mTOR, Tau and Neurodegeneration

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Abstract

The mechanistic target of rapamycin (mTOR) is a protein kinase which, upon activation, triggers the synthesis of proteins, including the Tau protein. Hyperactive mTOR, thus Tau over-production, has been demonstrated to increase the risk for Alzheimer's disease and other neurodegenerative disorders. As discussed in Paper 2, excessive Tau proteins (especially the 4-repeat isoform) can cause hyperexcitability. Therefore, hyperactive mTOR should promote hyperexcitability. This novel mechanism is now well established. Since hyperexcitability is an early sign of neurodegeneration, the link among mTOR, Tau, hyperexcitability and neurodegeneration provides further evidence for the notion that neurodegeneration originates from hyperexcitability.

Introduction

mTOR refers to "mechanistic (or mammalian) target of rapamycin". It has been demonstrated to play pivotal roles in a wide range of human diseases, including diabetes (Gong et al., 2014), cancer (Selvarajah et al., 2015), and neurodegeneration. This paper focuses on neurodegeneration, particularly its association with hyperactive mTOR, over-production of Tau proteins and hyperexcitability. Hyperexcitability could be the origin of neurodegeneration, as it is an early sign of Alzheimer's disease and other neurodegenerative disorders (see Paper 2).

The principal function of mTOR is protein synthesis, in response to a variety of signals: glucose, amino acids, insulin, growth factors, cytokines, protein misfolding, etc. mTOR is a protein kinase that catalyzes protein phosphorylation. Upon activation, it can phosphorylate two major targets, p70 ribosome S6 kinase1 (S6K1) and eukaryotic initiation factor 4E-binding protein 1 (4EBP1), for the initiation of protein synthesis from mRNA to a globular protein. Since the normal function of a protein requires correct folding, mTOR and its regulatory proteins have the capability to sense a misfolded protein and trigger the synthesis of chaperones (e.g. heat shock proteins HSP70, HSP90, etc.) to

ensure accurate folding from the amino acid chain to a three dimensional structure (Qian et al., 2010; Conn and Qian, 2011). However, persistent mTOR activation by the misfolded pathological proteins (e.g. mutated, oxidized or aberrantly phosphorylated) may cause diseases.

