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Review

mTOR signaling in tumorigenesis

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ABSTRACT

mTOR (the mechanistic target of rapamycin) is an atypical serine/threonine kinase involved in regulating major cellular functions including growth and proliferation. Deregulation of the mTOR signaling pathway is one of the most commonly observed pathological alterations in human cancers. To this end, oncogenic activation of the mTOR signaling pathway contributes to cancer cell growth, proliferation and survival, highlighting the potential for targeting the oncogenic mTOR pathway members as an effective anti-cancer strategy. In order to do so, a thorough understanding of the physiological roles of key mTOR signaling pathway components and upstream regulators would guide future targeted therapies. Thus, in this review, we summarize available genetic mouse models for mTORC1 and mTORC2 components, as well as characterized mTOR upstream regulators and downstream targets, and assign a potential oncogenic or tumor suppressive role for each evaluated molecule. Together, our work will not only facilitate the current understanding of mTOR biology and possible future research directions, but more importantly, provide a molecular basis for targeted therapies aiming at key oncogenic members along the mTOR signaling pathway.

Contents

Abbreviations: mTOR, the mechanistic target of rapamycin or the mammalian target of rapamycin; PIKK, phosphoinositide 3-kinase related protein kinase; ATM, ataxia-telangiectasia mutated; ATR, ataxia-telangiectasia and rad3-related; DNAPK, DNA-dependent protein kinase; Raptor, regulator-associated protein of mammalian target of rapamycin; mLST8, mammalian lethal with sec-13 protein 8; Rictor, rapamycin-insensitive companion of mTOR; mSin1 (MAPKAP1), mammalian stress-activated map kinase-interacting protein 1; DEPTOR, DEP domain containing mTOR-interacting protein; PRAS40, proline-rich Akt substrate 40 kDa; Protor1/2, protein observed with rictor 1 and 2; SGK, serum/glucocorticoid regulated kinase; 4E-BP1, eukaryotic translation initiation factor 4E (eIF4E)-binding protein 1; S6K, S6 kinase; SREBP, sterol regulatory element-binding protein; LKB1, liver kinase B1; TBC1D7, tre2-bub2-cdc16 1 domain family, member 7; AMPK, AMP-activated protein kinase; GAP, GTPase-activating protein; BHD, Birt–Hogg–Dubé; Rheb, ras homologue enriched in brain; FLCN, folliculin; KO, knockout; Tg, transgenic; ODC, ornithine decarboxylase; FGF, fibroblast growth factor; VEGF, vascular endothelial growth factor; HSCs, hematopoietic stem cells; IRS1, insulin receptor substrate 1; IGF-1, insulin-like growth factor; Grb10, growth factor receptor-bound protein 10; FAS, fatty acid synthase; ULK1, uncoordinated 51-like kinase 1; Atg13, mammalian autophagy-related gene 13; DAP1, death-associated protein 1; TFEB, transcription factor EB; ROS, reactive oxygen species; PH, pleckstrin homology; PDK1, phosphoinositide-dependent kinase 1; Pten, phosphatase and tensin homologue; APC, adenomatous polyposis coli; PLD, phospholipase D; REDD1, regulated in development and DNA damage responses 1

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1. Introduction

Rapamycin is an immune-suppressant drug extracted from a bacterial strain isolated on the Easter Island [1]. In 1991, a genetic screen for rapamycin-resistant mutations in budding yeast *Saccharomyces cerevisiae* led to the discovery of both *TOR1* and *TOR2* genes [2], the yeast homologues of mammalian mTOR. Subsequent biochemical studies in mammalian cells further led to the identification of a ~290 kDa protein, which was termed mTOR (mechanistic target of rapamycin, also known as the mammalian target of rapamycin) [3–5]. mTOR is an atypical serine/threonine kinase that belongs to the PIKK (phosphoinositide 3-kinase related protein kinase) super-family, which includes multiple members of large-size kinase proteins that are involved in nutrient sensing (mTOR) and DNA repair [ATM (ataxia-telangiectasia mutated), ATR (ataxia-telangiectasia and Rad3-related) and DNAPK (DNA-dependent protein kinase)] [6].

In yeast, two *TOR* genes have been identified and termed as *TOR1* and *TOR2*, both of which participate in two separate protein complexes TORC1 and TORC2, respectively [7]. Notably, both TOR1 and TOR2 are found in the TORC1 complex that mainly regulates cell growth; whereas only TOR2 is found in the TORC2 complex, which is important for cell cycle-dependent polarization of the actin cytoskeleton [8]. On the other hand, in mammalian cells, there is only one *mTOR* gene identified thus far [3,4]. Furthermore, as an evolutionarily conserved kinase, mTOR functions largely as the catalytic subunit of two distinct protein kinase complexes, designated as mTORC1 (mTOR complex 1) and mTORC2 (mTOR complex 2), respectively [9].

