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Malignant Brain Aging: The Formidable Link Between Dysregulated Signaling Through Mechanistic Target of Rapamycin Pathways and Alzheimer's Disease (Type 3 Diabetes)

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Abstract

Malignant brain aging corresponds to accelerated age-related declines in brain functions eventually derailing the self-sustaining forces that govern independent vitality. Malignant brain aging establishes the path toward dementing neurodegeneration, including Alzheimer's disease (AD). The full spectrum of AD includes progressive dysfunction of neurons, oligodendrocytes, astrocytes, microglia, and the microvascular systems, and is mechanistically driven by insulin and insulin-like growth factor (IGF) deficiencies and resistances with accompanying deficits in energy balance, increased cellular stress, inflammation, and impaired perfusion, mimicking the core features of diabetes mellitus. The underlying pathophysiological derangements result in mitochondrial dysfunction, abnormal protein aggregation, increased oxidative and endoplasmic reticulum stress, aberrant autophagy, and abnormal post-translational modification of proteins, all of which are signature features of both AD and dysregulated insulin/IGF-1-mechanistic target of rapamycin (mTOR) signaling. This article connects the dots from benign to malignant aging to neurodegeneration by reviewing the salient pathologies associated with initially adaptive and later dysfunctional mTOR signaling in the brain. Effective therapeutic and preventive measures must be two-pronged and designed to 1) address complex and shifting impairments in mTOR signaling through the re-purpose of effective anti-diabetes therapeutics that target the brain, and 2) minimize the impact of extrinsic mediators of benign to malignant aging transitions, e.g., inflammatory states, obesity, systemic insulin resistance diseases, and repeated bouts of general anesthesia, by minimizing exposures or implementing neuroprotective measures.

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CONFLICT OF INTEREST

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SUPPLEMENTARY MATERIAL

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Keywords

Aging; Alzheimer's disease; brain; mTOR; neurodegeneration; neuroinflammation; type 3 diabetes; vascular disease; white matter

ALZHEIMER'S DISEASE: THE BIG PICTURE

Clinical features and diagnostic aids

Alzheimer's disease (AD) accounts for 70% to 80% of chronic progressive dementia-associated neurodegeneration. The clinical course including deterioration of multiple integrative sensory activities, combined with multi-modal neuroimaging approaches [1–3] are used to delineate brain structural, biochemical, and functional deficits. Diagnostic specificity has improved through the use of positron emission tomography scans to quantify amyloid-β (Aβ) and phospho-Tau (pTau) accumulations in the brain [1, 2], the results of which serve to select subjects for clinical trials, and monitor disease progression and treatment responses [1, 2]. In addition, cerebrospinal fluid (CSF) with simultaneous serum assays that assess brain expression, processing, and clearance of Aβ and pTau [4–7], function as biomarkers [8]. Nonetheless, the post-mortem brain examination remains the diagnostic gold standard for resolving complex cases that result from the overlapping occurrence of two or more forms of neurodegeneration and superior accuracy given the nearly 1000-fold greater sensitivity and specific of histopathology compared with neuroimaging [9, 10]. Nonetheless, the combined use of neuroimaging, clinical diagnostics, and the continually evolving array of CSF and serum-based biomarkers have greatly improved our diagnostic acumen and expanded eligibility for early interventional treatments [9].

Clinical diagnostic challenges-mild cognitive impairment

The seemingly unstoppable rising incident rates of neurodegenerative diseases, including AD, together with prolonged survival account for our current global chronic disease pandemic. By 2050, the worldwide prevalence of AD is expected to reach 115 million [11]. The culprits of this crisis are largely shouldered by the field's lack of consensus about etiology, pathogenesis, and best means of remediating or preventing disease progression despite more than 40 years of intense investigation. Our learning curve is stalled by insufficient understanding of AD's protean clinical profiles, beginning from its yet-to-be-established onset, the full spectrum of AD neuropathology including its heterogeneous features, and the inter-relationships between AD and systemic, i.e., non-central nervous system (CNS) pathologies [12, 13].

The triple-pronged challenge of diagnosing the earliest stages of AD is rooted in its prolonged asymptomatic (silent) period, ill-defined prodromal interval of slowly progressive and difficult-to-characterize neurobehavioral changes that evolve over years, possibly one or two decades, and considerable overlap with "normal" aging [14]. The preclinical silent period goes undetected until work-related, home-life, or social task errors get exposed. Intelligent people often hide their difficulties for years, delaying the discovery of problems linked to financial mismanagement and declines in planning and organizational executive

functions. Neurobehavioral problems can be subtle or simply dismissed as exaggerated baseline personality quirks until embarrassing circumstances scream concern. Mild cognitive impairment (MCI), frequently associated with forgetfulness and inattentiveness, can be a feature of normal aging or a manifestation of early AD, although the predisposition to AD is eventually revealed by neurocognitive and neuroimaging studies [15]. In addition, MCI coupled with significant cerebrovascular risk factors is not strongly predictive of future AD [16]. Correspondingly, in a postmortem study, CNS vasculopathy accompanied by classical albeit mild to moderate AD pathology was associated with early-stage AD, whereas without AD lesions, CNS vasculopathy was not associated with cognitive impairment [17]. In essence, MCI's isolated presence is not diagnostic and does not reliably predict AD. Instead, its detection warrants clinical monitoring over time for evidence of progression. The composite clinical profile that marks the impending transition from MCI to AD includes a progressive decline in short-term memory, cognition, social skills, thinking ability, behavioral functions, and capacity to independently perform daily activities [18–21].

Therapy and caretaker challenges

Therapeutic interventions should be initiated at the earliest possible stages of neurodegeneration to prevent further cognitive and behavioral declines and possibly remediate the disease. A diagnosis of early-stage AD is also desirable for clinical trials designed to assess the effectiveness of novel therapies. However, MCI's overlap with normal aging and early-stage AD can confound interpretations of trial outcomes since the absence of clinical progression could reflect aging-associated non-responses rather than successful therapeutic intervention. Moreover, the therapeutic window can be distorted by AD mimics such as psychiatric disorders and polypharmacy complications. In short, the field needs additional strategies to access and utilize data pertaining to a broad array of neurobehavioral and cognitive dysfunctions, along with objective biomarkers to reliably detect proneness to AD and other neurodegenerative diseases.

An MCI diagnosis justifies thorough evaluation and monitoring for patient reassurance and management. Furthermore, even a suspicion of MCI should alert patients and caretakers to minimize circumstances that exacerbate cognitive decline such as elective surgical procedures requiring general anesthesia, heavy alcohol drinking, tobacco smoking, poorly controlled hypertension or diabetes mellitus, increased risk of falling and head trauma, and continued use of un-needed or potentially harmful drugs, either prescribed or unregulated. "MCI" that does not progress could be a manifestation of "normal aging" or isolated cerebrovascular disease. On the other hand, its misinterpretation or underdiagnosis could result in missed opportunities to treat very early-stage diseases. This matter is of particular concern for highly intelligent people with immense cognitive reserves and capacities to hide deficits until their declines accelerate (https://platinum-communities.com/2017/12/01/5-ways-elderly-can-hide-dementia-symptoms/; https://www.apa.org/news/press/releases/2004/01/alzheimers-iq) [22, 23]. Sadly, the first signs of AD may be appreciated after their severities become moderate or high-level and beyond the optimum therapeutic window [22, 23]. As AD progresses, functions required for communication, self-care, independence, and enjoyment of life deteriorate. The rising number of cases has become socioeconomically burdensome. To exit from this destructive vortex, we must unpack its

components and deal with the multifaceted features of AD together with the obvious requirement for multi-pronged therapeutic interventions. The next section focuses on the full neuropathologic spectrum of AD.

ALZHEIMER'S DISEASE NEUROPATHOLOGY

Typical brain structural pathologies

The earliest descriptions of AD pathology highlighted the hallmark features of brain atrophy, neuronal loss, and abundant accumulations of extracellular and perivascular cortical plaques, intracellular neurofibrillary tangles (NFTs), and reactive astrocytes [24, 25]. Their characteristic and non-random regional distributions within selected cortical areas, basal forebrain, medial temporal structures, and hippocampal formation correlate with clinical and neurobehavioral abnormalities and distinguish AD from other forms of neurodegeneration. However, diversified research revealed critical mechanistic structural and molecular pathologies that led to experimental models for hypothesis testing. NFTs, along with dystrophic neurites, and neuropil threads, initially identified using silver impregnation techniques, were later found to contain aberrantly hyperphosphorylated tau along with other neuronal cytoskeletal proteins and to have ultrastructural features corresponding to paired-helical filaments (PHFs), the abundances of which correlate with dementia severity [26]. Another game-changing discovery stemmed from the isolation and chemical characterization of brain amyloid as the insoluble Aβ C-terminal proteolytic cleavage product of amyloid-β protein precursor (AβPP) [27]. Subsequent research showed that in addition to Aβ plaques, AD brains harbor increased Aβ fibrils, peptides, and potentially neurotoxic oligomers [28, 29]. Paradoxically, Aβ plaques appear not to be toxic and instead may sequester neurotoxic Aβ oligomers and fibrils [30]. Furthermore, evidence suggests that toxic Aβ may induce tau hyperphosphorylation and neuritic pathology that correlate with dementia [28, 29].

Effects of familial and genetic susceptibilities

Although the vast majority of AD occurrences are sporadic, accounting for 90% to 95% of cases [31, 32] the relatively small 5 to 10% subset of the cases is burdened by genetic risk factors or heritable gene mutations. The genetic or familial forms of AD result in higher levels of Aβ accumulations in the brain. Apolipoprotein E4 (*APOE* ε4) is the most common familial susceptibility gene for late-onset AD [32]. Another less common AD susceptibility gene detected in microglia is the triggering receptor expressed on myeloid cells-2 (*TREM2*) [30]. Both *APOE4* and *TREM2* exacerbate AD risk by their associated increases in Aβ accumulation [33, 34]. Presenilin 1 (PS1) and PS2 are catalytic components of the γ-secretase complex, which functions with β-secretase/BACE1 to cleave AβPP and generate Aβ [32]. Higher levels of BACE1 and γ-secretase activities increase Aβ production, which in combination with reduced proteolytic degradation by insulin-degrading enzyme and neprilysin, mediate neurotoxic Aβ oligomer and fibril accumulations [35, 36]. However, the neuropathology of AD extends far beyond the presence and severity of Aβ and pTau accumulation. All cell types are affected by the underlying processes. Brief descriptions of how neurons, oligodendrocytes, astrocytes, microglia, and microvessels are damaged in AD follow below.

Neuronal pathology

In AD, neuronal pathology is characteristically associated with altered phosphorylation and processing of tau. The resulting disassociation of tau from axonal microtubules leads to their destabilization, adversely affecting axonal structure and transport [37, 38]. In neuronal cytoplasm, disassociated aberrantly hyperphosphorylated tau forms neurotoxic fibrils and insoluble NFTs, representing neuropathological hallmarks that correlate with cognitive impairment and dementia [37, 39]. Neuronal death and synaptic degeneration or dysfunction are additional pathologies that correlate with cognitive impairment [40–42], but remain difficult to quantify in standardized fashions. Despite their characteristic presence in AD, tau-associated lesions lack specificity because similar lesions occur in other neurodegenerative diseases including frontotemporal lobar degeneration, dementia with Lewy bodies, and progressive supranuclear palsy.

Oligodendrocyte pathology

Oligodendrocyte pathology has not been well-studied, despite significant progressive white matter atrophy and degeneration from the early stages of AD [43–47]. Emerging evidence suggests that the impaired function and survival of oligodendrocytes and oligodendrocyte progenitor cells (OPCs) mediate white matter degeneration [48–53]. Significant myelin protein and lipid abnormalities have been identified in human and experimental models of AD [54, 55]. Although both phospholipids and sphingolipids are affected [54, 56], reductions in sulfatides and increases in ceramides correlate with cognitive impairment and neurodegeneration [57–59]. Early-stage breakdown of myelin with oligodendrocyte dysfunction [60] coincides with the progression of NFT pathology [47, 49, 61, 62]. Furthermore, dysfunction of oligodendrocytes and OPCs compromises their phagocytosis of Aβ [50, 63], potentially contributing to Aβ build-up. However, opposing data suggest that Aβ toxicity contributes to oligodendrocyte dysfunction and myelin breakdown [50]. Additional studies are needed to clarify the pathophysiology and pathogenesis of glial cell dysfunction in relation to neurodegeneration [30].

Astrocytes and microglia

Neuroinflammatory responses in astrocytes and microglia are consistent components of AD neuropathology. In “quiescent brains”, the homeostatic functions of astrocytes and microglia include mopping up extracellular glutamate to prevent excitotoxic injury, elaborating cytokines needed to support various neuronal functions, including cell survival, and catabolic degradation of Aβ [30, 64]. Functional impairment of astrocytes or microglia compromises glutamate homeostasis and renders neurons vulnerable to excitotoxic injury mediated by overactivation of ionotropic glutamate receptors such as N-methyl-D-aspartate (NMDA) [65], reduces degradation of Aβ facilitating its neurotoxic accumulation [65], and drives neuroinflammatory responses with increased generation of pro-inflammatory cytokines that exacerbate neurodegeneration [65, 66], damage synaptic connections, and promote neuronal death [30, 64, 67–69]. Of note is that variant and mutant isoforms of the *APOE* and *TREM2* AD susceptibility genes likely increase the risk for AD by failing to guard against neuroinflammation and Aβ accumulation [33, 34, 70].

