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Review in Depth

Interrogating the Etiology of Sporadic Alzheimer's Disease Using Aging Rhesus Macaques: Cellular, Molecular, and Cortical Circuitry Perspectives

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Abstract

Aging is the most significant risk factor for neurodegenerative disorders such as Alzheimer's disease (AD) associated with profound socioeconomic and personal costs. Consequently, there is an urgent need for animal models that recapitulate the age-related spatial and temporal complexity and patterns of pathology identical to human AD. Our research in aging nonhuman primate models involving rhesus macaques has revealed naturally occurring amyloid and tau pathology, including the formation of amyloid plaques and neurofibrillary tangles comprising hyperphosphorylated tau. Moreover, rhesus macaques exhibit synaptic dysfunction in association cortices and cognitive impairments with advancing age, and thus can be used to interrogate the etiological mechanisms that generate neuropathological cascades in sporadic AD. Particularly, unique molecular mechanisms (eg, feedforward cyclic adenosine 3′,5′-monophosphate [cAMP]-Protein kinase A (PKA)-calcium signaling) in the newly evolved primate dorsolateral prefrontal cortex are critical for persistent firing required for subserving higher-order cognition. For example, dendritic spines in primate dorsolateral prefrontal cortex contain a specialized repertoire of proteins to magnify feedforward cAMP-PKA-calcium signaling such as *N*-methyl-D-aspartic acid receptors and calcium channels on the smooth endoplasmic reticulum (eg, ryanodine receptors). This process is constrained by phosphodiesterases (eg, PDE4) that hydrolyze cAMP and calcium-buffering proteins (eg, calbindin) in the cytosol. However, genetic predispositions and age-related insults exacerbate feedforward cAMP-Protein kinase A-calcium signaling pathways that induce a myriad of downstream effects, including the opening of K^+ channels to weaken network connectivity, calcium-mediated dysregulation of mitochondria, and activation of inflammatory cascades to eliminate synapses, thereby increasing susceptibility to atrophy. Therefore, aging rhesus macaques provide an invaluable model to explore novel therapeutic strategies in sporadic AD.

Keywords: Aging, Alzheimer's disease, Calcium, Pyramidal cells, Tau

Aging represents the primary risk factor for neurodegenerative disorders such as Alzheimer's disease (AD). Epidemiological studies have revealed that ~10% of individuals over the age of 65 develop AD, and the prevalence increases significantly with advancing age and is associated with cognitive impairment. The rising prevalence of AD is compounded by a rapidly aging population and is predicted to impose a huge financial burden on healthcare systems globally. As a result, there is an urgent need to develop effective preventative therapeutic strategies to ameliorate cognitive decline with advancing age to augment health span and quality of life.

The neuropathological hallmarks of AD include extracellular deposits of amyloid Aβ plaques and intracellular neurofibrillary tangles (NFTs) comprising hyperphosphorylated tau. Current hypotheses postulate that these pathological phenomena are interconnected, as Aβ oligomers can drive tau phosphorylation (1–3), and accumulations of phosphorylated tau may increase the production of Aβ (4,5), thus establishing vicious cycles that lead to the hallmark toxic phenotypes and the destruction of synapses that mediate memory and cognition. Human AD studies have revealed that cognitive deficits correlate with NFTs, but not Aβ plaques (6), suggesting that understanding the etiology of tau phosphorylation and how it emerges in the aging association cortex is particularly critical in elucidating the pathogenesis of AD. Tau normally serves to assemble and stabilize microtubules (7,8), but with increasing phosphorylation, tau detaches from microtubules and aggregates, and with hyperphosphorylation, fibrillates within dendritic shafts to form NFTs that then proceed to invade the cell soma. The neuron eventually dies from autophagic degeneration, leaving a "ghost tangle" (reviewed in (5)).

Classic neuroanatomical studies have revealed that tau pathology in AD shows a stereotypic progression across the cortical hierarchy. Tau pathology preferentially affects glutamatergic neurons in the limbic and association cortices, beginning in the perirhinal and entorhinal limbic cortices, and proceeding to the neocortical association areas with advanced age, but only afflicting neurons in the primary sensory cortex at end-stage disease (9–12). A growing body of literature supports the notion that phosphorylated tau in AD and other tauopathies can traffic between neurons to propagate along anatomically connected cortical networks via excitatory

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synapses (13–22). Understanding the selective vulnerability of these highly interconnected glutamatergic neurons remains an ongoing area of investigation in the field and might provide critical signs regarding cell-type specificity of neuropathology in AD.

