Special Issue: Direct Reprogramming

Brief Review

Direct reprogramming

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Recent studies have revealed that the fates of cells can be forcibly converted from the original cell source to a completely different cell type by artificial manipulation of the gene expression patterns in cells. This phenomenon is called “direct reprogramming” and is attracting a great deal of attention in the fields of biology and medicine. To induce such direct cell-fate conversion, transcription factors that determine the fate of a cell are introduced into another type of cell and forcibly expressed. These special transcription factors are generally known as “master transcription factors”, and enable the reconstitution of a cell-type-specific transcriptional network by activating and suppressing the expressions of multiple genes that decide the properties of cells. In line with this definition, it can be said that the generation of induced pluripotent stem (iPS) cells also represents a case of direct reprogramming. However, to prevent confusion of terms in this field of science, it is widely accepted that direct cell-fate conversion without passing through a state of iPS cells is specified as direct reprogramming.

The concept of master transcription factors has been supported by several previous studies, including the identification of MyoD as a factor capable of inducing the program for muscle cell fate in mouse fibroblasts[1)]. However, the most significant information in this area of research could be considered to arise from the generation of iPS cells, which clearly showed that the creation of a core transcriptional network based on a set of master transcription factors is important for fate-conversion of cells[2)]. In fact, since the generation of mouse iPS cells, many researchers have sought to identify sets of transcription factors that can induce the conversion of mouse fibroblasts into non-fibroblastic cells, including neuronal cells, cardiomyocytes, and hepatocytes. As a result of these efforts, studies on direct reprogramming have extended worldwide and developed more than expected, and recent progresses in this field have enabled cell-fate conversion not only in animals, but also in humans.

In this special issue, several groups engaged in studies of direct reprogramming present their data as original articles or summarize their previous findings as review articles. With regard to the direct reprogramming of fibroblasts to hepatocytes, we report data showing the early process of the conversion of mouse embryonic fibroblasts to hepatocyte-like cells, designated induced hepatocyte-like (iHep) cells, by live-cell imaging, immunofluorescence staining, and quantitative polymerase chain reaction (qPCR) analyses. Unexpectedly, our data demonstrated that direct reprogramming of fibroblasts to iHep cells began immediately after the introduction of master transcription factors for hepatocyte differentiation into fibroblasts. These findings suggest that iHep cells can be prepared rapidly when these cells are required for studies, therapies, and screening of drugs for patients with liver diseases.

Drs. Miyamoto and Ieda at Keio University describe recent findings regarding direct reprogramming of mouse and human fibroblasts to cardiomyocyte-like (iCM) cells. In addition to several transcription factors, microRNAs were also effective for the conversion of human fibroblasts into iCM cells by suppressing fibroblast-specific features. Moreover, cardiac fibroblasts residing in the mouse heart could be directly converted into iCM cells by forced expression of master transcription factors for cardiomyocyte differentiation *in vivo*, and these cells ameliorated cardiac function after acute myocardial infarction. It is expected that these new technologies will develop into hopeful avenues toward heart regeneration.

The research team of Dr. Suzuki at RIKEN comprises a group of experts in the analysis of cell-type-specific transcriptional networks. They are working on a comprehensive transcriptome analysis for functional annotation of the mammalian genome (FANTOM) and developing a systemic approach to identify sets of transcription factors that can create core transcriptional networks to induce fate-conversion of cells. Using their system, they found a set of master transcription factors that can induce conversion of human fibroblasts into monocyte-like cells. This type of approach will be a powerful tool for revealing cell-type-specific transcriptional networks and paring down the candidates for critical transcription factors that determine the fate of cells.

Studies on direct reprogramming of the fates of cells have just begun to increase, and therefore many mysteries and possibilities remain largely hidden within this phenomenon. I hope that this special issue will provide an opportunity for readers to become involved with this new technology and contribute toward the development of their own research regarding inflammation and regeneration.

References

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