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Rapamycin and Alzheimer disease: a hypothesis for the effective use of rapamycin for treatment of neurodegenerative disease

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ABSTRACT

In 2019 we summarized work relating to the potential use of rapamycin for treating Alzheimer disease (AD). We considered the commentary necessary because use of rapamycin in people with AD is a very real prospect and we wanted to present a balanced view of the likely consequences of MTOR (mechanistic target of rapamycin kinase) inhibition in the AD brain. We concluded that use of rapamycin, an MTOR inhibitor that increases macroautophagy/autophagy, could hold promise for prevention of AD if used early enough. However, MTOR inhibition appeared ineffectual in resolving existing amyloid pathology in AD mouse models. In this View article, we update these observations with new studies that have used rapamycin in AD models and provide evidence both for and against its use in AD. We also discuss rapamycin in the light of new research that describes rapamycin-induced autophagic stress in the aging brain and autophagic stress as the origin of the amyloid plaque itself. We conclude that rapamycin will have complex effects on the brain in AD. Further, we hypothesize that lysosomal degradative capacity in the brain will likely determine how effective or detrimental rapamycin will be as a treatment of AD.

Abbreviations: AD: Alzheimer disease; APP: amyloid beta precursor protein; MAPT/tau: microtubule associated protein tau; MTOR: mechanistic target of rapamycin kinase; MTORC1: mechanistic target of rapamycin kinase complex 1.

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We previously responded [1] to a call for the use of rapamycin – a partial allosteric inhibitor of MTOR complex 1 (MTORC1) – as a treatment for Alzheimer disease (AD) that was predicated on promising data from preclinical models [2]. Our opposing view to this call argued that where rapamycin appeared capable of preventing AD pathology, it was administered before or very early in disease progression [1,3]. This is problematic because by the time a person is diagnosed with dementia that is caused by AD, amyloid plaques have been developing for nearly two decades and significant MAPT/tau (microtubule associated protein tau) pathology/tauopathy is also present [4,5]. Indeed, rapamycin fails to change neuropathology when used late in the disease course in a mouse model [3]. Determining exactly how rapamycin interacts with the hallmarks of AD is important as tangle pathology made up of aggregated MAPT correlates with cognitive decline [6], and amyloid plaques made up of aggregated amyloid-β peptides associate with poor memory performance, even in people who do not meet the criteria for dementia [7]. We further argued that in the later stages of AD, rapamycin may enhance pathology by exacerbating autophagic stress – when the generation of autophagic cargoes exceeds the lysosome's capacity for clearance (Figure 1A,B). By and large, most of the benefits of rapamycin that relate to amyloid and MAPT pathology/tauopathy in preclinical models of AD support its use in preventing, not treating, disease. Since we wrote our commentary in 2019, studies have been published which both support and counter the use of rapamycin for AD. Here, we provide an update on how rapamycin could be useful for AD by reviewing these data from an autophagy and lysosomal perspective.

First, it is critical to note that one study that found a beneficial role for MTOR inhibition (via loss of a single *MTOR* allele) in mice that overexpress mutant APP (amyloid beta precursor protein) (Tg2576) was retracted [8]. In addition, important new studies show that amyloid plaques are a result of autophagic stress [9] and that rapamycin may produce autophagic stress *in vivo* [10]. Other new papers detailing the use of rapamycin in AD mouse models have shown conflicting and surprising results [11–14]. We have summarized these papers, along with older studies and their mouse models in Table 1 [15–26].