Nonhuman primates (NHPs) have provided an invaluable model system to probe the neurobiology underlying amyloid and tau pathology in AD. Particularly, aging NHPs provide an opportunity to examine the generation of tau pathology in its native course in sporadic AD in the absence of familial, autosomal dominant mutations. There are striking differences in the magnitude of AD-related neuropathology across NHP species (eg, marmosets, vervets, rhesus macaques, chimpanzees) along the evolutionary lineage, and it is intriguing to note that the extent of pathology correlates with the expansion of the association cortex across species reaching a pinnacle in humans (4,12,23–27). Extensive research has been conducted in rhesus macaques, which provide an indispensable model to illuminate the early etiological mechanisms mediating amyloid and tau pathology. For example, aging rhesus monkeys naturally develop Aβ plaques (28,29) and NFTs (28) resulting in age-related cognitive deficits (30) without having to introduce the mutations that cause autosomal dominant disease, and thus are ideal for studying the changes in aging association cortex that lead to early-stage pathology. In addition to amyloid and tau pathology, aged macaques also show additional signs of AD-like degeneration and age-related phenotypes, including large autophagic vacuoles in dendrites, mitochondrial dysfunction, activation of inflammatory cascades and microglial engulfment, synapse loss, argyrophilia, profound aggregation of late-phase lysosomes, and dystrophic neurites (28). These questions require NHPs, as rodents have a rudimentary association cortex and require transgenic mutations to induce neuropathology with limited tau pathology. Furthermore, rodents are limited in their ability to perform complex cognitive operations that are unique to primates. The use of perfusion-fixed tissue, not possible in humans, also provides remarkable clarity for observing phosphorylated proteins in their native location and interaction with subcellular organelles with nanometer resolution, including multiple key epitopes of phosphorylated tau. This article will review research in rhesus macaques conducted by multiple research groups and provide evidence of how aging monkeys can be leveraged to explore the pathophysiology of AD, various cellular and molecular phenotypes of aging, and age-related cognitive decline to enhance our discovery of novel therapeutic targets. Rhesus macaques have also been invaluable in elucidating the contribution of multiple factors (eg, dietary factors, sexual dimorphism, nutrition, exercise, immune activation) in impacting trajectories with advancing age, although these topics have been extensively reviewed by other groups and are beyond the purview of the Review (31–34).

Aging Rhesus Monkeys Recapitulate Amyloid and Tau Pathology in AD

Histological examination of *postmortem* human AD brain has revealed how cortical tau pathology in AD originates in layer pre-α of the perirhinal cortex and the layer pre-α (Layer II) cell islands of the entorhinal cortex (ERC; (9,12,36). Cortical tau pathology then emerges in pyramidal cells in deeper layers of the ERC, in the hippocampus, and in the association cortex, with pyramidal cells in the primary sensory and motor cortex only impacted in terminal stages of the illness (11,12,35). Rhesus monkeys with advanced age intrinsically recapitulate AD-like early-stage cortical tau pathology with the same *qualitative* pattern and sequence observed in human AD patients, with neuropathology emerging in the ERC Layer II cell islands (4). Similar to humans, tau pathology later develops in pyramidal cells in the association cortices, whereas the primary visual cortex (V1) remains unaffected until the end stages of the disease (4,23). With significantly advanced age, rhesus macaques exhibit classic NFTs in the ERC and dorsolateral prefrontal cortex (dlPFC; [4]), comprising paired helical filaments with periodicity and blunt ends identical to those in human AD patients, and which are labeled by the AT8 antibody used to clinically diagnose AD. Similar patterns of tau pathology with advancing age have also been seen in marmosets (25), vervet monkeys (27), baboons (36), and chimpanzees (26), where the degree of pathology corresponds with the extent of evolutionary expansion of the association cortex. Furthermore, the tremendous elaboration of glutamatergic synapses across evolutionary phylogeny could be a critical factor in mediating the generation of tau pathology to ultimately manifest in degenerative cascades in humans (37,38). NHPs also naturally develop amyloid plaques with advancing age, which are qualitatively identical to human AD patients (4,26,29,39–41). However, current hypotheses in the field purport that tau phosphorylation is a critical precipitating factor in the etiology of AD as longstanding neuroanatomical studies across human life span show that tau pathology begins about a decade before the formation of Aβ (42) and tau pathology, but not Aβ, correlates with progressive gray matter loss (43) and cognitive impairment (44). Furthermore, the recent case study of an AD patient with a rare, combined PS1 and Christchurch ApoE3 mutation, who did not develop dementia in spite of the extensive formation of Aβ, but very restricted tau pathology, supports the prevailing idea that aberrant tau is a key disease-inducing mechanism (45).