Vascular pathology

Impairments in brain perfusion have been well-established in AD. The most notable consequences include progressive declines in cerebral blood flow, oxygen utilization, and glucose metabolism [71, 72]. The extent to which vascular disease represents a primary, secondary, or coincidental unrelated pathology in AD remains unresolved due to confusion about its mechanisms and relationships to other aspects of neurodegeneration. The extremely high prevalence of cerebral vascular pathology, which was detected in over 80% of postmortem brains with AD [73] supports the concept that cerebral vascular disease is indeed one of the dominant AD pathologies.

In AD, there are two main types of microvascular pathology that can occur independently or overlap with one another: Aβ and non-Aβ [44, 74–77]. Aβ angiopathy affects vessels in the cerebral cortex and leptomeninges, and not white matter [78–80]. In contrast, non-Aβ vascular degeneration occurs in micro-vessels, including capillaries, arterioles, and venules distributed throughout the brain. In AD, non-Aβ vascular pathology is commonly detected in the cerebral cortex, white matter, and subcortical nuclei. Non-Aβ microvascular disease is characterized by fibrotic thickening of vessel walls (sclerosis), loss of endothelial cells, thickening of basement membranes, attrition of perivascular tissue [81], reduced vascular density (micro-vasculopenia), and increased vascular coiling [82]. Mural sclerosis can cause extreme narrowing of vascular lumens and reduced vasoresponsiveness, restricting perfusion, including in times of high metabolic demand [83]. Chronic hypoperfusion of white matter causes ischemic injury ranging from myelin loss to fiber attrition, and in extreme cases, leukoaraiosis and micro-infarcts [43, 84, 85]. Other consequences of microvascular pathology include weakening and increased permeability of vessel walls, like the vascular degeneration that occurs in diabetic nephropathy [86]. Leakiness of microvessels enables toxins and inflammatory mediators from the periphery to enter the brain and cause perivascular tissue injury and attrition [72, 87–93].

The clinical relevance of the cerebral vascular disease component of AD has been highlighted by clinical and postmortem studies. In the Gothenburg study, mental slowness and executive function deficits were associated with white matter vascular dysfunction and pathology but not cortical vasculopathy [94]. Since Aβ vasculopathy does not occur in white matter structures, and instead is restricted to gray matter, non-Aβ associated white matter microvascular disease must be regarded as an important component of AD, and a significant additive or synergistic factor contributing to cognitive decline. An earlier postmortem study showed that at least 40% of brains with AD also had cerebrovascular disease and microvascular lesions, whereas no cases with similar degrees of cerebrovascular disease but devoid of AD pathology had clinical dementia [17]. Furthermore, cases with combined AD and microvascular pathology had dementia levels that were like cases of “pure” AD despite higher densities of NFTs and Aβ plaques in the latter. These findings support the concept that clinically manifested AD results from either classical AD pathology or combined AD plus non-Aβ microvascular disease. In essence, cerebrovascular pathology, particularly microvascular disease, can additively or synergistically mediate AD pathogenesis, but in general, is not sufficient to cause clinical AD in the absence of classical AD structural lesions [17]. Together, the clinical, postmortem, and pathophysiological mechanistic studies

support the concept that both Aβ and non-Aβ vasculopathies are highly relevant to AD progression, raising concern about any dismissal of non-Aβ CNS vasculopathy as a pathogenic mediator of cognitive impairment, particularly in early-stage AD or MCI, and the exclusion of such affected subjects from clinical trials.

Take-away points

Although classical neuropathological lesions abound in corticolimbic structures particularly in the earliest stages of AD, the neurodegeneration process advances over time, resulting in relatively widespread cerebral involvement. AD-related pathologies are protean and extend far beyond the signature lesions marked by abundant NFTs and Aβ accumulations. We have yet to standardize the detection and quantification of other complex neuronal pathologies like neuritic dystrophy, aberrant neuritic growth, synaptic disconnection, and loss of synaptic plasticity, which affect many neurons that lack NFT neurodegeneration but correlate with dementia severity. White matter degeneration occurs early, progresses with disease severity, and is associated with fiber rarefaction and myelin loss. The consequences include attenuation or destruction of intra and inter-cortical connections and slowing of conductivity and processing speeds. However, both cortical and white matter degeneration are consistently accompanied by astrocytic and microglial cell activation and microvascular disease. Astrocytic pathology compromises the glial-vascular network and blood-brain barrier, and together with activated microglia, contributes to a neuroinflammatory environment. Microvascular disease is perhaps the least understood due to its overlap with normal aging and poor correlation with Aβ neuroimaging and cognitive impairment. Determining the contributions of Aβ versus non-Aβ microvascular disease to the development and progression of AD-related cognitive decline will require focused research together with a broadening of concepts surrounding disease pathogenesis.

Although AD is largely sporadic in occurrence, research focused on genetic risk factors and gene mutations provides opportunities to investigate specific pathogenic mechanisms that collaborate with aging to trigger dementia-associated pathologies that are virtually identical to those observed in non-genetic forms of the disease. Ultimately, the effectiveness of AD treatments will require an improved understanding of both the pathology and pathogenesis. However, it is critically important that we identify the boundaries between normal aging and the onset of neurodegeneration, i.e., the silent window leading up to the emergence of MCI that will likely progress to AD. Aging caused by wear, tear, and winding down of biological clocks should be regarded as benign. Aging linked to progressive impairment of essential functions such as activities of daily living, should be regarded as malignant, and a precursor to AD or other forms of neurodegeneration. The next segment describes normal, benign brain aging for later comparison with malignant aging/neurodegeneration.

BENIGN AGING: FEATURES AND MECHANISMS

Benign brain aging

Aging is a natural component of life’s arc and therefore benign. However, when aging triggers or enables the development of AD or other forms of neurodegeneration, the transformation could be regarded as malignant. Understanding how benign aging

differs from malignant aging could provide clues about pivotal mediators of accelerated deterioration and loss of functions needed for independent living. The analysis of genetic risk factors and gene mutations in relation to the transition from benign to malignant aging and then neurodegeneration could enlighten us about specific triggers or mediators of cognitive impairment that begin or become problematic in middle age. This section of the review draws distinctions between benign (normal) and malignant aging, given the latter's propensity to progress to degeneration.

The natural time-dependent shifts in human brain structure and function resemble a frustum (flat-topped pyramid). Normal stepwise growth and development of the brain is analogous to the steeply tiered upslope of the Pyramid of the Sun. The relatively stable but event-filled period of healthy adult brain function corresponds to the pyramid's broad upper plateau, marred by divots, crevices, dents, and small craters reflecting opportunities to falter, but also self-correct through healing. The benign brain aging that ensues is gradual although micro-erratically tortuous in pursuit of a coarsely tiered but overall gentle downward slope that resembles the Pyramid of the Moon, which is about 50% less steep than the Pyramid of the Sun. (Both pyramids are in Teotihuacan, Mexico.) In contrast, malignant brain aging has a steep, accelerated, irreversible (thus far) downhill course leading to inevitable neurodegeneration. For benign brain aging, mental and physical processing slow down, become less resilient and agile and require more rest compared with the young brain. Tolerance for benign aging is linked to the preserved capacity to enjoy life, engage in social discourse, remain physically active, and utilize perceptive and analytical thought processes.

Other, more varied post-frustrum paths can be forged by transitions from benign to malignant aging at different points on the descent, due to one or more significant "second hits", i.e., injurious or traumatic events or exposures. Ample data support the concept that aging-associated downward trajectories can shift from gentle to steeper slopes at any stage, the telltales of which are marked by accelerated cognitive declines that precipitously lead to dementia. Causal factors include small strokes, repeated bouts of general anesthesia, hypoxia, head trauma [95–98], prolonged use of strong anticholinergic medications, heavy alcohol consumption, and metabolic disorders linked to insulin resistance. Cognitive impairments can be worsened by chronic, intermittent, and unpredictable stress, e.g., post-traumatic stress disorder [99] via excess glucocorticoid hormone release [100, 101]. Furthermore, outcomes of the Coronavirus Disease 2019 (COVID-19) pandemic suggest that prolonged social isolation also can trigger cognitive decline in the elderly [102]. Characteristic manifestations of malignant aging include progressive neurobehavioral dysfunction with reduced processing and recovery speeds, loss of mental nimbleness and cognitive reserve, and impaired capacity to learn, recall, and communicate. The accompanying brain atrophy with loss of neurons, synaptic connectivity, and neuronal plasticity translates to impairments in thinking and mentation, analytical skills, social discourse, and capacity to enjoy life and self-care.

Global disparities in aging

Among countries with the healthiest aging, Japan and Switzerland lead as their populations enjoy at least 10 years longer than the average durations of disease-free living and average

lifespans to the mid-80 s, whereas, in Papua New Guinea, population aging is accelerated by the mid-40 s, and the mean life expectancy is in the mid-60 s. The shortest mean life expectancy of 57 years is in Western Africa (https://worldpopulationreview.com/country-rankings/life-expectancy-by-country). Malignant brain aging challenges victims, caretakers, medical/nursing providers, and the pharmaceutical industry due to its multifaceted roots, clinical and pathological manifestations, and both the known and unknown precipitating or exacerbating environmental/exposure factors experienced on the frustrum's plateau and beyond. Fatigued by the hunt to resolve these problems forces us to confront two over-arching questions: 1) Is there anything we can do to purchase a stable and virtually immutable benign brain aging trajectory while still on the middle-age plateau of the frustum? 2) Is it possible to halt or prevent accelerated cognitive declines and either protect residual or regain recently lost functions following events that shift the path from benign to malignant aging? Reviewing the vulnerable brain cellular targets of aging, both benign and malignant, could help clarify the breadth of required preventive or therapeutic remediation, as well as explain why single-pronged medicinal targeting will never work.

Brain cell targets of aging- mediators and consequences

All brain cell types are vulnerable to the effects of aging. The consequences of cell loss with limited replacement capacity, declining function, and mediators of aging at the cellular levels are reviewed below and summarized in relation to malignant aging and neurodegeneration in Table 1.

Neurons

Neuronal attrition and synaptic disconnection are inevitable consequences of brain aging. Accompanying declines in plasticity compromise nimbleness in learning, memory, and behavior. Unlike the efficient turnover or replacement of aged or damaged epithelial cells in the gastrointestinal tract, skin, and liver, the process of replacing degenerated or dead neurons in the mature brain, even prior to senescence, is inefficient and largely ineffective due to limited capacity for neurogenesis. Instead, functions are largely restored through the re-growth of inter-neuronal connections and the re-establishment or re-modeling of circuits. However, aging-related wear and tear can hinder the efficacy of these processes. Stroke, ischemia, general anesthesia, head trauma, infection, and inflammatory disorders are among the many potential episodic second hits that pose life-long threats to the maintenance of normal brain function. Furthermore, such events can additively or synergistically accelerate aging and promote neurodegeneration by raising the bar of effort required to address larger fields of damage due to neuronal loss, neuritic process retraction, and degeneration. On the other hand, avoiding or minimizing related injuries could serve as one of the main avenues of neuroprotection. At its core, the capacity of aging neurons to thrive, maintain functional connectivity, and utilize the tools of plasticity is governed by responsiveness to insulin, IGF, and other trophic factors that are needed for metabolic homeostasis and neuroprotection.

Oligodendrocytes

Oligodendrocytes are abundantly distributed in white matter where their primary function is to maintain myelin for efficient neurotransmission. White matter atrophy occurs with normal/benign aging but is substantially more pronounced with malignant aging/

neurodegeneration. Although not well understood, the mechanisms of white matter degeneration are likely linked to oligodendrocyte dysfunction with attendant alterations in myelin integrity. Like neurons, oligodendrocytes are predominantly postmitotic and terminally differentiated and therefore have limited capacity to regenerate. However, functional losses caused by aging, injury, or death of mature oligodendrocytes can be compensated by cellular repair mechanisms that restore myelination and myelin integrity. In addition, OPCs can be recruited to replenish oligodendrocyte populations and normalize neuronal conductivity. However, like neurons, survival, maintenance, and function of oligodendrocytes are trophic factor-dependent and require continuous stimulation by insulin, IGF's, neurotrophins, or interleukins [103, 104].

