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Synergy between amyloid-beta and tau in Alzheimer's Disease

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ABSTRACT

Alzheimer's Disease (AD) patients present with both extracellular amyloid-beta (Aβ) plaques and intracellular tau-containing neurofibrillary tangles in the brain. For many years, the prevailing view of AD pathogenesis has been that changes in Aβ precipitate the disease process, and initiate a deleterious cascade involving tau pathology and neurodegeneration. Beyond this 'triggering' function it has been typically presumed that Aβ and tau act independently and in the absence of specific interaction. However, accumulating evidence now suggests otherwise and contends that both pathologies have synergistic effects. This could not only help explain negative results from anti-Aβ clinical trials but also suggests that trials directed solely at tau may need to be reconsidered. Here, drawing from extensive human and disease model data, we highlight the latest evidence base pertaining to the complex Aβ-tau interaction, and underscore its crucial importance to elucidating disease pathogenesis and the design of next generation AD therapeutic trials.

MAIN

Widespread deposition of amyloid-beta (Aβ) plaques in the neocortex and a hierarchically organized pattern of neurofibrillary tangles (composed largely of tau aggregates) in limbic and cortical association areas are the neuropathologic hallmarks of Alzheimer's Disease (AD). Genetic studies, indicating that mutations in the amyloid precursor protein (APP) or in enzymes that generate Aβ instigate autosomal dominantly inherited AD, clearly implicate Aβ as a critical disease initiator, but tangles are more closely related to neuronal loss and clinical symptoms[1]. Glial cell activation and neuroinflammation accompany tangles and plaques in the cortex, and, like tangles, parallel clinical symptoms[2].

The question of how plaques relate to tangles has recently come into sharp focus, with numerous clinical trials directed at reducing Aβ failing to substantially modify clinical symptoms or the course of disease despite the same therapies being largely curative in mouse models of AD that harbour a causative gene (e.g. mutant APP with or without mutant presenilin-1 (PS1); see **Box 1** for therapeutic considerations). These findings suggest that the removal of plaques *per se* is not sufficient to unequivocally improve brain function and enhance cognition, nor slow AD progression. Perhaps the most parsimonious explanation lies in the fact that such mouse models have only plaques, whereas patients in clinical trials possess plaques, tangles, and substantial neuronal/synaptic degeneration. We suggest that a deeper understanding of the interrelationship between Aβ and tau, present in the human patients but not in mice, may not only be crucial to elucidating the failure of previous therapeutic strategies and understanding AD progression, but also critical to informing the next generation of clinical trials.

Aβ and tau: cause and effect, or pathogenic interaction?

Current disease models suggest that Aβ, either as plaques, or as nonfibrillar, soluble, oligomeric forms, initiates a pathophysiological cascade leading to tau misfolding and assembly that spreads throughout

the cortex, ultimately resulting in neural system failure, neurodegeneration and cognitive decline. This 'linear' model is seemingly corroborated by observations that carriers of Aβ-enhancing genetic forms of AD (i.e., mutant APP and PS1/2, APOE4 and Down's syndrome), in which Aβ accumulates earlier in disease, are associated with a dramatic hastening in age of onset but a comparable rate of progression of clinical symptoms, relative to sporadic illness[3, 4]. However, this suggests there is an "Aβ-dependent" (impacting age of onset) and an "Aβ-independent" (impacting rate of progression) phase of disease[5]. If so, anti-Aβ therapies might be of minimal benefit to change the rate of progression once symptoms are present, the outcome measure of all current AD clinical trials.

Experimental support for this model comes from a human neural stem-cell derived 3D-culture system, in which overexpression of mutant APP and PS1 (in the absence of a tau mutation) induced Aβ and tau aggregation, with tau pathology downstream of Aβ[6]. Blocking Aβ production in cultures (using β- or γ-secretase inhibitors) prevented formation of tau pathology. Similar findings were reported in organoid brain cultures of AD-patient derived induced pluripotent stem cells[7, 8]. In the 3xTg-AD mouse model that develops both Aβ and tau pathology, plaques developed before tangles, and antibodies directed against Aβ reduced early, but not late-disease, tau alterations [9]. Interestingly, several APP models exhibit some degree of Aβ-induced tau hyperphosphorylation, especially in dystrophic neurites near plaques, and increased tau cerebrospinal fluid (CSF) levels, even in the absence of expression of a human tau transgene[10]. Additionally, β-secretase inhibition prevented the age-related increase of tau in the CSF of APP mice[11]. In contrast to the view that there is no particular interaction between Aβ and tau beyond the induction function of the former, several lines of experimental and clinical evidence now indicate that the role of Aβ is more complex, such that its presence enhances tau phenotypes throughout the disease course[12], and that the functional consequences of Aβ and tau occur in late stages of the disease[13]. This implies that the most efficacious approach to slow AD may be to combine anti-Aβ and anti-tau therapies. It is notable that anti-tau immunotherapy and antisense

therapy for tau are already in clinical trials, suggesting that combination therapies may be realistic possibilities both experimentally and clinically.

Clinical observations and insights

Plaques are initially deposited in the neocortex, in particular in medial prefrontal and medial parietal regions[14]. Cortical plaques are widespread 10-20 years before clinical symptoms emerge, and both autopsy-based and recent Aβ-positron emission tomography (PET)-studies suggest that up to 40% of cognitively normal individuals have profuse plaque deposition in the brain[15, 16]. Tau aggregates are commonly found in the medial temporal lobe after 60 years of age, probably starting in the entorhinal cortex (EC) and propagating to hippocampus (HC) and beyond to limbic and association areas as the disease progresses from an asymptomatic/preclinical phase to devastating dementia[1, 17, 18]. Notably, tau pathology can occur in isolation already in childhood (e.g. in locus coeruleus), but the significance of this finding for AD remains controversial[19]. Experimental data from multiple laboratories suggest that the anatomical pattern of tau spread may be partly explained by misfolded tau being released from neurons and taken up by connected cells, leading to tau propagation between cells that might then recruit endogenous tau to the misfolded state (referred to as the 'prion-like' properties of tau)[20]. This model has appeal as a similar phenomenon has been implicated in Parkinson's disease and other neurogenerative disorders[20, 21]. Importantly, spread of tau pathology into association cortices is associated with the presence of widespread plaques[22], suggesting that either plaques precede tangles in the cortex by chance, or that plaques act synergistically on tangles, leading to a situation in which tangle spread to the cortex is more likely.

A recent study combining resting-state functional magnetic resonance imaging (fMRI) and tau/ Aβ-PET in cognitively normal individuals reported that the likelihood of tau spread outside of the EC was augmented by the presence of cortical Aβ[23]. Further support for Aβ-dependent propagation of tau pathology into the cortex through direct neuronal connections (rather than expansion of the

pathology into neighbouring, unaffected regions), comes from another longitudinal study in which tau/Aβ-PET was combined with diffusion tensor imaging (DTI) of large fibre tracts. This study in older individuals revealed that Aβ accumulation facilitates tau spread into the posterior cingulate cortex (PCC) through the cingulum bundle, a major white matter tract that connects the HC with the cingulate gyrus[24], and that the convergence of tau and Aβ in the PCC over a 6-year period was associated with a strong decline of episodic memory (**Figure 1**). These data agree with a PET-study in cognitively normal individuals showing that Aβ-tau interaction (but not Aβ or tau alone) accelerated cognitive decline[25]. Furthermore, tau accumulation in the inferior temporal cortex of cognitively normal older individuals was accelerated in the presence of Aβ, with tau deposition related to cognitive decline during a 7-year follow-up[26]. A synergistic association between Aβ and tau predicting longitudinal memory decline was also demonstrated in a CSF biomarker study of individuals aged 50-90 years, in which total tau and phosphorylated-tau (p-tau) levels correlated with cognitive performance only when Aβ-deposition (as evidenced by low CSF Aβ) was contemporaneously present[27].

