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Alteration of scaffold: Possible role of MACF1 in Alzheimer's disease pathogenesis

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disease, with the sign of sensory or motor function loss, memory decline, and dementia. Histopathological study shows AD neuron has irregular cytoskeleton and aberrant synapse. Amyloid-β (Aβ) is believed as the trigger of AD, however, the detailed pathogenesis is not fully elucidated. Microtubule-actin crosslinking factor 1 (MACF1) is a unique giant molecule which can bind to all three types of cytoskeleton fibers, different linkers/adaptors, as well as various functional proteins. MACF1 is a critical scaffold for orchestrating the complex 3D structure, and is essential for correct synaptic function. MACF1's binding ability to microtubule depends on Glycogen synthase kinase 3 Bate (GSK3β) mediated phosphorylation. While GSK3β can be regulated by the binding of Aβ and the receptor Paired immunoglobulin-like receptor B (PirB), possibly via Protein phosphatase 2A (PP2A). So based on literature search and logic analysis, we propose a hypothesis: Aβ binds to its receptor PirB, and triggers cytosol PP2A, which might activate GSK3β. GSK3β might further phosphorylates microtubule-binding domain (MTBD) of MACF1, causes the separation of microtubule and MACF1. Thus MACF1 might lose the control of the whole cytoskeleton system, synapse might change and AD might develop. That is Aβ-PirB-PP2A-GSK3β-MACF1 axis might give rise to AD. We hope our hypothesis might provide new clue and evidence to AD pathogenesis.

Introduction

Alzheimer's disease (AD), a type of neurodegenerative disease, is becoming more serious in modern world, paralleling with the growing life expectancy [1]. Patients suffered from AD show progressive sensory, or motor function loss, memory decline, and dementia. Typical AD brain specimen shows histopathological sign of amyloid plaques, and neurofibrillary tangles, which accounts for synaptic loss, neurite shrink, and in the late stage, brain atrophy [2,3]. Gradual accumulation of amyloid-β (Aβ) is believed as the main pathogenesis and hallmark of AD [4]. However, the exact mechanism linking Aβ to synaptic decrease is still under investigation.

As a specialized cell type, neuron owns two different spiked neurites, axon and dendrite. The joint point of one neuron to another, typically an axon to a dendrite, termed synapse, is the structure where neuronal network forms and memory stored [5,6]. Neuronal shape and synaptic function largely depend on cytoskeleton system, including three major categories: microtubule, microfilament and intermediate filament. These fibrous structure always keeps a dynamic balance between polymerization and disassembly, participates in building cellular outline, localizing organelles and transporting particles [7,8]. A widely accepted opinion is that AD neurons suffer from pathological change in cytoskeleton system, resulting in altered stability, impaired synaptic plasticity, and malfunction [7,8]. In the complex fibrous network, microtubule-actin crosslinking factor 1 (MACF1) plays a central role joining different filaments and other related proteins together.

MACF1, also known as actin-crosslinking family 7 (ACF7), belongs to Spectraplakin family, serves as an adaptor or linker protein. MACF1 is a real giant protein (~608 kDa), and expressed widely in human body including nervous system [9]. Its huge molecular weight endows a very intricate structure with different motifs/domains binding to correlated targets (Fig. 1) [10]. MACF1 is one of the rare proteins can simultaneously bind to all three types of cytoskeleton fibers, as well as connect with many other adaptors and functional proteins. Thus MACF1 acts as the scaffold within the cell and supports correct assembly and function of fibers. Studies show MACF1, in general, is necessary for cytoskeleton localization and stability, protein-cytoskeleton interaction, intracellular transportation [11,12]. Focused on nervous

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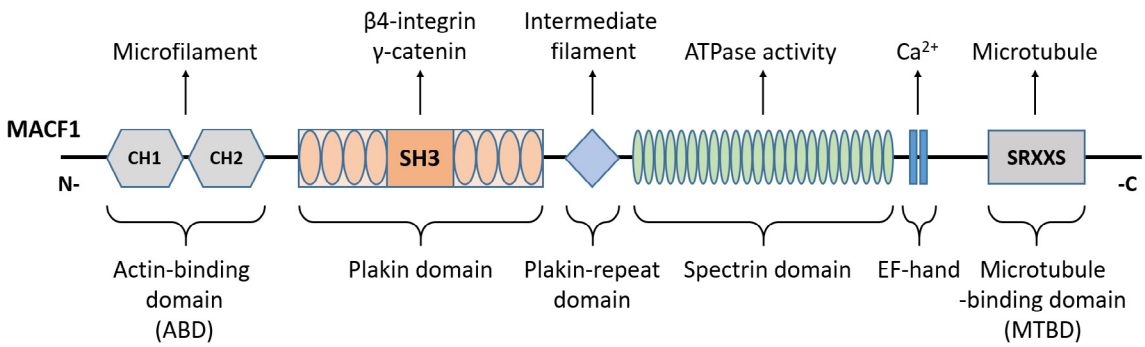

