MicroRNA cocktail helps turn skin cells into stem cells

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Stem cells are ideal tools to understand disease and develop new treatments; however, they can be difficult to obtain in necessary quantities. In particular, generating induced pluripotent stem (iPS) cells can be an arduous task because reprogramming differentiated adult skin cells into iPS cells requires many steps and the efficiency is very low – researchers might end up with only a few iPS cells even if they started with a million skin cells.

A team at Sanford-Burnham Medical Research Institute (Sanford-Burnham) set out to improve this process. In a paper published February 1 in The *EMBO Journal*, the team identified several specific microRNAs (miRNAs) that are important during reprogramming and exploited them to make the transition from skin cell to iPS cell more efficient.

"We identified several molecular barriers early in the reprogramming process and figured out how to remove them using miRNA," said Tariq Rana, Ph.D., director of the RNA Biology program at Sanford-Burnham and senior author of the study. "This is significant because it will enhance our ability to use iPS cells to model diseases in the laboratory and search for new therapies."

"Our study not only presents new mechanistic insights about the role of non-coding RNAs during somatic cell reprogramming but also provides proof of principle using microRNAs as great enhancers for iPS cell generation," added Zhonghan Li, graduate student and first author of the study.

MiRNAs are small strands of genetic material that may play a major role in many diseases by gumming up protein production. In this study, Dr. Rana and his colleagues observed that three groups of miRNAs, including two known individually as miR-93 and miR-106b, are activated as part of a defense mechanism that occurs when cells are stressed by the standard skin cell reprogramming process. Digging deeper, they determined that miR-93 and miR-106b target two proteins called Tgfbr2 and p21, which slow up the path to iPS cells by halting the cell cycle – the cell's process of duplicating its DNA and dividing into two identical "daughter" cells – and promoting cell death.

Not only does this finding reveal more about the genetic underpinnings of iPS cell formation, but the researchers took advantage of this new information to speed up the process. When they added extra miR-93 and miR-106b to skin cells, Tgfbr2 and p21 were blocked, more cells survived, and iPS cells were more readily obtained.

"In some respects, this work may be regarded as a landmark contribution to the field of stem cell biology in general and cellular reprogramming in particular," said Evan Y. Snyder, M.D., Ph.D., director of Sanford-Burnham's Stem Cells and Regenerative Biology program. "Up until now, cellular differentiation and de-differentiation has focused principally on the expression of genes; this work indicates that the strategic non-expression of genes may be equally important. The work has demonstrated that miRNAs do function in the reprogramming process and that the generation of iPSCs can be greatly enhanced by modulating miRNA action. In addition to helping us generate better tools for the stem cell field, such findings inevitably facilitate our understanding of normal and abnormal stem cell behavior during development and in disease states."

More information: Original paper Li Z, Yang CS, Nakashima K, Rana TM. Small RNA-mediated regulation of iPS cell generation. *The*

EMBO Journal. February 1, 2011. www.nature.com/emboj/journal/v … ull/emboj20112a.html