AD cognitive decline is typically preceded by several years by reduced brain glucose metabolism and regional atrophy. One longitudinal study combining Aβ, tau and fluorodeoxyglucose (FDG)-PET in cognitively normal individuals showed that the combination of cortical Aβ and tau (but not Aβ or tau individually) is associated with hypometabolism of the PCC, which in turn predicts memory decline[28]. Similarly, the interaction between Aβ-tau, but not their independent effects, was reported to drive cortical hypometabolism[29]. Moreover, neocortical and HC atrophy in cognitively normal or AD individuals was best predicted by the cooperative effects of tau and Aβ[30], and, likewise, EC atrophy in asymptomatic/mildly symptomatic individuals was strongly associated with the interaction of Aβ and tau[31]. Lastly, data from the AD Neuroimaging Initiative (ADNI) cohort has indicated tau-related cortical thinning to be robustly enhanced only in the presence of Aβ[32].

Several forms of tau might contribute to tau spreading, uptake and aggregation, and arguably lead to tau-induced toxicity. Recent human post-mortem data has demonstrated that the presence of Aβ

accelerates the formation of a rare soluble species of high-molecular weight (HMW) hyperphosphorylated tau, which in experimental studies appears to be a competent substrate for the inter-cellular spread[33]. Indeed, AD patients, exhibiting typical Aβ-plaque and tau tangle burden, were associated with increased HMW tau levels relative to individuals that exhibited equivalent tau burdens but negligible amounts of Aβ (i.e., individuals with primary age-related tauopathy, PART[17]), [12] (**Figure 1**). Similar forms of soluble oligomeric seed-competent tau have been identified by other laboratories[34]. Genetic factors, importantly, appear to modulate pathology progression across neuronal circuits. A recent study combining tau/Aβ-PET with human gene expression data provided further evidence for cooperation between Aβ and tau[35] by revealing that tau and Aβ progression are related to common gene sets associated with lipid metabolism genes, such as APOE, and also to gene ontology category-specific sets, such as dendrite-related genes for Aβ and axon-related genes for tau, and that β-secretase is as a major driver of tau propagation.

Mechanistic lessons from AD models

Evidence from multiple models and experimental settings provides strong support for Aβ-tau synergy (see **Box 2** for limitations of current animal models). In cell culture, the addition of Aβ to human cells expressing (wild-type) tau resulted, after a 5-day period, in tau aggregate formation in the form of paired helical filaments (PHF), the major components of tangles[36]. Cortical and/or hippocampal Aβ injections (both synthetic or brain-derived) into P301L-mutant tau mice accelerated tangle formation, not only near the injection site but also in synaptically-connected areas[37, 38]. Similarly, injection of human brain-derived PHFs into APP/PS1 mice (5xFAD model) enhanced cortical tau propagation compared to injections into wild-type mice[39]. Notably, PHF injection exacerbated tau pathology particularly near plaques. This latter aspect was further investigated in another study, in which HC injections of tau seeds derived from AD-brain homogenates into APP^{NL-F}-knock-in (KI) and 5xFAD mice induced tau aggregation, especially in plaque-associated dystrophic neurites, leading to the

development of 'neuritic' plaques (i.e., Aβ-deposits with associated neurofibrillary tau-dystrophic neurites)[40]. This finding was independently confirmed [41], reinforcing the idea that plaques provide a microenvironment that promotes tau aggregation and propagation, and hence disease progression.

Accordingly, multiple laboratories have reported that cross-breeding of tau and APP (with or without PS1) overexpressing mice results in enhanced tau pathological phenotypes relative to parental lines. For example, crossing APP (Tg2576 model) with tau producing P301L mice (JNPL3 model) led to dramatic acceleration of tangle formation in EC, olfactory cortex and amygdala but, remarkably, also in regions that rarely exhibit tangles in JNPL3 controls[42]. Similarly, experiments involving cross-breeding of APP23 with JNPL3 mice have demonstrated that enhanced tangle formation predominates in high plaque burden areas, consistent with results from tau-injection experiments[38]. Furthermore, the magnitude and rate of tau propagation from EC to downstream regions was augmented in rTauEC mice (which primarily express P301L-tau in layer II of medial EC) crossed with APP/PS1 mice (APPswe/PS1dE9 model), and was paralleled by enhanced cell loss[43]. Crossing the same APP/PS1 model with another P301L-tau line (rTg4510 model) accelerated the formation of p-tau, and enhanced the amount of seed-competent HMW tau, tangle number, and gliosis[12]. Importantly, recent work has indicated that extracellular soluble, but not intracellular, Aβ mediates synergistic effects on tau phenotypes[44].

While many of the studies involving cross-breeding of mouse lines have not reported alterations in Aβ characteristics, such as plaque number and biochemical measures of Aβ-40/42, there are noteworthy reports of tau increasing Aβ-pathology, suggesting that tau and Aβ may reciprocally modulate each other under certain circumstances. Indeed, in APP/PS1-rTauEC mice, plaque numbers and areas increased, and plaque-related neuritic dystrophy was enhanced, compared to APP/PS1 siblings[43]. Larger plaque areas and enhanced neuritic dystrophy were also described upon crossing APP/PS1 mice with the wild-type tau expressing rTg21221 line[45]. Furthermore, enhanced plaque burden was reported in a cross between Tg2576 mice and the VLW-tau model[46]. In contrast, cross-breeding of

5xFAD with Thy-Tau22 mice resulted in dramatic reductions in plaque burden, probably due to activation of phagocytic microglia[47]. Similar plaque reductions were also found in 12-months old APP/PS1-rTg4510 mice, with residual plaques being, surprisingly, larger in size[12]. Here, tau transgene suppression 'rescued' the decrease in plaque numbers in APP/PS1-rTg4510 mice, suggesting a direct effect of tau (or a tau related event) on plaque formation. It remains unclear how differences in Aβ pathology in the presence of tau can be explained, but variability in background strains or APP/Aβ characteristics, leading to variable microglia responses, as well as confounding effects of neurodegeneration and reduction of the APP-overexpressing cell population, may be potential mechanisms of action.

Neural system functional consequences of Aβ-tau interactions: antagonism versus synergy

Soluble Aβ causes neuronal hyperexcitability leading to impaired network oscillations, epileptiform activity, and overt seizures[48]. Multiple mechanisms, such as Aβ-dependent impaired glutamate reuptake, inhibitory GABAergic interneuron dysfunction, abnormal ion channel modulation and structural dendritic degeneration, have been reported[48, 49]. Several forms of Aβ-related hyperexcitability are dependent on endogenous tau levels, as genetic deficiency of tau confers protection against these phenotypes[50, 51]. This beneficial effect is explained by a loss of the tyrosine kinase Fyn resulting in a reduced number of postsynaptic glutamate receptors[52], thereby reducing synaptic overexcitation.

In contrast, emerging evidence suggests that tau suppresses neuronal activity independently of tangle formation. In-vivo patch-clamp and multiphoton microscopy studies have consistently reported decreased spontaneous action-potential firing of cortical neurons in rTg4510 and P301S tau mice[13, 53, 54]. In turn, several in-vitro studies have corroborated these observations and provided valuable mechanistic insights. For example, one study revealed that tau binding to synaptogyrin-3 reduces

synaptic neurotransmitter release[55], and other work in rTg4510-brain slices showed that a distal relocation of the axon initial segment reduces action potential firing[56]. Postsynaptic mechanisms, including a reduction in the number of glutamatergic receptors, have been reported[57, 58], and tau pathology appears to selectively target excitatory neurons[59]. Emerging evidence also indicates that tau suppresses nuclear transcription[60-62] and protein translation[63]. It should be noted that the presence of tau may, under certain conditions, be associated with no change of neuronal activity[64] or even hyperexcitability[65-67]. Several reasons could explain such variability, including the fact that different tau models and background strains were used, different tau concentrations (as, for example, suggested for rTauEC mice) or age-related effects, and that different laboratories used different experimental techniques and preparations.

