Scientists succeed in manipulating stem cells into liver and pancreas precursor cells

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Scientists from the Genome Institute of Singapore (GIS) in A*STAR have developed a novel method of directing human pluripotent stem cells (hPSCs) into highly pure populations of endoderm, a valuable cell type that gives rise to organs including the liver and pancreas.

These cells are highly sought-after for therapeutic and biotechnological purposes, but have been historically difficult to attain from hPSCs. The ability to generate pure endoderm at higher yields from hPSCs is a key and important step towards the use of stem cells in clinical applications.

The discovery, published in the prestigious scientific journal *Cell Stem Cell* in January 2014, was led by Dr Bing Lim, Senior Group Leader and Associate Director of Cancer Stem Cell Biology at the GIS, Dr Lay Teng Ang, a postdoctoral fellow from Dr Lim's lab, and Kyle Loh, a graduate student at Stanford University School of Medicine.

hPSCs are stem cells that can generate over 200 distinct cell types in the human body. They respond to multiple external protein instructions to differentiate into other cell types. Therefore, generating one single cell type from hPSCs, and a pure population of that given cell type, is delicate as hPSCs have a tendency to also form other types of cells.

Employing a highly systematic and novel approach, the group screened for proteins and chemicals that promote the formation of a single desired cell type, and concurrently block induction of unwanted cell types. This strategy uncovered a combination of triggers that could drive hPSCs

towards pure populations of endoderm. The valuable cells produced and the insights gained from this work have brought stem cells one step closer to clinical translation and furthered basic research into the understanding of how cell fates are specified during stem cell differentiation.

Prof Thomas Graf, Coordinator of the Differentiation and Cancer Programme at the Center for Genomic Regulation, Barcelona, commented, "Using this novel strategy, the work beautifully shows how hPSCs can be guided to differentiate into the endoderm cells at high efficiencies. The strategy described should be more widely applicable to other desired cell types."

Next, leveraging the highly pure population of endoderm cells, the team utilised GIS' expertise in next-generation sequencing as well as bioinformatics and accurately characterised the transcriptional and enhancer states of these highly pure cells. Enhancers are DNA elements that can become activated to increase the expression of flanking genes. In hPSCs, a category of dormant enhancers was reported to be pre-configured before subsequently becoming activated when the cells differentiate.

Dr Shyam Prabhakar, Group Leader of Computational and Systems Biology, and Associate Director of Integrative Genomics at the GIS said, "Our new results indicate that the reality is more complex. Beyond current scientific knowledge, we found a larger superset of inactive enhancer states, all of which have the ability to convert to an active state upon cell differentiation."

The study not only provides a more comprehensive model of enhancer regulation of cellular differentiation, it also provides a valuable resource for the scientific community. Prof Ken Zaret of the Department of Cell and Developmental Biology at the University of Pennsylvania said, "The

rich trove of genomic data from their hESC work beautifully illustrates the power of having developed a rigorous developmental system that will serve as a resource for years to come".

Dr Lim added, "This unprecedented access to highly pure population of endodermal cells attracts pharmaceutical companies, who are interested in further making human liver cells to tests drug toxicities."

GIS' Executive Director Prof Ng Huck Hui said, "This is a beautiful piece of work to delineate the early events in cell fate decision. The findings will enable researchers to obtain high quality endodermal cells for future applications."

More information: "Efficient Endoderm Induction from Human Pluripotent Stem Cells by Logically Directing Signals Controlling Lineage Bifurcations." Kyle M. Loh, Lay Teng Ang, Jingyao Zhang, Vibhor Kumar, Jasmin Ang, Jun Qiang Auyeong, Kian Leong Lee, Siew Hua Choo, Christina Y.Y. Lim, Massimo Nichane, Junru Tan, Monireh Soroush Noghabi, Lisa Azzola, Elizabeth S. Ng, Jens Durruthy-Durruthy, Vittorio Sebastiano, Lorenz Poellinger, Andrew G. Elefanty, Edouard G. Stanley, Qingfeng Chen, Shyam Prabhakar, Irving L. Weissman, Bing Lim. *Cell Stem Cell* - 09 January 2014. DOI: 10.1016/j.stem.2013.12.007

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