Role of Apolipoprotein E in Alzheimer’s disease: mini review

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Abstract

Alzheimer’s Disease (AD) is one of the most common neurodegenerative diseases. Apolipoprotein E 4 (APO E ε4) gene is a genetic risk factor for AD. The encoded protein apo E ε4 predisposes its carriers to AD by influencing the metabolic of amyloid and other factors. APO E ε4, of which massive biological and genetic evidence has been accumulated, is sure to be a hot topic for AD study and the development of target therapeuticals.

Introduction

AD (Alzheimer's disease) is one of the most common neurodegenerative diseases and the leading cause of dementia [1-3]. Apo E (apolipoprotein E) was found to be involved in the pathogenesis of AD in 1991 by Warren Strittmatter when he searched AD-associated amyloid-binding proteins in the cerebrospinal fluid [4]. Allen Roses and his wife confirmed that apo E4 is a genetic risk factor for AD afterward [5]. It was found subsequently that apo E4 is the genetic risk factor for late-onset AD (LOAD, onset age >65 years old, which is a predominant type); while early-onset AD (accounting for 5%-10%) may be associated with other genes including APP (Amyloid precursor protein), PS1 (Presenilin 1) and PS2 (Presenilin 2) [6]. Human apo E has three subtypes (type 1, type2 and type4); the carrying rates of the three subtypes are 7%-8%, 78% and 14%-15% respectively [6]. In white people, those carrying ε4/ε4 homozygote have a nearly 15-fold increased risk of developing AD compared with those with ε3/ε3 homozygote; In African Americans, the risk in the people with ε4/ε4 genotype increased by 10 folds compared

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with those with ε3/ε3 [7].

Although apo E has been found associated with AD for more than 20 years, the understanding of the role of apo E in AD is still limited. How does apo E ε4 increases the risk of AD, current studies suggest two involved pathways; the first one is amyloid-related, that is, apo E ε4 greatly promotes the deposition of Aβ in the brain; the other is amyloid non-related [8]; it is thought that when neurons are subjected to stress, the increase of apo E is one of the repair mechanisms; however, the increase of harmful subtype will injure the mitochondria and cytoskeleton [1, 9].

This article reviewed the role of apo E in AD and their correlation and provided some suggestions and thoughts for further research and clinical application of apo E.

1. Relationship between apo E-related Lipids and AD

Apo E, firstly known as a member of apolipoproteins, participates in the transfer of lipids including cholesterol in the body. The protein is consisted of 299 amino acids and included three subtypes; while apo E gene is located at chromosome 19 [6]. Apo E is a member of ligand family of low-density lipoprotein receptor (LDLR). In the central nervous system, most apo E proteins are produced by astrocytes. The protein can bind to cholesterol and other lipids and transport these lipids into neurons through receptor-mediated endocytosis. The major receptors of apo E in the central nervous system are LDLR and LRP1 (low density lipoprotein receptor-related protein 1) [10].

1.1.1. Cholesterol and apo E

In animal model of high-fat, high-cholesterol (HFHC) diet, brain cholesterol level is elevated, especially in the elderly animals that carry the ε4 gene [6]. However, the increase of cholesterol level is not so significant in the brain of the patients with early-stage AD. Diet may increase peripheral cholesterol level. Despite that the correlation of the cholesterol regulation in peripheral and central system is still unclear, with aging and progression of AD, many factors such as oxidative stress, infection, cardiovascular diseases and diabetes can promote oxidation of cholesterol, phospholipids and other lipids, which alters the normal functions of the membrane and accelerates the formation and aggregation of Aβ.

It has been known that oxidized cholesterol (O-Cholesterol, oxysterols) in the central nervous system is mostly formed locally instead of being transported from the periphery. However, some highly-polar oxidized cholesterol can also pass through the blood brain barrier (BBB). Moreover, oxidized cholesterol can regulate the expression of apo E by binding to liver X receptor, and acting as a messenger molecular, 24-OH Chol can induce cholesterol exocytosis of astrocytes mediated by apo E. In the cerebrospinal fluid, 24-OH Chol level is positively correlated with apo E level [6]. However, a large amount of cholesterol (sphingolipid) is inherently present in the central nervous system, and there is no significant difference in the central cholesterol level between AD group and control group. The subcellular cholesterol levels are also difficult to
measure [10]; therefore, whether the interaction of cholesterol and apo E is associated with AD still needs further studies to elucidate.

