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Review

The dark sides of amyloid in Alzheimer's disease pathogenesis

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ABSTRACT

Although widely explored, the pathogenesis of Alzheimer's disease (AD) has yet to be cleared. Over the past twenty years the so call amyloid cascade hypothesis represented the main research paradigm in AD pathogenesis. In spite of its large consensus, the proposed role of β-amyloid (Aβ) remain to be elucidated. Many evidences are starting to cast doubt on Aβ as the primary causative factor in AD. For instance, Aβ is deposited in the brain following many different kinds of injury. Also, concentration of Aβ needed to induce toxicity *in vitro* are never reached *in vivo*. In this review we propose an amyloid-independent interpretation of several AD pathogenic features, such as synaptic plasticity, endo-lysosomal trafficking, cell cycle regulation and neuronal survival.

1. Introduction

Alzheimer's disease (AD) is the most common form of dementia, with an estimated 24 to 35 million people affected worldwide [1]. Although it has been widely explored, the pathogenesis of AD has yet to be cleared. According to the view that interprets many neuropsychiatric disorders as neurotransmitter dysfunctions, during the seventies and early eighties AD was looked at as a cholinergic deficit involving the cholinergic projection from the basal forebrain neuronal population (the nucleus basalis magnocellularis of Meynert) to the cortex and hippocampus [2], similarly to Parkinson disease (PD) which was shown to be due to the degeneration of the nigrostriatal dopaminergic fibers. Since the cholinergic hypothesis of AD was developed, once again similarly to PD, a pharmacological approach based on inhibitors of cholinesterases addressed to increase the cholinergic tone in AD brain was adopted. Later on, over the past twenty years, when a more complex way to look at the neurodegenerative diseases caught on, the so call amyloid cascade hypothesis [3] became the main research paradigm in AD pathogenesis.

Amyloid β protein (Aβ), the major constituent of the senile plaques (SP) [4] is, together with neurofibrillary tangles (NFT), the hallmark for the neuropathological confirmation of AD [5]. Aβ is a peptide that has between 39 and 42 amino acid chains; the 42 amino acids form aggregates more avidly and is thought to be implicated in the pathogenesis of the disease and is the basis of the amyloid hypothesis. Aβs are products of the proteolytic cleavage of amyloid precursor protein (APP), a ubiquitous, glycosylated, sulfated, and phosphorylated integral membrane protein [6]. The amyloid hypothesis infers the presence of two distinct pathways for APP hydrolysis: the "amyloidogenic" and the "non-amyloidogenic" pathway. The first pathway is initiated by the β-secretase enzyme, an identified aspartyl protease (BACE 1 and 2) which cleaves the extracellular region of APP [7–9]. Subsequently, γ-secretase, a multiprotein complex containing at least presenilin 1, presenilin 2 and nicastrin, hydrolyses APP in the middle of its transmembrane domain [10–12]. The large, soluble APP ectodomain, APPs-β and Aβs are released extracellularly. The alternative pathway of APP hydrolysis is referred to as "non-amyloidogenic"

Abbreviations: Aβ, amyloid β protein; NFT, neurofibrillary tangles; APP, amyloid precursor protein; PSs, presenilins; NICD, Notch intracellular domain; mTOR, mammalian Target of Rapamycin; PP2A, protein phosphatase 2; GSK-3, glycogen synthase kinase-3; CTFS, cytosol-soluble peptides containing; AICD, APP intracellular domain; CTFs, carboxy terminal fragments (CTFs); MVEs, multivesicular endosomes; ILVs, intraluminal vesicles

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and is initiated by α-secretase, which cleaves APP within the Aβ domain precluding the formation of Aβ. In this case, the γ-secretase activity produces P3, a 24 or 26 amino acid containing peptide, and APPs-α, a large soluble protein released extracellularly [13,14]. α-Secretase cleavage is the major pathway of APP processing, which is mediated by a disintegrin and metalloproteinase ADAM10 or ADAM17 [15].

The pathogenic role of Aβ in AD is sustained by several lines of evidence. The main support comes from the observation that mutations in APP or in presenilins genes, leading to overexpression of Aβ, are associated with familial forms of AD (FAD). Furthermore, transgenic mice harboring the human mutations bear strong similarity to AD and finally, Aβ is shown to be toxic to neurons in culture and when administered intracerebrally to experimental animals. In accordance with this hypothesis, Aβ emerges as a molecule with a variety of cytotoxic effects. For instance, Aβ is able to affect the mitocondrial redox activity [16] to increase the production of free radicals [17], to damage the intracellular calcium homeostasis [18], to induce the formation of selective calcium channels [19], to induce the release of cytokines [20], to increase the effects of other toxic agents such as excitatory aminoacids [21] or lack of glucose [22], and to increase the enzymatic activity of phospholipases A2, C and D [23]. More interestingly, it was also shown that Aβ is able to negatively regulate the synthesis and release of ACh from the basal forebrain cholinergic system [24,25].

