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Review Article

Role and Agents Regulating the Mammalian Target of Rapamycin to Prevent the Progression of Dementia in Alzheimer's Disease

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Abstract

The prevalence of late onset Alzheimer's disease (AD), one of the most common causes for dementia in elder people, is alarmingly increasing worldwide. Various signaling pathways such as oxidative stress, inflammation, and apoptosis are involved in the formation of amyloid beta (Aβ) and tau proteins which are demonstrated as the hall mark of this irreversible disease. Elevated mammalian target of rapamycin (mTOR) signaling has been reported in the pathophysiology of many human ailments including AD. mTOR is a serine-threonine protein kinase in the phosphoinositol/protein kinase B pathway which has role in the cellular growth process and survival. The effect is mediated through the up regulation of protein synthesis and down regulation of autophagy. mTOR is the catalytic subunit of complexes mTORC1 and mTORC2. mTORC1 regulates the cell growth and metabolism whereas mTORC2 is involved in the organization of cytoskeleton. Overwhelming research on this complex signaling machinery during the last decade revealed that mTORC1 enhances the formation of Aβ and decreases its degradation. Furthermore, mTORC1 increases the synthesis and phosphorylation of tau proteins. Both these neurotoxic compounds cause the synaptic plasticity in the preclinical AD patients. Therefore, regulation of mTORC1 may render beneficial effect in preventing the progression of AD mainly at the early stage. Rapamycin and curcumin were demonstrated as inhibitors of mTORC1 and, thereby, showed neuroprotection in experimental AD models. This review article discusses the role of mTORC1 and the agents that target this complex to prevent the formation and progression of AD.

Keywords: Mammalian Target of Rapamycin; Alzheimer's Disease; AMP Dependent Protein Kinase; PI3K/Akt Pathway

Introduction

Alzheimer's disease (AD) is one of the most common forms of dementia in elder people which is contributing an estimated 60-80% of all cases [1]. An alarmingly increasing prevalence in AD during the last decade has revealed that more than 80 million people all over the world may be affected by this incurable disease by 2040 [2]. Although progresses have been made in the etiology, diagnosis and treatment, the exact molecular pathophysiology of AD remains elusive. Formation of amyloid beta, tau protein phosphorylation, formation of amyloid plaque and neurofibrillary tangle and apoptosis were reviewed as the major molecular mechanism associated with the disease [3,4]. Oxidative stress and inflammation in astrocytes were demonstrated as the etiological factors [5]. Experimental evidences revealed that mammalian target of rapamycin (mTORC), a significant molecule involved in the coordination of inflammatory signals during hypoxia, in neurons and astrocytes has been proposed to be involved in AD. mTOR is a serine-threonine kinase which belongs to the phosphoinositol 3-kinase (PI3K)-related kinase family protein. It acts as the downstream signaling molecule in the PI3K/Akt pathway which is activated by growth factors and insulin. Two distinct multi-protein complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) are reported [6]. The mTOR signaling pathway integrates both intracellular and extracellular signals generated from amino acids, growth factors, oxygen level and energy status. This complex has long been proposed in the pathophysiology of human ailments including cancer and diabetes mellitus. A recent review highlights the significance of mTORC1 pathway as a possible therapeutic target for brain vasculoprotection in AD [7]. Since several pathways are explained in the mechanism for AD, Sahoo., *et al.* recently recommends 'Combination-drugs-multi-targets' as a possible strategy [8]. Despite many phytochemicals that target the NF-κB proved as effective in the inflammation-based AD therapy [9], only a few mTORC1 targeting agents were demonstrated in AD models. Therefore, discussing the role and agents targeting the mTORC1 complex signaling machinery will be worthwhile contribution to this field. This review article discusses the role of mTORC1 in the formation and progression of AD and agents targeting this complex.

