Hitting the Golden TORget: Curcumin's Effects on mTOR Signaling

Article *in* Anti-cancer agents in medicinal chemistry · December 2012

DOI: 10.2174/1871520611313070004 · Source: PubMed

3 authors, including:

Hongyu Zhou
Chinese Academy of Sciences
35 PUBLICATIONS **1,331** CITATIONS
SEE PROFILE

Shile Huang
Louisiana State University Health Sciences Cen…
131 PUBLICATIONS **5,251** CITATIONS
SEE PROFILE

Send Orders for Reprints to reprints@benthamscience.net

988 *Anti-Cancer Agents in Medicinal Chemistry,* **2013,** *13,* **988-994**

Hitting the Golden TORget: Curcumin's Effects on mTOR Signaling

Christopher S. Beevers[1,*], Hongyu Zhou[2] and Shile Huang[3,4,*]

[1]*Department of Pharmacology, Ross University School of Medicine, Picard-Portsmouth, Commonwealth of Dominica, West Indies;* [2]*Kunming Institute of Botany, Chinese Academy of Sciences, 132 Lanhei Road, Kunming, Yunnan Province, 650201, People's Republic of China;* [3]*Department of Biochemistry and Molecular Biology, and* [4]*Feist-Weiller Cancer Center, Louisiana State University Health Sciences Center, Shreveport, Louisiana, USA*

Abstract: The polyphenol natural product curcumin possesses a plethora of biological and pharmacological properties. For years, much interest has been placed in the development and use of curcumin and its derivatives for the prevention and treatment of cardiovascular, diabetic, and neurodegenerative diseases, as well as cancer. Increasing evidence suggests that curcumin displays amazing molecular versatility, and the number of its proposed cellular targets grows as the research continues. The mammalian target of rapamycin (mTOR) is a master kinase, regulating cell growth/proliferation, survival, and motility. Dysregulated mTOR signaling occurs frequently in cancer, and targeting mTOR signaling is a promising strategy for cancer therapy. Recent studies have identified mTOR as a novel target of curcumin. Here we focus on reviewing current knowledge regarding the effects of curcumin on mTOR signaling for better understanding the anticancer mechanism of curcumin. The emerging studies of mTOR signaling and clinical studies on curcumin with cancer patients are also discussed here.

Keywords: Curcumin, mTOR, Akt, Cancer, Cell proliferation, Cell death.

CURCUMIN

Phytochemicals are plant-based molecules that are non-nutritive in nature, but possess beneficial pharmacological actions in the human body when ingested [1]. Over the past decades, interest in the potential use of phytochemicals as chemopreventive and chemotherapeutic agents has grown both scientifically and publically, with the greatest amount of attention being paid to their potential application in the fight against cardiovascular disease and cancer [1]. Turmeric, a spice produced from the rhizome of the perennial Asian herb *Curcuma longa*, has been especially popular in this growing interest in botanical pharmacology, owing to its distinguished and long history as a therapeutic agent in Oriental medicine for several thousand years. In this capacity, turmeric has been utilized topically for the treatment of open wounds, skin tumors, and inflammatory conditions, while orally ingested forms have been used to remedy gastrointestinal disorders and other internal ailments [1, 2].

Analyses of turmeric have identified its major chemical constituents as a family of polyphenolic compounds called the curcuminoids, which include curcumin [1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione], curcumin II (demethoxycurcumin), and curcumin III (bis-demethoxycurcumin) [1, 2]. Curcumin is the most biomedically potent chemical component in turmeric, and it comprises approximately 2-8% of most turmeric preparations [1, 2]. Hundreds of scientific studies conducted over the past 30 years have extensively studied the chemical, biochemical, pharmacological, and clinical properties of curcumin [1, 2]. The vast majority of these investigations have specifically attempted to elucidate the potential chemopreventive and chemotherapeutic value of this phytochemical in the battle against human diseases, particularly neurodegenerative disorders, inflammatory conditions, gastrointestinal disorders, cardiovascular diseases, and cancer [1, 2].

*Address correspondence to these authors at the Department of Pharmacology, Ross University School of Medicine, 630 US Hwy 1, North Brunswick, NJ 08902, USA; Tel: +1-767-255-6368; Fax: +1-767-445-5897; E-mail: cbeevers@rossmed.edu.dm; Shile Huang, Ph.D., Department of Biochemistry and Molecular Biology, Louisiana State University Health Sciences Center, 1501 Kings Highway, Shreveport, LA 71130-3932, USA; Tel: +1-318-675-7759; Fax: +1-318-675-5180; E-mail: shuan1@lsuhsc.edu

Curcumin (molecular weight: 368.37) possesses a conjugated double bond heptadienone linker containing a bis-α,β-unsaturated β-diketone moiety [1]. This linker joins together the molecule's two methoxyphenol rings [1]. The diketone moiety undergoes tautomerization in a pH-dependent fashion [1]. The bis-keto tautomer displays potent Brønsted acid activity, while the enol tautomer functions as a powerful Lewis Base [3]. Curcumin is insoluble in water, but is soluble in organic solvents such as acetone, ethanol, and dimethylsulfoxide (DMSO) [2]. In neutral/alkaline solutions the compound displays a dark red color, while in acidic solutions it adopts a vibrant yellow color [2]. Curcumin is extremely unstable in phosphate-based buffers, normal cell culture media, and most alkaline solutions, while it is extremely stable in acidic solutions [1, 2, 4].

A number of clinical trials have addressed the safety and pharmacokinetics of curcumin in humans. The safety and tolerability of curcumin at high doses are well established [5-7]. In patients with high-risk or pre-malignant lesions, oral dose ranging from 500 to 8,000 mg/day for 3 months are well tolerated [6]. However, the *in vivo* bioavailability of curcumin is poor, due to a combination of poor aqueous solubility, poor gastrointestinal absorption, efficient first pass metabolism, and rapid elimination [8, 9]. After oral dosing, curcumin is metabolized into several chemical species, including curcumin glucuronide, curcumin sulfate, hexahydrocurcumin, tetrahydrocurcumin, and dihydrocurcumin [10]. One of the current major initiatives in the field of curcumin study has been the manipulation and optimization of the compound's pharmacokinetic characteristics *via* the development of curcumin derivatives and curcumin-drug vehicle combinations that display greatly enhanced absorption and systemic bioavailability, and many of these studies appear to be very promising [10, 11].

Without question, the most intensive study of curcumin has been exploration of its pharmacodynamic profiles, namely its mechanisms of action, pharmacological actions, and pharmacological effects, and how these profiles are potentially translated into clinical use and responsiveness. Those studies have been carried out extensively *in vitro* (human cell lines) and *in vivo* (both animals and humans), and have been thoroughly reviewed [1, 2, 9, 10, 12, 13]. Consistent with the strong pre-clinical evidence of its pharmacological activities, curcumin has been in early clinical trials for

1875-5992/13 $58.00+.00

treatment of a variety of human diseases, including rheumatoid arthritis [14, 15], ulcerative colitis , Alzheimer's disease [15], multiple myeloma [15], pancreatic cancer [15, 16], and colon cancer [2, 15]. Here we only focus on reviewing some clinical trials related to cancer.

