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Alzheimer's enzyme acts as a tumor suppressor

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Researchers at Burnham Institute for Medical Research have provided the first evidence that gamma-secretase, an enzyme key to the progression of Alzheimer's, acts as a tumor suppressor by altering the pathway of epidermal growth factor receptor (EGFR), a potential treatment target for cancer. Expedited to publication online by *Proceedings of the National Academy of Sciences*, these findings reveal a limitation of targeting gamma-secretase for treatment of Alzheimer's and potentially other diseases.

Amyloid precursor protein (APP) is found inside all cells. Though its function is unknown, it is associated with Alzheimer's in the following way. APP can be cleaved by the enzymes beta-secretase and gamma-secretase, sequentially. Upon gamma-secretase cleavage, amyloid-beta (AB) peptides are dispelled into the extracellular matrix region and eventually aggregate into senile plaques, characteristic of Alzheimer's.

Residing inside cells, gamma-secretase is a complex of four proteins, including a family of proteins known as the presenilins (PS). Mutations in PS are found in approximately 5% of individuals suffering Alzheimer's, resulting in early onset of the disease.

At the center of the activities governing AB production is gamma-secretase, the subject of intensive interest as a potential therapy target for Alzheimer's. Mice deficient in PS/gamma-secretase activity tend to develop skin cancer. EGFR is known to be upregulated in a variety of tumors, including various skin cancers. Elevated EGFR levels in tumors

are linked with poor clinical prognosis and tumor resistance to chemotherapy. EGFR is therefore the subject of intensive investigation by pharmaceutical companies as a potential treatment target for cancer.

The Xu laboratory set out to determine whether there might be a correlation between PS/gamma-secretase activity and EGFR. They examined mice with reduced PS gene dosage and found that there is an inverse relationship between the level of EGFR and PS. They discovered that APP intracellular domain (AICD), another cleavage product of PS/gamma-secretase, negatively regulates transcription of the EGFR gene by binding the gene's promoter region. They also demonstrated that deficient levels of APP correlate with increased levels of EGFR.

"Alzheimer's disease and cancer are two of the most important medical research areas today", said Huaxi Xu, associate professor and program director at Burnham. "We believe that our studies, which reveal a key role of Alzheimer's PS/gamma-secretase-generated APP metabolite AICD in gene transcription and in EGFR-mediated tumorigenesis, should have a significant impact on both fields of research."

Source: Burnham Institute