The effect of co-expression of both APP/Aβ and tau on neuronal function was investigated in two recent studies. One study, from our laboratories[13], employed in-vivo multiphoton Ca^{2+}-imaging of cortex in APP/PS1 crossed with rTg4510 or rTg21221 mice, and revealed that Aβ-dependent neuronal hyperexcitability is blocked by the presence of tau, which instead suppresses neuronal activity (**Figure 2**). This result suggests that, from the perspective of neural circuit activation, tau and Aβ have antagonistic effects. However, further investigation importantly revealed synergistic circuit-level interactions, as tau-dependent hypoexcitability was dramatically accelerated in the APP/PS1-rTg4510 mice relative to rTg4510 siblings. Additionally, in the presence of Aβ, tau suppression was less effective in mitigating the neuronal hypoexcitability phenotype. We subsequently found that, in the presence of Aβ, tau suppression was also ineffective in reducing the numbers of activated microglia[68]. Our results are consistent with another study employing in-vitro electrophysiology[69], which demonstrated that Aβ-expression in the EC resulted in hyperexcitability, whereas tau expression led to suppression of activity. Aβ/tau co-expression also suppressed activity as the tau phenotype seemed to dominate. It is noteworthy that tau aggregates or neurofibrillary tangles were not required for the functional neuronal effects both in-vitro and in-vivo. Indeed, the finding that soluble tau species may have

greater consequences for neuronal dysfunction than insoluble fibrils is further supported by recent in-vivo Ca^{2+}-imaging experiments in P301S mice[53]. In that study, cortical injection of tau preformed fibrils to induce tangle formation in a subset of layer 2/3 neurons revealed that both tangle-containing and tangle-free cells showed a comparable suppression of spontaneous activity. Another study employing fMRI in mice demonstrated that soluble (wild-type) tau also reduces brain network functional connectivity[70], consistent with fMRI imaging of human individuals with tau pathology[71].

Synaptic plasticity and strength, in the form of long-term potentiation (LTP) and long-term depression (LTD) of excitatory synaptic transmission, has been extensively studied in AD models. One recent in-vivo study in rat HC showed that soluble Aβ and tau had antagonistic effects on LTD, with Aβ lowering the threshold for LTD induction, and tau increasing the threshold for LTD induction, but also blocking Aβ-dependent effects. The authors also reported synergistic effects on LTP, as subthreshold doses of soluble tau dramatically enhanced Aβ-dependent inhibition of LTP[72]. It is widely believed that impaired synaptic plasticity in AD promotes synapse elimination and, in the HC of the $hAPP_{SL}$/hTau model, dendritic spine loss is accompanied by accelerated memory decline and is enhanced compared to single-transgenic siblings[73]. Similarly, cross-breeding of the APP_{OSK} model with wild-type tau mice (tau264 model) resulted in an earlier onset, enhanced HC synapse loss and spatial memory impairment, relative to the APP parental strain[74]. Other functional cellular impairments, such as defects in mitochondrial function and mitophagy (i.e., degradation of damaged mitochondria), as well as impaired axonal transport, have been observed in the presence of Aβ and/or tau[75-77], and the combination of Aβ and tau has indicated synergistic effects in these cellular phenotypes[78-80]. Indeed, a synergistic reduction of mitochondrial membrane potential, ATP synthesis and respiration, as well as enhanced reactive oxygen species (ROS) production, was observed in APPxtau crosses (APP/PS2-pR5 model) when compared to each parent strain[81]. Finally, multiple studies have demonstrated that Aβ and tau interact to promote cognitive decline in mouse models. Behavioural phenotypes occur earlier and are more severe in several APPxtau crosses, compared to their single-transgenic siblings[73,

[74, 82]. Interestingly, one study has reported that co-expressing APP and mutant tau in *Caenorhabditis elegans* resulted in marked neuronal and cognitive impairment and strongly reduced lifespan relative to single transgene controls[83]. Another recent study extended this result by demonstrating that tau wild-type protein is sufficient for the synergistic effects[84].

Putative mechanisms underlying Aβ-tau synergy

Direct Aβ-tau interactions. Current data indicates that Aβ synergistic effects on tau aggregation and neuronal physiology are pervasive phenomena, since they can occur in mice before plaques and tangles substantially appear [12, 13], can be mediated by extracellular soluble Aβ [44], and be manifest in wild-type proteins, expressed at physiological levels, in humans[12]. Aβ can induce tau oligomer formation[85], with the presence of both plaques and soluble Aβ enhancing the seeding effect of PHF tau aggregates[39, 44]. In a cell-free assay, Aβ was found to directly promote tau aggregation by cross-seeding[86] and counteracted through peptide-based inhibition of a core segment of Aβ which also, surprisingly, reduced self-seeding[87]. Previous in-vitro studies have demonstrated binding and co-aggregation of Aβ and tau, and, in the intact brain, the presence of Aβ leads to tau becoming relatively protease resistant, suggesting that Aβ promotes a physical change in tau (i.e. posttranslational modifications, conformation or oligomerization)[68]. These data beg the question: are these effects due to a direct interaction, and if so, where do both species interface? Both Aβ and tau target synapses, and synapses from tau null animals are protected from Aβ damage[52]. Intriguingly, site-specific phosphorylation of tau on threonine-205 conferred a similar protection, not only contrasting the long-held view that all tau phosphorylation is detrimental, but also reinforcing the notion of tau-Aβ interactions[88]. While several studies have reported that pathological Aβ and tau aggregates can, in principle, co-localize in neurons and synaptic terminals in both human post-mortem tissue and 3xTg mice, with increased interaction in later disease stages[89], a recent quantitative array tomography study of human post-mortem tissue, as well as APP/PS1-rTg21221 mice, reported that synapses were

positive for both Aβ and (wild-type) tau in less than 0.02% of cases[61]. These data argue against a major physical interaction of both proteins at the synapse (or that the interacting species are microscopically invisible). Alternatively, Aβ and tau could interact indirectly through their impact on neuronal physiology (i.e., activating kinases, reducing tau degradation, modulating excitability and gene expression) and glial activation.

Microglia as contributors/intermediates. Genes expressed in microglia including TREM2 have emerged as major risk factors in AD, implying that the innate immune system impacts the disease process. Microglial activation is a key neuropathological feature of AD, and cases that are clinically more benign tend to have less glial activation[90]. It is well known that plaques and earlier, soluble forms of Aβ, trigger microglial activation and the release of pro-inflammatory cytokines including interleukin-1β and tumor necrosis factor-α (TNF-α), as well as ROS and nitrogen species[91]. In turn, tau overexpression drives microglial activation, even preceding tangle formation[92]. These data, along with the observation that young APP/PS1-rTg4510 mice without plaques and tangles have a synergistically enhanced tau aggregation phenotype, suggest that the phenotype may be an early consequence of microglial changes that have been directly implicated in the facilitation of tau patho-progression[93, 94]. Indeed, microglial depletion protects against tau pathology propagation from EC to dentate gyrus (DG) in the PS19 tau model and rescues tau-dependent DG hypoexcitability[95]. Microglia are capable of uptake and decomposition of seed competent tau[96], albeit ineffectively[97], and tau uptake may reciprocally lead to microglial activation. Bystanding microglia that do not take up tau, but are proximal to tau-containing neurons, may also become reactive and form aberrant somatic junctions with neurons, through which tau might be inter-cellularly transferred[98]. In human brain, microglia cluster around tangles, suggesting that microglia migrate towards the tau-positive neurons. Activated microglia may play a direct role in repackaging tau into exosomes, or an indirect role in enhancing tau phosphorylation, for example via pro-inflammatory cytokine signalling[93, 99]. However, an opposing viewpoint is not necessary mutually exclusive: activated microglia could induce neurodegeneration

leading to tau hyperphosphorylation and aggregation as a consequence of the neuronal injury[100]. Tau mice lacking the 'anti-inflammatory' microglial protein CX3CR1 show enhanced microglial activation and accelerated onset and progression of tau pathology[93, 99]. However, microglia might also neutralize Aβ or toxic tau species, acting to delay propagation and neurodegeneration, since TREM2 deletion and secondary loss of plaque-associated microglia enhanced tau pathology seeding and spreading, suggesting that TREM2 mitigates tau pathology by directing microglia to contain plaques[41]. In 5xFAD/Thy-Tau22 crosses there was a strong increase in microgliosis, astrogliosis and cytokine production[47], while APP/PS1-rTg4510 mice did not exhibit increased microglia numbers *per se*[12] but more active microglia phenotypes compared to the rTg4510 parental line. Genes related to the complement system, implicated in aberrant synapse pruning in AD[101], were synergistically upregulated in APP/PS1-rTg21221 mice when compared to their single-transgenic siblings[61]. Interestingly, in the APP/PS1-rTg21221 line, the upregulation of inflammatory markers expressed by microglia was reduced by tau suppression, suggesting that tau might in fact contribute to increased inflammatory response nominally attributed to Aβ. While the above data position microglia as potential intermediaries of Aβ-tau synergy (**Figure 3**), additional research is needed to determine whether, and to what extent, differing mouse-model genetic backgrounds impact on microglial activation profiles and tau propagation patterns. Finally, we note that astrocytes and oligodendrocytes may also play a role in the glial response to tau since they can take up tau, and tau fibrils are known to accumulate in astrocytes (and oligodendrocytes) in several tauopathies[102, 103].