A phase I study evaluated the toxicology, pharmacokinetics, and biologically effective dose of curcumin in 25 patients with various types of high-risk or pre-malignant lesions [6]. After an initial dose of 0.5 g curcumin daily, the dose was increased to as much as 8 g daily for 3 months. There was no treatment-related toxicity up to 8 g/day. Histological improvement of precancerous lesions was observed in 1 of 2 patients with recently resected bladder cancer (decreased dysplasia and inflammation), 1 of 6 patients with intestinal metaplasia of the stomach (fewer goblet cells), 1 of 4 patients with cervical intraepithelial neoplasm (decreases in hyperkeratosis, parakeratosis), 2 of 7 patients with oral leukoplakia, and 2 of 6 patients with Bowen's disease, indicating a biologic effect of curcumin in the chemoprevention of cancer [6].

Two clinical phase I dose-escalation studies have investigated the use of curcumin therapy in patients with advanced colorectal cancer [7, 17]. In the pilot study, 15 patients received an oral capsule of *Curcuma* extract at doses between 440 and 2,200 mg/day, containing 36-180 mg of curcumin, for up to 4 months [7]. The compound was well tolerated, and dose-limiting toxicity was not observed. The lymphocytic biomarker glutathione S-transferase (GST) activity showed a 59% decrease with ingestion of low-dose (440 mg/day) of *curcuma* extract, and radiologically stable disease was demonstrated in 5 patients for 2-4 months of the study period [7]. In a subsequent study in a similar population, Sharma *et al.* further explored the pharmacology of curcumin administered in capsules compatible with curcumin doses between 0.45 and 3.6 g/day for up to 4 months [17]. Three biomarkers of the potential activity of curcumin were measured in patient blood leukocytes: GST activity, levels of deoxyguanosine adduct M(1)G, and PGE_2 production induced *ex vivo*. In blood samples taken 1 h after the dose on Days 1 and 29, consumption of 3.6 g of curcumin daily decreases inducible PGE_2 production by 62% and 57%, respectively, when compared with levels observed immediately before administering the drug [17]. Consequently, the 3.6 g dose was chosen for further evaluation in phase II trial in cancers outside the gastrointestinal tract [17].

In another clinical trial, 25 patients with advanced pancreatic cancer received 8 g curcumin orally every day, and 21 of them exhibited evaluable responses [16]. Of note, one patient achieved disease stabilization for 18 months, and another patient had a brief, but marked, tumor regression (73%) accompanied by 4- to 35-fold increases in serum cytokine levels (IL-6, IL-8, IL-10 and IL-1 receptor antagonists) [16]. Downregulated expression of NF-κB, COX-2, and phosphorylated signal transducer and activator of transcription 3 (Stat3) by curcumin in peripheral blood mononuclear cells from patients were also observed [16]. In an interesting, but uncontrolled study of 62 patients with oral cancerous lesions, topical curcumin application produced remarkable symptomatic relief in patients. Dry lesions were noted in 70% of the cases, and a reduction in lesion size and pain was observed in 10% of patients [18]. Currently, a search on the web of http://clinicaltrials.gov shows that there are 17 clinical trials investigating the preventive or therapeutic efficacy of curcumin in cancer patients. Five studies have completed, and 12 are ongoing. Hopefully, these ongoing trials over the next few years will provide a better understanding of the anticancer potential of curcumin in patients with different cancers.

Preclinical studies in cell culture and in animal models strongly support that curcumin has the ability to exert anti-cancer actions, including inhibiting cell proliferation/growth and motility [2, 13, 19], inducing cell death, and inhibiting angiogenesis [2, 13, 19, 20]. These studies also suggest that curcumin possesses amazing molecular versatility as evidenced by the large number of proposed drug receptors for the compound, including plasma membrane-bound receptors, proteases, transporters, apoptotic factors, kinases, transcription factors, and adhesion molecules [2, 12]. While it remains a possibility that curcumin is in fact interacting with this large range of molecules, a more plausible explanation is that curcumin predominately targets only a few key cell regulators, and these actions spill over to affect many different pathways, factors, and processes within the cell. Identifying these key cellular regulators, however, remains challenging due to the seemingly diverse molecular promiscuity of the compound. Recently, the mammalian target of rapamycin (mTOR) has been identified as a novel molecular target of curcumin, which may in fact represent one of these central targets due to the fact that mTOR stands at the center of numerous key cellular processes (cell growth/proliferation, survival and motility), almost all of which are affected to some degree by curcumin.

mTOR

The serine/threonine protein kinase mTOR is composed of 2549 amino acids and has a molecular mass of 289 kDa [21]. Numerous studies demonstrated that cellular conditions that are sufficient to suppress *in vivo* mTOR kinase activity do not affect the *in vitro* kinase activity of purified mTOR [21, 22]. This led to the conclusion that mTOR functions *in vivo* as the catalytic subunit of one or more supramolecular protein complexes that control the intrinsic kinase activity of mTOR [23]. Subsequent studies have confirmed this original hypothesis to be true and so far have identified at least two such complexes (Fig. **1**): mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) [24].

mTOR lies downstream of numerous cell surface receptors, including the insulin receptor, the insulin-like growth factor type 1 receptor (IGF-1R), the epidermal growth factor receptor, and many others [20, 25-27]. Activation of these receptors stimulates the activity of phosphatidylinositol 3-kinase (PI3K) which facilitates the events necessary for the plasma membrane association and initiation of activation of the serine/threonine protein kinase Akt/protein kinase B (Akt/PKB) [28, 29] (Fig. **1**). Upon association with the plasma membrane, Akt undergoes two key stimulatory phosphorylation events [30]. The most important of these occurs at Ser^{473} by the action of mTORC2, which is composed of mTOR, rapamycin insensitive companion of mTOR (Rictor), G-protein β-subunit like protein (GβL), mammalian Sin1 (mSin1), protein observed with Rictor-1 and -2 (protor-1 and protor-2), and DEP domain containing mTOR-interacting protein (DEPTOR) [31-33] (Fig. **1**). Following this event and other activating modifications, Akt undergoes full activation and can phosphorylate a large number of cellular targets. One of these is the tuberous sclerosis complex 2 (TSC2) [25]. Akt phosphorylates TSC2 at several locations [25, 34, 35], inhibiting TSC2 GTPase activating protein (GAP) activity on the small GTPase ras homolog enriched in brain (Rheb) [25, 35]. Once Rheb is locked in the bound-guanosine triphosphate (GTP) state, it becomes active and in turn activates mTORC1 through direct binding and stimulation of its kinase activity [25, 35-37].

mTORC1 is composed of mTOR, regulatory associated protein of mTOR (Raptor), GβL, proline-rich Akt1 substrate of 40 kDa (PRAS40), and DEPTOR [23, 25, 38, 39]. mTORC1 signals to two primary downstream targets, p70 S6 kinase 1 (S6K1) and eukaryotic translation initiation factor 4E (eIF4E)-binding protein 1 (4E-BP1) [25] (Fig. **1**). S6K1 is a serine/threonine protein kinase that is involved in regulation of cell growth and G_1 cell cycle progression [40, 41]. S6K1 undergoes several activating phosphorylation events, including mTORC1-mediated phosphorylation of Thr^{389} [41], an event that correlates best with S6K1 activity [42]. Activated S6K1 was originally thought to regulate protein synthesis through

