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Apolipoprotein E in Alzheimer's Disease

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Abstract

The pathophysiology of Alzheimer's disease (AD) is related with the ongoing deterioration of brain lipid homeostasis, in which the cholesterol transporter apolipoprotein E (APOE) plays a key role. Plasma protein APOE might be additionally associated with AD due to its capability to bind the amyloid protein. There are three principal isoforms: APOE2, APOE3 and APOE4, encoded by three different alleles (ε2, ε3, ε4). Among them, APOE4 is recognized as the toxic form involved in AD development and progression. In fact, the presence of the ε4 allele correlates to an increase of about three times in the risk of developing the disease in late onset forms, both familiar and sporadic. For this reason, APOE4 has been often highlighted as a promising therapeutic target. Nevertheless, recent studies also suggest that the reduction of APOE protein levels, regardless of the isoform present, might be beneficial to deal with AD progression.

Herein we report a brief overview of the proposed roles of APOE and in particular of ApoE4 in the insurgence and development of AD. In particular, its intervention in amyloid-β dependent and independent processes are examined. New therapeutic approaches for AD exploiting APOE as a target are finally discussed.

Keywords: *Apolipoprotein E; APOE4; Alzheimer's Disease; Cholesterol Homeostasis; Aβ-APOE Interaction; APOE Based Treatments*

Introduction

Alzheimer's disease (AD) is one of the most common types of dementia, with 24 million people affected worldwide [1]. Its incidence is highly related to age as well as multiple risk factors.

More specifically, AD is a progressive neurodegenerative disease of the central nervous system (CNS). It is characterized by cognitive decline with two anomalous hallmarks in the patients' brain, namely extracellular senile plaques and intracellular neurofibrillary tangles (NFTs) [2,3]. The major constituents of senile plaques are insoluble aggregates of amyloid-β (Aβ) peptide, while the NFTs are mainly composed of microtubule-associated tau protein in its hyperphosphorilated state [4,5].

A large number of studies support the hypothesis that the AD pathophysiology is also associated with the dysregulation of brain lipid homeostasis and vascular changes [6], with cholesterol alterations being related to senile plaques formation and impaired phosphorylation of tau protein [7].

In this context, apolipoprotein E (APOE) is believed to play a key role in cholesterol homeostasis in the normal and injured central nervous system, being the most important protein of its family to coordinate, mobilize and redistribute such lipid in the brain [6,8]. The cholesterol is fundamental for repair, growth and maintenance of myelin and neuronal membranes [9], for this reason the APOE role is essential during development or after injury.

In detail, the human APOE is a lipid transport glycoprotein coded by the polymorphic ApoE gene, mapped at the chromosome 19q13.2. In humans, three major allelic variants exist: ε2, ε3 and ε4, that derive from single nucleotide polymorphisms (SNPs) rs429358 (T/C) and

rs7412 (C/T) at exon 4. The most widespread is ε3, being represented in 78% of the population, while ε3 and ε2 account for only 14% and 7% of the genotypes respectively [10]. They encode the three major protein isoforms, APOE2, APOE3, and APOE4, that differ from each other in aminoacid residues at the 112th and 158th positions as follows: APOE2 contains Cys 112 and Cys 158, APOE3 Cys 112 and Arg 158 and APOE4 Arg 112 and Arg 158 [11]. The combination of these mutations results in different three-dimensional structures, affecting the protein intervention in processes such as synaptic plasticity and cognitive aging [12,13].

APOE interventions in AD

Due to the increased occurrence of ε4 allele in late-onset AD patients (40%) compared to that among healthy individuals [14], ApoE isoforms differential roles in AD pathogenesis have been extensively investigated. Major evidences have been found that ε4 allele carriers are at increased risk of developing late-onset AD, with respect to ε3 and ε2 carriers [15-19]. This effect is dose-dependent, with ε4/ε4 homozigous individuals having a higher risk with respect to heterozigous (ε4/ε3 or ε4/ε2) ones [14]. In addition, there are evidences that, even though much less prevalent, possession of an ε2 allele is protective against AD risk [20,21].

In particular, APOE4 seems to increase risk of AD and cognitive decline through both Aβ-dependent and independent processes. Concerning the Aβ pathway, many studies highlighted the association with senile plaques deposition. In particular, a large study on a broad AD population strongly suggested that ε4 allele possession correlates with increased levels of neuritic plaques, in a dose-dependent manner [22]. Interactions might occur at various stages of the Aβ cascade. In particular, it has often been hypothesized that APOE plays a pivotal role in Aβ clearance, possibly by endocytosis of Aβ-APOE complexes via the low density lipoprotein receptors [23]. Because native ε4 protein is much less affine to Aβ than ε3 and ε2 isoforms [24,25], it might be unable to efficiently clear it and thus favour extracellular aggregates accumulation. Moreover, immunoreactivity tests showed that APOE co-deposits with Aβ in senile plaques [26], suggesting an active role of the protein in triggering aggregation and deposition, possibly in an isoform-dependent manner [27]. Finally, it was demonstrated that it stimulates the production itself of Aβ: APOE4 can in fact promote APP endocytosis at a much higher extent than APOE3, resulting in the acceleration of Aβ production, aggregation and deposition in the brain [28].

