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A Perfect sTORm: The Role of the Mammalian Target of Rapamycin (mTOR) in Cerebrovascular Dysfunction of Alzheimer's Disease: A Mini-Review

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Abstract
Cerebrovascular dysfunction is detected prior to the onset of cognitive and histopathological changes in Alzheimer's disease (AD). Increasing evidence indicates a critical role of cerebrovascular dysfunction in the initiation and progression of AD. Recent studies identified the mechanistic/mammalian target of rapamycin (mTOR) as a critical effector of cerebrovascular dysfunction in AD. mTOR has a key role in the regulation of metabolism, but some mTOR-dependent mechanisms are uniquely specific to the regulation of cerebrovascular function. These include the regulation of cerebral blood flow, blood-brain barrier integrity and maintenance, neurovascular coupling, and cerebrovascular reactivity. This article examines the available evidence for a role of mTOR-driven cerebrovascular dysfunction in the pathogenesis of AD and of vascular cognitive impairment and dementia (VCID) and highlights the therapeutic potential of targeting mTOR and/or specific downstream effectors for vasculoprotection in AD, VCID, and other age-associated neurological diseases with cerebrovascular etiology.

Introduction

Alzheimer's disease (AD) and vascular cognitive impairment and dementia (VCID) are the leading causes of dementia among the elderly, with AD and VCID amounting to approximately 60 and 20% of all dementia cases, respectively. While specific lesions and histopathological hallmarks define AD and VCID and relatively "pure" cases of AD and VCID can be identified in the clinic, the presentation of most AD and VCID cases is heterogeneous, and thus, diagnosis can present a challenge. This is because symptoms, risk factors, and etiologies of AD and VCID are partially overlapping and coexist in the majority of cases. Not surprisingly, pathologies common to both types of dementia are cerebrovascular in nature [1].

Brain vascular dysfunction is also involved in the etiology of related dementias, including Lewy body dementia and Parkinson disease. Indeed, cerebrovascular dysfunction is one of the earliest events in these dementias, best exemplified by diminished cerebral blood flow (CBF) [2, 3]. A recent study incorporating large datasets from the AD Neuroimaging Initiative (ADNI) suggested that vascular dysfunction indicated by decreased CBF may be the first abnormal biomarker in AD progression, as well as the one that shows the largest magnitude of change [4].

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A significant barrier to effective treatments for AD, which are currently unavailable, is that we still do not sufficiently understand the mechanisms that drive its onset and progression. While the neuronal contributions to AD pathogenesis have been extensively studied, cerebrovascular mechanisms of AD, which show substantial overlap with those of VCID, are only partially understood. Prominent cerebrovascular changes in AD include chronic hypoperfusion [4], increased blood-brain barrier (BBB) permeability [5], impaired neurovascular coupling [6], and diminished cerebrovascular reactivity [7].

The mechanistic/mammalian target of rapamycin (mTOR) may be a critical effector of cerebrovascular dysfunction in AD and potentially other dementias [8–10]. mTOR is a major signaling hub that integrates nutrient/growth factor availability with cellular metabolism. mTOR also regulates the rate of aging across phyla, including invertebrates and mammals [11]. Rapamycin, an mTOR inhibitor, is the first drug that has been experimentally proven to slow down the rate of aging in mice [12]. Work from our lab [8, 10, 13, 14] and others [15] has identified mTOR as a major regulator of cerebrovascular damage and dysfunction in AD. While mTOR has a critical role in the regulation of cellular metabolism through actions at multiple signaling pathways, some mTOR-dependent mechanisms are uniquely specific to the regulation of cerebrovascular function. These include the control of CBF, BBB integrity and maintenance, neurovascular coupling, and cerebrovascular reactivity. This review will discuss the role of mTOR in the control of cerebrovascular function with a specific emphasis on dysregulation in AD and VCID.

mTOR and CBF Deficits in AD and Other Dementias

Chronic cerebral hypoperfusion, as evidenced by dysfunctional and/or reduced CBF, occurs prior to cognitive impairments, brain atrophy, amyloid β (Aβ) accumulation, and a clinical diagnosis of AD [4]. Experimental evidence suggests that cerebral hypoperfusion produces cognitive impairments, synaptic alterations, and Aβ oligomerization [16]. Further, primary vascular deficits lead to Aβ accumulation and tau hyperphosphorylation [17]. Therefore, it has been proposed that brain microvascular dysfunction and loss of cerebrovascular density may trigger the imbalance in the levels of hyperphosphorylated tau and fibrillar Aβ observed in AD, both of which are associated with a further disruption of cerebrovascular function. This concept has been formulated as the "two-hit" hypothesis of AD [5].

