Preamyloid Lesions and Cerebrovascular Deposits in the Mechanism of Dementia: Lessons from Non- β -Amyloid Cerebral Amyloidosis

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Abstract

The importance of amyloid plaques in the pathogenesis of dementia is usually centered on β -amyloid ($A\beta$) and its role in Alzheimer's disease (AD). However, since fibrillar plaques correlate poorly with neurodegeneration, challenging their importance in the mechanism(s) of dementia, investigators turned their focus to the importance of soluble oligomers and the role of preamyloid and cerebrovascular deposits. Two non- $A\beta$ cerebral amyloidoses, familial British and Danish dementias (FBD and FDD), share many aspects of AD, including cognitive impairment and the presence of neurofibrillary tangles in limbic areas. The lack of compact plaques in FDD and in many areas in FBD further questions the importance of these lesions in the mechanism of dementia. The main components of the deposits – ABri and ADan – are structurally unrelated to $A\beta$ and yet they all have a high tendency to oligomerize and assemble into amyloid fibrils in vitro and form ion-like channels in lipid membranes. Thus, different amyloid species have the capability to induce similar neuropathological changes, which are neither exclusive for $A\beta$ nor dependent on the presence of compact plaques. These findings reaffirm the notion that non- $A\beta$ amyloidoses constitute alternative models to study the role of preassembled amyloid subunits in neuronal death.

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Alzheimer's disease (AD) is traditionally considered a disorder of plaques and tangles, criteria that were extended from the field of diagnosis to the area of basic research on the molecular mechanism(s) of the disease. In spite of all the attention these two lesions have received, their primary role in the pathogenesis of the disease remains unclear. The amyloid cascade hypothesis originally proposed fibrillization of β -amyloid ($A\beta$) as the likely cause of AD [1] but it soon became evident that amyloid plaques correlate poorly in number, time of appearance and distribution with neurodegeneration or cognitive impairment [2], issues that questioned their importance in the mechanism(s) of dementia. Over the last decade, investigations shifted to two traditionally neglected and understudied lesions, preamyloid and cerebrovascular deposits, in an effort to assess their contribution as significant elements to disease pathogenesis. In the case of preamyloid lesions, attention focused on whether prefibrillar $A\beta$ species constituted the active elements that ultimately caused the synaptic loss and dementia associated with AD. Although the precise molecular identity of these soluble nonfibrillar species remains unsettled, cumulative evidence suggests that these forms are indeed the effectors leading to neuronal injury. Stable oligomers of $A\beta_{42}$ have been identified in cell culture models, in amyloid precursor protein transgenic mice, and have been isolated from the human brain, plasma, and cerebrospinal fluid under disease conditions correlating better with the severity of neurodegeneration. In vitro experiments with nonfibrillar structures suggest that these assemblies are

not only neurotoxic but also likely to affect cellular plasticity and memory loss early in the disease progress through synaptic targeting and alterations in the synaptic structure (reviewed in Hardy [3] and Walsh and Selkoe [4]).

Cerebrovascular dysfunction is being increasingly recognized as a major contributor to AD pathogenesis. In particular, amyloid deposition in cerebral vessels – collectively known as cerebral amyloid angiopathy (CAA) – is emerging as an important participant in neurodegeneration. Although it is clear that the relation CAA-dementia is complex and probably encompasses a range of different pathogenic mechanisms, to date, vascular deposits and not parenchymal plaques appear to be more sensitive predictors of dementia [5]. A β vascular deposition affects not only medium and small cerebral arteries and arterioles, in which they frequently replace the normal vessel architecture, but very often the degenerating endothelium of capillaries in which thinning and fragmentation of the basement membrane and breakdown of the blood-brain barrier translates into disturbances of cerebral metabolism, reduced cerebral blood flow and neural metabolic changes contributing to neuronal damage and cognitive impairment. Many aspects of CAA in early- and late-onset AD still remain unclear, among them the dichotomy leading to the preferential vascular deposition of A β ₄₀ in contrast to the parenchymal localization of A β ₄₂, the favored vascular compromise associated with familial A β genetic variants, as well as the puzzling observation that some of these vasculotropic variants solely present with hemorrhage or stroke while others are mainly associated with dementia (reviewed in Ghiso and Frangione [6]).