A tremendous advantage of research involving NHPs is the prospect of interrogating neuropathology using perfusion-fixed brains with negligible postmortem interval, which allows the detection of early-stage tau phosphorylation that is often lost in human brains due to rapid dephosphorylation by phosphatases and membrane degradation postmortem (46). Perfusion fixation allows ultrastructural visualization of early-stage, soluble phosphorylated tau epitopes that are lost in postmortem human tissue, as well as more advanced, fibrillated tau species. We have taken advantage of this opportunity to implement high-spatial-resolution immunoelectron microscopy (immunoEM) to examine the earliest stages of tau pathology in situ, and to investigate the molecular and cellular mechanisms in aging association cortex that mediate tau hyperphosphorylation. For example, we have visualized early-stage phosphorylated pS214-tau aggregating on microtubules, within glutamate synapses, and on the calcium-containing smooth endoplasmic reticulum (SER), beginning in middle age in ERC, and at later ages in dlPFC (23,28,47). Protein kinase A (PKA)-mediated phosphorylation of tau at S214 is a particularly important step in the cascade of tau pathology in AD, as it causes tau to detach from microtubules and aggregate in dendrites (4,23,48), and primes tau for hyperphosphorylation by GSK3β (49,50). ImmunoEM has been particularly instrumental in revealing pS214-tau

trafficking between neurons within omega bodies in ERC layer II in middle-aged macaques and in layer III dlPFC in aged macaques (28). pS214-tau trafficking was only seen near excitatory (28), but not inhibitory synapses, consistent with the notion of tau spreading, uptake, and aggregation occurring in highly interconnected glutamatergic circuits, leading to tau-induced toxicity (15,17,18,51–53). Our ongoing studies suggest that rhesus macaques can be used to examine the emergence of tau phosphorylated at threonine 217 (pT217-tau) in aging association cortex (38,47). pT217-tau is a particularly important phosphorylation epitope on tau as it is emerging as a promising new in vivo biomarker for AD in cerebrospinal fluid (CSF) and plasma, superior to pT181-tau in correlations with PET measures of tau and Aβ (54–58), correlating with disease stage and progression (59), and allowing early identification of at-risk presymptomatic individuals (54,59–61). In the oldest monkeys, we find AT8-labeled fibrils in dendrites, which eventually invade the perisomatic compartment, paralleling the degenerative process in humans (28). Intriguingly, across the primate lineage, rhesus macaques express both 3R and 4R isoforms in the brain (62), identical to human AD, but markedly different from rodents and even marmosets, and therefore provide an ideal opportunity to understand the contribution of 3R and 4R tau isoforms in the generation of neurofibrillary tangle pathology.

Cellular and Molecular Mechanisms Underlying Tau Phosphorylation in AD

A critical question that is central to understanding the pathophysiology of AD lies in elucidating why tau pathology preferentially afflicts glutamatergic neurons in association cortices. Based on a large body of work, we have hypothesized that glutamatergic neurons in association cortices have unique molecular features that allow these cells to partake in higher-order cognition, yet predispose these cells to neurodegeneration with advanced age (63). Our aging research has focused on the rhesus macaque dlPFC, which mediates top-down regulation of higher-order cognition, including working memory, executive function, abstract thought, and regulation of emotion. The seminal work from Goldman-Rakic, Arnsten, Fuster, and colleagues has revealed how neurons in the rhesus macaque dlPFC represent position in visual space across the delay period of a working memory task, maintaining neuronal firing without bottom-up sensory stimulation (64). These "Delay cells" are spatially tuned and are involved in persistent firing for their preferred spatial position (65). This persistent firing arises from extensive, recurrent excitatory circuits in deep layer III of the dlPFC with NMDAR synapses on dendritic spines, with lateral inhibition to sculpt the information held in working memory stores (66–70). The dendrites of dlPFC layer III pyramidal cells greatly expand during primate evolution, including significant increases in dendritic spine density for integration of excitatory inputs (71,72) and these cortical circuits are particularly vulnerable with advancing age showing profound atrophy of dendritic spines and dendrites (73–75), which is associated with cognitive decline (76).