Underlying the CBF reductions observed in AD are decreases in regional and global vascular density [18]. mTOR drives cerebromicrovascular density loss, leading to profound CBF deficits, by decreasing microvascular nitric oxide (NO) bioavailability in brains of mice modeling AD [8] through inhibition of NO synthase (NOS) activity. Therefore, mTOR attenuation with rapamycin induces endothelium-dependent cortical vasodilation via NO release [8]. In agreement with this notion, prior in vitro studies showed that mTOR inhibits endothelial NOS (eNOS) phosphorylation and activation and NO-dependent arterial vasodilation [19]. Moreover, a link between the inhibition of mTOR and the activation of eNOS had been suggested by studies showing that Akt, which phosphorylates eNOS and increases NO production, can be activated by rapamycin treatment [20] and, conversely, that activation of mTOR results in Akt inhibition [20].

Aβ, causally implicated in AD, is generated in the brain by cleavage of the amyloid precursor protein (APP) in association with neuronal activation [21]. Aβ is released at synaptic sites into the interstitial fluid [21]. Several physiological mechanisms act to prevent Aβ accumulation, but the largest contributor is transvascular Aβ clearance, as over 85% of Aβ is continuously cleared out of the brain through the BBB [5]. Disruption of transvascular Aβ clearance leads to accumulation of Aβ in the brain, causing AD-like pathophysiological changes [22].

Consistent with a critical role of microvascular integrity and function in Aβ removal from the brain, systemic mTOR inhibition reduces Aβ levels in the brain and improves cognitive function in mouse models of AD [14], even after the onset of AD-like deficits [8]. In these AD models, mTOR promotes the accumulation of Aβ in the brain by inhibiting autophagy [14, 15] and by decreasing Aβ clearance as a result of decreased vascular density and reduced CBF [8]. The preservation of vascular density and vascular function that is observed as a result of mTOR attenuation in AD models may be sufficient to decrease brain Aβ and improve cognitive outcomes in AD and VCID. For instance, physical exercise, which restores adequate brain perfusion, reduces both Aβ deposition and tau phosphorylation [23] in models of AD and other tauopathies. Thus, these studies support the notion that cerebral hypoperfusion has a critical and potentially initiating role in the etiology of AD.

In agreement with a central role of mTOR-driven loss of cerebrovascular integrity and decreased cerebral perfusion in the etiology of neurological diseases of aging be-

yond AD, studies from our laboratory have shown that mTOR is involved in brain vascular disintegration and subsequent CBF deficits and cognitive impairment in low-density lipoprotein receptor knockout ($LDLR^{-/-}$) mice, a well-established model of atherosclerosis that recapitulates the vascular dysfunction of VCID [9].

mTOR and BBB Breakdown in AD and Other Dementias

The BBB is formed by a monolayer of vascular endothelial cells that line the brain microvasculature and dynamically regulate the exchange of molecules between the peripheral circulation and the central nervous system. A critical function of the BBB is to restrict the entry of plasma components into the brain. Clinical and experimental studies indicate that BBB breakdown is one of the earliest events in the pathogenesis of AD [5]. Further, recent studies suggest that BBB breakdown may underlie early cognitive changes in mild cognitive impairment, as evidenced by increased BBB permeability in patients with mild cognitive impairment compared to age-matched controls [24].