Fig. 1. Structure of MACF1. From N- terminal of MACF1, it has actin-binding domain (ABD), Plakin domain, Plakin-repeat domain, 28 repeated Spectrin domain, EF-hand motif, MTBD domain. Among which, ABD directly bonds microfilament; Plakin domain contains SH3 motif and might interact with β4-integrin and γ-catenin; Plakin-repeat domain shares typical feature of intermediate filament binding; Spectrin domain shows ATPase activity; MTBD binds microtubule, and the affinity can be regulated by the phosphorylation of serine in SRXXS motif. Modified from [10].

system, MACF1 is found to be critical for neuron migration, neurite formation, synaptic function, and hippocampus-dependent learning and memory, which is also the most susceptible part in AD condition [13–16].

The microtubule-binding domain (MTBD) of MACF1 could be directly phosphorylated by Glycogen synthase kinase 3 Bate (GSK3β), and subsequently loses the ability to link microtubule [14,17,18]. Thus, with MTBD phosphorylation, MACF1 could not act as a central scaffold to orchestrate all different structural and functional molecules. This might have profound consequences in structural maintenance and dynamic change of neurite and synapse, which might lead to synaptic loss and plasticity reduction. Nevertheless, GSK3β activity is also de-regulated by accumulated extracellular Aβ binding to its high-affinity receptor, Paired immunoglobulin-like receptor B (PirB), possibly through Protein phosphatase 2A (PP2A) [19,20]. In other words, extracellular Aβ might induce the phosphorylation of MACF1, and cause the alteration of intracellular scaffold system, cytoskeleton and synapse.

The clues, ratiocination and hypothesis

The mechanism of AD development is not fully uncovered yet, however, numerous studies outline the profile of AD pathogenesis, as shown in Fig. 2. We could extract 5 chains of evidence from the clues:

Chain of evidence 1: Experimental observations show extracellular Aβ as a critical trigger of AD. Aβ has different receptors such as EphB, NMDAR and NGFR, however, one emerging molecule, PirB, has been verified to be connected with synaptic plasticity and AD, and it draws attention of many groups including us. And it has been shown the combination of Aβ with PirB could conduct intracellular pathway through PP2A [19,21–25].

Chain of evidence 2: Mutation study and inhibitor research show, at least in neural tissue, PP2A could regulate GSK3β activity by changing its phosphorylation status [20,26,27].

Chain of evidence 3: GSK3β has been shown to phosphorylate MTBD domain of MACF1, which then loses binding ability to microtubule, thus leads to alteration of cytoskeleton [10,18,28].

Chain of evidence 4: MACF1 is the central scaffold of different cytoskeletal molecules, orchestrating and maintaining synaptic structure, as well as activity [16].

Chain of evidence 5: It has been clearly proved and reviewed that Aβ could cause cytoskeletal/synaptic alteration, which leads to AD pathogenesis [29–31].

Inspired by literatures and the 5 chains of evidence above, we propose a hypothesis for AD pathogenesis: Extracellular Aβ binds to membrane PirB, and the latter activates cytosolic factor PP2A, and might further activate GSK3β. GSK3β then binds and phosphorylates serine residues in MTBD domain of MACF1, leads to the dissociation of microtubule from MACF1, and the change of cytoskeleton network. As a result, synapse might not keep the correct structure and function, leading to plasticity reduction, cognition loss and AD pathogenesis (Fig. 3).

Evaluation of the hypothesis

Cytoskeleton and AD

Synapse is the specialized structure for neural network, and the physical carrier of learning, memory, emotion and cognition. The formation, maintaining and modulation of synapse all relies on cytoskeleton system. The essence of AD is the disturbance of cytoskeleton, which is responsible for instability and loss of synapse, and clinical symptoms, such as memory loss, emotional change and dementia [7,8].

Microtubule is the inner support of neuronal process, localized in axon, pre-synaptic composition and dendritic stem. In axon, microtubule elongation direction is the same as axonal protrusion and leads to the growth of axon. In pre-synaptic composition, microtubule changes from linear, rod-like conformation to curvy conformation. Together with Spectrin, Anykrin and microfilament, microtubule outlines the button-like shape of pre-synaptic composition [32]. Microtubule could also bend and protrude from dendritic stem into dendritic spine, and the frequency of protrusion is correlated with synaptic function [8]. Microtubule is also the expressway within neuron. Cargo proteins, such as Kinesin family and Dynein, are able to carry substances/particles and move along microtubule for long distance [33,34]. Facilitated by linker proteins, such as EBs, CLIP170 and CAMSAP3, microtubule can interact with other components indirectly, regulate synaptic stability and function [35,36]. Microtubule stability is reduced in AD condition.