In mice, poorly acidified lysosomes that cannot efficiently clear autophagic material in neuronal bodies results in the storage of autophagic material in perikaryal blebs [9]. This gives the neuronal body a "flower-like" appearance that is referred to as "PANTHOS" (poisonous anthos). This stored autophagic material is a site of accumulation for amyloid-β peptides that eventually form amyloid fibrils and the amyloid plaque itself. In this way, autophagic stress leads to the formation of an amyloid plaque, which itself is the tombstone of a dying neuron. Indeed, in the human AD brain, amyloid plaques are highly enriched with lysosomal machinery which is likely to be a remnant of this process [27,28]. Consistent with autophagic stress acting upstream

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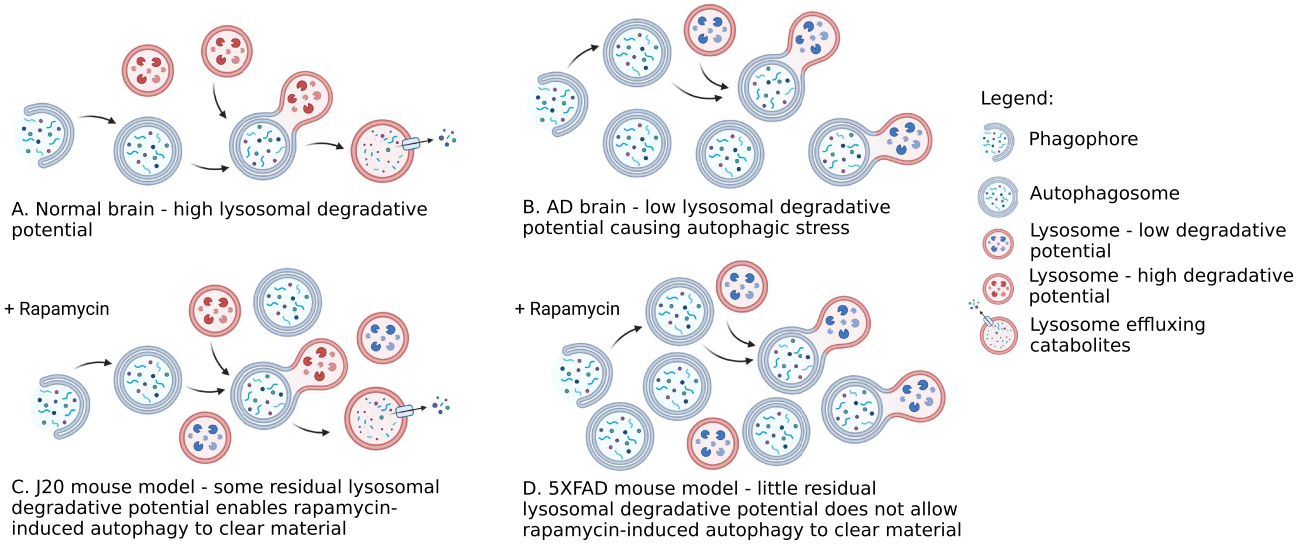

Figure 1. Lysosomal degradative potential and its interaction with AD and rapamycin – a hypothesis. (A) In a normal brain, autophagy is resolved by efficient lysosomes. (B) In AD, lysosomes have reduced degradative potential and autophagic material accumulates. (C) Recent work has shown that rapamycin can reduce amyloid plaque burden after plaques are established. We hypothesize this is because there is some lysosomal degradative potential in the system that can process increased autophagic flux stimulated by rapamycin. (D) In contrast, the failure of rapamycin to decrease amyloid plaques in recent papers that have used the 5XFAD mouse model could reflect lower lysosomal degradative potential.

of amyloid plaques, loss of ATG7 (autophagy related 7) in neurons abrogates the formation of amyloid plaques in the brain [29].

Given that rapamycin can activate autophagy [30], it may cause autophagic stress under conditions where lysosomes have low degradative potential. Rapamycin given to nine-month-old, but not four-month-old mice induces the appearance of astroglia in the hippocampus that are laden with SQSTM1/p62 (sequestosome 1)-positive inclusions [10]. This is consistent with an age-related decline in lysosomal degradative potential that renders specific cells more susceptible to autophagic stress. Rapamycin appears to cause autophagic stress in a subtype of aging cells yet, despite this, increases lifespan and prevents age-related cognitive decline [31,32]. This suggests that some organs or cell types may be more susceptible to autophagic stress than others. It is plausible that under conditions where lysosomes have high – or normal – degradative potential, induction of autophagy by rapamycin may be beneficial. However, in cells where the degrative potential of lysosomes is reduced, activating autophagy could be deleterious. In this regard, the use of rapamycin in AD is complicated by the fact that the degradative potential of neuronal lysosomes is attenuated, which in itself leads to amyloid plaque deposition [9].

