This Week in The Journal

APP- β CTF-Mediated Lysosomal Dysfunction in Down Syndrome

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(see pages 5255–5268)

Alzheimer's disease (AD) is characterized by the accumulation of β -amyloid peptides derived from amyloid precursor protein (APP). Because the APP gene is present on chromosome 21, people with trisomy 21 (Down syndrome) have an extra copy of the gene. Consequently, almost all develop AD at a relatively young age. Studying the effects of APP in young people with Down syndrome can therefore provide insights into the earliest pathological processes in AD. Importantly, many of these effects can be studied in peripheral cells, such as fibroblasts, from living donors.

Disruption of protein and lipid trafficking through endosomes occurs at early stages of AD and begins perinatally in people with DS. Endosomes are the main site of cleavage of APP by β -secretase, which generates a β -cleaved carboxy-terminal fragment (APP- β CTF) that is subsequently cleaved by γ -secretase to generate β -amyloid. The extra copy of APP in Down syndrome leads to excessive activation of endocytosis, enlargement of endosomes, and increased production of APP- β CTF.

The function of lysosomes, the organelles responsible for metabolizing damaged proteins and lipids, is also impaired in AD and, as Ying et al. now report, in people with Down syndrome. Lysosomal degradation of proteins was slowed in fibroblasts from people with Down syndrome, leading to accumulation of proteins in these organelles. Reduced proteolysis was attributable to an increase in the pH of lysosomes, which resulted in decreased activity of proteases that require low pH, including cathepsin D. These deficits were reversed by knocking down APP in fibroblasts.

APP- β CTF colocalized with cathepsin D in fibroblasts, and lysosomal APP- β CTF levels were higher in fibroblasts from people with Down syndrome than in controls. Notably, increasing APP- β CTF levels in control fibroblasts increased lysosomal pH and decreased cathepsin D activity.

In contrast, blocking β -secretase in Down syndrome cells reduced lysosomal pH to control levels.

These results suggest that elevated levels of APP- β CTF in Down syndrome and AD impair acidification of lysosomes and thus hinder proteolysis. The resulting accumulation of damaged or misfolded proteins may then disrupt other cellular functions. Thus, lysosomal dysfunction might be an early step in the pathological processes leading to cognitive decline in AD. This may help to explain why lowering β -amyloid levels has been unsuccessful in treating AD.

Pou4f1 (green) is expressed in most neurons (labeled with anti-tubulin antibody, red) in the apical portion of the spiral ganglion (circled) at embryonic day 14.5 (top), but is restricted to a subset of neurons at postnatal day 14 (bottom). See Sherrill, Jean, et al. for details.

Presynaptic Effects of *Pou4f1* in Spiral Ganglion Neurons

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(see pages 5284–5298)

Auditory information is carried from cochlear inner hair cells to brainstem auditory nuclei by spiral ganglion neurons (SGNs). SGNs can be subdivided into three groups based on their response threshold, spontaneous firing rate, and location of hair-cell innervation. Specifically,

SGNs with high thresholds have low spontaneous rates and form synapses on the medial (modiolar) side of the hair cells, whereas those with low thresholds have high spontaneous rates and innervate the lateral (pillar) side. The size and physiological properties of presynaptic specializations in hair cells also differ depending on SGN type: medially located synapses have larger synaptic ribbons, require greater depolarization for calcium-channel activation, and have larger maximal calcium influx than lateral synapses. How these differences in synapses and SGNs arise is unclear, but differences in transcription factor expression in SGNs might play a role.

One transcription factor that helps distinguish SGN subtypes is *Pou4f1*. *Pou4f1* is expressed in all SGNs early in embryonic development, but it becomes restricted to a subset (~30%) of SGNs after birth. Sherrill, Jean, et al. report that SGNs that retain *Pou4f1* expression typically form synapses on the medial side of inner hair cells. Not all SGNs that formed synapses medially expressed *Pou4f1*, however, suggesting that *Pou4f1* identifies only a subset of high-threshold SGNs.

Knocking out *Pou4f1* in SGNs starting on embryonic day 14.5 did not result in SGN death (unlike germline deletion), and it did not reduce the number of medial synapses on hair cells or noticeably impair auditory function. Surprisingly, although *Pou4f1* is not expressed in hair cells, the size of synaptic ribbons (where synaptic vesicles are tethered) in hair cells was reduced. Moreover, there was a small but statistically significant increase in the voltage sensitivity of calcium channels in hair-cell active zones, and this shifted the half-maximal calcium-channel activation to more hyperpolarized potentials. Finally, *Pou4f1* knock-out eliminated the medial-to-lateral gradient in maximum calcium influx at hair-cell synapses.

These results suggest that *Pou4f1* expression in a subset of high-threshold, low-spontaneous-rate SGNs affects the properties of presynaptic active zones. How these effects are mediated and how *Pou4f1* expression affects the properties of SGNs in which it is expressed remain to be determined.

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