Mammalian target of rapamycin

The complex structure of mTOR is constituted by several subunits [10]. Among the many structural subunits described for mTORC1, mTOR is the catalytic subunit. The others are regulatory subunits which include proline-rich AKT substrate 40 kDa (PRAS40), DEP-domain-containing mTOR-interacting protein (Deptor) and regulatory-associated protein of mTOR (Raptor) [11]. Among this, the PRAS40 and Deptor when recruited to the complex mTORC1 is inhibited. Furthermore, tuberous sclerosis protein 1/2 (TSC1/2) was also demonstrated as an inhibitor of mTORC1 [12]. The mTORC1activity is stimulated by amino acids (mainly leucine), growth factors, insulin, serum phosphatidic

acid and oxidative stress [13,14]. The cytokines including tumor necrosis factor-alpha (TNF-α), activate the IκB kinase-β which can inhibit TSC1 and, thereby, activates the mTORC1 [15]. The activated mTOR will produce a p70 ribosomal S6 kinase 1 dependent negative feedback loop which is explained as the main autoregulatory mechanism.

Hypoxia and low cellular energy status can inhibit the mTORC1 activity. During mild hypoxia, a reduction in the adenosine triphosphate level can activate the adenosine monophosphate kinase (AMPK), which promotes the activation of TSC1/2. Hypoxia can involve in the activation of TSC1/2 through transcriptional regulation of DNA damage response 1 [16] TSC1/2 inhibits the mTORC1 signaling. AMPK can also directly phosphorylate and inactivate the positive regulator, Raptor which finally inhibits the mTORC1 [17].

Role and agents regulating mTOR in Alzheimer's disease

Formation of amyloid beta (Aβ), tau proteins and their aggregated forms such as extracellular Aβ plaques and intracellular neurofibrillary tangles are demonstrated as the major hallmarks of AD. The formed Aβ can aggregate to form an oligomeric toxic form during the progression of the disease. It has been hypothesized that the synaptic dysfunction is initiated by soluble Aβ oligomers [18]. Aβ impairs the brain-derived neurotrophic factor induced signaling in cortical neurons and thus underlies the deficits of synaptic plasticity. This occurred at the early stage of AD before significant neuronal loss is evidenced [19]. Synaptic plasticity is a key contributor to declined learning and memory in severely impaired AD patients. The role of mTORC1 in AD is depicted in figure 1. Signal transduction pathways generated from the PI 3-K/Akt/mTOR cascade during the oxidative stress in brain can send signals to multiple cross talking pathways which are ultimately inducing neurodegeneration.

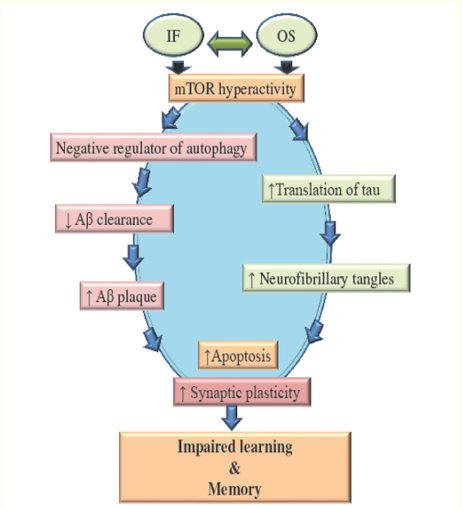

Figure 1: Inflammation (IF) and oxidative stress (OS) in neurons can hyper activate the mammalian target of rapamycin (mTORC1). Hyperactive mTORC1 inhibits the autophagy, increase the apoptosis, clearance of amyloid beta (Aβ) and enhance the translation of tau protein. These effect contribute to the formation of Aβ oligomer, neurofibrillary tangels and, thereby, leading to impaired cognitive functions..

The exact role of the hyperactive mTOR in the cognitive deficits associated with AD remains elusive. Hyperactive mTORC1 is closely associated with the level of soluble Aβ and tau proteins. mTORC1 increase the translation of tau proteins [20]. Furthermore, mTORC1 maintains the homeostasis of protein essential for the neural plasticity or regulates the translation such proteins. The hyperactivity of mTOR signaling has been shown to enhance the phosphorylation and reduce the dephosphorylation of tau protein in order to favor the formation of tangle [21]. The tau protein hyperphosphorylation favors the formation of neurofibrillary tangles. Evidence is pointed to the role of mTORC1 in reduced clearance of Aβ as well. Previous studies were demonstrated that mTORC1 is a negative regulator of autophagy therefore, hyperactivity of mTORC1 signaling is associated to the reduced the clearance of Aβ in the brain of AD [22,23]. Therefore, autophagy disorders may cause the accumulation of pathologically defective misfolded proteins in AD. Decreased mTORC1 activity up regulates the removal of dysfunctional cellular components via autophagy. Several recent evidences supported this.

