NEURODEGENERATIVE DISEASE

New insights into the origin of amyloid plaques

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Alzheimer's disease (AD) is characterized by the presence of tau filaments in intracellular neurofibrillary tangles and amyloid β (Aβ) peptides in extracellular senile plaques. Extensive research is ongoing to understand how, and when, Aβ plaques are forming in AD brains. Using a new transgenic mouse line and five mouse models of AD, a study in *Nature Neuroscience* shows that autophagy dysfunction in neurons precedes the formation of amyloid plaques. These findings further support the idea that the events kicking off plaque formation in AD occur within the cells and not outside.

Autophagy is the process responsible for the delivery of cellular debris such as damaged organelles and obsolete proteins to lysosomes (LY) for degradation. Autophagy dysfunction has been linked to several neurodegenerative disorders that are associated with accumulation of misfolded protein aggregates, but the role of autophagy dysfunction in AD pathogenesis is unclear.

Here, Lee et al. generated a transgenic mouse line expressing a dual fluorescent sensor to monitor autophagy in neurons in vivo. The sensor (tfLC3), which is composed of pH-resistant mRFP and pH-sensitive eGFP linked to LC3, a protein associated with autophagosomes (APs) and autolysosomes (ALs), produces different colors (yellow, orange or red) depending on the pH of the environment and the quenching of the GFP signal. By using a third fluorophore (blue) to label LY, the team was able to identify poorly acidified ALs (pa-ALs), which are APs that fuse with an LY but fail to acidify adequately, indicating autophagy dysfunction.

Vesicle quantification on confocal-imaged brain sections of tfLC3 mice crossed with a mouse model of AD revealed that AL acidification deficits developed before β-amyloid deposit. Analysis of five mouse models of AD revealed that compromised neurons massively accumulate pa-ALs containing APP-βCTF/Aβ around the nucleus, forming large membrane blebs that resemble petals of a flower. This unique pattern, which was termed PANTHOS (poisonous "anthos" (flower)) by the investigators, was detected in neurons of AD mice prior to plaque formation.

"We establish quantitatively that PANTHOS neurons are the origin of the vast majority of senile plaques in AD mouse models, thus prompting a reconsideration of the conventionally accepted sequence of events in plaque formation in AD," write the investigators who also indicate that their autophagy probe could be useful to characterize changes in autophagy in other neurodegenerative disease models.

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