REVIEW OF CURCUMIN EFFECTS ON SIGNALING PATHWAYS IN CANCER

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ABSTRACT

Cancer is a major health problem in the United States. In recent years, the use of natural dietary supplements for cancer prevention and treatment has received considerable attention. One such natural dietary supplement is curcumin, a major constituent of the herb called turmeric, a common spice used in Indian food. Turmeric is the dried ground rhizome of the perennial herb *Curcuma longa* Linn of the ginger family. Extensive studies relating to its potential role in cancer prevention and treatment suggest that curcumin consumption may reduce the risk of cancer. Curcumin prevents cancer development and progression by interfering with several cell signaling pathways which are commonly associated with cancer cell proliferation and metastasis. Its intervention in NF-κB, MAPK, Akt, p53 and steroid receptor pathways has already been established, while its involvement in other pathways is still under investigation. Curcumin also has potent radio-sensitizing activity, and its use in combination with radiation based therapy may provide a better treatment outcome in cancer patients. The herbal product curcumin is now emerging as a new hope in the fight against cancer.

Key words

Cancer, curcumin, cancer prevention, herbs for cancer, signaling pathways

INTRODUCTION

Curcumin is a major active constituent of turmeric, which is a well-known herb in the ancient Indian System of Medicine "Ayurveda"(Nadkarni and Nadkarni 1976). Turmeric is the dried ground rhizome of the perennial herb *Curcuma longa* Linn of the ginger family. It is called turmeric in English, Haldi or Haridra in Hindi, and Ukon in Japanese. The color of turmeric powder is orange yellow and it tastes a little sour. The role of some of these natural dietary supplements on human health is the subject of scientific investigation. A review of the literature revealed that turmeric is useful in treating a variety of ailments and metabolic disorders (Khanna 1999). More than two hundred and fifty research papers relating to curcumin were published in the past year according to a search

of the U.S. National Library of Medicine. The U.S. National Institutes of Health has four clinical trials underway to study curcumin for treatment of pancreatic cancer, multiple myeloma, colorectal cancer and Alzheimer's disease. In this article, we specifically describe the effects of curcumin on signaling pathways that highlights some vital roles of curcumin in the treatment of cancer.

BIOLOGICAL PROPERTIES

Turmeric has drawn world-wide attention for its medicinal properties originating back to 1815 (Vogel and Pelletier 1815). It was first chemically characterized in 1910 (Lampe, V. et al. 1910). The active constituent of turmeric is curcumin, also known as C.I. 75300 or Natural Yellow 3, (1E, 6E)-1, 7-bis (4 hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione. It can exist in two tautomeric forms, keto and enol. The keto form is preferred in solid phase and the enol form in solution (Figure 1). Curcumin and its metabolites, mainly tetrahydrocurcumin, hexahydrocurcumin, glucuronides (Holder, Plummer et al. 1978), and essential oil, isolated from turmeric rhizome, are being investigated for the prevention and treatment of cancer. Curcumin is a natural, nontoxic food constituent. On irradiation with visible light, curcumin proves to be phototoxic for *Salmonella typhimurium* and *Escherichia coli*, even at very low concentrations. The observed phototoxicity makes curcumin a potential photosensitizing drug which might find application in the phototherapy of psoriasis, cancer, bacterial and viral diseases (Tonnesen, de Vries et al. 1987).

Extensive research in the last 30 years has indicated that curcumin has both preventive and therapeutic abilities for cancer. Beside antioxidant, anti-inflammatory, cancer chemo-preventative, and potential chemotherapeutic properties,

Figure 1. Turmeric (Curcuma longa L) plant, turmeric root, turmeric powder and structures of different active ingredients (curcumin) and some common biological effects exerted by curcumin.

curcumin also protects against various forms of stress, cataract formation, alcohol-induced liver injury, drug-induced myocardial toxicity, bowel diseases, lung injury, nephrotoxicity and stroke. Multiple biological activities of curcumin are shown in Figure 1.

