Journal Club

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Regulation of Synaptic Amyloid- β Generation through BACE1 Retrograde Transport in a Mouse Model of Alzheimer's Disease

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Review of Ye et al.

Alzheimer's disease (AD) is a neurodegenerative disease characterized by the presence of intraneuronal fibrillary tangles consisting of hyperphosphorylated tau, and extracellular deposits (neuritic plaques) of β -amyloid ($A\beta$; Chia and Gleeson, 2011). It is hypothesized that the pathogenesis of AD stems, in part, from the production and accumulation of the neurotoxic 42 aa fragment of $A\beta$ ($A\beta_{42}$), and to a lesser extent a shorter 40 aa fragment of $A\beta$ ($A\beta_{40}$; Kuperstein et al., 2010). Specifically, AD-related dystrophic neurites accumulate $A\beta$ fragments at presynaptic terminals leading to synapse loss and subsequent cognitive deficits; however, elucidating the mechanisms responsible for $A\beta$ accumulation remain elusive (Butterfield et al., 2002; Swerdlow, 2007; Chia and Gleeson, 2011). $A\beta$ fragments are generated by cleavage of amyloid precursor protein (APP) by both β -site amyloid precursor protein cleaving enzyme 1 (BACE1), a β -secretase, and γ -secretases, with BACE1 being the rate-limiting enzyme (Luo et al., 2001; Ye and Cai, 2014).

Due to the observed presynaptic accumulation of $A\beta$ in AD patients and mouse models, it has been hypothesized that a large percentage of APP produced in the cell body is trafficked by fast anterograde transport to distal portions of the axon where it is processed by BACE1 within late endosomes (Takahashi et al., 2004; Wu et al., 2011).

Late endosomes are membranous packages that transport endocytosed material along microtubules from the distal axon to the cell body, where the endosome and its contents are either degraded by lysosomes or fuse with the plasma membrane to release its contents into the extracellular space (van Weert et al., 1995). Ye and Cai (2014) recently reported that BACE1 accumulates in late endosomes that cluster at presynaptic terminals of hippocampal neurons in the human APP (hAPP) transgenic mouse model of AD, which produces amyloid pathology in mice comparable to human AD, and in AD patient brains. Given that the lumen of late endosomes is acidic, which is necessary for optimal BACE1 activity (Das et al., 2013), this finding is consistent with the hypothesis that $A\beta$ fragments are produced at the presynaptic terminal within late endosomes (Ye and Cai, 2014; Ye et al., 2017).

It has been hypothesized that accumulation of $A\beta$ fragments at presynaptic terminals of dystrophic neurites results from

defective retrograde transport, specifically of cargo directed for lysosomal degradation (Ye and Cai, 2014). Retrograde transport of late endosomes depends on the protein snapin, which promotes coupling between endosomes and dynein motors (Cai et al., 2010). Ye and Cai (2014) showed that cultured neurons from mice expressing hAPP along with a mutation that disrupted snapin–dynein interaction displayed aberrant retrograde transport of BACE1-containing late endosomes. Anterograde transport was unaltered, as evidenced by distal axonal accumulation of BACE1 (Ye and Cai, 2014). Thus, a defective retrograde transport system in hAPP mice and AD patient brains may provide an explanation for presynaptic accumulation of BACE1-containing late endosomes due to the inability of the neuron to target late endosomes for lysosomal degradation, resulting in distal BACE1 accumulation and continual processing of APP into $A\beta$ fragments.

The role of retrograde transport in presynaptic $A\beta$ accumulation has also been examined *in vivo* using hAPP mice, which show distal axonal $A\beta_{42}$ accumulation, reduced synaptic density in the hippocampus, and deficits in spatial and nonspatial learning (Ye and Cai, 2014). These mice also displayed a dysfunctional retrograde transport system, determined by accumulation of BACE1-containing late endosomes at presynaptic terminals.

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As mentioned previously, postmortem AD patient brains also display accumulations of BACE1-containing late endosomes at presynaptic terminals; however, snapin levels are not altered in either hAPP mice or AD patients (Ye et al., 2017).

Given that BACE1 is the rate-limiting enzyme responsible for the production of A β fragments at presynaptic terminals (Ye and Cai, 2014), levels of BACE1 are elevated in AD patient brains (Yang et al., 2003), and BACE1-containing late endosomes accumulate at presynaptic terminals in hAPP mice and AD patient brains, it is reasonable to conclude that increasing clearance of BACE1-containing late endosomes from the presynaptic terminal may reduce processing of APP and thus decrease the amount of A β fragment production and neuritic plaque formation. Thus, Ye et al. (2017) proposed that overexpressing functional snapin may enhance retrograde transport of BACE1 and thus attenuate production of A β .

