Role of Curcumin in Cancer Therapy

Although our knowledge of cancer biology has advanced a great deal, neither the incidence of cancer nor the rate of death due to cancer has changed in the last 50 years. Most drugs currently available for the treatment of cancer have limited potential because they are very toxic, highly inefficient in treating cancer, or highly expensive and thus beyond the reach of the majority. Treatments without these disadvantages are needed. Curcumin is one such agent; derived from turmeric (*Curcumin longa*), it has been used for thousands of years in the Orient as a healing agent for variety of illnesses. Research over the last few decades has shown that curcumin is a potent antiinflammatory agent with strong therapeutic potential against a variety of cancers. Curcumin has been shown to suppress transformation, proliferation, and metastasis of tumors. These effects are mediated through its regulation of various transcription factors, growth factors, inflammatory cytokines, protein kinases, and other enzymes. It also inhibits proliferation of cancer cells by arresting them in various phases of the cell cycle and by inducing apoptosis. Moreover, curcumin has the ability to inhibit carcinogen bioactivation via suppression of specific cytochrome P450 isozymes, and to induce the activity or expression of phase II carcinogen detoxifying enzymes, which may account for its cancer chemopreventive effects. Curcumin has been shown to have protective and therapeutic effects against cancers of the blood, skin, oral cavity, lung, pancreas, and intestinal tract, and to suppress angiogenesis and metastasis in rodents. The current review focuses on the molecular mechanisms by which curcumin mediates its effects against various cancers. Curcumin is the most active component of turmeric, a botanical agent derived from the dried rhizome of the turmeric plant (*Curcuma longa*), a perennial herb belonging to the ginger family that is cultivated extensively in south and southeast tropical Asia. The rhizome, or root, is processed into turmeric powder, which is 2% to 5% curcumin. Turmeric is widely consumed in the Indian subcontinent, south Asia, and Japan.[1] It has a variety of uses;

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it is a popular dietary spice and pigment (it is one of the ingredients of curry powder), and in India is employed as a folk medicine for the treatment of various illnesses. It is used in the textile and pharmaceutical industries and in Hindu religious ceremonies.[2] The ancient texts of Ayurveda (the science of long life) and traditional Chinese medicine describe the use of turmeric for the prevention and cure of several health problems and to improve general well-being. Turmeric's pharmacological safety is accepted, considering that it has been consumed as a dietary spice, at doses up to 100 mg/d, for centuries.[3] Traditional Indian medicine still practiced today uses it for biliary disorders, anorexia, cough, diabetic wounds, hepatic disorders, rheumatism, and sinusitis.[4] The old Hindu texts describe it as an aromatic stimulant and carminative.[5] A household remedy for local inflammation combines powdered turmeric and slaked lime. In some parts of India, turmeric powder is taken orally for the treatment of sore throat. In the United States, curcumin is used as a coloring agent in cheese, spices, mustard, cereals, pickles, potato flakes, soups, ice cream, and yogurt.

Over 1700 papers on curcumin have been published over the last 50 years. Extensive investigation has indicated that curcumin reduces blood cholesterol[6-12]; prevents low-density lipoprotein oxidation[13-15]; inhibits platelet aggregation[16,17]; suppresses thrombosis[18] and myocardial infarction[19-22]; suppresses symptoms associated with type II diabetes,[23-27] rheumatoid arthritis,[28] multiple sclerosis,[29] and Alzheimer's disease[30,31]; inhibits HIV replication[32-36]; enhances wound healing[37-39]; protects from liver injury[40]; prevents cataract formation[41]; protects from pulmonary toxicity and fibrosis[42-45]; has therapeutic effects in leishmaniasis[46-48]; and has antiatherosclerotic activity.[49,50] Moreover, there is extensive literature suggesting that curcumin has potential in the prevention and treatment of a variety of cancers.

