Journal club

FROM MYOD1 TO IPS CELLS

Most of the undergraduates that I teach have heard about the generation of induced pluripotent stem (iPS) cells from somatic cells by the enforced expression of transcription factors. However, few of them are aware of the previous discoveries that led to the insight that transcription factors can change cell fate. An elegant set of experiments led to the discovery of myoblast determination protein 1 (MYOD1) as a key determinant of muscle cell fate and got me interested in the field of epigenetics and reprogramming.

A key finding that provided the basis for the identification of MYOD1 was the observation by Taylor and Jones that the treatment of fibroblast cell lines with the DNA analogue 5-azacytidine induced their conversion into adipocytes, chondrocytes and myogenic cells.

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The recognition that 5-azacytidine blocks DNA methyltransferases raised the possibility that the demethylation of genes in fibroblasts causes their phenotypic switch into these specialized cell types.

Lassar *et al.* formally proved that structural DNA changes are indeed responsible for the myogenic conversion of fibroblasts by demonstrating that transfected genomic DNA from 5-azacytidine-treated cells, but not from untreated cells, could induce myogenic features in fibroblasts. Finally, Davis *et al.* used ‘subtractive hybridization’ to identify the elusive myogenic factor (or factors) and pulled out three candidates (MYOD1, MYOA and MYOH), of which only MYOD1 harboured myogenic activity when overexpressed in fibroblasts.

These experiments exemplify the laborious steps that it takes to go from an initial observation to the identification of a gene that is involved in a cellular process. Moreover, these papers were influential in the field of cellular reprogramming as they established a conceptual framework for the recent discoveries of induced pluripotency and transcription factor-induced ‘transdifferentiation’ of one differentiated cell type into another.

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ORIGINAL RESEARCH PAPERS Taylor, S. M. & Jones, P. A. Multiple new phenotypes induced in 10T1/2 and 3T3 cells treated with 5-azacytidine. *Cell* **17**, 771–779 (1979) | Lassar, A. B., Paterson, B. M. & Weintraub, H. Transfection of a DNA locus that mediates the conversion of 10T1/2 fibroblasts to myoblasts. *Cell* **47**, 649–656 (1986) | Davis, R. L., Weintraub, H. & Lassar, A. B. Expression of a single transfected cDNA converts fibroblasts to myoblasts. *Cell* **51**, 987–1000 (1987)
FURTHER READING Stadtfeld, M. & Hochedlinger, K. Induced pluripotency: history, mechanisms, and applications. *Genes Dev.* **24**, 2239–2263 (2010)