Neuronal activity changes. As highlighted, Aβ causes neuronal hyperexcitability, which in turn enhances Aβ pathology, in what could be a vicious cycle promoting early abnormal Aβ-deposition in the brain. Additionally, there seems to be a positive correlation between (untreated) chronic epilepsy and the extent of tau pathology in the brain[104]. Indeed, neuronal hyperactivity enhances tau secretion from neurons, and secreted tau can be internalized by recipient cells, where it subsequently seeds additional tau. In rTg4510 mice, optogenetic HC activation resulted in increased tau pathology and cell

loss in the stimulated region[105]. Increased tauopathy following neuronal stimulation was also found in rTauEC mice after 6 weeks of chemogenetic EC activation[105], and stimulation of tau-expressing subiculum and EC enhanced tau spreading to distal, anatomically connected, regions[106]. In APP-J20/rTauEC crossed mice, 6 weeks of chemogenetic inhibition of EC, itself in a hyperexcitable state owing to mild Aβ pathology, resulted in reduced propagation of tau pathology towards DG and HC[107]. Hyperexcitability enhances Ca^{2+}-influx into neurons leading to downstream Ca^{2+}-elevations that can aberrantly stimulate signalling cascades, including the activation of protein kinases and calcineurin-mediated pathways (**Figure 4**). Their activation can mediate local synaptic changes and post-translational modifications of tau and other proteins, and also modify nuclear gene expression[108]. Data from APP/PS1-rTg2122 mice, suggesting that Aβ synergistically enhances tau-dependent downregulation of neuronal and synaptic genes[60-62] are consistent with this notion, and may explain the observed accelerated hypoexcitability phenotype[13] (**Figure 4a,b**). Interestingly, while tau suppression prevented further downregulation of those genes, it did not restore normal gene expression levels in APP/PS1-rTg21221 mice[61]. Other downstream consequences of abnormally elevated neuronal Ca^{2+}, including mitochondrial dysfunction, impaired synaptic transmission and plasticity, as well as oxidative stress, have been extensively reviewed elsewhere[5, 109].

Additional modifiers of Aβ-tau synergy. Several additional processes likely modulate Aβ-tau interactions, including vascular changes (**Box 3**), ageing (**Box 4**), lipid metabolism, myelination, vesicle trafficking, autophagy, proteasome function, endosomal transport and mitochondrial function, since at least some experimental data are suggestive of both independent and interacting effects of Aβ or tau on each of these processes. Indeed, lipid-metabolism related genes are related to the spread of both Aβ and tau pathology in human AD[35], and recent tau/Aβ-PET revealed a synergistic interaction between APOE4 status and Aβ levels on tau burden in the brain, as well as levels of p-tau in CSF, with the strongest effects seen in homozygous APOE4 carriers[110]. The LDL-receptor-related-protein 1 (LRP1) appears ideally positioned to modify Aβ-tau synergy, since it can not only bind tau and mediate

its neuronal uptake and spread, but also interact directly with APP, Aβ and APOE4, thereby regulating Aβ production and clearance[111, 112]. Another receptor recently implicated in Aβ-tau synergy is the cellular prion protein, which is upregulated in several Aβ/tau models[44, 61] and, importantly, also in human AD brains, particularly in those exhibiting cognitive decline[47]. Soluble Aβ and tau (and also α-synuclein, itself enhanced in the presence of Aβ[113] and capable of cross-seeding tau in-vitro and in-vivo[114]) can directly bind to the prion receptor, leading to impaired synaptic plasticity and neurite degeneration[115], and activation of kinases including Fyn, which itself can enhance tau phosphorylation. Finally, even nanomolar amounts of Aβ can shift α_{2A}-adrenergic receptor signalling towards enhanced activity of the 'tau kinase' glycogen synthase kinase (GSK)-3β, resulting in enhanced tau phosphorylation[116]. Blockade of α_{2A}-receptors in APP/PS1 and APP-KI mice reduced Aβ-burden, diminished microglial activation and tau hyperphosphorylation (in particular in the plaque microenvironment), and enhanced cognition. These studies underscore the complex relationships between variant molecular, cellular and systemic (disease) mechanisms, and suggest that distinct disease manifestations (i.e., tau propagation or circuit dysfunction) cannot be explained in isolation, but are instead rooted in complex interactions that recurrently impact neural systems.

Conclusions and future directions

Therapeutic development in AD has been entrenched in the notion that Aβ and tau are co-existing species that are temporally, but not synergistically, related. However, compelling experimental and clinical data have emerged which supports a co-pathogenic interaction between Aβ and tau in AD, that not only manifests throughout the disease course, but also fundamentally drives disease progression. It is therefore tempting to speculate that reconceptualizing AD in terms of Aβ-tau synergy may provide a vital therapeutic context (**Box 1**) in which to rationalize past failures and inspire future successes. Nevertheless, it is clear that our knowledge of Aβ-tau synergy remains in its infancy with several outstanding unknowns, including the aetiology of within-model inconsistencies or the

contributory role of other critical processes such as glial activation, that must be explained before the complexities of a decades long evolution of neurodegeneration can be modelled under such a framework. Moreover, further insight is needed into how additional biological variables, including vascular changes (**Box 3**) and ageing-related processes (**Box 4**), among others, can modulate Aβ-tau synergy, and a major challenge will be to disambiguate mechanisms most critical to Aβ-tau synergies (and their downstream effects such as accelerated tau propagation and neural circuit impairment) from those playing only minor supporting roles. Experimental strategies that allow finely tuned loss or gain of function manipulations in candidate cell types, such as microglia, in combination with monitoring of cellular functional states and tracking of pathological protein species with sensitive biosensors, will be crucial to elucidating their precise role in the context of Aβ and tau modes. Parallel transcriptomic profiling of cell populations (e.g. by means of *in-situ* sequencing) will also enable complementary molecular insights, and drive translational discoveries by linking animal model readouts to human data. As always, translating animal-derived findings, especially those relying on overexpression models, to a clinical context, must be carried out judiciously and tempered by firm consideration and anchoring to human data. As a result, we will need animal (and cellular) models to more realistically capture the spatiotemporal evolution of Aβ and tau pathology and other hallmarks of AD, and which allow incorporation of the complex genetic and environmental variables that modify disease phenotypes (**Box 2**). We will also need to better consider how other pathological proteins (e.g., α-synuclein and/or TDP-43) and pathologies (e.g., cerebrovascular disease and/or hippocampal sclerosis), that are often present in the aged AD brain, can potentiate the synergistic interactions between Aβ and tau. Such progress should therefore extend beyond biological models into the realm of in-silico approaches, in which existing and novel data-sets, themselves reciprocally informed by computational read-outs, may be fully exploited to confirm and identify new mechanistic pathways. Since most real-world systems are inherently non-linear, we must move away from our focus on linear solutions, such as triggers and 'silver-bullets', in order to meet the challenge of understanding a disorder as complex as AD. In this regard, computational tools such as machine-learning will no doubt

prove invaluable and, in combination with continued development of fine-resolution in-vivo imaging technologies, will help to establish which, and to what extent, variant disease processes can be targeted and modulated. Ultimately, while much is yet to be elucidated, Aβ-tau synergy has been sign-posted by the burgeoning evidence base to be a prime candidate for further investigation.

