# Scientists learn how to avoid a roadblock when reprogramming cells

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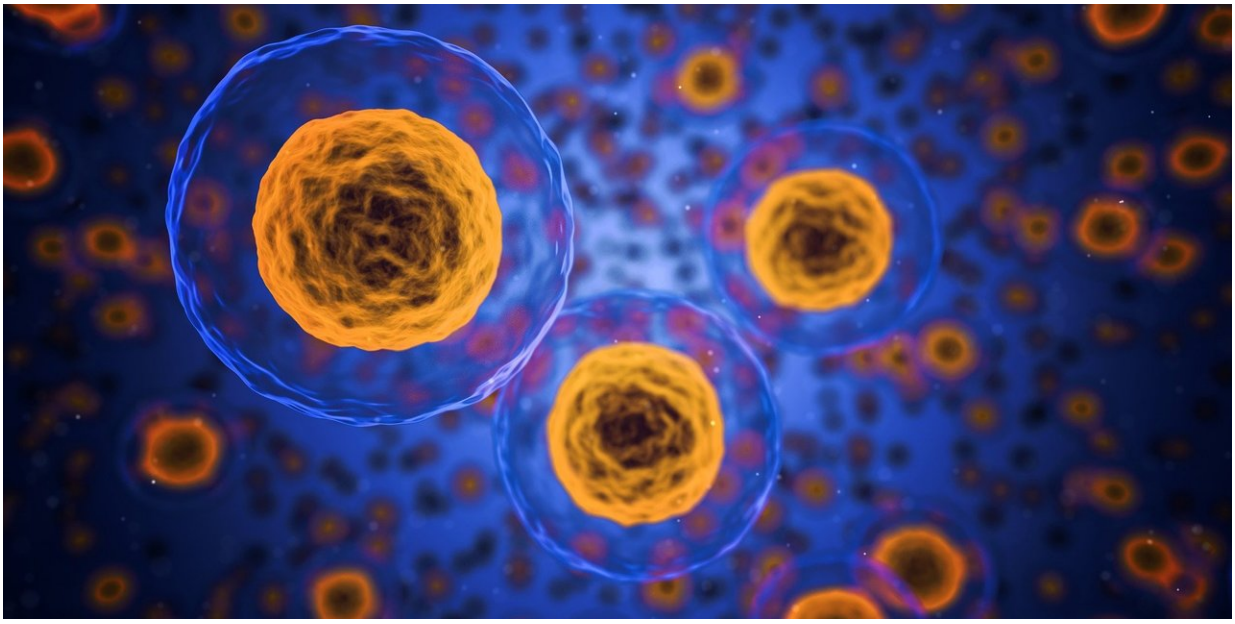

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Over a decade ago, Shinya Yamanaka and Kazutoshi Takahashi made a discovery that would revolutionize biomedical research and trigger the field of regenerative medicine. They learned how to reprogram human adult cells into cells that behave like embryonic stem cells. Scientists were shocked that something so complex could be done so simply, and they had thousands of questions.

The reprogrammed cells are known as induced pluripotent stem cells (iPSCs). Researchers can create iPSCs from a patient's blood or skin cells, and use these patient-specific cells to study diseases or even create new tissues that could be transplanted back into the patient as therapy.

Initially, Nobel Laureate and Gladstone Senior Investigator Yamanaka, MD, PhD, and Staff Research Investigator Takahashi, PhD, identified four genes—abbreviated as O, S, K, and M—that cause cells to transform into iPSCs. The genes O, S, and K were known to help the cells become pluripotent, which allows them to produce any other cell type in the body.

The role of gene M (short for MYC), however, was unclear. They knew that by adding MYC, they could reprogram cells 10 percent more efficiently. But they didn't know why.

Twelve years later, Yamanaka and Takahashi finally defined the role of MYC in this important reprogramming process, answering several lingering questions. Their findings are published today in the scientific journal *Cell Reports*.

They discovered that MYC helps cells get around a significant roadblock in the process. They also found that, in some instances, MYC isn't actually needed for adult cells to successfully transform into iPSCs.

