MEDIA RELEASE
FOR IMMEDIATE RELEASE

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SINGAPORE SCIENTISTS DISCOVER REJUVENATION FACTORS
Findings will advance our understanding of how cellular metabolism changes during aging and during rejuvenation after egg fertilisation

SINGAPORE – Scientists from A*STAR's Genome Institute of Singapore (GIS) have discovered metabolic rejuvenation factors in eggs. This critical finding furthers our understanding of how cellular metabolism changes during aging, and during rejuvenation after egg fertilisation.

When a sperm fertilises an egg to create a baby, two adult cells combine to form a new embryo. A similar process of combining an egg's cytoplasm with an adult cell nucleus led to the cloning of Dolly the sheep. However, the metabolic factors underlying this fascinating process had remained unclear.

A new study from GIS suggests that old mitochondria – the oxygen-consuming metabolic engines in cells – are roadblocks to cellular rejuvenation. By tuning up a gene called Tcl1, which is highly abundant in eggs, researchers were able to suppress old mitochondria to enhance a process known as somatic reprogramming, which turn adult cells into embryonic-like stem cells.

GIS researchers found that Tcl1 does its job by suppressing mitochondrial polynucleotide phosphorylase, thereby inhibiting mitochondrial growth and metabolism.

Findings from the study were published in the scientific journal *Cell Reports.*

Stem cell researchers had known that egg (or oocyte) cytoplasm contains some special unknown factors that can reprogramme adult cells into embryonic-like stem cells, either during egg-sperm fertilisation or during artificial cloning procedures like those that created Dolly the sheep. While the Nobel Prize winner Dr Shinya Yamanaka had invented a technology called induced pluripotent stem cell (iPSC) reprogramming to replace the ethically controversial oocyte-based reprogramming technique, oocyte-based reprogramming was still deemed superior in complete cellular reprogramming efficiency.

To address this shortfall, the GIS team led by Dr Khaw Swea-Ling, Dr Lim Bing and Dr Ng Shyh-Chang combined oocyte factors with the iPSC reprogramming system. Their bioinformatics-driven screening efforts[1] led to two genes: Tcl1 and its cousin Tcl1b1. After a deeper investigation, the team found that the Tcl1 genes were acting via the mitochondrial enzyme, PnPase.

"We were quite surprised, because nobody would have thought that the key to the oocyte's reprogramming powers would be a mitochondrial enzyme. The stem cell field's conventional wisdom suggests that it should have been some other signalling genes instead," said corresponding author of the research, Dr Ng Shyh-Chang.

Tcl1 is a cytoplasmic protein that binds to the mitochondrial enzyme PnPase. By locking PnPase in the cytoplasm, Tcl1 prevents PnPase from entering mitochondria, thereby suppressing its ability to promote mitochondrial growth and metabolism. Thus, an increase in Tcl1 suppresses old mitochondria's growth and metabolism in adult cells, to enhance the somatic reprogramming of adult cells into embryonic-like stem cells.

Cracking the mystery of reprogramming factors in oocytes is an important milestone. These new insights could boost efficacy of the alternative, non-oocyte-based iPSC techniques for stem cell banking, organ and tissue regeneration, as well as further our understanding of how cellular metabolism rejuvenates after egg-sperm fertilisation. This could help address both the aging and the fertility problems of modern societies.

GIS Executive Director Prof Ng Huck Hui said, "This is an exciting step forward in the study of cellular aging. Although accumulated defects in mitochondrial metabolism were known to cause cellular aging, no solutions were available. Shyh-Chang's team has uncovered a molecular pathway to solve this problem".

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[1] While the researchers attempted to deconstruct the mechanisms of oocyte-based reprogramming, no human oocytes or embryos were used or destroyed in the process as the screening effort was bioinformatics database-driven.

IMAGE
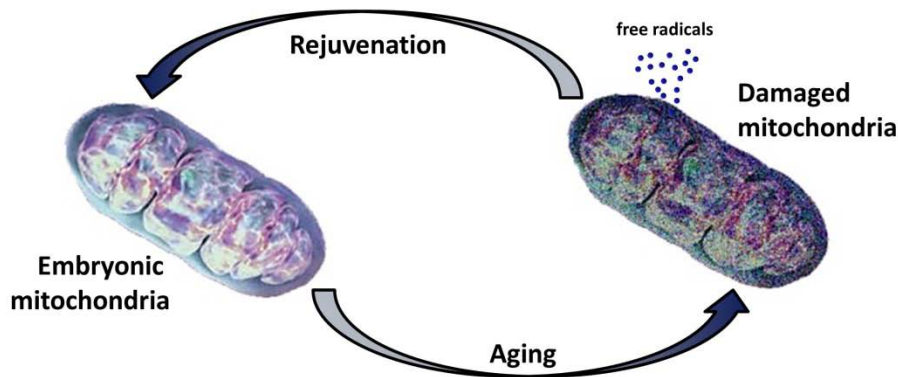
Mitochondria during cellular aging

Notes to Editor:

The research findings described in this media release can be found in the scientific journal *Cell Report*s, under the title, "Oocyte Factors Suppress Mitochondrial Polynucleotide Phosphorylase to Remodel the Metabolome and Enhance Reprogramming" by KHAW Swea-Ling[1,2], CHUA Min-Wen[1], KOH Cheng-Gee[2,3,*], LIM Bing[1], NG Shyh-Chang[1,*]

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Full text of the *Cell Report*s paper can be accessed online from: http://www.cell.com/cell-reports/fulltext/S2211-1247(15)00792-5

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About the A*STAR's Genome Institute of Singapore (GIS)

The Genome Institute of Singapore (GIS) is an institute of the Agency for Science, Technology and Research (A*STAR). It has a global vision that seeks to use genomic sciences to achieve extraordinary improvements in human health and public prosperity. Established in 2000 as a centre for genomic discovery, the GIS will pursue the integration of technology, genetics and biology towards academic, economic and societal impact.

The key research areas at the GIS include Human Genetics, Infectious Diseases, Cancer Therapeutics and Stratified Oncology, Stem Cell and Regenerative Biology, Cancer Stem Cell Biology, Computational and Systems Biology, and Translational Research.

The genomics infrastructure at the GIS is utilised to train new scientific talent, to function as a bridge for academic and industrial research, and to explore scientific questions of high impact.

For more information about GIS, please visit www.gis.a-star.edu.sg.

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As a Science and Technology Organisation, A*STAR bridges the gap between academia and industry. Our research creates economic growth and jobs for Singapore, and enhances lives by contributing to societal benefits such as improving outcomes in healthcare, urban living, and sustainability.

We play a key role in nurturing and developing a diversity of talent and leaders in our Agency and Research Institutes, the wider research community and industry.

A*STAR oversees 18 biomedical sciences and physical sciences and engineering research entities primarily located in Biopolis and Fusionopolis.

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