mTOR Signaling Pathways

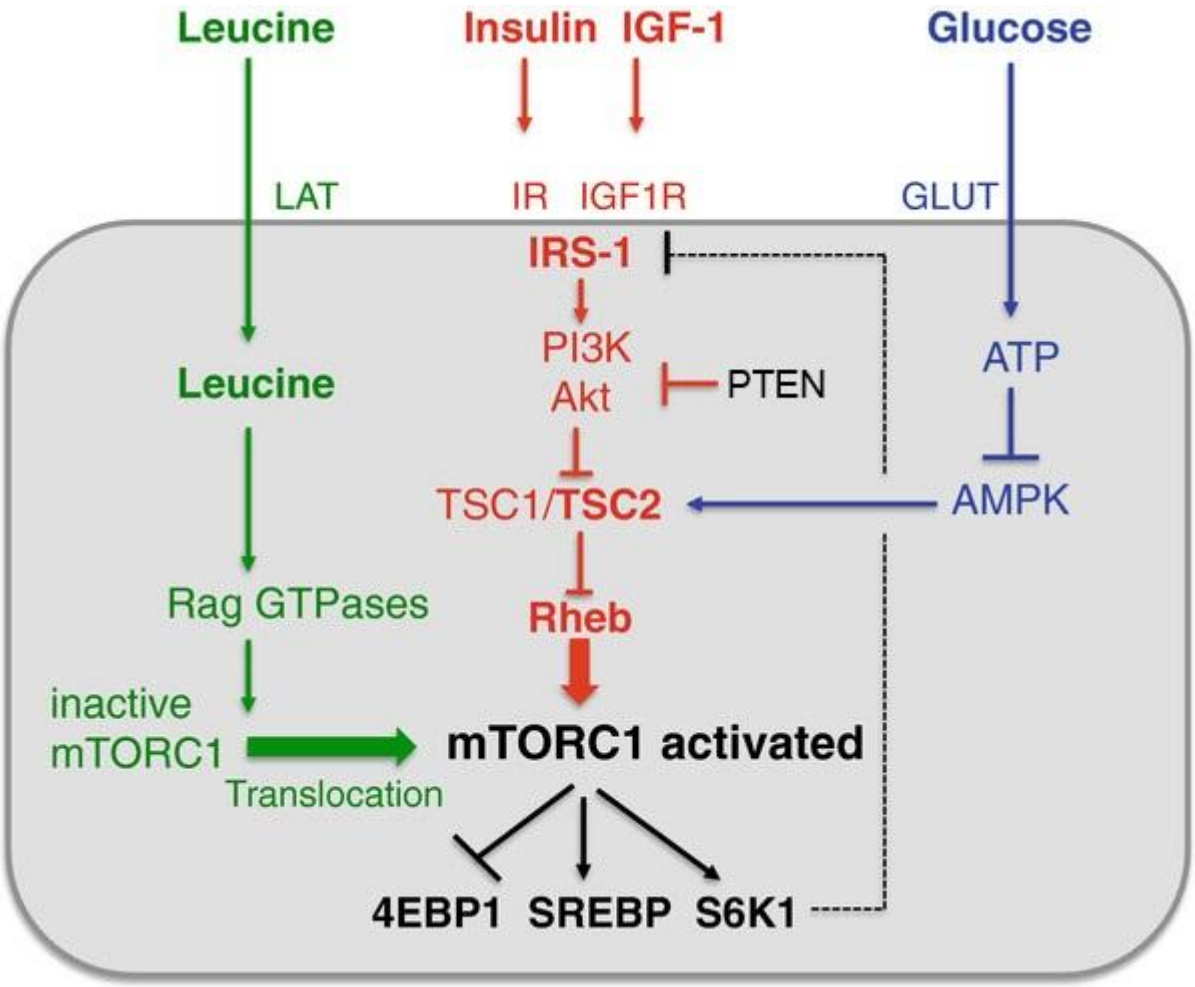

Figure 1. Schematic diagram of major pathways leading to the activation of mTORC1. Protein misfolding may activate mTORC1 via Raptor (not shown). [Source: Melnik et al., 2012]

In mammalian cells, mTOR exists in two functionally and structurally distinct multiprotein complexes: mTORC1 and mTORC2. mTORC1 consists of mTOR, Raptor, PRAS40, and mLST8 while mTORC2 comprises mTOR, Rictor, mSIN1, and mLST8. Rapamycin can inhibit mTORC1, but its effect on mTORC2 is more complex. Tau proteins are produced from the activation of mTORC1.

Figure 1 shows the major pathways leading to the activation of mTORC1. The misfolded proteins can also activate mTORC1, possibly via Raptor (Qian et al., 2010). Generally, the activation of mTORC1 requires two parallel processes: (1) activation of Rheb (Ras homolog enriched in brain) which is a GTP-binding protein, and (2) translocation of inactive mTORC1 to late endosome or lysosome where active Rheb is located (Melnik et al., 2012). The second process can be induced by amino acids, in particular, leucine. Rheb is negatively regulated by tuberous sclerosis complex (TSC1 or TSC2) which, in turn, is subject to regulation of Akt (protein kinase B) and AMPK (AMP-activated protein kinase).

mTOR and Neurodegeneration

Hyperactive mTOR increases the risk for neurodegenerative disorders, such as Alzheimer's disease (Pei and Hugon, 2008; Gouras, 2013), Huntington's disease (Pryor et al., 2014), amyotrophic lateral sclerosis (ALS) (Manuel and Heckman, 2011), and Parkinson's disease (Lan et al., 2016). Below are some of the factors that can lead to hyperactive mTOR.

- **Glucose:** Glucose may pass the blood-brain barrier (Simpson et al., 1999) to activate mTOR in neurons. Diabetes is characterized by high level of glucose in the blood. This explains why diabetes is a risk factor for Alzheimer disease (Moran et al., 2015). Furthermore, the widely used anti-diabetic drug, metformin, inhibits mTOR activity (Gong et al., 2014).
- **Leucine:** Leucine is a branched chain amino acid (BCAA) commonly used by athletes to stimulate muscle growth. It has been shown to increase the risk for ALS (Manuel and Heckman, 2011).
- **Tau mutation:** The frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) is caused by mutations of the Tau protein, which may result in conformational change (Jicha et al., 1999; Frost et al., 2009), thereby leading to mTOR activation. In support of this mechanism, rapamycin (a potent mTOR inhibitor) has been demonstrated to attenuate the progression of Tau pathology in P301S Tau transgenic mice (Ozcelik et al., 2013).
- **Huntingtin mutation:** In Huntington's disease, the huntingtin gene (*HTT*) is mutated so that its protein product contains larger number of repeated glutamines. The mutation potentiates mTOR activity (Pryor et al., 2014).
- **SOD1 (superoxide dismutase 1) mutation:** SOD1 mutation is the most common form of familial ALS. It is an antioxidant, but SOD1 knockout mice do not develop

ALS, suggesting that the toxicity of SOD1 mutation is not related to loss of normal function, but rather to a toxic gain-of-function (Quinlan, 2011). The mutant protein is misfolded (Rotunno et al., 2014; Fujisawa et al., 2015), which may trigger mTOR activation, consistent with the finding that rapamycin suppresses hyperexcitability induced by SOD1 mutation (Manuel and Heckman, 2011; Carunchio et al., 2010).