1.1.2. Sulfatide and apo E
Sulfatide (SL) is another lipid associated with apo E. Apo E assists SL transport in the central nervous system and maintains its balance. When this effect is abnormal, it can lead to the decrease of SL, further cause ceramide (a kind of sphingolipid) decreased [10]. The decrease of ceramide may occur in the early stage of AD, and the protection of nerve fibers is weakened, which in turn will affect the transmission of nerve impulses.

1.1.3. Dipalmitoyl phosphatidyl choline and apo E
Aβ tends to accumulate in the dipalmitoyl phosphatidyl choline (DPPC)-rich region of the membrane; this part of the membrane then encapsulates Aβ; the binding of apo E to DPPC stabilizes this structure and makes it transport safely. When reaching the target cells, apo E binds to LDL receptor to mediate endocytosis, and Aβ can successfully enter the target cells. Apo E plays a guard role throughout the process. This effect can be weakened by reducing dietary intake of DPPC, and cellular oxidative stress can also be reduced [10]. This role has a great relationship with the aggregation and degradation of Aβ, which was described in detail later.

2. Different and Common Features of the E Subtypes of apo E

2.1. The Structural Differences between the Subtypes
There are three subtypes of apo E, namely ε2, ε3 and ε4 [9]. Although ε4 is the major risk factor for LOAD, most patients with AD carry ε3 (78%). They have only two amino acid residue differences in their composition; in ε2, the position 112 and 158 were both cysteine (Cys); in ε3, the cysteine of 158 is replaced by arginine (Arg), and in ε4, both positions are arginine. In terms of the effect on LOAD, opposite to ε4 which is a risk factor for AD, ε2 has protective effect and ε3 is relatively neutral [6, 10, 11]. It has been known that Cys can induce the post-translational modification of proteins, for example, chelating with metal ions and fold, which plays an important role in the production of proteins. The three subtypes have very different effects on LOAD. Therefore, J Abrams et al supposed that Cys may play a switch role in the development of AD [12]. In subsequent studies, they found that the Cys112 site of ε3 is more likely to bind to the LDL receptor after S-nitrosylation by NOS1, and this modification is very active in brain tissue [11]. This is indeed an exciting breakthrough, but ε2 and ε3 both have Cys in position 112, why is NOS1 effect particularly significant for ε3? Moreover, whether there are other mechanisms to alter protein functions in addition to the replacement of amino acids? The in vivo binding capacity of apo E subtypes to LDL receptor is still unclear.

2.3 Association-dissociation Behavior of apo E
The complete structure of wild-type apo E is unknown until now. The apo E monomer contains two domains to be connected by a 40aa
length protease-sensitive hinge structure [13].

Apo E includes N-terminal (1-191, the change from Cys to Arg occurs in this region) and C-terminal (221-299, the region responsible for the binding of apo E to lipids) [14, 15]. Garai et al found that wild-type apo E shows a dynamic binding-dissociation process in vitro, that is, monomer-dimer-tetramer, and the process is associated with the concentration of apo E in environmental solvent [16]. When the concentration of apo E is ≤200 nM, apo E exists as monomer/dimer form predominantly, and the number of ε3 is much more than ε2 and ε4 [14]. Whether the dominance of the number of ε3 may cause a false impression that ε3 has a stronger binding capacity? Another question is, the concentration of Apo E in the cerebrospinal fluid (CSF) is ≈150 nM, apo E is mostly in the form of lipoprotein complex, whether the association-dissociation behavior is as same as in vitro? in vivo environment is more complicated than in vitro and affected by more factors; however, the finding indicates a possibility of reducing the negative effect of apo E by changing its subtype to achieve prevention and therapeutic effect [17].