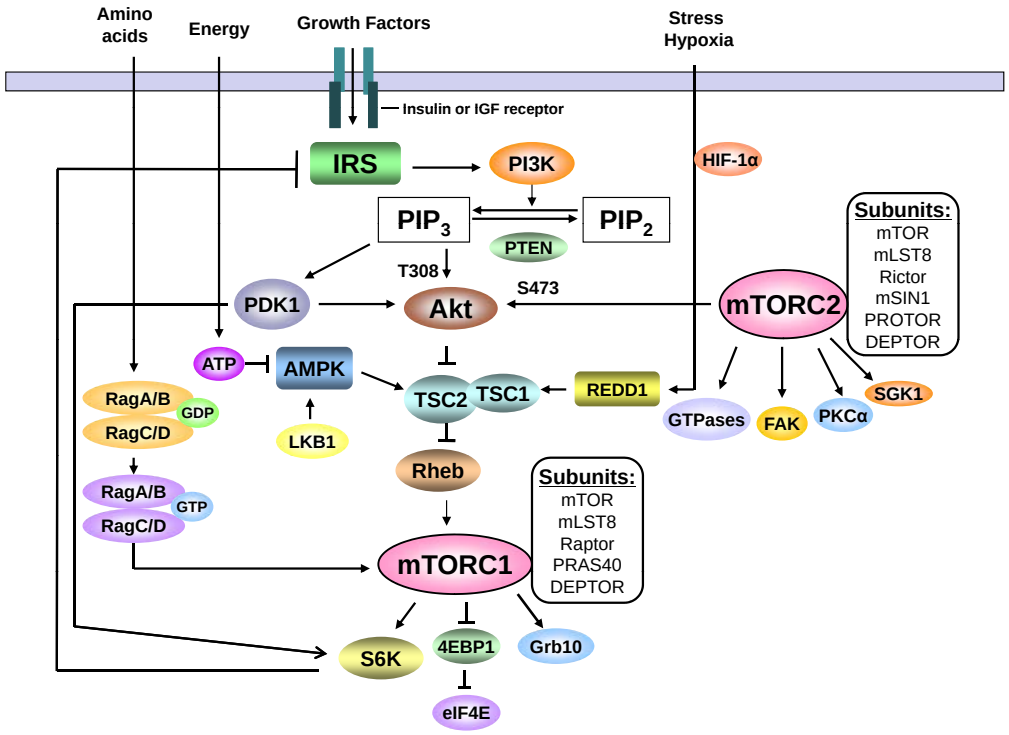

Fig. (1). The mTOR signaling pathway. mTOR functions as two distinct signaling complexes, mTORC1 and mTORC2. mTOR signaling regulates multiple cellular processes by sensing nutrients, energy, growth factors and stress. Arrows represent activation, whereas bars represent inhibition. IRS, insulin receptor substrates; PIP_2, phosphatidylinositol (4, 5)-bisphosphate; PIP_3, phosphatidylinositol-3, 4, 5-trisphosphate; PDK1, phosphoinositide-dependent kinase 1; TSC, tuberous sclerosis complex; Rheb, Ras homolog enriched in brain; AMPK, AMP-activated kinase; Grb10, growth factor receptor-bound protein 10.

phosphorylation of the 40S ribosomal subunit, which has been suggested to increase the translational efficiency of a class of mRNA transcripts with a 5'-terminal oligopolypyrimidine sequence [43]. Recently, it has been further proposed that the mechanism by which S6K1 regulates translation is likely by phosphorylation of eIF4B at Ser^{422} [44], which causes it to associate with eIF3 and promotes eIF4F complex formation [45, 46]. 4E-BP1 binds eIF4E, preventing it from participating in cap-dependent translation initiation [47]. Phosphorylation of 4E-BP1 by mTORC1 stimulates protein synthesis through the release of eIF4E from 4E-BP1, allowing eIF4E to associate with eIF4G and other relevant factors to promote cap-dependent translation [47, 48].

mTOR truly functions as a master cellular regulator. It acts as a sensor of growth factor stimuli [25], nutrient [23, 49], energy [49], redox [50], and oxygen levels [51, 52] (Fig. **1**). mTOR controls numerous cellular processes such as cell proliferation [53], cell growth (size) [23, 54], cell motility [55], cell survival [56, 57], and metabolism [53]. In humans, dysregulated mTOR signaling is implicated in a wide range of disease processes [53, 58, 59], including tuberous sclerosis [53, 60], diabetes [61, 62], obesity [62], lymphangiomyelomatosis [63], and most types of cancer [58, 62, 64, 65]. mTORC1 and mTORC2 are essential complexes, as downregulation of Raptor, Rictor, and mSin1 leads to embryonic lethality [66, 67]. mTORC1 regulates, to varying degrees, transcription [53, 68, 69], translation initiation [25, 48], nutrient transport [56, 70], autophagy [71-73], and ribosome biogenesis [74, 75]. mTORC2 controls actin cytoskeleton organization, cell shape [76, 77], and cell motility *via* its effects on the Rho-type GTPases [76], focal adhesion proteins, and protein kinase C (PKC) [77]. mTORC2 also regulates cell survival *via* activation of Akt and serum- and glucocorticoid-inducible kinase 1 (SGK1) [32, 78] and the subsequent regulation of its numerous cellular targets, including the Foxo family of transcription factors [79] and the apoptosis-regulating Bcl-2 family of proteins such as BAD [80].

CURCUMIN AND mTOR: THE GOLDEN COUPLE

The worlds of curcumin and mTOR first collided in studies conducted in rhabdomyosarcoma (RMS) cell lines [20]. Curcumin inhibited proliferation and induced apoptosis of RMS cells in a concentration-dependent manner (2.5-40 μM) [20]. Curcumin inhibition of cell proliferation was related to the arrest of cells in the G_1/G_0 phase of the cell cycle [20]. Curcumin also blocked the basal and IGF-1-stimulated cell motility of these RMS cells [20]. It has been well documented that RMS is a type of cancer that possesses as one of its major genetic/molecular features the upregulation and dysregulation of the IGF-1R/PI3K/Akt/mTOR signal transduction cascade [20, 55, 81]. Of note, rapamycin, the first identified inhibitor of mTORC1 signaling, successfully inhibits the proliferation/growth, motility, and survival of RMS cells [55, 57, 82, 83]. This information drove the authors to investigate whether or not curcumin might be acting on some component of the IGF-1R/PI3K/Akt/mTOR pathway. Subsequent experiments demonstrated that curcumin inhibited the IGF-1-stimulated, mTORC1-mediated phosphorylation of S6K1 and 4E-BP1 at low concentrations (~2.5 μM), and the IGF-1-stimulated, mTORC2-mediated phosphorylation of Akt at higher concentrations (>40 μM) in RMS cells [20]. Similar results were also observed in prostate (DU145), breast (MCF-7), and cervical (HeLa) cancer cell lines [20].