Caccamo., *et al.* demonstrated that genetic reduction of mTORC1 could ameliorate the cognitive decline in AD. Hyper activation of PI3K/Akt/mTOR pathway can lead to the disease progression due to the reduction in autophagy in the inferior parietal lobe of preclinical AD patients [24]. AD is found to be developed in Down's syndrome where Di Domenico., *et al.* demonstrated the activation of mTORC1 signaling contributes to the Aβ and neurofibrillary tangles generation [25].

Elevated reactive oxygen species and pro-inflammatory cytokines, such as TNF-α level can trigger the mTOR signaling in AD patients. These processes are enhanced during diabetes, one of the well-known risk factors for AD. Oxidative stress pathways that involve the PI 3-K/Akt/mTOR cascade can lead to cellular injury through the increased apoptosis and decreased autophagy [26,27]. The presence of apoptotic proteins was demonstrated in Alzheimer's disease models [28]. Apoptotic DNA fragmentation and caspase activation is also evidenced in the brain of AD patients [29]. Apoptosis of neuron may be independent of the onset of autophagy. In neurodegenerative disorders, autophagy can render protection [30]. Autophagy is necessary for the clearance of mutated α-synuclein toxicity in neurons [31]. This was evident from the studies in Parkinson's disease where autophagy protects against neuronal cell loss and α-synuclein toxicity [30].

Therefore, the deficit due to the hyper activity of mTORC1 can be attenuated by therapy using the specific inhibitors of this signal complex. Several clinical trials demonstrated the beneficial anticancer effects from inhibiting the PI3K/Akt/mTOR signaling pathway by agents such as sirolimus, everolimus, temsirolimus and ridaforolimus (deforolimus) [32-34]. However, clinical trials using specific inhibitors of mTORC1 in subjects with early AD have not yet been evaluated. Recent results from the National Institute on Aging Interventions Testing Program have shown that pharmacologically reducing mTOR signaling with rapamycin increases the median and maximal lifespan in genetically heterogeneous mice [35]. Curcumin was demonstrated to significantly decrease the expression of PI3K/mTOR protein levels and increased the autophagy and, thereby, showed neuroprotection in APP/PS1 double

transgenic mice [36]. Epigallocatechin gallate was effective in AD as an agent decrease the Aβ generation as well as interfering in its assembly to the toxic form [37,38]. Like epigallocatechin gallate, several other natural compounds such as caffeine and resveratrol were also demonstrated as inhibitors of mTOR, but their effect on mTORC1 complex in an *in vivo* AD model or clinical trials remains elusive [39].

Conclusion and Future Perspectives

Signal transduction pathway of the PI 3-K/Akt/ mTOR cascade can positively regulates the cell growth and proliferation by promoting many anabolic processes. During oxidative stress, multiple pathways are affected that involve the PI 3-K/Akt/mTOR signaling that ultimately interface with programmed cell death and autophagy. While enhancing the apoptosis and limiting the autophagy, hyper activation of mTORC1 will favor the deposition of abnormal dysfunctional proteins like Aβ in nerve cells. Hence, the removal of Aβ is possible by maintaining the process of autophagy which can be achieved through selectively inhibiting the activity of mTORC1. Activation of mTORC1 can lead to increase translation of tau protein and its phosphorylation. Suppression of mTORC1 activity reduced the Aβ oligomerisation, formation of tau proteins and, thereby, rescued the memory deficits. But the exact role of mTOR complex and the associated therapeutic intervention in AD patients is limited. Therefore, further studies using agents with the multi targeted activity in combination with the standard drugs are essential.

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Volume 2 Issue 1 April 2018