Neurodegeneration 'clumping proteins' common in aging process

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Many proteins that form insoluble clumps in the brains of people with Alzheimer's and other neurodegenerative diseases are also found in healthy individuals and clump together as a normal part of aging. According to a surprising new finding by researchers at the University of California, San Francisco, the discovery in the *C. elegans* roundworm refutes a widespread belief that these clumps are unique to degenerative disease and created by proteins specific to those diseases. The team also found that gene manipulations that extend the lifespan of *C. elegans* prevent the formation of these insoluble aggregates. These findings will appear next week in the online, open-access journal *PLoS Biology*.

In many neurodegenerative diseases, such as Alzheimer's and Huntington's, clumps of proteins known as aggregates appear in the patients' brains as the degeneration progresses. Those clumps contain some proteins that are unique to the specific disease (such as Abeta in Alzheimer's), intertwined with many others that are common in healthy individuals. For years, those common proteins were thought to be accidental inclusions in the aggregates, much as a sea turtle might be caught in a seine of fish. In fact, they may not be innocent bystanders at all, but instead their presence may influence the course of neurodegenerative disease.

"If you take people with Alzheimer's and look at their aggregates, there are many other proteins in the clump that no one has ever paid much attention to," said UCSF Professor Cynthia Kenyon, PhD, director of the Larry L. Hillblom Center for the Biology of Aging at UCSF and senior

author of the paper. "It turns out that about half of these proteins are aggregating proteins that become insoluble as a normal part of aging."

The team found that in the presence of proteins specific to Huntington's disease, these aggregators actually sped up the course of the disease, indicating that they could be fundamental to its progression. These findings indicate that widespread protein insolubility and aggregation is an inherent part of aging and that it may influence both lifespan and neurodegenerative disease. The presence of insoluble protein aggregates has long been a hallmark of protein aggregation diseases such as Alzheimer's, Huntington's and amyotrophic lateral sclerosis (ALS) disease. The team, led by first author Della C. David, PhD, a postdoctoral scholar in the UCSF Department of Biochemistry and Biophysics, asked a simple question that had never been asked before: do normal proteins form insoluble clumps when normal, healthy individuals age? They identified roughly 700 proteins in a normal *C. elegans* worm that become insoluble with age.

These insoluble proteins are highly over-represented in the aggregates found in human neurodegeneration, according to the paper. Yet even in the healthy aging worms, these proteins had a propensity for clumping and forming hard, rocklike structures. Their aggregation was significantly delayed or even halted by reducing insulin and IGF-1 hormone activity, whose reduction is known to extend animal lifespan and to delay the progression of Huntington and Alzheimer's disease in animal models of neurodegenerative diseases. The researchers found that many of the proteins that become insoluble during normal aging are proteins already known to accelerate the aging process and to influence the aggregation of the major disease proteins.

While there are indisputable differences between worms and humans, the roundworm *C. elegans* (*Caenorhabditis elegans*) often has led the way in advancing our understanding of human biology, notably in such areas

as the mechanism of cell death, insulin pathways, the genes involved in cancer, and aging.

More information: David DC, Ollikainen N, Trinidad JC, Cary MP, Burlingame AL, et al. (2010) Widespread Protein Aggregation as an Inherent Part of Aging in C. elegans. PLoS Biol 8(8): e1000450. doi:10.1371/journal.pbio.1000450