Glutathione precursor GlyNAC reverses premature aging in people with HIV

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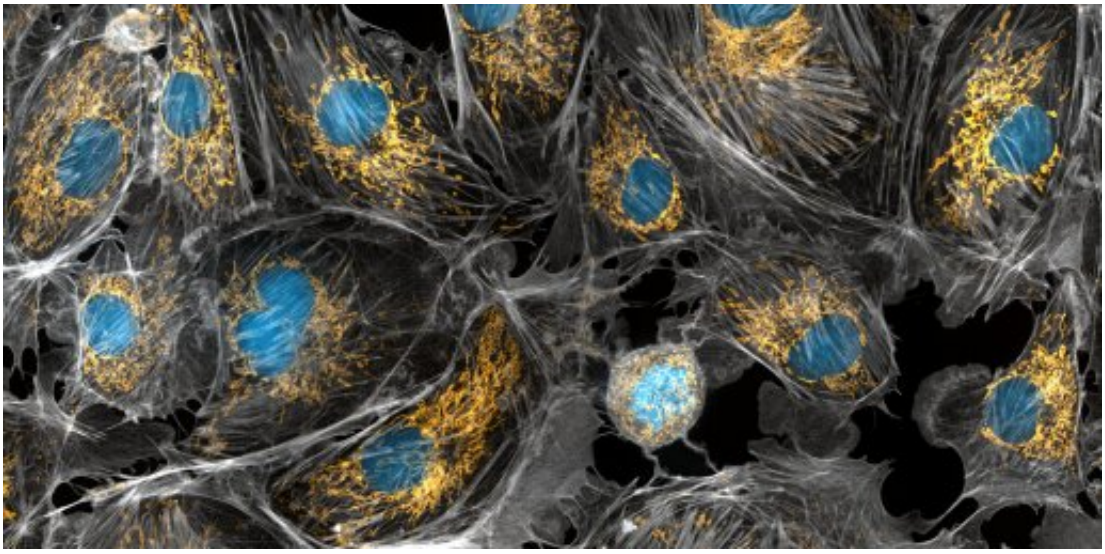

Mitochondria are golden. They are the batteries of the cell, generating the energy cells need to do their tasks and to stay alive. Researchers have studied mitochondria for some time because when these cell organelles don't perform as well as they should, several diseases develop. This is a photograph of cow cells taken with a microscope. The mitochondria were stained in bright yellow, the cell nuclei in blue and the cytoskeleton in gray. Credit: National Institute of General Medical Sciences.

Premature aging in people with HIV is now recognized as a new, significant public health challenge. Accumulating evidence shows that people with HIV who are between 45 to 60 years old develop characteristics typically observed in people without HIV that are more

than 70 years of age. For instance, declining gait speed, physical function and cognition, mitochondrial aging, elevated inflammation, immune dysfunction, frailty and other health conditions are significantly higher in people with HIV when compared to age- and sex-matched uninfected people.

At Baylor College of Medicine, endocrinologist Dr. Rajagopal Sekhar, associate professor of medicine-endocrinology, and his team have found themselves in the right place at the right time to study premature aging in people with HIV. For the last 20 years, they have been studying natural aging in older humans and aged mice in the Section of Endocrinology, Diabetes and Metabolism of the Department of Medicine. Also, for the last 17 years, Sekhar has been active in HIV research, and has been providing clinical care for patients at the HIV clinic at Thomas Street Health Center, a part of Houston's Harris Health System, where he runs the sole endocrinology and metabolism clinic.

Sekhar's years-long expertise, knowledge and interest in metabolic disorders affecting HIV patients and a parallel track investigating non-HIV people have resulted in the publication of significant discoveries regarding the metabolic complications in aging, HIV and diabetes, and has guided numerous clinical trials that together provide a better understanding of why we age.

"The work presented here, published in the journal *Biomedicines*, builds a bridge between laboratory bench and bedside by showing proof-of-concept that supplementing people with HIV specifically with a combination of glycine and N-acetylcysteine, which we call GlyNAC, as precursors of glutathione, a major antioxidant produced by the body, improves multiple deficits associated with premature aging," said Sekhar.

Why we age?

For several decades, experimental evidence has supported two theories for aging. The free radical theory and the mitochondrial theory propose that elevated free radicals (oxidative stress) and mitochondrial dysfunction, respectively, are at the core of geriatric aging. Both, elevated oxidative stress and mitochondrial dysfunction, are present in people with HIV.

Free radicals, such as reactive oxygen species, and the mitochondria are physiologically connected. The mitochondria are like the batteries of the cell, they produce the energy needed for conducting cellular functions. The body transforms the food we eat into sugar and fat, which the mitochondria burns as fuel to produce energy.

However, one of the waste products of cellular energy generation is free radicals, which are highly reactive molecules that can damage cells, membranes, lipids, proteins and DNA. Cells depend on antioxidants, such as glutathione, to neutralize these toxic free radicals. When cells fail to neutralize free radicals, there is an imbalance between the radicals and the antioxidant responses, leading to harmful and damaging oxidative stress.