Microfilament is short, thin, rod-like structure, is the main cytoskeleton molecule in dendritic spine and pre-synaptic composition [37]. With linkers, microfilament can weave a 3D network. For instance, Formin mediates the linear connection of microfilament, while Arp2/3 induces the branching and further regulates the volume of synapse [38]. Microfilament is crucial for short-distance transport, along which, Myosin V, Myosin VI could deliver receptors such as AMPAR, NMDAR, mGluR to synaptic membrane [39–41]. Collaborated with adaptors, eg. Adducin, Tmods, interacting with other molecules, microfilament modulates synaptic structure and function, and is essential for neural plasticity [37]. However, in AD condition, microfilament network is disorganized.

MACF1 is the central scaffold for cytoskeleton system

MACF1 is a ~608 kDa giant protein with different domains, can link microtubule, microfilament, intermediate filament, adaptors/linkers, and functional proteins [10] (Fig. 1). Start from N- terminal of

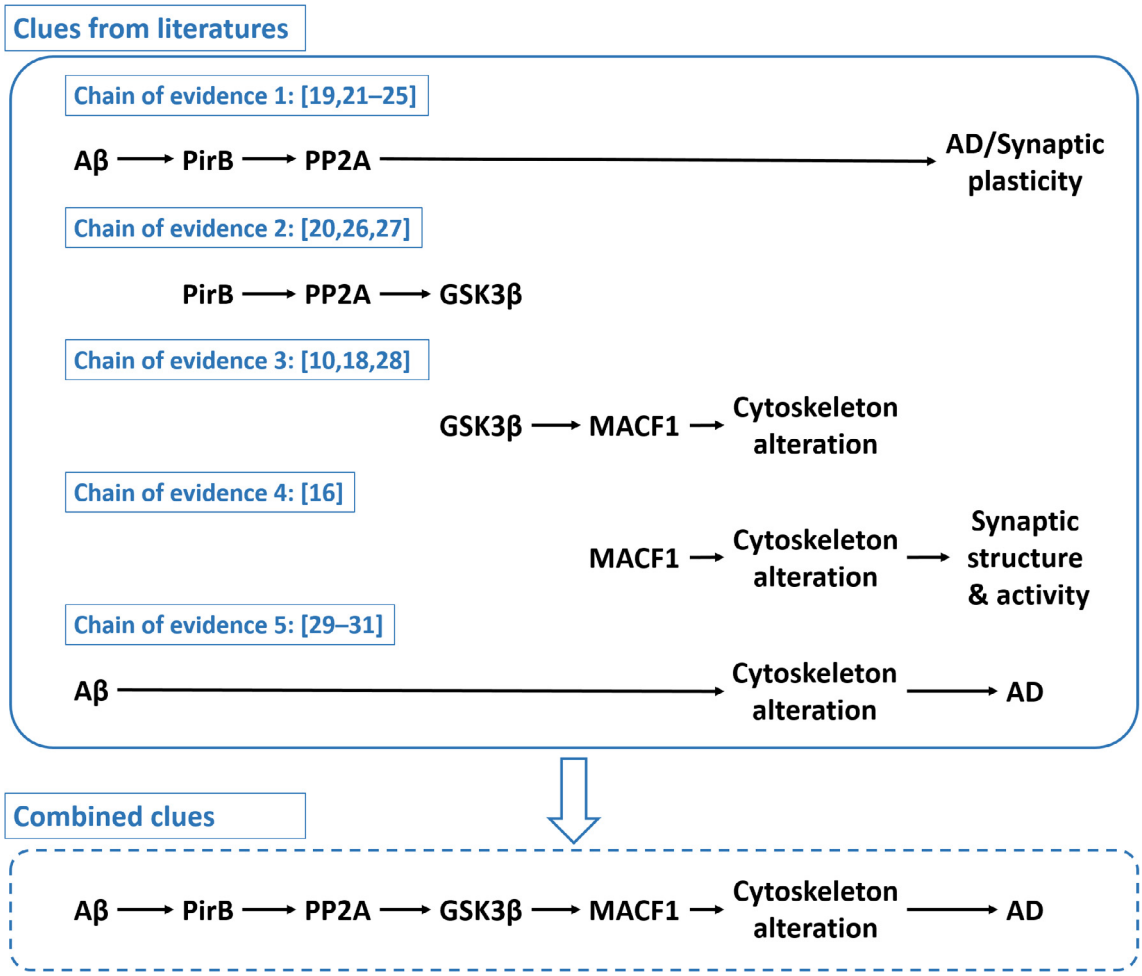

Fig. 2. Chains of evidence extracted from literature. 5 chains of evidence. The corresponding cited articles are labeled in brackets.