New research on how rapamycin interacts with MAPT pathology/tauopathy has confirmed previous results that indicated rapamycin can prevent but not reverse accumulation of aggregated MAPT [3]. Rapamycin prevents the accumulation of MAPT pathology/tauopathy in the cerebral cortex of transgenic mice that overexpress $MAPT^{P301S}$ but only when administered early (from two- to five-months) but not later (from 3.5- to five-months) in disease progression [14]. Intriguingly, in the brainstem, where MAPT pathology/tauopathy precedes that of the cerebral cortex, rapamycin does not have an impact on the MAPT burden. Remarkably, where rapamycin cannot reduce cortical MAPT pathology/tauopathy when applied from 3.5- to five-months of age, a brain-permeable MTOR kinase inhibitor called PQR530 can [14].

Although rapamycin cannot reduce established MAPT pathology/tauopathy, one study has shown it can reduce established pathology in a transgenic amyloidosis model. Two months of rapamycin treatment reduces amyloid accumulation in the brain of J20 transgenic mice that overexpress mutant APP [13]. Importantly, treatment with rapamycin began at 10-months of age, long after the initiation of amyloid plaque deposition, which likely began three- to five-months earlier [22]. This approach demonstrated that rapamycin can also correct a deficit in neurovascular coupling (a process whereby blood flow is adjusted according to neuronal activity). This shows that in the context of this model, rapamycin can be beneficial for AD-related pathology.

Another research paper demonstrated that seizures invoked by pentylenetetrazol causes an increase in amyloid plaques in the 5XFAD AD mouse model [11], which develop amyloid plaques from two-months of age [25]. The relationship between seizures, amyloid-β and MTOR is complex. Experimentally-induced seizures increase the expression of amyloidogenic pathway proteins and amyloid-β production is enhanced by increased synaptic transmission [11,33,34]. Seizures are associated with increased MTORC1 activity in neurons [11], and loss-of-function mutations in proteins that make up the GATOR1 complex – a major negative regulator for MTORC1 – cause focal epilepsy in humans [35]. Consistent with this, in kindled 5XFAD mice, rapamycin treatment from 3.5- to seven-months of age prevents seizures and seizure-related increases in amyloid plaque burden [11]. It has been hypothesized that amyloid-β pathology and seizures both share neuronal MTORC1 activity as a pathological effector and this results in a positive feedback loop that rapamycin

Table 1. Studies that have tested the effect of rapamycin on AD hallmarks in mouse models.