Upon the publication of these results, numerous other investigations began confirming the interaction of curcumin with the mTOR pathway. Curcumin treatment of human prostate cancer cells (PC3) lead to a dose- and time-dependent decrease in the transcriptional expression of the p53 ubiquitin E2 ligase murine double minute 2 (MDM2), and this was mediated *via* curcumin action on the PI3K/mTOR/ETS2 pathway [84]. Curcumin induced G_2/M cell cycle arrest and autophagy in two human malignant glioma cell lines (U87-MG and U373-MG) [85]. These effects were

related to curcumin inhibition of mTORC2 (as indicated by the phosphorylation of Akt) and activation of the ERK pathway, as reconstitution of Akt activity and inhibition of ERK (use of PD98059) prevented curcumin-mediated autophagy [85]. Curcumin treatment also prevented growth of these tumor cells *in vivo* by inducing autophagy [85]. Curcumin was able to decrease the transcriptional and translational expression of mTOR, Raptor, and Rictor in human colorectal cancer cells (HCT116) [86]. Lim *et al.* suggested that curcumin-mediated inhibition of mTOR signaling could be the result of its function as a protonophoric uncoupler and activator of F_0F_1-ATPase, thus leading to 5'-AMP-activated protein kinase (AMPK) activation and its induction of mTOR inhibition [87]. Curcumin was able to attenuate irradiation-mediated activation of Akt and mTOR phosphorylation in human intestinal micro-vascular endothelial cells and this correlated with curcumin-mediated induction of apoptosis [88]. The compound was able to block basal and nicotine-stimulated mTORC1 signaling in human head and neck squamous cell carcinoma cell lines (PCI15a and SCC40) and this correlated with inhibition of cell proliferation, invasion, and migration [89]. A study conducted in adenoid cystic carcinoma cells suggested that curcumin inhibitory action on both mTOR signaling and the NF-κB pathway may be related to cross-talk *via* the PI3K/Akt/IκB kinase network [90]. Curcumin was able to inhibit mTORC1 signaling in autosomal dominant polycystic kidney disease, even in the presence of a deletion of the gene encoding polycystin-1 (PC1), a molecular genotype that results in an activated mTOR pathway phenotype [91]. Curcumin also inhibited mTORC1 signaling in human leiomyosarcoma cells (SKN), an event that was correlated with decreased cell growth/ proliferation and induction of apoptosis [92], and this activity of curcumin was enhanced when it was administered in combination with epigallocatechin-3-gallate (EGCG) [93]. The compound also successfully abrogated mTORC1 signaling in squamous cell carcinoma cells *in vivo* [94]. Curcumin, as well as rapamycin and several other compounds, successfully enhanced the efficiency of reprogramming somatic cells into induced pluripotent stem cells, more than likely *via* inhibition of the IGF-1/mTOR signaling pathway [95].

To date, at least two major studies [26, 96] have been undertaken to determine the mechanism of action by which curcumin disrupts mTORC1 and mTORC2 signaling. The first was conducted by Yu *et al.* utilizing human prostate cancer cells (PC3) [96]. This study demonstrated that curcumin inhibited the mTORC2- and PDK1-mediated phosphorylation of Akt and the mTORC1-mediated phosphorylation of S6K1 and 4E-BP1 at similar concentrations [96]. This study also found that curcumin stimulated the phosphorylation and activity of AMPK, which serves as a positive regulator of TSC2 [96]. Use of a PI3K-rescue agent and a phosphatidylinositol-dependent kinase 1 (PDK1) *in vitro* kinase assay revealed that curcumin action on the complexes of mTOR was independent of PI3K and PDK1, while overexpression of Akt did not prevent curcumin inhibition of mTORC1-mediated S6K1 and 4E-BP1 phosphorylation [96]. Overexpression of wild-type and dominant-negative AMPK and pretreatment of cells with the AMPK inhibitor compound C did not block curcumin abrogation of mTORC1-mediated phosphorylation of its two major downstream targets [96]. Genetic and siRNA knockdown of TSC2 also failed to interfere with curcumin-mediated inhibition of mTORC1 activity [96]. Finally, use of the serine/threonine protein phosphatase inhibitors calyculin A and okadaic acid was able to reverse curcumin inhibition of both mTORC1 and mTORC2 signaling, suggesting that curcumin might be acting directly as an activator of protein phosphatase 2A (PP2A), thus leading to inhibition of the mTOR pathway [96]. This is indeed a possibility because PP2A functions as the major phosphatase responsible for the dephosphorylation of the mTORC1 substrates S6K1 [97, 98] and 4E-BP1 [99], and the mTORC2 substrate Akt [97, 100].

The second study was carried out primarily in RMS cells by Beevers *et al.* [26]. This study also showed that the IGF-1R, the PDK1, and the AMPK/TSC2 pathways did not play a role in curcumin-mediated inhibition of mTORC1 and mTORC2 signaling [26]. However, PP2A was found not to be involved in curcumin action on the mTOR pathway, as the use of okadaic acid, expression of dominant-negative PP2A, and shRNA-mediated downregulation of PP2A was unable to prevent curcumin inhibition of mTORC1 and mTORC2 signaling in rhabdomyosarcoma cells [26]. Whether the discrepancy between the studies [26, 96] is related to different cell lines or experimental conditions used remains to be defined. Of interest, Beevers *et al.* observed that low concentrations of curcumin (2.5 μM) blocked the kinase activity of the mTORC1 by disrupting mTOR-Raptor interaction and that higher concentrations of the compound (40 μM) inhibited the kinase activity of the mTORC2 by disrupting mTOR-Rictor interaction [26]. This concentration-dependent effect of curcumin on the two complexes of mTOR fits data concerning the nature of the two complexes. The interaction of mTOR with Raptor in the mTORC1 is a weak and dynamic association, facilitating the large amount of control that is needed over mTORC1 activity [23], while the mTOR-Rictor interaction in the mTORC2 appears to be a much stronger and more static association [77]. At that time (2008), these results suggested that curcumin was the first, and currently only, identified compound to exert activity against both complexes of mTOR specifically by disrupting complex partner interactions.

CONCLUSIONS

mTOR is a master kinase that controls cell proliferation/growth, survival, and motility. Over the past 6 years, mTOR has emerged as an exciting and novel molecular target for curcumin, particularly in cancer cell lines. It appears that curcumin inhibits both mTORC1 and mTORC2, but in a concentration-dependent manner. There exist some discrepant findings regarding the mechanism by which curcumin inhibits mTOR signaling pathways. The findings have opened the doors to many different avenues of research into the interactions between curcumin and mTOR and the cellular processes and factors affected by this interaction. Obviously, much work remains to be done, including identifying the exact mechanism by which curcumin disrupts mTOR activity and complex formation/ stability and whether or not these results can translate over into other disease states and/or normal human tissue as well. Obviously, the ultimate aim of these molecular studies would be to attempt to replicate these discoveries within *in vivo* cancer models in animals. Greater demonstration of successful replication of these results in animal models may provide the necessary stimulus to induce the initiation of clinical trials in humans using various formulations/ derivatives of curcumin as chemotherapeutic and/or chemopreventive agents against many types of cancer.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

This work was supported in part by NIH (CA115414 to S. Huang), and American Cancer Society (RSG-08-135-01-CNE to S. Huang).