Progressive white matter degeneration occurs in nearly all neurodegenerative diseases [84, 105–108] and manifested by alterations in myelin glycoprotein and lipid expression [56, 109–111]. Loss of oligodendrocytes broadly impacts white matter myelin integrity because each oligodendrocyte myelinates multiple axons. Besides compromising neuronal conductivity and processing speeds, oligodendrocyte dysfunction and myelin loss render axons and dendrites vulnerable to extracellular fluid environmental toxins, further compromising synaptic connections and efficiency of neurotransmission. Like neurons, sporadic or incidental insults triggered by hypoxia, ischemia, inflammation, or metabolic dysregulation can compromise oligodendrocyte function and myelin integrity and fast-forward aging-associated white matter degeneration.

Astrocytes

Astrocytes are multifaceted. They support neurons, neuritic process growth, and the generation and maintenance of structural matrices for glial-vascular networks, the blood-brain barrier [104], and neurovascular coupling [112]. Insulin and IGF receptor signaling networks support these positive astrocyte functions [113, 114]. In addition, protective trophic factor stimulation modulates glutamate-mediated neurotoxicity, cellular stress [115], and glial scar formation [114]. Aging-associated declines in circulating levels of IGF-1 and responsiveness to insulin and IGF-1 increase the generation of reactive oxygen species (ROS) and uncouple the relationship between brain blood flow and glucose utilization [115]. In addition, associated increases in insulin/IGF-1 resistance compromise the integrity of the blood-brain barrier and neurovascular coupling [112]. Aging-related impairments in glial-vascular networks lead to excessive proliferation and activation of astrocytes, glial scarring, and pro-inflammatory cytokine activation. These responses impede neuronal growth and repair, promote senile plaque formation, and exacerbate pro-inflammatory cytokine production [115]. In essence, aging-associated insulin resistance and IGF-1 deficiency or withdrawal compromise astrocytes' capacity to protect neurons from stress and injury induced by ROS. Therefore, insulin, IGF, and other trophic factor deficiencies and receptor resistances contribute to neurodegeneration by compromising astrocytic functions needed to protect neurons and oligodendrocytes from extracellular toxins and metabolites, preserve local perfusion, and deliver nutrients to the brain. Sporadic injuries or 'second hits' can adversely impact astrocyte functions, causing their responses to shift from positive to reactive or negative, and thereby promote synaptic disconnection, axonal degeneration, neuroinflammation, blood-brain barrier disruption, and glutamate dyshomeostasis [113].

Microglia

Microglia, like astrocytes, in their nonactivated, quiescent, healthy brain states have roles in surveying the microenvironment, synaptic pruning, and axonal remyelination. Persistent tissue injury and cellular stress provoke proliferative, pro-inflammatory, and phagocytic actions [116–118] that cause or exacerbate dystrophic processes linked to neurodegeneration. In addition, tissue injury-induced microglial activation can drive astrocytes to respond and generate scar tissue that interferes with the restoration of synaptic connections. Like neurons, oligodendrocytes, and astrocytes, microglia are responsive to IGF-1 which quiesces their injury-associated activation [114]. With aging and related impairments in insulin and IGF-1 signaling, microglia become more activated as evidenced by their increased proliferation and cytokine production.

Vasculature

Aging compromises flow through large- and medium-caliber arteries by reducing their luminal diameters through progressive deposition of atherosclerotic plaque and fibrotic diminution of vascular wall compliance. Aging also negatively impacts the structural and functional integrities of the brain's microvascular networks by causing vascular and perivascular sclerosis with luminal narrowing, reduced compliance, proneness to thrombosis, and increased capillary leakage. This type of microvascular pathology is not unique to the brain, as it is prominently featured in diabetes mellitus and systemic arterial hypertension. The main consequences of aging-related cerebrovascular pathology include impaired delivery of oxygenated blood and nutrients needed to maintain cellular viability and metabolism, increased rates of ischemic injury, and stroke-proneness due to the greater ease of occluding narrowed lumens with embolus or thrombus.

Dysfunction of the neurovascular unit, which is composed of brain microvascular endothelial cells, neuronal processes, microglia, astrocytes and pericytes [119], leads to chronic hypoperfusion, nutrient shortage, waste build-up, and oxidative injury. Furthermore, endothelial cell dysfunction disrupts the blood-brain barrier, rendering neurons and oligodendrocytes susceptible to toxin exposures due to their increased ingress, reduced selectivity of molecule delivery, and inefficient clearance. The functional integrity of the neurovascular unit relies on intact insulin/IGF-1 signaling through phosphatidylinositol-3-kinase (PI3K)-Protein Kinase B (Akt) pathways [74]. Insulin and IGF-1 support astrocyte functions needed to mediate neurovascular coupling and regionally micro-adjust blood flow [112, 120]. Therefore, aging-associated declines in responsiveness to insulin and IGF-1 likely contribute to brain hypo-perfusion and vascular cognitive decline [112]. Attendant impairments in signaling through insulin/IGF networks lead to metabolic dysfunction, excessive cell death, and astrocyte- and microglia-mediated inflammation [119]. Impaired functioning of the microvascular unit and blood-brain barrier help drive the transition from benign to malignant brain aging [119].

Beyond brain aging: Mechanisms relevant to the central nervous system

Aging affects cells, tissues, and organ systems throughout the body. Like the brain, systemic aging is mediated by complex interactive effects of environment x genes, leading to gradual but progressive declines in structure and function once the middle-age plateau has been

reached. Several examples of aging-associated non-CNS pathologies and their consequences are discussed below. It is noteworthy that the repeating mantra echoes the concept that impairments in insulin/IGF-1 signaling mechanisms and the associated increases in oxidative stress, DNA damage, and inflammation coordinate the aging cascade, irrespective of organ or tissue type. Prior to dissecting the intracellular mediators of impaired insulin/IGF-1 signaling in relation to neurodegeneration, a brief discussion of senescent processes in other organs and tissues will reinforce the goal of supporting related pathways to minimize transitions from benign to malignant aging.

Muscle

In skeletal muscle, aging is characterized by progressive declines in mass and strength [121]. Sarcopenia (atrophy) is accompanied by fat infiltration (myosteatosis) and mitochondrial dysfunction, rendering muscles weakened and fragile [122, 123]. However, the pathophysiological contributions of insulin resistance and impaired oxidative metabolism to aging- and obesity-associated declines in skeletal muscle structural and functional integrity can be reversed or prevented by exercise training [124], especially resistance exercises which reverse aging-associated muscle weakness, mitochondrial impairment [125], and insulin resistance [126].

Peripheral nervous system

In peripheral nerves, aging-associated functional declines interfere with daily sensory, motor, or autonomic functions and increase the risk of falling with injury. Aging-associated peripheral neuropathy is caused with axonal atrophy with loss of myelinated and unmyelinated nerve fibers, mainly small caliber, along with demyelination, remyelination, and myelin balloon figures. Axonal atrophy is marked by reduced expression of major myelin proteins and axonal transport of cytoskeletal proteins in peripheral nerves, resulting in declines in conduction velocity, muscle strength, sensory discrimination, autonomic responses, and endoneurial blood flow [127]. Although regenerative capacity persists across the lifespan, the process slows with aging [127] and prolongs post-injury neuropathic symptoms. Senescent failure of peripheral nerve functions contributes to age-related decay of muscle quality and muscle function [128]. Polyneuropathies in aged adults are often associated with diabetes mellitus or chronic alcoholism, both of which are linked to impairments in insulin and IGF-1 signaling [129–132].

Skin

The definition of skin aging has not reached consensus, although roles for intrinsic (genetic, chronological age) and extrinsic modifiable factors (sun, UV exposure, smoking, diet) are well recognized [133]. Besides increased laxity with wrinkling, aging- attenuation of the rete ridges reduces the skin’s capacity to perfuse/nourish the epidermis, resulting in atrophy and reduced resistance to shearing force injury [134]. Aging dermal fibroblasts are deficient in normal extracellular matrix production, and instead acquire pro-adipogenic attributes that are responsive to metabolic factors, including caloric restriction [134], linking the effects to reduced insulin sensitivity, dysregulated metabolism and increased inflammation, which further drive insulin resistance [135].

Bone and joints

Aging reduces bone mass and strength due to unbalanced and excessive resorption by osteoclasts vis-à-vis inadequate deposition by declining populations of osteoblasts [136]. Chondrocytes and articular cartilage are the main targets of joint aging [137]. Mechanistically, senescing chondrocytes are less responsive to IGF-1 which is needed for matrix production [138]. Loss of smooth lubricated articular cartilage surfaces impacts gliding joint motion, impairs function, and irritates pain fibers [138]. Aging-associated joint erosion from osteoarthritis is strongly modified by inflammation, cellular senescence, mitochondrial dysfunction, stress, and impairments in energy metabolism [137, 138]. The development of osteoarthritis renders joints more susceptible to other factors that lead to abnormal biomechanics, e.g., injury and obesity [138].

Cardiovascular system

Aging-associated arteriosclerotic and atherosclerotic cardiac and cardiovascular pathologies lead to heart failure, coronary artery disease, arrhythmias, cardiomyopathies, and myocardial infarction, which together account for the high worldwide rates of cardiovascular morbidity, disability, and mortality among the elderly [139]. The main underlying risk factors include chronic systemic arterial hypertension, diabetes mellitus, hyperlipidemia, and obesity. Cardiovascular structures diseased by arteriosclerosis or atherosclerosis stiffen and become less compliant, compromising blood flow and oxygen/nutrient exchange. Insulin resistance is a strong predictor of atherosclerosis and arteriosclerosis due to injury and stress mediated by high, possibly toxic local levels of insulin [140].

Immune system

Aging-related weakening of the immune system increases vulnerability to infection and reduces tumor surveillance. In the respiratory tract, aging contributes to chronic airway damage and pulmonary fibrosis, reducing exercise tolerance and increasing proneness to life-threatening infections.

Liver

In the liver, aging reduces the capacity for repair and regeneration, particularly following drug, alcohol, or medication toxicities [141].

Endocrine organs

Aging of endocrine organs halts hormonal production, reducing trophic factor stimulation throughout the body and significantly contributing to hypothyroidism, diabetes mellitus, and end-stage renal disease.

Kidneys

Aging-associated declines in renal function compromise the efficacy of filtration and capacity to remove toxic metabolites.

Gut

In the gastrointestinal tract, aging impacts the gut microbiome's taxonomic composition, leading to significant changes in carbohydrate metabolism and amino acid synthesis with attendant dysregulation of the immune system [142].

The bottom line is that the aging process in multiple organs and tissues has common threads including 1) impaired secretion or production of positive trophic or signaling molecules; 2) reduced responsiveness to trophic factors, chiefly insulin and IGF-1; 3) increased oxidative and other cellular stresses; 4) mitochondrial dysfunction; 5) inflammation; and 6) proneness to second hits. The common thread is that insulin resistance is the main culprit driving non-CNS aging-related pathologies. Insulin resistance coupled with mitochondrial dysfunction and stress drive activate pro-inflammatory responses in adipose tissue and cause insulin resistance possibly cause immune dysfunction and inflammation of adipose tissue drives insulin resistance [143, 144].

TRANSITION FROM BENIGN TO MALIGNANT BRAIN AGING

Stages, enablers, and mediators

Aging (senescence) can be divided into three stages: benign, intermediate, and malignant. Lessons from various species have taught that benign senescence is likely mediated by low levels of insulin and IGF resistance, the effects of which are worsened by wear and tear-induced mitochondrial DNA damage, oxidative stress, and impairments in microvascular perfusion. However, despite increased vulnerability to the effects of injury due to reduced efficiency of repair, adaptive measures enable endurance and recovery from mild or transient insults, e.g., physical trauma, infection, or inflammation, with the maintenance of the benign senescent phenotype. However, with subacute or chronic conditions that compromise mitochondrial function or promote cellular stress and inflammation senescing CNS cells become poised for metabolic dysregulation due to the co-existing declines in insulin and IGF-1 trophic factor availability and responsiveness relative to the non-aged state [112].

Transition forces

The transition from benign to intermediate senescence is likely enabled or driven by superimposed lifestyle factors and exposures such as obesity, ultraviolet radiation, smoking, excessive alcohol consumption, and hypertension, or repeated second hits, e.g., physical trauma, infection, and inflammatory processes, that exacerbate insulin resistance, oxidative stress, DNA damage, or deficiencies in microvascular perfusion. Lowering the threshold for aging-associated cellular and tissue damage increases the efforts required to repair, recover, and homeostatically restore benign senescence. Cumulative effects of incomplete recovery cause permanent cellular pathology marked by constitutively higher levels of insulin/IGF-1 resistance, mitochondrial dysfunction, oxidative stress, and DNA damage. Correspondingly, longevity is linked to the intactness of the related networks, and adaptive/compensatory mechanisms generally are sufficient to overcome the adverse impacts of mild, transient insults and restore cellular homeostasis.

