Has the amyloid cascade a central role in Alzheimer's disease pathogenesis?

M. Di Luca

Dept. Pharmacological and Biomolecular Sciences, Università degli Studi di Milano, via Balzaretti 9, 20133 Milan

Alzheimer's disease (AD) accounts for approximately half of the dementia cases on a global scale and is characterized by progressive memory loss and severe cognitive decline. These clinical features are associated with extracellular deposition of amyloid-β (Aβ) peptide, formation of intracellular neurofibrillary tangles of hyperphosphorylated tau protein as well as neuronal and synaptic loss in the cerebral cortex and hippocampus.

Currently, the state-of-the art of AD knowledge is stuck to the amyloid hypothesis, which posits that Aβ has an early and vital role in AD pathogenesis since it triggers a cascade of events leading to synaptic dysfunction, tau pathology and neuronal loss. A quarter of a century of research on Aβ has produced a wealth of evidence that its accumulation in brain regions serving memory and cognition contributes strongly to the development of AD. Support has come from neuropathological, genetic, biochemical, animal modelling and biomarker analysis.

This view of the disease is appealing because it suggests a several equally clear paths by which AD might be prevented and cured. However, AD is associated with a complex biology and biochemistry, as well as a pattern of brain degeneration that cannot be resolved by a simple linear disease model. Indeed, there are growing amounts of evidence, including a number of failed clinical trials, suggesting that the model is probably not sufficient to explain AD pathogenesis.

Here, we will describe the current knowledge of AD pathogenesis mechanisms, providing a complete picture of strengths and weakness of the amyloid cascade. In addition we will address alternative models of disease process and the potential novel perspectives of therapeutic treatment.