Wiping the slate clean: Erasing cellular memory and resetting human stem cells

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Babraham Institute scientists, in collaboration with colleagues at the Cambridge Stem Cell Institute and the European Bioinformatics Institute, have published findings today in the journal *Cell* giving hope that researchers will be able to generate base-state, naïve human stem cells for future medical applications. The study demonstrates that human stem cells can be reverted back to a base state, losing characteristics that mark them as belonging to a specific cell lineage and instead regaining the identify of a non-specialised cells with unrestricted potential (pluripotency) to develop into any cell type.

The study's lead researchers, based at the Wellcome Trust-Medical Research Council Stem Cell Institute in Cambridge, reset human stem cells back to a pluripotent state. Previous work in mice had described the characteristics of base-state mouse stem cells and the group were able to show that these characteristics were largely shared by reset human pluripotent stem cells, giving confirmation that these human cells were indeed reverted to a naïve state.

Part of this analysis involved looking at the epigenetic regulation in the base-state human stem cells. This analysis was performed by Dr Gabriella Ficz, Professor Wolf Reik and their colleagues at the BBSRC-supported Babraham Institute, Cambridge, UK. Epigenetics refers to the range of DNA modifications that affect gene expression but are not sequence-based. For example, chemical methyl tags on DNA can silence gene expression. Cells gain epigenetic markers as they assume a defined cell identify. Therefore, early embryo cells show a low level of

methylation, corresponding to their lack of commitment to a particular cell fate. Last year, the Babraham group discovered a large-scale loss of methylation from the genome of reset mouse embryonic stem cells.

Ficz and Reik were able to show that, overall, the reset human stem cells showed a loss of methylation marks throughout the genome; they essentially had their epigenetic memories wiped clean. This low level of DNA methylation demonstrated their similarity to early embryonic cells and thus was a strong indication of their regained pluripotency.

Dr Gabriella Ficz, who undertook the epigenetic analysis of the cells as a post-doctoral researcher in Professor Reik's group, said: "This study brings us one step closer to the ultimate aim in regenerative medicine of using patient-derived cells to avoid immune rejection in cell and organ replacement therapies. It's all about finding out what the cell needs in order to survive and multiply while making sure that they have lost the memory of the tissue they came from. Both conditions need to be fulfilled for successful use of embryonic stem cells in tissue generation."

Professor Wolf Reik, Group Leader at the Babraham Institute continued: "We can liken this reprogramming to giving cells amnesia so they forget any previous developmental decisions they have made. Returning them to this state means that we can then control their cellular decisions, allowing us to generate the particular types of cells needed. This area has huge medical potential, for example, being able to provide reset stem cells back to a patient that we can be confident will develop into the correct cell type as required, for example, nerve cells."

Professor Michael Wakelam, Director of the Babraham Institute added: "This research is an enormous step forward in answering questions about whether human stem cells can be reset to a ground state and the feasibility of maintaining pluripotency. It is also an excellent demonstration of the importance of collaborative research making the

most of the extensive and complementary expertise that can be found in Cambridge."

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More information: Takashima *et al.* (2014). Resetting transcription factor control circuitry towards ground state pluripotency in human. *Cell*. http://www.cell.com/cell/abstract/S0092-8674(14)01099-X

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