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Longevity and rejuvenation effects of cell reprogramming are decoupled from the loss of somatic identity

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Motivation and Aim: Transient somatic cell reprogramming has been proposed as a perspective rejuvenation intervention [1]. However, its association with the mechanisms of aging and longevity at molecular level remains unclear. Here we conducted a meta-analysis of time-series gene expression data and identified robust transcriptomic signature of reprogramming of mouse and human cells.

Methods and Algorithms: We gathered 41 gene expression datasets of time-course cell reprogramming from mouse and human cells. We used meta-analysis technique (mixed effects model) to aggregate multiple datasets into one reprogramming signatures. By comparing them to the signatures of aging and lifespan extending interventions, we revealed genes and functional processes associated with rejuvenation and longevity effects of reprogramming. We also trained multi-tissue transcriptomic aging clocks developed for humans and mice to indicate which particular combination of reprogramming factors provides rejuvenation effects.

Results: We observed significant co-regulation of genes perturbed by reprogramming and established lifespan-extending interventions, including those involved in DNA repair and inflammation. On the other hand, age-related gene expression changes were reversed during reprogramming, as confirmed by multi-tissue transcriptomic aging clocks. Importantly, the longevity and rejuvenation effects induced by reprogramming were mainly independent from the changes associated with the gain of pluripotency.

Conclusion: Overall, this work reveals specific molecular mechanisms associated with reprogramming induced rejuvenation at gene expression level and provides instruments for discovery of new geroprotective interventions that induce rejuvenation effect of reprogramming without posing the risk of pluripotency and neoplasy.

References

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