What confers heightened vulnerability of dlPFC microcircuits to neurodegeneration with advancing age? Decades of in vivo physiology and cell-type-specific molecular characterization from Arnsten and colleagues in rhesus macaques have revealed how glutamatergic synapses on dendritic spines in deep layer III dlPFC exhibit evidence of magnified intracellular calcium release (38,77,78), where cyclic adenosine 3′,5′-monophosphate [cAMP] signaling increases calcium release from the SER (called the spine apparatus when it elaborates in the dendritic spine) into the cytosol (23). Calcium is released from the SER through multiple calcium channels such as IP3 receptors and ryanodine receptors (eg, RyR2). The data support the idea that dlPFC dendritic spines, particularly in layer III, contain the molecular machinery for cAMP-PKA signaling to enhance the release of calcium from the SER, which in turn can increase cAMP production, creating feedforward signaling (reviewed in [77]). At a functional level, the local generation of intracellular calcium release near the glutamatergic synapse may help to maintain the PSD in a depolarized state needed for NMDAR-dependent persistent firing. However, exacerbated levels of cAMP-calcium signaling induce detrimental effects, opening nearby potassium channels (eg, HCN, KCNQ) to reduce firing (79–81). This constraining mechanism might provide necessary negative feedback in a recurrent excitatory circuit to suppress the generation of seizures, to dynamically gate network inputs, and to take the PFC "offline" during uncontrollable stress when elevated levels of stress-induced catecholamines significantly increase cAMP-calcium signaling (80,82,83).

There is a multitude of regulatory mechanisms that can control feedforward cAMP-calcium signaling in aging association cortices. For example, phosphodiesterases (PDE4s) hydrolyze cAMP once it is generated, and calbindin binds cytosolic calcium released within the cell, or when calcium undergoes influx through NMDAR2B-containing dendritic spines (23,79,84). Moreover, noradrenergic alpha-2AR and mGluR3 are positioned in postsynaptic compartments on the plasma membrane of dendritic spines to inhibit cAMP production (23,79,84). Intriguingly, there are molecular gradients in several of these calcium-regulatory components (eg, PDE4D, mGluR3, calbindin) showing increases in transcript and protein expression across cortical hierarchy and during primate evolution (85,86). With advanced age, we have discovered that a decrement in expression or inhibition of these calcium-regulatory mechanisms (87) and/or induced by inflammation (77) manifests in dysregulated cAMP-calcium signaling in the aging association cortex (23,87–89) (Figure 1). This drives calcium "leak" from PKA-phosphorylated RyR2 (pRyR2) from the SER into the cytosol described in AD (4,91), which causes calcium dysregulation (92,93). Furthermore, we have observed reduced calcium binding in the cytosol as the calcium-binding protein, calbindin, which is lost with age from pyramidal cells and associated with increased NFT pathology in AD (88,89) (Figure 1). We have also observed cell-type-specific and subcompartment-specific alterations with aging, as PDE4D immunoreactivity was absent in dendritic spines and shafts of pyramidal cells in aged macaque dlPFC but preserved in astroglial cells (47,94). Protracted calcium dysregulation within the cytosol leads to the activation of the calcium-dependent protease calpain, which disinhibits a critical kinase, GSK3β, normally suppressed by PKA (95,96) to induce hyperphosphorylation of tau and mediate autophagic neurodegeneration (97). Loss of proteostasis and impairments in the autophagy-lysosomal and ubiquitination pathway in