Both mTORC1 and mTORC2 complexes share common subunits including mTOR and mLST8 (mammalian lethal with sec-13 protein 8, also known as GβL) [10–12], whereas mTORC1 contains its unique subunit, Raptor (regulator-associated protein of mammalian target of rapamycin), and the specific components including Rictor (rapamycin-insensitive companion of mTOR) and mSin1 (mammalian stress-activated map kinase-interacting protein 1, also termed MAPKAP1) define mTORC2 [13–16] (Fig. 1). Critically, both Raptor and Rictor serve as scaffolding proteins to regulate the assembly, localization and substrate binding of mTORC1 and mTORC2, respectively [17]. However, it appears that mLST8 is essential for the mTOR/Rictor, but not the mTOR/Raptor interaction, while the underlying molecular mechanism is not fully understood [18]. Sin1 is also considered as a scaffolding protein regulating the assembly and activity of mTORC2 [15,19,20], while the detailed complex organization remains largely elusive in part due to the lack of structural evidence for the mTORC2 holo-enzyme. Furthermore, other additional regulatory components have also been reported to be involved in mTOR complex function [17]. For example, DEPTOR (DEP domain containing mTOR-interacting protein) acts as an endogenous mTOR inhibitor that expresses at low levels in most cancers [21]. Unlike DEPTOR, which inhibits both mTORC1 and mTORC2, PRAS40 (proline-rich Akt substrate 40 kDa) binds the mTOR kinase domain in a phosphorylation-dependent manner and only suppresses the kinase activity of mTORC1 [22,23]. On the other hand, Protor1/2 (protein observed with Rictor 1 and 2) binds Rictor, and is only present in mTORC2, to increase the mTORC2-mediated activation of SGK-1 (serum/glucocorticoid regulated kinase-1) [24,25].

The mTOR signaling pathway is pivotal in regulating major cell functions including cell growth, proliferation and metabolism [17]. To this end, mTORC1 and mTORC2 have been shown to play critical yet functionally distinct roles in controlling different cellular processes. Specifically, mTORC1 largely regulates protein translation and cell metabolism through sensing intra-cellular as well as extra-cellular stimuli, such as stress, nutrients, energy, oxygen levels and growth factors [7,17]. In addition, it also directly phosphorylates many downstream targets including 4E-BP1 (eukaryotic translation initiation factor 4E binding protein 1), S6K (S6 kinase), SREBP (sterol regulatory element-binding protein) and autophagy components to promote protein and lipid synthesis, lysosome biogenesis, energy metabolism and to inhibit autophagy [17]. On the other hand, mTORC2 is less sensitive to nutrients but largely responsive to extra-cellular growth factors [13,14]. However, the exact molecular mechanism for how mTORC2 senses extra-cellular growth factor stimulation is still largely unclear, while the only available knowledge is that ribosome association of mTORC2 is critical for its activation [17]. Nonetheless, once mTORC2 is activated, it phosphorylates major downstream target proteins including AGC family of kinases, such as Akt, SGK and PKC (protein kinase C) [26] to further augment the kinase cascade to exert their cellular functions.

Consistent with a critical role in regulating cell growth and metabolism, deregulation of the mTOR signaling is commonly observed in human cancers [27–29]. To this end, mutations or loss-of-function of upstream regulator genes such as *TSC1/2* (tuberous sclerosis complex 1/2) or *LKB1* (liver kinase B1) have been closely linked to clinical tumor syndromes including the Tuberous Sclerosis complex and the Peutz–Jeghers syndrome, respectively [30,31]. More importantly, hyper-activation of PI3K and Akt, or genetic loss or mutation of *PTEN* (phosphatase and tensin homologue), a negative suppressor of the PI3K signaling, have been observed in many types of human cancers [32]. Given that hyper-activation of the mTOR pathway in cancer contributes significantly to cancer initiation and development, targeting the oncogenic mTOR pathway components could potentially be an effective cancer treatment strategy [17]. In fact, FDA (Food and Drug Administration) has approved rapamycin and its analogs Temsirolimus and Everolimus for the treatments of certain types of tumors including renal cell carcinoma and mantle cell lymphoma [33]. However, considering rapamycin and its analogs have only reached modest efficacy in current clinical trials, an in-depth further understanding of the molecular mechanisms for the mTOR signaling pathway, as well as identifying new therapeutic targets along this signaling cascade may provide fruitful targets for cancer therapy [17,34].

Thus in this review, we summarize the available genetic mouse models for both the mTORC1 and mTORC2 complexes. Furthermore, we also explore their upstream regulators or downstream targets to define a clear functional role for these critical molecules in their physiological settings as well as in tumorigenesis, which will provide insights for