The BBB is maintained by intercellular tight junctions that reduce the permeability of the brain endothelium [5]. Aβ induces changes in tight junction protein expression, resulting in BBB disruption [25]. Additionally, vascular Aβ accumulation is associated with degeneration of cellular components of the vasculature, including endothelial cells, smooth muscle cells, and pericytes [26]. Although cerebral microvascular accumulation of misfolded forms of tau in AD and other tauopathies has been documented [27, 28], how the accumulation of misfolded tau in cerebromicrovasculature contributes to cerebrovascular dysfunction in AD is currently unknown. Some studies have suggested, however, that vascular tau accumulation may contribute to BBB breakdown in AD and in other tauopathies [29], suggesting that both Aβ and pathogenic forms of tau contribute to BBB disintegration in AD.

mTOR attenuation reduces or prevents BBB breakdown in several models of age-associated neurological disorders, suggesting a broad role of mTOR in BBB dysfunction in age-related brain disease states. mTOR inhibition with rapamycin attenuates BBB breakdown in rat models of cerebral ischemia-reperfusion injury [30, 31], subarachnoid hemorrhage [32], and pharmacologically induced status epilepticus during the chronic phase [33]. These studies illustrate a key role of mTOR in BBB breakdown in several different models of age-associated neurological disease. The exact mechanisms by which mTOR promotes BBB breakdown, however, have not yet been sufficiently studied. Evidence exists that mTOR inhibition with rapamycin maintains adequate levels of tight junction protein expression in cultured cells [31]. Additionally, recent work using in vivo models suggests that BBB breakdown may follow an mTOR-dependent increase in matrix metalloproteinase 9 activity [30], which is involved in the degradation of the extracellular matrix and has been associated with various pathological processes, including cerebral hemorrhage and BBB disruption in AD [25]. These studies provide support for the notion that mTOR activity may have a critical role in BBB breakdown in age-associated neurological disorders, including prominently AD and VCI. Despite the abrogation of BBB breakdown, however, attenuation of mTOR activity increased cortical infarct volume in an ischemia-reperfusion model [34], suggesting that mTOR activation may be necessary for neuronal survival after cerebral ischemia and reperfusion. A potential use of mTOR inhibitors preventively for stroke, or in individuals affected by diseases associated with a high risk of cerebral ischemia [34], like diabetes, might thus be limited. Because of the urgent need for interventions to slow down or block the progression of AD and other dementias, and the potential for the use of mTOR inhibitors in aged individuals without major undesirable side effects [35], there is a pressing need for additional research to precisely define the mechanisms of mTOR-dependent BBB disintegration and to precisely determine the functional and cognitive consequences of BBB restoration by mTOR inhibition in models of various neurological disorders. BBB breakdown may be one of the earliest events in AD progression [24]. Thus, understanding the mechanisms by which mTOR regulates BBB integrity may be important to devise *early* interventions to delay or block the development of AD.

mTOR and Neurovascular Uncoupling in AD

Rapid increases in blood flow to areas of the brain with high neuronal activity are required to maintain cellular homeostasis and function. This is accomplished through neurovascular coupling, a homeostatic response mediated by complex intercellular signaling events involving neurons, astrocytes, vascular smooth muscle cells, and endothelial cells [36]. Significant neurovascular coupling deficits are observed in patients with AD [6], and these

deficits are recapitulated in several different mouse models of AD [37, 38]. NO production via activation of the neuronal form of NOS (nNOS) contributes significantly to the neurovascular coupling response by inducing local vasodilation in response to neuronal activation [6]. Dysfunctional neurovascular coupling in mouse models has been reported to occur both from reduced neuronal NO production [39] as well as from a diminished CBF response to otherwise unimpaired NO signaling [38]. Thus, differences in timing or in levels of Aβ accumulation or the concomitant expression of human tau forms in different mouse models may impact neurovascular coupling and lead to cerebrovascular dysfunction through different mechanisms. Further studies are needed to better define the mechanisms underlying neurovascular coupling impairment in AD.