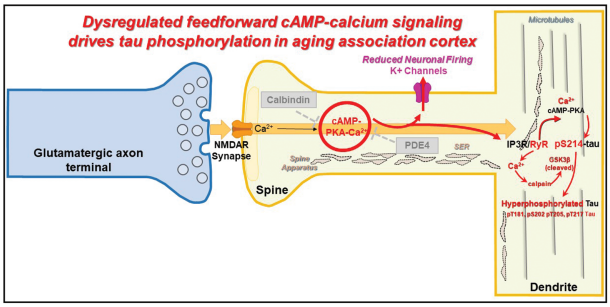

Figure 1. Schematic illustrating how dysregulated cAMP-calcium signaling in dorsolateral prefrontal cortex Layer III cortical circuits leads to tau phosphorylation with advancing age. Under normal conditions, feedforward cAMP-calcium signaling is held in check by phosphodiesterases (PDE4s) localized in postsynaptic compartments in dendritic spines, which hydrolyze cAMP, and calcium-buffering protein calbindin, which sequesters intracellular cytosolic calcium. Calcium levels rise through multiple sources, including the calcium conductance of *N*-methyl-D-aspartic acid (NMDAR) channels (specifically composed of NR2B subunits) as well as release from internal storage within the smooth endoplasmic reticulum (SER), called the spine apparatus once it extends into the dendritic spine. However, age-related decrease in calcium-regulatory proteins, PDE4, and calbindin, leads to exacerbated feedforward cAMP-calcium signaling which induces several downstream effects, including opening of K^+ channels (90), and tau phosphorylation. Protein kinase A (PKA) directly phosphorylates tau at the critical S214 residue, which causes tau to detach from microtubules and aggregate in dendrites (4,23,48). Calcium "leak" from PKA-phosphorylated RyR2 (pRyR2) from the SER into the cytosol in dendritic spines and shafts further drives dysregulated cAMP-calcium signaling and leading to activation of calcium-dependent protease calpain which cleaves the N-terminus of GSK3β kinase to induce hyperphosphorylation at multiple phosphorylation epitopes, including T181, S202/T205 (labeled by AT8), and T217.

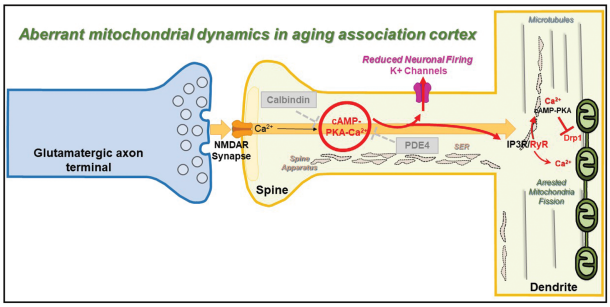

Figure 2. Schematic illustrating how dysregulated cAMP-calcium signaling in dorsolateral prefrontal cortex layer III cortical circuits leads to aberrant mitochondrial dynamics. Our data have revealed how calcium overload with advanced age leads to mitochondrial dysfunction (eg, incomplete fission), resulting in a phenotype called "Mitochondria-on-a-string" (MOAS). Within the dendritic shafts of glutamatergic-like pyramidal neurons of layer III of the dlPFC of aged rhesus macaques, we have observed MOAS with pinched constricted regions next to the calcium-containing smooth endoplasmic reticulum (SER). Fission is initiated by the dynamin-like GTPase, dynamin-related protein 1 (Drp1; also known as DLP1; [115]), which translocates from the cytosol into the outer mitochondrial membrane (OMM), where it interacts with its primary receptor—mitochondrial fission protein 1 (Fis1). Drp1 oligomers assemble into rings and spirals around the OMM, leading to the final membrane constriction and scission (100–102). The efficacy of Drp1 in fission is determined by its GTPase activity, which is inhibited by elevated PKA signaling with advancing age (103,104).

aging and AD would further compound the aggregation of hyperphosphorylated tau (98,99).

Aberrant Mitochondrial Dynamics in Aging Association Cortex

Exacerbated cAMP-calcium signaling can produce a myriad of deleterious effects, including in organelles such as mitochondria (87) (Figure 2). Mitochondria are crucial organelles that sustain neuronal function by controlling energy metabolism, cellular respiration, reactive oxygen species (ROS) generation and elimination, and modulating calcium flux. They are highly dynamic organelles, undergoing fission and fusion in an activity-dependent fashion (105). We have reported marked changes in mitochondrial morphology in dlPFC pyramidal neurons from aged rhesus macaques (106). Specifically, immunoEM paired with 3D reconstruction from serial sections revealed mitochondria with different size profiles characterized by thin segments that intermingle with enlarged segments, a phenotype we described as mitochondria-on-a-string (MOAS), indicative of impaired mitochondrial fission (Figure 2). Identical MOAS phenotypes have been demonstrated in the postmortem hippocampus of human subjects with AD, and in mice with human autosomal dominant genetic mutations (107). Similarly, presynaptic mitochondrial abnormalities in aging macaque dlPFC, indicative of pathology, have been shown to contribute to synaptic and cognitive impairment (108). Mitochondrial dysfunction and pathology have been identified in the dlPFC and other brain regions as part of the progression in postmortem human AD brains, suggesting compromised mitochondrial bioenergetics is a key driver of disease progression (109–111).