REFERENCES

[1] Sharma, R. A.; Gescher, A. J.; Steward, W. P. Curcumin: the story so far. *Eur. J. Cancer*, **2005**, *41*, 1955-1968.

[2] Aggarwal, B. B.; Kumar, A.; Bharti, A. C. Anticancer potential of curcumin: preclinical and clinical studies. *Anticancer Res.*, **2003**, *23*, 363-398.

[3] Jovanovic, S. V.; Boone, C. W.; Steenken, S.; Trinoga, M.; Kaskey, R. B. How curcumin works preferentially with water soluble antioxidants. *J. Am. Chem. Soc.*, **2001**, *123*, 3064-3068.

[4] Tonnesen, H. H.; Karlsen, J. Studies on curcumin and curcuminoids. VI. Kinetics of curcumin degradation in aqueous solution. *Z. Lebensm. Unters. Forsch.*, **1985**, *180*, 402-404.

[5] Shankar, T. N.; Shantha, N. V.; Ramesh, H. P.; Murthy, I. A.; Murthy, V. S. Toxicity studies on turmeric (Curcuma longa): acute toxicity studies in rats, guineapigs & monkeys. *Indian J. Exp. Biol.*, **1980**, *18*, 73-75.

[6] Cheng, A. L.; Hsu, C. H. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. *Anticancer Res.*, **2001**, *21*, 2895-2900.

[7] Sharma, R. A.; McLelland, H. R.; Hill, K. A.; Ireson, C. R.; Euden, S. A.; Manson, M. M.; Pirmohamed, M.; Marnett, L. J.; Gescher, A. J.; Steward, W. P. Pharmacodynamic and pharmacokinetic study of oral Curcuma extract in patients with colorectal cancer. *Clin. Cancer Res.*, **2001**, *7*, 1894-1900.

[8] Anand, P.; Kunnumakkara, A. B.; Newman, R. A.; Aggarwal, B. B. Bioavailability of curcumin: problems and promises. *Mol. Pharm.*, **2007**, *4*, 807-818.

[9] Sharma, R. A.; Steward, W. P.; Gescher, A. J. Pharmacokinetics and pharmacodynamics of curcumin. *Adv. Exp. Med. Biol.*, **2007**, *595*, 453-470.

[10] Beevers, C. S.; Huang, S. Pharmacological and clinical properties of curcumin. *Botanics: Targets and Therapy*, **2011**, *1*, 5-18.

[11] Basnet, P.; Skalko-Basnet, N. Curcumin: an anti-inflammatory molecule from a curry spice on the path to cancer treatment. *Molecules*, **2011**, *16*, 4567-4598.

[12] Zhou, H.; Beevers, C. S.; Huang, S. The targets of curcumin. *Curr. Drug Targets*, **2011**, *12*, 332-347.

[13] Gupta, S. C.; Kim, J. H.; Prasad, S.; Aggarwal, B. B. Regulation of survival, proliferation, invasion, angiogenesis, and metastasis of tumor cells through modulation of inflammatory pathways by nutraceuticals. *Cancer Metastasis Rev.*, **2010**, *29*, 405-434.

[14] Deodhar, S. D.; Sethi, R.; Srimal, R. C. Preliminary study on antirheumatic activity of curcumin (diferuloyl methane). *Indian J. Med. Res.*, **1980**, *71*, 632-634.

[15] Hatcher, H.; Planalp, R.; Cho, J.; Torti, F. M.; Torti, S. V. Curcumin: from ancient medicine to current clinical trials. *Cell Mol. Life Sci.*, **2008**, *65*, 1631-1652.

[16] Dhillon, N.; Aggarwal, B. B.; Newman, R. A.; Wolff, R. A.; Kunnumakkara, A. B.; Abbruzzese, J. L.; Ng, C. S.; Badmaev, V.; Kurzrock, R. Phase II trial of curcumin in patients with advanced pancreatic cancer. *Clin. Cancer Res.*, **2008**, *14*, 4491-4499.

[17] Sharma, R. A.; Euden, S. A. Phase I clinical trial of oral curcumin: biomarkers of systemic activity and compliance. *Clin. Cancer Res.*, **2004**, *10*, 6847-6854.

[18] Kuttan, R.; Sudheeran, P. C.; Josph, C. D. Turmeric and curcumin as topical agents in cancer therapy. *Tumori*, **1987**, *73*, 29-31.

[19] Hanif, R.; Qiao, L.; Shiff, S. J.; Rigas, B. Curcumin, a natural plant phenolic food additive, inhibits cell proliferation and induces cell cycle changes in colon adenocarcinoma cell lines by a prostaglandin-independent pathway. *J. Lab. Clin. Med.*, **1997**, *130*, 576-584.

[20] Beevers, C. S.; Li, F.; Liu, L.; Huang, S. Curcumin inhibits the mammalian target of rapamycin-mediated signaling pathways in cancer cells. *Int. J. Cancer*, **2006**, *119*, 757-764.

[21] Dennis, P. B.; Jaeschke, A.; Saitoh, M.; Fowler, B.; Kozma, S. C.; Thomas, G. Mammalian TOR: a homeostatic ATP sensor. *Science*, **2001**, *294*, 1102-1105.

[22] Hara, K.; Yonezawa, K.; Kozlowski, M. T.; Sugimoto, T.; Andrabi, K.; Weng, Q. P.; Kasuga, M.; Nishimoto, I.; Avruch, J. Regulation of eIF-4E BP1 phosphorylation by mTOR. *J. Biol. Chem.*, **1997**, *272*, 26457-26463.

[23] Kim, D. H.; Sarbassov, D. D.; Ali, S. M.; King, J. E.; Latek, R. R.; Erdjument-Bromage, H.; Tempst, P.; Sabatini, D. M. mTOR interacts with raptor to form a nutrient-sensitive complex that signals to the cell growth machinery. *Cell*, **2002**, *110*, 163-175.

[24] Zhou, H.; Huang, S. The complexes of mammalian target of rapamycin. *Curr. Protein Pept. Sci.*, **2011**, *11*, 409-424.

[25] Hay, N.; Sonenberg, N. Upstream and downstream of mTOR. *Genes Dev.*, **2004**, *18*, 1926-1945.

[26] Beevers, C. S.; Chen, L.; Liu, L.; Luo, Y.; Webster, N. J.; Huang, S. Curcumin disrupts the Mammalian target of rapamycin-raptor complex. *Cancer Res.*, **2009**, *69*, 1000-1008.

[27] Johnston, S. R. Targeting downstream effectors of epidermal growth factor receptor/HER2 in breast cancer with either farnesyltransferase inhibitors or mTOR antagonists. *Int. J. Gynecol. Cancer*, **2006**, *16 Suppl 2*, 543-548.

[28] LeRoith, D.; Roberts, C. T., Jr. The insulin-like growth factor system and cancer. *Cancer Lett.*, **2003**, *195*, 127-137.

