A newly discovered anti-senescence function of vitamin B2

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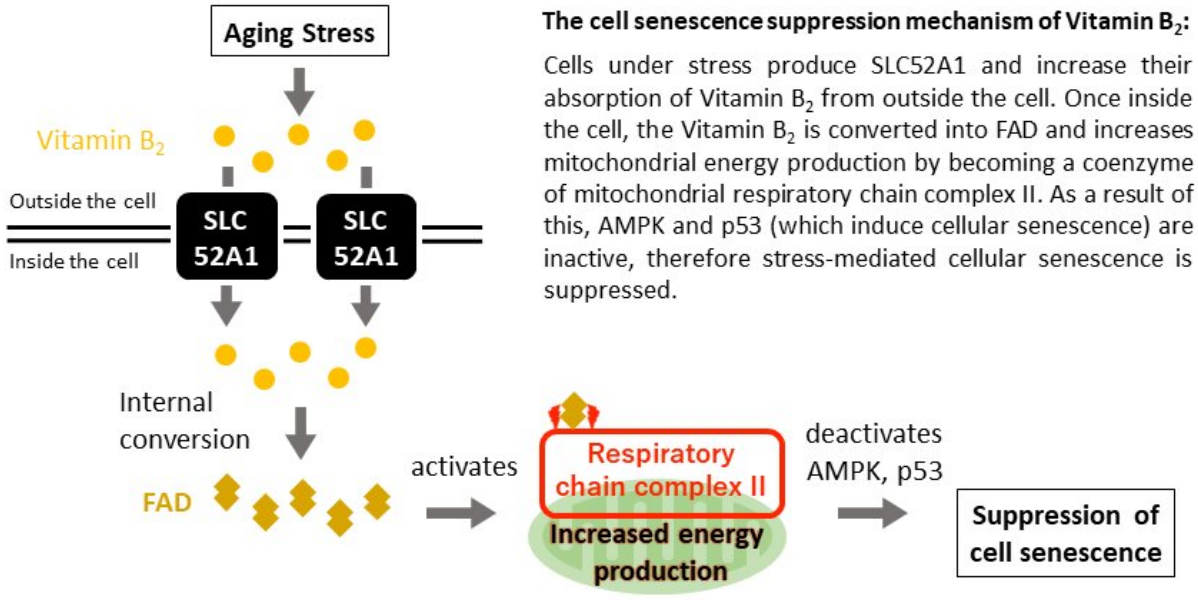

Credit: Kobe University

A group of Kobe University researchers have revealed that adding Vitamin B2 to cells that have been exposed to aging stress increases the mitochondria's ability to produce energy and prevents cell aging. The research group included Professor KAMADA Shinji and Research Associate NAGANO Taiki of the Biosignal Research Center.

It has previously been shown that the accumulation of old (i.e. senescent)

cells in the body causes age-related disorders and whole-body aging. Therefore, there is the potential to prevent and ameliorate age-related disorders and extend people's healthy lifespans using supplements and medicines containing Vitamin B2 to suppress cell senescence.

These research results were published in *Molecular Biology of the Cell* on November 1, 2021.

Main points

- The aging of the body is caused by the accumulation of old (i.e. senescent) cells. Experiments on mice have shown that age-related disorders can be prevented or treated by suppressing this accumulation.
- This research group discovered an anti-aging phenomenon whereby the cell's ability to absorb Vitamin B2 is increased in response to stress.
- Vitamin B2 suppresses cell senescence by activating the mitochondria, which produces energy.
- More detailed investigation into the relationship between Vitamin B2 and the suppression of aging could lead to the development of simple and safe treatment plans for age-related disorders that incorporate meal plans and supplements.

Research Background

Japan is a super-aged society and as a result, research into aging is becoming increasingly important to resolve the accompanying medical and welfare issues, and to help people live healthily for longer. The process by which the body ages is not completely understood, however the aging of the cells that make up the body has been revealed to be one factor. As the cell division cycle continuously repeats, the telomere

regions at the end of each chromosome get shorter, eventually resulting in cellular senescence, which is when the cell loses the ability to divide. Later research revealed that the reduction of telomere regions is not the only factor involved, and that various types of stress (such as DNA damage and reactive oxygen outbreaks) can also trigger cell senescence. It is thought that the aged cells resulting from this stress exposure accumulate inside the body as it grows older.

