Survival mode that protects cells when oxygen is low also slows aging (w/Video)

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From left to right is Dr. Ranjana Mehta, George Sutphin and Dr. Matt Kaeberlein in the laboratory where they and their team discovered a biochemical pathway that slows aging in nematodes. Credit: Leila Gray

A biochemical pathway that helps keep cells alive when oxygen is low also plays a role in longevity and resistance against some diseases of old age, according to a report to be published April 16 in the journal *Science*.

A cell's protective reaction to a drop in oxygen is called the hypoxic response. Researchers at the University of Washington (UW) have found that nematode worms live longer if their genetic make-up permits their cells to turn on the hypoxic response under normal oxygen conditions.

Not only do these worms live longer, the researchers noted, their cells

are relatively free from the toxic proteins that accumulate and clump together as an animal ages.

Dr. Matt Kaeberlein, UW assistant professor of pathology and the senior author on the study, said that defining cellular mechanisms that prevent accumulation of these proteins may point to new therapeutic targets for devastating diseases that often accompany old age in people. Toxic protein aggregations, he explained, are seen in the brain cells of those with Alzheimer's disease, Huntington's disease, and several other degenerative conditions that afflict the elderly.

The co-lead authors, Dr. Ranjana Mehta and Dr. Katy Steinkraus, uncovered the life-extending role of the hypoxic response while studying the mechanism by which dietary restriction slows aging in nematodes. Dietary restriction has been shown to increase life span in many different organisms, including worms, flies and mice. Kaeberlein's group had previously found that dietary restriction also protects against toxic protein aggregation in nematode models of Huntington's and Alzheimer's diseases. To their surprise, however, genetic experiments mapped the hypoxic response to a previously unknown longevity pathway, different from dietary restriction.

"The research findings suggest that the hypoxic response promotes longevity and reduces the accumulation of toxic proteins by a mechanism that is distinct from both dietary restriction and insulin-like signaling. It appears to be an alternative pathway," Kaeberlein said. "However, we don't know if future studies might reveal that all of these different genetic pathways converge somewhere down the line into a common mechanism for delaying the effects of age."

The key factor that controls the hypoxic response is called HIF. HIF is regulated by another protein called VHL-1, which tags HIF to be destroyed by a cellular machine called the proteasome. Destruction of

HIF by VHL-1 keeps the hypoxic response "off" when oxygen is present. The UW researchers bred worms that could not produce VHL-1, leading to persistence of HIF even in the presence of high oxygen levels. They found that these worms, which were able to turn on the hypoxic response under normal oxygen conditions, lived about 30 percent longer than worms whose cells made VHL-1.

They also found that animals lacking VHL-1 were resistant to the toxic proteins known to cause Alzheimer's and Huntington's diseases, and that their cells accumulated less of an age-pigment called lipofuscin. Lipofuscin is thought to be one indicator of an animal's health during aging. According to Kaeberlein, "These observations may suggest that the hypoxic response not only increases life span, but also lengthens health span and protects against the molecular processes that lead to neurodegenerative diseases in people." Health span refers to the period of an organism's life that is relatively free of disease.

The authors note that the hypoxic response, including HIF and VHL-1, is very well conserved in organisms from nematodes to humans, raising the possibility that modulating HIF activity may be useful for treating some age-associated diseases, and perhaps even slowing aging, in people. Kaeberlein cautions, however, that "mutation of VHL-1 is associated with a variety of tumors, and any therapies targeted toward activation of HIF would most likely need to be specific for cells that are not rapidly dividing, such as brain cells or muscle cells."

"What we're focused on now," says Mehta, "is figuring out how HIF is protecting the animals from aging." In both worms and people, HIF regulates the activity of several factors involved in growth and resistance to stress. "One or more of these factors must be the key."

Kaeberlein agrees. "This is a completely new pathway for aging and age-associated disease. If we can understand at a very detailed level how HIF

is slowing aging, we may be able to use that information to develop effective therapies for treating age-associated diseases in people."

Source: University of Washington (news : web)