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AUTHOR CONTRIBUTIONS

M.A.B. and B.T.H. conceived the original idea and wrote the paper.

COMPETING INTERESTS

The authors declare no competing interests related to this project.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this review article as no datasets were generated.

CODE AVAILABILITY STATEMENT

No custom code was used in this review.

FIGURE LEGENDS

Figure 1: Aβ plaques accelerate tau spreading and cognitive decline in human AD

Top panel, Tau tangles (*red*) in the absence of concurrent cortical plaques are present in brain stem nuclei (e.g., locus coeruleus) and the parahippocampal gyrus, which includes the EC, of many cognitively normal aged individuals (i.e., those with primary age-related tauopathy). In AD, the presence of cortical plaques (*blue*) correlates with neuronal tau propagation from the parahippocampal gyrus into neocortical areas, including medial parietal and medial prefrontal cortex[18, 24]. *Bottom panel*, human AD cases with plaques and tangles show a dramatically enhanced formation and propagation of bioactive, high molecular weight (HMW) forms of tau (*right box*) relative to human cases with tangles alone (*left box*)[12].

Figure 2: The interaction between Aβ and tau enhances neural circuit impairment

Compared to the healthy brain (*left*), the cellular microenvironment adjacent to plaques (*middle*) is characterized by hyperactive neurons, microglia activation and spine loss (inset). The impairments are largely reversible following suppression of Aβ or endogenous tau. In-vivo multiphoton imaging has revealed that the combined presence of Aβ and tau pathology in the neocortex (*right*) is associated with suppressed neuronal activity, as well as enhanced microglia activation and spine loss[13, 73]. Suppression of Aβ or tau pathology alone is not effective in rescuing these functional impairments.

Figure 3: Microglia may be critical intermediates of Aβ-tau synergy

Depicted are mechanisms by which microglia might contribute to enhanced bioactivity and spreading of tau in the presence of Aβ. Soluble Aβ and other factors, such as release of cytokines by senescent oligodendrocytes near plaques[117], can activate microglia. Activated microglia may take up tau, process it and release it in a more bioactive form. Neurons may take up released tau (possibly through an interaction with LRP1[112]), and in turn release tau into the neuropil in an activity-dependent manner.

Neuronal activity is enhanced by multiple mechanisms including Aβ-mediated block of glutamate re-uptake[49], impaired synaptic inhibition[48], or BBB-breakdown resulting in extravasation of neurotoxic products (e.g. albumin, illustrated) and activation of astrocytic TGF-β signaling[118, 119]. Additional mechanisms by which microglia might contribute to tau seeding and propagation include the release of cytokines, chemokines and NO that enhance tau phosphorylation, and perhaps direct transfer through microglia-neuron somatic junctions[98]. Note that Aβ can also directly seed tau[85, 86].

Figure 4: Aβ and tau pathways may converge at the level of gene expression

a) Transcriptional dysregulation in crossed APPxtau models (green trace) exceeds that observed in APP (moderate gene changes, red trace) or tau (mild gene changes, blue trace) mice, and outstrips that which would be expected from the combined effect of APP and tau (black dashed trace), suggesting Aβ-tau synergy at the level of gene expression[61]. **b)** While gene upregulation in APPxtau models is concordant with that in either APP or tau mice, APPxtau models exhibit increased downregulation of genes compared to APP or tau models alone (black arrow), indicating an interaction between Aβ and tau in downregulating gene expression[61]. **c)** Aβ-mediated glutamate re-uptake blockade results in increased action-potential firing[49], which is associated with an influx of Ca^{2+} via L-type voltage gated Ca^{2+}-channels (L-VGCC). Other sources of Ca^{2+}-influx are Ca^{2+}-permeable AMPA and NMDA receptors, and Ca^{2+}-release from internal stores (e.g., endoplasmic reticulum, ER). Ca^{2+}-elevations stimulate a signalling cascade, which includes the activation of the Ras-mitogen-associated protein kinase (MAPK), Ca^{2+}/calmodulin-dependent protein kinases (CaMK), and calcineurin-mediated signalling pathways that have multiple effects, ranging from posttranslational modifications of proteins (e.g. tau) and alterations in cell surface trafficking of neurotransmitter receptors, to the initiation and modulation of transcriptional cascades. Tau itself modulates transcriptional activity via multiple mechanisms including impairment of nucleocytoplasmic transport and dysregulation of transposable elements[120, 121]. In addition, tau acts as a critical intermediate of Aβ-induced overexcitation by Fyn-dependent stabilization of NMDA receptors, and Fyn activation can

independently promote the local translation and phosphorylation of tau[52]. Aβ-mediated NMDA receptor overactivity as well as stimulation of α_{2a}-receptors leads to activation of GSK3-β[116].

Box 1: Therapeutic implications – when does the effect of Aβ on tau occur, and is it reversible?

Evidence suggests that HMW tau load, tangle burden, and tau uptake/aggregation activity are increased in APP/PS1-rTg4510 mice compared to rTg4510 siblings, but only at earlier disease stages (4-6-months), and not in older animals (12-months) that have fully established plaques and tangles[12]. This age-dependent disparity in tau bioactivity raises the possibility that pathological tau processes ultimately become Aβ-independent, and suggests that Aβ reduction could slow the rate of tangle formation, propagation and neurodegeneration in early, but not necessarily later, phases of AD. Few studies have examined the role of anti-Aβ therapy in the context of Aβ/tau models, but are consistent with the idea of an Aβ-dependent and independent phase[5]. In the 3xTg model that has both APP and tau overexpression, antibodies directed against Aβ reduced early tau alterations, but not at later stages of the disease due to the clearance of tau pathology being dependent on its phosphorylation state[122]. Anti-oligomeric Aβ-antibodies were also effective in reducing plaques and tau hyperphosphorylation, and microglia activation, and improved cognition in the same mouse line[123] - a likely prophylactic effect taking place prior to substantial tau accumulation. Similarly, early active immunization against Aβ also prevented Aβ and tau accumulation in the 3xTg model[124]. Whether anti-Aβ treatment alone can rescue neuronal dysfunction in mice that have established plaque and tangle pathology has not been tested, but is, in our opinion, unlikely, given that the combination of Aβ and tau leads to a phenotype that is different than Aβ alone, and which is dominated by tau-dependent neuronal silencing[13]. Indeed, tau suppression was incapable of rescuing tau-dependent neuronal silencing in two APPxtau models (at least during the 6 weeks of applied treatment)[13], and was unable to reduce the number of tau-positive neurons in 12-month APP/PS1-rTg4510 animals to the level seen in treated rTg4510 mice, despite similar decreases in levels of soluble tau[68]. These studies reinforce the notion of Aβ-tau synergy and indicate that combined anti-Aβ and anti-tau therapies may be the most effective way to improve neuronal function (by reducing Aβ effects, and also decreasing tau

formation and increasing its rate of clearance). Moreover, since tau is more stable in the presence of Aβ, with both a presumed longer half-life and increased bioactivity[68], a combinatorial therapeutic approach implemented at early stages of the disease would exploit the inverse relationship between rate of tau turnover and presence of Aβ and in which therapeutic tau clearance would be reciprocally enhanced by concurrent anti-Aβ therapy.