The results from Ye et al. (2017) demonstrated that in hAPP mice overexpressing snapin, levels of BACE1-containing late endosomes at the presynaptic terminal were reduced, as evidenced by increased localization of these endosomes in cell bodies, compared with clustering at the presynaptic terminal in control hAPP mice without snapin overexpression. This finding implies that snapin overexpression in hAPP mice reinstates retrograde transport of late endosomes. Consequently, snapin overexpression significantly reduced distal accumulation of A β 40, as evidenced by reduced neuritic plaque formation and synapse loss.

Because A β aggregation and accumulation at presynaptic terminals is hypothesized to be one of the main factors responsible for the cognitive deficits, such as memory loss, present in AD patients (Rajasekhar et al., 2015), Ye et al. (2017) hypothesized that snapin overexpression in hAPP mice may lead to improved cognition. Indeed, hAPP mice overexpressing snapin demonstrated significant improvements in nonspatial memory (novel object recognition), spatial memory (shorter latency time in the Morris water maze), and contextual fear conditioning compared with hAPP mice without snapin overexpression.

Given the cognitive benefits associated with introducing functional snapin protein into hAPP mice, these results present a possible therapeutic approach to treating patients with AD. Interestingly, defective intracellular trafficking has been linked to

late-onset AD (Chia and Gleeson, 2011). This should encourage future studies to determine the mechanisms responsible for defective intracellular trafficking in AD, with the goal of producing treatments to reinstate intracellular transport of cargo. For example, it would be of interest to determine whether patients with late-onset AD possess a dysfunctional snapin protein, and whether snapin dysfunction contributes significantly to cognitive deficits in this specific patient population. If this patient population is found to possess dysfunctional snapin, a gene therapy approach to introduce a functional form of the protein becomes a viable treatment option to reduce the rate of neurodegeneration.

There are other possible mechanisms that can contribute to poor retrograde transport, and importantly, may lead to other novel therapeutic approaches; one in particular is the tau hypothesis. Tau is a microtubule-associated phosphoprotein that functions to promote the formation of microtubules and stabilize their structure by remaining bound to microtubules at its proline rich microtubule-binding domain (Wang et al., 2014). Hyperphosphorylation of tau disrupts its affinity for microtubules causing it to remain in an unbound state and form aggregates in the form of neurofibrillary tangles, predominately in the cell body (Wang et al., 2014). Therefore, it is possible that a lack of axonal microtubule-bound tau can destabilize the microtubule structure, affecting retrograde axonal transport along microtubules. Additionally, mutations in the dynein motor may contribute to defective retrograde transport due to poor late endosome-dynein coupling, as evidenced by research in motor-neuron disease (Hafezparast et al., 2003; Ravikumar et al., 2005).

Despite the important findings from this study, there were a few limitations and knowledge gaps that remain to be explained. It is believed that a higher intracellular ratio of A β 42/A β 40 is implicated with greater neurotoxicity, mainly due to the hydrophobicity of A β 42 and thus higher propensity to aggregate compared with A β 40 (Kuperstein et al., 2010). The authors, however, only quantified A β 40 levels in hAPP mice and AD patient brains. The addition of presynaptic A β 42 quantification analysis in hAPP mice overexpressing snapin and control hAPP mice would have increased the impact of their findings, due to the pathogenic implications of the A β 42 fragment. Additionally, snapin is believed to play a role in the fusion between late endosomes and

lysosomes (Cai et al., 2010; Yuzaki, 2010). If this is the case, it is likely that overexpressing snapin would not only enhance retrograde transport of late endosomes, but could also enhance the rate of lysosomal degradation. An increase in the clearance of autophagosomes could have beneficial intracellular effects, as there would be enhanced removal of unwanted metabolic waste, damaged cellular structures, and macromolecules, which would contribute to the overall health and longevity of the cell (Rahman and Rhim, 2017).

In conclusion, the cognitive improvements demonstrated by Ye et al. (2017) in hAPP mice with snapin overexpression highlights the importance of functional retrograde axonal transport and its beneficial effects on cognition in AD model mice. Specifically, the reduction of presynaptic BACE1 and A β 40 likely contributed to the decrease in synapse loss and A β plaque formation, leading to improved cognition. Future research in AD should determine the precise mechanisms responsible for dysfunctional retrograde transport and how they can be corrected; leading to the development of a clinical treatment strategy aimed at improving retrograde transport within AD-affected neurons in the brain, with the goal of enhancing lysosomal degradation of pathological cellular components related to AD. As evidenced by Ye et al. (2017), enhanced retrograde transport in AD patients may reduce distal A β aggregation in dystrophic neurites, thereby attenuating synapse loss and slowing cognitive decline in patients who suffer from AD.

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