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Genetically reprogramming biological clocks: one step closer to the Fountain of Youth

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Imagine telling explorers of the New World that the Fountain of Youth was hidden in their cells. That's probably what Kristen C. Browder's team could say after successfully reversing the biological clock of living mice. According to their results, the secrets of rejuvenation seem to be buried in the heart of each of our cells, in other words, in our genes.

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Aging, the cruel fate from which no one can escape, is associated with drastic physiological changes amplified by the increased expression of genes related to cell damage. This uncontrolled expression contributes to the natural aging of our organs and tissues which gradually lose the ability to perform their vital functions. Modern medicine has already succeeded in considerably extending our lifespan, and reprogramming cells to rejuvenate them appears to be a potential new tool to counteract the effects of aging.

Cellular reprogramming using transcription factors (proteins that control gene expression) enables cells to be rejuvenated by restoring their genetic features to a younger stage. This tool intervenes in the epigenetic patterns, which are reversible chemical modifications of our DNA acquired during development and influenced by our environment all along our life, and especially by aging. These reversible changes affect gene expression and can therefore serve as markers of biological age measurable with “epigenetic clocks”. The scientists are particularly interested in reversing age-related epigenetic changes using ‘reprogramming factors’, which can restore younger epigenetic patterns in cells, therefore reversing the "biological clock".

To rejuvenate the cells, the researchers used Yamanaka reprogramming factors, which are a combination of 4 transcription factors, usually abbreviated as OSKM. Using these transcription factors on cell cultures allowed the researchers to reprogram and reset the identity of cells. As a result, differentiated cells revert to their youthful undifferentiated (stem cell) stage.

To assess the effects of reprogramming in the organism, the scientist studied three different types of mice: mice with Hutchinson-Gilford progeria

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syndrome causing accelerated aging, healthy wild-type mice, and healthy mice genetically modified to artificially induce the expression of OSKM factors. Mice are treated for short and repeated intervals to avoid tumors and loss of cellular identity, resulting in partial reprogramming. To further investigate the effects of partial reprogramming, healthy mice were treated either long-term for 10 months or short-term for 1 month, and at different ages.

To figure out whether the effects of age could be reversed, they measured biological age using epigenetic clocks on several tissues. The scientists measured changes in gene expression due to the OSKM factors using RNA sequencing. In addition, they identified age-related biomarkers in the blood to detect any physiological changes. Finally, the results were compared to untreated mice to certify that alterations are caused by the expression of OSKM factors.

Results show that partial reprogramming reduces cellular aging in mice without any significant side effects. Indeed, after the treatment, progeria mice show reduced aging in a part of the hypothalamus involved in episodic memory. In addition, a decrease in fibrosis in the skin is observed (poor wound healing resulting in scars). Most impressively, their lifespan was extended.

The epigenetic clocks revealed a reduced biological age for several organs in long-term treated genetically modified mice. Indeed, the epigenetic patterns of the skin and kidneys of these mice are similar to the patterns observed in younger animals. This made the researchers wonder what the effects of partial reprogramming are on the ability for the skin to heal. Indeed, they found a decrease of scarring in long-term treated and progeria mice, thus bringing back the capacity to heal wounds in the skin to a younger stage. They also found a reduced expression of genes naturally overexpressed with aging. These genes are mainly related to inflammation and senescence (the decrease in vital activity associated with age). Finally, analysis of the blood showed that in general age-related biomarkers were reduced in long-term genetically treated mice. This suggests that the mice were overall rejuvenated by the procedure.

In conclusion, the success in performing cellular reprogramming on animals without significant side effects is a big step, but many questions remain. Cellular partial reprogramming shows an interesting way to prevent age-related diseases. However, not all organs react the same to this technique and limitations are known concerning the capacity of old cell to react to partial reprogramming naturally resulting in skepticism about the real ability of rejuvenating entire organisms. Furthermore, epigenetic patterns being also influenced by the personal life background, they could represent a limitation in the efficiency of the technique.

The Fountain of Youth may not have been discovered yet, but this tool could open the door for new treatments of certain medical conditions, such as progeria and burn injuries.