The Institute of Medical Science
The University of Tokyo

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Research News

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GLS1 inhibitor that selectively removes senescent cells ameliorated age-associated tissue dysfunction and diseases such as arteriosclerosis

Senescent cells accumulate in organs during aging, promote tissue dysfunction, and cause numerous aging-related diseases like cancer. The cells arise through a process called “cellular senescence”, a permanent cell cycle arrest resulting from multiple stresses.

A collaborative research group led by Professor Makoto Nakanishi of the Institute of Medical Science, The University of Tokyo (IMSUT), and co-researchers(※)has identified an inhibitor of the glutamate metabolic enzyme **GLS1(*1)** so that its administration selectively eliminates senescent cells in vivo. They confirmed that the GLS1 inhibitor eliminated senescent cells from various organs and tissues in aged mice, ameliorating age-associated tissue dysfunction and the symptoms of obese diabetes, arteriosclerosis, and NASH. The results of this research were published in "*Science*" on January 15, 2021.

Previous studies have shown that genetically engineering removal of senescent cells from aged mice delays the onset of geriatric diseases such as arteriosclerosis and renal damage, and extends healthy life expectancy. However, those studies have not led to identifying useful drug candidates.

Professor Nakanishi said," Our results can contribute to the development of new anti-aging therapies that remove senescent cells by targeting these cells' metabolic characteristics.".

Lysosomal membranes hold the key to senescent cell removal

The research team has developed a new method for producing purified senescent cells to search for genes essential for senescent cells' survival. This new method activates the p53 gene in the G2 phase, which can efficiently induce cellular senescence.

They used purified senescent cells to search for genes essential for senescent cells' survival, then identified GLS1, which is involved in glutamine metabolism, as a potential candidate gene.

When they examined the effect of GLS1 inhibitor on the mortality of senescent cells, senescent cells were more sensitive to GLS1 inhibition due to damage to the lysosomal membrane and decreased intracellular pH. When they administered GLS1 inhibitors to aged mice, senescent cells in various tissues and organs were removed, and the aging phenomenon was significantly improved.

0rganelles called **lysosomes(*2)** play an essential role in the regulation of intracellular pH. The team analyzed the dynamics of lysosomes and found the vital fact that damage to the lysosomal membranes in senescent cells lowers intracellular pH.
For details of the research, please see the paper.

Expectations for innovative anti-aging therapies and treatments for geriatric diseases

The results of this study show more interesting results. As aging progresses, motor function declines due to muscle loss, and metabolic disorders due to adipose tissue atrophy occur. But, when the research team injected GLS1 inhibitors into mice suffering age-related disorders, the progression of these age-related symptoms was suppressed. Moreover, GLS1 inhibitors were able to relieve the symptoms of obese diabetes, arteriosclerosis, and **NASH(*3).**

According to the team, GLS1 inhibitors are currently in clinical trials as effective cancer treatments. "We hope that innovative anti-aging therapies and treatments for geriatric diseases will be developed that can remove senescent cells by treatment with GLS1 inhibitors," said Professor Nakanishi.

※Co-researches

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Makoto Suematsu (Professor, Department of Biochemistry, Keio University School of Medicine)

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Makoto Arita (Team leader, Laboratory for Metabolomics, RIKEN Center for Integrative Medical Sciences)

Masataka Sugimoto (Director, Research Institute, National Center for Geriatrics and Gerontology)

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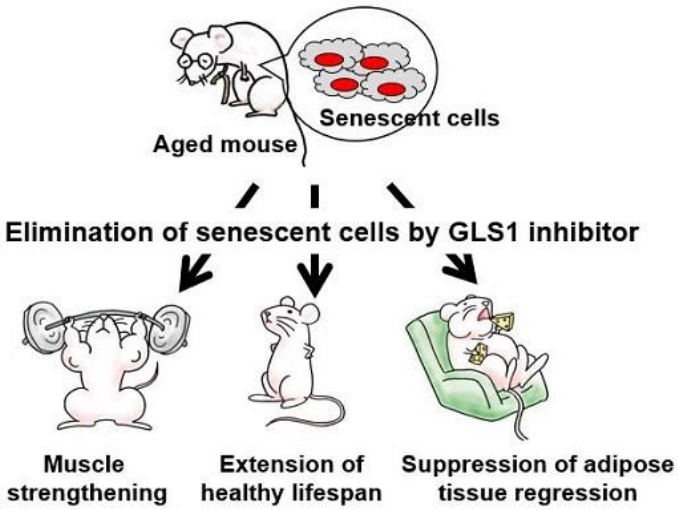

Outline of this study : The research team identified a GLS1 inhibitor that selectively removes senescent cells, found that administration of the GLS1 inhibitor improves age-related tissue dysfunction and the symptoms of obese diabetes, arteriosclerosis, and NASH.

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Research Notes

(*1) GLS1

Abbreviation for glutaminase 1. A type of amidohydrolase enzyme that produces glutamic acid and ammonia from glutamine.

(*2) Lysosomes

One of the membrane-enclosed organelles of eukaryotes. The lumen of lysosomes is acidified to around pH 5 and contains hydrolases, allowing the organelle to perform intracellular digestion.

(*3) NASH

A disease in which fat accumulates in the liver in an alcohol-independent manner, causing inflammation and fibrosis. As it progresses, it causes cirrhosis and liver cancer.

About the research

1) Journal Article

Yoshikazu Johmura*, Takehiro Yamanaka$, Satotaka Omori$, Teh-Wei Wang$, Yuki Sugiura, Masaki Matsumoto, Narumi Suzuki, Soichiro Kumamoto, Kiyoshi Yamaguchi, Seira Hatakeyama, Tomoyo Takami, Rui Yamaguchi, Eigo Shimizu, Kazutaka Ikeda, Nobuyuki Okahashi, Ryuta Mikawa, Makoto Suematsu, Makoto Arita, Masataka Sugimoto, Keiichi I. Nakayama, Yoichi Furukawa, Seiya Imoto, and Makoto Nakanishi*, "Senolysis by glutaminolysis inhibition ameliorates various age-associated disorders", *Science*, Vol. 371, Issue 6526, pp. 265-270, January 15, 2021.
(*corresponding co-authors, $the second co-authors)
DOI: 10.1126/science.abb5916
URL : https://science.sciencemag.org/content/371/6526/265

2) Publication Journal

Science
https://science.sciencemag.org/

3) Contact

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https://www.amed.go.jp/en/news/newsreleases_2020.html

・Project for Elucidating and Controlling Mechanisms of Aging and Longevity

https://www.amed.go.jp/en/program/list/15/01/003.html

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About IMSUT (The Institute of Medical Science, The University of Tokyo)

The Institute of Medical Science, The University of Tokyo (IMSUT) evolved from its origin, the Institute for Infectious Disease in 1967. The mission of IMSUT is to advance basic knowledge underlying infectious diseases, cancer and other intractable diseases and ultimately to control them. IMSUT consists of about 165 faculty members, 224 graduate students coming from various schools such as medicine, science, agriculture, pharmaceutical science, and engineering to develop more effective interdisciplinary research in basic life science and genomic medicine.
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