The morphological alterations in mitochondria indicate that MOAS may arise from impairments in mitochondrial fission due to dysregulation of the mitochondrial fission machinery. Our findings suggest that mitochondrial division is initiated, producing constricted segments in the mitochondrial body, but that the process of fission is unable to proceed to completion, ie, resulting in "unfinished fission" (Figure 2). This hypothesis is consistent with the findings that "pinched" segments were associated with (a) calcium-associated SER cisterns, which have been shown to encircle mitochondria to initiate constriction and are thought to play an active role in defining the positions of mitochondrial division sites (112,113) and (b) Drp1, the GTPase that is recruited to constriction sites and subsequently cuts the mitochondrial membrane, and Fis1, its primary receptor on the outer mitochondrial membrane (114–116).

Mitochondrial fission is part of a quality-control mechanism whereby damaged mitochondrial components are segregated from healthy components, followed by mitochondrial division and mitophagy (105). A balance between mitochondrial fusion versus fission is also necessary for limiting the production of toxic ROS and for normal cellular metabolism, whereas disruptions in these processes affect the cell and may be implicated in neurodegenerative diseases (117–119). In vitro studies have also shown that irregular mitochondrial fission may be a part of a pathological process that impairs mitochondrial membrane permeability (ie, opens mitochondrial permeability transition pores), resulting in the release of cytochrome c in cytoplasm and activation of caspases that, in turn, initiate apoptotic or necrotic cell death pathways (120–122). Impairments in mitochondrial dysfunction

are associated with decreased mitochondrial respiration and increased oxidative stress along with lipid peroxidation and glycolysis (110,111). Rodent and human AD studies show that mitochondrial oxidative stress occurs early in the disease process in AD (123–125), and mitochondrial oxidative stress is associated with increased phosphorylation of tau (126). Based on multiple studies, it has been suggested that MOAS may arise from excessive calcium flux and bioenergetic stress leading to dysregulated mitochondrial fission (127,128). Furthermore, calcium overload of mitochondria can indirectly initiate the generation of pro-inflammatory cytokines, such as activation of the NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome (129,130), ultimately leading to synaptic loss with advanced age. In sum, these findings are consistent with the idea that mitochondrial dysfunction is an early signature of pathology in neurodegeneration resulting in hypometabolism and cognitive deficits (131).

Activation of Inflammatory Cascades to Induce Atrophy of Glutamatergic Synapses in Aging Association Cortex

A defining feature of aging involves significant changes to both the innate and adaptive immune systems. Recent evidence suggests that activation of inflammatory cascades in brain aging contributes significantly to atrophy of cortical circuits that are critical for higher-order cognition and ensuing risk for neurodegeneration. For example, although glial cells play an important physiological role in supporting network activity, aberrant activation of astrocytes and microglia has been shown to induce inappropriate elimination of synapses under pathological conditions (132,133).

The molecular mechanisms that drive the activation of inflammatory pathways with aging are an important arena of discovery. Particularly, the complement cascade signaling pathway is an important mechanism that has garnered extensive attention. Complement signaling is one of the key arms of the innate immune system, allowing the immune system to rapidly recognize and eradicate foreign antigens (134). The classical pathway of complement activation is initiated by C1q, which leads to the activation of downstream complement components, importantly C3 and C4, which can recruit microglia through their cognate receptors to "tag" vulnerable synaptic elements (135). Rodent and human studies have revealed a dramatic upregulation of synapse-associated C1q transcript and protein during aging and in AD, which plays a role in age-related memory dysfunction (136,137). Aberrant reactivation of complement cascade signaling pathways also has been implicated in various neurodegenerative disorders including Parkinson's disease (138,139). In mouse models of AD, C1q is necessary for soluble β-amyloid oligomers to induce synapse elimination prior to plaque formation (140). Likewise, prominent accumulation of C1q has been observed near the postsynaptic density (PSD) of Tau-P301S mice and in postmortem AD brain, changes that are associated with the microglial engulfment of synaptic components (141). C3 and C3a receptors (C3aR1) are also positively correlated with cognitive decline and Braak tau staging in human AD brains (142). Furthermore, in mouse models of frontotemporal dementia caused by progranulin deficiency, there is a remarkable upregulation in C1q expression in microglia, resulting in concomitant tagging of dysfunctional synapses by C3 and phagocytosis (143). On the contrary, the reduction of complement cascade signaling pathways using genetic and/or antibody-mediated inhibition of C1q leads to rescue of synaptic alterations, neuroinflammation, and degenerative signatures (140–142).

