Dementia from Plaques

The summary of the following thread of documents is as follows:

- Tau and beta-amyloid plaques are bioidentic aggregations of the amyloids that are the amino acid neurotransmitters that are subjected to copy error mutation.
- Copy errors create kinases; aggregations of the amino acids into plaques; i.e. the liquid to solid fibrous tangles in the second document
- Our copy error explanation identifies the copper - zinc based process using enzyme to "disassemble" lipids, carbohydrates and amino acids (aka kinases). In other words, these enzymes can "disassemble" the solid plaques and treat tau/beta-amyloid dementias.

Our findings for the aggregation of tau into plaques and the means of resolving the problem are outlined in the information affixed to this article for use as part of discussions with interested parties.

https://www.sciencedaily.com/releases/2017/07/170705184054.htm

First look at atomic structures of protein tangles found in Alzheimer's disease

Date:

July 5, 2017

Source:

Indiana University

Summary:

The most detailed view yet of tau protein structures found in Alzheimer's disease has been provided by a team of scientists.

New research by scientists at the MRC Laboratory of Molecular Biology in the United Kingdom and Indiana University School of Medicine gives the most detailed view yet of tau protein structures found in Alzheimer's disease.

The team of the MRC scientists -- led by Michel Goedert, MD, PhD, and Sjors Scheres, PhD -- along with IU Distinguished Professor Bernardino Ghetti, MD, and Assistant Research Professor Holly Garringer, PhD, of the IU School of Medicine Department of Pathology and Laboratory Medicine, are the first to present high-resolution structures of tau filaments from the brain of a patient with a confirmed diagnosis of Alzheimer's disease.

Dr. Ghetti said their findings, published online July 5 in *Nature*, represent one of the major discoveries of the past 25 years in the field of Alzheimer's disease research.

"This is a tremendous step forward," Dr. Ghetti said. "It's clear that tau is extremely important to the progression of Alzheimer's disease and certain forms of dementia. In terms of designing therapeutic agents, the possibilities are now enormous."

Tau proteins are a stabilizing element in healthy brains, but when they become defective, the proteins can form bundles of filaments -- or tangles -- known as the primary markers of Alzheimer's and other neurodegenerative diseases. But tau filaments are invisible at the light microscope, Dr. Ghetti said, and without high-resolution images showing their atomic structure, it has been difficult to decipher their role in the development of these diseases.

That's why the research team used an imaging technique called cryo-electron microscopy, which studies samples at very low temperatures, to see atomic-level detail in the structures of these proteins. Dr. Ghetti and Dr. Garringer studied multiple brain areas and DNA of the Alzheimer's disease patient to facilitate the analysis of tau proteins by cryo-electron microscopy.

Dr. Ghetti said the new images and analysis could help scientists better understand the molecular mechanisms that cause Alzheimer's disease and identify new strategies for the prevention, diagnosis and treatment of this and other neurodegenerative diseases.

Dr. Ghetti is an international leader in research on the neuropathology of dementia. He is the founder and first director of IU School of Medicine's Indiana Alzheimer Disease Center (1991 to 2013), leader of the neuropathology of dementia laboratory and the founder of the International Society for Frontotemporal Dementias (2011).

Dr. Goedert is internationally known for his contribution to the biology of tau and other proteins involved in neurodegeneration.

Dr. Scheres is one of the most advanced experts in the study of the structure of protein machinery.

Story Source:

Materials provided by **Indiana University**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Anthony W. P. Fitzpatrick, Benjamin Falcon, Shaoda He, Alexey G. Murzin, Garib Murshudov, Holly J. Garringer, R. Anthony Crowther, Bernardino Ghetti, Michel Goedert, Sjors H. W. Scheres. **Cryo-EM structures of tau filaments from Alzheimer's disease**. *Nature*, 2017; DOI: 10.1038/nature23002

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Transitioning of tau from liquid to solid is the result of excessive anabolic activity due and copy error mutations that prevent autophagy (catabolic activity). The process can be verified using the following.

http://www.mcfip.net/upload/Epigenetics%20-%20DNA%20Repair%20-%20Copy%20Errors.pdf

Obviously, the significance of mitigating tau aggregation cannot be over emphasized?

https://www.sciencedaily.com/releases/2017/07/170706143143.htm

A biophysical smoking gun

Scientists begin to unravel how the protein tau transitions from a soluble liquid state to solid fibrous tangles

Date:

July 6, 2017

Source:

University of California - Santa Barbara

Summary:

While much about Alzheimer's disease remains a mystery, scientists do know that part of the disease's progression involves a normal protein called tau, aggregating to form ropelike inclusions within brain cells that eventually strangle the neurons. Yet how this protein transitions from its soluble liquid state to solid fibers has remained unknown -- until now.

While much about Alzheimer's disease remains a mystery, scientists do know that part of the disease's progression involves a normal protein called tau, aggregating to form ropelike inclusions within brain cells that eventually strangle the neurons. Yet how this protein transitions from its soluble liquid state to solid fibers has remained unknown -- until now.

Discovering an unsuspected property of tau, UC Santa Barbara physical chemist Song-I Han and neurobiologist Kenneth S. Kosik have shed new light on the protein's ability to morph from one state to another.

Remarkably, tau can, in a complex with RNA, condense into a highly compact "droplet" while retaining its liquid properties. In a phenomenon called phase separation, tau and RNA hold together, without the benefit of a membrane, but remain separate from the surrounding milieu. This novel state highly concentrates tau and creates a set of conditions in which it becomes vulnerable to aggregation. Kosik and Han outline their discoveries in the journal *PLOS Biology*.

"Our findings, along with related research in neurodegeneration, posit a biophysical 'smoking gun' on the path to tau pathology," said Kosik, UCSB's Harriman Professor of Neuroscience and co-director of the campus's Neuroscience Research Institute. "The signposts on this path are the intrinsic ability

of tau to fold into myriad shapes, to bind to RNA and to form compact reversible structures under physiologic conditions, such as the concentration, the temperature and the salinity."

The researchers found that, depending on the length and shape of the RNA, up to eight tau molecules bind to the RNA to form an extended fluidic assembly. Several other proteins like tau are known to irreversibly aggregate in other neurodegenerative diseases such as amyotrophic lateral sclerosis, more commonly known as Lou Gehrig's disease.

"There is an interesting relationship between intrinsically disordered proteins that are predisposed to become neurodegenerative -- in this case tau -- and this phase separation state," said Han, a professor in UCSB's Department of Chemistry and Biochemistry. "Is this droplet stage a reservoir that protects tau or an intermediate stage that helps transform tau into a disease state with fibrils or both at the same time? Figuring out the exact physiological role of these droplets is the next challenge."

Subsequent analysis will consist of an intensive search for the counterpart of tau droplets in living cells. In future work, the researchers also want to explore how and why a cell regulates the formation and dissolution of these droplets and whether this represents a potential inroad toward therapy.

Story Source:

Materials provided by **University of California - Santa Barbara**. Original written by Julie Cohen. *Note: Content may be edited for style and length.*

Journal Reference:

1. Xuemei Zhang, Yanxian Lin, Neil A. Eschmann, Hongjun Zhou, Jennifer N. Rauch, Israel Hernandez, Elmer Guzman, Kenneth S. Kosik, Songi Han. **RNA stores tau reversibly in complex coacervates**. *PLOS Biology*, 2017; 15 (7): e2002183 DOI: 10.1371/journal.pbio.2002183