CURCUMIN AND CANCER

Cancer is a major health problem in the United States. It is not just one disease, but a complex family of diseases. The term cancer actually encompasses more than 100 diseases that affect many different tissues and cell types. All cancers start from normal cells that have gone awry. Cancer is simply an abnormal tissue made of abnormal cells. In 2000, Douglas Hanahan and Robert Weinberg (Hanahan and Weinberg 2000) described six major characteristics of cancer cells, i.e. self-sufficiency in growth signals, insensitivity to anti-growth signals, evading apoptosis, limitless replicating potential, sustained angiogenesis and tissue invasion and metastasis. Various studies on curcumin have shown promising results in effectively intervening and/or controlling most of these hallmarks of cancer progression as shown in Figure 2. Curcumin, with its chemo-preventative and anti-carcinogenic properties, offers hope for the care and cure of several types of cancers, such as gastric, colon, stomach, liver, lung, duodenum, oral (Tanaka, Makita et al. 1994), skin (Conney, Lysz et al. 1991) breast (Wang and Wieder 2004), cervical, and prostate cancers (Lin, Shi et al. 2006). Several studies indicate that curcumin slows the development and growth of numerous types of cancer cells. Topical application of curcumin has also been shown to inhibit chemical carcinogenesis of the skin by Conney et al (Conney, Lysz et al.

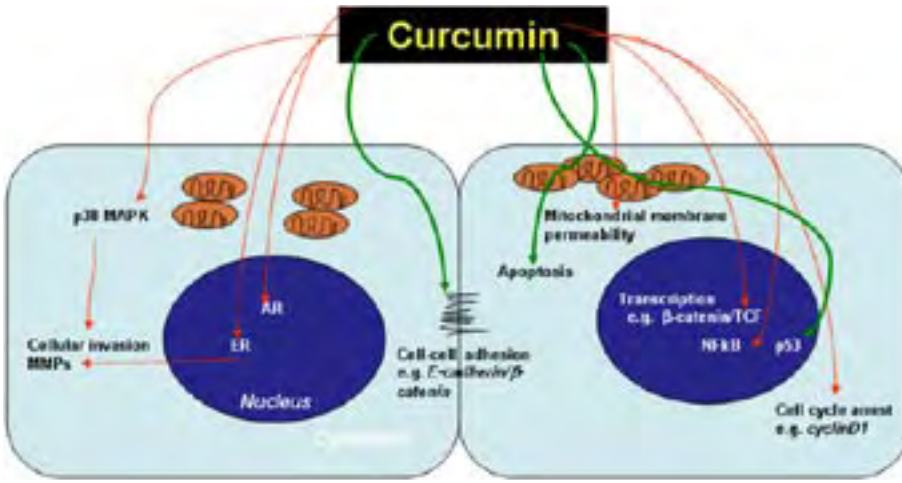

Figure 2. Schematic representation of curcumin modulated signaling pathways that are involved in cancer pathogenesis and progression. Green arrows represent activation and red arrows represent inhibition of the pathway. (AR=Androgen Receptor, ER=Estrogen Receptor, MMPs= Matrix Metalloproteinases)

1991; Conney 2003). Curcumin affects diverse cellular processes of cancer cells. An ethanol extract of turmeric, "Curcuma longa," as well as an ointment of curcumin (its active ingredient) were found to produce remarkable symptomatic relief in patients with external cancerous lesions. Reductions in smell and itching were noted in 90% and 100% of the cases respectively (Kuttan, Sudheeran et al. 1987). Dry lesions were observed in 70% of the cases, and a small number of patients (10%) had a reduction in lesion size and pain. In many patients the effect continued for several months. An adverse reaction was noticed in only one of the 62 patients evaluated (Kuttan, Sudheeran et al. 1987).

