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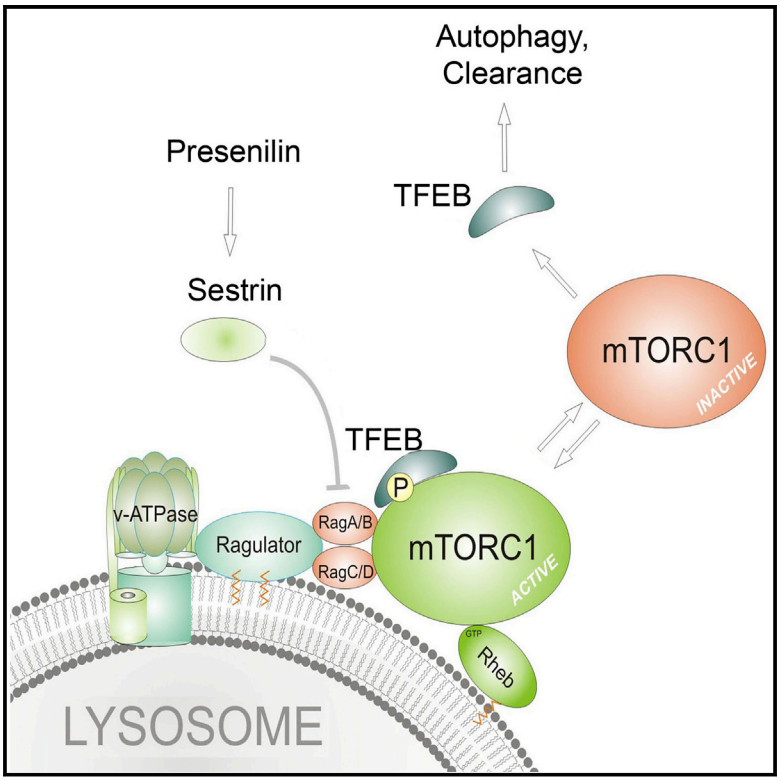
Dysregulation of Nutrient Sensing and CLEARance in Presenilin Deficiency

Graphical Abstract



Highlights

- Presenilin (PS)-knockout or AD mutations attenuate CLEAR network activity
- Amino-acid-sensing function of mTORC1 is dysregulated in PS-deficient cells
- Increase of cellular calcium or Sestrin2 re-regulates mTORC1 and CLEAR activity
- Dysregulated mTORC1 accounts for low autophagy in PS deficiency

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In Brief

Reddy et al. find that the amino-acid-sensing function of mTORC1 is dysregulated in cells deficient in the AD-associated presenilin proteins. Constitutively active mTOR in these cells inhibits CLEAR network activity, leading to degeneration. Attenuation of the CLEAR network leads to the onset of AD-like pathophysiology in vivo.

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Dysregulation of Nutrient Sensing and CLEARance in Presenilin Deficiency

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SUMMARY

Attenuated auto-lysosomal system has been associated with Alzheimer disease (AD), yet all underlying molecular mechanisms leading to this impairment are unknown. We show that the amino acid sensing of mechanistic target of rapamycin complex 1 (mTORC1) is dysregulated in cells deficient in presenilin, a protein associated with AD. In these cells, mTORC1 is constitutively tethered to lysosomal membranes, unresponsive to starvation, and inhibitory to TFEB-mediated clearance due to a reduction in Sestrin2 expression. Normalization of Sestrin2 levels through overexpression or elevation of nuclear calcium rescued mTORC1 tethering and initiated clearance. While CLEAR network attenuation in vivo results in buildup of amyloid, phospho-Tau, and neurodegeneration, presenilin-knockout fibroblasts and iPSC-derived AD human neurons fail to effectively initiate autophagy. These results propose an altered mechanism for nutrient sensing in presenilin deficiency and underline an importance of clearance pathways in the onset of AD.

INTRODUCTION

Alzheimer disease (AD) is the most common neurodegenerative disorder of our time. Functional abnormalities of autophagosomes and lysosomes have been identified as some of the early pathological features in AD brains, preceding the hallmark deposits of amyloid and Tau tangles (Nixon and Yang, 2011). Enlargement of endosomal compartments containing amyloid precursor protein (APP) peptides (Takahashi et al., 2002), lysosomal deficits, and progressive accumulation of autophagic vacuoles are widely observed in AD human samples and corresponding mouse models (Cataldo et al., 1997; Nixon and Yang, 2011; Nixon et al., 2005). The link between AD and the lysosomal system is strengthened by observations that polymorphisms in several cathepsin genes increase the risk for AD (Bhojak et al., 2001; Papassotiropoulos et al., 1999) and deletions of lysosomal protease inhibitors cystatin B/C largely ameliorate symptoms in AD mouse models (Mi et al., 2007; Yang et al., 2011, 2014).

Impaired auto-lysosomal system, along with the consequential disruption of molecular trafficking and cellular signaling (Dobrowolski and De Robertis, 2011; Sorkin and von Zastrow, 2009; Taelman et al., 2010), is strongly linked to neurodegeneration (Komatsu et al., 2006; Lipinski et al., 2010; Nixon, 2013). Efficient (macro)autophagy is required to remove aggregated proteins and defective organelles, whose accumulation associates with a number of human diseases like AD, Parkinson disease, and amyotropic lateral sclerosis (Nixon, 2013). Autophagy is strictly dependent on lysosomal function that is driven by the nutritional status of the cell. Specifically, amino acids are sensed by lysosomes through a protein complex (vacuolar ATPase, Ragulator complex, and the Rag heterodimers A/B and C/D) that tethers the mechanistic target of Rapamycin complex 1 (mTORC1) to their membranes (Laplante and Sabatini, 2012; Nnah et al., 2015). The small GTPase Rheb (Ras homolog enriched in brain) activates mTORC1 on lysosomal membranes if TSC1/2 (tuberous sclerosis 1/2 complex) is inactivated by growth factor signaling (Inoki et al., 2003; Tee et al., 2003). Thus, mTORC1 activity is regulated by amino acid levels (as readily monitored by tethering of the complex to lysosomal membranes) and cellular signaling. Activity of mTORC1 has a direct effect on the biogenesis of lysosomes and autophagosomes through TFEB (transcription factor EB). TFEB is regulated by mTORC1 and positively regulates the activity of the CLEAR (coordinated lysosomal expression and regulation) gene network encoding for lysosomal and autophagosomal genes (Sardiello et al., 2009; Settembre et al., 2012). Under normal feeding conditions, active mTORC1 phosphorylates TFEB allowing it to remain in the cytoplasm. When cells starve, mTORC1 displaces from the lysosomal membranes, is no longer active, and is unable to phosphorylate TFEB that then translocates into the nucleus to directly bind to promoter elements containing the CLEAR sequence (Settembre et al.,

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