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# Novel mouse gene reduces major pathologies associated with Alzheimer's disease

November 11 2009

A new study reveals that a previously undiscovered mouse gene reduces the two major pathological perturbations commonly associated with Alzheimer's disease (AD). The research, published by Cell Press in the November 12 issue of the journal *Neuron,* finds that the novel gene interacts with a key cellular enzyme previously linked with AD pathology, thereby uncovering a new strategy for treating this devastating disorder.

AD is an incurable neurodegenerative disease characterized by a pathological accumulation of extracellular sticky amyloid beta (A{beta}) protein plaques and intracellular hyperphosphorylated tau protein aggregations, called neurofibrillary tangles (NFT), in the brain. Previous research has suggested that glycogen synthase kinase-3 (GSK-3), an enzyme that is essential for many critical cellular functions, may play a role in both A{beta} plaque and NFT generation.

"Because GSK-3 regulates two major pathological hallmarks of AD, manipulation of its activity is an attractive potential therapeutic strategy for AD," explains senior study author Dr. Huaxi Xu, professor and acting director of the Neurodegenerative Disease Research Program at the Burnham Institute for Medical Research in La Jolla, California. "Identification of new genes involved in these processes will be instrumental in developing novel AD therapeutics."

Using a sophisticated genetic screening approach that finds genes based on their functions, Dr. Xu and colleagues identified the novel mouse

gene Rps23r1. RPS23R1 protein reduced levels of A{beta} and hyperphosphorylated tau by interacting with the well known adenylate cyclase/cAMP/PKA signaling pathway and inhibiting GSK-3 activity. Remarkably, the AD-like pathologies of transgenic AD mice were improved after crossing them with Rps23r1 transgenic mice.

Additionally, the researchers demonstrated that RPS23R1 also exerts its function in human cells, suggesting that RPS23R1 signaling pathways are active in humans. "While it is not yet known whether there are functional analogs of RPS23R1 in humans, further elucidation of RPS23R1 functions and mechanism of action may prove to be important for developing new strategies for combating AD and other diseases, including cancer and diabetes, in which the PKA and GSK-3 signaling pathways are centrally involved," concludes Dr. Xu.

The authors also reported that the mouse Rps23r1 gene, whose human counterpart has not yet been identified, was created during evolution through a process called retroposition, in which a gene is "duplicated" through the reverse transcription of mRNA and the "duplicate" is placed in a different location in the cell's DNA. Although most retroposition events result in non-functional duplicates (called pseudogenes), in rare cases, retroposed genes, like Rps23r1, can become functional.

"From the point of view of treating Alzheimer's disease, if we can express the mouse gene in human brain cells, we may be able to control the buildup of amyloid beta and tau neurofibrillary tangles," said Dr. Xu. "From an evolutionary point of view, we have found an example of a retroposed gene that took on a completely new function."

Source: Cell Press (news : web)