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Editorial
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Inhibitors of PI3K/AKT/mTOR Signaling Pathway as a Novel Targeted Therapy for Cancer

Thekkuttuparambil Ananthanarayanan Ajith*

Department of Biochemistry, Amala Institute of Medical Sciences, Kerala, India

Editorial

There are various cytoplasmic cross talking signaling pathways possible in the target cell. The phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway (PI3K/AKT/mTOR pathway) plays a pivotal role in the pathophysiology of cancer. mTOR is a serine/threonine protein kinase involve in the downstream of the PI3K signaling pathway, regulating the cellular process such as growth, proliferation, motility and survival. These processes are accomplished through the regulation of transcription and protein translation. Furthermore, mTOR has also been demonstrated as an inhibitor of autophagy. In eukaryotic cells, two distinct mTOR complexes have identified, TORC1 and TORC2. The substrates for these complexes are different and, thus, they have distinct physiological functions [1].

There are six components of mTORC1. Among them mTOR is the catalytic subunit and others such as proline-rich AKT substrate 40kDa (PRAS40), DEP-domain-containing mTOR-interacting protein (Deptor) and regulatory-associated protein of mTOR (Raptor) are regulatory components. When PRAS40 and Deptor recruited to the complex, mTORC1 is inhibited. Raptor regulates the assembly of mTORC1 complex by recruiting substrates for mTOR [2,3]. Activated Akt can directly phosphorylate PRAS40 which will reduce its binding to Raptor and, thereby, activate the mTORC1. Another pathway through which Akt activates the mTORC1 is mediated through IκB kinase-β (IKKβ) mediated through its association with the Raptor. IKKβ can also phosphorylate to inactivate the tuberous sclerosis protein 1 which results in the activation of mTORC1. Therefore, signals generated from the growth factors can activate the PI3K/Akt/mTOR pathway and proliferate the cells. The mTORC2 comprises seven different proteins and can phosphorylate the serine/threonine protein kinase Akt/PKB resulting in the complete activation of Akt [4]. A consistent activation of mTOR will produce a p70 ribosomal S6 kinase 1 (p70S6K1) dependent negative feedback loop as the autoregulatory mechanism. Further, Deptor can negatively regulate the mTORC2 activity.

mTOR are regulated by a wide range of signals. The activity of mTORC1 is stimulated by insulin, growth factors, essential amino acids leucine and also by oxidative stress [5,6]. A chronic inflammation that exists in the microenvironment of the cancer cell releases pro-inflammatory cytokines, tumor necrosis factor-alpha which in turn activates inhibitor kappa kinase-beta (IKKβ). IKKβ later interacts with and inactivates the tuberous sclerosis protein 1 leading to the activation of mTORC1 [7]. The Akt activity can be blocked by the phosphatase and tensin homolog deleted from chromosome 10, SH2 domain-containing inositol phosphatase, and carboxyl-terminal modulator protein.

mTORC1 activation inhibits the autophagic proteins autophagy related gene 13 and UNC-51 like kinase 1/2 through phosphorylation that finally prevent the autophagy. Studies have demonstrated that PI 3-K/Akt/mTOR pathway ultimately interface with programmed cell death. Upon activation, mTORC1 phosphorylates its downstream targets p70S6K which in turn phosphorylate and inactivate the pro-apoptotic protein BAD. While anti-apoptotic protein Bcl-2/Bcl-x_L expression increases. Both Bcl-2 and Bcl-xL proteins inhibit cytochrome c release through the mitochondrial pore and finally inhibit the activation of caspase cascade.[8] The antiapoptotic effect mTOR can also be mediated though the activation of Akt which inhibits the “pro-apoptotic” proteins such as FoxO3a, glycogen synthase-kinase 3β and PRAS40. Aberrant activation of the PI3K/mTOR pathway was evidenced in many cancers as well. Akt activity is enhanced in the T cell leukemia/lymphoma and also in B cell [9]. The expression of mTOR increased in glioblastomas resulting in poor survival [10].

Therefore, targeting the PI3K/AKT/mTOR signaling pathway can block the growth and survival of cancer cells. Agents were demonstrated to inhibit selectively mTORC complexes 1 or both

Correspondence:
Ajith TA, Professor of Biochemistry, Department of Biochemistry, Amala Institute of Medical Sciences, Kerala, India.
E-mail: *taajith@rediffmail.com*
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mTORC1 and mTORC2 or targeting PI3K. Inhibition of mTORC1 and mTORC2 can lead to autophagy or apoptosis. Furthermore, inhibition of mTORC2 alone prevents phosphorylation of Ser-473 site on AKT and result in arrests of cells in G1 phase of the cell cycle. Sathe et al, recently concluded that combining the inhibitors of PI3K/mTOR with AKT or PDK1 can induce the apoptosis, decreased colony formation, cell viability and growth of tumor xenografts [11]. mTOR inhibitors such as sirolimus, temsirolimus, everolimus and ridaforolimus have demonstrated as antitumor agents in several malignancies [12]. Temsirolimus, everolimus are used in the treatment of in renal cell carcinoma [11] mainly in advanced renal cell carcinoma and also in breast cancer [13]. Ridaforolimus (deforolimus) is another selective mTORC1 inhibitor, showed benefit in women with advanced or recurrent endometrial cancer [12].

Recent clinical trials demonstrated the effectiveness of combination therapy. Fukumoto et al. demonstrated the stronger anti-proliferative effect of rapamycin in combination with MAPK/ERK (MEK) inhibitor than rapamycin monotherapy on OUMS-27 cells [14]. However, one of the recent randomized controlled trials revealed the efficiency of using inhibitors of PI3K pathway for advanced solid tumours. While comparing the effect of single PI3K/AKT/mTOR pathway inhibitor therapy with either other targeted therapies alone or combination therapy using inhibitors of PI3K/AKT/mTOR pathway plus other targeted therapies, no significant improvement in the progression-free survival was observed [15]. Inhibition of the mTOR complex such as disruption of mTORC2 produces the diabetic-like symptoms of decreased glucose tolerance and insensitivity to insulin [16]. Furthermore, individual drugs produce adverse effect such as peripheral edema, hypertriglyceridemia and hypertension were observed in ~30% of patients treated with rapamycin, interstitial lung disease and hypertension have noticed in organ transplanted patients when treated with sirolimus and everolimus. This emphasize the need of further studies in which more specific inhibitors of PI3K/AKT/mTOR signaling pathway with limited adverse drug reaction.

Despite various natural compounds including curcumin, epigallocatechin gallate, resveratrol and caffeine were demonstrated as inhibitors of mTOR in cells in culture no clinical trials are available to demonstrate their effect or their use as dietary supplements [17]. Therefore, more focused future studies are warranted to explore the targeting therapy of PI3K/AKT/mTOR signaling pathway.

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