Mouse model[1]	Likely age AD hallmark present from[1]	Treatment age range	Effect	Study reference
		Amyloid plaque models		
J20 (PDGF-APPSw,Ind)	Amyloid plaques: 5–7 months of age [22]	Rapamycin: 4–7 months of age	Reduced $A\beta_{42}$	[21]
J20 (PDGF-APPSw,Ind)	Amyloid plaques: 5–7 months of age [22]	Rapamycin: 16 weeks beginning at 7 months	Reduced amyloid plaques and cerebral amyloid angiopathy	[18]
APP/PS1	Mouse not clearly referenced	Temsirolimus: 60 days from 5 months of age	Reduced amyloid plaques and soluble and insoluble $A\beta_{42}$	[16]
J20 (PDGF-APPSw,Ind)	Amyloid plaques: 5–7 months of age [22]	Rapamycin: 10–12 months of age	Reduction of amyloid plaques and $A\beta_{42}$	[13]
5XFAD	Amyloid plaques: 2 months of age [25]	Rapamycin: 3.5–7 months of age	No change in amyloid plaques or $A\beta_{42}$ in non-kindled model	[11]
5XFAD	Amyloid plaques: 2 months of age [25]	Rapamycin: 3–6 months of age	Increased $A\beta_{42}$	[12]
5XFAD	Amyloid plaques: 2 months of age [25]	Rapamycin: 4–6 months of age	Increased $A\beta_{42}$	[12]
5XFAD; microglia-specific *Tsc1* conditional knockout	Undefined	Rapamycin: 2–3 months of age, animal killed at 6 months of age	No change in amyloid plaques or $A\beta_{42}$	[12]
5XFAD; microglia-specific *Tsc1* conditional knockout	Undefined	Rapamycin: 4–6 months of age, animal killed at 6 months of age	Increased amyloid plaques and $A\beta_{42}$	[12]
5XFAD; microglia-specific *Tsc1* conditional knockout	Undefined	Rapamycin: 3–6 months of age, animal killed at 6 months of age	Increased amyloid plaques and $A\beta_{42}$	[12]
		MAPT pathology models		
hTau.P301S	Sarkosyl-insoluble MAPT aggregates: 4 months of age [24]	Rapamycin: 0.75–5.5 months of age	Reduced MAPT tangles and sarkosyl insoluble MAPT aggregates	[19]
hTau.P301S	Sarkosyl-insoluble MAPT aggregates: 4 months of age [24]	Rapamycin: 3–4.5 months of age	Reduced MAPT tangles and sarkosyl insoluble MAPT aggregates	[19]
P301S	Mouse not clearly referenced	Temsirolimus: 60 days from 5 months of age	Reduced phospho-MAPT epitopes	[17]
AAV vector expressing $MAPT^{P301L}$ injected into mouse brain	NA	Rapamycin: 5 weeks of treatment starting 4 days after viral delivery	Reduced trans-synaptic spread of human MAPT	[20]
hTau.P301S	Sarkosyl-insoluble MAPT aggregates: 4 months of age [24]	Rapamycin: 2–5 months of age	Reduction of phospho-MAPT epitopes, and sarkosyl insoluble MAPT aggregates	[14]
hTau.P301S	Sarkosyl-insoluble MAPT aggregates: 4 months of age [24]	Rapamycin: 3.5–5 months of age	No change in phospho-MAPT epitopes, and sarkosyl insoluble MAPT aggregates	[14]
hTau.P301S	Sarkosyl-insoluble MAPT aggregates: 4 months of age [24]	PQR530: 3.5–5 months of age	Reduction of phospho-MAPT epitopes	[14]
rTg4510	MAPT tangles: 4 months of age [26]	Rapamycin: 2.5–5.5 months of age	Reduction of phospho-MAPT epitopes, no change in sarkosyl insoluble MAPT aggregates	[14]
		Dual Amyloid plaque/MAPT pathology models		
3xTg	Amyloid plaques: 6 months of age; MAPT aggregates: 12–15 months of age [23]	Rapamycin: 10 weeks beginning at 6 months	Reduced $A\beta_{42}$, reduced phospho-MAPT epitopes	[15]
3xTg	Amyloid plaques: 6 months of age; MAPT aggregates: 12–15 months of age [23]	Rapamycin: 2–18 months of age	Reduced amyloid plaques, $A\beta_{42}$, and phospho-MAPT epitopes	[3]
3xTg	Amyloid plaques: 6 months of age; MAPT aggregates: 12–15 months of age [23]	Rapamycin: 15–18 months of age	No change in amyloid plaques, $A\beta_{42}$, or phospho-MAPT epitopes	[3]

[1]Zygosity of AD transgenes is sparsely reported and may modify relationship between age and pathology

disrupts [11]. However, rapamycin does not decrease amyloid plaque burden in 5XFAD mice where seizures are not induced by pentylenetetrazol.

In another study, rapamycin treatment in 5XFAD mice increases amyloid-β_{42} accumulation after treatment from three- to six-months of age. Hyperactivation of MTORC1 signaling specifically in microglia from 5XFAD mice via conditional deletion of *Tsc1* (TSC complex subunit 1) reduces amyloid-β_{42} accumulation and amyloid plaque burden. Intriguingly, these mice appear to be more sensitive to rapamycin-induced increases in amyloid-β_{42} accumulation and amyloid plaque burden than 5XFAD control mice [12]. The same study revealed that TREM2 (triggering receptor expressed on myeloid cells 2) expression in microglia is also positively controlled by MTORC1 activity. This finding in itself lends great complexity to how MTOR inhibitors are used in AD given that TREM2 is important for the brain's immune response to amyloid plaques and microglial autophagy [36].