"The free radicals produced during fuel burning in the mitochondria can be compared to some of the waste products produced by a car's combustion engine, some of which are removed by the oil filter," Sekhar said. "If we don't change the oil filter periodically, the car's engine will diminish its performance and give less mileage."

Similarly, if the balance between free radical production and antioxidant response in cells consistently favors the former, in time cellular function could be disrupted. Glutathione helps cells keep oxidative stress in balance, it keeps the oil filter clean. GlyNAC helps the cell make glutathione.

Sekhar and his colleagues have been studying mitochondrial function and glutathione for more than 20 years. Their findings, and those of other researchers, have shown that glutathione is the ultimate natural antioxidant.

Interestingly, compared to those in younger people, glutathione levels in older people are much lower, and the levels of oxidative stress are much higher. Glutathione levels also are lower and oxidative stress is higher in conditions associated with mitochondrial dysfunction, including aging, HIV infection, diabetes, neurodegenerative disorders, cardiovascular disorders, neurometabolic diseases, cancer, obesity and other conditions.

"When the mitochondrial batteries are running low on power, as a medical and scientific community, we do not know how to recharge these batteries," Sekhar said. "Which raised the question, if the levels of glutathione were restored in cells, would the mitochondria be recharged and able to provide power to the cell? Would restoring mitochondrial functioning improve conditions associated with mitochondrial dysfunction?"

Restoring glutathione

Restoring glutathione in cells was not straightforward because glutathione cannot work if taken orally for the same reasons that diabetic patients cannot eat insulin. It would be digested before it reached the cells. Also, providing glutathione in the blood cannot correct glutathione deficiency because every cell makes its own.

"Glutathione is a small protein made of three building blocks: amino acids cysteine, glycine and glutamic acid. We found that people with glutathione deficiency also were deficient in cysteine and glycine, but not glutamic acid," Sekhar said. "We then tested whether restoring deficient glutathione precursors would help cells replenish their

glutathione. But there's another catch, because cysteine cannot be given as such, we had to supplement it in another form called N-acetylcysteine."

In past studies, Sekhar and his colleagues determined that supplementing GlyNAC, a combination of glycine and N-acetylcysteine, corrected glutathione deficiency inside the cells of naturally aged mice to the levels found in younger mice. Interestingly, the levels of glutathione and mitochondrial function, which were lower in older mice before taking GlyNAC, and oxidative stress, which was higher before GlyNAC, also were comparable to those found in younger mice after taking GlyNAC for six weeks.

The same results were observed in a small study in older humans who had high oxidative stress and glutathione deficiency inside cells. In this case, taking GlyNAC by mouth for 2-weeks corrected the glutathione deficiency and lowered both oxidative stress and insulin resistance (a pre-diabetic risk factor).

In past clinical trials, Sekhar provided GlyNAC to small groups of people to correct a nutritional deficiency, and produced encouraging evidence supporting further studies of the value of this approach to restoring mitochondrial function in clinical trials.

Improving premature aging in people with HIV

In the current study, Sekhar and his colleagues conducted an open-label clinical trial that included six men and two women with HIV, and eight age-, gender- and body mass index-matched uninfected controls, all between 45 and 60 years old. The people with HIV were on stable antiretroviral therapy and had not been hospitalized for six months prior to the study.

Before taking GlyNAC, the group with HIV, compared with the controls, was deficient in glutathione and had multiple conditions associated with premature aging, including higher oxidative stress; mitochondrial dysfunction; higher inflammation, endothelial dysfunction and insulin resistance; more damage to genes; lower muscle strength; increased belly fat and impaired cognition and memory.

The results are encouraging. GlyNAC supplementation for 12 weeks improved all the deficiencies indicated above. Some of the improvements declined eight weeks after stopping GlyNAC.

"It was exciting to see so many new beneficial effects of GlyNAC that have never been described before. Some of the most encouraging findings included reversal of some measures of cognitive decline, a significant condition in people with HIV, and also improved physical strength and other hallmark defects," Sekhar said.

"It was encouraging to see that GlyNAC can reverse many of these hallmark defects in people with HIV as there is no current treatment known to reverse these abnormalities. Our findings could have implications beyond HIV and need further investigation," Sekhar said.

Overall, these findings in HIV patients provide proof-of-concept that dietary supplementation of GlyNAC improves multiple hallmarks of aging and that glutathione deficiency and oxidative stress could contribute to them.

Encouraged by these results, Sekhar has continued his investigations by testing the value of GlyNAC supplementation for improving the health of the growing older population, and has completed an open label trial, and another NIH-funded, double-blind, placebo-controlled trial in older adults.

"The results from these recently completed trials support the findings of the HIV study," said Sekhar, who is currently the Principal Investigator of two NIH-funded randomized clinical trials studying the effect of GlyNAC in older humans with mild cognitive impairment, and with Alzheimer's disease.

More information: Premranjan Kumar et al, Supplementing Glycine and N-acetylcysteine (GlyNAC) in Aging HIV Patients Improves Oxidative Stress, Mitochondrial Dysfunction, Inflammation, Endothelial Dysfunction, Insulin Resistance, Genotoxicity, Strength, and Cognition: Results of an Open-Label Clinical Trial, *Biomedicines* (2020). DOI: 10.3390/biomedicines8100390

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