Limits of the amyloid cascade hypothesis in the pathogenesis of Alzheimer disease, lessons from randomized controlled trials

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Randomized controlled trials (RCT) with immunotherapy against amyloid have given controversial and, at the end, unsatisfactory results. These human experiments were soundly based on the hypothesis that Alzheimer disease (AD) is causally linked to the deposition of beta-amyloid (Aβ) into brain plaques: the so called 'amyloid cascade'. According to this hypothesis the process of accumulation of Aβ -may be through oligomers that represent the immature forms of neurofibrillary Aβ- causes the neurodegeneration that determines AD and contrasting and even halting the process of aggregation of Aβ should also have beneficial effects on the disease. For these kind of reasoning the controversial, unsatisfactory results of the RCT on immunotherapy against Aβ are particularly disappointing and have raised a renewed scientific debate about the solidity and completeness of the Aβ cascade hypothesis for explaining the pathogenesis of AD or better of dementia due to Alzheimer disease. Actually animal models that develop cerebral Aβ amyloid plaques show phenotypic features very far from that observed in human AD. Even more puzzling is the fact that Aβ deposition is a necessary condition for AD -some researcher consider this a circular reasoning- but is not sufficient to cause the disease. Some, certainly defective, estimates show that about one third of persons with brain Aβ plaques do not have dementia with increasing numbers at older ages. This longstanding observation is generally explained with the argument that Aβ deposition precedes of many years – may be of decades- the development of symptoms of dementia, and this has been a strong argument in favor of considering Aβ as a biomarker of the disease clinically useful for early detection. However up to now there is no convincing evidence that Aβ deposition is inevitably followed, soon or later, by dementia. There are a number of other evidences contrary to the Aβ cascade hypothesis that, at the moment, cannot disprove it, however there is no doubt that, particularly for therapeutic purposed, this hypothesis should be discussed and refined.