Curcumin is an orange–yellow crystalline powder practically insoluble in water and ether but soluble in ethanol, dimethylsulfoxide, and acetone. Curcumin was first isolated in 1815 by Vogel[51]; in 1870 it was isolated in crystalline form and identified as 1,6-heptadiene-3,5-dione-1,7-bis(4-hydroxy-3-methoxyphenyl)-(1E,6E) or diferuloylmethane.[52] The feruloylmethane skeleton of curcumin was confirmed in 1910 by the initial work and synthesis by Lampe.[53,54] Curcumin has a melting point of 183°C; its molecular formula is $C_{21}H_{20}O_6$ and molecular weight 368.37. Besides curcumin, turmeric contains other chemical constituents known as the curcuminoids.[55] The curcuminoids impart the characteristic yellow color to turmeric. The major curcuminoids present in turmeric are demethoxycurcumin, bisdemethoxycurcumin, and the recently identified

cyclocurcumin.[56] Commercial curcumin contains about 77% curcumin, 17% demethoxycurcumin, and 3% bisdemethoxycurcumin as its major components.

Why Does Curcumin Have Anticancer Effects?

Cancer is a hyperproliferative disorder marked by metastasis into the vital organs of the body through invasion and angiogenesis. Curcumin blocks the transformation, proliferation, and invasion of tumor cells. The biochemical pathways involved in the carcinogenesis process have been investigated extensively over the last four decades. Numerous studies over the last two decades have demonstrated that curcumin targets several steps in these biochemical pathways, thus showing immense promise for the treatment of cancers.

Curcumin suppresses the growth of several tumor cell lines, including drug-resistant lines.[57] It suppresses the expression of cyclin D1, which is deregulated in a wide variety of tumors. Cyclin D1 is a component subunit of cyclin-dependent kinases (CDK) 4 (Cdk4) and 6 (Cdk6), which are rate limiting in progression of cells through the cell cycle.[57] Curcumin also induces apoptosis in tumor cells by activating caspase-8, which leads to cleavage of Bid, thus resulting in sequential release of mitochondrial cytochrome C and activation of caspase-9 and caspase-3, which leads to activation of poly ADP ribose polymerase (PARP) and apoptosis of tumor cells.

Curcumin also suppresses the activation of several transcription factors that are implicated in carcinogenesis.[58] It suppresses the activation of nuclear factor kappa B (NF-κB), activator protein 1 (AP-1), and at least two of the signal transducer and activator of transcription proteins (STAT3, STAT5), and modulates the expression of early growth response protein 1 (Egr-1), peroxisome proliferator-associated receptor gamma (PPAR-γ), β-catenin, and Nrf-2. Curcumin also modulates expression of genes involved in cell proliferation, cell invasion, metastasis, angiogenesis, and resistance to chemotherapy.[58] It has been shown to downregulate the expression of Bcl-2, *Bcl*XL, cyclooxygenase 2 (COX-2), matrix metalloproteinase (MMP)-9, tumor necrosis factor (TNF), cyclin D1, and the adhesion molecules.[59] Numerous studies in animals have demonstrated that curcumin has potent chemopreventive activity against a wide variety of tumors. This review presents several lines of evidence from *in vitro*, *in vivo*, preclinical, and clinical studies to suggest that curcumin has great potential in the prevention and treatment of cancer.