A second line of research has focused on the role of APOE in cholesterol metabolism and homeostasis, whose dysregulation has often been associated with AD. The crucial role of such substance in axons growth and modelling of synapses might explain the correlation [29]. This is not, however, the only connection with AD disease pathogenesis: for example, abnormal metabolites of cholesterol oxidation were also found to accelerate amyloids formation [30]. In this complex net, APOE isoform-dependent interaction with cholesterol is crucial. In particular, it was shown that APOE4 is less efficient in transporting cholesterol from neuronal cells and astrocytes to the CNS compared to APOE3 [31], fact that might be directly associated with AD risk and progression. APOE intervention in cholesterol metabolism is not completely detached from Aβ pathway either. In fact, cholesterol levels also modulate γ-secretase activity and thus Aβ production via APP cleavage [32]. This process reportedly depends on the specifically expressed isoform as well.

Furthermore, APOE4 is associated with a number of other processes implied in AD risk and development. In particular, it triggers inflammatory cascades that cause neurovascular dysfunction, including blood–brain barrier breakdown, leakage of blood derived toxic proteins into the brain and reduction in the length of small vessels [33]. Also, it is associated with dysfunctional neurogenesis, by impairment of hilar interneurons containing γ-aminobutirric acid maturation [34]. A truncated fragment of APOE4, resulting from a proteolytic cleavage following stress or injury, increases tau hyperphosphorylation, promoting intracellular neurofibrillary tangles (NFTs) formation, cytoskeletal disruption and mitochondrial dysfunction [18,35-39]. Moreover, immunoreactivity tests show that APOE is co-deposited not only to the senile plaques but also to vascular amyloids and NFTs of AD patients [7,18,40].

Novel treatments targeting APOE pathways

Based on all these findings on APOE4 toxic functions, the lowering of its expression is believed to be beneficial in APOE ε4 carriers with cognitive decline during AD, even though additional preclinical studies are needed for a full confirmation. Generally concerning APOE protein and regardless of the isoform, there has been intense debate on whether potential AD therapeutics should increase or decrease its

levels [41-43]. Many studies clearly indicate that higher levels of APOE increase the risk of developing AD [21]. Accordingly, it was demonstrated that the deletion of the endogenous murine APOE gene causes a dramatic decrease in fibrillary and total Aβ deposition in amyloid precursor protein (APP) in transgenic mouse models [44]. Besides, APOE mRNA and protein levels are elevated in brains of Alzheimer's subjects compared to controls [45,46] and have been demonstrated to correlate with Aβ aggregation and accumulation [47]. However, other studies indirectly suggest that increasing, rather than decreasing, human APOE levels would be the right therapeutic approach [48]. This might, in fact, compensate the reduced APOE functions in Aβ metabolism and cholesterol homeostasis for AD patients. For example, administration of agonists of liver X receptor and retinoid X receptor -which modulate ApoE expression- were found to increase the protein levels and contextually facilitate Aβ clearance [48,49]. Further studies are thus required to clarify which is the convenient approach with respect to APOE3 and APOE2.

Beside these, a number of other therapeutic strategies are currently studied. The first one aims at disrupting the Aβ-APOE interaction. It relies on the observation that APOE is co-deposited in senile plaques and the hypothesis that deposition would not happen when impeding the interaction. This has been firstly achieved with an $A\beta_{12-28}$ peptidomimetic [50], but could in principle be done with antibodies and small molecules as well. While searching for APOE-interacting entities, however, attention should be paid at not disrupting other APOE functions. Another approach relies on APOE4 modification so as to obtain an APOE3-like structure [12]. This strategy is based on the argument that not APOE, but specifically APOE4 levels should be lowered. Several compounds have been tested that interact with the APOE4 Aβ-binding domain, producing good results in terms of decreasing the Aβ levels [51]. Finally, APOE receptors instead of the protein itself have been highlighted as targets for novel AD therapies, to restore the correct lipid homeostasis and improve Aβ clearance [52].

Conclusion

In conclusion, a large number of studies have highlighted many putative roles of APOE, and in particular APOE4, in AD. These range from direct interaction with the toxic Aβ peptide to cholesterol homeostasis, protein tau hyperphosphorilation and a number of other processes exacerbating the disease course. While it seems clear that they are mostly isoform-dependent, with APOE4 being the harmful isoform and APOE2 being possibly protective, details are still missing in the general picture. For example, a relevant issue to be addressed is whether high levels of APOE are harmful in AD patients, regardless of the isoform. Nevertheless, many therapeutic strategies have been proposed that exploit these insights on APOE. These range from inhibiting Aβ-APOE interaction, to exclusively modifying APOE4 structures, to interfering with APOE receptors activity.

Even though ApoE genotype is not considered a predictive feature for Alzheimer's, it can still indicate a predisposition to develop the disease. For this reason, genetic data can be extremely valuable to obtain a differential diagnosis. As for other conditions, risks awareness enables to undertake therapeutic action in advance, although, in the case of AD no curative treatments are currently available.

For this reasons, APOE pathogenicity with respect to AD and its roles in the disease insurgence and progression should be further investigated, so as to exploit the results for early diagnosis and development of new therapeutic approaches.

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