Discovery may open new therapeutic avenues for degenerative diseases of the brain and eye

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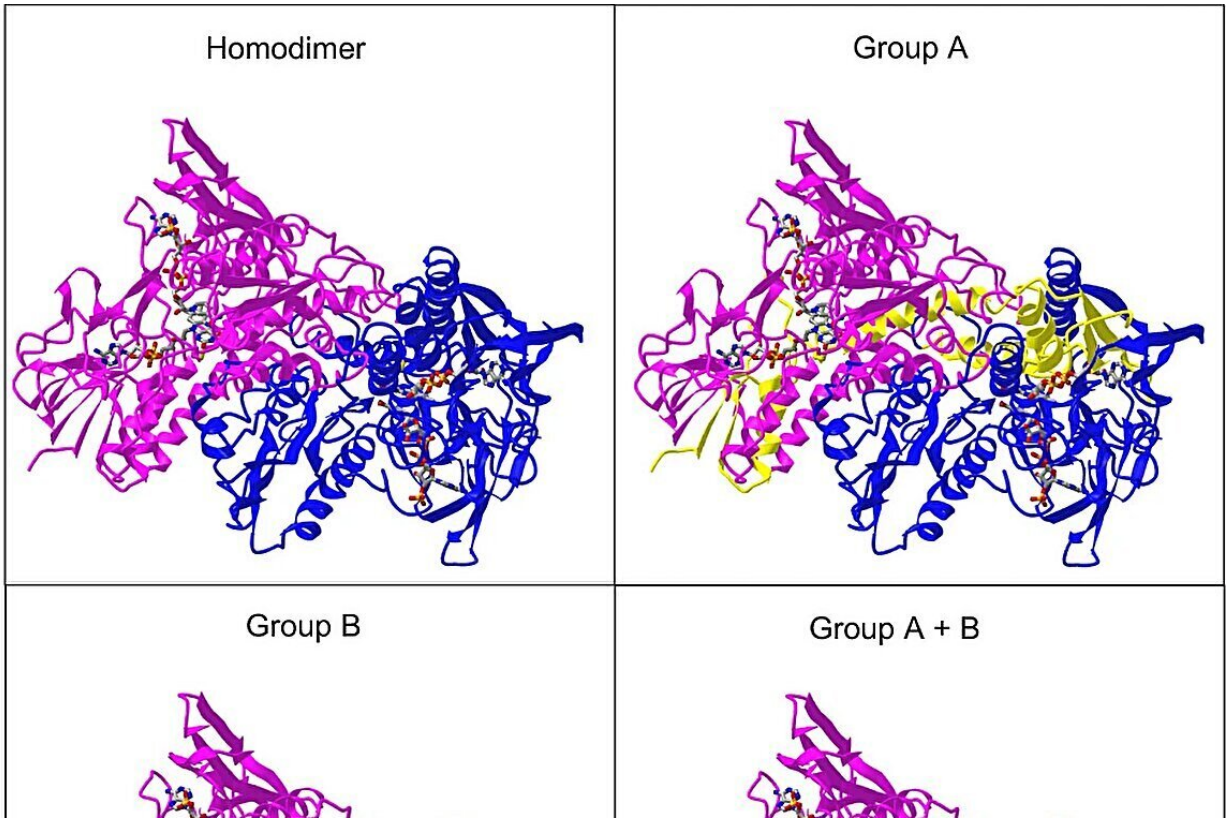

The regions affected by ELV-N34 are in close contact with the FAD pocket and the interface zone. The alignment of the peptides with the secondary structure of the TXNRD1 (Fig. S6 and Tables S6–S9) fell into two groups displayed as group A (yellow) and group B (green). The upper left quadrant shows the homodimer 3D (PDB ID: 2ZZC) rendition obtained by X-ray crystallography and available on NCBI (https://www.ncbi.nlm.nih.gov/Structure/icn3d/full.html?&mmdbid=76017&bu=1&showanno=1&source=full-feature). The right upper and the left down quadrants depict the groups A and B highlighted respectively (yellow and

green) and the right down quadrant illustrates the whole zone affected by ELV-N34 that in the 3D representation appears as a continuous region. Credit: *Cell Death & Disease* (2023). DOI: 10.1038/s41419-023-06334-6

Scientists at LSU Health New Orleans' Neuroscience Center of Excellence, led by Nicolas Bazan, MD, Ph.D., Boyd Professor and Director, have identified a new mechanism that regulates a protein key for cell survival. It appears to protect against the excessive oxidative stress that precedes the development of neurodegenerative diseases of the brain and eye. Results are published in the journal *Cell Death & Disease*.

"This discovery goes beyond the commonly studied transcriptional modulation, suggesting its impact on protection against oxidative stress-related diseases and extension of lifespan," notes Dr. Bazan, who is also the Ernest C. and Ivette C. Villere Chair for Retinal Degenerations and Bollinger Family Professor in Alzheimer's Disease. "We found that Elovanoid-34 modulates the activity of the protein, TXNRD1, which is central to the initiation cascade of oxidative stress."

Elovanoid-34 is part of a class of molecules in the brain discovered by the Bazan lab that synchronize cell-to-cell communication and neuroinflammation-immune activity in response to injury or disease. Elovanoids are bioactive chemical messengers made from omega-3, very long-chain polyunsaturated fatty acids. They are released on demand when cells are damaged or stressed.

Oxidative stress occurs when there is an imbalance between free radicals and antioxidant defenses to detoxify them. It can lead to cell and tissue damage and the onset of diseases.

The research team, which included scientists from the Swiss company Biognosys AG, identified the proteins affected by Elavamoid-34. Using proteomics, they screened 130,000 protein sequences corresponding to 4,749 proteins and discovered that only one changed in structure upon contact with Elovanoid-34.

Researchers found that TXNRD1 is a crucial component of the antioxidant system, Glutathione, and targets a regulator of Ferroptosis, a type of cell death. This is particularly the case in Age-Related Macular Degeneration, where the support cells of the photoreceptors of the light in the retina succumb to excessive oxidative stress conditions.

These cells, called retinal pigment epithelial (RPE) cells, can be rescued from death by Elovanoid-34, stopping the neurodegeneration of the retina and blindness. The current study uses human RPE cells, which were developed in the Bazan lab.

"This breakthrough discovery opens new therapeutic avenues for various pathologies and the promotion of successful aging of the nervous system," concludes Dr. Bazan.

LSU Health New Orleans Neuroscience Center co-authors also included Drs. Jorgelina Calandria, Surjyadipta Bhattacharjee, Sayantani Kala-Bhattacharjee, and Pranab K. Mukherjee. Co-authors from Biognosys AG included Yuehan Feng, Jakob Vowinckel and Tobias Treiber.

"The present discovery opens a new dimension to understanding the complex multifactorial process of aging," adds Dr. Bazan. "The gradual decline of functions in aging does engage excessive oxidative stress further magnified by co-morbidities such as diabetes and cardiovascular disorders. In fact, a clear connection is revealed by the present discovery because elovanoids also target neuronal cell senescence and epigenetic signaling."

"Overall, the protein discovered now to be a site of brain and retina (and likely other organs) protection by elovanoids opens avenues of targeted therapeutics for age-related diseases, stroke, ALS, and traumatic brain injury, as well as to sustain healthy, successful aging."

More information: Jorgelina M. Calandria et al, Elovanoid-N34 modulates TXNRD1 key in protection against oxidative stress-related diseases, *Cell Death & Disease* (2023). DOI: 10.1038/s41419-023-06334-6

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