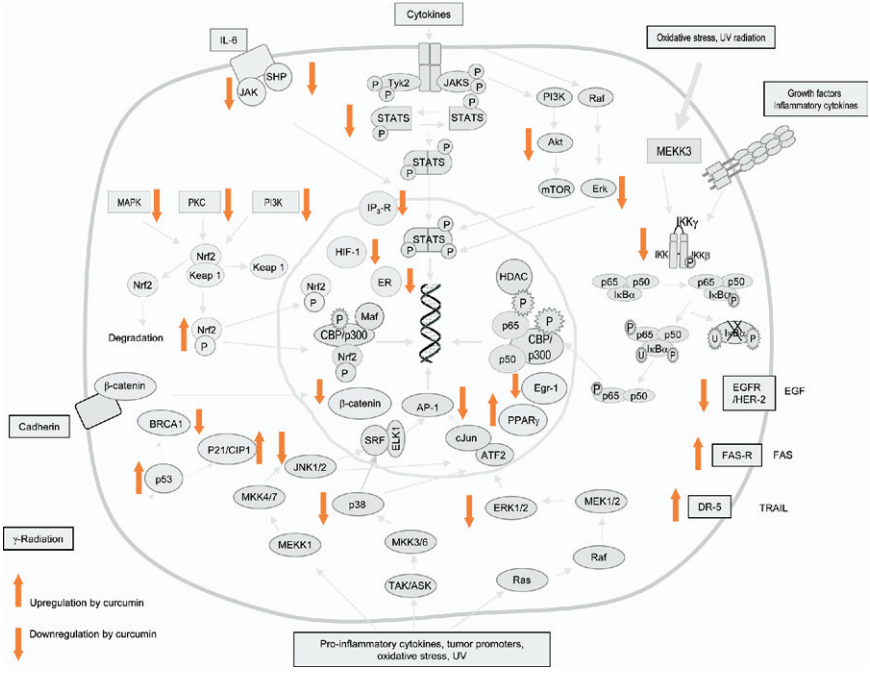

FIG 1. Targets of curcumin. Abbreviations: MEKK, MAPK/ERK kinase kinase; IKK, IκB kinase; IκB, inhibitory kappa B; CBP, CREB-binding protein; HDAC, histone deacetylase; P, phosphorylation; U, ubiquitination; MAPK, mitogen activated protein kinase; MEK, MAPK/ERK kinase; MKK, MEK kinase; ERK, extracellular signal regulated kinase; JNK, cJun N-terminal kinase; TAK/ASK, transforming growth factor-β-activated /apoptosis signal-regulated kinase; PI3K, phosphatidylinositol-3-kinase; ISRE, IFN-stimulated responsive element; GAS, γIFN activation site; mTOR Mammalian target of rapamycin; PKC, protein kinase C; Keap, Kelch-like ECH-associated protein 1. (Color version of figure is available online.)

Molecular Targets of Curcumin

Carcinogenesis is a multistep process in which several biochemical pathways and hundred of molecules are deregulated. These include the growth factors, growth factor receptors, transcription factors, cytokines, enzymes, and genes regulating apoptosis and proliferation. Curcumin has been shown to target several of the molecules involved in carcinogenesis, as described in the following sections (Fig 1).

Transcription Factors

NF-κB. NF-κB is a family of five closely related proteins which are found in several dimeric combinations and bind to the κB sites on DNA.[60] Under resting conditions, NF-κB dimers reside in the cytoplasm. On

activation by free radicals, inflammatory stimuli, cytokines, carcinogens, tumor promoters, endotoxins, gamma-radiation, ultraviolet (UV) light, or x-rays, NF-κB is translocated to the nucleus, where it induces the expression of more than 200 genes that have been shown to suppress apoptosis and induce cellular transformation, proliferation, invasion, metastasis, chemoresistance, radioresistance, and/or inflammation. Many of these activated target genes are critical to establishment of the early and late stages of aggressive cancers, including those encoding expression of cyclin D1, apoptosis suppressor proteins such as bcl-2 and bcl-XL, and proteins required for metastasis and angiogenesis, such as matrix metalloproteinases and vascular endothelial growth factor (VEGF).

The identification of the p50 subunit (v-REL) of NF-κB as a member of the reticuloendotheliosis family of viruses provided the first evidence that NF-κB is linked to cancer. Several groups, including ours, have shown that activated NF-κB suppresses apoptosis in a wide variety of tumor cells,[61-63] and it has been implicated in chemoresistance.[61] Furthermore, the constitutively active form of NF-κB has been reported in human breast cancer,[64-66] pancreatic cancer,[67,68] head and neck squamous cell carcinoma,[69] multiple myeloma,[70] mantle cell lymphoma,[59] and melanoma.[71]

We showed that curcumin suppresses the activation of NF-κB induced by various tumor promoters, including phorbol ester, TNF, and hydrogen peroxide.[72] Subsequently, others showed that curcumin-induced downregulation of NF-κB is mediated through suppression of IκBα kinase (IKK) activation.[73,74] Recently, we showed that curcumin down-regulated cigarette smoke-induced NF-κB activation through inhibition of IKK in human lung epithelial cells.[75] We also have demonstrated that curcumin suppresses constitutively active NF-κB in multiple myeloma, head and neck cancers, pancreatic cancers, and mantle cell lymphoma.[59] We found that curcumin suppresses the paclitaxel-induced NF-κB pathway in breast cancer cells and inhibits lung metastasis of human breast cancer in nude mice.[76] Suppression of NF-κB by curcumin led to downregulation of cyclin D1, COX-2, and MMP-9. Philip and coworkers[77] reported that curcumin down-regulates osteopontin-induced NF-κB-mediated pro-MMP-2 activation through IκBα/IKK signaling.[77] Curcumin arrested cell growth at the G_2/M phase and induced apoptosis in human melanoma cells by inhibiting NF-κB activation.[78]

