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mTOR signaling in aging and neurodegeneration: At the crossroad between metabolism dysfunction and impairment of autophagy

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ABSTRACT

Compelling evidence indicates that the mammalian target of rapamycin (mTOR) signaling pathway is involved in cellular senescence, organismal aging and age-dependent diseases. mTOR is a conserved serine/threonine kinase that is known to be part of two different protein complexes: mTORC1 and mTORC2, which differ in some components and in upstream and downstream signalling. In multicellular organisms, mTOR regulates cell growth and metabolism in response to nutrients, growth factors and cellular energy conditions. Growing studies highlight that disturbance in mTOR signalling in the brain affects multiple pathways including glucose metabolism, energy production, mitochondrial function, cell growth and autophagy. All these events are key players in age-related cognitive decline such as development of Alzheimer disease (AD). The current review discusses the main regulatory roles of mTOR signalling in the brain, in particular focusing on autophagy, glucose metabolism and mitochondrial functions. Targeting mTOR in the CNS can offer new prospective for drug discovery; however further studies are needed for a comprehensive understanding of mTOR, which lies at the crossroads of multiple signals involved in AD etiology and pathogenesis.

1. Introduction

Considerable evidence indicates that Alzheimer disease (AD) may be classified as an age-related metabolic neurodegenerative disease. Indeed, the brain is an organ with highly active energy metabolism in human body. Although the adult brain accounts for only 2% of total body weight, it utilizes approximately 20% of total body oxygen consumption and 25% of total body glucose in the resting awake state (Sokoloff, 1999). Glucose is virtually the sole fuel for the adult brain under physiological conditions (Bouzier-Sore et al., 2006). However, in addition to glucose other alternative substrates, including ketone bodies, glycogen and amino acids may be used as energy fuel under certain circumstances. Intriguingly, among the mechanisms proposed to be central to neuronal loss, the impairment in energy metabolism is a pathophysiological feature of AD and its occurrence precedes cognitive dysfunction and pathological alterations even for decades (Cunnane et al., 2011; Jack et al., 2008; Reiman et al., 1996). Thus, much effort is given to elucidate the etiological factors and consequences associated with altered energy metabolism that may likely provide valuable clues for treatment strategies and diagnostic approaches in AD (Chen and Zhong, 2013).

The mammalian target of rapamycin (mTOR) signaling pathway is an attractive candidate to study with respect to both aging and energy balance because it has the potential to affect a large number of processes that could be crucial in age-related degenerative phenomena. For example, mTORC1 is activated by growth factors, amino acids, and cellular energy status to regulate protein synthesis, autophagy, mitochondrial function, lipogenesis, ketogenesis, and glucose homeostasis.

Neurons are differentiated cells with polarized cell bodies. Their viability and function is closely connected to the availability of trophic factors as well as active metabolism. In addition, neurons, because of their extreme polarization, size and post-mitotic nature, may be particularly sensitive to the accumulation of aggregated/damaged cytosolic compounds, or membranes, and depend on autophagy for survival (Tooze and Schiavo, 2008).

Insight into mTOR signaling may provide a comprehensive means to counteract both aging and age-related diseases. Here, we review the major regulatory roles of mTOR on autophagy, glucose metabolism and mitochondrial function in the brain and how these intricate pathways may affect aging and neurodegeneration.

2. mTOR: complexes and signaling network

2.1. mTORC 1/2 complexes

mTOR is a serine/threonine protein kinase of 2549 amino acids, that belongs to the phosphatidylinositol 3-kinase-related kinase protein