- **Inflammation:** Inflammation produces cytokines which may stimulate mTOR (Lee et al., 2007), thus increasing the risk for Alzheimer disease and other age-related disorders (Tilstra et al., 2011).
- **Vitamin D deficiency:** Vitamin D is an mTOR inhibitor (Lisse and Hewison, 2011). This explains why vitamin D deficiency is linked to Alzheimer's disease (Littlejohns et al., 2014), Parkinson's disease (Ng and Nguyen, 2012) and amyotrophic lateral sclerosis (Long and Nguyen, 2013; Gianforcaro and Hamadeh, 2014).
- **Traumatic brain injury:** Traumatic brain injury activates mTORC1 to stimulate neural stem cell proliferation for brain repair (Wang et al., 2016). However, mTOR activation increases the risk for neurodegeneration. Boxing fighters often suffered from concussive brain injury, resulting in mTOR activation (Zhu et al., 2014). This could contribute to the Parkinson's disease with Muhammad Ali.

mTOR and Hyperexcitability

The activation of mTOR has been shown to increase Tau production (Caccamo et al., 2013; Tang et al., 2013; Tang et al., 2015). As discussed in Paper 2, excessive Tau proteins (especially the 4-repeat isoform) may give rise to hyperexcitability. Therefore, hyperactive mTOR should promote hyperexcitability. This novel mechanism is supported by the following observations.

- Mutations in tuberous sclerosis complex (TSC1 or TSC2) result in Tau up-regulation and epilepsy (Sarnat and Flores-Sarnat, 2015). TSC1 and TSC2 are the crucial negative regulators of mTOR. Their loss of function may activate mTOR, leading to seizures (Uhlmann et al., 2002).
- Mutations in the PI3K/AKT/mTOR pathway cause epilepsy-associated diseases (Lee et al., 2012; Poduri et al., 2012; Jansen et al., 2015).

- PTEN (phosphatase and tensin homolog on chromosome ten) is known to inhibit the PI3K/AKT/mTOR pathway. Mutations in PTEN promote mTOR activation, thereby increasing the risk for epilepsy (Garcia et al., 2014).
- DISC1 (Disrupted-In-Schizophrenia 1) is another negative regulator for mTOR signaling (Kim et al., 2009). Its knockdown results in hyperexcitability (Zhou et al., 2013).
- The GATOR1 complex (composed of DEPDC5, NPRL2 and NPRL3) can inhibit mTOR by negatively regulating Rag GTPase (Bar-Peled et al., 2013). Mutations in GATOR1 are associated with focal epilepsy and cortical dysplasia (Baulac et al., 2015; Sim et al., 2015; Ricos et al., 2015).
- Vitamin D is an mTOR inhibitor (Lisse and Hewison, 2011). Its deficiency is highly prevalent in epilepsy patients (Jiang et al., 2015).
- Peroxisome proliferator-activated receptor γ (PPAR-γ) is a transcription factor that suppresses mTOR expression (Vasheghani et al., 2015; Dell'Accio and Sherwood, 2015) and increases PTEN expression (Farrow and Evers, 2003). Pioglitazone, a PPAR-γ agonist, has been demonstrated to protect rats from status epilepticus by inhibiting the mTOR signaling pathway (San et al., 2015).

Discussion

Mounting evidence has suggested that hyperactive mTOR may lead to Tau over-production and neuronal hyperexcitability. This agrees with the MT Model that hyperexcitability arises from the interaction between Tau and microtubules at the axon initial segment (AIS). However, it has been well documented that mTOR plays a key role in synaptic plasticity which can also affect excitability. In this regard, experimental studies found that mTOR hyperactivation is not always associated with enhanced synaptic transmission (Lasarge and Danzer, 2014; Wang et al., 2015). Furthermore, the mTOR-induced hyperexcitability is likely to originate from persistent Na^+ current, I_{NaP} (Manuel and Heckman, 2011; Carunchio et al., 2010). The major source of I_{NaP} is the ionic current through non-inactivating Na^+ channel, Nav1.6, which is located predominantly at AIS and nodes of Ranvier (O'Brien and Meisler, 2013).