Downregulation of Notch signaling by curcumin may be a novel strategy for the treatment of patients with pancreatic cancer.[79] The Notch-1 signaling pathway is associated mechanistically with NF-κB activity during curcumin-induced cell growth inhibition and apoptosis of

pancreatic cells. A recent report suggested, however, that the curcumin-induced apoptosis is mediated through impairment of the ubiquitin proteasome system. Curcumin disrupts ubiquitin proteasome function by directly inhibiting the enzyme activity of the proteasome's 20S core catalytic component. This direct inhibition of proteasome activity causes an increase in half-life of IκBα that ultimately leads to downregulation of NF-κB activation. The curcumin-induced proteasomal malfunction might be linked with both antiproliferative and antiinflammatory activities.[80]

NF-κB plays important roles in inflammation, cell proliferation, apoptosis, and oncogenesis. The ability of curcumin to suppress activation of NF-κB is of particular interest in cancer.

STAT. STAT proteins are signaling molecules with dual functions that were discovered during studies on interferon (IFN) gamma-dependent gene expression.[81] They can be activated by phosphorylation through janus kinase (JAK) or cytokine receptors, G-protein-coupled receptors, or growth factor receptors [such as epidermal growth factor receptor (EGFR)]; by platelet-derived growth factor receptors (PDGF) that have intrinsic tyrosine kinase activity; or by intracellular nonreceptor tyrosine kinase recruitment.[82,83] Of the seven STAT proteins identified so far, constitutively activated STAT3 and STAT5 have been implicated in multiple myeloma, lymphomas, leukemias, and several solid tumors, making these proteins logical targets for cancer therapy. These STAT proteins contribute to cell survival and growth by preventing apoptosis through increased expression of antiapoptotic proteins, such as bcl-2 and bcl-X_L. Recently, STAT3 was shown to be a direct activator of the *VEGF* gene, which is responsible for increased angiogenesis. Elevated STAT3 activity has been detected in head and neck squamous cell carcinoma,[84] leukemias,[85] lymphomas,[86] and multiple myeloma.[87]

Bharti and coworkers[87] demonstrated that curcumin inhibited interleukin (IL) 6-induced STAT3 phosphorylation and consequent STAT3 nuclear translocation. Curcumin had no effect on STAT5 phosphorylation but inhibited IFN-α-induced STAT1 phosphorylation. The constitutive phosphorylation of STAT3 found in certain multiple myeloma cells was also abrogated by treatment with curcumin. Curcumin was more efficient and more potent than the well-characterized JAK2 inhibitor AG490. In addition, dexamethasone-resistant multiple myeloma cells were found to be sensitive to curcumin. Overall, these results demonstrated that curcumin is a potent inhibitor of STAT3 phosphorylation and that this plays a role in curcumin's suppression of multiple myeloma proliferation. Recently, we showed that curcumin suppresses the constitutive and

IL-6-inducible STAT3 pathway in head and neck squamous cell carcinoma cells.[87]

Li and coworkers[88] showed that curcumin suppressed oncostatin-M-stimulated STAT1 phosphorylation, DNA-binding activity of STAT1, and c-Jun N-terminal kinase (JNK) activation without affecting JAK1, JAK2, JAK3, ERK1/2, or p38 phosphorylation. Curcumin also inhibited oncostatin M-induced expression of the *MMP-1*, *MMP-3*, *MMP-13*, and tissue inhibitor metalloproteinase 3 (*TIMP-3*) genes. Treatment of activated T cells with curcumin inhibited IL-12-induced tyrosine phosphorylation of JAK2, tyrosine kinase 2, STAT3, and STAT4 transcription factors.[29] Inhibition of the JAK-STAT pathway by curcumin resulted in a decrease in IL-12-induced T-cell proliferation and Th1 differentiation. The STAT5 signaling pathway may be involved in the proliferation of primary chronic myelogenous leukemia cells. Curcumin has been shown to inhibit cellular proliferation and the expression of *STAT5* mRNA, and to downregulate the activation of STAT5 in primary chronic myelogenous leukemia cells[89] and K562 leukemia cells.[90]