## The Power of Three Discoveries

To reprogram cells, scientists typically add four genes (O, S, K, and MYC) to a dish containing adult cells. This allows the cells to start multiplying, which is a distinctive feature of stem cells. But after three days, the cells suddenly encounter a roadblock and stop multiplying, or proliferating. Then, on day seven, the cells start multiplying again and go on to become iPSCs.

If the researchers don't add MYC to the dish, the cells go through the same process, but they never overcome the obstacle, so they cannot successfully convert into iPSCs.

"We realized that MYC seems to help cells get around this roadblock, and that this needs to happen for adult cells to turn into iPSCs, but we still didn't quite understand how MYC did that," explained Takahashi. "Interestingly, we were able to figure it out thanks to three discoveries that happened independently in the lab, while people were working on different things."

The first discovery helped them find an early indicator of a cell's potential to finish reprogramming. It also allowed them to easily identify when the roadblock would occur, providing a valuable time reference for the subsequent findings.

The second discovery stemmed from a separate project on a protein called LIN41. The scientists found that if they replaced MYC with LIN41 in the cocktail of genes involved in reprogramming—meaning if they used O, S, K and LIN41—they could convert adult cells into iPSCs with the same efficiency.

"This was strange because it meant that, contrary to what we believed, MYC isn't necessary for cells to reprogram efficiently," said Tim Rand, MD, PhD, staff scientist at Gladstone and a first author of the study. "It turns out that adding LIN41 altogether avoids the onset of the roadblock that prevents cells from converting into iPSCs."

The team found that when they use the combination of O, S, K, and LIN41, the adult cells don't stop proliferating after the third day. Instead, they continue to multiply as if nothing happened and successfully complete the reprogramming process. This is because LIN41 blocks another protein, called p21, which causes the roadblock.

The third discovery proved to be even more astonishing. It showed that, in a particular cell line, neither MYC nor LIN41 are needed to enhance reprogramming.

The scientists went through the same process using tumor-derived cells that continuously multiply. Then, they removed LIN41, and nothing happened. Puzzled, they tried to remove MYC and, once again, nothing changed.

"That result was very shocking to me," said Rand. "Given everything we thought we knew about MYC and LIN41 at the time, we couldn't comprehend how these genes were so beneficial in somatic cell reprogramming, but absolutely useless in tumor reprogramming. Eventually, when we realized how it fit in, it was such useful information. It made us realize that certain cell types can fortuitously accomplish the role of MYC and LIN41 during reprogramming—to disable the p21 response. If I could relive that day over again, I would make sure it was a big celebration."

Rand and the rest of the team realized that without p21, there is no roadblock, so LIN41 is not needed to avoid it. They also showed that MYC is mainly useful because it activates LIN41. So, without the p21 roadblock, MYC isn't needed either.

## Bringing Clarity to a Complex Process

Through these multiple discoveries, the Gladstone scientists noticed that the reprogramming process involves many genes and proteins important for cancer biology. In fact, they believe the roadblock trying to prevent cells from multiplying is the same one that tries to prevent cancer from spreading.

"When cancer biologists add certain factors to a cell that should drive it

toward cancer, the cell panics and, to protect itself, it stops multiplying," said Takahashi. "We think the same thing is happening here, because cells are reacting to reprogramming as if it were cancer. It's not that they're trying to block the cells from transforming into iPSCs, but they've simply never been exposed to this process before and don't know how to react."

The new study explains many important activities involved in cellular reprogramming, and debunks certain leading theories about the role of MYC in this process.

"For a long time now, the entire field was collecting data on MYC, LIN41, and other genes and proteins without knowing what most of it meant," said Yamanaka, who is also director of the Center for iPS Cell Research and Application (CiRA) at Kyoto University, and professor at UC San Francisco. "Our study finally allows us to clearly understand all the data and address questions about the roles and importance of many of these elements."

With a clearer picture of the reprogramming process in hand, the field of regenerative medicine can now build upon these findings to answer the next set of burning questions.

**More information:** Tim A. Rand et al. MYC Releases Early Reprogrammed Human Cells from Proliferation Pause via Retinoblastoma Protein Inhibition, *Cell Reports* (2018). DOI: 10.1016/j.celrep.2018.03.057

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