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Endolysosome and autophagy dysfunction in Alzheimer disease

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ABSTRACT

Abnormalities of the neuronal endolysosome and macroautophagy/autophagy system are an early and prominent feature of Alzheimer disease (AD). *SORL1* is notable as a gene in which mutations are causal for a rare, autosomal dominant form of AD, and also variants that increase the risk of developing the common form of late-onset AD. In our recent study, we used patient-derived stem cells and CRISPR engineering to study the effects of *SORL1* mutations on the endolysosome and autophagy system in human forebrain neurons. *SORL1* mutations causal for monogenic AD are typically truncating mutations, and we found, using stem cells generated from an individual with dementia due to a heterozygous *SORL1* truncation mutation, that this class of mutation results in SORL1 haploinsufficiency. Reducing SORL1 protein by half results in disrupted endosomal trafficking in patient-derived neurons, which we confirmed by studying the endolysosomal system in isogenic CRISPR-engineered *SORL1* heterozygous null neurons. We also found that *SORL1* homozygous null neurons develop more severe phenotypes, with endosome abnormalities, lysosome dysfunction and defects in the degradative phase of autophagy. Endolysosome and autophagy defects in *SORL1* mutant neurons are dependent on *APP*, a key AD gene, as they are rescued by extracellular antisense oligonucleotides that reduce APP protein.

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Dysfunction of the endolysosomal-autophagy network is emerging as an important pathogenic process in AD. We have previously reported that mutations in *APP* and *PSEN1* that are causal for autosomal dominant, early-onset monogenic AD, lead to significant defects in lysosome function and autophagy in human iPSC-derived neurons. The presence of these changes within relatively young neurons, combined with the ability to induce these phenotypes by acute γ-secretase inhibition in healthy neurons, indicates that these defects are an early event in monogenic AD pathogenesis. However, the contribution of dysfunction in these systems to pathogenesis of the late-onset, sporadic form of the disease is less clear. Recent genome-wide association studies have identified single nucleotide polymorphisms in several genes with roles in the endolysosomal and autophagy systems as affecting disease risk, including *SORL1* (sortilin related receptor 1). This finding was followed by the key discovery that loss-of-function mutations in this gene are a rare cause of autosomal-dominant AD, suggesting that *SORL1* is involved in the pathogenesis of both monogenic and late-onset AD.

In our recent study [1], we studied how truncating mutations in *SORL1* affect the initiation and progression of AD, using human stem cell-derived neuronal models. We found that human cortical neurons derived from an individual with dementia due to a heterozygous *SORL1* truncating mutation have half of control levels of SORL1 protein, demonstrating that these mutations cause haploinsufficiency. Human forebrain neurons expressing this mutation have disrupted endosomes, but no detectable changes in lysosomal function. We used CRISPR-Cas9-mediated genome engineering to generate an isogenic *SORL1* null allelic series in human neurons. Consistent with the findings in the patient-derived *SORL1* heterozygous mutant neurons, we observed a significant increase in both the number and average size of early endosomes in *SORL1* heterozygous null neurons. Furthermore, we found that complete loss of SORL1 results in a more severe phenotype and leads to significant defects in endosome, lysosome and autophagosome function.

This phenotype includes a marked reduction in the level of lysosomal CTSD (cathepsin D) activity in *SORL1* null neurons compared with isogenic controls. Impaired lysosomal clearance can lead to downstream changes in autophagy, including accumulation of autophagic vesicles. Therefore, we carried out a number of studies of autophagy in *SORL1* homozygous null human neurons. Measuring autophagic flux using a well-established quantitative western-blot approach, we found that the degradative phase of autophagy is compromised in *SORL1* null neurons. Lastly, we demonstrated that the endolysosome and autophagy defects are dependent on APP protein as these defects can be rescued by extracellular antisense oligonucleotides selectively targeting *APP* mRNA. This last result places *SORL1* in the same cellular pathway as *PSEN1* and *APP* for AD pathogenesis and highlights the potential efficacy of therapeutics that reduce APP levels in slowing disease initiation or progression.

Autophagy activation has been proposed as a promising therapeutic strategy for AD. However, many questions remain to be answered regarding its beneficial role in disease pathogenesis. For example, which step(s) of the autophagic-lysosomal pathway should be targeted? How would the

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upregulation of autophagy disturb the delicate balance between autophagosome formation and lysosomal degradation? Our data suggested that targeting canonical autophagy induction may be counterproductive in the face of lysosomal clearance deficits and reduced autophagosome degradation, by further overburdening the already failing lysosomes and thus exacerbating autophagic accumulation in axons. Rapamycin, an FDA-approved drug, enhances autophagosome biogenesis and has shown promising effects in ameliorating the development of amyloid pathologies and memory deficits in a mouse model of AD. In contrast, administration of rapamycin after the formation of amyloid plaques fails to rescue the cognitive deficits in a mouse model of AD. Based on our recent data, we propose that either reducing input of APP to the endolysosome or increasing expression of SORL1 at the early disease stages may represent alternative productive therapeutic strategies to attenuate autophagic defects in AD. Overall, our study suggests that dysfunction of the endolysosomal–autophagic system represents a convergent mechanism shared by monogenic and sporadic forms of AD. As such, this work establishes a foundation for future investigation into cellular pathways enhancing autophagy and lysosomal proteolytic activity as an approach to ameliorating neurodegeneration in AD.

Disclosure statement

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Reference

[1] Hung C, Tuck E, Stubbs V, et al. SORL1 deficiency in human excitatory neurons causes APP-dependent defects in the endolysosome-autophagy network. Cell Rep. 2021;35(11):109259.