3. Effect of apo E on Aβ

As mentioned above, one of the apo E-associated pathways involves Aβ. Many studies also confirm the existence of subtle relationship between them. Aβ is a proteolytic product of transmembrane protein APP after secondary cleavage, and is also a major component of firstly-discovered biomarker of AD [18]. Apo E affects the function of astrocytes in the clearance of Aβ although the role of ε4 remains unclear [10]. Peripherally, there is a LXR (liver X receptor)-ABCA1 (ATP binding cassette transporter A1)-apo E regulatory axis [21], also known as "peripheral deposition" clearance pathway of apo E.
Aβ, which regulates the clearance of Aβ after being transported to liver and kidney. Studies have shown that antagonists of X receptor can induce the increase of ABCA1 and apo E to reduce Aβ deposition [10, 22]. Unfortunately, there is a substantial amount of cholesterol (sphingolipids) in the central nervous system inherently [23], and there is no significant difference in central cholesterol level between AD and control group. The subcellular level of cholesterol is also difficult to determine due to technical limitations [10]; therefore, the effect of apo E on Aβ clearance is still inconclusive [24, 25].

Effect of apo E Aβ aggregation: in addition to Aβ clearance, apo E also has certain effects on Aβ formation. Current studies suggest that the soluble oligomerization state of Aβ is more neurotoxic than that in precipitated plaques. Hashimoto et al found central apo E could stabilize Aβ oligomers, especially ε4, to protect them from degeneration or being cleared by phagocytes. The binding site of apo E to Aβ is Δ243-272, which is just the domain to bind lipids [15]. It is reasonable to speculate that apo E bond to lipids can increase the level of soluble Aβ oligomers in the central nervous system and synergize the neurotoxicity of the latter. This is not apo E specific since Apo J and apo A/I also have such an effect. Whether other apolipoprotein families are also involved in AD needs further studies.

In summary, apo E is associated with both Aβ production and its clearance. We also know that apo E involves in the pathogenesis and progression from multiple aspects. Recently, Roses et al identified TOMM40 gene, which encodes a channel protein on the mitochondrial outer membrane, nearing the coding region of apo E gene. An adjacent regulatory gene q523 is associated with the expression level of TOMM40 [31] and APO E. The role of q523 in the population carrying APO EΔ3 is being investigated [1, 7]. In addition, it is found that apo E4 may also be a risk factor for PD, epilepsy and other diseases, and is associated with poor prognosis of brain amyloid plaque deposition site shows certain injury and the prognosis of non-interventional

4. Correlation between apo E and Gender

It has been found that DHCR24/seladin-1, a protein involved in lipid biosynthesis, and having neuroprotective and anti-apoptotic effects, can affect the risk of AD in male. Its expression decreases in certain brain areas [26, 27]. In fact, two-thirds of LOAD patients are female; the situation may be associated with the decrease of estrogen after menopause; while estrogen may be a protective factor for AD. It is found that in female not carrying ε4 subtype, estrogen can actually reduce the degree of cognitive decline [28], but this effect is not obvious in female carrying ε4. In addition, middle-age female have more Aβ deposits than male, which is particularly significant in those carrying ε4 compared with ε2 and ε3 [29, 30]. This opens up a new thought for using estrogen to fight AD.

5. Outlook

Apo E involves in the pathogenesis and progression from multiple aspects. Recently, Roses et al identified TOMM40 gene, which encodes a channel protein on the mitochondrial outer membrane, nearing the coding region of apo E gene. An adjacent regulatory gene q523 is associated with the expression level of TOMM40 [31] and APO E. The role of q523 in the population carrying APO EΔ3 is being investigated [1, 7]. In addition, it is found that apo E4 may also be a risk factor for PD, epilepsy and other diseases, and is associated with poor prognosis of brain amyloid plaque deposition site shows certain injury and the prognosis of non-interventional
HIV infection [1]; the effect of apo E on Aβ is particularly significant in post-traumatic cellular model [32].

In conclusion, in-depth research into the APO E regulatory network will enhance our understanding of the pathogenesis of AD and provide useful information for the prevention and treatment of AD.

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