Researchers can reprogramme cells to original state for regenerative medicine

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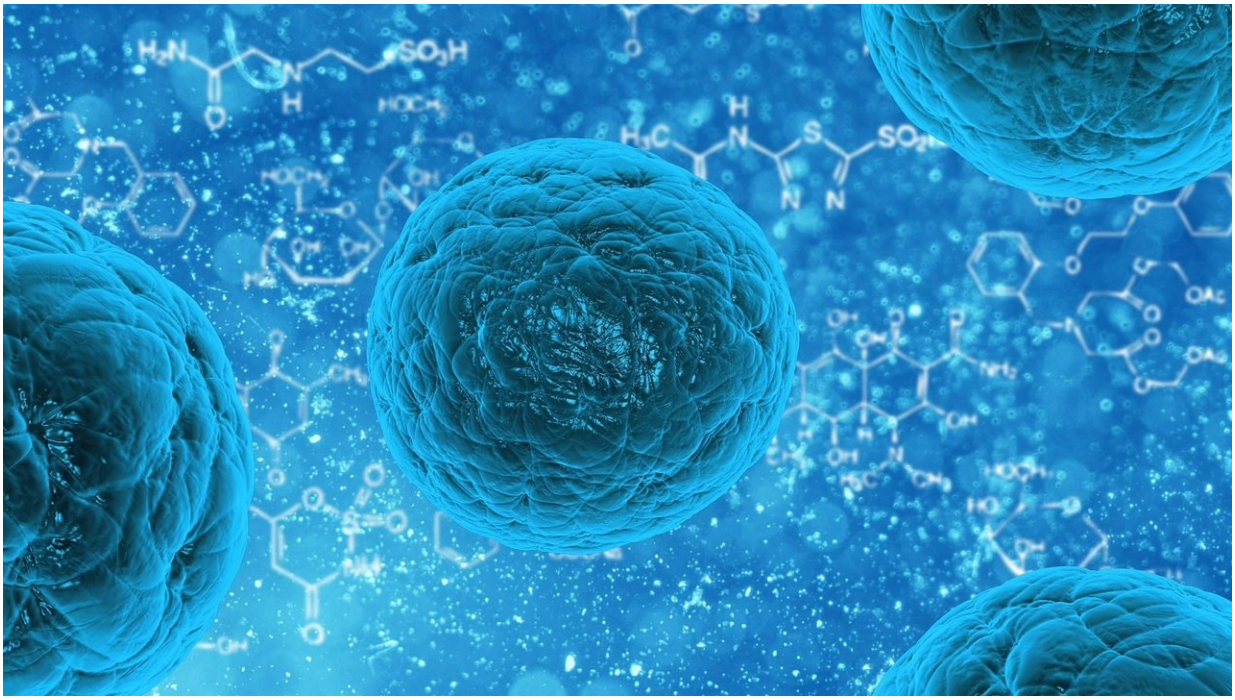

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Early mammalian development is a highly complex process involving elaborate and highly coordinated biological processes. One such process is zygotic genome activation (ZGA) which occurs following the union of the sperm and egg, marking the beginning of life. The resultant early embryos, termed 'zygotes' are capable of generating the entire organism, a property known as totipotency.

Totipotent cells sit atop the developmental hierarchy and have the greatest potency of all cell types, giving it limitless therapeutic potential. Surpassing pluripotent embryonic stem cells, which are only able to differentiate into all cell types within the embryo, the totipotent zygote loses its totipotency as it matures into pluripotency.

Scientists at the National University of Singapore's Yong Loo Lin School of Medicine have now found a way to manipulate pluripotent cells into acquiring the totipotent capacity previously thought to exist only in the zygote. This not only provides key insights into how totipotency is formed and the earliest events in mammalian development, but opens new doors for potential cell therapies that were previously unexplored.

The study identified a totipotency-inducing factor—Negative Elongation Factor A (NELFA), which is capable of driving pluripotent embryonic stem cells into totipotency in a petri dish. NELFA achieves this feat by causing specific changes in the gene regulatory and metabolic networks of the cell. Specifically, NELFA has the ability to reactivate certain genes that are only active in the zygote but otherwise silent in embryonic stem cells. NELFA is also able to alter the energy using pathways in the pluripotent stem cells. All these changes will result in pluripotent stem cells reverting into a totipotent-like state.

Discovering this method of inducing totipotency in cells outside of the embryo also provides a means to engineer cells with maximum cell plasticity for therapeutic purposes. This increases the potential applications of regenerative medicine, especially in cell replacement therapies.

According to Assistant Professor Tee Wee Wei, the lead investigator in this study, the eventual goal of this research is to translate the findings into the development of rapid and efficient cellular reprogramming strategies for clinical application, such as in the treatment of debilitating

diseases and developmental disorders.

More information: Zhenhua Hu et al, Maternal factor NELFA drives a 2C-like state in mouse embryonic stem cells, *Nature Cell Biology* (2020). DOI: 10.1038/s41556-019-0453-8

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