Since mTOR is a key driver of cerebrovascular damage and disintegration in several mouse models of AD [8, 10] and in a model of VCI [9], it is reasonable to hypothesize that mTOR contributes, at least indirectly, to neurovascular coupling deficits in these models. Very little is known at present, however, about the role of mTOR in the regulation of neurovascular coupling. Interestingly, some of the mechanisms that underlie neurovascular uncoupling, including oxidative stress [40] arising from increased NADPH-derived reactive oxygen species (ROS) production [41], are regulated by mTOR. Specifically, mTOR drives the increase in ROS observed after ischemic injury in rat brain [31]. Furthermore, ROS itself activates the Akt/mTOR pathway in the brain [42], suggesting a feedforward mechanism involving mTOR and ROS production that leads to neurovascular uncoupling and cerebrovascular dysfunction. Indeed, a recent unbiased quantitative mass spectrometry-based proteomic study showed that proteomic alterations in the hippocampus, involving myelination, dendrite homeostasis, and oxidative stress, were associated with the upregulation of ribosomal proteins and mTOR in animals heterozygous for a null allele of tuberous sclerosis complex 1 ($Tsc1^{+/-}$ mice) [43], a negative regulator of mTOR. These studies further showed that the observed proteomic changes were a direct consequence of increased mTOR activity since treatment of $Tsc1^{+/-}$ mice with rapamycin was sufficient to normalize levels of proteins related to oxidative stress, myelin homeostasis, and protein synthesis that were altered in control-treated $Tsc1^{+/-}$ mice. These data strongly support a direct role of mTOR in the regulation of oxidative stress in the hippocampus, as well as in the regulation of myelin homeostasis in the brain, the latter having been well established through the regulation of oligodendrocyte maturation.

mTOR and Cerebrovascular Reactivity in AD

Vasomotor reactivity, or the ability of vessels to dilate and constrict in response to physiologic or pharmacological stimuli, is mediated by coordinated responses of vascular endothelium and smooth muscle cells. Endothelium-dependent vasomotor reactivity is decreased in patients with AD and VCID [7], and smooth muscle cells degenerate in AD [44]. Most studies addressing mechanisms of vascular smooth muscle dysfunction in AD have used a mouse model of AD (Tg2576) that expresses the Swedish familial AD-mutated form of APP (APP_{Swe}). Tg2576 mice develop extensive vascular lesions recapitulating cerebral amyloid angiopathy (CAA), the accumulation of fibrillar Aβ within the cerebrovasculature. CAA is highly prevalent in AD, but can also accumulate to a lesser extent during normal aging, and is associated with brain microhemorrhages. Tg2576 mice recapitulate the age-dependent increase in vascular fibrillar Aβ burden that is associated with altered vascular smooth muscle cell morphology and the loss of vascular smooth muscle cells in vascular segments with high Aβ load [45]. CAA-like lesions in Tg2576 mice decrease smooth muscle cell-dependent responses necessary for relaxation and subsequent vasodilation in response to NO. These deficits are detectable prior to overt loss of vascular smooth muscle in Tg2576 mice [45]. Studies in the Swedish-Arctic APP transgenic (APP_{SweArc}) mouse model of AD, however, did not reveal deficits in the smooth muscle-dependent component of vasoreactivity but found significant decreases in NO bioavailability that accounted for the overall deficit in vascular reactivity documented in this model [46]. These data suggest that Aβ negatively impacts several functions of different microvascular cell compartments and that specific functional consequences of Aβ exposure are related to differences in timing of Aβ expression and accumulation, as well as its specific localization in different transgenic mouse models of AD.

AD and VCID are characterized by an insensitivity to endothelium-dependent vasodilation, and these deficits are causally linked to decreased vascular reactivity in AD. The endothelium-dependent component of brain microvascular dilation depends on the synthesis of NO by eNOS within brain microvascular endothelial cells. In agreement with a critical role of brain vascular endothelial dysfunction in the cerebrovascular deficits of AD, changes in eNOS activity have been linked to AD pathology. Accumulation of both Aβ and neurofibrillary tangles is associated with reduced eNOS expression in the brain

capillaries of human patients with AD and with endothelial cell apoptosis [47]. Loss of eNOS activity can in turn promote tau phosphorylation in a mouse model of AD [48], suggesting that the accumulation of AD pathology and the dysregulation of eNOS may be linked in a feed-forward loop. However, the mTOR inhibitor rapamycin induces eNOS phosphorylation, restores endothelium-dependent vasodilation, and produces NOS-dependent restoration of baseline CBF [8].