Intrinsic versus extrinsic factors governing transition

That trajectory toward malignant brain aging is enabled by both intrinsic and extrinsic factors. Intrinsic enablers are facts of life and impossible to modify. Extrinsic enablers correspond to the effects of lifestyle choices and exposures that are potentially within modifiable reach. The most notable intrinsic enablers include progressive advancement in chronological age, inherited gene mutations or allelic variants such as presenilin mutations, *APOE* ε4 genotypes, and Down syndrome, each of which has been associated with impairments in brain insulin, IGF-1, and related polypeptide expression and signaling [32, 33, 70, 145, 146], and increased genetic susceptibility to the effects of extrinsic factors and exposures. The extrinsic enablers of malignant brain aging include systemic metabolic disorders such as obesity, diabetes mellitus, non-alcoholic fatty liver disease (NAFLD), and metabolic syndrome, cerebrovascular pathologies, repeated bouts of general anesthesia, head trauma, and severe inflammatory states such as with COVID-19 infections, early life exposures to particle 2.5 in air pollution [147, 148], and chronic exposure/consumption of nitrosamine-containing products [149–152]. The emergence and progression of chronic deficits in trophic factor signaling, particularly via insulin and IGF-1, challenge and ultimately prevent cellular function resets to former healthier states.

Enabling role of impaired insulin/IGF signaling mechanisms

Rooted in all the above aging-associated enablers of benign-to-malignant aging transition are pathophysiological processes linked to dysregulated insulin/IGF-1 signaling through cellular metabolic, growth, and survival pathways, leading to mitochondrial dysfunction, abnormal protein aggregation, increased oxidative and endoplasmic reticulum stress, aberrant autophagy, and abnormal post-translational modification of proteins, all of which are signature features neurodegeneration [153]. Aberrant post-translational modifications of molecules render them non-functional. Attendant adverse effects on enzymes, macromolecules, and a range of cellular processes exacerbate neuroinflammation, oxidative stress, and trophic factor receptor resistances. Early onset and progressive impairments in insulin and IGF trophic factor supply, receptor responsiveness, and downstream intracellular signaling are well-established as features of AD neurodegeneration [154–163].

Malignant aging-arrival

In essence, the transition from benign to malignant aging is marked by dysregulated energy metabolism superimposed on states of cellular stress and inflammation [164]. Unmitigated, these same pathologies force the transition from malignant aging to neurodegeneration via a self-reinforcing loop in which each component pushes the others [153], culminating in signaling impairments that disrupt pro-growth, pro-survival, anti-stress, anti-inflammatory, and anticell death mechanisms. Energy deficits caused by mitochondrial dysfunction and DNA damage worsen oxidative injury and drive destructive pro-inflammatory, pro-stress, and pro-death pathways. Cellular dyshomeostasis promotes cell loss, synaptic disconnection, and deficits in neuronal plasticity, and accompanying pro-inflammatory and pro-stress mechanisms activate unfolded protein responses that further drive pro-stress and pro-death responses as characteristically occur with neurodegeneration [165, 166].

Type 3 diabetes concept of AD

Over the past several decades, extensive research confirmed that the pathophysiology of AD extends well beyond Aβ and pTau accumulations. Important to this revelation were the findings in humans that AD is associated with significant impairments in brain glucose utilization [153, 167, 168], energy metabolism, trophic factor expression and responsiveness, and signal transduction networks stemming from the insulin and IGF-1 receptors and extending downstream through PI3K-Akt pathways [154, 162, 169]. Moreover, the discoveries that dysregulated insulin/IGF-1 signaling impairments arise early, progress with severity of AD [154], and correlate with *APOE* ε4 genotype [170] provide substantive support in favor of a causal relationship. In addition, clinical studies demonstrating improvements in memory, cognition, and brain metabolism following insulin administration [171–174] reinforce the importance of intact brain insulin/IGF-1 signaling networks as critical mediators of cognitive function.

In many respects, the fundamental metabolic and related pathophysiologies identified in AD, including mitochondrial dysfunction, cellular stress, inflammation, autophagy, and activation of unfolded protein response mechanisms, are reminiscent of diabetes mellitus [30, 164, 165, 175, 176] (Table 2). However, since the deficiencies in brain insulin correspond to type 1 diabetes, while the impairments in receptor responsiveness, i.e., insulin resistance, corresponded to type 2 diabetes, the co-existence of both pathologies in AD led to the concept that AD should be regarded as a distinct form of brain-predominant diabetes, and thusly was dubbed, “Type 3 Diabetes” [169, 175]. Correspondingly, epidemiologic studies in elderly humans and experimental animal models have consistently demonstrated that dysfunctional brain insulin signaling characterized by brain insulin resistance results in cognitive decline with clinical features reminiscent of AD [177]. Furthermore, AD phenotypic features of cognitive impairment, with or without Aβ burdens, are significantly correlated with systemic metabolic disorders and insulin resistance, including in patients with type 2 diabetes mellitus, metabolic syndrome, polycystic ovarian syndrome, and NAFLD [165, 178]. These disease states share with sporadic AD increased inflammation, oxidative stress, and mitochondrial dysfunction [30, 165, 178]. Defective insulin signaling with systemic insulin resistance drives neuroinflammation and may play a significant role in AD pathogenesis [164, 179].

Experimental models of type 3 diabetes

Fortunately, the availability of experimental models generated by intracerebral-ventricular injection of streptozotocin (icv-STZ) or chronic high-fat diet feeding helped enhance our understanding of how insulin resistance leads to neurodegeneration. The icv-STZ treatments cause AD-type neurodegeneration with cognitive impairment, brain atrophy affecting all the known targets in AD, increased Aβ deposits, tau phosphorylation, neuroinflammation, oxidative stress, and mitochondrial dysfunction in the cortex [149, 150, 180–182]. In addition, icv-STZ causes significant deficits in brain glucose utilization and metabolic abnormalities reminiscent of diabetes mellitus but localized in the brain [183–186].

Chronic high fat feeding, in addition to obesity, causes cognitive impairment, brain atrophy, increased tau phosphorylation, oxidative stress, neuroinflammation [116, 117,

187, 188], and deficits in cholinergic function [189]. However, the AD-type pathology is less severe in the obesity compared with the icv-STZ model, and Aβ deposition has not been observed unless combined with low-dose nitrosamine exposures [152]. Taken together, these findings align with the emerging dual profiles of AD/type 3 diabetes: one associated with progressive and eventually severe dementia and neuroimaging detectable increased Aβ burdens, and the other characterized by cognitive-behavioral abnormalities but without substantial or even detectable Aβ. However, both groups exhibit brain insulin signaling impairments, but the latter tends to be associated with systemic insulin resistance diseases including type 2 diabetes, obesity, and NAFLD. The Type 3 Diabetes hypothesis is supported by the findings that: 1) icv-STZ-mediated neurodegeneration was remediated by treatment with insulin sensitizer drugs that have dual anti-inflammatory effects, namely peroxisome proliferator-activate receptor (PPAR) agonists [180–182, 190]; 2) humans with early-stage AD exhibit improvement of cognitive function and reduced AD biomarker indices by exercise routines that restore insulin responsiveness [191–197]; 3) anti-Aβ, anti-inflammatory, or antioxidant monotherapies have not proven effective for reversing or stabilizing clinical AD or Aβ-plaque-independent neurodegeneration [198–201], although early encouraging results from the latest Phase III anti-Aβ clinical trial using Donanemab showed significantly lower percentages of cognitive decline relative to placebo, after 1-year of treatment (https://investor.lilly.com/news-releases/news-release-details/lillys-donanemab-significantly-slowed-cognitive-and-functional).

Rationale for addressing type 3 diabetes in relation to dysregulated signaling through the mechanistic target of rapamycin (mTOR)

In both human cases and experimental models of AD, the dominant abnormalities identified in relation to impairments in insulin/IGF-1 intracellular signaling involve PI3K-Akt pathways that mediate neuronal plasticity, cell survival, energy metabolism, and cellular homeostasis. However, earlier segments of this review highlighted the need to understand the full spectrum of AD pathology given that all brain cell types and tissues are affected by benign aging, malignant aging, and neurodegeneration, but their differential responses shift with disease progression. Compensatory adaptive responses must be distinguished from pro-degenerative reactions and managed accordingly. Furthermore, emerging science pertaining to mTOR pathway regulation and crosstalk continues to inform about how dysregulated signaling broadly impacts fundamental cellular processes including protein synthesis, myelin generation and maintenance, cell survival, energy metabolism, mitochondrial function, autophagy, nutrient uptake, inflammation, oxidative stress, and plasticity, all of which are altered in AD.

Relevance of mTOR pathway dysregulation in AD-type neurodegeneration is further suggested by the findings of: 1) worsened cognitive impairment, Aβ load in senile plaques, and stress-induced neuronal injury with reduced brain levels of phosphorylated insulin receptor and IRS-1, and signaling through Akt, mTOR, 70 kDa ribosomal protein S6 kinase (p70S6K), extracellular signal-regulated kinase-1/2 (ERK1/2), and Phosphatase and tensin homolog (PTEN) in AβPP/PS1 mice [202]; and 2) Rapamycin-induced amelioration of AD pathology in a systemic diabetes-STZ model [203] in which the therapeutic responses were associated with reductions in hippocampal mTOR/p70S6K [203]. These diametrically

opposed experimental outcomes speak to the nature of the models. The first produced the spectrum of pathologies most often identified in moderate to severe AD and associated with broadly inhibited insulin/IGF-1 signaling through mTOR, whereas the second was more reminiscent of obesity/peripheral insulin resistance medicated cognitive decline and incomplete or modest AD-type pathology, together with inappropriate over-activation of mTOR. The take-home message is that beyond the concept of type 3 diabetes is the need to gain thorough understanding of how mTOR signaling either modulates or is modulated by aging neurodegeneration. Efforts must be made to evaluate the impact of dysregulated overactivation versus inhibition of mTOR pathways in different cell types and tissues in the brain in relation to benign aging, malignant aging, and neurodegeneration to optimize management at different stages of type 3 diabetes. To this end, the principal components of the mTOR signaling network and their alterations in aging and neurodegeneration are reviewed below.

THE MECHANISTIC (MAMMALIAN) TARGET OF RAPAMYCIN AND ITS DYSREGULATION AS A MEDIATOR OF MALIGNANT BRAIN AGING AND TYPE 3 DIABETES

Pathway overview

The mTOR signaling network is extremely complex and inter-connected with many other pathways. Its differential and at times, opposing roles during maturation, aging, and degeneration add to the complexity of how impairments in signaling might be managed to support brain function in different circumstances. Interest in mTOR stems from its critical roles in regulating insulin and IGF-1 signal transduction along metabolic, growth, anti-inflammatory and pro-survival pathways, and evidence for its relevance to all brain cell types affected by malignant aging/neurodegeneration. Correspondingly, strong evidence suggests that significant impairments in the expression and function of upstream modulators of mTOR in the Insulin/IGF1-PI3K-Akt pathway alter mRNA and protein expression and protein phosphorylation relevant to AD in humans and experimental models [204, 205]. The paradox to bear in mind is that while studies have demonstrated prolonged longevity via inhibition of insulin and mTOR [205], even enhancement of cognition or reversal of experimental AD by rapamycin [203], progressive and established AD in both humans and experimental models are associated with brain insulin resistance [12, 117, 154, 162, 163, 176, 182, 206–208]. The bulk of this review addresses abnormalities in mTOR signaling in relation to brain insulin resistance and its consequences linked to malignant aging and neurodegeneration.

In brief, mTOR signaling is mediated by two main complexes termed mTORC1 and mTORC2 in which mTOR functions as the central catalytic subunit. mTORC1 is sensitive to rapamycin and mTORC2 is not. The mTORC1 complex is composed of mTOR, Raptor, mammalian lethal with SEC13 protein 8 (mLST8), proline-rich Akt substrate of 40 kDa (PRAS40), and DEP domain-containing mTOR interacting protein (Deptor) and localized in endosomal and lysosomal membranes. mTORC2 is composed of mTOR bound to Rictor, Protor-1/2, mammalian stress-activated MAP kinase interacting protein 1 (mSIN1), mLST8,

and Deptor, and associated with the plasma and ribosomal membranes [209]. mTOR's impact on cell growth, plasticity, and responses to stress is mediated by control of protein synthesis its regulation of mRNA translation, and protein degradation via autophagy [210]. mTORC1 is regulated broadly by stimuli such as growth factors (Insulin/IGF-1), stressors including hypoxia and nutrients, and energy status, while mTORC2 is largely regulated by growth factor stimulation. Therefore, both mTORC1, which ultimately modulates energy metabolism and responses to stress, and mTORC2 which has important roles in cell growth and survival, are potential targets of malignant aging because impairments in insulin/IGF-1 signaling would likely compromise the activation of both pathways [205].

Function and dysfunction of mTOR signaling in AD

Most of the prior research detailing roles for dysregulated signaling through insulin and IGF pathways in AD characterized abnormalities in trophic factor expression, receptor responsiveness, and downstream relays through insulin receptor substrate (IRS) proteins, PI3K, Akt, and glycogen synthase kinase-3 (GSK-3). However, within the past several years, comprehensive analysis of further downstream signaling responsible for cell survival, growth, protein synthesis, autophagy, homeostasis, and metabolism in other systems has provided information that should be extended to the CNS in relation to aging and neurodegeneration. This section elucidates aging- and AD-related dysfunction of the major mTOR pathway components expressed in the brain. The roles of major mTOR pathway proteins and phosphoproteins and their functions in the brain are summarized in Supplementary Table 1.