A hypothesis for the disparity between the results shown in J20 and 5XFAD mouse models could be that rapamycin induces autophagy in both: whereas J20 mice have residual lysosomal degradative potential that clears incoming cargo, 5XFAD mice do not (Figure 1C,D). But why would 5XFAD have less lysosomal degradative potential than the J20 model? An explanation can be found in the fact that 5XFAD mice express mutant PSEN1 that is known to interfere with lysosomal gene expression via MITF (melanocyte inducing transcription factor) family transcription factor-CLEAR element interactions [37].

Where does this new research leave the field? While rapamycin has numerous positive effects on biological aging outside of autophagy and could even ameliorate these aspects of aging in AD, it is important to note that AD is a deeply lysosomal disease both genetically [38] and biochemically [9]. AD specifically targets lysosomal degradative potential, and this is likely to render neurons vulnerable to the autophagy-enhancing effects of rapamycin. With this in mind,

experiments that seek to use rapamycin should pay very close attention to (i) the aspects of pathology they are attempting to address, and (ii) whether lysosomes in the respective model are still functional. Scientists should also focus on measurement of lysosomal function in vivo. It is likely that rapamycin will be effective when there is remaining lysosomal degradative potential. However, we hypothesize that diminished lysosomal degradative potential will predict the inability of rapamycin to ameliorate AD-related pathology and perhaps even exacerbate the likelihood of harm. Regardless, moving forward with informed use of rapamycin, or a related compound, early in disease could provide a much-needed tool for clinicians. Recent progress has been seen with antibody-based therapies – lecanemab and aducanumab – that target amyloid-β protofibrils and fibrils, and slow cognitive decline in clinical trials. However, the clinical significance of the magnitude of these effects has been questioned, and some people suffer from severe side effects [39]. It is worth noting here that an autophagy-based approach to AD could be superior to antibody-related interventions as, if lysosomal degradative potential permits, it would simultaneously target multiple AD-related pathologies.

In sum, recent research that has used rapamycin in preclinical AD mouse models has shown mixed results that appear model dependent, where rapamycin's effects range from beneficial to deleterious. Future research could utilize other models such as human induced-pluripotent stem cell-derived brain organoids that recapitulate the pathological signs of AD [40]. More interestingly, autophagic stress has been formally identified as propagating AD-related pathology, which could be exacerbated by rapamycin. We hypothesize that measurement of lysosomal degradative potential, and thus the likelihood of rapamycin causing autophagic stress, will be an important tool for clinical translation.

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Figure 1 was created using BioRender.com.

Disclosure statement

TJS holds the following patents: Methods and products for assessing lysosomal flux. Australia (Provisional) 2,019,903,187; 2,019,904,822; PCT/AU/2020/050908; United Kingdom GB2204321.0; USA 17/637,494.

