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Amyloid β-interacting partners in Alzheimer's disease: From accomplices to possible therapeutic targets

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ABSTRACT

Alzheimer's disease (AD) is one of the most devastating neurodegenerative diseases in modern society because of insurmountable difficulties in early diagnosis and lack of therapeutic treatments. AD pathogenesis is tightly linked to the abnormal accumulation and aggregation of amyloid β (Aβ), seemingly the main causative factor of AD; however, intensive research on Aβ has not yet explained the complexity of AD pathogenesis. Consequently, the role of other supportive partners of Aβ have been elucidated and evaluated in the etiology of AD, and their potential molecular mechanisms have emerged as possible therapeutic targets. In this review, we compile information regarding Aβ-interacting partners in normal conditions and AD pathology, and analyze their etiological roles in diverse areas. Furthermore, we integrate this information into suggestions for probable clinical applications for AD diagnosis and therapeutics. We include Aβ-interacting partners localized to the cell surface and intracellular and extracellular compartments of different cell types ranging from the central nervous system to peripheral regions. Additionally, we expand the range of Aβ-interacting partners by including not only proteins, but also inorganic substances like metals, expecting that one of these partners may yield a critical breakthrough in the field of AD diagnostics and therapeutic drug development.

Contents

Abbreviations: AD, Alzheimer's Disease; Aβ, amyloid beta; ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale; MMSE, Mini-Mental State Examination; ApoE, Apolipoprotein E; APP, amyloid precursor protein; BBB, blood brain barrier; RXR, retinoid X receptor; PPARγ, peroxisome proliferator-activated receptor gamma; LXR, liver X receptor; ApoJ, apolipoprotein J; LRP, low-density lipoprotein receptor-related protein; HDL, high density lipoproteins; SAP, serum amyloid P component; PP2A, protein phosphatase 2A; RAGE, receptor for advanced glycation end products; ERK, extracellular signal-related kinases; NF-κB, nuclear factor kappa B; MMP, matrix metalloprotease; NMDA, N-methyl-D-aspartate; $p75^{NTR}$, the 75-kD neurotrophin receptor; TrkA, tyrosine kinase receptor A; SEC receptor, serpin-enzyme complex receptor; α7nAChR, α7 nicotinic acetylcholine receptor; MAPK, mitogen-activated protein kinase; PI3-k, phosphatidylinositol 3-kinase; EphB2, ephrin type-B receptor 2; PrP, prion protein; LilrB2(PriB), leukocyte immunoglobulin-like receptor B2; ERAB, endoplasmic reticulum-associated Aβ peptide binding protein; PTB domain, phosphotyrosin-binding domain; Hsp, heat shock protein; mPTP, mitochondrial permeability transition pore; ABAD, Aβ-binding alcohol dehydrogenase; VDAC, voltage-dependent anion channel; ANT, adenine nucleotide translocase; TOM, translocase of the outer membrane; hPreP, presequence protease; Drp1, dynamin related protein 1; Fis 1, fission protein 1; PreP, presequence protease; TLR, toll-like receptor; MAP3K, mitogen-activated protein 3 kinases; JNK, c-Jun N-terminal kinases; mFPR2, mouse G-protein coupled formyl peptide receptor; M-CSF, macrophage-colony stimulating factor; CAA, cerebral amyloid angiopathy; PKC, protein kinase C; PYK2, calcium sensitive tyrosine kinase; SR, scavenger receptor.

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1. Introduction

Alzheimer's disease (AD) is one of the most concerning neurodegenerative diseases in present society due to the lack of early diagnostic methods and therapeutic remedies. Amyloid β (Aβ) plaques are regarded as the main etiological hallmark of AD. Plaque formation begins with abnormal production or impaired clearance of Aβ and consequent accumulation and aggregation, leading to formation of Aβ plaques in the brain (Mawuenyega et al., 2010; Querfurth and LaFerla, 2010). Increased Aβ levels are tightly associated with synaptic dysfunctions and neuronal network perturbations, which are regarded as the main cause of cognitive impairment in AD (Palop and Mucke, 2010). Contrary to AD, in other types of dementia aggregated forms of Aβ are not present, suggesting that aggregation of Aβ peptides is a peculiar characteristic of AD, and plays a pivotal role in its pathogenesis. Therefore, inhibition of Aβ aggregation or its effects may be a key solution to prevent the initiation of AD or slow down its etiological progression.

Accumulating evidence suggests that Aβ elicits its deleterious effects, including toxicity on cellular and synaptic functions, through binding to certain molecular partners. However, other molecules may interact with Aβ and prevent the Aβ-mediated toxic effects. Therefore, Aβ-interacting proteins and molecules are tightly associated with diverse aspects of AD pathophysiology. Firstly, numerous Aβ-interacting proteins play a critical role in influencing the lifespan of Aβ via regulating Aβ generation, aggregation, disaggregation, and degradation (Bohrmann et al., 1999; Clinton et al., 2010; Hone et al., 2003). Certain Aβ-interacting proteins are capable of modulating the amyloidogenic and catabolic process by interacting with Aβ (Fagan et al., 2002; Ono et al., 2012). Other Aβ-interacting proteins either enhance or inhibit Aβ aggregation by maintaining Aβ in a free or bound form, respectively (Clinton et al., 2010; Schwarzman and Goldgaber, 1996). This process is critical in AD pathogenesis, because abnormally accumulated Aβ, usually the free form of Aβ, aggregates to form neurotoxic Aβ, whereas bound forms do not tend to aggregate (Bohrmann et al., 1999). Secondly, Aβ-interacting partners, localized in both intra/extracellular compartments and on the cell surface, typically serve as mediators for Aβ-triggered signaling (activation or inhibition) (Freir et al., 2011; Sturchler et al., 2008), which is closely linked to synaptic dysfunction and neuronal toxicity. Thirdly, Aβ directly binds to certain enzymes that are critical in cell dynamics, and modulates their activities and functions (Chen and Yan, 2007; Hernandez-Zimbron et al., 2012; Lustbader et al., 2004), which leads to the breakdown of cellular homeostasis and further toxicity. Aβ-interacting partners attract a great interest, as they might help in understanding the pathophysiology of AD, and therefore, comprehensive assessment of Aβ-interacting proteins and their diverse roles is necessary for developing therapeutic agents for AD targeting these proteins. Careful investigation of Aβ-interacting partners may provide valuable information to understand Aβ-mediated cellular toxicity in AD and promising first-line interventions to delay or prevent disease progression by modulating these regulatory partners.