We have characterized the expression and subcellular localization of the initiating complement signaling protein, C1q, in the aging macaque dlPFC and rat medial PFC (mPFC), with a focus on the Layer III circuits known to exhibit age-related loss of dendritic spines (144). We found a large increase in the expression of C1q with advancing age in the rhesus monkey dlPFC, and corroborated this finding in rat mPFC. At the anatomical level, we confirmed dense glial localization of C1q. These findings are consistent with previous RNA-sequencing and immunohistochemistry studies in rodent and human brain (136,145–147), suggesting C1q in glial cells, indicating that the protein may be inherently synthesized in this cell type. In addition, we observed C1q localization within pyramidal neurons, particularly in dendritic spines and shafts (144). Specifically, C1q was located near the synaptic membrane in dendritic spines and near dysmorphic MOAS within shafts (Figure 3). These findings support observations in hippocampal neurons, where calcium overload of mitochondria has been shown to activate inflammatory caspase-3 actions (148), which may be associated with increased levels of C1q (149,150). Intriguingly, C1q was evident on the calcium-storing spine apparatus and near or within glutamatergic synapses (144). The subcompartment-specific localization of C1q within neurons might engage other immune pathway receptors, such as major histocompatibility complex I (151,152). Our findings lend credence to the notion that C1q may signal from within pyramidal neurons to initiate phagocytosis by reactive glia and that aberrant reactivation of inflammatory cascades with aging may lead to neurodegeneration and ensuing cognitive deficits. Glial cells such as microglia and astrocytes might be particularly susceptible to cellular senescence, which leads to the inhibition of key intracellular signaling pathways, further driving the release of pro-inflammatory cytokines with aging (153,154). Senescent glial cells have been shown to be particularly important in

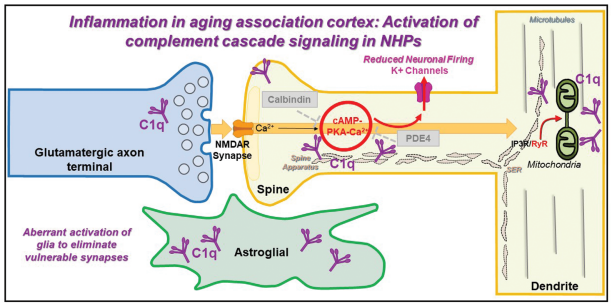

Figure 3. Age-related alterations in complement cascade C1q signaling in dorsolateral prefrontal cortex Layer III. C1q expression accumulates in glia and postsynaptically in dendritic spines and dendritic shafts, with a sparser expression in axon terminals. Within dendritic spines, C1q aggregates in perisynaptic and extrasynaptic subcompartments in association with the spine apparatus of glutamatergic synapses. Within dendritic shafts, C1q aggregates in close proximity to dysmorphic mitochondria. We hypothesize that the rise in complement C1q signaling in the aged dlPFC may be due to age-related dysregulation of feedforward cAMP-PKA-calcium signaling but may also cause calcium overload of mitochondria and the initiation of inflammatory actions to eliminate dysfunctional neuronal elements and synapses by microglia-mediated phagocytosis (144).

driving AD pathology by precluding the ability of glial cells to encapsulate Aβ plaques, ultimately contributing toward cognitive decline (153). In fact, clearance of senescent glial cells with first-generation senolytics has been shown to prevent gliosis, hyperphosphorylation of tau, and NFT pathology in a tau-transgenic mouse model of AD (155). Genetic risk factors for sporadic AD such as ApoE4 can further exacerbate the development of neuroinflammation and tau pathology (156), suggesting the intersection between inflammatory pathways and hyperphosphorylation of tau (157), and these phenotypes may be amplified in primates as opposed to rodents (158). Rhesus macaques all carry the ApoE4 risk allele and provide an invaluable opportunity to dissect the contribution of this genetic risk factor in the native course of the illness, and how it intersects with amyloid and tau pathology (159).

Role of Stress Signaling in Aggravating Feedforward, cAMP-Calcium Signaling with Advancing Age

Multiple studies have provided convincing evidence of how physiological and psychological stress with advancing age can ultimately lead to the loss of synapses on dendritic spines and the weakening of higher cognitive abilities. The association cortices that mediate higher-order cognition are particularly modulated by catecholamines, norepinephrine (NE), and dopamine (DA), which can rapidly activate intracellular stress signaling pathways to weaken synaptic connections and impair cognition (78,82,160). Acute psychological stress results in significantly reduced working memory-related activity in the dlPFC and less deactivation of the default mode network due to supraoptimal levels of catecholamines (161). Similarly, chronic stress exposure leads to sustained weakening of network connections by calcium-cAMP-PKA-K^+ signaling, leading to the removal of spines and dendrites (162–165), findings validated in humans (166). Both acute and chronic stress can potently drive cAMP-calcium signaling via catecholamines acting through NE alpha-1 adrenergic receptors (α1-AR) and DA-1 receptors to mediate Gq-IP3R-mediated calcium-protein kinase C signaling and Gs-cAMP-PKA signaling, respectively.

