Cell aging can be slowed by oxidants

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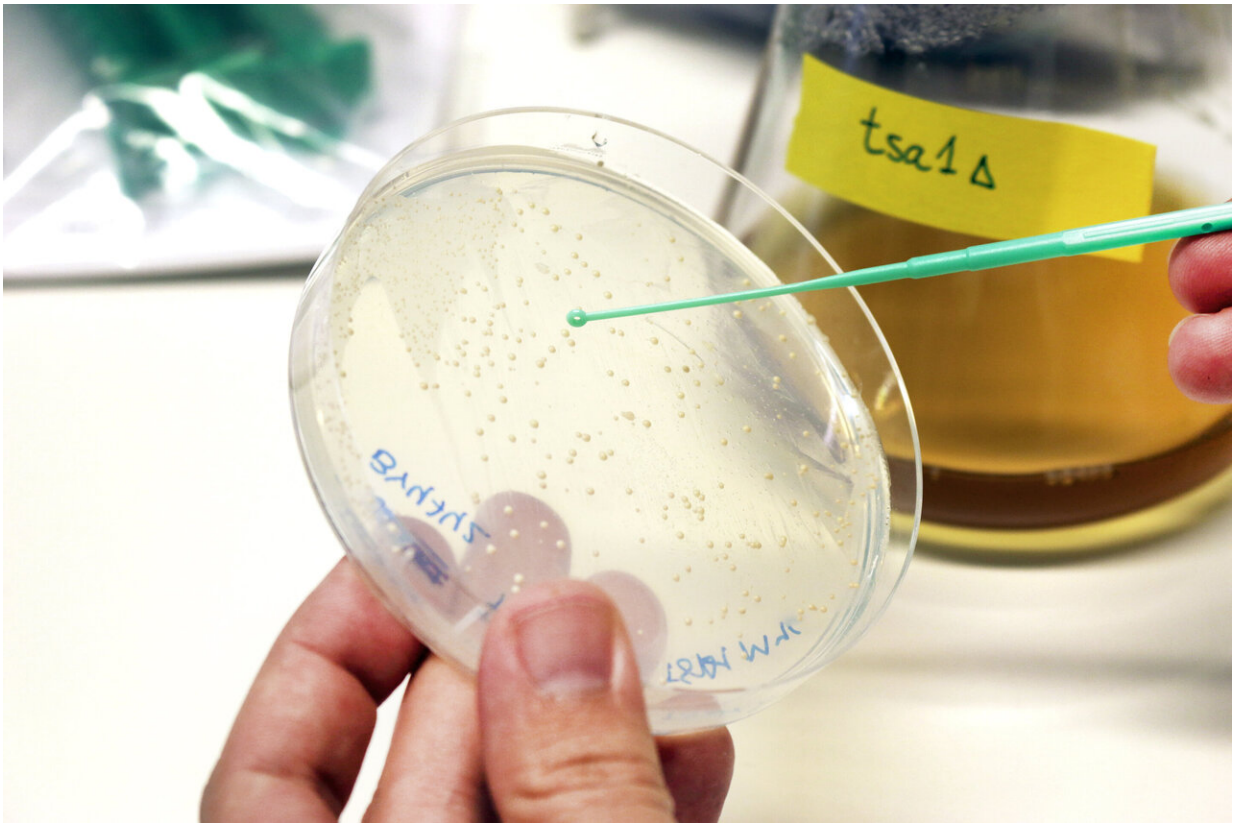


Yeast can be grown on both solid and liquid nutrition medium and is a good model system for studying ageing. Yeast cells share many molecular mechanisms with cells in more complex organisms, yet it is easy to change their DNA and study different genes' functions. Yeast also produces many generations in a short time. Credit: Martina Butorac/Chalmers University of Technology

At high concentrations, reactive oxygen species—known as

oxidants—are harmful to cells in all organisms and have been linked to aging. But a study from Chalmers University of Technology, Sweden, has now shown that low levels of the oxidant hydrogen peroxide can stimulate an enzyme that helps slow down the aging of yeast cells.

One benefit of antioxidants, such as vitamins C and E, is that they neutralize reactive oxygen species—known as oxidants—which may otherwise react with important molecules in the body and destroy their biological functions. Larger amounts of oxidants can cause serious damage to DNA, cell membranes and proteins for example. Our cells have therefore developed powerful defense mechanisms to get rid of these oxidants, which are formed in our normal metabolism.

It was previously believed that oxidants were only harmful, but recently, scientists have begun to understand that they also have positive functions. Now, the new research from Chalmers University of Technology shows that the well-known oxidant hydrogen peroxide can actually slow down the aging of yeast cells. Hydrogen peroxide is a chemical used for hair and tooth whitening, among other things. It is also one of the metabolically produced oxidants that is harmful at higher concentrations.

