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# Rescuing the golgi puts brakes on Alzheimer's progression

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Alzheimer's disease (AD) progresses inside the brain in a rising storm of cellular chaos as deposits of the toxic protein, amyloid-beta (Aβ), overwhelm neurons. An apparent side effect of accumulating Aβ in neurons is the fragmentation of the Golgi apparatus, the part of the cell involved in packaging and sorting protein cargo including the precursor of Aβ. But is the destruction the Golgi a kind of collateral damage from the Aβ storm or is the loss of Golgi function itself part of the driving force behind Alzheimer's?

This was the question for Yanzhuang Wang, Gunjan Joshi, and colleagues at the University of Michigan, Ann Arbor, as they set out to uncover the mechanism damaging the Golgi, using a transgenic mouse and tissue culture models of AD to look at what was going on.

The unsurprising part of the answer was that rising levels of Aβ do lead directly to Golgi fragmentation by activating a cell cycle kinase, cdk5. The surprising part of the answer was that Golgi function can be rescued by blocking cdk5 or shielding its downstream target protein in the Golgi, GRASP65. The even more surprising answer was that rescuing the Golgi reduced Aβ accumulation significantly, apparently by re-opening a normal protein degradation pathway for the amyloid precursor protein (APP). To Wang et al, this suggested an entirely new line of attack for drugs hoping to slow AD progression.

Speaking at the ASCB/IFCB Meeting in Philadelphia, the researchers now say that Golgi fragmentation is in itself a major—and until now an

unrecognized—mechanism through which Aβ extends its toxic effects. They believe that as Aβ accumulation rises, damage to the Golgi increases, which in turn accelerates APP trafficking, which in turn increases Aβ production. This is a classic "deleterious feedback circuit," they say. By blocking cdk5 or its downstream target, that circuit can be broken or greatly slowed. "Our study provides a molecular mechanism for Golgi fragmentation and its effects on APP trafficking and processing in AD, suggesting Golgi as a potential drug target for AD treatment," the Michigan researchers report.

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