News and Research Communications

Research identifies key genetic link in the biology of aging

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CORVALLIS, Ore. – New research at Oregon State University suggests it may be possible to slow age-related disease with new types of treatments.

Scientists have tracked the syndromes associated with aging to their biochemical roots, and identified a breakdown in genetic communication as part of the problem. The findings imply that aging happens for a reason, and that while aspects of it may be inevitable, there could be ways to slow down disease development.

The newest study relate to a protein, Nrf2, that helps regulate gene expression and the body's reaction to various types of stressors. The research was published in Free Radical Biology and Medicine, in work supported by the National Institutes of Health and the Medical Research Foundation of Oregon.

"We're very excited about the potential of this area of research," said Tory Hagen, corresponding author on this study, and the Helen P. Rumbel Professor for Health Aging Research in the Linus Pauling Institute and the OSU Department of Biochemistry and Biophysics in the College of Science.

"At least one important part of what we call aging appears to be a breakdown in genetic communication, in which a regulator of stress resistance declines with age," Hagen said. "As people age and their metabolic problems increase, the levels of this regulator, Nrf2, should be increasing, but in fact they are declining."

Nrf2 is both a monitor and a messenger, OSU researchers say. It's constantly on the lookout for problems with cells that may be caused by the many metabolic insults of life – oxidative stress, toxins, pollutants, and other metabolic dysfunction.

When it finds a problem, Nrf2 essentially goes back to the cellular nucleus and rings the alarm bell, where it can "turn on" up to 200 genes that are responsible for cell repair, detoxification of carcinogens, protein and lipid metabolism, antioxidant protection and other actions. In their report, the scientists called it a "longevity-assurance" factor.

Nrf2 is so important that it's found in many life forms, not just humans, and it's constantly

manufactured by cells throughout the body. About half of it is used up every 20 minutes as it performs its life-protective functions. Metabolic insults routinely increase with age, and if things were working properly, the amount of Nrf2 that goes back into the nucleus should also increase to help deal with those insults.

Instead, the level of nuclear Nrf2 declines, and the OSU scientists say they have discovered why.

"The levels of Nrf2, and the functions associated with it, are routinely about 30-40 percent lower in older laboratory animals," said Kate Shay, director of the Healthy Aging Core Laboratory at OSU and co-author on this study. "We've been able to show for the first time what we believe is the cause."

The reason for this decline, the scientists said, is increasing levels of a micro-RNA called miRNA-146a.

Micro-RNAs have been one of the most profound scientific discoveries of the past 20 years. They were once thought to be "junk DNA" because researchers could see them but they had no apparent biological role. They are now understood to be anything but junk – they help play a major role in genetic signaling, controlling what genes are "expressed," or turned on and off to perform their function.

In humans, miRNA-146a plays a significant role. It can turn on the inflammation processes that, in something like a wound, help prevent infection and begin the healing process. But with aging, this study now shows that miRNA-146a expression doesn't shut down properly, and it can significantly reduce the levels of Nrf2.

This can cause part of the chronic, low-grade inflammation that is associated with the degenerative diseases that now kill most people in the developed world, including heart disease, cancer, diabetes and neurological disease.

"The action of miRNA-146a in older people appears to turn from a good to a bad influence," Shay said. "It may be causing our detoxification processes to decline just when we need them the most."

Some of the things found to be healthy for individuals, in diet or lifestyle, may be so because they help to conserve the proper balance between the actions of miRNA-146a and Nrf2, the OSU researchers said. Alternatively, it may be possible to reduce excessive levels of miRNA-146a with compounds that interfere with its function. There may also be other micro-RNAs associated with this process, they said, that need further research.

"Overall, these results provide novel insights for the age-related decline in Nrf2 and identify new targets to maintain Nrf2-dependent detoxification with age," the researchers wrote in their conclusion.

About the Linus Pauling Institute: The Linus Pauling Institute at OSU is a world leader in the study of micronutrients and their role in promoting optimum health or preventing and treating disease. Major areas of research include heart disease, cancer, aging and neurodegenerative disease.

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