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Biology 12 /15

Case Study: Cell Organelles and Their Functions

In the past, biologists looked for clues to again and human disease by studying organs, tissues and cultures of cells. With more powerful microscopes and more sophisticated means of chemical analysis, biologists can focus on smaller elements of living things: the organelles within individual cells. Read the following scientific journal articles. Use your knowledge of cell organelles and their functions to answer the following questions about some of the current research that links cell organelles with certain conditions of aging and disease.

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

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. The research, published this month in the 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.

Story Source:

The above post is reprinted from materials provided by **University of Tsukuba**. *Note: Materials may be edited for content and length.*

Journal Reference:

1. Osamu Hashizume, Sakiko Ohnishi, Takayuki Mito, Akinori Shimizu, Kaori Iashikawa, Kazuto Nakada, Manabu Soda, Hiroyuki Mano, Sumie Togayachi, Hiroyuki Miyoshi, Keisuke Okita, Jun-Ichi Hayashi. **Epigenetic regulation of the nuclear-coded GCAT and SHMT2 genes confers human age-associated mitochondrial respiration defects**. *Scientific Reports*, 2015; 5: 10434 DOI: 10.1038/srep10434

Questions

1. Scientists studied DNA molecules taken from mitochondria in the cells of older people. These mitochondrial DNA molecules differed from the mitochondrial DNA taken from the cells of younger people.
    a. What is the function of mitochondria in a healthy cell?

    b. In view of this cellular function, why does it make sense that mitochondria might be different in the cells of older people?

2. There are more mitochondria in cells that need a lot of energy, such as heart muscle cells. Some researchers have begun to study mitochondrial DNA in the heart cells of different age groups. What do you think researchers discovered in the mitochondrial DNA taken from the heart cells of older adults?

3. Researchers have found mutated mitochondrial DNA in people suffering from Kearns-Sayre syndrome. The syndrome causes paralysis of the eye muscles, difficulty in walking and heart problems. What is the connections between Kearns- Sayre syndrome and the role of mitochondria in cell function?

Lysosomes May Contribute to Alzheimer's Disease

New research from Yale University shows lysosomes, the "garbage disposal" systems of cells, can fail and perhaps contribute to Alzheimer's disease.

Lysosomes, the "garbage disposal" systems of cells, are found in great abundance near the amyloid plaques in the brain that are a hallmark of Alzheimer's disease. Scientists have long assumed that their presence was helpful — that they were degrading the toxic proteins that trigger amyloid plaque formation.

However, in Alzheimer's patients, these lysosomes lack the ability to do their jobs properly, and instead of helping, the accumulation of lysosomes may even contribute to the disease, Yale University researchers report the week of June 29 in the Proceedings of the National Academy of Sciences.

The new findings raise the possibility that coaxing lysosomes to do their jobs could help to prevent the toxic processes that eventually destroy the minds of Alzheimer's patients.

Scientists first noted the presence of large numbers of lysosomes at amyloid plaques more than a half century ago. This new study suggests the lysosomes that build up in neurons that contact amyloid plaques are abnormally enriched with β-secretase, the enzyme that initiates the production of the toxic amyloid β peptide. These dysfunctional lysosomes lack the ability to degrade β-secretase, the researchers said.

"We think this represents a vicious circle," said Swetha Gowrishankar, a postdoctoral scientist who led the research in the laboratory of Shawn Ferguson, assistant professor of cell biology

The lysosomes cannot mature because amyloid plaques block the ability of lysosomes to travel within neuronal axons, which in turn results in the local accumulation of more β-secretase and the formation of more amyloid β peptide, the researchers believe.

The team will next use genetic strategies to restore neuronal lysosome maturation and function in mouse models

of Alzheimer's disease in order to determine whether this protects against the development of disease pathology. The researchers also note lysosome dysfunction has been linked to other neurodegenerative diseases including Parkinson's disease and frontotemporal dementia.

The labs of Pietro De Camilli, the John Klingenstein Professor of Neuroscience and Professor of Cell Biology, and Jaime Grutzendler, associate professor of neurology, also contributed to this study. All these investigators are members of the Yale Program in Cellular Neuroscience, Neurodegeneration, and Repair.

Funding support for this research was provided by the National Institutes of Health, Howard Hughes Medical Institute, the Ellison Medical Foundation, and The Consortium for Frontotemporal Dementia Research.

Source: Bill Hathaway, Yale University

Journal Reference:

Swetha Gowrishankar, Peng Yuan, Yumei Wu, Matthew Schrag, Summer Paradise, Jaime Grutzendler, Pietro De Camilli, and Shawn M. Ferguson. **Massive accumulation of luminal protease-deficient axonal lysosomes at Alzheimer's disease amyloid plaques** *Proceedings of the National Academy of Sciences of the United States of America*, vol. 112 no. 28, E3699–E3708, doi: 0.1073/pnas.1510329112

Question:

1. Some researchers now believe that Alzheimer's disease is caused by the release of destructive enzymes into the cytoplasm of nerve cells. The enzymes are thought to be released by organelles whose membranes ruptured as they were trying to digest harmful proteins. Which organelles do you think are responsible for the release of these destructive enzymes? Why?

Changes in Hepatic Enzymes and Organelles in Alcoholic Liver Disease

Liver biopsy specimens obtained from patients with alcoholic liver disease of varying severity were assayed for lysosomal and microsomal enzyme activities, the results being compared with values previously obtained in control subjects.

Analytical subcellular fractionation by sucrose-density-gradient centrifugation was performed on extracts of the biopsies and the properties of the lysosomes, plasma membrane, biliary canaliculi and endoplasmic reticulum membranes were determined. Increased activities of plasma membrane marker enzymes, particularly γ-glutamyl transpeptidase believed to be localized to the biliary canalicular membrane, were demonstrated. These findings were most marked in alcoholic cirrhosis. The centrifugation studies revealed no abnormalities in the properties of these membranes.

Although the total activities of the endoplasmic reticulum marker enzyme neutral α-glucosidase were unaltered in alcoholic liver disease, centrifugation studies showed a decrease in the density distribution of the membrane-bound enzyme in cirrhosis indicating an increase in the proportion of smooth endoplasmic reticulum membranes. Chronic ethanol intake resulted in an increased number of smooth endoplasmic reticulum in the liver cell, related to the effect of ethanol on lipid metabolism.

Apart from a small decrease in activity of certain acid hydrolases in fatty liver and in cirrhosis the activities of the lysosomal enzymes were unaffected by alcoholic liver disease.

Measurements of lysosomal integrity and density-gradient-centrifugation studies revealed no significant abnormalities in the various patient groups apart from increased stability and reduced equilibrium density of certain lysosomes in fatty liver. It is concluded that lysosomal disruption is not implicated in the pathogenesis of alcoholic liver disease.

Journal Reference:

1. Carol A. Seymour, T. J. Peters, **Clinical Science** Oct 01, 1978, 55 (4) 383-389; DOI: 0.1042/cs0550383

Question:

1. In the liver cells of a person who died from alcoholism, an extremely dense network of smooth endoplasmic reticulum was found. Why do you think this was so?