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Inhibition of PI3K/Akt/mTOR Signaling by Natural Products

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Mammalian target of rapamycin (mTOR) lies downstream of the type I insulin-like growth factor receptor (IGFR), a transmembrane tyrosine kinase [1-4]. In response to ligand binding, IGFR is activated *via* autophosphorylation of multiple tyrosine residues. Activated IGFR in turn phosphorylates the insulin receptor substrates 1-4 (IRS1-4) and src- and collagen-homology (SHC) adaptor proteins, which can trigger multiple downstream signal transduction pathways including PI3K pathway [1-4]. Phosphorylated IRS recruits the p85 subunit of PI3K and signals to the p110 catalytic subunit of PI3K, resulting in activation of PI3K. Activated PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-trisphosphate (PIP3) [1-4]. This pathway is negatively regulated by PTEN (phosphatase and tensin homolog on chromosome ten), a dual-specificity protein and lipid phosphatase. Increased PIP3 binds to the pleckstrin homology (PH) domain of Akt and, in combination with additional Ser/Thr phosphorylation of Akt by phosphoinositide-dependent kinase 1 (PDK1) and mTOR complex 2 (mTORC2), results in full activation of Akt [1-4]. Subsequently, activated PI3K or Akt may positively regulate mTOR, leading to increased phosphorylation of ribosomal p70 S6 kinase (S6K1) and eukaryotic initiation factor 4E (eIF4E) binding protein 1 (4E-BP1), the two best-characterized downstream effector molecules of mTOR [1-4]. Studies have placed tuberous sclerosis complex (TSC) 1/2 as a modulator between PI3K/Akt and mTOR [5-7]. The TSC1/2 complex acts as a repressor of mTOR function [8-10]. TSC2 has GTPase-activating protein (GAP) activity towards the Ras family small GTPase Rheb (Ras homolog enriched in brain), and TSC1/2 antagonizes the mTOR signaling pathway *via* stimulation of GTP hydrolysis of Rheb [11-13]. Rheb activates mTOR by antagonizing its endogenous inhibitor, FK506 binding protein 38 (FKBP38) [14], though this remains controversial [15]. The TSC can also be activated by energy depletion through the activation of AMPK [1-4]. This, in turn, activates the TSC, which catalyzes the conversion of Rheb-GTP to Rheb-GDP and thus inhibits mTOR [1-4]. Recently, Rag proteins have been described to link amino acid sensing and the regulation of mTORC1 activity [16-18]. mTOR functions at least as two complexes (mTORC1 and mTORC2) in mammalian cells [1-4]. mTORC1 is composed of mTOR, mLST8 (also termed G-protein β-subunit-like protein, GβL, a yeast homolog of LST8), PRAS40 (proline-rich Akt substrate 40 kDa) and raptor (regulatory-associated protein of mTOR) [19-24], whereas mTORC2 consists of mTOR, mLST8, mSin1 (mammalian stress-activated protein kinase-interacting protein 1), rictor (rapamycin insensitive companion of mTOR), and protor (protein observed with rictor, also named PRR5, proline-rich protein 5) [25-32]. mTORC1 is sensitive to energy, amino acids, growth factors, and oxygen levels, as well as rapamycin, regulates phosphorylation of p70 S6 kinase 1 (S6K1) and eukaryotic initiation factor 4E (eIF4E) binding protein 1 (4E-BP1), and controls protein and lipid synthesis, cell growth, proliferation, survival and motility [1-4, 19-24]. In contrast, mTORC2 is only sensitive to growth factors and prolonged (>24 h) rapamycin exposure in

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certain cases, mediadtes phosphorylation/activity of Akt [25,27,28,30,31], serum and glucocorticoid-inducible kinase 1 (SGK1) [33], PKCα [29], focal adhesion proteins [26,29,34] and small GTPases [26,35], and regulates cell survival and the actin cytoskeleton [1-4, 25-35]. However, rapamycin inhibition of mTORC1-mediated S6K1 may decrease IRS-1 phosphorylation, which results in IRS-1 accumulation, thereby activating PI3K/Akt [36,37]. Most recent studies further indicate that mTORC1 interacts with ULK1/2-ATG13-FIP200 complex and phosphorylates ULK1/2 and ATG13, regulating autophagy [38-40]. Both mTORC1 and mTORC2 interact with a negative regulator DEPTOR [41]. Although the cellular functions of the mTOR complexes remain to be determined, current data indicate that mTOR is a central controller for cell growth, proliferation, survival/autophagy, and motility [1-4].

