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The emergence of Ephexin5 as a therapeutic target in Alzheimer's disease

Emily K. Cook¹, Gabrielle L. Sell², Thomas B. Schaffer³, Seth S. Margolis^{1,4}

¹Department of Biological Chemistry, The Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA

²Center for Neuroscience, University of California, Davis, California 95618, USA

³Research and Development, Columbia Biosciences Corporation, Frederick, MD 21703, USA

⁴Solomon H. Snyder Department of Neuroscience, The Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA

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Introduction

Alzheimer's Disease (AD) is an age-related neurodegenerative illness characterized by progressive memory loss, impairment of cognitive function, and the development of plaques of insoluble amyloid precursor protein fragments and neurofibrillary tangles of Tau protein [1] [2]. It is estimated that in 2018, 5.7 million people in the United States are living with Alzheimer's, most of whom are 65 years old, with costs of care accumulating to \$277 billion [3]. The prevailing hypothesis views the accumulation of the β -amyloid protein ($A\beta$) as a precipitating event in the pathogenesis of AD [4]. Increased $A\beta$ production is thought to disrupt neuronal function and ultimately lead to cell death [5]. However, it is becoming increasingly evident that the etiology of Alzheimer's Disease is more complex than previously appreciated [6]. Neuropathological studies have established excitatory synaptic loss as the best correlate of the pattern and severity of cognitive deficits observed in AD [7]; [8]; [9]. Furthermore, the loss of synapses in AD appears to be substantially greater than that predicted by the loss of neurons alone, and the onset of cognitive impairments and memory loss, the earliest clinical manifestations of AD, precede massive neuronal degeneration [10].

Corresponding author: Seth S. Margolis, The Johns Hopkins School of Medicine, Department of Biological Chemistry, Wood Basic Science Building Room 517, 725 N. Wolfe St., Baltimore, MD 21205, USA, Phone: 410-502-5362, smargol7@jhmi.edu.

Declaration of interest

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Taken together, we consider that *synapse loss represents a key initial event in the onset of AD*.

Current treatments for Alzheimer's disease

Despite research advancements in recent years, there is no cure for AD and cholinesterase inhibitors and a N-methyl-D-aspartate (NMDA) antagonist are the only drugs that are approved by the U.S. Food and Drug Administration (FDA) to treat AD [6]. These drugs treat only the symptoms of AD, not the underlying pathology, and show modest efficacy [11]; [12]. There currently a number of compounds in clinical trials to treat AD, many of which are anti-A β or anti-Tau therapies [6]. Since strategies to treat AD, such as lowering A β , have performed only modestly in recent clinical trials, the identification of alternate targets that are independent of amyloid load is critical for progress in the development of AD therapeutics. Such approaches may work independently to treat AD or in conjunction with current A β therapies. This alternative view is evident, as compounds entering clinical trials show less bias towards anti-tau and anti-amyloid therapies, and NIH funding for amyloid based therapies decreased from 27% in 2008 to 18% in 2017 [6].

Ephexin5 in AD

Recent progress in the Alzheimer's field has revealed a promising drug target, Ephexin5 (*Arhgef15*), that acts to restrict excitatory synapse development. Ephexin5, a guanine nucleotide-exchange factor (GEF) that activates the small G-protein RhoA, is present at the excitatory synapse in developing neurons [13]; [14]. Post development, Ephexin5 is rapidly phosphorylated by the Ephrin B receptor tyrosine kinase B2, EphB2, and is then targeted for proteasome-dependent degradation by the E3 ubiquitin ligase, UBE3A. Subsequently, Ephexin5 protein levels remain low into adulthood [13]. It has been demonstrated that EphB2 signaling is downregulated in the J20 mouse model of AD, and over-expression of EphB2 rescues the defects seen in the same model [15]. This suggests that a better understanding of the role of EphB2 signaling in synapse development may offer new possibilities for treating AD.

It was previously found that Ephexin5 expression is activated in the CA1 region of the hippocampus in patients with early stages of AD [16]. Sell et al. also found that Ephexin5 expression is upregulated by two to three fold in human AD brains and is elevated in the hippocampus of the J20 AD mouse models [17]. Additionally, A β -triggered neuronal damage is now recognized as a central feature of AD pathology [18] and treating cultured mouse neurons or stereotaxic injection in brains of wild-type (WT) mice with soluble A β was sufficient to increase Ephexin5 expression [17]. Importantly, genetic removal of endogenous Ephexin5 from J20 AD mice ameliorates cellular, behavioral, and physiological deficits in the AD animals [17]. Further, acute reduction of endogenous Ephexin5 protein levels via lentivirus-mediated shRNA expression in a subset of dentate gyrus granule cells of adult AD mice was sufficient to rescue a learning and memory phenotype in these animals [17]. Previous studies have determined that in AD there is pathological elevation in the activity of RhoA [19]. Thus, Ephexin5 is hypothesized to link two characteristic biochemical pathways of AD pathophysiology: the A β -induced decrease in EphB2 signaling and elevated

RhoA activation. The precise mechanism of how these events are accomplished is not yet understood [Figure 1].

Expert Opinion

Previous studies have suggested the importance of RhoA GEFs in the progression of AD and as potential drug targets to treat AD [20]. The study by Sell et. al, is among the few to test this hypothesis and goes on to identify a new and critical RhoA GEF, Ephexin5, to be relevant to AD-associated synaptic pathology and cognitive dysfunction. Moreover, an intriguing feature of Ephexin5, distinct from other potential drug targets, is that its expression is very low in healthy adult tissue and generally enriched in hippocampus [17]. This suggests that Ephexin5 is a comparatively specific therapeutic target owing to its pathological elevation in expression. Future targets of this nature may prove to be very safe, as they likely will limit effects of inhibition on healthy cells. Thus, it is feasible to generate an inhibitor, proteolysis-targeting chimera, or negative allosteric modulator of Ephexin5 in order to provide a new and critical avenue for therapeutic intervention for treating AD and test our hypothesis that treating AD in humans can be accomplished through correcting synapse pathology.

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Figure 1.

A: In healthy brains, EphB2 receptors dimerize and are activated in response to interaction with ligands such as Ephrins [13]. Active EphB2 receptors can phosphorylate the RhoA GEF Ephexin5 [13]. Ephexin5 is then ubiquitinated and targeted for proteasomal degradation. This prevents Ephexin5 from activating RhoA to inhibit spine formation and thus leading to “spine permissive” conditions. **B:** In Alzheimer’s disease, EphB2 expression is downregulated by Amyloid Beta [15]. Thus, Ephexin5 is likely less inhibited by EphB2 phosphorylation and subsequent proteasomal degradation. This is evident by the pathological accumulation of Ephexin5 in AD mouse and human brains [17]. This elevated Ephexin5 leads to “spine restrictive” conditions. The most likely explanation of this is due to Ephexin5 activating RhoA which is considered to be a major contributor to AD pathology. Based on our current understanding, Ephexin5 is a novel, A β -independent drug target that targets key pathways underlying AD and is likely to have limited off target effects due to its low expression in healthy tissue. Created with BioRender.