In agreement with a central role of cerebrovascular dysfunction in the early stages of AD progression, young adult carriers of the ApoE4 allele show reduced cerebrovascular reactivity before developing detectable cognitive impairments [49]. Interestingly, mTOR attenuation is sufficient to preserve cerebrovascular integrity and function in ApoE4 transgenic mice [10], suggesting that mTOR is a critical driver of early cerebrovascular dysfunction in a model of sporadic AD associated with ApoE4 carrier status. Since mTOR activity reduces NOS-dependent cerebromicrovascular NO bioavailability, mTOR inhibitors may be efficacious for the preservation of cerebrovascular function as an early treatment and intervention in AD.

Intriguing recent studies (reviewed in [50]) have suggested that overactivation of the renin-angiotensin system may underlie cerebrovascular dysfunction in AD. Angiotensin (Ang)-II and Ang-III levels are higher in AD patients compared to age-matched control subjects, and Ang-III is strongly associated with both Aβ and phosphorylated tau pathology [51]. In agreement with an important role of the renin-angiotensin axis in AD pathogenesis, it has been reported that centrally acting angiotensin-converting enzyme inhibitors temporarily delay progression of AD cognitive deficits [52], and recent studies in mouse models of AD showed that the beneficial effects of the angiotensin receptor blocker losartan on cognitive performance and cerebrovascular function may be related to its selective blockage of the Ang-IV receptor [53]. Furthermore, overactivation of Ang-II has been shown to contribute to cerebrovascular pathogenesis in stroke through vasoconstriction, activation of proinflammatory factors, and increased oxidative stress in the parenchyma [54]. Ang-II strongly activates mTOR, and blockade of its receptor, the angiotensin type I receptor, reduces activity of the mTOR pathway [55], which can ameliorate cerebral microcirculatory changes to improve brain perfusion [56]. Additionally, it was shown that mTOR inhibition with rapamycin prevented in vitro aortic endothelial cell dysfunction induced by Ang-II, including preservation of eNOS phosphorylation, NO production, and vasodilation [57]. Taken together, these data suggest that improvements in cerebrovascular function from therapeutic interventions targeting the renin-angiotensin system in AD may at least partially result from the direct inhibition or downregulation of mTOR activity.

Conclusions and Perspectives

Recent studies highlight the role of cerebrovascular dysfunction in the pathogenesis of AD and VCID. Given that cerebrovascular dysfunction can be detected prior to the onset of cognitive impairments, presentation of AD-associated pathologies, and a diagnosis of AD [4], there has been recent interest in exploring the potential of CBF deficits as a noninvasive biomarker for risk of AD development, as well as a target for intervention early in the pathogenesis of AD. Our laboratory and others have identified the mTOR pathway as a potential target for brain vasculoprotection in AD and VCID [8–10, 14]. Since mTOR-dependent cerebrovascular dysfunction is not limited to AD models, the mTOR pathway may be a suitable target for early intervention in several different disorders beyond AD that have cerebrovascular dysfunction as a common etiology.

Adverse effects of rapalogs at doses used in oncology or organ transplantation may be of concern [58]. Thus, it is crucial that the mechanisms of rapamycin- and rapalog-induced neuroprotection and vasculoprotection are elucidated to enable the design of better strategies, such as the use of existing drugs, or development of new ones, that target key effectors of rapamycin-induced neuroprotection and/or vasculoprotection while avoiding potential undesirable side effects. However, a relatively recent study showed that a 6-week course of rapamycin enhanced the response to the influenza vaccine by about 20% in elderly volunteers over 65 years of age, without significant adverse events [35]. These findings underscore the need for additional exploratory proof-of-concept studies in the elderly, which would be the target population for interventions aimed at blocking or delaying AD progression early during development of the disease. Since mTOR inhibitors are available clinically, translational studies of dementias with cerebrovascular dysfunction could follow quickly. As these studies are performed, rapamycin- or rapalog-based therapies to treat AD can be designed that take advantage of strategies such as intermittent administration, as well as personalized dosage and frequency of treatment.

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Disclosure Statement

The authors have no conflicts of interest to report.

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