Variant form of amyloid beta hinders amyloidogenesis, development of Alzheimer's disease

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Alzheimer's disease causes misfolding and aggregation of a protein fragment known as amyloid beta and its deposition as plaques in the brain. This process triggers a cascade of event that leads to neurodegeneration. A new study has found that the deadly transformation of amyloid beta into neurotoxic aggregates can be prevented through its interaction with a variant form of the amyloid beta itself. This opens up new prospects for therapies for the disease.

Alzheimer's disease is the most frequent form of dementia in the elderly. It is usually sporadic, but a small proportion of cases are familial, linked to mutations in the Aβ precursor protein (APP), presenilin 1 or presenilin 2 genes. The mutations identified previously increase aggregation and/or the production of Aβ, and have an autosomal dominant pattern of inheritance with complete penetrance, meaning that only one allele of the gene needs to be mutated in order to produce the disease.

The study by Di Fede and colleagues published in the March 13 issue of *Science* is based on the identification of a new APP mutation that has an autosomal recessive pattern of inheritance, meaning it causes disease only in the rare cases where both alleles of the gene have the defect - individuals with only one copy of the mutated allele remain healthy even into old age.

To investigate the mechanism by which the recessive mutation causes disease, the authors used cell models and synthetic Aβ peptides with and without the amino acid change induced by the genetic defect. Incubation of Aβ with the normal human sequence produced amyloid fibrils similar to those deposited in Alzheimer patients' brains. The peptide containing the novel mutation was more prone to amyloid formation than the normal peptide. However, most significantly, when the mutated and normal peptides were incubated together no amyloid formed by either the mutated or the normal form of Aβ. This is in line with the observation that heterozygous carriers do not develop the disease, even at a very late age.

Much remains to be clarified but these new data offer a basis for designing therapeutic strategies based on modified Aβ peptides for both the sporadic and genetic forms of Alzheimer's disease.

Source: Carlo Besta National Neurological Institute