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Kinesin light chain-1 variant E disrupts axonal transport and A β generation in Alzheimer's disease

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Although many studies have shown that fast axonal transport is disrupted in neurodegenerative diseases, mechanism(s) leading to the disruption and the direction of the cause $\leftrightarrow$ effect arrow have been unclear. For example, expression of Familial Alzheimer's Disease-causing mutations in APP or Presenilin genes, or exposure of cells to the product of PS-dependent APP cleavage—the A β peptide—impairs axonal transport, including that of APP protein itself. Recently, Morihara and colleagues used transcriptome analysis of various mouse strains, each carrying an APP transgene in a different background, to discover the reasons for their different levels of A β accumulation [1]. They found that kinesin light chain-1 splice variant E (KLC1vE) is a modifier of A β accumulation, and is overexpressed in Alzheimer's disease brain. Furthermore, overexpression or knockdown of KLC1vE in neuroblastoma cells increases or decreases production of A β , respectively. In the current paper “Atlas stumbled: Kinesin light chain-1 variant E triggers a vicious cycle of axonal transport disruption and amyloid- β generation in Alzheimer's disease” by Gan et al., three members of the team provide an insightful and thorough review of the literature on kinesin light chain structure and function and on microtubule involvement in neurodegeneration, with particular focus on axonal transport [2]. They then present and discuss three non-mutually exclusive hypotheses for how KLC1vE may alter A β accumulation and contribute to Alzheimer's disease pathology and dementia. Specifically:

- A. KLC1vE enrichment may reduce APP transport, leading to intra-neuronal A β accumulation.
- B. KLC1vE enrichment may reduce APP transport, which then triggers an ER stress response that activates the amyloidogenic pathway.
- C. KLC1vE enrichment may impair transport of other KLC1 cargos that regulate amyloidogenesis, promoting A β retention within the secretory pathway.

Each of these ideas is reasonable, is consistent with our current knowledge, and, most important, is testable. For example apolipoprotein ER2 (ApoER2), c-Jun NH2-terminal kinase-associated leucine zipper protein (JLP), and cal-syntenin have been shown to be involved in amyloidogenesis, and their transport may be impaired by KLC1vE. Furthermore, glycogen synthase kinase-3 β (GSK3 β), which upregulates β -secretase expression and phosphorylates APP at T668 Gan et al.—and thus promotes cleavage by the

amyloidogenic pathway to generate more A β peptide—is activated by ER stress, and may further impair transport of neuropeptides and organelles by inhibitory phosphorylation of associated kinesins. Indeed, A β directly binds to and inhibits certain microtubule motors that are essential for mitosis and for the transport of many receptors to the cell surface [3]. This inhibition leads to chromosome mis-segregation and the production of aneuploid neurons—whose specific loss accounts for 90% of the neuro-degeneration in Alzheimer’s disease—and to neurons whose response to neurotrophins and neurotransmitters is greatly attenuated [4, 5]. As KLC1vE increases intracellular A β accumulation, more inhibition of kinesin 5 and other A β -sensitive motors should ensue, with further disruption of both neurogenesis and neuronal function.

Together the ideas and results of the current paper and the previous genetic/transcriptome identification of KLC1vE’s involvement in A β accumulation support the conclusion that disruption of microtubule-dependent transport in neurons—specifically by KLC1vE—can lead to neuronal dysfunction by affecting the production and accumulation of A β , which in turn can lead to further microtubule based transport defects, in a vicious cycle of increasing pathology. Clearly, the overexpression of KLC1vE in Alzheimer’s disease brain, and the consequent increase in A β accumulation, has many pathological repercussions, and is a promising new target for therapeutic intervention.

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