Study demonstrates cells can acquire new functions through transcriptional regulatory network

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Researchers at the RIKEN Omics Science Center (OSC) have successfully developed and demonstrated a new experimental technique for producing cells with specific functions through the artificial reconstruction of transcriptional regulatory networks. As an alternative to induced pluripotent stem cells, the technique promises to enable faster and more efficient production of functional cells for use in cancer therapy and a variety of other areas.

Starting with the first-ever production of induced pluripotent stem cells (iPS cells) in 2006, cell reprogramming - the genetic conversion of cells from one type to another - has revolutionized stem cell research and opened the door to countless new medical applications. Inducing such reprogramming, however, is difficult, inefficient and time-consuming, involving a largely hit-or-miss process of selecting candidate genes.

In the current study, the OSC research team explored an alternative to iPS cells based on the use of transcriptional regulatory networks (TRNs), networks of transcription factors and the genes they regulate. Previous research by the team characterized the dynamic regulatory activities of such transcription factors during cellular differentiation from immature cell (monoblast) to developed (monocyte-like) cell using human acute monocytic leukemia cell lines (THP-1). Their findings led them to hypothesize that functional characteristics of the cell-type are maintained by its specific TRN.

Their new paper builds on this hypothesis, establishing a series of new methods for identifying transcription factors (TFs) for the monocyte network, which play a key role in inducing cell-specific functions. Four core TF genes of the monocyte TRN, identified using this approach, were introduced into human fibroblast cells, expression of which activated monocytic functions including phagocytosis, inflammatory response and chemotaxis. Genome-wide gene expression analysis of this reprogrammed cell showed monocyte-like gene expression profile, demonstrating that reconstruction of a functional TRN can be achieved by introducing core TRN elements into unrelated cell types.

Published in the journal *PLoS ONE*, the newly-developed methods open the door to a new form of direct cell reprogramming for clinical use which avoids the pitfalls of embryonic stem (ES) and induced pluripotent stem (iPS) cells, charting a course toward novel applications in regenerative medicine and drug discovery.

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