Box 2: Limitations of existing models to study Aβ-tau interactions

A caveat concerning all animal studies pertains to their technical limitations and correspondence to human AD. The typical approach in aforementioned studies has been to combine overexpressing models of mutant APP and tau. Recent advances have included the development of more 'physiological' non-overexpressing models (e.g., KI models but also wild-type mice injected with human AD-derived proteins), but while APP-KI models are in widespread use, tau-KI mice have only recently become available[125]. It will thus be important to continuously validate new models against evolving genetic, molecular, cellular and circuit findings from humans. A related issue of note, with regard to currently available tau models, is the fact that many of these mice overexpress frontotemporal dementia-related mutant tau (e.g., P301L-tau) which, although leading to tangle formation, has different structural and functional properties than those associated with tau found in human AD. Furthermore, transgene insertional effects may also confound the observed tauopathy-like phenotypes in transgenic models[126]. It is, however, reassuring that crosses between APP models and mice that have regulatable wild-type tau overexpression (e.g., rTg21221 model) show similar synergies between Aβ and tau[13, 61]. Furthermore, mutant APP overexpression, and to a lesser extent the Swedish mutation in APP-KI mice, is not only associated with an overproduction of Aβ, but also of other APP-derived fragments, such as β-CTF, which may have Aβ-independent effects on tau phenotypes. Finally, transgenes in several crosses (e.g., Tg2576/JNPL3 or APP23/JNPL3) are not driven by the same promoter, which may lead to differential transgene dosage and/or spatiotemporal expression that, together with differences in background strains and the limited lifespan of rodents, should be considered when interpreting results.

Box 3: Vascular contributions to Aβ-tau synergy

Vascular impairment may be an early phenomenon in AD, preceding neurodegeneration and cognitive decline[127]. That vascular abnormalities accompany plaques and tangles in AD appears to be rather the norm than the exception, and experimental studies support the idea that vascular dysregulation, capillary inflammation and blood-brain barrier (BBB) disruption are important phenotypes in both Aβ and tau models. Decreased cerebral blood flow is commonly observed in AD[127] and cerebrovascular hypoperfusion may exacerbate synergistic neuropathological changes in the disease. For example, experimentally-induced hypoperfusion promotes Aβ oligomerization in wild-type rodents[128] and facilitates Aβ aggregation and plaque deposition in APP mice[129], whilst also enhancing tau hyperphosphorylation in wild-type rodents and 3xTg mice[130]. In turn, Aβ exerts, presumably pericyte-mediated, vasoconstrictive effects[131] and tau pathological changes can induce cerebrovascular remodeling[132], blood vessel abnormalities[133] and BBB breakdown[134]. Pericyte degeneration, oft-observed in AD, leads to increased Aβ levels and the atypical development of tau pathology and neurodegeneration that is nominally absent in APP mice[135]. Moreover, perivascular mechanisms may contribute to tau clearance, similar to that proposed for Aβ, and both may slow down in ageing (**Box 4**) and AD. BBB breakdown is also a part of normal ageing and is exacerbated in cases with cognitive impairment, independent of Aβ or tau[136]. Two recent studies have shown that the age-dependent impairment of the BBB can initiate neuronal hyperexcitability and seizures via activation of astrocytic transforming growth factor (TGF)-β receptors by albumin and possibly other blood-derived substances[118, 119]. Also, systemic inflammation induces neuronal hyperexcitability mainly through CC chemokine ligand-2 production from the PDGFRβ-positive mural cells of blood vessels (rather than microglia or astrocytes)[137]. Other changes in the systemic circulation including plasma proteins, microbial metabolites and immune cells, can have pleiotropic effects on virtually all cell types in the brain and thereby contribute to age- and disease-related brain dysfunction[138]. Finally, cardiovascular risk factors are also risk factors for AD, and poor cardiovascular health is related to accelerated

cognitive decline. For example, we are intrigued by a recent Aβ/tau-PET study in cognitively normal individuals, which demonstrated that the combination of high vascular risk (i.e. high blood pressure, presence of diabetes, high body mass index and smoking) and high brain Aβ burden dramatically enhanced tau pathology in the medial temporal lobe[139]. These data and others implicate cerebrovascular (dys-) function in AD as a potential key player in shaping Aβ-tau synergy, although the temporal placement of vascular impairment in the context of that synergy, and the detailed mechanism of the synergistic effects, remain to be determined.

Box 4: Ageing-related pathophysiology

Ageing has been categorized into several overlapping cellular and molecular processes, including DNA damage, epigenetic changes, loss of protein homeostasis, mitochondrial and lysosomal dysfunction, altered stress response, Ca^{2+}-dyshomeostasis, immune dysregulation, reduced neurogenesis, aberrant network activity, dysregulated energy metabolism, cellular senescence, telomer attrition and impaired circadian rhythms[140]. The role of ageing in neurodegenerative disease, and its impact on Aβ and tau, has been reviewed comprehensively elsewhere[140, 141], and here we can only highlight selected aspects:

DNA damage/impaired DNA repair. Nuclear and mitochondrial DNA damage is common and is counteracted, under normal conditions, by an extensive repair system. With age, and in the context of neurodegenerative disease, these repair mechanisms weaken and lead to accumulation of oxidative DNA damage. DNA damage has been linked to suppressed expression of essential genes associated with synaptic plasticity, vesicular transport and mitochondrial function[142]. Neuronal hyperactivity and excessive glutamatergic activity can damage DNA[143]. Both Aβ and tau also promote DNA damage, and modulation of DNA repair can alter the toxicity of these proteins[120]. We are intrigued by a report of increased neuronal dysfunction and loss, as well as cognitive deficits, in a cross between the 3xTg model and one with (moderately) defective DNA repair, and which implicates DNA damage as a contributor to Aβ-tau interactions[144].

Cellular senescence. Senescent cells, which are characterised by the expression of proteins p21 and $p16^{INK4A}$ as well as arrested cell proliferation, resistance to apoptosis, and production of a senescence-associated secretory pathway (SASP) that includes many proinflammatory cytokines, accumulate in aged brain tissue. A recent study has shown that tauopathy in PS19 mice promotes the accumulation of $p16^{INK4A}$-positive senescent astrocytes and microglia, and that clearance of the senescent cells, either through genetic manipulations or with a senolytic compound, blocks glial activation, tau hyperphosphorylation and tangles, as well as neurodegeneration[145]. Another study has described

senescence-associated genes to be upregulated in tangle-containing neurons of rTg4510 mice, and that removal of senescent neurons reduced tangle burden, neuronal loss, and the observed ventricular enlargement[146]. Finally, repeated back-crossing of pR5 tau mice onto a senescence-accelerated SAMP8 background accelerated pathological tau phosphorylation compared with the parent strain[147]. Remarkably, and in contrast to tau, Aβ triggers senescence of oligodendrocyte precursor cells, and senescent oligodendrocytes accumulate near plaques[117].

Chronic inflammation. It is increasingly clear that inflammation is not only reciprocally linked to the accumulation of Aβ and tau in the brain, but that normal ageing is also associated with immune activation and cell infiltration in the brain. Genes related to cellular stress and inflammation increase with age, whereas genes related to synaptic function, growth factors, and trophic support, decrease, possibly as a result of increased DNA damage with ageing[142]. There is an age-related upregulation of proinflammatory cytokines and concomitant downregulation of anti-inflammatory cytokines in the systemic circulation[138]. Microglia become progressively activated with increasing age, and not only do they begin producing ROS and secreting pro-inflammatory cytokines (e.g., interleukin-1β, interleukin-6 and TNF-α), but also lose the ability to phagocytose, possibly triggered by the formation of lipid droplets in the cells[148]. It is thus possible that young brains are predisposed to microglia-mediated tau-uptake and phagocytosis, in contrast to older brains where tau may persist in the neuropil and be more likely to be taken up by neurons. The complement cascade is also, notably, enhanced during ageing, and profoundly upregulated in the presence of both Aβ and tau[61], with the exaggerated activation potentially contributing to synapse loss in neurodegenerative disease[101].

