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The downward spiral of tau and autolysosomes

A new hypothesis in neurodegeneration

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A growing body of research has connected autophagy to neurodegenerative diseases such as Alzheimer disease (AD). In autopsied AD brain, large multivesicular bodies accumulate in neurons. Knockout mice deficient for key autophagy genes demonstrate age-dependent neurodegeneration. Most neurodegenerative diseases are characterized by accumulation of insoluble protein species; the type of protein and the location of aggregates within the nervous system help to define the type of disorder. It has been hypothesized that the inability to degrade such aggregates is a major causative factor in neuronal dysfunction and eventual neuronal death. As neurons are postmitotic and thus cannot regenerate themselves, mechanisms of protein clearance have received much attention in the field. The function of the ubiquitin-proteasome system (UPS) is impaired in models of neurodegeneration, and overexpression of chaperone proteins, such as those in the HSP70 family, leads to beneficial effects in many models of proteinopathies. Recently, studies of the effects of autophagy as a clearance mechanism have uncovered compelling evidence that inducing autophagy can alleviate many pathogenic and behavioral symptoms in animal and cellular models of neurodegeneration.

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MAPT/tau is expressed predominantly in axons where it binds to and stabilizes microtubules. However, insoluble aggregates of MAPT are found in several types of neurodegenerative diseases. Our report identified several autophagy genes as strong modifiers of neurodegeneration using an in vivo model expressing human MAPT in Drosophila. Several parts of the autophagy system including autophagosome induction (*Atg6*), lysosomal acidification (*Vha14*) and autolysosome formation (*white, brown, rosy*) were identified in our screen. Other groups have shown similar results with MAPT toxicity and lysosomal associated genes, including *benchwarmer* and the vacuolar ATPase subunit *v0a1*.

Although autophagy has been implicated in other proteinopathies, use of the same modifier alleles did not modify polyglutamine-induced degeneration in our experiments. This may suggest a specific, or perhaps a more sensitized, effect of autophagy dysregulation on MAPT pathology. The MAPT protein has several serine, threonine and tyrosine residues that can be phosphorylated, the majority of which decrease the binding affinity of MAPT to microtubules. As autophagosomes and lysosomes rely on microtubule-based networks for trafficking and eventually merge to form autolysosomes, a link between MAPT, microtubule trafficking and autolysosome formation can be made. In AD and other tauopathies, MAPT is hyperphosphorylated, which has led to the prevailing hypothesis that increased phosphorylation of MAPT is the root cause of pathology, causing *decreased* binding of MAPT to microtubules, which leads to destabilized microtubule networks and ensuing trafficking deficits within diseased neurons.

However, previous work from our lab has shown equivalent or increased toxicity using phosphorylation-resistant MAPT mutants. These isoforms have increased

binding affinity to tubulin as compared with wild-type MAPT in vivo. This indicates that when MAPT cannot dissociate from microtubules it is equally or more toxic than when MAPT is hyperphosphorylated and unable to bind to microtubules. MAPT has a much higher binding affinity for tubulin then either kinesin or dynein, the motor proteins needed for microtubule trafficking. Thus, an alternate hypothesis can be put forward that increased accumulation of soluble MAPT outcompetes binding of motor proteins to microtubule tracks, in what may be termed a "hyperbound" state of MAPT to microtubules. Lack of motor protein binding to microtubule tracks will cause major defects in trafficking and axonal transport. Of significant importance would be disruption of the merging of autophagosomes and lysosomes to form autolysosomes. This would result in increased autophagosome production but without the necessary acidic environment or proteases found within lysosomes to clear the contents of autophagosomes. Disruption of autolysosomal formation would lead to decreased degradation of a number of proteins including MAPT. More MAPT would accumulate, leading to further "hyperbound" MAPT and still further trafficking blocks, inducing a downward spiral of impaired microtubule trafficking and increased MAPT accumulation (**Fig. 1**). In this hypothesis, increased or "hyper" phosphorylation of MAPT is not the driving force of toxicity, but rather a cellular defensive mechanism to alleviate the burden of "hyperbound" MAPT disrupting microtubule trafficking.

However, a trigger is needed to induce a "hyperbound" state of MAPT. This may be from either increased levels of soluble MAPT or decreased ability to reduce the binding affinity of MAPT for microtubules.

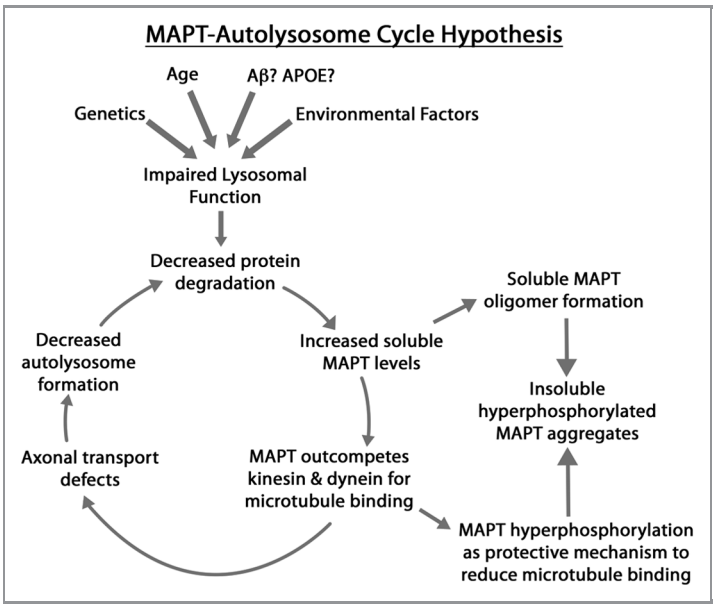

Figure 1. Several factors can contribute to reduced lysosomal and other protein degradation mechanisms. Once past a point of equilibrium, a positive feedback loop of MAPT accumulation and decreased autolysosome function is initiated that causes progressive worsening of reduced protein clearance and impaired axonal transport, which may explain several phenomena of neurodegenerative tauopathies. Hyperphosphorylation of MAPT and insoluble MAPT aggregation are by-products in this model that may further impair protein degradation processes or cause other deleterious effects.

If we focus on increased levels of MAPT as the main starting point, this too may also be due to autophagy/lysosomal dysfunction. MAPT can be degraded by several processes/proteins, including proteases, the UPS, and cathepsin cleavage in lysosomes. Impairment in any of these processes could lead to reduced turnover and increased accumulation of MAPT. The probability of such impairments increases with cellular and organismal age, and as neurons are postmitotic and ostensibly survive as long as the organism in which they function, neurons are particularly susceptible to reduced protein turnover efficiency. This may also explain, in part, the late age of onset of most tauopathies and the progressive degeneration thereafter. Other genetic and environmental factors, along with possible effects from β-amyloid (Aβ), can also contribute to reduced proteolytic efficiency.

In this model, several factors associated with neurodegeneration, including the soluble oligomers, oxidative stress, mitochondrial dysfunction, excitotoxicity, neurotrophins and cytokines, to name a few, are not addressed. However, the role of autophagy in tauopathies and other neurodegenerative diseases will continue to be the focus of much research in the near future, as the processes of neuronal health, protein turnover, and microtubule regulation appear to be closely tied to one another. We hope the model we provide serves to add further stimulus to this discussion.