MECHANISM OF ACTION

In vivo and *in vitro* studies have demonstrated curcumin's ability to inhibit carcinogenesis at three stages: tumor promotion, angiogenesis, and tumor growth. The molecular basis of the anti-carcinogenic and chemo-preventative effects of curcumin are attributed to its effect on several targets, including transcription factors, growth regulators, adhesion molecules, apoptotic genes, angiogenesis regulators cellular signaling molecules and androgen responsive genes (Duvoix, Morceau et al. 2003a; Duvoix, Morceau et al. 2003a; Duvoix, Blasius et al. 2005) (Figure 2). The ability of curcumin to induce apoptosis in cancer cells without cytotoxic effects on healthy cells contributes to the understanding of the anti-cancer potential of curcumin (Sarkar and Li 2004). However, the precise molecular mechanisms of its actions are not fully known. In order to determine curcumin efficacy and its precise mechanism of action, we must understand its molecular interactions and the intracellular signaling network involved in the process.

Curcumin and Nuclear Factor-kappaB (NF-kB) Pathway

Various studies have shown active involvement of the NF-kB pathway in signaling that is employed in controlling cancer cell growth, apoptosis, inflammation and stress response (Shishodia, Amin et al. 2005). There are several important molecules such as NF-kB, IkB, and IKK, which are known to be involved in NF-kB pathways. However, among all these protein molecules, NF-kB is the most important molecule in this pathway and has emerged as a major therapeutic target in cancer cells in recent years. It has been reported in a number of studies that curcumin restrained the expression of IKK, suppressed both constitutive and inducible NF-kB phosphorylation/activation and potentiated TNF-induced apoptosis (Bharti, Donato et al. 2003). Additionally, curcumin showed antioxidant and anti-cancer properties via regulation of the expression of genes required for activation of activator protein 1 (AP1) and NF-kB (Aggarwal, Kumar et al. 2003).

Effect of Curcumin on β-Catenin Signaling

Inappropriate activation of the β-catenin signaling pathway is linked to a wide range of cancers, including colorectal cancer, prostate cancer and melanoma. Abnormalities in the expression and functional activity of the E-cadherin/catenin complex is implicated in the development and progression of the majority of colon cancers by regulating cell polarity, differentiation, proliferation, migration and invasion (Wheelock and Johnson 2003), (Yap 1998). Curcumin prevents tumors in C57BL/6J-Min/+ (Min/+) mice by decreased expression of the oncoprotein ß-catenin with increased enterocyte apoptosis and proliferation in the enterocytes of the Min/+ mouse. These animals bear a germline mutation in the Apc gene and spontaneously develop numerous intestinal adenomas by 15 weeks of age. At a dietary level of 0.15%, curcumin decreased tumor formation in Min/+ mice by 63%. Jaiswal et al. (Jaiswal, Marlow et al. 2002) suggested that curcumin down-regulates β-catenin's transcriptional activity in HCT116 intestine cancer cells inducing G2/M arrest. Curcumin and its analog, CHC007, are good inhibitors of the β-catenin/TCF signaling pathway in kidney and colon cancer cells.

Protein Kinase D (PKD) family members are important modulators of several signal-transduction pathways in benign and malignant human diseases (Jaggi, Rao et al. 2003; Jaggi M. 2006). We have identified a novel interaction between E-cadherin/β-catenin and PKD1 (Jaggi, Rao et al. 2005). Studies from our laboratory have shown that the β-catenin is phosphorylated by PKD1 and that over-expression of PKD1 in cancerous cells leads to decreased β-catenin/TCF transcriptional activity (Jaggi and Balaji 2006). We are studying the effect of curcumin on the interaction between PKD1 and E-cadherin/β-catenin complex and on β-catenin transcription activity in colon, prostate and cervical cancer. An understanding of the effect of curcumin on the β-catenin signaling pathway will establish a mechanistic basis by which cell adhesion and proliferation can be manipulated in cancer cells.