AP-1. AP-1 is a transcription factor that is frequently associated with activation of NF-κB and has been closely linked with proliferation and transformation of tumor cells.[91] Curcumin has been shown to inhibit the activation of AP-1 induced by tumor promoters.[92] Activation of AP-1 requires the phosphorylation of c-jun through activation of stress-activated kinase JNK,[93] and curcumin suppresses the JNK activation induced by carcinogens.[94] Curcumin also interacts with the AP-1–DNA binding motif, thereby inhibiting activation of AP-1.[95]

Curcumin suppressed constitutive AP-1–DNA binding and transcriptional activity in an HTLV-1-infected T-cell line. It inhibited the growth of these cells by inducing cell cycle arrest followed by apoptosis. Suppression of the constitutively active AP-1 by curcumin may be due partly to its suppression of JunD expression.[96] Infection with high-risk human papillomaviruses (HPV) leads to development of cervical carcinoma, predominantly through the action of viral oncoproteins E6 and E7. Curcumin suppressed the expression of viral oncogenes *E6* and *E7* and down-regulated the binding of AP-1, an indispensable factor in efficient epithelial tissue-specific expression of the *HPV* gene.[97] Hydrogen peroxide stimulates proliferation and migration of human prostate cancer cells through activation of AP-1 and up-regulation of the heparin affin regulatory peptide (*HARP*) gene. Curcumin abrogated both hydrogen peroxide-induced *HARP* expression and LNCaP cell proliferation and migration.[98] Prusty and Das recently reported that curcumin down-

regulated AP-1 binding activity in tumorigenic HeLa cells.[99] IL-18-induced VEGF plays an important role in angiogenesis, and curcumin abrogated the effect of IL-18 on VEGF production in a dose-dependent manner.[100]

PPAR-γ. PPAR-γ is a member of the nuclear hormone receptor gene family that is activated by fatty acids and plays a role in insulin sensitivity and adipogenesis. Activation of PPAR-γ inhibits the proliferation of nonadipocytes. Xu and coworkers demonstrated that curcumin dramatically induced expression of the *PPAR-γ* gene and activated PPAR-γ in activated hepatic stellate cells.[101] Blockade of its transactivating activity by a PPAR-γ antagonist markedly decreased the effects of curcumin on inhibition of cell proliferation. Chen and coworkers recently reported that curcumin activation of PPAR-γ inhibited Moser cell growth and mediated suppression of *cyclin D1* and *EGFR* gene expression.[102] These results provided a novel insight into the roles and mechanisms of curcumin in inhibition of colon cancer cell growth and potential therapeutic strategies for treatment of colon cancer.

Androgen Receptor (AR) and AR-Related Cofactors. The AR is an intracellular steroid receptor that specifically binds testosterone and dihydrotestosterone. Curcumin has been shown to modulate the AR in prostate cancer cells. Nakamura and coworkers evaluated the effects of curcumin in cell growth, activation of signal transduction, and transforming activities of both androgen-dependent and androgen-independent cell lines. The prostate cancer cell lines LNCaP and PC-3 were treated with curcumin, and its effects on signal transduction and expression of AR and AR-related cofactors were analyzed. Their results showed that curcumin down-regulates transactivation and expression of AR, AP-1, NF-κB, and cAMP response element-binding protein (CBP). It also inhibited the transforming activities of both cell lines as evinced by reduced colony-forming ability in soft agar. These findings suggest that curcumin has a potential therapeutic effect on prostate cancer cells through downregulation of AR and AR-related cofactors AP-1, NF-κB, and CBP.[103] Curcumin also induced apoptosis in both androgen-dependent and androgen-independent prostate cancer cells through suppression of apoptosis suppressor proteins and AR.[104]

A number of curcumin analogs have been evaluated as potential AR antagonists against human prostate cancer cell lines PC-3 and DU-145, in the presence of AR and AR coactivator ARA70. Compounds 4 [5-hydroxy-1,7-*bis*(3,4-dimethoxyphenyl)-1,4,6-heptatrien-3-one], 20 [5-hydroxy-1,7-*bis*[3-methoxy-4-(methoxycarbonylmethoxy)phenyl]-1,4,6-