Hyperexcitability and Ca^{2+}-dyshomeostasis. Ageing promotes neuronal hyperexcitability[149] and enhanced Ca^{2+}-influx into neurons (e.g., through increased expression of L-type voltage-gated Ca^{2+}-channels) and release from internal stores, and prolonged Ca^{2+}-recovery kinetics following stimulation. Dysregulation of Ca^{2+}-homeostasis can further promote mitochondrial dysfunction, impaired synaptic transmission and plasticity and oxidative stress, and thereby contribute to age-related cognitive impairment. Impaired Ca^{2+}-buffering, reduced expression of Ca^{2+}-binding proteins,

and reduced Ca^{2+}-extrusion mechanisms, likely contribute to such impairments. Ca^{2+}-dysregulation and its secondary processes can directly affect tau phosphorylation, APP processing and lysosome function, and, in turn, tau and Aβ have been shown to further aggravate Ca^{2+}-dyshomeostasis[109]. Impaired Ca^{2+}-handling by aged neurons renders them more vulnerable to the effects of hyperexcitability. Interestingly, an age-dependent increase in intracellular Ca^{2+} has also been described in microglia, which may subsequently enhance Ca^{2+}-dependent processing and release of proinflammatory cytokines and nitric oxide which can cause oxidative damage to neurons[150].

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Figure 1

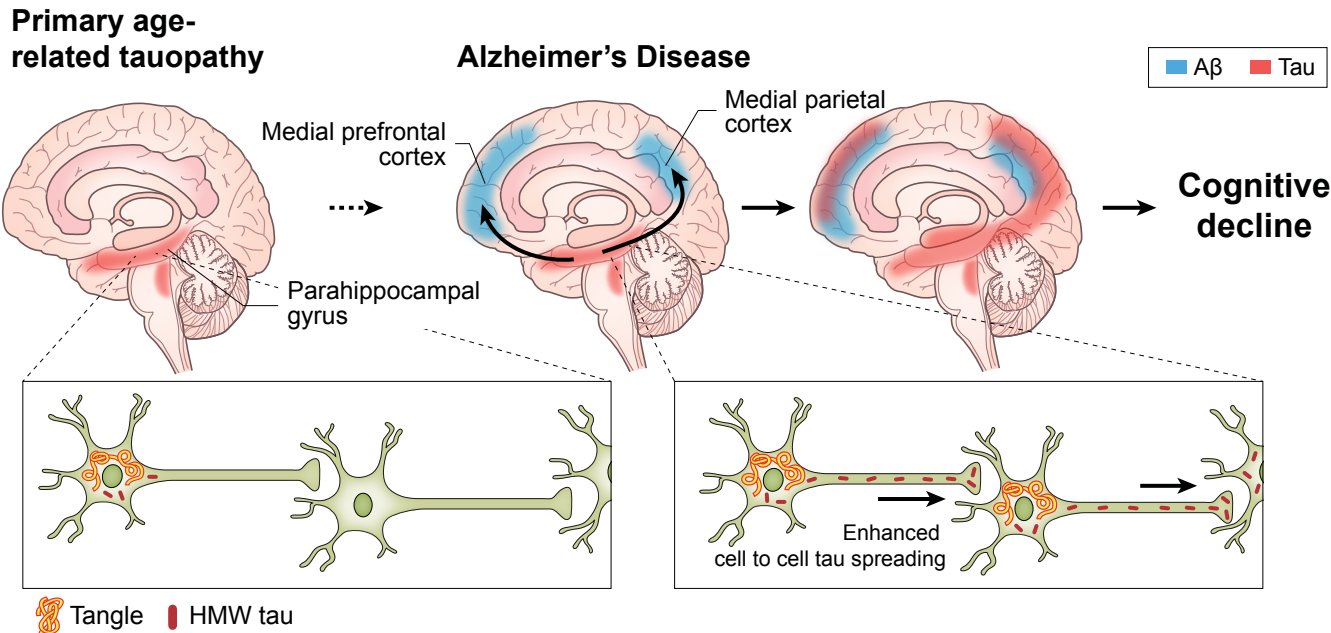

Primary age-related tauopathy
Alzheimer's Disease
Aβ
Tau
Medial prefrontal cortex
Medial parietal cortex
Parahippocampal gyrus
Cognitive decline
Enhanced cell to cell tau spreading
Tangle
HMW tau

Figure 2

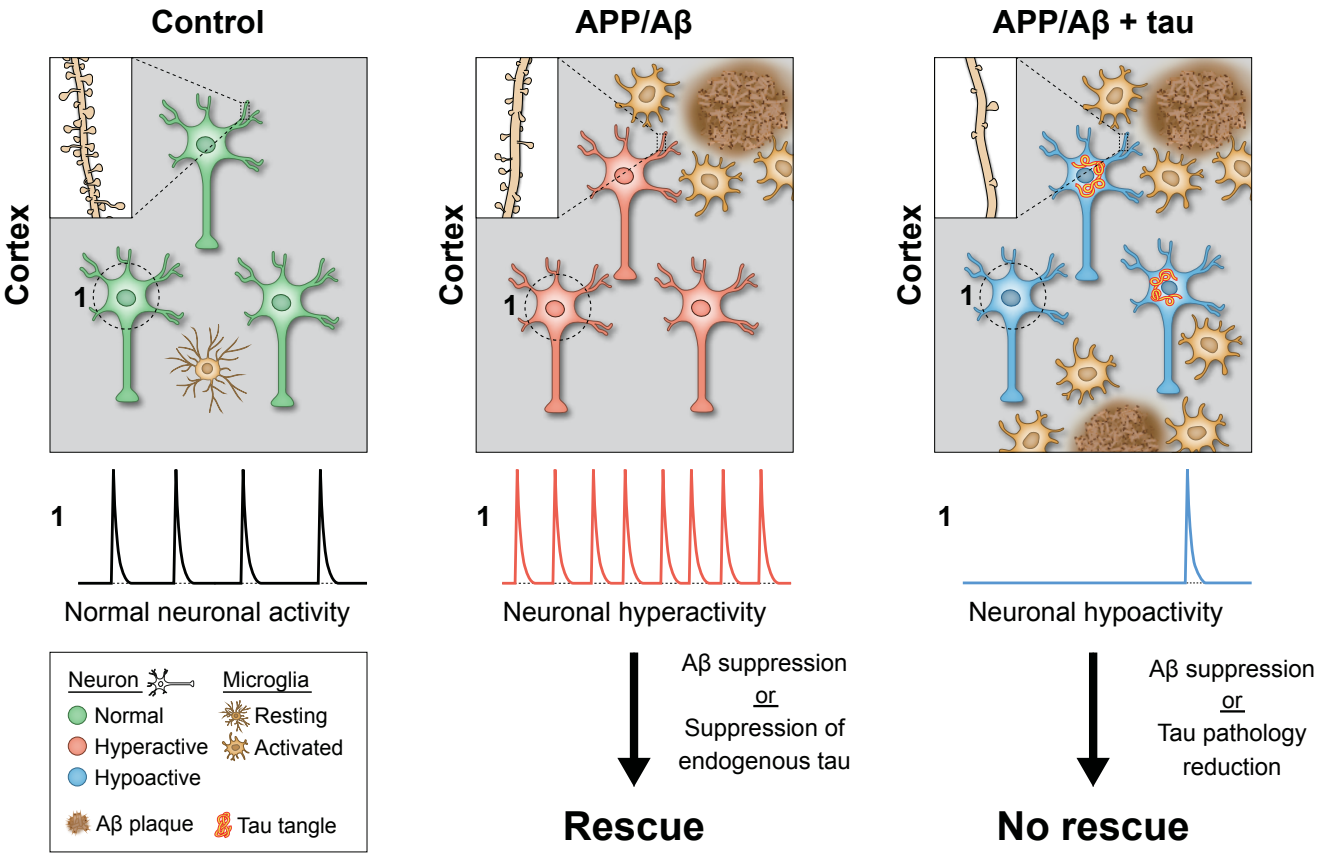

Control
APP/Aβ
APP/Aβ + tau
Cortex
1
Normal neuronal activity
Neuronal hyperactivity
Neuronal hypoactivity
Neuron
Normal
Hyperactive
Hypoactive
Microglia
Resting
Activated
Aβ plaque
Tau tangle
Aβ suppression
or
Suppression of endogenous tau
Rescue
Aβ suppression
or
Tau pathology reduction
No rescue