Effect of Curcumin on p53 Pathway

The p53 tumor suppressor and transcription factor is a vital regulator in many cellular processes including apoptosis, cell cycle control, cellular response to DNA-damage, genomic stability and signal transduction (Liu and Seidel-Dugan 2006). Aberrant expression of p53 is thought to be a hallmark of cancer cells. Its expression status is an important mediator in the cellular response to cancer therapeutic agents. It has been observed that curcumin induces apoptosis at G (2) phase of the cell cycle mammary epithelial carcinoma cells in which cyclin D1 is deregulated but does not affect mammary epithelial cells. Curcumin selectively increases p53 expression at G (2) phase in cancer cells and leads to cytochrome release from mitochondria, an essential requirement for apoptosis (Choudhuri, Pal et al. 2005). In experiments using p53-null as well as dominant-negative and wild-type p53-transfected cells, it has been established that curcumin induces apoptosis in carcinoma cells via a p53-dependent pathway (Choudhuri, Pal et al. 2005).

Mitogen Activated Protein Kinase (MAPK) Pathway and Curcumin Intervention:

The MAPK pathway has also been considered to be a potential target for cancer therapy and prevention. It has been reported that the MAPK pathway consists of a three step kinase system where a MAPKKK activates a MAPKK which activates a MAPK (ERK, JNK, and p38). This pathway results in the activation of cell growth, cell survival and the NF-kB pathway. Curcumin is known to modulate the MAPK signaling pathway and this might contribute to the inhibition of inflammation. Curcumin is able to attenuate experimental colitis through a reduction in p38 MAPK activity. Furthermore, curcumin has a strong repression of the PMA-induced phosphorylation of ERK, JNK, and p38 MAP kinases.

Curcumin and AKT Pathway

The Akt pathway plays a critical role in cell survival and cell growth. This pathway has been shown to be activated in various cancers. Akt is activated by phospholipid binding and phosphorylation at Thr308 by PDK1 and at Ser473 by PDK2. Activated Akt is known to promote cell survival by inhibiting apoptosis via inactivation of several pro-apoptotic factors including Bad, caspase-9 and Forkhead transcription factors. Recent studies have also shown that the NF-κB pathway is regulated by Akt via modulation of phosphorylation and activation of molecules involved in the NF-κB pathway. Therefore, Akt has also been considered to be an attractive target for cancer treatment and prevention. Studies have shown that the Akt signaling pathway is constitutively activated in human T-cell leukemia virus type I (HTLV-I)-infected T-cell lines and in primary adult T-cell leukemia (ATL) cells (Tomita, Matsuda et al. 2006). The effect of curcumin was investigated on Akt activity in HTLV-I-infected T-cell lines and primary ATL cells (Tomita, Kawakami et al. 2006). In these experimental studies curcumin was shown to decrease phosphorylation of PDK1 and thereby inhibit constitutive activation of Akt. Curcumin activated glycogen synthase kinase (GSK)-3beta, a downstream target of Akt kinase, by inhibiting phosphorylation of this protein. Curcumin reduced the expression of cell cycle regulators cyclin D1 and c-Myc proteins, which are both degraded by activated GSK-3beta. Thus, curcumin may have anti-cancer properties which are mediated, at least in part, by inhibiting Akt activity (Tomita, Kawakami et al. 2006).

Effect of Curcumin on Steroid Receptor Pathway

Curcumin has been found to regulate the molecules involved in the androgen receptor (AR) signaling pathway in cancer cells (Guo, Yu et al. 2006). The effects of curcumin on cell growth, activation of signal transduction, and transforming activities in both androgen-dependent and -independent cell lines have been evaluated. Curcumin down-regulates transactivation and expression of AR and AR-related cofactors (AP-1 and NF-κB), and reduces the ability to form colonies in soft agar. The results showed that some curcumin analogues possessed

potent anti-androgenic activities and were superior to hydroxyflutamide, which is the currently available anti-androgen used for the treatment of prostate cancer (Nakamura, Yasunaga et al. 2002; Yang, Zhang et al. 2005).

