
Tau

Tau is a protein that helps stabilize the internal skeleton of nerve cells (neurons) in the brain. This internal skeleton has a tube-like shape through which nutrients and other essential substances travel to reach different parts of the neuron. In Alzheimer's disease, an abnormal form of tau builds up and causes the internal skeleton to fall apart.

Tau tangles

These abnormal forms of tau protein cling to other tau proteins inside the neuron and form "tau tangles." Tau tangles and beta-amyloid plaques — large accumulations of microscopic brain protein fragments that slow a person's ability to think and remember — are hallmarks of Alzheimer's disease.

Tau research

Emerging evidence suggests that Alzheimer's-related brain changes may result from a complex interaction among abnormal tau and beta-amyloid proteins and several other factors. It appears that abnormal tau accumulates in specific brain regions involved in memory. As the amount of beta-amyloid in the brain increases, a tipping point is reached that causes abnormal tau to spread throughout the brain.

Until a few years ago, tau and beta-amyloid levels in a person with dementia could only be measured after the person had died. Now, however, tau and beta-amyloid levels can be measured in living individuals by analyzing samples of cerebrospinal fluid (CSF), the fluid surrounding the brain, and by using positron emission tomography (PET) scans and special dyes to show tau tangles and beta-amyloid plaques in the brain. Scientists are beginning to use CSF analysis and PET scans to study how possible tau and beta-amyloid interactions may speed the brain changes that ultimately result in memory loss and other symptoms of Alzheimer's dementia.

Researchers at the Mayo Clinic in Rochester, Minnesota, are using PET imaging and CSF testing to examine how brain health is affected by tau and beta-amyloid clumping. The researchers will measure protein levels in about 3,000 older individuals over time to determine how tau and beta-amyloid clumping — either alone or in combination — might influence (1) whether people in the study who have normal cognitive function develop mild cognitive impairment (MCI) and (2) whether people with MCI in the study eventually develop Alzheimer's disease. Results of the study could shed light on how cognitive decline occurs at the molecular level. The study could also provide important data for future clinical trials of therapies targeting tau, beta-amyloid or both. To date, the research team has found subtle but statistically significant differences in personality that coincide with the transition from preclinical Alzheimer's disease (before symptoms) to incident MCI. During that transition, researchers saw an increase in neuroticism and a decrease in openness, along with evidence of physical stress, depression, anxiety and irritability.

A study by scientists at University of California San Francisco Memory and Aging Center found that brain imaging of tau protein “tangles” reliably predicts the location of future brain cell death a year or more in advance. In contrast, the location of amyloid “plaques” did not predict how or where brain cell damage would occur.

Some studies have found that tau can also build up inside another type of brain cell called astrocytes. This is called age-related tau astroglipathy. Astrocytes are helper cells that serve many functions, including the maintenance of synapses, which enable neurons to communicate with each other. It is not yet known whether tau astroglipathy impairs brain function, but researchers are studying astroglipathy to find out how it might affect brain health. Other investigators are studying astroglipathy early in the dementia process and in multiple ethnic groups. They hope to better understand the role of tau accumulation in astrocytes and whether it increases an individual’s risk of cognitive decline.

Tau toxicity

Tau accumulation has been shown to promote brain cell damage and death in Alzheimer’s and other dementias, including frontotemporal dementia, but the exact processes that lead to this toxicity are unclear. Some studies suggest stress in the brain cell’s endoplasmic reticulum (ER), the part of the cell where proteins are produced, may play a role. Researchers have also discovered that disulfide bonds on certain amino acids act to stabilize tau and cause it to accumulate, an effect that worsened with increased oxidative stress (an imbalance between free radicals and antioxidants in the body). The identification of chemical targets triggering tau accumulation may lead to new treatments.

The APOE-tau connection

The apolipoprotein E (APOE) gene is responsible for the creation of a type of protein involved in metabolizing fat in the body. Certain forms of this gene have been found to increase risk of developing Alzheimer’s. To gain insight into the possible connection between the APOE gene and tau protein in promoting nerve cell death in Alzheimer’s, researchers are studying how the e4 form of APOE may worsen tau-related nerve cell death. Using mice genetically engineered to carry the e2, e3 or e4 forms of APOE, they will study which types of nerve cell death occur most frequently with the different forms of APOE. They will also test whether blocking certain biological processes prevents tau-related nerve cell death. Determining how APOE may be linked with tau-related nerve cell death could help scientists design targeted treatments to slow or prevent the damage and death of neurons in Alzheimer’s disease. One research team found that turning off the astrocyte APOE-e4, but not APOE-e3, just as tau started to accumulate not only stopped subsequent brain shrinkage but also slowed tau accumulation.

Drug treatments targeting tau

Researchers are investigating ways to prevent tau protein from forming into tangles, which ultimately destroys the neuron. One potential therapy in clinical trials that

targets tau protein is AADvac1. AADvac1 is a vaccine that stimulates the body's immune system to attack the abnormal form of tau protein that causes the internal skeleton of neurons to fall apart. If successful, it has the potential to help stop the progression of Alzheimer's disease. The change in several biomarkers (measurable biological changes that can show if a disease is present or a person is at risk) for Alzheimer's suggest AADvac1 may slow the progression of the disease. People receiving AADvac 1 also had positive changes in several cognitive tests. Based on these promising early results, the vaccine will continue to be studied in the next phase of clinical trials. Plans are being made for a phase 3 trial that will run for 24 to 30 months. (Drug is still in research; not available to the public.)

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