Insulin and IGF-1 trophic factors and receptors

Insulin is a master regulator of cell growth, energy metabolism, mitochondrial function, autophagy, oxidative stress, synaptic plasticity, and cognitive function. Insulin mediates these effects by functioning alongside its closely related molecule, insulin-like growth factor, type 1 (IGF-1). Impairments in insulin/IGF-1 signaling such as occur with insulin resistance diseases characteristically result in chronic inflammation, oxidative stress, dysregulated energy metabolism, mitochondrial dysfunction, and deficits in cognitive-behavioral functions [153, 157, 158, 165, 211], corresponding to the effects of aging. Therefore, it should not be a surprise that the maintenance of intact insulin and IGF-1 signaling is mechanistically linked to longevity, protein homeostasis, learning and memory, and protection from premature senescence.

Throughout the brain, insulin and IGF-1 transmit signals from their cell surface receptors via autophosphorylation and activation of intrinsic receptor tyrosine kinases [160, 212], followed by a sequence of phosphorylation events relayed through the multifunctional insulin receptor substrate types 1 and 2 (IRS-1/2) docking proteins, PI3K, Akt, and GSK-3 [30, 204, 213, 214]. Beyond these intermediate levels, insulin and IGF-1 mediate their regulatory effects on protein and lipid biosynthesis and degradation, gene expression, energy metabolism, cellular homeostasis, and a host of critical cellular functions such as survival, growth, motility, differentiation, repair, autophagy, cyto-protection, and neurotransmitter actions by engaging downstream components of the signaling network. Under normal circumstances, most of these signaling and cellular responses are tightly regulated through

the actions of kinases and phosphatases that alter phosphorylation states to rapidly, and for the most part, transiently enable or disable specific inter-molecular interactions and enzyme activities. However, chronic reductions in trophic factor supply or receptor responsiveness can have devastating effects on many critical cellular functions due to compromise of pathway activation or suppression needed to meet the intended goals of the signaling networks. The eventual failure of transient compensatory mechanisms leads to deficits in energy metabolism coupled with increased inflammation, oxidative stress, and proneness to cell death, all of which are fundamental cellular pathologies in AD.

All major cell types in the brain, including neurons, oligodendroglia, astrocytes, microglia, and microvascular networks are responsive to insulin and IGF-1 stimulation. Shared cellular responses include increased survival, growth, energy metabolism, repair, and homeostasis, and reduced stress and pro-apoptosis signaling. In addition, in neurons, insulin and IGF-1 stimulate plasticity, migration, and cholinergic function [157, 160, 176, 212]. For oligodendrocytes, IGF-1 more than insulin stimulates myelination and maintenance of myelin integrity [74]. Insulin and IGF-1 also positively impact homeostatic functions in quiescent astrocytes, microglia, and micro-vessels [74]. Correspondingly, the loss of trophic factors stimulation due to withdrawal or receptor resistance adversely impacts all cellular and structural elements in the CNS, the consequences of which include impairments in anti-inflammatory, antioxidant, anti-apoptotic, pro-growth, pro-survival, and pro-metabolic functions, and functional integrity of the microvascular network and blood-brain barrier.

In AD, early-stage and progressive declines in the expression and tyrosine phosphorylated levels of both insulin and IGF-1 receptors correspond with significant impairments in brain insulin and IGF-1 signaling and reduced levels of tyrosine phosphorylated IRS-1/2 [154, 162, 169]. The most substantial reductions in brain trophic factor and receptor expression and corresponding receptor tyrosine kinase activation occur with end-stage AD. The combined loss of both endogenous trophic factors and tyrosine phosphorylated receptors prompted the designation of AD as ‘Type 3 Diabetes’ [169, 175]. In addition to cortical atrophy with neuronal loss and increased abundance of tauopathy-associated lesions (which correlate with dementia severity), type 3 diabetes is associated with progressive white matter atrophy, increased activation of astrocytes, and microglial and microvascular pathology [74].

The findings in postmortem brains and brain tissue correspond with earlier studies that demonstrated impairments in cerebral glucose metabolism linked to neuronal damage [215], suggesting insufficiency in neuronal insulin and insulin receptor function. Subsequently, an elegant *in vivo* study provided solid evidence supporting the concept that impairments in brain insulin signaling with receptor resistance are features of AD neurodegeneration [162]. The now widely used intracerebroventricular streptozotocin (icv-STZ) model of AD has repeatedly demonstrated that cognitive impairment and neurodegeneration, including Aβ accumulation develop with brain insulin and IGF-1 deficiencies and resistances accompanied by impairments in signaling through IRS-1, PI3K, and Akt with increased activation of GSK-3β, oxidative stress, and neuroinflammation [182, 207]. Equally pertinent were the findings that treatment with PPAR agonists that addressed both the delta and gamma receptors expressed in the brain, and function as insulin sensitizers and antioxidants, prevented cognitive impairment and AD-type neurodegeneration in icv-STZ models [180–

182, 190, 216]. The PPAR-δ/γ agonist treatments restored insulin/IGF-1 signaling through PI3K-Akt while reducing GSK-3β activation, oxidative stress, neuroinflammation, effects that were associated with normalization of brain weight, white matter integrity, and cholinergic functions [180–182]. Correspondingly, experimental upregulation of PPAR-γ abates insulin resistance [217], and Rapamycin restores cognitive performance and mitochondrial dysfunction in the icv-STZ model [203]. Furthermore, PPAR agonist treatment of AD in humans has been rationally proposed, but as a monotherapy has not produced overt clinical improvement [218–221]. On the other hand, recent evidence suggests that novel small molecule dual targeting of PPAR-δ/γ (T3D-959) [222], or both insulin-related metabolic and inflammatory dysfunction [223, 224] have shown promise in placebo-controlled clinical trials for patients with early stage AD.

Insulin receptor substrate

IRS, IRS-1/2, are major docking proteins that transmit signals downstream from the insulin and IGF-1 receptors to mediate cell growth, survival, energy metabolism, homeostatic, anti-stress, and repair functions [157, 160, 176, 212]. These outcomes are achieved via receptor tyrosine kinase phosphorylation of IRS-1/2, which signals downstream through PI3K-Akt [225–228]. PI3K signaling through Pyruvate dehydrogenase kinase 1 (PDK1) phosphorylates the tuberous sclerosis complex 1/2 (TSC1/2) and PRAS40 [229], and serine phosphorylation of TSC1/2 releases TSC's inhibition on mTOR/mTORC signaling [229]. In contrast, serine phosphorylation of IRS-1/2 provides negative feedback such that its inhibitory effects cause insulin resistance and mitochondrial dysfunction [225].

Studies of AD brains have detected reduced expression of IRS-1/2 mRNA transcripts [162, 175] or proteins, reduced tyrosine phosphorylated IRS-1/2, or increased serine phosphorylated IRS-1/2 [207]. These abnormalities could account for the associated impairments in PI3K/Akt signaling with reduced levels of serine phosphorylated Akt, reflecting lower levels of Akt kinase activity, and reduced levels of serine-phosphorylated GSK-3β, reflecting increased activation of GSK-3β kinase [230], which promotes oxidative stress, tau phosphorylation, pro-apoptosis mechanisms, and mitochondrial dysfunction [30]. Certainly, inhibition of IRS-1/2 signaling due to reduced receptor tyrosine kinase activation of IRS-1/2 would be consistent with the evidence for insulin/IGF-1 resistance in AD brains. On the other hand, some reports suggest that IRS-1/2 gets inactivated via feedback inhibition of insulin/IGF-1 due to over-activation of the serine/threonine kinase Akt and phosphorylation of its downstream targets, including mTOR [214]. Correspondingly, increased levels of two mTOR downstream targets, p70S6K and 4EBP1, were detected in brains with AD MCI, and in Down syndrome (DS), with and without dementia [231]. These points are discussed below. Since the opposing concepts of direct IRS-1/2 inhibition versus negative feedback inhibition could suggest disparate therapeutic interventions, additional studies are needed to delineate the facts in relation to the development and progression of AD in humans.

Akt (protein kinase B)

Akt is a serine/threonine kinase that stimulates that stimulates growth, survival, and energy metabolism in neurons and oligodendrocytes [225, 230, 232]. Inhibition of

Akt decreases neuronal and oligodendrocyte functions [233–237] including myelination, which is intricately involved in mTOR signaling [238, 239]. Akt kinase activation via phosphorylation on T308 or S473 differentially modulates mTOR signaling. PI3K-PDK-mediated phosphorylation on T308 leads to the phosphorylation of TSC1/2 at S939 and T1462, and downregulation of the GTPase activating potential of tuberin, the gene product of the TSC2, as well as inhibition of Ras homolog enriched in brain (RHEB), a potent regulator of the mTOR signaling [238, 240, 241]. Akt kinase activation due to phosphorylation at S473 inhibits TSC1/2 and PRAS40 [229] with activation of mTORC2 kinase [242]. Akt kinase is also an important negative regulator of GSK-3β and PTEN. Aberrantly increased GSK-3β and PTEN are associated with tau hyperphosphorylation and formation of PHF-associated dementia-linked pathologies, including dystrophic neurites, NFTs, and neuropil threads.

Nearly all studies agree that in AD Akt kinase activity is altered with dysregulation of PI3K-Akt-mTOR signaling. However, the results fall into two seemingly opposite camps: one suggests that increased PI3K-Akt signaling with inhibition of GSK-3β and PTEN leads to overactivation of mTOR with impairments in autophagy, accounting for Aβ and pTau accumulations in the brain [204, 231]. The opposing argument is that PI3K-Akt signaling is inhibited, leading to GSK-3β over-activation, aberrant tau phosphorylation, and increased oxidative stress with attendant Aβ accumulation [204, 243]. These disparate conclusions may stem from the timing or stages of the disease examined, as well as the nature of experimental models.

The findings with respect to aging and similarities with early-stage AD may explain the Akt activation paradox. In an experimental aging model, subtle declines in spatial learning and memory, working memory, and behavioral flexibility were found associated with impairments in hippocampal synaptic remodeling [244]. Accompanying dysregulated signaling through Akt-mTORC1-p70S6K marked by increased levels of phosphorylated AMP, GSK-3β, and p70S6K with hyperphosphorylation of mRNA translational elongation factor 2 (TEF2) and AMP-activated protein kinase (AMPK), suggested that over-activation of these pathways occurs with aging [244]. Aging and AD were distinguished by the selectively increased levels of eIF2alpha phosphorylation in AD [244].

In another study, increased Akt activity in AD brains was suggested by the higher levels of *in vitro* GSK-3α/β fusion protein phosphorylation and accompanying elevated levels of serine-phosphorylated Akt immunoreactivity in degenerating pyramidal neurons and reactive astrocytes [245], although the results were not normalized to the total Akt protein levels. Mechanistically, independent reports linked brain accumulations of pathogenic forms of Aβ to aberrantly sustained overactivation of PI3K/Akt signaling, non-responsive insulin and IGF-1 receptors, and altered phosphorylation, conformation, and function of tau [214]. One hypothesis is that Aβ can over-activate the PI3K/Akt/mTOR axis, which plays a central role in proteostasis [231]. The proposed consequences include decreased autophagy, inhibition of IRS1 and GSK-3β activity, and increased mTOR signaling to promote the progression of AD neuropathology [231]. The further argument was that in AD, the accumulation of Aβ neurotoxic oligomers and hyperphosphorylated tau occurs due to impairments in the autophagy-mediated clearance of abnormal proteins [204]. Correspondingly, while reduced

autophagy (Beclin-1 and LC-3) was detected in brains with preclinical-AD, MCI, or AD and significantly increased levels of Aβ (1-42), hyperactivation of the PI3K/Akt/mTOR pathway and decreased phosphatase and tensin homolog were features of disease progression, i.e., MCI and AD, but not pre-clinical AD. Similarly, in DS brains, with and without AD pathology, the PI3K/Akt/mTOR axis was reported as hyperactivated relative to control. Finally, aberrant activation of the PI3K/Akt/mTOR axis may act in parallel with the Regulator of calcineurin 1 (RCAN1) in phosphorylating tau in DS and DS with AD [246]. Together these studies suggest that modulating PI3K/Akt to inhibit mTOR autophagy could be restored as a means of reducing AD neuronal degeneration [204].

