Dual-function protein switch can be tweaked to improve the effectiveness of cellular reprogramming

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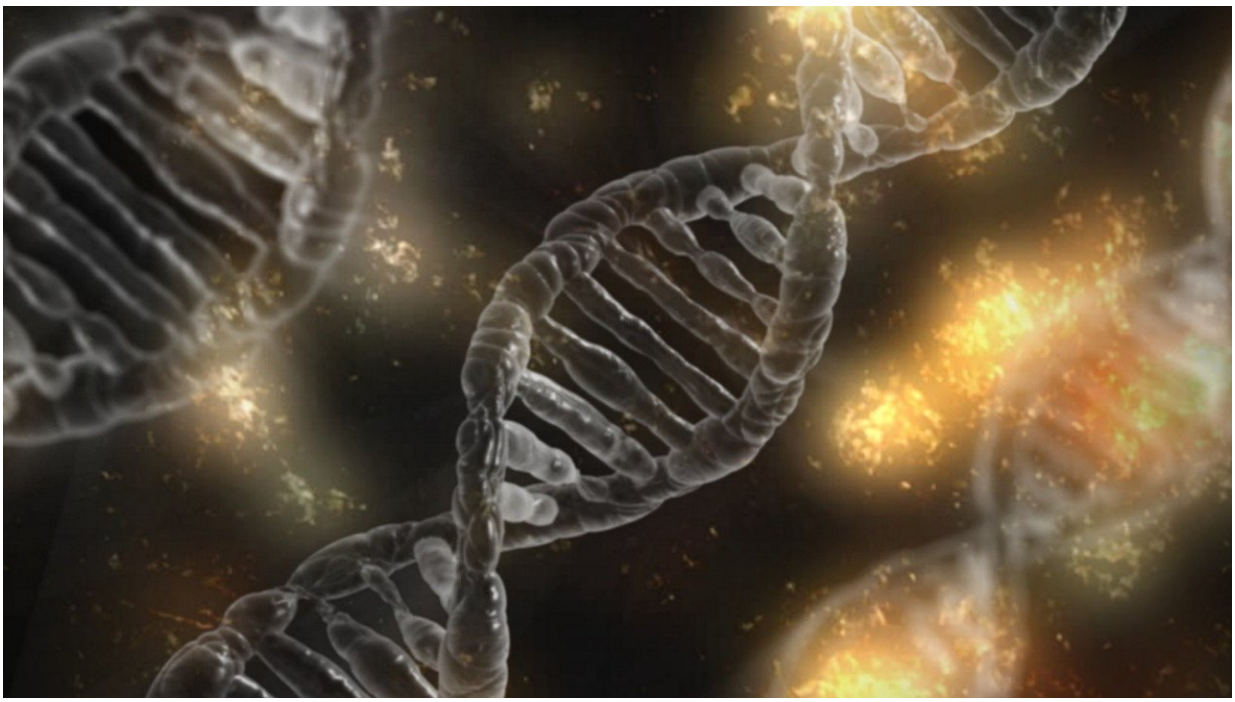

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Toggling the functions of a protein that regulates gene expression during cellular reprogramming ensures cell fate conversion, an A*STAR study has found.

Understanding how cell fate is maintained is key for improving the efficiency with which induced pluripotent stem cells, iPSCs, can be derived from patients' somatic cells and differentiated into tissue-specific cell types for the treatment of medical conditions such as leukemia or spinal cord injury.

The histone variant, H3.3, is a protein that has previously been shown to activate gene transcription during cellular differentiation, but its exact role in cell fate transition was unclear. Jonathan Yuin-Han Loh at the A*STAR Institute of Molecular and Cell Biology in Singapore and colleagues have investigated the effect of H3.3 in the transformation of mouse embryonic fibroblasts into iPSCs and hematopoietic progenitor cells, as well as in the differentiation of stem cells into neurons.

In all three scenarios they found that H3.3 has a dual role: it maintains parent cell identity in the early stages of reprogramming, and aids cell fate transition at later stages. This switch in function is regulated by the histone chaperone Hira, which deposits H3.3 on specific DNA regions, and an epigenetic modification involving the addition of methyl groups to two lysine residues. "Our results were both surprising and unexpected, because H3.3 seems to work as a universal regulator of cell fate," says Loh.

When the team overexpressed transcription factors known to induce the conversion of fibroblasts into pluripotent stem cells, they found that genes associated with fibroblast function were enriched with H3.3. Transiently reducing the expression of H3.3 at this early stage of reprogramming significantly improved the induction of pluripotency, indicating that H3.3 can impede cell fate conversion.

However, as reprogramming progressed, H3.3 became bound to genes associated with pluripotency. Reducing its expression at late stages of reprogramming reduced the reprogramming efficiency suggesting that

H3.3 is essential for establishing the new pluripotent cell fate.

Interestingly, when the team tried to differentiate embryonic stem cells into neurons, reducing the levels of H3.3 led to the loss of expression of genes involved in the maintenance of pluripotency and an increase in the expression of neuronal genes, confirming its role in cell lineage transition.

As Loh explains, "our discovery suggests a way to convert skin cells to stem cells with higher efficiency, simply by tweaking the levels of H3.3". Further understanding the processes driving cell fate transition will improve the efficiency with which cells can be reprogrammed for therapeutic purposes.

More information: Hai-Tong Fang et al. Global H3.3 dynamic deposition defines its bimodal role in cell fate transition, *Nature Communications* (2018). DOI: 10.1038/s41467-018-03904-7

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