Boosting the potency of a broccoli-related compound yields a possible treatment for AMD

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broccoli

Buck researchers boosted the potency of a broccoli-related compound by ten times and identified it as a possible treatment for age-related macular degeneration (AMD), the leading cause of vision loss affecting more than 10 million older Americans. The research, published in *Scientific Reports*, also highlights the role of lipid metabolism in maintaining the health of the retina, reporting that palmitoleic acid also had protective effects on retinal cells in culture and in mice.

The "good-for-you" compound in broccoli which prompted the inquiry is indole-3-carbinol (I3C), which is currently being studied for cancer prevention. I3C helps clear cells of environmental toxins by activating the aryl hydrocarbon receptor (AhR) protein which upregulates pathways

involved in chemical detoxification. AhR, which declines with age, is important for detoxifying the retina. Previous studies show that AhR-deficient mice develop a condition which looks extremely similar to AMD. When contemplating the possibility of boosting AhR via broccoli's I3C, Buck faculty and lead author Arvind Ramanathan, PhD, knew there was a challenge - I3C is weak activator of AhR. So he used the chemical scaffold of I3C to do a 'virtual' screen of a publicly-available database of millions of compounds to find those that were related to I3C but would bind to AhR with more strength. His team came up with 2,2?-aminophenyl indole (2AI) which is ten times more potent than I3C.

"2AI protected human retinal cells in culture from stress," said Ramanathan. "And it also protected retinal cells in mice from light-mediated damage. We are very excited about the potential for 2AI and look forward to developing it further." Ramanathan is also excited about the possibility of finding more potent versions of other naturally occurring molecules that show health benefits for age-related diseases. "You would have to eat an unreasonable amount of broccoli and other cruciferous vegetables to get enough of a protective effect to impact AMD," he said. "This method allows us to capitalize on nature's wisdom to find related molecules that can deliver therapeutic benefit."

"2AI prevented cell death in the retinas of mice that were exposed to light stress," said Buck faculty and co-senior author Deepak Lamba, MBBS, PhD, who is developing stem-cell based therapies for degenerative eye diseases. "Our next step is to study the functional outcomes of treatment with 2AI, something I am eager to do because environmental stress is the major contributor to age-related vision loss."

Ramanathan said data from the study suggests that at least some of the protective effects of the AhR activation may come via lipids. "We know that eating a diet rich in fish and omega fatty acids reduces the risk of

AMD, even though we don't fully understand the mechanisms involved." Ramanathan said in this study, 2AI increased levels of the omega-7 lipid palmitoleic acid (PA) suggesting it could be a downstream signal in the anti-inflammatory pathway. Ramanathan said injecting PA also had protective effects on retinal cells in culture and in mice. PA is found in a variety of food including nuts, fish, dairy and vegetable oils. It is found at high concentrations in macadamia and sea buckthorn oil.

More information: Mark A. Gutierrez et al, A novel AhR ligand, 2AI, protects the retina from environmental stress, *Scientific Reports* (2016). DOI: 10.1038/srep29025

Provided by Buck Institute for Research on Aging

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