Over a decade of research into aging has revealed that senescent cells have the harmful ability to cause functional decline in every organ in the body. Furthermore, it has been discovered that it is possible to prevent or ameliorate age-related disorders that occur more frequently as people get older, such as cancer, cardiovascular disease, Alzheimer's and diabetes, by preventing the accumulation of senescent cells. There is intense competition worldwide to develop medicines that will extend people's healthy lifespan by preventing this accumulation, however such a drug has yet to be made available due to various issues such as side effects.

Vitamins, on the other hand, are essential micronutrients that are required to keep the human body functioning normally. As the human body cannot synthesize vitamins they must be absorbed from food and drink. Vitamin B2 (also known as riboflavin) is prevalent in foods such as meat, eggs and dairy products and is an important vitamin for energy generation and metabolism. Deficiency causes symptoms such as swelling in the mouth and anemia. On the other hand, there are no negative effect associated with overconsumption of vitamin B2 as it is soon excreted by the body. Even though vitamin B2 is an essential nutrient for maintaining health, no research has been carried out into its relationship with aging. This research team commenced research into the effects of vitamin B2 on aging in the hope that if an everyday vitamin could suppress cell senescence, this would contribute towards making low-cost and safe anti-aging drugs available.

Research Methodology

The research team discovered a phenomenon whereby resistance to cellular senescence occurred as a result of increasing the amount of SLC52A1 produced. SLC52A1 is the protein responsible for transporting vitamin B2 into cells (vitamin B2 transporter). When SLC52A1 production was increased, cellular senescence did not occur immediately even under stress conditions (where human cells were treated with a drug to injure the DNA and induce aging). Following on from this, the researchers conducted an experiment where they exposed the cells to stress and then increased the amount of vitamin B2 in the culture solution. They found that resistance to senescence increased in accordance with the amount of vitamin B2 in the solution. Inside the cell, vitamin B2 is converted into a substance called Flavin Adenine Dinucleotide (FAD), a coenzyme that promotes the chemical reactions necessary for biological activities such as energy production. In fact, the amount of FAD in cells exposed to stress increased, which resulted in the vitamin B2 that had been transported into the cells to be converted into FAD, thus suppressing senescence.

Next, the research team focused on the mitochondria to investigate the mechanism behind FAD's suppression of cellular senescence. It is known that functional decline in mitochondria causes cellular senescence, and that FAD is essential for energy production in mitochondria as it functions as a respiratory chain complex II coenzyme. When the researchers investigated the response of the mitochondria, they were surprised to find that mitochondrial activity temporarily increased in cells subjected to stress, with the subsequent decline in activity resulting in senescence. Furthermore, the researchers were able to maintain the high level of stress-mediated mitochondrial activity by increasing the amount of vitamin B2 in the culture solution, which also allowed a high level of anti-aging to be maintained.

Finally, the researchers sought to illuminate how mitochondrial activity and anti-aging are connected. To do this, they investigated the activity of the enzyme AMPK, which detects when there is insufficient energy inside a cell, and discovered that AMPK activity is suppressed by mitochondrial activity. Conversely, suppressing mitochondrial activity with a drug caused AMPK to be activated, and sends signals to the protein p53, that induces cellular senescence) to stop cell division thus resulting in an aged state. The above results reveal that Vitamin B2 increases mitochondrial activity in cells exposed to stress and prevents aging by suppressing the functions of AMPK and p53.

Further Developments

Vitamin B2 is easily absorbed from food and supplements and is quickly expelled from the body if too much is consumed. Therefore, it is hoped that simple and safe treatments for age-related disorders can be developed that utilize the cellular anti-aging property of vitamin B2 that was revealed by this study. Next, the research team will conduct animal experiments to confirm the anti-aging effect of vitamin B2, with the aim of eventually developing medicine.

More information: Taiki Nagano et al, Riboflavin transporter SLC52A1, a target of p53, suppresses cellular senescence by activating mitochondrial complex II, *Molecular Biology of the Cell* (2021). DOI: 10.1091/mbc.E21-05-0262

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