We have been studying two hereditary disorders known as chromosome 13 dementias – familial British and Danish dementias (FBD and FDD) – which reinforce the viewpoint that plaque burden is not indicative of dementia, while highlighting the relevance of nonfibrillar lesions and vascular involvement in the disease pathogenesis. Patients with FBD or FDD show extensive pre-amyloid deposits, widespread CAA with perivascular plaques and neurofibrillary tangle pathology in limbic areas. Both disorders originate in genetic defects at or near the stop codon of the 13q14.3 *BRI2* gene, namely a Stop-to-Arg mutation in FBD and a 10-nucleotide duplication insertion immediately before the stop codon in FDD (reviewed in Rostagno et al. [7]). Regardless of the nucleotide changes, the final outcome is common to both diseases: the genesis of an extended precursor featuring a C-terminal piece that does not exist in normal condi-

tions. The de novo created amyloid peptides, ABri and ADan, are C-terminal proteolytic fragments of this larger-than-normal precursor molecule, generated mainly by the action of the proprotein convertase furin. Both BRI2-related amyloid peptides show no sequence identity with any known amyloid protein, share 100% homology within the first 22 residues but are completely different in the 12 C-terminal amino acids, characteristics that allowed the generation of specific antibodies used for the topographical characterization of the deposited proteins [8, 9]. ABri and ADan differ from A β in length and primary structure and yet all share an array of post-translational modifications, a great propensity to oligomerize and form fibrils in vitro, as well as the ability to assemble into morphologically compatible ion-channel-like structures and elicit single ion channel currents in reconstituted lipid membranes [10], suggestive of their ability to induce common pathogenic pathways.

In spite of the structural differences among A β , ABri and ADan, the neurofibrillary tangles present in FBD and FDD are very similar, if not identical, to those found in AD. In all cases, tangles are immunoreactive with several antihyperphosphorylated tau antibodies, ultrastructurally composed of paired helical filaments, and display an indistinguishable electrophoretic migration pattern among the three disorders [7]. Amyloid deposits and neurofibrillary tangles primarily coexist in the limbic structures although amyloid burden is also evident in other areas not affected by tangle pathology. As in AD, there is no complete overlap between these two pathologies, and neurons from some structures with significant parenchymal amyloid load (e.g. the cerebellum) remain resistant to neurofibrillary tangle formation. This lack of complete overlap of tau and amyloid pathologies in FBD and FDD is puzzling and indicates that, although amyloid/preamyloid deposits are of paramount importance, the mechanism of neurodegeneration is complex and likely involves additional factors and/or interrelationships among different cellular pathways.

The BRI2-linked hereditary disorders also question the importance of amyloid plaques in the mechanism of cell toxicity: plaques are absent in FDD and in certain brain areas in FBD whereas both disorders overwhelmingly feature parenchymal preamyloid lesions. These diffuse deposits are more soluble than the fibrillar lesions; they can be extracted in water-based buffers in the presence of mild detergents and do not require the use of formic acid. Western blot and size exclusion chromatography studies reveal that these extracts are enriched in oligomeric species with the potential to trigger neuronal

toxicity [11]. In addition to the preamyloid deposits, chromosome 13 dementias also share a broad vascular compromise which undoubtedly contributes to the process of neurodegeneration. Closely resembling FDD, cases of the Iowa variant of amyloid precursor protein (a single D-to-N substitution at position 23 of A β) also present with a predominant vascular compromise coexisting with scattered preamyloid deposits, abundant neurofibrillary tangles and dystrophic neurites in the presence of remarkably few mature plaques. In spite of the lack of compact plaques, Iowa patients – similar to FDD cases – develop progressive, early-onset AD-like memory impairment with no reported episodes of clinically manifest intracerebral hemorrhage regardless of the overwhelming vascular amyloid deposition [12].

In conclusion, both A β and non-A β cerebral amyloidoses emphasize the primary importance of amyloid in the process of neurodegeneration which is certainly neither exclusive for A β nor dependent on the presence

of compact plaques. Based on their neuropathological phenotypes we propose that FBD and FDD are excellent models to study early steps of peptide oligomerization/fibrillization and the role of preamyloid and cerebrovascular deposits in the process of neurodegeneration. Evidence indicates that different amyloid species have the capability to induce similar neuropathological changes leading to the same scenario, neuronal loss and dementia. BRI2-related dementias provide excellent alternative paradigms to assess the molecular mechanisms by which unrelated peptides likely adopt similar altered amyloidogenic configurations and trigger comparable downstream detrimental effects in neuronal cells.

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