

Downregulation of Ubiquitin Carboxyl-terminal Hydrolase L1 (*UCHL1*) Expression in the Pathogenesis of Alzheimer's Disease

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Abstract

The pathogenesis of Alzheimer's disease (AD) has not been definitely confirmed so far. As a result, a cure for AD is lacking, and current treatments are limited to modest symptomatic relief. Accumulation of damaged proteins and formation of protein aggregates are found in AD brains, suggesting impairment of protein degradation is contained by the pathogenesis of AD. Impairment of ubiquitin-proteasome system has been found in Alzheimer Disease. Here we demonstrate ubiquitin carboxyl-terminal hydrolase L1 (*UCHL1*) which plays a role in neuronal ubiquitination/de-ubiquitination machinery participates in the pathogenesis of AD.

Keywords: *UCHL1*; Alzheimer's disease; Pathogenesis

Public Significance Statement

This article reveals that increase of *UCHL1* protein levels may be an efficient therapeutic strategy for AD, as well as other neurodegenerative diseases.

Introduction

Alzheimer's disease (AD) is one of the most common neurodegenerative disorders in humans. The brains of patients with Alzheimer's disease are histopathologically characterized by two hallmark lesions: amyloid- β -containing plaques and neurofibrillary tangles (NFTs), implying that something in the degradative systems did not work properly.

Protein ubiquitination/de-ubiquitination has emerged as an important mechanism for regulating a variety of cellular processes, including protein degradation [1]. Dysfunction of this system, leading to neuronal degeneration by accumulation of damaged protein and formation of protein aggregates [2], have been reported in the pathogenesis of AD [3].

Ubiquitin carboxyl-terminal hydrolase L1 (*UCHL1*), belonging to a family of deubiquitinating enzymes (DUBs)[4], plays an important role in protein ubiquitination/de-ubiquitination [5]. It is interesting that AD brains are found to show prominent *UCHL1* immunostaining associated with neurofibrillary tangles and levels of soluble Uch-L1 inversely proportional to the number of tangles [6]. Collectively, these different lines of evidence support a role for *UCHL1* in the pathogenesis of AD.

Literature Review

Decreased levels of *UCHL1* and AD

It is all known that extracellular amyloid- β -containing senile plaques and intracellular neurofibrillary tangles (NFTs) consisting of tau are pathological hallmarks of AD [7]. A possible link between *UCHL1* and AD is suggested by reports of decreased levels of *UCHL1* in postmortem AD brain and decreased levels of *UCHL1* were inversely proportional to tangle numbers [6]. *UCHL1* is downregulated in cells exposed to A β [8]. Moreover, levels of *UCHL1* are decreased in AD

model mice [9]. As stated above, levels of *UCHL1* are decreased in whether AD patients or AD models (cells and mice).

AD is characterized clinically by progressive memory loss and cognitive impairment. Reduction in memory is confirmed in gracile axonal dystrophy (*gad*) mice, which do not express *UCHL1* [10]. These results imply downregulation of *UCHL1* contribute to the progress of AD.

Diminished hydrolase activity and AD

Accumulating findings indicate dysfunction of *UCHL1* hydrolase is linked to neurodegenerative disease. The Ile93Met mutation in the UCH-L1 gene, which leads to 50% reduction in hydrolytic activity, is expected to contribute to the genetic aetiology of PD patients [11]. It's reported that loss of function of the neuronal ubiquitin hydrolase *UCHL1* leads to early-onset progressive neurodegeneration [12]. Oxidative stress-induced damage becomes much more pronounced in age-associated pathologies, including AD [13]. Intriguingly, *UCHL1* is a target of oxidative damage and the hydrolase activity of oxidative modification of *UCHL1* was reduced to about 40–80% [3]. Exogenous wide-type *UCHL1* reestablish normal synaptic plasticity and improves associative memory in APP/PS1 mice (AD mice mode), while exogenous C90S mutant UCHL has no function [9]. These results suggest hydrolase activity of *UCHL1* could counteract certain symptoms in AD.

A β production increase and AD

A β is cleaved from amyloid- β protein precursor (APP) by

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β -amyloid cleavage enzyme 1 (BACE1) and γ -secretase that exert a range of neurotoxic effects that are considered to be important to the evolution of the pathology. Overexpression of ubiquitin carboxyl-terminal hydrolase L1 (*UCHL1*) is observed to decrease A β by promoting APP degradation and delays Alzheimer's progression *in vivo* [14]. BACE1 half-life is reduced in cells overexpressing *UCHL1* and decreased A β levels are found, while inhibition of *UCHL1* significantly increases BACE1 protein level *in vitro* [8,15]. These researches suggest downregulation of *UCHL1* increase A β production by impairing APP and BACE1 degradation that contributes to the pathology of AD.

Discussion and Conclusion

A close connection between downregulation of *UCHL1* and mechanisms of the pathology of AD is well documented. Some lncRNAs have been detected to have a say in regulating *UCHL1* levels, thus documenting possible mechanisms of decreased *UCHL1* levels in AD patients [16-18]. Grape seed procyanidin b2 is observed to increase *UCHL1* levels in the research of cardiovascular diseases [19]. Taken together, these findings show that increase of *UCHL1* protein levels may be an efficient therapeutic strategy for AD, as well as other neurodegenerative diseases.

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