Zeitschrift: Jahresbericht / Schweizerische Akademie der Medizinischen Wissenschaften = Rapport annuel / Académie suisse des sciences médicales = Rapporto annuale /Accademia svizzera delle scienze mediche

Herausgeber: Schweizerische Akademie der Medizinischen Wissenschaften

Band: - (1989)

Artikel: Molecular biology of Alzheimer's disease

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DOI: https://doi.org/10.5169/seals-308364

MOLECULAR BIOLOGY OF ALZHEIMER'S DISEASE

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Alzheimer's disease is a degenerative disorder of the central nervous system that results in a progressive loss of memory and other intellectual functions beginning in middle to late life (ALZHEIMER, 1907; for reviews, see PRICE, 1986, ABRAHAM and POTTER, 1989). Alzheimer's disease appears to occur both sporadically and in a familial (autosomal dominant) form with an overall prevalence estimated to be approximately 600 per 100,000. No clear evidence for an environmental, dietary, or infectious agent in the etiology of Alzheimer's disease has been found. Nor is there an effective treatment for preventing or arresting the neurodegenerative process.

The entry of molecular biology into the field of Alzheimer's disease has led to a great increase in our knowledge in the last few years. Several proteins involved in the neuropathology have been identified and their genes are providing a promising approach to finding the genetic defect underlying the familial forms of the disorder.

One of the main neuropathological lesions that characterize the brains of Alzheimer's disease patients is the neuritic or senile plaque, which consists of a spherical core of extracellular protein filaments surrounded by a halo of degenerating nerve cell processes. Extracellular protein filaments similar to those in the cores of neuritic plaques also occur in the walls of meningeal and intracortical blood vessels. The proteinaceous deposits in the cores of neuritic plaques and in blood vessels are referred to by the generic term "amyloid" – generally defined as an aggregate of extracellular 6–10 nm protein filaments that has certain tinctorial properties.

The first identified constituent of Alzheimer amyloid deposits was purified and sequenced from the amyloid in meningeal blood vessels (GLENNER and WONG, 1984). This protein, termed the β-protein, also proved to be the major constituent of the cores of the neuritic plaques of Alzheimer's disease and Down's syndrome (MASTERS et al., 1985, SELKOE et al., 1986) and served as the beachhead for cloning the gene encoding this protein. Four groups, independently and at nearly the same time, succeeded in using oligonucleo-

tide probes designed on the basis of the β-protein sequence to screen human brain cDNA libraries and obtain the corresponding gene for the Alzheimer's β-amyloid protein precursor (βAPP) (GOLDGABER et al., 1987, KANG et al., 1987, TANZI et al., 1987, ROBAKIS et al., 1987). Analysis of an apparently full-length clone showed the precursor of the β-protein to be a 695 amino acid protein which resembles a cell surface receptor (KANG et al., 1987). The β-protein is a small portion of this polypeptide near its carboxy terminus, and includes part of the putative membrane spanning region and part of the adjacent extracellular domain.

a_1-antichymotrypsin (ACT) in Alzheimer amyloid deposits

In a second, parallel line of experimentation, another component of the amyloid deposits of the cores of neuritic plaques and the walls of selected meningeal and cortical blood vessels in Alzheimer's disease brains was shown to be the serine protease inhibitor, a_1-antichymotrypsin (ABRAHAM, SELKOE, and POTTER, 1988). ACT was also found to be part of the similar amyloid filaments present in the brains of Down's syndrome patients and very aged normal humans and monkeys. The possibility that ACT plays a role in the formation of Alzheimer amyloid deposits was suggested by the specificity of its localization and the tightness of its association with the amyloid fibers: (1) only ACT, but not other related protease inhibitors, was detected in Alzheimer amyloid, (2) ACT was not present in the cerebral amyloid of Creutzfeldt-Jakob disease, and (3) immunogold electron microscopy localized ACT on extensively purified and extracted amyloid fibers.

The origin of amyloid proteins in Alzheimer's disease

Whether proteins contributing to amyloid deposits in Alzheimer's disease are synthesized locally, or are derived from a blood-borne precursor, has been a matter of some debate because it may bear on the pathogenesis of the disease (for discussion, see ABRAHAM, SELKOE, and POTTER, 1988). With respect to the β-protein precursor, its expression can be found not only in neurons in the brain but in cells of various tissues, including spleen, kidney and heart. Thus, the neurons of the brain appears to be the most likely source of the β-protein found in Alzheimer amyloid deposits, but it is not yet possible to exclude the possibility that the βAPP also circulates in the blood and reaches the brain through a defective blood-brain barrier.

The presence of ACT in Alzheimer amyloid deposits also opened the

question of the origin of this protease inhibitor. Because ACT is present in high concentration in the blood, a likely source of the inhibitor in Alzheimer's amyloid deposits is the circulation. However, we also found that both ACT messenger RNA and soluble ACT protein were greatly elevated in Alzheimer's disease grey matter, especially those areas most affected by neuropathology. *In situ* hybridization studies showed that reactive astrocytes in the region of neurodegeneration are actively synthesizing ACT (PASTERNAK et al., in press).

Role of proteases and inhibitors in amyloid formation

Proteases and their inhibitors, including α_1-antichymotrypsin, exist in a dynamic equilibrium in many tissues of the body (for review, see ABRAHAM, SELKOE, and POTTER, 1988). There is a delicate balance in the organism between proteases and their inhibitors associated with various physiological processes. Any alteration in activity, amount or location of a protease inibitor such as ACT could disrupt the dynamic maintenance of the local architecture or function of brain tissue. For example, a local excess of ACT might prevent a normal brain protease from clearing abnormal cleavage products of the β-protein precursor. Also the fact that ACT forms a complex with its target protease that cannot be dissociated by boiling in SDS and β-mercaptoethanol could explain the inclusion of the inhibitor in the Alzheimer amyloid filaments. Indeed, we have recently shown that the β-protein itself resembles the active site of serine proteases and binds to ACT in vitro to form an SDS-stable complex (unpublished).

Is α_1-antichymotrypsin part of a brain "acute phase response"?

Since the concentration of ACT in the blood can increase 2–4fold in a few hours as part of the body's acute phase response to various types of inflammation, it was possible that the increase in ACT mRNA and protein we detected in AD represented a similar general response associated with pathological states in the central nervous system. We therefore asked whether ACT-positive cells also arose in areas of neuropathology associated with diseases unrelated to Alzheimer's disease or Down's syndrome. In Huntington's and Parkinson's disease, stroke and brain malignancy, astrocytes immunolabeled for α_1-antichymotrypsin were found surrounding the areas of pathology (ABRAHAM, SHIRAHAMA, and POTTER, in preparation). From these results we conclude that the overexpression of ACT in the brain is

not *per se* a characteristic of Alzheimer's disease. Nor is it sufficient to cause ACT-associated amyloid deposition. Instead, ACT and its expression must either be aberrant in Alzheimer's disease, or its increased expression must be coupled with aberrant processing of the β-protein precursor protein in order for characteristic Alzheimer-like amyloid to form.

We consider it a particularly intriguing possibility that the overexpression of the protease inhibitor a_1-antichymotrypsin in the various types of brain pathology may reflect a brain "acute phase" response not unlike the acute phase response elicited by inflammation in the periphery.

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