Biophysicists discover how 'Australian' mutation leads to Alzheimer's disease

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Illustration. Alzheimer's. Credit: Elena Khavina and @tsarcyanide, MIPT Press Office

A team of scientists from the Moscow Institute of Physics and Technology (MIPT) and Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry (IBCh RAS) studied one hereditary genetic mutation to discover general molecular mechanisms that may lead both to early onset of Alzheimer's disease and to the form of the disease caused by age-related changes in human body. Understanding these mechanisms is necessary for developing new targeted treatments for this neurodegenerative disease that is becoming ever more widespread across developed countries' aging populations. The study findings were published in *ACS Chemical Biology*.

Dementia is a syndrome in which there is deterioration in memory, thinking, behavior, and the ability to perform everyday activities. Alzheimer's disease is the most common form of dementia and may contribute to 60-70% of cases, according to WHO fact sheet. This makes dementia a public health priority, with substantial funds allocated to fight it by both governments and pharmaceutical companies. Prominent politicians such as Margaret Thatcher and Ronald Reagan were afflicted with Alzheimer's disease in their later years. Alzheimer's disease is most common in people over the age of 65 but people aged 40 or even younger are sometimes diagnosed with it as well. Approximately 10-15% of early onset cases are caused by inherited predisposition. Integrated studies of hereditary, or "familial" mutations may give researchers a clue about key mechanisms of Alzheimer's disease pathogenesis, in particular, its initial steps.

Alzheimer's disease is associated with accumulation of pathogenic amyloid-? peptides into amyloid plaques within brain tissue. These peptides are short (about 40 amino acids) fragments of amyloid precursor protein (APP) that spans through membrane of brain cells. APP protein is cleaved by various enzymes as part of neuron activity. The sequential cleavage of the "large" APP protein (biological function of which is still not fully understood) by ?- and ?-secretase enzymes produces amyloid-? peptides which in small amounts are probably necessary for sustaining brain functions. However, ?-secretase cuts the APP chain (within neuron membranes) into consecutive fragments of slightly varying length, thus producing relatively "pathogenic" and "non-pathogenic" forms of amyloid-? peptides. The main pathogenic form consists of 42 amino acid residues (A?42), while the less pathogenic form consists of 40 residues (A?40). The A?42/A?40 ratio in healthy humans is not high, standing at approximately one to nine. A higher A?42/A?40 ratio indicates an excessive production of A?42 which leads to the neurodegenerative disorder. Researchers are currently testing a hypothesis that amyloid-? peptides are active participants of innate immunity of the human nervous system and their increased production may be caused by various inflammations and brain injuries. At the same time, a lot of familial mutations associated with early onset of Alzheimer's disease have been found in the transmembrane (TM) domain of APP.

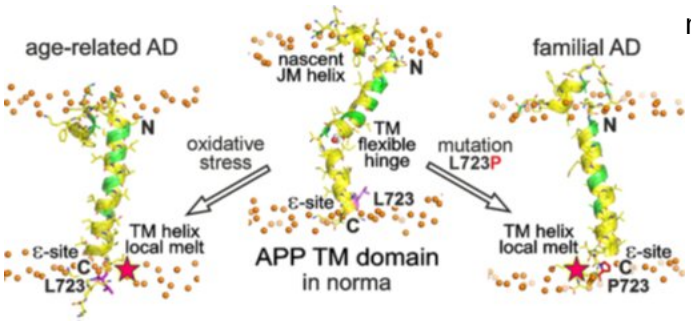

Illustration of molecular mechanisms behind pathogenesis of familial and age-related forms of Alzheimer's disease. Credit: Eduard V. Bocharov et al.; *ACS Chemical Biology*

This research aimed to study the "Australian" familial mutation (L723P) within the APP TM domain that is the cause of early onset of Alzheimer's disease. The scientists studied the structural-dynamic behavior of the mutant APP TM domain against the wild-type by the aid of protein engineering, high-resolution nuclear magnetic resonance (NMR), and computer simulations. NMR spectroscopy was used to compare wild-type APP peptide with its mutant by such parameters as "helicity" of the amino acid polypeptide chain, its bending and flexibility, as well as the accessibility to lipids and water molecules. The researchers discovered L723P mutation to cause local melt of the last turn of APP TM domain helix and also straighten and stabilize the domain in the center of lipid membrane. Apart from that, it was noted that mutation increases accessibility of the domain to water molecules, which shifts the "frame" of its cleavage by ?-secretase, thus switching between alternative ("pathogenic" and "non-pathogenic") cleavage cascades. This leads to growing A?42/A?40 ratio and general concentration of amyloid-? within brain tissue.

Senior research staff at Laboratory for Aging and Age-Related Neurodegenerative Diseases, MIPT, and Laboratory of biomolecular NMR-spectroscopy, IBCh RAS, Eduard Bocharov, commented:

"It goes without saying that this study touches upon just a few of causes for the multifactorial disorder that is Alzheimer's disease. The molecular mechanisms of its pathogenesis are being researched in numerous laboratories all over the world. In particular, a special attention in paid to studying the "key player"—the amyloid precursor protein, as well as its sequential cleavage by secretases within neuron membranes. We described a cascade of events happening within and around the cell membrane as APP is cut by ?-secretase enzyme complex. We have thus used a single "Australian" mutation to reveal molecular mechanisms behind the pathogenesis that may lead both to early onset of Alzheimer's and the age-related form of the disease."

The study findings suggest a straightforward mechanism of Alzheimer's disease pathogenesis associated with the impact of "Australian" mutation on the structural-dynamic behavior of APP TM domain. This is what leads to the pathological cleavage of APP by secretases and the increased accumulation of pathogenic amyloid-? around neurons. Worth noting is the fact that age-related onset of Alzheimer's disease can be explained by similar mechanisms, where the effect of mutation is replaced by the impact of local environmental factors, such as oxidative stress or membrane lipid composition including cholesterol saturation. A detailed understanding of the molecular mechanisms regulating generation of amyloidogenic peptides is essential for development of novel treatment strategies targeted at the primary stage of the Alzheimer's disease pathogenesis.

More information: Eduard V. Bocharov et al, Familial L723P Mutation Can Shift the Distribution between the Alternative APP Transmembrane Domain Cleavage Cascades by Local Unfolding of the ?-Cleavage Site Suggesting a Straightforward Mechanism of Alzheimer's Disease Pathogenesis, *ACS Chemical Biology* (2019). DOI: 10.1021/acschembio.9b00309

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