

## **The Pathogenic Role of Defective Endosomal-Lysosomal Function in Alzheimer's Disease**

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Genes regulating the lysosomal network are implicated in pathogenesis of multiple adult onset neurodegenerative diseases. In some of these disorders, including Alzheimer's disease (AD), dysfunction arises early and is progressive, intersecting with further declines due to cellular aging and ultimately initiating neuron death. The three genes that cause early-onset familial Alzheimer's disease (FAD) -- presenilins 1, 2 (*PS1*, *PS2*) and amyloid precursor protein (*APP*) – corrupt lysosomal function via different mechanisms, while promoting  $\beta$ -amyloid peptide production or impeding its clearance through the endosomal-lysosomal pathway. *Rescuing* impaired lysosomal proteolysis in AD mouse models ameliorates autophagy/lysosomal pathology, amyloid burden, and memory deficits underscoring the pathogenic significance of lysosomal dysfunction. Lysosomes require *PSEN1* to assemble vATPase and effect acidification necessary for normal hydrolase activation. Loss of PS1 function conferred by FAD mutations, which elevates lysosomal pH, greatly accelerates lysosomal and autophagy pathology, amyloidogenesis, and neurodegeneration. *PSEN2* and *APP* mutations (or *APP* duplication as in Down syndrome) also disrupt lysosomal function, including acidification, by other mechanisms. Beyond regulating substrate hydrolysis, lysosomal pH modulates the large lysosomal stores of calcium. The lysosomal pH rise in AD patient fibroblasts and AD models induces calcium efflux via TRPML1 ion channels, which elevates cytosolic calcium levels. The resulting activation of calpains and the protein kinases cdk5 and JNK mediates AD-related pathological events, including increased exocytosis and selectively impaired retrograde transport of endolysosomes leading to AD-like axonal dystrophy. Inhibiting TRPML1 substantially reverses these calcium-dependent abnormalities but does not rescue autophagy. By contrast, restoring acidification reverses both calpain and autophagy abnormalities. *APP* mutations and *APP* triplication (in Down syndrome) that cause early-onset AD also impair endolysosomal function, including lysosomal acidification, by mechanisms mediated by the  $\beta$ -secretase-cleaved C-terminal domain of APP. Blocking signaling from this APP metabolite reverses endolysosomal anomalies, which appear very early in AD and are a cause of cholinergic neurodegeneration. Support: National Institute on Aging