Figure 3

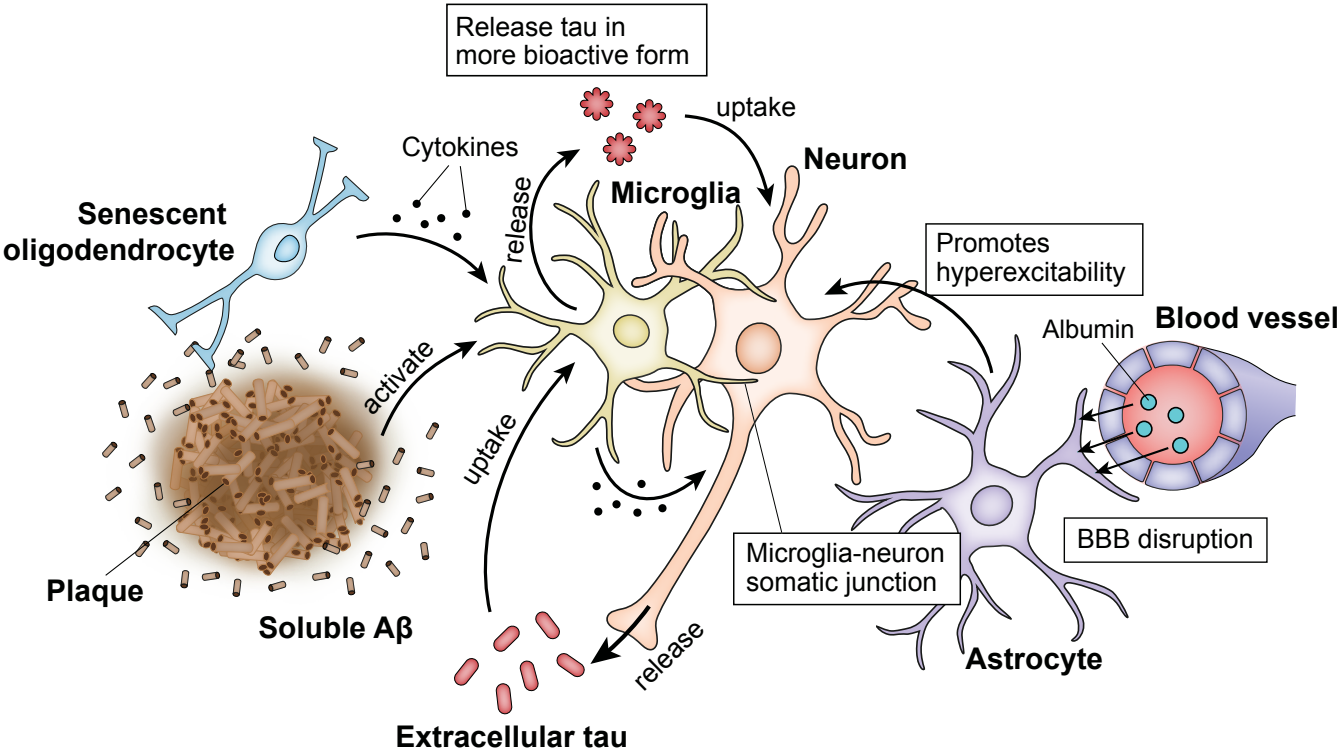
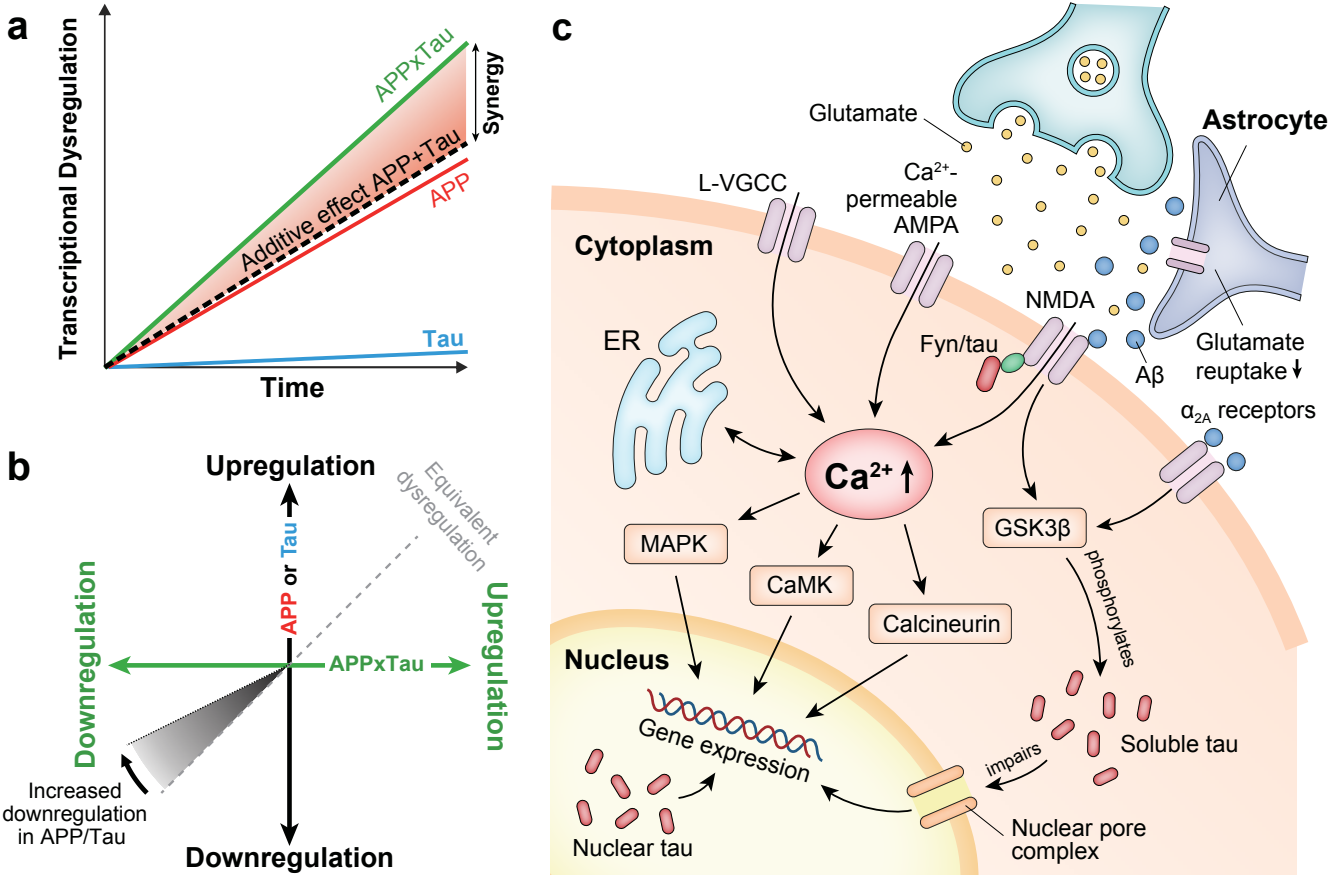

Release tau in more bioactive form
uptake
Neuron
Cytokines
release
Microglia
Senescent oligodendrocyte
Promotes hyperexcitability
Albumin
Blood vessel
activate
uptake
Microglia-neuron somatic junction
BBB disruption
Plaque
Soluble Aβ
release
Astrocyte
Extracellular tau

Figure 4


a
Transcriptional Dysregulation
APPxTau
Synergy
Additive effect APP+Tau
APP
Tau
Time
b
Upregulation
Equivalent dysregulation
APP or Tau
Downregulation
APPxTau
Upregulation
Increased downregulation in APP/Tau
Downregulation
c
Glutamate
Astrocyte
L-VGCC
Ca2+-permeable AMPA
Cytoplasm
NMDA
ER
Fyn/tau
Glutamate reuptake
Aβ
α2A receptors
Ca2+
MAPK
GSK3β
CaMK
Calcineurin
phosphorylates
Nucleus
Gene expression
impairs
Soluble tau
Nuclear tau
Nuclear pore complex