, enabling the study of normal development and regenerative medicine.

Totipotency is the ability of a cell to generate every cell type in the early embryo as well as the embryo's supporting structures, including the placenta. This ability is typically only found during the first few cell divisions of an embryo.

To date, mouse stem cell lines in a pluripotent state have been made. However, these cells can only make other cell types in the embryo or the placenta, but not both.

Criteria for assessment of totipotency

A team of researchers from Karolinska Institutet in Sweden, The Hospital for Sick Children (SickKids) in Canada and the KU Leuven in Belgium has provided a set of criteria to assess whether a mouse stem cell line shows true totipotency.

Together, they determined three criteria for a mouse stem cell line to be totipotent:

- The cells' genetic activity, or gene expression profiles, need to be closer to that of an earlier embryo rather than pluripotent stem cells.
- The cells should be able to readily transform into placental stem cells or into an early embryo-like structure in an artificial environment.
- Most importantly, the cells should be able to contribute to the placenta as well as the fetus when returned into the environment of an early embryo.

The team tested two different mouse stem cell lines that had been reported as potentially totipotent and assessed them using their criteria.

"While both lines showed some gene expression differences from pluripotent stem cells, they didn't look like totipotent early embryo cells and didn't make certain functional cells in the placenta," says Fredrik Lanner, assistant professor at the Department of Clinical Science, Intervention and Technology, Karolinska Institutet, and division of obstetrics and gynecology, Karolinska University Hospital and one of the corresponding authors.

"Ultimately, we found the search for a totipotent stem cell is not over. My laboratory is now particularly interested in extending these studies to the human and intensify our efforts towards establishment of human totipotent stem cells to better model early human embryo development," he says.

Resource for the scientific community

The research has resulted in a clear set of criteria to validate any new cell

lines. In addition, the team also developed a comprehensive analysis of gene expression and regulation at the single cell level for embryos and different pluripotent stem cell lines. The researchers believe this will be a valuable resource for the scientific community.

More information: Eszter Posfai et al. Evaluating totipotency using criteria of increasing stringency, *Nature Cell Biology* (2021). DOI: 10.1038/s41556-020-00609-2

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