Max Planck Institute for Molecular Biomedicine

Press Release

August 11, 2013

# Two distinct types of reprogramming

## "Oct4", the main switch protein of pluripotency is not essential for totipotency

**Reprogramming somatic cells to all-rounder cells is on everybody's lips – last year the Nobel Prize for Physiology or Medicine was awarded to two scientists, Sir John Gurdon and Shinya Yamanaka, for their achievements in the field of reprogramming. Yamanaka showed in 2006 that somatic cells can be reprogrammed to a pluripotent state with the help of four factors, one of them being Oct4. More than forty years ago, Gurdon had demonstrated in his cloning experiments with frog's eggs that somatic cells can, after all, be reprogrammed – to totipotency that is. Now scientists of Hans Schöler's group at the Max Planck Institute (MPI) for Molecular Biomedicine in Münster have demonstrated that reprogramming with factors (to pluripotency) and reprogramming with an egg (either by fertilisation or by cloning) are fundamentally different: Oct4, the main switch protein in Yamanaka-style reprogramming, is not required to establish totipotency (Nature Cell Biology, Epub ahead of print on August 11, 2013).**

In other words – when scientists add Oct4 to specialized somatic cells, the cells will be reprogrammed to pluripotent all-rounder cells that resemble embryonic stem cells. They can develop to any cell type of the body. Oct4 is, however, not necessary to get totipotent cells, which have the potential to develop to a complete organism.

"Our study shows that cloning leads to totipotency with or without Oct4, while reprogramming cells for pluripotency is not possible without Oct4, " explains Professor Dr. Hans Schöler. "This is an important finding, also with regards to the German Embryo Protection Act. It shows that both methods of reprogramming are fundamentally different. Reprogramming by the Yamanaka-method brings specialized somatic cells to a pluripotent state. For the induction of totipotency, there must be other mechanisms independent of Oct4. If these two processes were to involve the same mechanisms, totipotent cells could perhaps be formed by applying the Yamanaka-method – such cells might then be subject to the German Embryo Protection Act."

For quite some time, scientists have ascribed Oct4 an important role in early embryonic development – after all, the protein is present in the egg. To study the role of Oct4 in the transition from totipotency to pluripotency, the Max Planck researchers had to deactivate Oct4 in the egg. To do this, they used a genetically modified mouse model in which the protein Oct4 was eliminated only in the eggs. "Contrary to the established premise that Oct4 is crucial for the early embryonic stages of development, the mice without Oct4 were as fertile as those with Oct4," according to Guangming Wu PhD, first author of the study. "In other words, it was still possible to activate the totipotency of the fertilised eggs, as in normal fertilisation," he adds.

Another established assumption was that the fate of the cells in the early embryo is decided by the balance between the protein Oct4 and its antagonist, the protein Cdx2. According to this assumption, Oct4 would turn the cells into embryoblast cells, from which the foetus would later form. Cdx2, on the other hand, would transform the cells into trophoblasts, a subsequent part of the placenta. Consequently, without Oct4, there would be an empty trophoblast envelope. The researchers found that despite the elimination of Oct4, an embryo with an embryoblast formed. However, the cells quickly lost their pluripotency. Wu explains, "There must therefore be other factors that determine the fate of the cells in the early embryo. Identifying the factors that are decisive for embryonic cloning and pluripotency will be the subject of future research."

**Original publication:**
Guangming Wu, Dong Han, Yu Gong, Vittorio Sebastiano, Luca Gentile, Nishant Singhal, Kenjiro Adachi, Gerrit Fischedick, Claudia Ortmeier, Martina Sinn, Martina Radstaak, Alexey Tomilin and Hans R. Schöler
Establishment of totipotency does not depend on Oct4A
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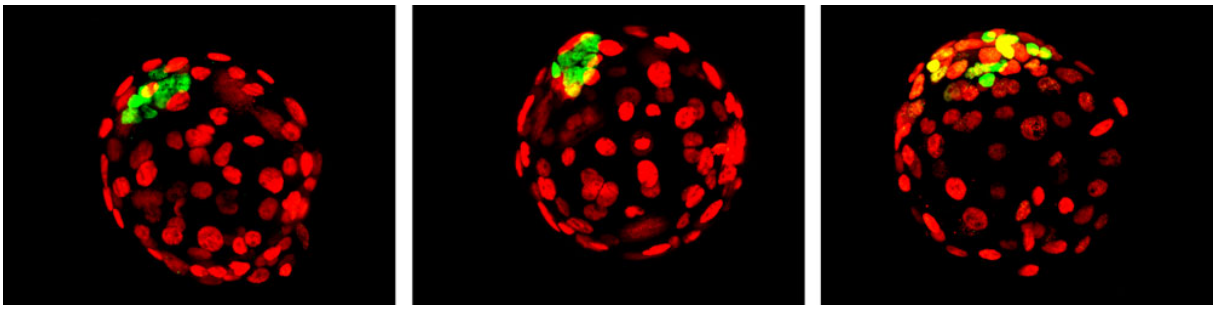
**Press photos**
Photos concerning the press release will be made available at request. You can ask for the photos by e-mail to the office of Professor Schöler or to Dr. Jeanine Müller-Keuker.

**Guangming Wu, PhD**

mpi-muenster_g-wu.jpg
Credit: MPI Münster / JMK



**No matter of balance: Oct4 does not determine cell fate**

Left: normal maus embryo, middle: mouse embryo witout the maternal Oct4, right: maus embryo without maternal and paternal Oct4
Despite the lack of Oct4, cells of the embryoblast (green: Nanog protein; red: cells of the trophoblast) are developed. In this stage, an embryoblast is present, however, it is not intact anymore.

mpi-muenster_Oct4_Totipotenz.jpg
Credit: MPI Münster / G. Wu