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References

[1] Carosi JM, Sargeant TJ. Rapamycin and Alzheimer disease: a double-edged sword? Autophagy. 2019 Aug;15(8):1460–1462.
[2] Kaeberlein M, Rapamycin GV. Alzheimer's disease: time for a clinical trial? Sci Transl Med. 2019 Jan 23;11(476):476.
[3] Majumder S, Richardson A, Strong R, et al. Inducing autophagy by rapamycin before, but not after, the formation of plaques and tangles ameliorates cognitive deficits. PLoS One. 2011;6(9):e25416.
[4] Roberts BR, Lind M, Wagen AZ, et al. Biochemically-defined pools of amyloid-β in sporadic Alzheimer's disease: correlation with amyloid PET. Brain. 2017;140(5):1486–1498.
[5] Ossenkoppele R, Leuzy A, Cho H, et al. The impact of demographic, clinical, genetic, and imaging variables on tau PET status. Eur J Nucl Med Mol Imaging. 2021 Jul;48(7):2245–2258.
[6] Ossenkoppele R, Smith R, Mattsson-Carlgren N, et al. Accuracy of tau positron emission tomography as a prognostic marker in preclinical and prodromal alzheimer disease: a head-to-head comparison against amyloid positron emission tomography and magnetic resonance imaging. JAMA Neurol. 2021 Aug 1;78(8):961–971.
[7] Jansen WJ, Ossenkoppele R, Tijms BM, et al. Association of cerebral amyloid-β aggregation with cognitive functioning in persons without dementia. JAMA Psychiatry. 2018 Jan 1;75(1):84–95.
[8] Belfiore ACR, Oddo S. Retraction notice to "Genetically reducing mTOR signaling rescues central insulin dysregulation in a mouse model of Alzheimer's disease" [Neurobiology of Aging Volume 68, August 2018, Page 59-67]. Neurobiol Aging. 2021 Aug;104:139.
[9] Lee JH, Yang DS, Goulbourne CN, et al. Faulty autolysosome acidification in Alzheimer's disease mouse models induces autophagic build-up of Aβ in neurons, yielding senile plaques. Nat Neurosci. 2022 Jun;25(6):688–701.
[10] Lee E, Jung Y-J, Park YR, et al. A distinct astrocyte subtype in the aging mouse brain characterized by impaired protein homeostasis. Nature Aging. 2022 Oct 01;2(8):726–741.
[11] Gourmaud S, Stewart DA, Irwin DJ, et al. The role of mTORC1 activation in seizure-induced exacerbation of Alzheimer's disease. Brain. 2021;145(1):324–339.
[12] Shi Q, Chang C, Saliba A, Bhat, M.A et al. Microglial mTOR Activation Upregulates Trem2 and Enhances β-Amyloid Plaque Clearance in the 5XFAD Alzheimer's Disease Model. J Neurosci. 2022;42:27:5294–5313. DOI:10.1523/JNEUROSCI.2427-21.2022
[13] Van Skike CE, Hussong SA, Hernandez SF, et al. mTOR attenuation with rapamycin reverses neurovascular uncoupling and memory deficits in mice modeling alzheimer's disease. J Neurosci. 2021 May 12;41(19):4305–4320.
[14] Morawe MP, Liao F, Amberg W, et al. Pharmacological mTOR-inhibition facilitates clearance of AD-related tau aggregates in the mouse brain. Eur J Pharmacol. 2022 Sep;30 (934):175301.
[15] Caccamo A, Majumder S, Richardson A, et al. Molecular interplay between mammalian target of rapamycin (mTOR), amyloid-beta, and Tau: effects on cognitive impairments. J Biol Chem. 2010 Apr 23;285(17):13107–13120.
[16] Jiang T, Yu JT, Zhu XC, et al. Temsirolimus promotes autophagic clearance of amyloid-β and provides protective effects in cellular and animal models of Alzheimer's disease. Pharmacol Res. 2014 Mar;81:54–63.
[17] Jiang T, Yu JT, Zhu XC, et al. Temsirolimus attenuates tauopathy in vitro and in vivo by targeting tau hyperphosphorylation and autophagic clearance. Neuropharmacology. 2014 Oct;85:121–130.
[18] Lin AL, Zheng W, Halloran JJ, et al. Chronic rapamycin restores brain vascular integrity and function through NO synthase activation and improves memory in symptomatic mice modeling Alzheimer's disease. J Cereb Blood Flow Metab. 2013 Sep;33 (9):1412–1421.
[19] Ozcelik S, Fraser G, Castets P, et al. Rapamycin attenuates the progression of tau pathology in P301S tau transgenic mice. PLoS One. 2013;8(5):e62459.
[20] Siman R, Cocca R, Dong Y. The mTOR inhibitor rapamycin mitigates perforant pathway neurodegeneration and synapse loss in a mouse model of early-stage alzheimer-type tauopathy. PLoS One. 2015;10(11):e0142340.
[21] Spilman P, Podlutskaya N, Hart MJ, et al. Inhibition of mTOR by rapamycin abolishes cognitive deficits and reduces amyloid-beta

