Scientists reverse aging in human cell lines and give theory of aging a new lease of life

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Professor Hayashi who is called "White Lion" by his students because of his white hair and big voice

Can the process of aging be delayed or even reversed? Research led by specially appointed Professor Jun-Ichi Hayashi from the University of

Tsukuba in Japan has shown that, in human cell lines at least, it can. They also found that the regulation of two genes involved with the production of glycine, the smallest and simplest amino acid, is partly responsible for some of the characteristics of aging.

Professor Hayashi and his team made this exciting discovery while in the process of addressing some controversial issues surrounding a popular theory of aging. This theory, the mitochondrial theory of aging, proposes that age-associated mitochondrial defects are controlled by the accumulation of mutations in the mitochondrial DNA.

Abnormal mitochondrial function is one of the hallmarks of aging in many species, including humans. This is mostly due to the fact that the mitochondrion is the so-called powerhouse of the cell as it produces energy in a process called cellular respiration. Damage to the mitochondrial DNA results in changes or mutations in the DNA sequence. Accumulation of these changes is associated with a reduced lifespan and early onset of aging-related characteristics such as weight and hair loss, curvature of the spine and osteoporosis.

There is, however, a growing body of conflicting evidence that has raised doubts about the validity of this theory. The Tsukuba team in particular has performed some compelling research that has led them to propose that age-associated mitochondrial defects are not controlled by the accumulation of mutations in the mitochondrial DNA but by another form of genetic regulation.

Noriben, which looks like mitochondria

The research, published this month in the prestigious journal *Nature*'s *Scientific Reports*, looked at the function of the mitochondria in human fibroblast cell lines derived from young people (ranging in age from a fetus to a 12 year old) and elderly people (ranging in age from 80-97 years old). The researchers compared the mitochondrial respiration and the amount of DNA damage in the mitochondria of the two groups, expecting respiration to be reduced and DNA damage to be increased in the cells from the elderly group. While the elderly group had reduced respiration, in accordance with the current theory, there was, however,

no difference in the amount of DNA damage between the elderly and young groups of cells. This led the researchers to propose that another form of genetic regulation, epigenetic regulation, may be responsible for the age-associated effects seen in the mitochondria.

Epigenetic regulation refers to changes, such as the addition of chemical structures or proteins, which alter the physical structure of the DNA, resulting in genes turning on or off. Unlike mutations, these changes do not affect the DNA sequence itself. If this theory is correct, then genetically reprogramming the cells to an embryonic stem cell–like state would remove any epigenetic changes associated with the mitochondrial DNA. In order to test this theory, the researchers reprogrammed human fibroblast cell lines derived from young and elderly people to an embryonic stem cell-like state. These cells were then turned back into fibroblasts and their mitochondrial respiratory function examined. Incredibly, the age-associated defects had been reversed - all of the fibroblasts had respiration rates comparable to those of the fetal fibroblast cell line, irrespective of whether they were derived from young or elderly people. This indicates that the aging process in the mitochondrion is controlled by epigenetic regulation, not by mutations.

The researchers then looked for genes that might be controlled epigenetically resulting in these age-associated mitochondrial defects. Two genes that regulate glycine production in mitochondria, CGAT and SHMT2, were found. The researchers showed that by changing the regulation of these genes, they could induce defects or restore mitochondrial function in the fibroblast cell lines. In a compelling finding, the addition of glycine for 10 days to the culture medium of the 97 year old fibroblast cell line restored its respiratory function. This suggests that glycine treatment can reverse the age-associated respiration defects in the elderly human fibroblasts.

These findings reveal that, contrary to the mitochondrial theory of aging,

epigenetic regulation controls age-associated respiration defects in human fibroblast cell lines. Can epigenetic regulation also control aging in humans? That theory remains to be tested, and if proven, could result in glycine supplements giving our older population a new lease of life.

More information: "Epigenetic regulation of the nuclear-coded GCAT and SHMT2 genes confers human age-associated mitochondrial respiration defects," *Scientific Reports* 5, Article number:10434 DOI: 10.1038/srep10434

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