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(PIKK) family (Jung et al., 2010). mTOR is an ubiquitously expressed protein, mainly localized into cytoplasm that modulates among other cell processes proliferation, mortality, survival and protein synthesis (Abelaira et al., 2014). Phosphorylation at Thr-2446, Ser-2448 and Ser-2481 within the kinase catalytic domain (KIN) domain of mTOR are correlated with overall higher levels of mTOR activity. Adjacent to the KIN domain is the FKBP12 rapamycin-binding domain (FRB), the site of inhibitory interaction between rapamycin and mTOR. The binding of rapamycin to FKBP12 disturbs mTOR–protein complex formation, thus impairing mTOR activity (Hoeffer and Klann, 2010). mTOR is known to be part of two different protein complexes: mTORC1 and mTORC2, which differ in some components, in upstream and downstream signalling, and in responsiveness to rapamycin treatment (Fig. 1). Both mTOR complexes share the catalytic mTOR subunit, the mammalian lethal with sec-13 protein 8 (mLST8), the DEP domain containing mTOR-interacting protein (Deptor), and the Tti1/Tel2 complex (Wullschleger et al., 2006). In contrast, regulatory-associated protein of mammalian target of rapamycin (Raptor) and proline-rich Akt substrate 40 kDa (PRAS40) are specific to mTORC1, while rapamycin-insensitive companion of mTOR (Rictor), mammalian stress-activated map kinase-interacting protein 1 (mSin1), and protein observed with rictor 1 and 2 (Protor) are specific of mTORC2 (Laplante and Sabatini, 2012; Takei and Nawa, 2014).

The main characteristic component of mTORC1 is raptor, a scaffold protein that regulates complex assembly and substrate recognition. Raptor is a 150 kDa protein that binds to TOR signalling (TOS) motif-containing proteins, carrying them to the mTOR catalytic domain in order to phosphorylate mTOR downstream proteins such as the p70S6Ks, 4EBPs, and STAT3 (Hoeffer and Klann, 2010). Moreover, raptor is essential as an amino acid sensor, thus regulating the subcellular localization of mTORC1 (Sancak et al., 2008). Raptor competes with rapamycin for binding to the FRB domain, assembles the mTORC1 complex and activates its catalytic activity (Hoeffer and Klann, 2010). PRAS40 and Deptor are negative regulators of mTORC1. PRAS40 regulates the interaction between mTOR and Raptor and negatively regulates mTOR signalling by blocking mTORC1 access to its substrates. When mTORC1 is activated, it is able to directly phosphorylate and reduce PRAS40 and DEPTOR function (Dunlop and Tee, 2009).

mTORC2 contains the rapamycin-insensitive companion of mTOR (Rictor) and as the name indicates is resistant to acute rapamycin treatment, although, prolonged rapamycin exposure impairs the mTORC2 complex. In addition, newly synthesized Rictor is susceptible to rapamycin, suggesting that only preformed mTORC2 is resistant to rapamycin, perhaps through steric occlusion, blocking access to the FRB. The function of Sin1, another unique protein component of the mTORC2 complex, is not clear but retains an essential function because deletion of Sin1 is embryonically lethal. TORC2 plays a role in organization of the actin cytoskeleton, but also phosphorylates Akt, which both activates TORC1 and inhibits FOXO nuclear recruitment (Crino, 2011; Hoeffer and Klann, 2010; Laplante and Sabatini, 2012).

The heterodimer consisting of tuberous sclerosis 1 and 2 (TSC1 and TSC2) is a key upstream regulator of mTOR. TSC1/2 functions to constitutively inhibit mTORC1/2 via Rheb (Ras-homolog expressed in brain), a Ras family guanosine triphosphatase GTPase by stimulating the conversion of active Rheb-GTP to inactive Rheb-GDP (Wullschleger et al., 2006). Several kinases control, by phosphorylation, the activity of TSC1/2, regulating the heterodimer formation. Depending on the phospho-acceptor amino acid residues, these phosphorylation events culminate in either mTOR inhibition or activation (Takei and Nawa, 2014). GSK3β (glycogen synthase kinase 3β) also phosphorylates TSC2, activating TSC1/2 and thus inhibiting mTORC1 (Takei and Nawa, 2014).

