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Short Communication
Published: 29 Mar, 2018

Journal of Molecular and Cellular Biology Forecast

Dynamin, Emerging Therapeutic Targets for Alzheimer's Disease

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Abstract

Dynamin family proteins are large GTPases implicated in the fission of emerging buds from the parent membrane. Studies showed that mutations in dynamin genes are associated with human diseases, such as centronuclear myopathy, Charcot-Marie-tooth disease, and Alzheimer disease. In the present review, we discuss the molecular mechanism of amyloid beta pathology caused by loss-of-function of dynamin family proteins as well as the therapeutic potential of dynamins for Alzheimer disease.

Alzheimer Disease

Alzheimer's disease (AD), a neurodegenerative disorder that was first described by Alois Alzheimer in 1906 [1], is accompanied by abnormal accumulation of neurofibrillary tangles (NFTs) and amyloid plaques in the brains of AD patients [2,3]. Worldwide, more than 47 million people live with AD and its associated symptoms [4,5]. NFTs are cytosolic aggregates of abnormally phosphorylated tau proteins, which negatively affects microtubule dynamics, thereby compromising axonal transport and in turn inducing neuronal loss [6] in the AD brains. Unlike NFTS, amyloid plaques form in the extracellular space as a result of association of amyloid beta (Aβ). Abnormal accumulation of Aβ is due to an overexpression of BACE1 [7], defected process of endocytosis of Aβ aggregates, and inefficient degradation of Aβ by microglia, perivascular macrophages and astrocytes [4,8].

Dynamins and Dynamin-Related Protein 1 (Drp1) with Alzheimer Disease

Among others, dynamin family proteins play a fundamental role in the pathology of amyloid plaques. It is well known that dynamins catalyze the scission process of endocytic vesicles, via using energy driven by GTP hydrolysis. Defects in endocytosis, mediated by expression of dominant negative dynamin 1 (Dyn1 K44A) in Hela cells, are associated with high levels of APP at the cell surface and accumulation of Aβ, due to an increase in the secretion of endogenous Aβ [9]. This result is consistent with previous discoveries made by two groups of researchers in that endocytic or exocytic defects are linked to overproduction of Aβ [10,11]. In contrast, Carey and coworkers reported that expression of dyn1 K44A in huam embryonic kidney cells led to a reduction in Aβ release [12]. To resolve this controversy a group of researchers introduced SiRNA targeting dyn1 in neuroblastoma cells and found that the endocytic defect by dyn1 knockdown efficiently reduces levels of external Aβ [13], consistent with the results by Carey et al. [12]. Interestingly, levels of BACE1 at the plasma membrane increased according to their fluorescence microscopic analysis, but its level at the endosome was reduced. In light of finding that low productivity of Aβ was correlated with lower BACE1 concentration in the endosome in dyn1 knockdown cells, they proposed that endosomal BACE1 plays more important role in Aβ pathology [13]. Based on these observations, dynamin 1 can serve as an Aβ-lowering therapeutic target without manipulating other key enzymes implicated in Aβ pathology. This idea is feasible because the treatment with dynasore, a dynamin GTPase inhibitor, in lieu of dyn1 knockdown, led to a phenotype reminiscent of dyn1 knockdown cells [13]. Preclinical and clinical treatments with dynamin SiRNA or dynasore and its related dynamin GTPase inhibitors as well as a virus-mediated delivery of dyn1 dominant negative genes (including dyn1 K44A) are required to further develop dynamin-based therapeutics for Alzheimer disease.

Dynamin 2 is another classical dynamin expressed in neuronal cells, and single nucleotide polymorphisms located in DNM2 are associated with sporadic AD [14], suggesting that DNM2 is a genetic factor among many others contributing to AD. Similar to the dominant negative

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Received Date: 12 Mar 2018
Accepted Date: 26 Mar 2018
Published Date: 29 Mar 2018

Citation: Kim K. Dynamin, Emerging Therapeutic Targets for Alzheimer's Disease. J Mol Cell Biol Forecast. 2018; 1(1): 1006.

ISSN 2643-7953

dyn1 experiment mentioned above, Kamagata and coworkers overexpressed dyn2 K44A mutant and observed that levels of amyloid precursor protein (APP) at the cell surface increased, in agreement with the previous finding by Chyung and Selkoe [9]. However, additional experiments are required to reveal the direct relationship regarding levels of Aβ and dynamin 2. Finally, dynamin 3 the third member of three classical dynamins, which is also present in neurons, appears not to play a significant role in regulating endocytosis, rather functioning with actin dynamics required for axonal growth cone formation [15]. However, it was found that in dyn 1 and dyn 3 double knock-out mouse model the loss of dyn 3 worsened the phenotype produced by the loss of dyn 1 [16], which indicates a functional redundancy between dyn 1 and dyn 3. More systemic study in the future would reveal the potential involvement of dyn 3 in Alzheimer pathology.

Dynamin-related protein 1 (Drp1), a dynamin-like GTPase implicated in mitochondrial division, also play a role in Aβ pathology. Studies showed that Drp1 interacts with Aβ and phosphorylated tau, which causes excessive fragmentation of mitochondria and leading to synaptic degeneration in AD neurons [17,18], suggesting a connection of dysregulation of mitochondria dynamics to AD pathology. Indeed, reduction of Drp1 expression in Drp1+/-xAβPP mice appears to mitigate the severity of Aβ accumulation [19], signifying that development of Drp1-based therapeutics for treating AD is feasible.

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