Several studies of postmortem brains with AD have demonstrated that signaling through Akt is significantly reduced and GSK-3β increased as evidenced by reduced levels of pS473-Akt and pS9/21-GSK-3β [154, 162, 169, 204]. Similarly in intracerebral STZ models of AD, Akt phosphorylation is significantly reduced together with elevated levels of unphosphorylated GSK-3β (active) [182]. Downstream signaling through mTOR/mTORC1 was also inhibited. Concomitantly increased levels of pTau, neuroinflammation, and oxidative stress were also observed. Inhibition of Akt signaling in both gray and white matter structures would account for the pro-stress, pro-apoptosis signaling, perturbations in energy metabolism detected by neuroimaging, and mitochondrial dysfunction reported for AD brains as well as many models of AD. Conceivably, the disparate findings with respect to Akt and mTOR may be related to alterations that occur in different subcellular compartments. In this regard, mTORC1 is localized in endosomal and lysosomal membranes [209, 247] whereas mTORC2 is associated with the plasma and ribosomal membranes [209]. The mTORC1 and mTORC2 signaling networks mediate complex functions such that dysregulation can cause aberrant growth or cell death, enhanced or impaired energy metabolism, clearance or accumulation of abnormal proteins, collapse or reorganization of the cytoskeleton. Additional studies are needed to delineate how the PI3K-Akt to mTOR/mTORC1/2 signaling pathways are modulated at different stages of neurodegeneration and within various cell types and subcellular compartments.

Glycogen synthase kinase-3

GSK-3 has two main subtypes, alpha and beta. These multifunctional serine/threonine kinases are ubiquitously expressed in eukaryotes, regulating a broad spectrum of signaling pathways in response to the activation of receptor tyrosine kinases, Wnt, and G-protein-coupled receptors. Outcomes of GSK-mediated signaling include regulating cell cycle progression and glycogen metabolism. Signaling via GSK-3 is typically mediated by phosphorylation and inhibition of constitutively negative regulatory controls [248].

GSK-3α and GSK-3β have distinct subcellular localizations and functions. GSK-3α is primarily localized in the nucleus and functions by downregulating G1 cyclins, suppressing E2F and markers of cell proliferation [249], and possibly protecting against aging-associated brain pathologies [250] or modulating neurobehavioral/psychiatric functions [251] including depression [252]. Serine-21 phosphorylation of GSK-3α inactivates the kinase [249], which when mediated by Interleukin-1β activation of inhibitor of Kappa B (IKKi) results in Akt activation of mTOR [253]. Regarding its potential role in AD, one report suggested that the

inhibition of GSK-3α reduced Aβ production [254] but in a separate study, no evidence was found that either GSK-3α or GSK-3β mediated control of AβPP processing in the brain [255]. In an early study that utilized transfected COS cells, over-expression of GSK-3α or GSK-3β decreased tau's electrophoretic mobility, reminiscent of PHF-tau in AD [256]. However, subsequent immunohistochemical staining studies failed to co-localize GSK-3α or GSK-3β within the NFT-rich region of the hippocampal formation in AD brains [257]. Further research utilizing more advanced approaches is needed to uncover potential roles for aberrant GSK-3α in relation to neurodegeneration.

GSK-3β is ubiquitously expressed in the CNS and functions as a master regulator of signaling through multiple major pathways including Canonical Wnt (β-catenin), Notch, receptor tyrosine kinases, G-protein coupled receptor, and sonic hedgehog [230, 248], modulating critical functions such as neurogenesis, plasticity, and synaptic transmission [258,259]. Excessive activation of GSK-3β, i.e., high levels of the constitutively active, un-phosphorylated protein, is a feature of neurodegenerative diseases [207, 254, 260–262]. GSK-3β inhibits mTORC1-mediated expression of synaptic proteins and neuronal proteins needed for post-injury regeneration [263, 264], axon formation, neuronal migration, and cytoskeleton regulation [265]. GSK-3β mediates its effects in part by targeting and phosphorylating PTEN for negative feedback on Akt [233, 237, 266, 267]. GSK-3β is negatively regulated by Serine-9 phosphorylation [230] through the actions of Akt, protein kinase A (PKA), and 90 kDa ribosomal protein S6 kinase 1 (P90RSK) [268], which is critical for the positive regulation of neuronal and oligodendrocyte responses to insulin and IGF-1 receptor tyrosine kinase signaling through IRS1/2-PI3K-Akt-mTOR [213].

Dysregulated GSK-3β has been implicated in the pathogenesis of AD pathologies including tau hyperphosphorylation, impairments in synaptic plasticity, and Aβ neurotoxicity. Tau hyperphosphorylation linked to PHF pathologies including dystrophic neurites and NFTs in AD [254] is associated with increased activation of GSK-3β, as well as other kinases including cyclin-dependent kinase-5 and p38 mitogen-activated protein kinase (MAPK) [30, 256]. Correspondingly, GSK-3 was shown to be prominently increased in neuronal cell bodies and processes and co-localized with neurofibrillary changes in AD brains [269]. At the same time, neuronal phosphatase activity was found to be reduced, which could account for excessive GSK-3β activity [270]. Beyond neuronal degeneration, abnormal tau also has been detected in oligodendrocytes and astrocytes [269], expanding our understanding of the extent to which tauopathy impacts neurodegeneration.

GSK-3β's role in Aβ accumulation and neurotoxicity has been suggested by the findings in experimental models. Evidence suggests that Aβ activates GSK-3β through impairment of phosphatidylinositol-3 (PI3)/Akt signaling, and that Aβ-activated GSK-3β induces hyperphosphorylation of tau, NFT formation, neuronal death, synaptic loss, and memory deficits [254]. Furthermore, inhibition of GSK-3 can reduce Aβ production [254].

The STZ model of AD which causes cognitive impairment with brain metabolic dysregulation through insulin and IGF-1 receptors, PI3K, Akt, and downstream signaling networks exhibits dysregulation of GSK-3β activity that varies with the time course of the model, but also leads to increased Aβ deposition in plaques and vessels [149, 271].

Like AD which shares most molecular, biochemical, and signal transduction abnormalities with diabetes mellitus, intracerebroventricular STZ causes tau phosphorylation linked to increased GSK-3β activity, inhibition of Akt, increased oxidative stress, pro-apoptosis mechanisms, neuroinflammation, oligodendrocyte pathology, and white matter atrophy and degeneration [149, 182, 207, 272, 273], all of which are linked to dementia [12].

Phosphatase and tensin homologue deleted from chromosome 10 (PTEN).— PTEN is a dual protein tyrosine and lipid phosphatase that has inhibitory actions on PI3K-Akt, MAPK, mTORC1, and mTORC2 [274]. PTEN dephosphorylates PI3,4,5 and PI3,4, inhibiting PI-dependent kinase activation of Akt, downregulating cell growth, proliferation, motility, survival, and plasticity, and promoting apoptosis [232, 259, 275–277]. PTEN's inhibition of MAPK compromises neurite outgrowth and causes growth cone collapse [236, 258, 278]. PTEN's inhibitory effects on mTORC1 are due to reductions in PI3K-Akt, but its inhibitory effects on mTORC2 are effectuated by targeting Rictor's association with mTOR [279]. In contrast, the loss of PTEN activity positively affects neuronal functions marked by enhanced proliferation, migration, survival, plasticity, and morphology [275]. These responses are achieved by constitutively active protein kinase (Casein kinase 2; CK2) phosphorylation of PTEN which inhibits function by reducing PTEN's membrane interactions and lipid binding [280, 281], and GSK-3β phosphorylation [213] which inhibits PTEN's function despite stabilization of the protein [281]. Therefore, despite increased stabilization of PTEN protein by CK2 and GSK-3β, its functional inhibition enhances mTOR signaling.

In AD, immunohistochemical staining studies demonstrated altered PTEN cellular and subcellular distributions with increased immunoreactivity in oligodendrocytes and astrocytes, reduced neuronal labeling [282], and excessive recruitment of PTEN into synapses correlating with synaptic depression [277]. Reduced PTEN was most conspicuous in damaged neurons that exhibited classical neuritic pathology, i.e., neuropil threads, dystrophic neurites, or NFTs [283, 284]. To interpret the altered distributions of PTEN in relation to associated impairments in downstream signaling through Akt/mTOR requires other considerations as to whether the aberrantly expressed PTEN has phosphatase activity. As mentioned CK2 and GSK-3β phosphorylation renders PTEN enzymatically inactive [280, 281], yet phosphatase-dead (mutant) PTEN increases tau aggregation and impairs neurite outgrowth [283] while experimental overexpression of PTEN alters tau phosphorylation, increases taumicrotubule association, and decreases the formation of tau aggregates. Tau's ability to interact with PTEN, together with the finding that experimental deletion of tau (mouse model) causes insulin resistance and impairs synaptic plasticity, suggest that Tau-PTEN interactions are important for metabolic signaling [208] and implicate PTEN malfunction as a mediator of tau pathology in degenerative/insulin resistance diseases like AD, diabetes mellitus [285]. Complicating the scenario is evidence that at some stages of AD-type neurodegeneration, the PI3K/Akt/mTOR pathway may be hyper-activated vis-a-vis PTEN inhibition and impairments in autophagy in brains with MCI or AD relative to normal aging or preclinical AD [231]. Similarly, in early, pre-AD DS, brain insulin resistance develop is associated with mTOR hyper-activation which appears to be driven by PTEN inhibition [274]. Such findings have suggested that therapeutic inhibition

of mTOR is a viable strategy for AD. However, the ultimate transition to inhibition of mTOR signaling in the later stages of AD could be exacerbated by that approach. Another factor to consider is the potential role of PTEN-induced kinase 1 (PINK1).

PINK1, a mitochondrial serine/threonine kinase that recruits parkin to target and rid cells of damaged, dysfunctional mitochondria by autophagy [286], may have a critical role in PTEN-mediated impairments of mTOR signaling. PINK1's neuroprotective properties include its ability to promote degradation of abnormally accumulated tau and rescue neuronal loss, synaptic damage, cognitive impairment, and mitochondrial dysfunction via the lysosome pathway and ubiquitin-proteasome system, as demonstrated in a mouse model of tauopathy [286]. In addition, PINK1 may lessen Aβ accumulation in plaques [286]. Correspondingly, PINK1 dysfunction is integrally related to neurodegeneration. For example, in several genetic forms of early onset Parkinson's disease, PINK1 mutations result in failure to protect cells from stress-induced mitochondrial dysfunction or apoptosis, and lead to mitochondrial accumulations of misfolded proteins [287]. PINK1 dysfunction may also have roles in mitochondrial dysfunction and altered mitophagy linked to neurodegeneration [288, 289] associated with motor neuron disease (amyotrophic lateral sclerosis), Huntington's Disease, and AD [286, 288–293]. Regarding AD, Aβ accumulation, which could be mediated by reduced PINK1 function, drives PTEN (inactive) accumulation at synapses, inducing synaptic depression and perturbing memory [294]. Regardless of mechanisms, PINK1-mitochondrial dysfunction with attendant increased oxidative stress and dysregulated metabolism, unfolded protein response, and autophagy mark impairments in mTOR signaling needed for homeostasis and function of every cell type within the brain.

Tuberous sclerosis complex protein 2 (TSC2; TSC1/2)

TSC is a critical regulator of mTOR signaling. The tuberous sclerosis gene encodes tuberin, a tumor suppressor, growth inhibitory protein, and an upstream regulator of mTOR. Tuberin's interaction with hamartin forms the TSC multi-protein complex that includes TSC2, TSC1, and TBC1D1 (TBC1 domain family member 1; conserved domain discovered In Tre2/Bub2/Cdc16; GTPase-activating). TSC1 and TSC2 regulation of mTOR is mediated through mTORC1 and mTORC2 via differential phosphorylation and kinase activation with outcomes such as increased dendritic arborization, axonal outgrowth, neuronal migration, and cortical lamination [295].

Non-phosphorylated TSC2 constitutively inhibits mTORC1 and its downstream activation of S6K [295–297]. Insulin and IGF-1 signaling through Akt [295, 297] and Erk1/2 [296–298] promote Ser-939 phosphorylation of TSC2, releasing its inhibitory hold on mTORC1 and S6K [296–298]. PRAS40 phosphorylation of TSC also disinhibits mTOR/mTORC1 signaling [299]. Another regulatory mechanism involves the stabilization of TSC2 and prevention of its ubiquitin-mediated proteasomal degradation by interacting with TSC1 [298]. The resulting TSC1-TSC2 heterodimeric complex physically associates with and activates mTORC2, while braking mTORC1 via RHEB GTP hydrolysis to RHEB-GDP [300]. Additional levels of TSC regulation occur via phosphorylation of TSC2 on Ser-1387 by AMPK, Thr-1227 by Wnt, and Ser-1345 via GSK-3β, and Wnt signaling through

GSK-3β to phosphorylate TSC, each of which stabilizes the TSC1-TSC2 complex and brakes mTORC1 [296, 301, 302].

In the brain, TSC1 and TSC2 regulate mTOR via the mTORC1 and mTORC2. Serine phosphorylated mTORC1/2 kinase activates mTOR, promoting mitochondrial function, cytoskeletal organization, cell migration, dendrite formation, glial differentiation, and lipid and protein metabolism while inhibiting autophagy [247, 303, 304]. TSC1 and TSC2 complexes promote dendritic arborization, axonal outgrowth, neuronal migration, and cortical lamination [295]. AMPK and GSK-3 activation of TSC1:TSC2 provide negative feedback inhibition of S6K in response to energy stress/depletion [295–297]. ROS and hypoxia increase GSK-3β activation and downregulate mTORC1, leading to increased synaptogenesis [263].