2.2. PI3K/AKT axis

The PI3-K/Akt/mTOR is involved in cell response to growth factors such as insulin, insulin-like growth factors (IGFs) and epidermal-derived growth factor receptors (EGFRs) through the activation of phosphoinositide-3 kinase (PI3-K). The growth factor signalling that regulates mTORC1 mainly involves the insulin/insulin-like growth factor (IGF-1), which binds to IGF-1R/IR, 2α–2β subunit tyrosine kinase receptors and triggers tyrosine phosphorylation and activation of the insulin receptor substrate (IRS) family to activate PI3-K. PI3-K bound to IRS converts phosphatidylinositol-4,5-phosphate (PIP_2) in the cell membrane to phosphatidylinositol-3,4,5-phosphate (PIP_3) (O'Neill, 2013). PIP_3 accumulation is antagonized by the lipid phosphatase PTEN (Wullschleger et al., 2006). Increased PIP_3 levels recruit Akt to the membrane, where it is activated by phosphorylation of Thr-308 and Ser-473 by phosphoinositide-dependent kinase-1 (PDK-1), mTORC2 and DNA-PK. In turn, Akt phosphorylates and inactivates TSC2, which as noted above is a negative regulator of mTORC1 (Fig. 2) (Franke, 2008a,b).

A primary negative-feedback inhibitory pathway exists whereby sustained activation of mTOR/p70S6K suppresses Akt activity (O'Neill, 2013). This mechanism acts through mTOR-mediated serine phosphorylation of IRS-1, to induce IRS-1 inactivation and degradation, thus eliminating coupling of PI3-K/Akt to the insulin and IGF-1 receptors and other activating receptors. This process is a major cause of insulin resistance (Shah et al., 2004; Tanti and Jager, 2009). In addition, mTORC2 phosphorylates Akt at Ser-473 to activate the system, but also promotes Akt degradation. Similarly JNK and inflammatory pathways (e.g. TNFα) antagonize and can turn off PI3-K/Akt, modulating IRS-1 activity (Tanti and Jager, 2009). Growth factors also activate mTORC1 through the Ras signaling pathway effectors ERK1/2 and p90 ribosomal S6 kinase 1 (Alayev and Holz, 2013).

mTORC2 controls the members of the AGC subfamily of kinases including Akt, serum- and glucocorticoid-induced protein kinase 1

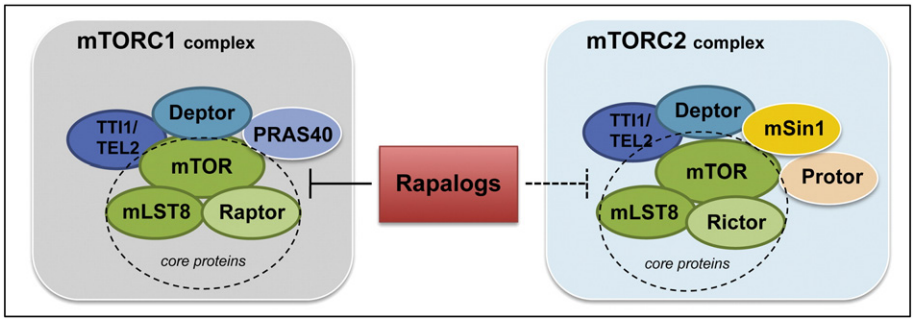

Fig. 1. mTOR complexes. TOR Complex 1 (mTORC1) is composed of mTOR, regulatory-associated protein of mTOR (Raptor), mammalian lethal with sec-13 protein 8 (mLST8) (core proteins) and the non-core components proline-rich Akt substrate 40 kDa (PRAS40), the DEP domain containing mTOR-interacting protein (Deptor) and the TTI1/TEL2 complex. This complex functions as a nutrient/energy/redox sensor and controlling protein synthesis. mTOR Complex 2 (mTORC2) is composed of mTOR, rapamycin-insensitive companion of mTOR (Rictor), mLST8, and the non-core proteins mammalian stress-activated protein kinase interacting protein 1 (mSin1), Deptor, TTI1/TEL2 and protein observed with rictor 1 and 2 (Protor). The mTORC2 signaling pathway is less defined than the mTORC1 signaling pathway.