[29] Carver, D. J.; Aman, M. J.; Ravichandran, K. S. SHIP inhibits Akt activation in B cells through regulation of Akt membrane localization. *Blood*, **2000**, *96*, 1449-1456.

[30] Kohn, A. D.; Takeuchi, F.; Roth, R. A. Akt, a pleckstrin homology domain containing kinase, is activated primarily by phosphorylation. *J. Biol. Chem.*, **1996**, *271*, 21920-21926.

[31] Frias, M. A.; Thoreen, C. C.; Jaffe, J. D.; Schroder, W.; Sculley, T.; Carr, S. A.; Sabatini, D. M. mSin1 is necessary for Akt/PKB phosphorylation, and its isoforms define three distinct mTORC2s. *Curr. Biol.*, **2006**, *16*, 1865-1870.

[32] Sarbassov, D. D.; Guertin, D. A.; Ali, S. M.; Sabatini, D. M. Phosphorylation and regulation of Akt/PKB by the rictor-mTOR complex. *Science*, **2005**, *307*, 1098-1101.

[33] Pearce, L. R.; Huang, X.; Boudeau, J.; Pawlowski, R.; Wullschleger, S.; Deak, M.; Ibrahim, A. F.; Gourlay, R.; Magnuson, M. A.; Alessi, D. R. Identification of Protor as a novel Rictor-binding component of mTOR complex-2. *Biochem. J.*, **2007**, *405*, 513-522.

[34] Peterson, R. T.; Desai, B. N.; Hardwick, J. S.; Schreiber, S. L. Protein phosphatase 2A interacts with the 70-kDa S6 kinase and is activated by inhibition of FKBP12-rapamycinassociated protein. *Proc. Natl. Acad. Sci. U. S. A.*, **1999**, *96*, 4438-4442.

[35] Garami, A.; Zwartkruis, F. J.; Nobukuni, T.; Joaquin, M.; Roccio, M.; Stocker, H.; Kozma, S. C.; Hafen, E.; Bos, J. L.; Thomas, G. Insulin activation of Rheb, a mediator of mTOR/S6K/4E-BP signaling, is inhibited by TSC1 and 2. *Mol. Cell*, **2003**, *11*, 1457-1466.

[36] Long, X.; Lin, Y.; Ortiz-Vega, S.; Yonezawa, K.; Avruch, J. Rheb binds and regulates the mTOR kinase. *Curr. Biol.*, **2005**, *15*, 702-713.

[37] Long, X.; Ortiz-Vega, S.; Lin, Y.; Avruch, J. Rheb binding to mammalian target of rapamycin (mTOR) is regulated by amino acid sufficiency. *J. Biol. Chem.*, **2005**, *280*, 23433-23436.

[38] Kim, D. H.; Sarbassov, D. D.; Ali, S. M.; Latek, R. R.; Guntur, K. V.; Erdjument-Bromage, H.; Tempst, P.; Sabatini, D. M. GbetaL, a positive regulator of the rapamycin-sensitive pathway required for the nutrient-sensitive interaction between raptor and mTOR. *Mol. Cell*, **2003**, *11*, 895-904.

[39] Sancak, Y.; Thoreen, C. C.; Peterson, T. R.; Lindquist, R. A.; Kang, S. A.; Spooner, E.; Carr, S. A.; Sabatini, D. M. PRAS40 is an insulin-regulated inhibitor of the mTORC1 protein kinase. *Mol. Cell*, **2007**, *25*, 903-915.

[40] Dufner, A.; Thomas, G. Ribosomal S6 kinase signaling and the control of translation. *Exp. Cell Res.*, **1999**, *253*, 100-109.

[41] Pullen, N.; Thomas, G. The modular phosphorylation and activation of p70s6k. *FEBS Lett.*, **1997**, *410*, 78-82.

[42] Weng, Q. P.; Kozlowski, M.; Belham, C.; Zhang, A.; Comb, M. J.; Avruch, J. Regulation of the p70 S6 kinase by phosphorylation *in vivo*. Analysis using site-specific anti-phosphopeptide antibodies. *J. Biol. Chem.*, **1998**, *273*, 16621-16629.

[43] Pause, A.; Belsham, G. J.; Gingras, A. C.; Donze, O.; Lin, T. A.; Lawrence, J. C., Jr.; Sonenberg, N. Insulin-dependent stimulation of protein synthesis by phosphorylation of a regulator of 5'-cap function. *Nature*, **1994**, *371*, 762-767.

[44] Raught, B.; Peiretti, F.; Gingras, A. C.; Livingstone, M.; Shahbazian, D.; Mayeur, G. L.; Polakiewicz, R. D.; Sonenberg, N.; Hershey, J. W. Phosphorylation of eucaryotic translation initiation factor 4B Ser422 is modulated by S6 kinases. *Embo J.*, **2004**, *23*, 1761-1769.

[45] Shahbazian, D.; Roux, P. P.; Mieulet, V.; Cohen, M. S.; Raught, B.; Taunton, J.; Hershey, J. W.; Blenis, J.; Pende, M.; Sonenberg, N. The mTOR/PI3K and MAPK pathways converge on eIF4B to control its phosphorylation and activity. *Embo J.*, **2006**, *25*, 2781-2791.

[46] Holz, M. K.; Ballif, B. A.; Gygi, S. P.; Blenis, J. mTOR and S6K1 mediate assembly of the translation preinitiation complex through dynamic protein interchange and ordered phosphorylation events. *Cell*, **2005**, *123*, 569-580.

[47] Gingras, A. C.; Raught, B.; Sonenberg, N. Regulation of translation initiation by FRAP/mTOR. *Genes Dev.*, **2001**, *15*, 807-826.

[48] Gingras, A. C.; Raught, B.; Gygi, S. P.; Niedzwiecka, A.; Miron, M.; Burley, S. K.; Polakiewicz, R. D.; Wyslouch-Cieszynska, A.; Aebersold, R.; Sonenberg, N. Hierarchical phosphorylation of the translation inhibitor 4E-BP1. *Genes Dev.*, **2001**, *15*, 2852-2864.

[49] Tokunaga, C.; Yoshino, K.; Yonezawa, K. mTOR integrates amino acid- and energy-sensing pathways. *Biochem. Biophys. Res. Commun.*, **2004**, *313*, 443-446.

[50] Sarbassov, D. D.; Sabatini, D. M. Redox regulation of the nutrient-sensitive raptor-mTOR pathway and complex. *J. Biol. Chem.*, **2005**, *280*, 39505-39509.

[51] Magagnin, M. G.; van den Beucken, T.; Sergeant, K.; Lambin, P.; Koritzinsky, M.; Devreese, B.; Wouters, B. G. The mTOR target 4E-BP1 contributes to differential protein expression during normoxia and hypoxia through changes in mRNA translation efficiency. *Proteomics*, **2008**, *8*, 1019-1028.

[52] DeYoung, M. P.; Horak, P.; Sofer, A.; Sgroi, D.; Ellisen, L. W. Hypoxia regulates TSC1/2-mTOR signaling and tumor suppression through REDD1-mediated 14-3-3 shuttling. *Genes Dev.*, **2008**, *22*, 239-251.