Experimental evidence suggests that curcumin exerts multiple different suppressive effects on human breast carcinoma cells *in vitro*. In ER-positive MCF-7 cells, curcumin treatment showed an effective suppression of the downstream genes of the ER pathway, including pS2 and TGF-beta (transforming growth factor). In addition, curcumin exerts strong anti-invasive effects in the ER-negative MDA-MB-231 breast cancer cells (Shao, Shen et al. 2002). These anti-invasive effects appear to be mediated through the down-regulation of MMP-2 (matrix metalloproteinase) and the up-regulation of tissue inhibitor metalloproteinase-1 and 2 (TIMP-1 and TIMP-2). These are molecules that have often been implicated in regulating tumor cell invasion.

CURCUMIN MODULATES RADIO-SENSITIVITY IN CANCER CELLS

Curcumin shows a growth inhibitory effect in a broad range of cancers as well as in TPA-induced skin cancers in animal models. The effect of curcumin has been investigated in radiosensitization in the p53 mutated prostate cancer cell line PC-3. Curcumin at 2 and 4 μM concentrations in combination with radiation showed significant enhancement of radiation-induced clonogenic inhibition and apoptosis. It has also been reported that curcumin inhibits TNF-alpha-induced NF-κB activity that is essential for Bcl-2 protein induction. In PC-3 prostate cancer cells, radiation induced up-regulation of TNF-alpha and NF-κB activity, and resulted in the induction of Bcl-2 protein. Radiation treatment in combination with curcumin showed a strong inhibition of Bcl-2 protein expression via down-regulation of TNF-alpha-mediated NF-κB activity. In addition, a significant activation of cytochrome c, caspase-9 and caspase-3 were also observed in curcumin combined radiation treatments. However, Bax protein expression remained constant in PC3 cells after radiation and/or curcumin treatments. Effective modulation in the expression of these proteins by curcumin caused the enhanced radiosensitization in these cancer cells. These observations clearly demonstrate that curcumin has a potent radio-sensitizing activity, and its use in combination with radiation based therapy may provide a better treatment outcome in cancer patients.

PHARMACOLOGICALLY SAFE AND EFFECTIVE DOSE OF CURCUMIN

At pre-clinical and clinical levels, curcumin has been found to be safe at 3.6 -10 g per day (Aggarwal, Kumar et al. 2003; Sharma, Euden et al. 2004; Sharma, Gescher et al. 2005). Systemic pre-clinical studies funded by the Prevention Division of the U. S. National Cancer Institute found no adverse effects in rats, dogs or monkeys in doses of up to 3.5 g/kg BW, administered for up to 3 months

(Shankar, Shantha et al. 1980). A daily oral dose of 3.6 g of curcumin results in pharmacologically effective levels in colorectal tissue with negligible distribution of the parent drug in hepatic tissue or other tissues of the gastrointestinal tract (Garcea, Berry et al. 2005). No toxicity was observed in a study where a high dose of oral curcumin was administered (up to 8 g curcumin daily for 3 months) to patients with pre-invasive malignant or high-risk pre-malignant conditions (Cheng, Hsu et al. 2001).

Due to lack of any substantial data in favor of a dose response relationship for a biomarker of curcumin's activity, several observations in human volunteers and patients suggest that curcumin may possesses systematic biological activity at low oral doses. In a small study, a single oral dose of 20 mg curcumin appeared to induce contraction of the gall bladder, assessed by ultrasound scanning in human volunteers, compared to amylum placebo (Rasyid, Rahman et al. 2002).

PROSPECTIVE

The data generated from *in vitro* experiments and *in vivo* preclinical and clinical trials indicates that curcumin exerts inhibitory effects on carcinogenesis and tumor progression suggesting that it has enormous potential in the prevention, care, and cure of cancer. There are nearly 50 different chemotherapy drugs that are being used for the treatment of cancer. Some of them are complementary and some are not. These anticancer drugs have low efficacy and severe side effects. Curcumin is one of the safest natural products which controls proliferation, apoptosis, angiogenesis and metastasis. In conclusion, curcumin is now emerging as a new hope in the fight against cancer.

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