Scientists discover switch to speed up stem cell production

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A team of scientists from Genome Institute of Singapore (GIS) of the Agency for Science, Technology and Research (A*STAR) have shown how proteins involved in controlling genes work together to carry out their functions in stem cells and demonstrated for the very first time, how they can change interaction partners to make other types of cells. The work highlighted the collaborative nature of modern biology in which techniques and knowledge from bioinformatics analysis, structural biology, biochemistry and stem cell molecular biology were used together to find the specific amino acid within the protein that facilitated the molecular switch between stem cells and other types of cells. This discovery, published in the journal *Stem Cells*, has implications for generating stem cells more efficiently for biomedical applications and could help facilitate the development of treatments for diseases such as diabetes, Parkinson's disease, and Huntington's disease.

Dr Larry Stanton, Deputy Director for Research Affairs and Senior Group Leader of the Stem Cell and Developmental Biology department at GIS, together with Dr Prasanna Kolatkar, Dr Ralf Jauch, Dr Irene Aksoy and other colleagues from GIS, were able to take a protein, Sox17, which normally makes gut cells, and convert it into making stem cells by changing a single amino acid. Significantly, the "new" Sox17 protein was able to make stem cells at five times the normal rate. The scientists were also able to take Sox2, a protein that normally creates stem cells and a close relative of Sox17, and convert it into making gut cells.

Dr Larry Stanton, one of the co-leaders of the project, said, "This research is a modification of the old theory that there are few native transcription factors which can help to make induced pluripotent stem cells. We show that one can take a transcription factor without IPS cell forming activity and in fact make it much more potent."

Dr Prasanna Kolatkar, Dr Stanton's partner in the research, "This is the first time inter-conversion of cell developmental programs has been demonstrated. Furthermore, this functional switch change was implemented by mutating a single amino acid thus showing the atomic level of understanding of the mechanism. There are many groups worldwide working on aspects of transcription factors and stem cells, as well as other groups focusing on the biochemistry and structural biology of transcription factors. What distinguishes our group is the unique integrative and collaborative science at GIS enabling us to bridge the gap between the two disciplines to study the science of transcription factors in stem cells."

"This is an elegant study combining a range of approaches from bioinformatics to in vivo studies to switch protein functions with a tweak of just a single amino acid," said Dr Ian Chambers, Professor of Pluripotent Stem Cell Biology at the University of Edinburgh. "By carefully comparing the biochemical properties of one of the keepers of pluripotent identity, Sox2 and the related pluripotency destroying factor, Sox17, Jauch and co-workers have made the stunning discovery that these divergent biological functions are caused largely by the identity of a single amino acid side chain in the DNA binding domain of the Sox proteins that interfaces with the transcription factor Oct4 and determines the selectivity of the Oct4/Sox binary complex for DNA. This is precisely the type of analysis that will be required to obtain the deep understanding of control of stem cell identity that is absolutely essential if we are to properly and safely use pluripotent stem cells for regenerative strategies."

Dr Alan Colman, Executive Director of the Singapore Stem Cell Consortium at the Institute of Medical Biology, A*STAR, said, "Transcription factor (TFs) interactions with genomic DNA are one of the main elements that define cell identity during development and in adult organisms. One of the mysteries of the field is how structurally similar TFs can have very diverse effects. In a remarkable piece of work that combines diverse techniques such as X-ray crystallography, gene mutagenesis and functional analysis, my colleagues at the A*STAR Genome Institute and the Nanyang Technological University show that the change of a single amino acid can cause TFs to assume a completely different functional character."

Continued Dr Colman, "This piece of truly elegant and insightful work is evidence of what can happen when talent from diverse fields come together to achieve breakthroughs in research. I am confident that scientists at A*STAR will continue to step across the boundaries of traditional research disciplines and produce exciting and groundbreaking work as Singapore strives towards being Asia's Innovation Capital."

More information: *Stem Cells*: "Conversion of Sox17 into a Pluripotency Reprogramming Factor by Re-engineering its Association with Oct4 on DNA".

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