levels in a mouse model of Alzheimer's disease. PLoS One. 2010 Apr 1;5(4):e9979.
[22] Mucke L, Masliah E, Yu G-Q, et al. High-level neuronal expression of $a\beta_{1-42}$ in wild-type human amyloid protein precursor transgenic Mice: synaptotoxicity without Plaque Formation. J Neurosci. 2000;20(11):4050–4058.
[23] Oddo S, Caccamo A, Shepherd JD, et al. Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Abeta and synaptic dysfunction. Neuron. 2003 Jul 31;39(3):409–421.
[24] Delobel P, Lavenir I, Fraser G, et al. Analysis of tau phosphorylation and truncation in a mouse model of human tauopathy. Am J Pathol. 2008 Jan;172(1):123–131.
[25] Oakley H, Cole SL, Logan S, et al. Intraneuronal beta-amyloid aggregates, neurodegeneration, and neuron loss in transgenic mice with five familial Alzheimer's disease mutations: potential factors in amyloid plaque formation. J Neurosci. 2006 Oct 4;26 (40):10129–10140.
[26] Santacruz K, Lewis J, Spires T, et al. Tau suppression in a neurodegenerative mouse model improves memory function. Science. 2005 Jul 15;309(5733):476–481.
[27] Hassiotis S, Manavis J, Blumbergs PC, et al. Lysosomal LAMP1 immunoreactivity exists in both diffuse and neuritic amyloid plaques in the human hippocampus. Eur J Neurosci. 2018 May;47(9):1043–1053.
[28] Cataldo AM, Nixon RA. Enzymatically active lysosomal proteases are associated with amyloid deposits in Alzheimer brain. Proc Natl Acad Sci U S A. 1990 May;87(10):3861–3865.
[29] Nilsson P, Loganathan K, Sekiguchi M, et al. Abeta secretion and plaque formation depend on autophagy. Cell Rep. 2013 Oct 17;5 (1):61–69.
[30] Rubinsztein DC, Nixon RA. Rapamycin induces autophagic flux in neurons. proceedings of the national academy of sciences. Proceedings of the National Academy of Sciences of the United States of America. 2010 Dec 07;107(49):E181–E181.
[31] Harrison DE, Strong R, Sharp ZD, et al. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. Nature. 2009 Sep 01;460(7253):392–395.
[32] Majumder S, Caccamo A, Medina DX, et al. Lifelong rapamycin administration ameliorates age-dependent cognitive deficits by reducing IL-1β and enhancing NMDA signaling. Aging Cell. 2012 March 01;11(2):326–335.
[33] Bero AW, Yan P, Roh JH, et al. Neuronal activity regulates the regional vulnerability to amyloid-β deposition. Nat Neurosci. 2011 Jun;14(6):750–756.
[34] Canet G, Zub E, Zussy C, et al. Seizure activity triggers tau hyperphosphorylation and amyloidogenic pathways. Epilepsia. 2022 Apr;63(4):919–935.
[35] Baldassari S, Picard F, Verbeek NE, et al. The landscape of epilepsy-related GATOR1 variants. Genet Med. 2019 Feb;21 (2):398–408.
[36] Ulland TK, Song WM, Huang SC, et al. TREM2 maintains microglial metabolic fitness in alzheimer's disease. Cell. 2017 Aug 10;170(4):649–663.e13.
[37] Reddy K, Cusack CL, Nnah IC, et al. Dysregulation of nutrient sensing and clearance in presenilin deficiency. Cell Rep. 2016 Mar 8;14(9):2166–2179.
[38] Gao S, Casey AE, Sargeant TJ, et al. Genetic variation within endolysosomal system is associated with late-onset Alzheimer's disease. Brain. 2018 Sep 1;141(9):2711–2720.
[39] Prillaman M. Alzheimer's drug slows mental decline in trial - but is it a breakthrough? Nature. 2022 Oct;610(7930):15–16.
[40] Gonzalez C, Armijo E, Bravo-Alegria J, et al. Modeling amyloid beta and tau pathology in human cerebral organoids. Mol Psychiatry. 2018 Dec 01;23(12):2363–2374.