Dysregulation of PI3K/Akt/mTOR pathway generates a favorable oncogenic environment and has been seen in a variety of transformed cells and human tumors [1-4]. High frequency of mutations of the components (such as *PTEN, TSC,* and *PI3K*) in this pathway is correlated to human malignant progression and poor prognosis [1-4]. A mutation of mTOR (L2431P) within an autoinhibitory domain of mTOR, resulting in constitutively activation of mTOR, has also recently been documented [42]. Of interest, the tumor cells that are addictive to PI3K/Akt/mTOR signaling are more sensitive to their inhibitors than normal cells [2-4]. Therefore, targeting PI3K/Akt/mTOR pathway has become a new and promising strategy to combat cancer.

While two rapalogs, CCI-779 (Temsirolimus) and RAD001 (Everolimus) that selectively inhibit mTORC1, have been approved for treatment of advanced renal cancer, other mTORC1 inhibitors and newly synthesized ATP-competitive mTORC1/2 inhibitors that inhibit both Akt and mTOR, are still in clinical trials for treatment of a variety of cancers [4]. Recent studies have demonstrated that a number of natural products (or nutraceuticals) isolated from plants (e.g. fruits, vegetables, spices, nuts, legumes, herbs, etc.) also inhibit PI3K/Akt/mTOR pathway, and exhibit potent anticancer activities. As most of the natural products occur in our diet every day, and are very safe, the results suggest that those natural products may be explored for cancer prevention and treatment. This special issue selects apigenin [43], curcumin [44], cryptotanshinone [45], fisetin [46], indoles (indole-3-carbinol and 3,3′-diindolylmethane) [47], isoflavones (genistein and deguelin) [48], quercetin [49], resveratrol [50], and tocotrienol [51]. First, we briefly summarize specific aspects of these compounds, including their origins, isolation, physical and chemical properties, structures, and medicinal uses, and finally, we focus on reviewing recent advances on their anticancer mechanisms, particularly related to inhibition of PI3K/Akt/mTOR as well as other oncogenic signaling pathways.

Apigenin, a family member of flavonoids, is abundant in fruits (oranges, apples, cherries, grapes), vegetables (onions, parsley, broccoli, sweet green pepper, celery, barley, tomatoes) and beverages (tea, wine). Here Tong *et al.* review recent studies of apigenin as an anticancer agent, and particularly discuss apigenin inhibition of PI3K/Akt/mTOR signaling [43]. Evidence suggests that apigenin inhibits PI3K/Akt/mTOR signaling either by direct inhibition of PI3K/Akt activity, or by indirect activation of AMPK-TSC axis.

Cryptotanshinone is one of the major tanshinones isolated from the roots of the plant *Salvia miltiorrhiza Bunge* (Danshen). Studies have shown that cryptotanshinone inhibits cell proliferation and induces cell death in a variety of cancer cells. Also, cryptotanshinone inhibits angiogenesis and lymphangiogenesis, suggesting that cryptotanshinone is a potential anticancer agent. However, because of its poor bioavailability, cryptotanshinone has not been in clinical trials for any cancer therapy. Here Chen *et al.* review recent findings, showing evidence that cryptotanshinone inhibits mTORC1-mediated phosphorylation of

S6K1 and 4E-BP1, but may inhibit or activate mTORC2-mediated Akt, depending on cell lines [44]. Further research is needed to address the underlying mechanisms.

Curcumin (diferuloylmethane), a polyphenol natural product of the plant *Curcuma longa*, is undergoing early clinical trials as a novel anticancer agent. However, the anticancer mechanism of curcumin remains to be elucidated. Numerous cellular targets have been proposed. However, none of them appears to be the primary target. Here Beevers *et al*. summarize recent findings and highlight that curcumin may execute its anticancer activity by primarily targeting Akt/mTOR signaling [45]. Curcumin, at low concentrations (< 40 μM) inhibits phosphorylation of S6K1 and 4E-BP1, two downstream effector molecules of mTORC1, while at high concentrations (>40 μM) inhibits phosphorylation of Akt, a substrate of mTORC2, in numerous cancer cell lines. Curcumin inhibition of Akt/mTOR signaling results from disrupting mTOR-raptor complex, and activating protein phosphatase 2A (PP2A).