Chronic stress signaling pathways also initiate and propagate inflammatory cascades. Dysregulated stress and inflammation can mediate the release of the enzyme glutamate carboxypeptidase II (GCPII), which hydrolyzes *N*-acetylaspartylglutamate (NAAG) to glutamate and *N*-acetylaspartate (NAA), and therefore elevates ambient glutamate levels at excitatory synapses (167). GCPII suppresses NAAG-induced activation of mGluR3, which is located in postsynaptic subcompartments in dlPFC Layer III microcircuits, further exacerbating feedforward, cAMP-calcium signaling locally within dendritic spines (84,168,169). We have recently shown that systemic administration and local infusion of 2-(3-mercaptopropyl) pentanedioic acid (2-MPPA), which inhibits GCPII, improved working memory performance in aged rats (170). In parallel studies conducted in rhesus macaques, systemic administration of 2-MPPA, significantly improved working memory performance without any toxic side effects, with the greatest enhancement in the oldest animals (169). Furthermore, inflammation can induce the generation and release of kynurenic acid from astrocytes (171), an endogenous metabolite that blocks NMDAR (172,173) and impairs PFC working memory function (174). In fact, various components of the kynurenine pathway are currently under investigation for therapeutic development in cognitive disorders, including aging and neurodegeneration (175). These studies highlight how multiple cellular and molecular mechanisms interact, converging ultimately in inducing the atrophy of dendritic spines and dendrites leading to cognitive impairment with advancing age.

Conclusions and Future Directions

These findings provide evidence of how NHPs can be used to probe the cellular, molecular, and circuit alterations in higher-order association cortices that mediate cognition and are particularly susceptible to undergoing atrophy with aging. Particularly, NHPs such as rhesus macaques provide an unprecedented opportunity to elucidate the natural course of tau pathology in aging association cortex in the absence of autosomal dominant mutations and assess novel disease-modifying pharmacological strategies to ameliorate cognitive deficits with advancing age. NHPs recapitulate cardinal features of AD pathophysiology, including synapse loss, mitochondrial dysfunction, and microglial and astrocytic activation in vulnerable brain regions.

The tremendous advances in molecular and genetic tools have paved the way for great strides in future NHP research. For example, exogenous injection of Aβ oligomers in adult rhesus macaques produces pathological features reminiscent of preclinical AD, with synaptic dysfunction, neuroinflammation, and even NFT pathology (40,41,176). Recent studies highlight the possibility of using genetic delivery of mutated tau in a region-specific manner in rhesus macaque brain to induce misfolded tau propagation and templating and the possibility of testing biomarkers in CSF and blood (177). Structural investigations involving cryo-EM and mass spectrometry-based proteomics of tau filaments, including detailed mapping of posttranslational modifications in AD, are revealing how tau fibril structure influences the diversity of tauopathy strains, and these studies will be particularly important in understanding the 3D architecture of tau propagation (178–180). The generation of genetically engineered transgenic NHPs, including marmosets and rhesus macaques, offers the possibility of introducing germline mutations and exogenous gene expression changes to evaluate how genetic risk factors in neurodegenerative diseases impact higher-order cortical circuits present in the primate brain (181–183). Innovations in optogenetics in NHPs, which use genetically coded light-gated ion channels, offer the unique opportunity to selectively activate or silence cell types and neural pathways to study cognitive operations (184,185). Finally, refinement of single-cell transcriptomics with RNA-sequencing across the evolutionary lineage in primates is offering clues regarding species-specific molecular differences across homologous neuronal, glial, and nonneuronal cell types (186–188), particularly relevant to illuminating why specific cortical circuits are vulnerable in neurological diseases such as AD (189). The undertaking and successful implementation of these multidisciplinary approaches to elucidate the neurobiology of neurodegenerative disorders will require a concerted effort from research institutions, funding agencies, and pharmaceutical industries to advance scientific discovery. These technical and conceptual developments might provide unique insight into

understanding the underlying cellular and molecular basis of devastating disorders like AD, to augment the development of intervention strategies.

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Conflict of Interest

None.

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