IS AMYLOID TARGETING REALLY THE ANSWER IN AD?

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According to the amyloid cascade hypothesis, accumulation of insoluble Aβ in the brain is the primary event driving AD pathogenesis. There are three main arguments supporting this theory. The first and possibly most convincing among them is the discovery of missense mutations causally related to some rare familial forms of early-onset AD. Yet twenty years of intensive research failed to establish a direct relationship between these mutations and the development of neuronal pathology even in these rare genetic forms of AD. A second argument refers to the analogy with peripheral amyloidosis-driven tissue dysfunction. Formation of protein fibrils with a characteristic cross β-sheet architecture is the key indicator for a wide variety of systemic amyloid diseases. The mechanisms by which peripheral amyloidosis is toxic and affect cell viability are still debated. Proposed molecular pathways include oxidative stress, apoptosis, disruption of cell membranes, and inactivation of functional proteins. The relevance of these peripheral models for the understanding of central nervous system pathologies is, however, doubtful. First, there is a remarkable organ-related polymorphism in amyloid aggregation and toxicity mechanisms. In the brain, cerebral amyloid angiopathy may co-exist with AD pathology. Although the chemical composition of Aβ deposits in vessels and parenchyma is quite similar, there are no pathogenetic relationships between the two types of pathology and their clinical effects are clearly separate. The third argument concerns the synaptic toxicity of Aβ oligomers. Soluble oligomers of Aβ may be responsible for synaptic dysfunction in AD animal models and in AD brain patients. Aβ oligomers cause long-term potentiation impairment and synaptic dysfunction in vitro experiments and animal models. Soluble Aβ dimers isolated from cortex of typical late-onset AD patients directly induce *in vitro* tau hyper-phosphorylation and neuritic degeneration, in absence of amyloid fibrils. However, human data are still controversial and reveal significant overlap between controls and AD cases; soluble Aβ levels in post-mortem tissues is higher in young healthy individuals than in elderly controls and AD cases. To date, the transient nature and the heterogeneity of Aβ oligomers species impede the efforts to define the molecular pathways of their toxic activity.

In vivo, the possibility to visualize compact Aß deposits using the 11C-labeled Pittsburg Compound B (PIB) imaging was possibly the most important advance in AD research during the last ten years. In patients with clinically overt AD, PIB-visualized deposits are stable despite cognitive deterioration and a substantial overlap exists between MCI and controls. A two-year follow-up of Aβ deposits in patients with AD revealed that they reach a plateau very early in the course of the disease, while degeneration of the neurons continues. Progression of PIB-visualized deposits is temporally and regionally unrelated to 2-[18F]fluoro-2-deoxy-D-glucose (FDG) PET and magnetic resonance imaging (MRI) changes in AD. Combining serial PIB PET and MRI scans in normal, MCI and AD subjects, a dissociation between the rate of Aβ positive deposits and that of neurodegeneration (atrophy on MRI) has been showed. Moreover, Aβ deposition occurred prior to clinical decline, and clinical symptoms appeared coupled to neurodegeneration but not to Aβ deposition.

The amyloid cascade supporters suggest that soluble Aβ accumulation is the “primum movens” of AD acting predominantly at the synaptic level. Negative data of immunization may simply reflect that his intervention comes too late. Alternatively and as the tau supporters affirm, the paucity of cognitive results in preliminary immunization trials may signify that tau pathology is temporally closer to the neurodegenerative events that result in dementia than Aβ aggregates. Recent data demonstrate that an unilateral focus to the amyloid hypothesis may help us to understand the “primum movens” of the disease but would not provide sufficient therapeutic benefits. Although difficult and time-consuming, invest on tau-related strategies is now mandatory. The recent focus on soluble forms of toxicity that may be active long before the formation of brain aggregates implies, however, that Aß- or tau-focused curative strategies would be effective only in very early and possibly preclinical stages of the disease when biological compromise is still avoidable.