Fisetin, a family member of flavonoids, occurs in fruits and vegetables, such as strawberries, apples, persimmons and onions. *In vitro* and *in vivo* studies have shown that fisetin is a potential anticancer agent, by inhibiting cell proliferation and inducing cell death in various cancer cells. Here Syed *et al*. summarize recent studies, showing evidence that the anticancer activity of fisetin is in part linked to inhibition of PI3K/Akt and mTOR and signaling pathways [46]. Mechanistically, fisetin downregulates expression of Raptor, Rictor, PRAS40, and mLST8, and subsequently decreases the formation of mTORC1 and mTORC2. Also, fisetin inhibits expression of the downstream targets of mTOR, such as S6K1, eIF4E, and 4E-BP1. Furthermore, fisetin decreases expression of regulatory (p85) and catalytic (p110) subunits of PI3K, activates AMPK, and decreases phosphorylation of Akt and mTOR.

Indoles are natural compounds in cruciferous vegetables such as broccoli, cauliflower, cabbage and brussels sprouts. Of indoles, indole-3-carbinol (I3C) and its *in vivo* dimeric product 3,3′-diindolylmethane (DIM) are potent compounds with anticancer properties. Here Ahmad *et al*. review the recent studies of anticancer mechanisms of the indoles [47]. It appears that I3C, DIM and their derivatives are able to inhibit PI3K/Akt/mTOR signaling pathway, as well as the downstream NF-κB, which helps explain their ability to inhibit invasion and angiogenesis, and the reversal of epithelial-to-mesenchymal transition (EMT) phenotype and drug resistance. The effects are derived from direct inhibition PI3K, Akt and mTOR activity. Further studies are required to unveil the detailed mechanism.

Isoflavones, a class of flavonoid phenolic compounds, are rich in soybean. In addition to other biological activities, isoflavones possess anticancer activities. This is evidenced by the roles of isoflavones in potentiating radio- or chemotherapy. Among isoflavones, genistein and deguelin have been well studied. Of note, genistein have been in phase II randomized bladder cancer chemoprevention trial. Here Ahmad *et al*. review the recent studies of anticancer activities of the isoflavones [48]. Multiple signaling pathways, including PI3K/Akt/mTOR pathway, are targeted by the isofalvones. However, the inhibitory effect of isoflavones on mTOR is only at the beginning of investigations. Also, the effect of genistein on Akt inhibition or activation remains to be defined.

Quercetin, a polyphenolic compounds, is mainly from consumption of tea, onions, red grapes, and apples in the daily life. In this specific issue, Brüning summarizes the findings, showing that quercetin acts an anticancer agent in part by inhibition of mTOR signaling [49]. Apparently, Quercetin inhibits mTOR signaling by inhibiting PI3K and Ras activity, activating AMPK, and upregulating TSC1. However, due to unfavorable bioavailability and

pharmacokinetics, new formulations or chemical modifications of quercetin are needed for clinical cancer therapy.

Resveratrol, a natural polyphenol rich in red grapes and red wine, possesses multifaceted health beneficial properties. Here Wu *et al*. summarize the anticancer activities of resveratrol, and the potential molecular mechanism related to inhibition of mTOR signaling [50]. Current knowledge implicates that resveratrol suppresses mTOR signaling in part by inhibiting PI3K/Akt, stimulating PTEN expression, activating AMPK-TSC1/2, and promoting DEPTOR-mTOR interaction.

Tocotrienols, members of vitamin E superfamily, exhibit not only strong antioxidant property, but also potent anticancer activity. Here Sylvester *et al*. summarize the studies of tocotrienols, and provide evidence that γ-tocotrienol is the most potent anticancer agent among the tocotrienols [51]. It is believed that the anticancer effect of γ-tocotrienol is mediated, at least in part, through the suppression of PI3K/PDK-1/Akt and NF B mitogenic signaling in neoplastic +SA mammary epithelial cells. γ-tocotrienol does not alter the expression or activity of PTEN or PP2A. How γ-tocotrienol inhibits PI3K/PDK-1/Akt remains to be elucidated.

Finally, it should be mentioned that many other natural products, such as caffeine (in caffee), epigallocatechin gallate (EGCG, in green tea), celastrol (in traditional Chinese medicine named “Thunder of God Vine”), butein (in the stems of *Rhus verniciflua*, used as a food additive and as an herbal medicine in Asia), capsaicin (in chili peppers), and β-elemene (from the traditional Chinese medicinal herb *Rhizoma zedoariae*), etc., have been reported to inhibit PI3K, Akt or mTOR signaling as well. However, due to limitation of time in editing this special issue, we cannot discuss them in details. Here Wang *et al*. briefly summarize the findings of numerous natural products that induce autophagy by inhibiting PI3K/Akt/mTOR signaling [52].

In conclusion, here we provide an overview of inhibition of PI3K/Akt/mTOR signaling by certain natural products. Understanding how the natural products inhibit PI3K/Akt/mTOR signaling may shed new insights on design and development of novel treatment and prevention of cancer.

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