Potential links between TSC2 dysregulation and neurodegeneration were suggested by the finding that TSC1 and TSC2 mutations cause hyperactivity of the mTOR pathway, and with aging, increases tau hyperphosphorylation [305]. Furthermore, evidence suggests that TSC2 may represent a molecular link between PKR and aberrant mTOR signaling in AD [306].

Mechanistic mTOR

mTOR signaling is mediated via two main complexes termed mTORC1 and mTORC2. mTORC1 is composed of mTOR complexed with Raptor, TSC, mLST8, PRAS40, and DEPTOR and localized in endosomal and lysosomal membranes [209, 247]. mTORC2 is composed of mTOR bound to Rictor, Protor-1/2, mammalian stress-activated MAP kinase-interacting protein 1 (mSIN1), mLST8 and DEPTOR [299] and associated with the plasma and ribosomal membranes [209]. Therefore, mTOR is at the center of both mTORC1 and mTORC2. Besides TSC-mediated regulatory controls, mTORC1 is negatively regulated by rapamycin, whereas mTORC2 is generally insensitive to rapamycin, except in non-acute states when mTOR is phosphorylated at Ser-2481 [210, 304]. Furthermore, differences in their subcellular localizations provide selectivity or specificity of mTORC1 versus mTORC2 as substrates for activation or inhibition [210]. Rapamycin's inhibitory effects on mTORC1 are likely mediated by destabilization of the mTOR-Raptor complex [307].

Serine phosphorylation of mTOR marks its activated state [304] such that mTOR phosphorylated at Ser-2448 by p70S6K [247] binds to Raptor, activating mTORC1 kinase, but when phosphorylated at Ser-2481 by Akt-S6K [304], mTOR interacts with Rictor and activates the mTORC2 kinase [303, 304]. Adding to the complexity of regulatory controls over cellular responses is the fact that ^{pS2448}-mTOR can bind to both Raptor and Rictor to activate mTORC1/mTORC2 signaling [247, 304]. In essence, the activation of mTOR/mTORC signaling is dictated by the expression levels and phosphorylation states of components within the complexes.

mTOR-controlled signaling is responsive to cellular nutrition, energy levels, and growth factor stimulation. mTORC1 is modulated by insulin, amino acids, and glucose, while mTOCR2 is regulated by insulin/IGF-1 signaling [209, 308]. Outcomes of insulin/IGF-1/Akt stimulated increases in ^{pS2448}-mTOR leading to mTOR/mTORC1 activation include enhanced cellular proliferation, growth, RNA translation, nutrient metabolism [309],

lipogenesis, and lipid storage [229], and inhibition of autophagy [298]. Insulin/IGF-1 activation of mTOR/mTORC1 via Akt phosphorylation of PRAS40 inhibits autophagy, whereas the inhibition of mTOR promotes autophagy [310]. Crosstalk between mTORC2 and mTORC1 occurs via insulin/IGF-1 stimulated Akt and attendant phosphorylation of TSC1/2 [311], which is permissive to mTORC1 pathway activation. In essence, mTORC1/2 has broad cellular effects that include promoting mitochondrial function, actin cytoskeleton organization, cell motility/migration, and lipid and protein metabolism while inhibiting autophagy [247].

In the nervous system, mTOR/mTORC1/2 signaling regulates many integrated physiological functions including neuronal development, synaptic plasticity, long-term memory storage, and cognition [210]. Such responses are differentially regulated trophic factor stimulation, particularly insulin/IGF-1, oxidative stress, inflammation, and injury, and the effects can vary with acute versus chronic disease states, development, aging, and proneness to neurodegeneration. Akt phosphorylates and activates mTORC2 [240, 247] leading to modulation of cell growth, synaptic plasticity [312], glial development, myelination, memory, cognition, and behavior [299, 309]. Furthermore, Akt's check on RHEB, enables activation of mTOR/mTORC1 [229]. mTOR's role in synaptic plasticity is protein synthesis-dependent, functioning through PI3K and the NMDA receptor to mediate long-term potentiation or metabotropic glutamate receptor for long-term depression [313].

Integrated signaling through mTOR/mTORC1/2, as well as cytokines, Wnt, and forkhead transcription factors, can modulate stem cell proliferation, tissue repair and longevity, synaptic growth, apoptosis, and autophagy. Correspondingly, stimulation with gingko biloba extracts which enhance Akt/mTOR signaling increase neurite outgrowth comparable to the effects of neurotrophic factor stimulation [314]. Paradoxically, the pro-growth and proliferative effects of mTOR can be detrimental to CNS recovery [315] and exacerbate aging and neurodegeneration [244, 311]. In this regard, some evidence suggests that aberrant overactivation of insulin/IGF-1 signaling is mechanistically linked to aging and neurodegeneration and that longevity, protein homeostasis, learning, and memory can be enhanced by reducing activation of Akt and downstream targets, including mTOR [210]. Furthermore, the restorative effects of mTORC1 inhibition may be linked to enhancing autophagy and blocking translation of neurotoxic proteins [316, 317]. This concept is reinforced by data showing that by reducing insulin/IGF-1 signaling such as by decreasing IGF-1 receptor levels or inhibiting mTOR activity, Aβ and tau protein homeostasis shifts towards less toxic protein conformations along with improvements in cognitive function and extends healthy lifespan [214].

The fundamental confusion about positive versus negative effects of mTOR pathway activation stem from seemingly inconsistent results of rapamycin treatment paradigms in animal models and various human disease states. Interpretations of rapamycin experimental results are confounded by the complexity of its actions including strength of association with various binding partners [313], and indirect inhibition of ribosome-activated mTORC2 via chronic blocking of mTORC1 ribosome biogenesis [210]. The latter highlights the point that contrary to original claims, rapamycin is not always a specific inhibitor of mTORC1. Another area of disagreement pertains to therapeutic versus adverse responses to rapamycin.

In essence, the critical variable seems to be whether the mTOR-mTOR1/2 pathway is hyper-activated as observed in early stages of AD and disorders of psychiatric, alcohol, substance abuse, or neurodevelopment-behavioral origins [318], or inhibited/impaired as has been reported for established or later-stage AD, both in humans and experimental models [182, 205, 231, 319], alcohol-related brain disease [320, 321], experimental metabolic disorder models [322], hypoxia [323], and AD models with impaired neuroplasticity/ synaptic function [324]. The aggregate picture suggests that some timing-related aspects of neurodegeneration are associated with hyperactivation of mTOR, whereas others are associated with its inhibition [204]. Therefore, targeting mTORC1/2 for CNS disease remediation requires oversight of programmed cell death (apoptosis), autophagy, and necroptosis pathways, notwithstanding potential harm inflicted by unintended opposing responses [325]. Since all cell types are responsive to mTOR pathway signaling, their varied responses can significantly impact the overall outcomes, a phenomenon that must be considered in relation to the potential therapeutic tweaking of mTOR to remediate disease at different stages.

Dysregulation of mTOR signaling is associated with many neurological and psychiatric disorders including neurodegenerative diseases such as AD [299], autism spectrum disorders, psychiatric disorders, mental retardation syndromes and drug and alcohol use disorders [313, 318]. Evidence from pre-clinical and limited clinical studies suggest mTOR/ mTORC1 hyperactivation contributes to the behavioral brain pathology, and therefore may benefit by therapeutic inhibition of the pathways with rapamycin [299]. However, the characteristics of dysregulated mTOR/mTORC1/2 signaling vary with human disease stage and experimental animal model due to shifts in the emphasis on axonal sprouting, axonal regeneration, myelination, dendritic spine growth [242, 299]. Therefore, in contrast to hyperactivation states, conditions that result in inhibition of axonal growth or regeneration would likely benefit by mTOR/mTORC activation rather than suppression [299]. Other factors contributing to the complexity of results include the tendency to focus on specific cell types and brain regions, with narrow probing of the mTOR/mTORC1/2 pathways. In AD, all brain cell types are impacted by neurodegeneration, accounting for the loss of neurons, neuronal plasticity, oligodendrocyte function, white matter myelin integrity, regulatory control on neuroinflammation and stress, and microvascular functions needed to maintain glial and neuronal vascular networks and the blood-brain barrier [12, 74]. In neurons, mTOR signaling regulates neuronal development, synaptic functions including plasticity, and dendrite formation, highlighting its role in memory, cognition, and behavior [299, 309]. In oligodendrocytes, Akt stimulates myelination via mTOR signaling [238, 239, 326] with Akt activation of mTORC2 and S6K [295]. In astrocytes, mTOR/mTORC2 drives cellular activation, differentiation, and clearing of extracellular glutamate, whereas hyperactivation of Rictor-containing mTORC2 increases brain gliogenesis [309]. Since mTOR broadly impacts cellular functions, clinical strategies for AD that implement mTOR must achieve parallel objectives of protecting neuronal, vascular, and immune cell survival in conjunction with preserving networks that determine memory and cognitive function [327, 328].

There is now strong evidence that metabolic dysregulation in AD is mediated by impairments in insulin/IGF-1 signaling downstream through PI3K-Akt with abnormalities

that resemble pathologies in diabetes mellitus and other insulin-resistance diseases [207]. Related deficits in growth, cell survival, energy metabolism, mitochondrial function, control of autophagy, and synaptic plasticity implicate roles for impaired mTOR signaling as downstream mediators of neurodegeneration [182, 207, 313]. Correspondingly, in human brains and rodent models with AD neurodegeneration, mTORC1 and mTORC2 proteins, enzymatic activities [319] and their downstream targets [182] were shown to be reduced, whereas, in cellular models of AD, inhibition of mTORC1 increased autophagic vesicles and reduced de novo protein synthesis [319]. Eukaryotic factors of initiation depend on ds RNA-dependent protein kinase (PKR) which shuts down protein synthesis and is upregulated in AD human and models and mTOR which regulates translation is downregulated in AD cellular and animal models [306].

The positive versus negative effects of altered mTOR signaling on synaptic plasticity required for learning and memory vary across studies, most likely due to mTOR's roles in integrating synaptic inputs of various types and needed to effectuate long-term synaptic efficacy and memory [318]. The analyses are further confused by the conflicting results of rapamycin treatments. However, collective analysis of the literature suggests that rapamycin's effects are complex rather than narrowly focused on mTORC1 inhibition. Instead, the findings suggest that rapamycin selectively inhibits mTORC1 in short-term models, but following long-term treatment, mTORC2 is inhibited [210]. In contrast to treatments inconsistent dysregulated mTOR signaling impaired mTOR signaling was associated with dysregulated synaptic plasticity and memory [207], cleavage of pSer2481-mTOR (mTORC2) and aberrant tau phosphorylation [207]. This suggests that restoration of mTOR signaling would improve synaptic plasticity and memory. The findings that repletion or over-expression of Rictor in primary neuronal cultures reversed Aβ's neurotoxicty and inhibitory effects of PDK-Akt [319], and that Aβ oligomers impair PI3K-Akt signaling through mTOR autophagy pathways [204], support the notion that dysregulated mTOR/mTORC signaling is relevant to AD pathogenesis. Beyond AD, studies suggest that mTOR's interactions with p70S6K, 4EBP1, GSK-3β, REDD1/RTP801, TSC1/TSC2, growth factors, Wnt, and forkhead transcription factor impact various neurodegenerative diseases including Parkinson's disease and Huntington's disease [325]. Since mTORC2/Rictor impacts cellular metabolism via Akt and S6K, one potential mTOR-targeting therapeutic strategy for AD and perhaps other degenerative diseases could be to restore mTORC2 and inhibit mTORC1 [319], reflecting fundamental impairments in nutrient sensing and cell growth control.

70. kDa p70 S6 kinase (P70S6K)

P70S6K is a cytoplasmic Ser/Thr kinase and major substrate for Akt-activated mTORC1 [247]. Akt mediates this process by Serine phosphorylation and kinase activation of mTORC1 [247], leading to the phosphorylation of p70S6K on T412 (within its catalytic domain extension). The resulting activated p70S6K enhances mRNA translation by increasing ribosome biosynthesis, modulates cell cycle progression, cell survival, and cell size in response to IGF-1 (mitogen) stimulation, and promotes anti-apoptotic and pro-survival mechanisms by inhibiting mitochondrial BAD via phosphorylation and activation of ribosomal protein S6 (RPS6) [329, 330]. On another level, Akt activity drives mTORC via phosphorylation-mediated disinhibition of TSC's constitutive hold on mTORC1. In its

non-phosphorylated state, heterodimerized TSC1-TSC2 inhibits mTORC1 and downstream activation of P70S6K [297]. Additional regulators of mTORC1-P70S6k signaling include: 1) S1261 phosphorylation of mTORC1, upregulating protein synthesis by promoting mTORC1-mediated phosphorylation of p70S6K and the eukaryotic initiation factor 4E binding protein 1 (4E-BP1) [331]; 2) mTORC phosphorylation of T389-p70S6K, driving its nuclear localization [332]; and 3) Leucine activation of P70S6K [312] with attendant stimulation of tau synthesis and phosphorylation in cortical neurons. Leucine-mediated phosphorylation and hyper-activation of p70S6K is considered a potential pathogenic mechanism in AD [333].