However, recent evidence suggests alternative mechanisms for AD pathogenesis and outline how Aβ, which is only one of the many products of the APP breakdown, may be regarded as a reactive entity to potentially pathogenic stimuli. Even the genes involved in Aβ metabolism, whose mutations may cause FAD, could be involved in additional mechanisms besides the ones associated with Aβ metabolism.

The aim of the present work is to reevaluate the role of Aβ in AD pathogenesis and to suggest possible alternative ways to look at the classic amyloid hypothesis proposed almost twenty years ago.

2. Is Aβ the primary culprit in AD?

In spite of the large consensus, the proposed role of Aβ in AD pathogenesis remains to be elucidated. Although several genetic evidence suggest an important pathogenic role for Aβ, a major remark that casts doubt on the amyloid hypothesis is the observation that just a small number of AD cases, comprised between 1% and 5%, are linked to a genetic mutation. The cause of most late-onset AD cases (LOAD) still remains unclear, as the likelihood of developing LOAD is linked to the interaction between environmental factors and a number of susceptibility genes such as the well known apolipoprotein E (APOE) gene [26,27]. Currently, more than 30 FAD mutations have been mapped on the APP gene. Interestingly, APP mutations of the London type, which cause relatively small increases in Aβ, induce AD at earlier ages than the Swedish mutation, which causes much higher increases in Aβ [28], suggesting that other mechanisms may be involved.

Another strong point against the arguments supporting the cause of senile plaques as main players in the etiology of AD is that, although long considered one of the hallmarks of AD, they are not specific to AD. The frequency of SP rises with the age in healthy controls [29] and the number of plaques in cognitively healthy people is comparable to the one observed in affected people [30]. Even in the AD population, there is only a weak correlation between plaque load and severity of dementia.

Perhaps more importantly, there is strong evidence of deposition of Aβ as a reaction to different kinds of brain injury, such as head trauma and cerebral ischemia. In general, data has demonstrated that stress, specifically of a type that can induce metabolic stress by lowering the energy supply, induces a Ca^{2+} overload and a consequent up-regulation of APP and its mRNA [31–37] suggesting that the overproduction of Aβ has to be regarded as a non-specific phenomenon.

A further remark that may question the validity of the amyloid hypothesis is the description of several pathological conditions including sporadic cerebral amyloid angiopathy [38] and hereditary cerebral hemorrhage with amyloidosis of Dutch type [39], which show levels of amyloid pathology similar to AD without any overt dementia, suggesting once again that amyloid alone is insufficient to cause neuronal loss and cognitive symptoms observed in AD.

Finally, further evidence that suggests an alternative way to consider the amyloid hypothesis comes from several clinical trials which used either active or passive immunization in order to stimulate the Aβ clearance from the brain of AD patients. Although immunization with Aβ-42 resulted in enhanced clearance of amyloid plaques, this did not prevent progressive neurodegeneration and cognitive deterioration [40]. Moreover, despite the evidence of a good safety profile and good signals of pharmacodynamic activity, even anti-Aβ monoclonal antibodies (bapineuzumab and solanezumab) did not demonstrate significant clinical effects in trials conducted on mild to moderate AD [41,42]. Even more significant is a recent study that compares the Fluorodeoxyglucose (FDG)-PET and Pittsburgh compound B (PIB)-PET patterns in three groups of AD variants (logopenic variant of Primary Progressive Aphasia (PPA), Posterior Cortical Atrophy (PCA) and early onset frontal variant) and suggests an only partial role of fibrillar Aβ deposition in determining clinical phenotypes. Although FDG-PET revealed a focal pattern of hypometabolism corresponding to these specific clinical aspects, PIB-PET detected a diffuse hypocaptation of the tracer without differences between the three groups. Therefore, it is not the distribution of cerebral amyloid deposition, but rather the position of the areas of focal hypometabolism to be related with distinct clinical features of the AD variants. Thus, the amyloid deposition only partially explains the overall clinic-anatomical heterogeneity of AD [43].

The role of Aβ as responsible for the cholinergic deficit in AD can also be questioned. For instance, in the brain of 8 months old transgenic Tg2576 mice, when there is no accumulation of Aβ yet, reduced binding levels of cortical and hippocampal M1 mAChR were observed [44]. Recent data shows as well that the reduced hippocampal release of ACh was due to a significant increase in the rate of high affinity choline uptake, suggesting a possible compensatory mechanism in response to an impairment of the cholinergic synapses [45,46].

In conclusion, it is critical that NFT burden correlates better than SP with cognitive decline, but the best correspondence is shown by cortical synaptic loss [29,47–50]. In fact, failure in synaptic transmission and further disturbance of the neuronal circuits is a significant pathogenic aspect of AD. Furthermore, it was demonstrated that extracellular deposition of fibrillar Aβ is not required for the development of synaptic function impairment. In particular, it was shown that overexpression of mutant human APP in the neurons of transgenic mice decreases the density of presynaptic terminals and neurons before these mice develop amyloid plaques [51].

3. Synaptic plasticity in AD

3.1. The role of presenilins

There is a growing body of evidence to show that presenilins (PSs) could be involved in synaptic plasticity. To support this role of PS1, there is data demonstrating that PSs are localized in

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