Molecular alliance that sustains embryonic stem cell state

4 March 2008

One of the four ingredients in the genetic recipe that scientists in Japan and the U.S. followed last year to persuade human skin cells to revert to an embryonic stem cell state, is dispensable in ES cells, thanks to the presence of a molecular alliance between a specific group of key proteins known as transcription factors, a research team led by the Genome Institute of Singapore (GIS) under the Agency for Science, Technology and Research (A*STAR) reports in the current issue of *Nature Cell Biology*.

The reprogramming factor - Klf4, one of the transcription factors that determine whether a cell's genes are active or silent - has at least two other sibling molecules that will substitute Klf4 to maintain a pluripotent embryonic stem (ES) cell state, the GIS-led team said.

Klf4 (also known as gut-enriched Krüppel-like factor or Gklf) belongs to the Krüppel-like factor (Klf) family of transcription factors that regulate numerous biological processes including proliferation, differentiation, development and apoptosis, or programmed cell death.

Since reprogramming mature cells to the ES state may provide a ready source of tissue for biomedical research and clinical treatment of diseases such as Parkinson's and diabetes, several laboratories, including GIS, are trying to better understand and finely tune the reprogramming process.

The team looks for clues for what these reprogramming ingredients are doing in ES cells.

"Klf4 has been a mysterious player among the four reprogramming factors. As taking out Klf4 in ES cells did not have any apparent effects, it is difficult to reconcile why such a potent reprogramming factor has no role in ES cell biology," said GIS scientist Ng Huck Hui, Ph.D., who headed the research team. Other members of the team include researchers from the National University of Singapore and University of Illinois at Urbana-Champaign.

The GIS research team found that when Klf4 was depleted, Klf2 and Klf5 took over Klf4's role. To understand the molecular basis of the Klf4 redundancy, the scientists studied the DNA binding and transcription activation properties of the three Klfs and found that the profiles of the three Klfs were strikingly similar.

"Most important, the data showed that the other Klfs were bound to the target sites when one of them was depleted." said Dr. Ng. "These Krüppel-like factors form a very powerful alliance that work together on regulating common targets. The impact of losing one of them is masked by the other two sibling molecules."

For example, Klfs were found to regulate the Nanog gene and other key genes that must be active for ES cells to be pluripotent, or capable of differentiating into virtually any type of cells. Nanog gene is one of the key pluripotency genes in ES cells.

"We suggest that Nanog and other genes are key effectors for the biological functions of the Klfs in ES cells," Dr. Ng said.

"Together, our study provides new insight into how the core Klf circuitry integrates into the Nanog transcriptional network to specify gene expression unique to ES cells.

The way these factors network with key genes in ES cells suggest a way of how Klf4 (along with the other three reprogramming factors) can jump-start the ES cell gene expression engine in adult cells," he noted.

Although these three Klfs are involved in diverse biological roles, their redundant roles have not

been previously appreciated.

"Dr. Ng and his colleagues at the Genome Institute of Singapore again have unraveled another intricacy of what makes a stem cell," said Edison Liu, M.D., Executive Director of GIS. "This work brings us closer to a detailed understanding of the genetic components of stemness."

Alan Colman, Ph.D., internationally recognized leader in stem cell research, said, "Klf4 is a transcription factor that came to prominence recently because it was one of four factors used to reprogram somatic cells back to the pluripotent state seen in embryonic stem cells.

"The mystery of the role of Klf4 has been revealed in studies by Huck Hui and colleagues," added Colman, Executive Director of the Singapore Stem Cell Consortium, which like GIS, is part of Singapore's A*STAR. "They show for the first time that Klf4 itself is not needed for the maintenance of the pluripotent state in ES cells; however, this is because the cells have a number of other Klf-like transcription factors that can substitute for Klf4."

Source: Agency for Science, Technology and Research, Singapore

APA citation: Molecular alliance that sustains embryonic stem cell state (2008, March 4) retrieved 21 October 2021 from https://phys.org/news/2008-03-molecular-alliance-sustains-embryonic-stem.html

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.