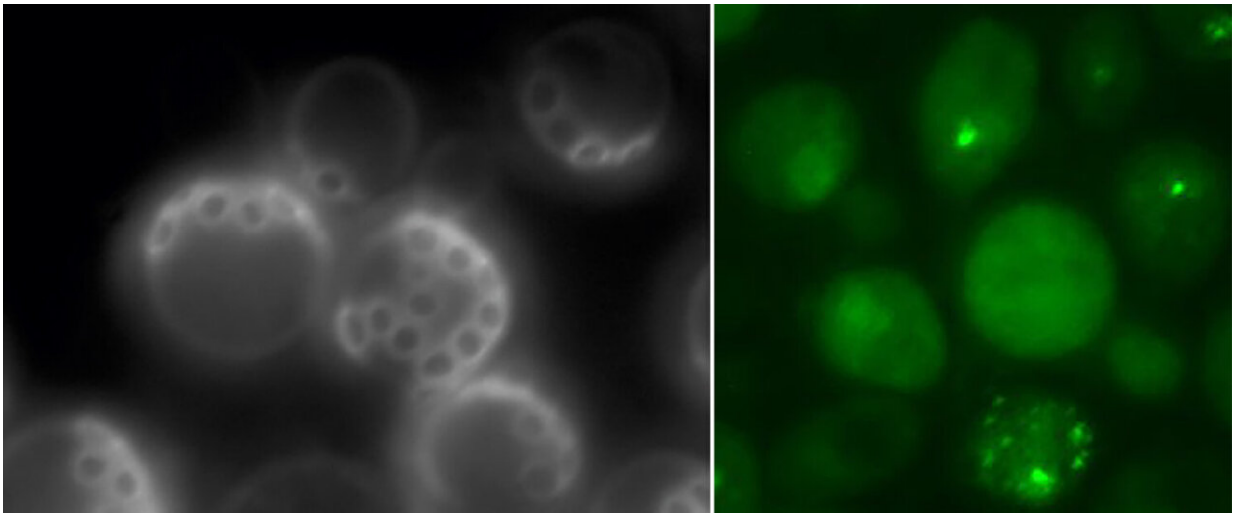
The Chalmers researchers studied the enzyme Tsa1, which is part of a group of antioxidants called peroxiredoxins.

"Previous studies of these enzymes have shown that they participate in yeast cells' defenses against harmful oxidants," says Mikael Molin, who leads the research group at Chalmers' Department of Biology and Biological Engineering. "But the peroxiredoxins also help extend the life span of cells when they are subjected to calorie restriction. The mechanisms behind these functions have not yet been fully understood."

Researchers have known that reduced calorie intake can significantly

extend the life span of a variety of organisms, from yeast to monkeys. Several research groups, including Mikael Molin's, have also shown that stimulation of peroxiredoxin activity in particular is what slows down the aging of cells in organisms such as yeast, flies and worms, when they receive fewer calories than normal via food.

"Now, we have found a new function of Tsa1," says Cecilia Picazo, postdoctoral researcher at the Division of Systems and Synthetic Biology at Chalmers. "Previously, we thought that this enzyme simply neutralizes reactive oxygen species. But now, we have shown that Tsa1 actually requires a certain amount of hydrogen peroxide to be triggered in order to participate in the process of slowing down the aging of yeast cells."



Yeast is a good model system for studying ageing. The researchers can easily determine the age of the cells by counting the bud scars, formed when they divide and form new cells by budding (left). As the yeast cells age, you can examine, for example, how proteins are damaged and aggregate (light spots in the image to the right), a process that in higher organisms can be linked to the degeneration of nerve or brain cells in, for example, Alzheimer's or Parkinson's disease. Credit: Mikael Molin/Chalmers University of Technology

Surprisingly, the study shows that Tsa1 does not affect the levels of hydrogen peroxide in aged yeast cells. On the contrary, Tsa1 uses small amounts of hydrogen peroxide to reduce the activity of a central signaling pathway when cells are getting fewer calories. The effects of this ultimately lead to a slowdown in cell division and processes linked to the formation of the cells' building blocks. The cells' defenses against stress are also stimulated, which causes them to age more slowly.

"Signal pathways which are affected by calorie intake may play a central role in aging by sensing the status of many cellular processes and controlling them," says Mikael Molin. "By studying this, we hope to understand the molecular causes behind why the occurrence of many common diseases such as cancer, Alzheimer's disease, and diabetes shows a sharp increase with age."

The fact that researchers have now come a step closer to understanding the mechanisms behind how oxidants can actually slow down the aging process could lead to new studies, for example looking for peroxiredoxin-stimulating drugs, or testing whether age-related diseases can be slowed by other drugs that enhance the positive effects of oxidants in the body.

The Chalmers researchers have shown a mechanism for how the peroxiredoxin enzyme Tsa1 directly controls a central signaling pathway. It slows down aging by oxidizing an amino acid in another enzyme, protein kinase A, which is important for metabolic regulation. The oxidation reduces the activity of protein kinase A by destabilizing a portion of the enzyme that binds to other molecules. Thus, nutrient signaling via protein kinase A is reduced, which in turn downregulates the division of cells and stimulates their defense against stress.

Other studies have also shown that low levels of reactive oxygen species can be linked to several positive health effects. These oxidants are formed in the mitochondria, the powerhouse of the cell, and the

mitohormesis process can be observed in many organisms from yeast to mice. In mice, tumor growth is slowed by mitohormesis, while in roundworms it has been possible to link both peroxiredoxins and mitohormesis to the ability of the type 2 diabetes drug metformin to slow cellular aging.

Metformin is also relevant in the hunt for drugs that can reduce the risk of older people being severely affected by COVID-19. Studies in China and the United States have yielded some promising results, and one theory is that metformin may counteract the deterioration of the immune system caused by aging.

More information: Friederike Roger et al, Peroxiredoxin promotes longevity and H2O2-resistance in yeast through redox-modulation of protein kinase A, *eLife* (2020). DOI: 10.7554/eLife.60346

Provided by Chalmers University of Technology