[53] Wullschleger, S.; Loewith, R.; Hall, M. N. TOR signaling in growth and metabolism. *Cell*, **2006**, *124*, 471-484.

[54] Fingar, D. C.; Salama, S.; Tsou, C.; Harlow, E.; Blenis, J. Mammalian cell size is controlled by mTOR and its downstream targets S6K1 and 4EBP1/eIF4E. *Genes Dev.*, **2002**, *16*, 1472-1487.

[55] Liu, L.; Li, F.; Cardelli, J. A.; Martin, K. A.; Blenis, J.; Huang, S. Rapamycin inhibits cell motility by suppression of mTOR-mediated S6K1 and 4E-BP1 pathways. *Oncogene*, **2006**, *25*, 7029-7040.

[56] Edinger, A. L.; Thompson, C. B. Akt maintains cell size and survival by increasing mTOR-dependent nutrient uptake. *Mol. Biol. Cell*, **2002**, *13*, 2276-2288.

[57] Huang, S.; Shu, L.; Easton, J.; Harwood, F. C.; Germain, G. S.; Ichijo, H.; Houghton, P. J. Inhibition of mammalian target of rapamycin activates apoptosis signal-regulating kinase 1 signaling by suppressing protein phosphatase 5 activity. *J. Biol. Chem.*, **2004**, *279*, 36490-36496.

[58] Inoki, K.; Corradetti, M. N.; Guan, K. L. Dysregulation of the TSC-mTOR pathway in human disease. *Nat. Genet.*, **2005**, *37*, 19-24.

[59] Tee, A. R.; Blenis, J. mTOR, translational control and human disease. *Semin. Cell Dev. Biol.*, **2005**, *16*, 29-37.

[60] Kwiatkowski, D. J. Tuberous sclerosis: from tubers to mTOR. *Ann. Hum. Genet.*, **2003**, *67*, 87-96.

[61] Manning, B. D. Balancing Akt with S6K: implications for both metabolic diseases and tumorigenesis. *J. Cell Biol.*, **2004**, *167*, 399-403.

[62] Dann, S. G.; Selvaraj, A.; Thomas, G. mTOR Complex1-S6K1 signaling: at the crossroads of obesity, diabetes and cancer. *Trends Mol. Med.*, **2007**, *13*, 252-259.

[63] Thedieck, K.; Polak, P.; Kim, M. L.; Molle, K. D.; Cohen, A.; Jeno, P.; Arrieumerlou, C.; Hall, M. N. PRAS40 and PRR5-like protein are new mTOR interactors that regulate apoptosis. *PLoS One*, **2007**, *2*, e1217.

[64] Guertin, D. A.; Sabatini, D. M. Defining the role of mTOR in cancer. *Cancer Cell*, **2007**, *12*, 9-22.

[65] Rubio-Viqueira, B.; Hidalgo, M. Targeting mTOR for cancer treatment. *Adv. Exp. Med. Biol.*, **2006**, *587*, 309-327.

[66] Guertin, D. A.; Stevens, D. M.; Thoreen, C. C.; Burds, A. A.; Kalaany, N. Y.; Moffat, J.; Brown, M.; Fitzgerald, K. J.; Sabatini, D. M. Ablation in mice of the mTORC components raptor, rictor, or mLST8 reveals that mTORC2 is required for signaling to Akt-FOXO and PKCalpha, but not S6K1. *Dev. Cell*, **2006**, *11*, 859-871.

[67] Polak, P.; Hall, M. N. mTORC2 Caught in a SINful Akt. *Dev. Cell*, **2006**, *11*, 433-434.

[68] Peng, T.; Golub, T. R.; Sabatini, D. M. The immunosuppressant rapamycin mimics a starvation-like signal distinct from amino acid and glucose deprivation. *Mol. Cell Biol.*, **2002**, *22*, 5575-5584.

[69] Mayer, C.; Grummt, I. Ribosome biogenesis and cell growth: mTOR coordinates transcription by all three classes of nuclear RNA polymerases. *Oncogene*, **2006**, *25*, 6384-6391.

[70] Roos, S.; Jansson, N.; Palmberg, I.; Saljo, K.; Powell, T. L.; Jansson, T. Mammalian target of rapamycin in the human placenta regulates leucine transport and is down-regulated in restricted fetal growth. *J. Physiol.*, **2007**, *582*, 449-459.

[71] Ramirez-Valle, F.; Braunstein, S.; Zavadil, J.; Formenti, S. C.; Schneider, R. J. eIF4GI links nutrient sensing by mTOR to cell proliferation and inhibition of autophagy. *J. Cell Biol.*, **2008**, *181*, 293-307.

[72] Mammucari, C.; Schiaffino, S.; Sandri, M. Downstream of Akt: FoxO3 and mTOR in the regulation of autophagy in skeletal muscle. *Autophagy*, **2008**, *4*, 524-526.

[73] Shinojima, N.; Yokoyama, T.; Kondo, Y.; Kondo, S. Roles of the Akt/mTOR/p70S6K and ERK1/2 signaling pathways in curcumin-induced autophagy. *Autophagy*, **2007**, *3*, 635-637.

[74] Martin, D. E.; Hall, M. N. The expanding TOR signaling network. *Curr. Opin. Cell Biol.*, **2005**, *17*, 158-166.

[75] Mayer, C.; Zhao, J.; Yuan, X.; Grummt, I. mTOR-dependent activation of the transcription factor TIF-IA links rRNA synthesis to nutrient availability. *Genes Dev.*, **2004**, *18*, 423-434.

[76] Jacinto, E.; Loewith, R.; Schmidt, A.; Lin, S.; Ruegg, M. A.; Hall, A.; Hall, M. N. Mammalian TOR complex 2 controls the actin cytoskeleton and is rapamycin insensitive. *Nat. Cell Biol.*, **2004**, *6*, 1122-1128.

[77] Sarbassov, D. D.; Ali, S. M.; Kim, D. H.; Guertin, D. A.; Latek, R. R.; Erdjument-Bromage, H.; Tempst, P.; Sabatini, D. M. Rictor, a novel binding partner of mTOR, defines a rapamycin-insensitive and raptor-independent pathway that regulates the cytoskeleton. *Curr. Biol.*, **2004**, *14*, 1296-1302.

[78] Garcia-Martinez, J. M.; Alessi, D. R. mTOR complex 2 (mTORC2) controls hydrophobic motif phosphorylation and activation of serum- and glucocorticoid-induced protein kinase 1 (SGK1). *Biochem. J.*, **2008**, *416*, 375-385.

[79] Plas, D. R.; Thompson, C. B. Akt activation promotes degradation of tuberin and FOXO3a *via* the proteasome. *J. Biol. Chem.*, **2003**, *278*, 12361-12366.

[80] Li, Y.; Tennekoon, G. I.; Birnbaum, M.; Marchionni, M. A.; Rutkowski, J. L. Neuregulin signaling through a PI3K/Akt/Bad pathway in Schwann cell survival. *Mol. Cell Neurosci.*, **2001**, *17*, 761-767.