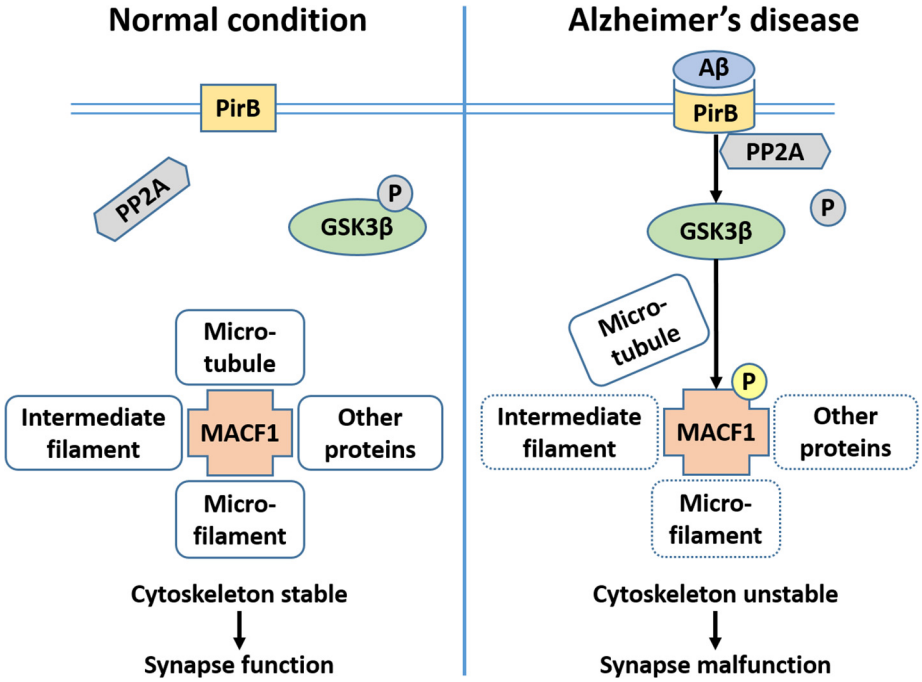

Fig. 3. The hypothesis. Extracellular Aβ might bind to membrane PirB, and the latter activates cytosolic factor PP2A, and might further activates GSK3β. GSK3β then binds and phosphorylates MTBD domain of MACF1, might lead to the dissociation of microtubule from MACF1, and the alteration of cytoskeleton network. As a result, the synapse could not keep the correct structure and function, leading to plasticity reduction, cognition loss and might lead to AD pathogenesis.

MACF1, it has actin-binding domain (ABD), Plakin domain, Plakin-repeat domain, 28 repeated Spectrin domain, EF-hand motif, MTBD domain. Among which, ABD directly bonds microfilament; Plakin domain contains SH3 motif and might interact with β4-integrin and γ-catenin; Plakin-repeat domain shares typical feature of intermediate filament binding; Spectrin domain shows ATPase activity; MTBD binds microtubule, and the affinity can be regulated by the phosphorylation of serine residues in SRXXS motif [10,18].

Besides connection to three types of cytoskeleton, due to complex structure, MACF1 is able to simultaneously bind to linkers/adaptors, such as EB1/3, CLASP2, CAMSAP3, ELMO1, DOCK180 and MAP1b, to regulate different physiological processes indirectly [42–45]. Thus MACF1 plays a central role in cell shape and structure maintenance. Via adaptors such as Rab11, Rab21 or TGN, MACF1 also participates in loading of vesicle, transport along microtubule and microfilament [28,46]. Experiments show MACF1 is related with hippocampus-mediated learning, which hints its relation to synaptic function [42,47]. Nevertheless, MACF1 influences protrusion outgrowth, and modulates Wnt/β-catenin pathway which is important for AD prevention [28,48–50].

An newly published paper have shown MACF1 serves as a synaptic scaffold and organizing center, crosslinking cytoskeleton proteins as well as adaptors such as EB1, MAP1b and Vinculin [16]. And MACF1 possesses the function of maintaining synaptic differentiation and transmission [16]. Thus the central scaffold role of MACF1 is probably related to AD, a disease with a sign of synaptic malfunction and loss.