The potential role of dysregulated p70S6K in AD-type neurodegeneration was suggested by several findings in experimental models and human brain studies. Using SH-Sy5y human neuroblastoma cells, p70S6K was shown to directly phosphorylate tau at S262, S214, and T212, and the findings in AD suggest a role for p70S6K activation as a mediator of aberrant Tau phosphorylation [334]. Furthermore, subjects with AD or MCI had elevated levels of two mTOR downstream targets, p70S6K and 4EBP1. In DS which consistently develops premature AD pathology, analysis of the early pre-AD signaling revealed altered or dysregulated mTOR signaling, supporting a role for this pathway in AD pathogenesis and progression [231]. In contrast to other studies that mainly focused on short-term or early AD pathology, in an intracerebral-ventricular STZ model of AD, late-stage neurodegeneration with deficits in spatial learning and memory was associated with profoundly reduced temporal lobe levels of total and T412-phosphorylated P70S6K [182]. Therefore, like Akt, over-activation of the mTOR/mTORC-p70S6K pathway may represent early responses or mediators of neurodegeneration, while at later, more advanced stages, the same signaling networks become inhibited, corresponding with sharp declines in energy metabolism, mitochondrial function, plasticity, growth, and survival mechanisms.

Ribosomal protein s6 kinase (RPS6)

RPS6K, the 40 S ribosomal protein kinase, upregulates protein synthesis, enhances lipid synthesis and mitochondrial biogenesis, and inhibits 4E-BP1 which inhibits protein synthesis and autophagy [335, 336]. RPS6 is activated via S235 and S236 phosphorylation by P70S6K [337], and $^{pS235/236}$-RPS6, the active form of S6, is a functional readout of mTORC1 activation of p70S6K [303, 304]. Activated RSP6 regulates cell size, growth, proliferation [335], neuronal activity [335], and synaptic plasticity [335]. $^{pS235/236}$-RPS6 provides negative feedback to IRS1-PI3K-Akt but is negatively regulated by protein phosphatase 1 (PP-1) dephosphorylation and inactivation of the kinase [335]. The role of RPS6 signaling in relation to AD has not been well studied.

MALIGNANT AGING-AD: SUMMARY AND CONCLUSIONS

Neurodegeneration is fundamentally rooted in a cluster of highly interrelated pathophysiologic processes that include dysregulated metabolism, especially mediated by insulin resistance and deficiency, activation of inflammatory cascades, mitochondrial dysfunction, oxidative stress, and free radical generation, and misfolding of cellular proteins. Each of these processes drives the others to propagate a self-reinforcing cascade [165, 166].

Neuronal death, disconnection, and loss of plasticity impair learning, memory, and behavior. Oligodendrocytes fail to maintain myelin integrity which is needed for efficient neuronal processing speeds. Astrocytes shift their functions from supportive to pro-inflammatory and lay down glial scar tissue that impedes neuronal growth and repair. Activated microglia alter their expression of cytokines and chemokines in favor of increased neuroinflammation. Compromised vascular and blood-brain barrier integrity disrupt nutrient/waste transport and worsen cellular dyshomeostasis. An abundance of data indicate that malignant aging and attendant neurodegeneration are likely mediated by fundamental defects in insulin's actions and aberrant cellular responses to insulin, mimicking the effects of diabetes mellitus [338], aptly termed, 'Type 3 Diabetes' [169, 175].

The take-home messages from this review are: 1) although genetic factors contribute to natural resistance or proneness to diseases, lifetime exposures, experiences, and their consequences are the only tangible preventable or reversible agents of malignant brain aging; and 2) once the malignant aging cascade gets established, a single-pronged intervention will not work because other contributing factors will continue to drive neurodegeneration. Future therapeutic strategies must accommodate requirements for triangulated righting of metabolic derangements, inflammation, and cellular stress. Given its broad impact on normal brain functions and the consequences of its dysregulation in aging and neurodegeneration, the Yinyang of mTOR must be considered to address functional integrity of all brain cell types to minimize shifts from benign to malignant aging and from malignant aging to neurodegeneration.

INTRINSIC VERSUS EXTRINSIC ENABLERS OF BENIGN TO MALIGNANT AGING AND AD TRANSITIONS

Two initial over-arching questions were posed: 1) Is there *anything* we can do to purchase a stable and virtually immutable benign brain aging trajectory while still on the middle-age plateau of the frustum? 2) Is it possible to halt or prevent accelerated cognitive declines and either protect residual or regain recently lost functions following events that shift the path from benign to malignant aging? The answers require that we address the intrinsic and extrinsic enablers of transitions from benign to malignant brain aging, and from malignant aging to neurodegeneration (Table 3).

Intrinsic factors

Intrinsic enablers, which include progressive advancement in chronological age, inherited gene mutations or allelic variants such as presenilin mutations, *APOE ε*4 genotypes, and DS are fundamentally immutable. However, knowing their propensities to be accompanied by progressive insulin and IGF resistances, the adverse effects of the intrinsic enablers may be dampened by early implementation of chronic, healthful lifestyle measures such as regular aerobic and resistance exercise training, habitual consumption of foods that support insulin sensitivity and avoidance of products that erode insulin responsiveness, and regular participation in activities that reduce overall stress, enhance social discourse and community, and fortify cognitive reserve, e.g. reading. Although earlier "interventions" make it easier to

establish habits, studies have shown benefits of adopting these approaches in later stages of life [191–197].

Extrinsic factors

Extrinsic enablers of malignant brain aging include systemic metabolic disorders such as obesity [176, 178, 339, 340], diabetes mellitus [341, 342], NAFLD [176, 178], and metabolic syndrome [176, 178], cerebrovascular pathologies [341], general anesthesia, particularly repeated bouts [343–348], cardiovascular disease impairing brain perfusion or causing ischemic injuries [349–352], pulmonary disease causing acute, subacute, or chronic hypoxic insults [353–356], head trauma [95–98], and severe inflammatory states such as COVID-19 infections [357, 358], and air pollution particulate matter exposures [147, 359]. In addition, growing evidence points toward environmental exposures such as nitrosamines [149, 150, 152, 360–362], pesticides, and herbicides as mediators or enablers of neurodegeneration [363–366]. Mindful opportunities to reduce, minimize, or avoid exposures to extrinsic enablers of malignant aging abound. Optimum management of systemic metabolic and hypertension-related disorders and disease states requires genuine collaboration with internal medicine and primary care providers. Repeated bouts of general anesthesia significantly contribute to cognitive decline and should be avoided or minimized after middle-age. Patients need to be made aware of their options and surgeons and anesthesiologists need to come on board with the concept to implement change. In this regard, it is noteworthy that major common orthopedic procedures such as hip or knee arthroplasty can be performed as day/outpatient surgeries without general anesthesia, e.g. with short-acting spinal anesthesia, enabling swifter recoveries [367] and potentially overall reductions in healthcare costs [368, 369]. Head trauma remains problematic. The development of chronic traumatic encephalopathy as a contributor to cognitive impairment, either alone or combined with other forms of neurodegeneration including AD has been well publicized in the media due to its relationship with contact sport-associated injuries [95–98]. Presumably those rates will decline, but the attention fails to address concerns for the broader population in which head trauma is largely caused by accidents or violence. Protocols to optimize the management of post-traumatic brain injuries are still in evolution.

Outside jobs: Environmental, exposure, and lifestyle factors

After systemic metabolic and hypertensive disorders, the potential adverse effects of environmental exposures on brain health, aging, and neurodegeneration are largely under-appreciated, yet virtually the entire world is impacted daily. Nitrosamine exposures via preservatives added to processed foods, tobacco smoking, and Betel quid consumption are significant, and experimentally, all have been shown to cause the full spectrum of insulin-resistance diseases including AD-type neurodegeneration [13, 149, 150, 152, 184, 186, 361, 362, 370]. Pesticides and herbicides, including Agent Orange constituents, are widely distributed worldwide for use in agriculture, or simply to green up and beautify lawns. Their connections with neurodegenerative diseases have received only spotty coverage compared with the attention given to their potential carcinogenic effects. Oddly, the main complex drivers of malignant aging and ultimately neurodegeneration, could be integrally related to environmental exposures, and therefore may not be readily managed with diet and exercise alone. Curves corresponding to their growing use and therefore human exposures over

time parallel trends in insulin resistance diseases and neurodegeneration. For us today, awareness, education and personal choices are critical to dampening the effects of extrinsic factor mediated transitions from benign to malignant aging and from malignant aging to neurodegeneration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Cellular targets and pathologies of brain aging and neurodegeneration

Neurons	1. Degeneration of synaptic connections and reduced plasticity 2. Cell death 3. Aberrant hyper-phosphorylation of tau and other cytoskeletal and associated proteins 4. Axonal loss and reduced neurotransmission 5. Insoluble neurotoxic fibril build-up 6. Oxidative stress, protein misfolding, and ubiquitination 7. Autophagy and mitophagy	1. Cognitive impairment 2. Neurobehavioral dysfunction 3. Impaired executive functions 4. Cortical atrophy 5. Neurofibrillary tangle and neuritic pathology 6. Aβ accumulation in plaques, fibril, and oligomers
Oligodendrocytes	1. Impaired oligodendrocyte function with altered expression of myelin lipids and glycoproteins 2. Reduced survival and replacement of oligodendrocytes 3. Loss of myelin integrity with degeneration of myelin and axons 4. Increased oxidative stress and lipid peroxidation	1. Cognitive impairment 2. Reduced speed of processing 3. White matter atrophy and degeneration of myelin and axons 4. Astrocyte and microglia activation via lipid peroxidation and stress-mediated tissue damage
Astrocytes	1. Impaired glutamate homeostasis- 2. Pro-inflammatory cytokine activation	1. Increased proneness to excitotoxic injury 2. Reduced Aβ degradation and increased Aβ build-up 3. Increased inflammatory-mediated neuronal and oligodendrocyte injury 4. Gliosis-Prevents re-establishment of inter-neuronal connections
Microglia	1. Impaired glutamate homeostasis- 2. Pro-inflammatory cytokine activation	1. Increased proneness to excitotoxic injury 2. Reduced Aβ degradation and increased Aβ build-up 3. Inflammatory-mediated neuronal and oligodendrocyte injury
Vascular	1. Microvascular networks 2. Cortical vessels-Aβ deposition-mural and perivascular 3. White matter vessels-arteriosclerosis with lumenal narrowing 4. Reduced micro-vessel density 5. Increased vascular permeability 6. Disrupted neurovascular unit	1. Impaired brain perfusion, nutrient delivery, and waste removal 2. Ischemic injury, especially white matter 3. Cortical micro-bleeds associated with Aβ 4. Myelin degradation 5. Microinfarcts 6. Neuroinflammation 7. Blood-brain barrier leakage and increased vulnerability to systemic-derived toxic factors

Table 2

Shared pathophysiological mechanisms: Alzheimer's disease, diabetes, and other insulin-resistance diseases

Insulin, IGF-1 Resistance	Impaired responsiveness to trophic factor stimulation Trophic factor deficiencies Impaired growth, metabolism, cell survival, homeostasis
Metabolic Deficiencies	Impaired carbohydrate and lipid metabolism Reduced energy production Altered cellular homeostasis. Increased lipid peroxidation, inflammation, and stress
Inflammation Cellular Stress: Endoplasmic reticulum Oxidative Nitrosative	Pro-inflammatory cytokine activation DNA, RNA Protein damage Adduct formation
Cell Injury/Death	Pro-apoptosis, anti-survival pathways activated
Mitochondrial Dysfunction	Reduced ATP (energy) production Increased reactive oxygen species (ROS) levels Inflammation, stress, autophagy, mitophagy Cell death
Vascular	Endothelial injury with increased proneness to luminal occlusion Smooth muscle degeneration-poor vascular compliance, restricted perfusion Reduced vascular wall integrity leading to leakage and tissue damage

Table 3

Enablers of malignant aging and neurodegeneration

Intrinsic factors
1. Aging 2. *APOE* ε4 3. Presenilin mutation 4. AβPP gene mutation 5. Down syndrome
Extrinsic Factors
1. Obesity 2. Diabetes mellitus 3. Insulin Resistance diseases (non-alcoholic fatty liver disease; metabolic syndrome) 4. Cerebrovascular pathologies 5. Infection 6. Head Trauma 7. Severe Inflammatory States 8. General anesthesia 9. Hypoxia 10. Cardiovascular events with hypoperfusion 11. Environmental a. Air pollution (particulate matter) b. Herbicides c. Pesticides 12. Lifestyle a. Nitrosamine exposures-preserved, processed foods b. Tobacco c. Head trauma d. Heavy alcohol consumption