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Researchers identify new group of proteins in the brains of Alzheimer's patients

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Researchers from Boston University School of Medicine (BUSM) have identified a novel group of proteins that accumulate in the brains of patients with Alzheimer's disease. These findings, which appear online in the *Journal of Neuroscience*, may open up novel approaches to diagnose and stage the progression likelihood of the disease in Alzheimer patients.

Alzheimer's disease is presumed to be caused by the accumulation of β-amyloid, which then induces aggregation of a neuronal protein, called tau, and neurodegeneration ensues. The diagnosis of Alzheimer's disease focuses on β-amyloid and tau protein, with much attention focusing on radiolabeled markers that bind to β-amyloid (such as the compound PiB). However, imaging β-amyloid is problematic because many cognitively normal elderly have large amounts of β-amyloid in their brain, and appear as "positives" in the imaging tests.

Therapeutic approaches for Alzheimer's disease generally have focused on β-amyloid because the process of producing a neurofibrillary tangle composed on tau protein has been poorly understood. Hence, few tau therapies have been developed. According to the researchers, this study makes important advances on both of these fronts.

The BUSM researchers identified a new group of proteins, termed RNA-binding proteins, which accumulate in the brains of patients with Alzheimer's disease, and are present at much lower levels in subjects who are cognitively intact. The group found two different proteins, both of which show striking patterns of accumulation. "Proteins such as

TIA-1 and TTP, accumulate in neurons that accumulate tau protein, and co-localize with neurofibrillary tangles. These proteins also bind to tau, and so might participate in the disease process," explained senior author Benjamin Wolozin, MD, PhD, a professor in the departments of pharmacology and neurology at BUSM. "A different RNA binding protein, G3BP, accumulates primarily in neurons that do not accumulate pathological tau protein. This observation is striking because it shows that neurons lacking tau aggregates (and neurofibrillary tangles) are also affected by the disease process," he added.

The researchers believe this work opens up novel approaches to diagnose and stage the likelihood of progression by quantifying the levels of these RNA-binding protein biomarkers that accumulate in the brains of Alzheimer patients.

Wolozin's group also pursued the observation that some of the RNA binding proteins bind to tau protein, and tested whether one of these proteins, TIA-1, might contribute to the disease process. Previously, scientists have demonstrated that TIA-1 spontaneously aggregates in response to stress as a normal part of the stress response. Wolozin and his colleagues hypothesize that since TIA-1 binds tau, it might stimulate tau aggregation during the stress response. They introduced TIA-1 into neurons with tau protein, and subjected the neurons to stress. Consistent with their hypothesis, tau spontaneously aggregated in the presence of TIA-1, but not in the absence. Thus, the group has potentially identified an entirely novel mechanism to induce tau aggregates de novo. In future work, the group hopes to use this novel finding to understand how neurofibrillary tangles for in Alzheimer's disease and to screen for novel compounds that might inhibit the progression of Alzheimer's disease.

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