MACF1 phosphorylation and GSK3β

As a really giant protein with many domains and motifs, it is no surprise that there are many phosphorylation sites on MACF1, eg. tyrosine residue at CH domain near N-terminal can be phosphorylated by Src/FAK complex [51]. More data points out the interaction between GSK3β and MACF1. Immunoprecipitation result verifies the direct physical contact between GSK3β and MACF1 [18,48,49]. Furthermore, there are 10 serine residues in 2 SRXXS motifs in MTBD domain, all of them are the substrates for GSK3β induced phosphorylation [18]. After MTBD phosphorylation, MACF1 cannot bind microtubules anymore, meanwhile the connection with microfilament and intermediate filament are not influenced [18]. However, MTBD phosphorylation wipes out the ability of simultaneously binding of all three types of cytoskeleton, leaves behind change of whole scaffold system.

Aβ-PirB interaction activates GSK3β

Aβ has many membrane-localized receptors, such as Apolipoprotein E, Clusterin, LRP1, Prion protein, Frizzled, TLR2 and PirB [52]. Among them, PirB is drawing increasing attention, as plenty of evidence hints the connection to synaptic plasticity and AD. PirB is a membrane protein, with high affinity to extracellular Aβ [19]. Basically, high level of PirB promotes AD pathogenesis, as many data shows: PirB expression is increased during aging, and negatively correlated to learning and memory [3,19]. Aβ-PirB binding causes impaired synapse formation, reduced synaptic plasticity [22,53]. On the contrary, knock out PirB would greatly promote the density of synapse, increase long-term potentiation (LTP) while repress long-term depression (LTD) [21]. And importantly, PirB intracellular domain could bind to PP2A, then PP2A removes the phosphate group on Ser9 of GSK3β, thus activates GSK3β [19].

Aβ-PirB-PP2A-GSK3β-MACF1 axis and AD

Concerning all the clues above, we propose a logic hypothesis: extracellular Aβ finds and binds its receptor PirB. This binding changes the conformation of PirB intracellular domain, which recruits and activates PP2A. PP2A then activates GSK3β, and the latter phosphorylates MTBD of MACF1. Afterwards MACF1 could not bind microtubule, and the multi-component scaffold alteration. Finally, without a correct scaffold, synapse might show malfunction or break down, AD might occur and develop.

Discussion

It has been well recognized that Aβ is a main trigger of AD, but the detailed downstream pathway is not fully clarified. Most researchers believe aberrant cytoskeleton system is the main outcome after Aβ accumulation, and causes the malfunction and reduction of synapse, and finally results in memory loss, emotional change and dementia. How does cytoskeleton system change in AD? One of the theory is Tau hyper-phosphorylation. Tau is a normal structural protein binding to and stabilizing microtubule [54–56]. Upon Aβ stimulation, Tau is hyper-phosphorylated, and separated from microtubule, leaving behind unstable microtubule. Tau hyper-phosphorylation is also mediated by GSK3β, and probably PP2A is also involved. However, AD pathogenesis is a very complex, very long procedure. It is not possible to be explained by a single molecule or theory. If we take into account all the facets of neuron, eg. energy consumption, oxidative pressure, cytokine stimulation, membrane composition, cytoskeleton, trophic factors and neuron-glia interaction, we probably find that AD is the overall summation of all factors. But we think cytoskeleton system is of particular importance, because it directly influences neurite and synapse formation, maintenance and function. Inspired from literature, we list 5 chains of evidence and logically we propose the possible critical role of MACF1 in AD. MACF1 is the central scaffold orchestrating cytoskeleton and related molecules, just like conductor in symphony for concert. Morphology and function is integrated anyway. Structure is the basis of certain function. Impaired synaptic function definitely meaning structural change, and *vice versa*, structural alteration defines functional variation or even functional loss. So MACF1 dysregulation might lead to the structural change of synapse and thus account for synaptic malfunction and development of AD. Although there is still a long way to lift the veil of AD, we hope our hypothesis could provide new clue and evidence to the truth.

Conclusion

AD pathogenesis is very complex and not fully elucidated. Based on literature study and logical analysis, we put forward a new hypothesis of MACF1 in AD: Aβ might bind to its receptor PirB, and trigger cytosol PP2A, which might activate GSK3β. GSK3β further phosphorylates MTBD domain of MACF1, might cause the dissociation of microtubule from MACF1. Thus MACF1 loses the control of the whole cytoskeleton system, synapse changes and AD develops. That is Aβ-PirB-PP2A-GSK3β-MACF1 axis might give rise to AD.

Declaration of Competing Interest

We have no conflict of interest to declare.

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