[81] Wan, X.; Helman, L. J. The biology behind mTOR inhibition in sarcoma. *Oncologist*, **2007**, *12*, 1007-1018.

[82] Wan, X.; Harkavy, B.; Shen, N.; Grohar, P.; Helman, L. J. Rapamycin induces feedback activation of Akt signaling through an IGF-1R-dependent mechanism. *Oncogene*, **2007**, *26*, 1932-1940.

[83] Hosoi, H.; Dilling, M. B.; Shikata, T.; Liu, L. N.; Shu, L.; Ashmun, R. A.; Germain, G. S.; Abraham, R. T.; Houghton, P. J. Rapamycin causes poorly reversible inhibition of mTOR and induces p53-independent apoptosis in human rhabdomyosarcoma cells. *Cancer Res.*, **1999**, *59*, 886-894.

[84] Li, M.; Zhang, Z.; Hill, D. L.; Wang, H.; Zhang, R. Curcumin, a dietary component, has anticancer, chemosensitization, and radiosensitization effects by down-regulating the MDM2 oncogene through the PI3K/mTOR/ETS2 pathway. *Cancer Res.*, **2007**, *67*, 1988-1996.

[85] Aoki, H.; Takada, Y.; Kondo, S.; Sawaya, R.; Aggarwal, B. B.; Kondo, Y. Evidence that curcumin suppresses the growth of malignant gliomas *in vitro* and *in vivo* through induction of autophagy: role of Akt and extracellular signal-regulated kinase signaling pathways. *Mol. Pharmacol.*, **2007**, *72*, 29-39.

[86] Johnson, S. M.; Gulhati, P.; Arrieta, I.; Wang, X.; Uchida, T.; Gao, T.; Evers, B. M. Curcumin inhibits proliferation of colorectal carcinoma by modulating Akt/mTOR signaling. *Anticancer Res.*, **2009**, *29*, 3185-3190.

[87] Lim, H. W.; Lim, H. Y.; Wong, K. P. Uncoupling of oxidative phosphorylation by curcumin: implication of its cellular mechanism of action. *Biochem. Biophys. Res. Commun.*, **2009**, *389*, 187-192.

[88] Rafiee, P.; Binion, D. G.; Wellner, M.; Behmaram, B.; Floer, M.; Mitton, E.; Nie, L.; Zhang, Z.; Otterson, M. F. Modulatory effect of curcumin on survival of irradiated human intestinal microvascular endothelial cells: role of Akt/mTOR and NF-{kappa}B. *Am. J. Physiol. Gastrointest. Liver Physiol.*, **2010**, *298*, G865-877.

[89] Clark, C. A.; McEachern, M. D.; Shah, S. H.; Rong, Y.; Rong, X.; Smelley, C. L.; Caldito, G. C.; Abreo, F. W.; Nathan, C. O. Curcumin inhibits carcinogen and nicotine-induced Mammalian target of rapamycin pathway activation in head and neck squamous cell carcinoma. *Cancer Prev. Res. (Phila)*, **2010**, *3*, 1586-1595.

[90] Sun, Z. J.; Chen, G.; Zhang, W.; Hu, X.; Liu, Y.; Zhou, Q.; Zhu, L. X.; Zhao, Y. F. Curcumin dually inhibits both mammalian target of rapamycin and nuclear factor-kappaB pathways through a crossed phosphatidylinositol 3-kinase/Akt/IkappaB kinase complex signaling axis in adenoid cystic carcinoma. *Mol. Pharmacol.*, **2011**, *79*, 106-118.

[91] Leonhard, W. N.; van der Wal, A.; Novalic, Z.; Kunnen, S. J.; Gansevoort, R. T.; Breuning, M. H.; de Heer, E.; Peters, D. J. Curcumin inhibits cystogenesis by simultaneous interference of multiple signaling pathways: *in vivo* evidence from a Pkd1-deletion model. *Am. J. Physiol. Renal Physiol.*, **2011**, *300*, F1193-1202.

[92] Wong, T. F.; Takeda, T.; Li, B.; Tsuiji, K.; Kitamura, M.; Kondo, A.; Yaegashi, N. Curcumin disrupts uterine leiomyosarcoma cells through AKT-mTOR pathway inhibition. *Gynecol. Oncol.*, **2011**, *122*, 141-148.

[93] Kondo, A.; Takeda, T.; Li, B.; Tsuiji, K.; Kitamura, M.; Wong, T. F.; Yaegashi, N. Epigallocatechin-3-gallate potentiates curcumin's ability to suppress uterine leiomyosarcoma cell growth and induce apoptosis. *Int. J. Clin. Oncol*., **2012**, [Epub ahead of print]

[94] Phillips, J. M.; Clark, C.; Herman-Ferdinandez, L.; Moore-Medlin, T.; Rong, X.; Gill, J. R.; Clifford, J. L.; Abreo, F.; Nathan, C. O. Curcumin inhibits skin squamous cell carcinoma tumor growth *in vivo*. *Otolaryngol. Head Neck Surg.*, **2011**, *145*, 58-63.

[95] Chen, T.; Shen, L.; Yu, J.; Wan, H.; Guo, A.; Chen, J.; Long, Y.; Zhao, J.; Pei, G. Rapamycin and other longevity-promoting compounds enhance the generation of mouse induced pluripotent stem cells. *Aging Cell*, **2011**, *10*, 908-911.

[96] Yu, S.; Shen, G.; Khor, T. O.; Kim, J. H.; Kong, A. N. Curcumin inhibits Akt/mammalian target of rapamycin signaling through protein phosphatase-dependent mechanism. *Mol. Cancer Ther*., **2008**, *7*, 2609-2620.

[97] Millward, T. A.; Zolnierowicz, S.; Hemmings, B. A. Regulation of protein kinase cascades by protein phosphatase 2A. *Trends Biochem. Sci.*, **1999**, *24*, 186-191.

[98] Westphal, R. S.; Coffee, R. L., Jr.; Marotta, A.; Pelech, S. L.; Wadzinski, B. E. Identification of kinase-phosphatase signaling modules composed of p70 S6 kinase-protein phosphatase 2A (PP2A) and p21-activated kinase-PP2A. *J. Biol. Chem.*, **1999**, *274*, 687-692.

[99] Nanahoshi, M.; Nishiuma, T.; Tsujishita, Y.; Hara, K.; Inui, S.; Sakaguchi, N.; Yonezawa, K. Regulation of protein phosphatase 2A catalytic activity by alpha4 protein and its yeast homolog Tap42. *Biochem. Biophys. Res. Commun.*, **1998**, *251*, 520-526.

[100] Dey, R.; Majumder, N.; Bhattacharjee, S.; Majumdar, S. B.; Banerjee, R.; Ganguly, S.; Das, P.; Majumdar, S. Leishmania donovani-induced ceramide as the key mediator of Akt dephosphorylation in murine macrophages: role of protein kinase Czeta and phosphatase. *Infect. Immun*., **2007**, *75*, 2136-2142.

Received: July 30, 2012 Revised: September 28, 2012 Accepted: November 30, 2012