heptatrien-3-one], 22 [7-(4-hydroxy-3-methoxyphenyl)-4-[3-(4-hydroxy-3-methoxyphenyl)acryloyl]-5-oxohepta-4,6-dienoic acid ethyl ester], 23 [7-(4-hydroxy-3-methoxyphenyl)-4-[3-(4-hydroxy-3-methoxyphenyl)acryloyl]5-oxohepta-4,6-dienoic acid], and 39 [*bis*(3,4-dimethoxyphenyl)-1,3-propanedione] showed potent antiandrogenic activities and were superior to hydroxyflutamide, the antiandrogen currently in use for the treatment of prostate cancer. Structure–activity relationship studies indicated that the *bis*(3,4-dimethoxyphenyl) moieties, the conjugated beta-diketone moiety, and the intramolecular symmetry of the molecules seem to be important factors related to antiandrogenic activity. The data further suggest that the coplanarity of the beta-diketone moiety and the presence of a strong hydrogen bond donor group were also crucial for the antiandrogenic activity, which is consistent with previous structure–activity relationship results for hydroxyflutamide analogs.[105]

CAMP Response Element-Binding Protein. p300/CBP, along with histone acetyltransferases (HAT), have been implicated in cancer cell growth and survival. Acetylation by HAT of specific lysine residues on the *N*-terminal tail of core histones results in uncoiling of the DNA and increased accessibility to transcription factor binding. In contrast, histone deacetylation by histone deacetylase represses gene transcription by promoting DNA winding, thereby limiting access to transcription factors. CBP and HAT represent novel, therapeutically relevant molecular targets for drug development.

Curcumin is a selective HAT inhibitor.[106] The α and β unsaturated carbonyl groups in the curcumin side chain function as Michael reaction sites, and the Michael reaction acceptor functionality of curcumin is required for its HAT-inhibitory activity. In cells, curcumin promotes proteasome-dependent degradation of p300 and the closely related CBP. In addition to inducing p300 degradation, curcumin inhibited the acetyltransferase activity of purified p300. Radiolabeled curcumin formed a covalent association with p300, but tetrahydrocurcumin displayed no p300-inhibitory activity, consistent with a Michael reaction-dependent mechanism. Curcumin was able to effectively block histone hyperacetylation induced by the histone deacetylase inhibitor MS-275 in both PC3-M prostate cancer cells and peripheral blood lymphocytes.

Balasubramanyam and coworkers found that curcumin is a specific inhibitor of the p300/CBP HAT activity but not of p300/CBP-associated factor, *in vitro* and *in vivo*.[107] Furthermore, curcumin could inhibit the p300-mediated acetylation of p53 *in vivo*. It specifically repressed p300/CBP HAT activity-dependent transcriptional activation. Curcumin

also could inhibit acetylation of HIV-Tat protein *in vitro* by p300 as well as proliferation of the virus in SupT1 cells. Thus, nontoxic curcumin, which targets p300/CBP, may serve as a lead compound in combinatorial HIV therapeutics. These data thus suggest curcumin as a novel compound for development of possibly therapeutic p300/CBP-specific HAT inhibitors.

Egr-1. Transient induction of the transcription factor Egr-1 plays a pivotal role in the transcriptional response of endothelial cells to the angiogenic growth factors VEGF and basic fibroblast growth factor (bFGF), which are produced by most tumors and are involved in angiogenesis. Pendurthi and coworkers investigated the effect of curcumin on Egr-1 expression in endothelial cells and fibroblasts[108] and showed that pretreatment of endothelial cells and fibroblasts with curcumin suppressed tetradecanoyl phorbol acetate (TPA) and serum-induced Egr-1 binding to the consensus Egr-1 binding site and also to the Egr-1 binding site present in the promoter of the tissue factor gene. Similarly, curcumin inhibited human colon cancer cell growth by suppressing expression of the *EGFR* gene through reducing the transactivation activity of Egr-1.[109] Curcumin also inhibited TPA-induced de novo synthesis of Egr-1 protein in endothelial cells. Suppression of Egr-1 protein expression in curcumin-treated cells stemmed from suppression of *Egr-1* mRNA. Curcumin inhibited serum- and TPA-induced expression of tissue factor and urokinase-type plasminogen activator receptor mRNA in fibroblasts. These results showed that curcumin suppresses the induction of Egr-1 and thereby modulates the expression of Egr-1-regulated genes in endothelial cells and fibroblasts. The downregulation of tissue factor by curcumin has also been demonstrated in bovine aortic endothelial cells.[95]

β-Catenin. β-Catenin is a central component of the cadherin cell adhesion complex and plays an essential role in the Wingless/Wnt signaling pathway. In the nucleus, β-catenin interacts with members of the TCF/LEF family of transcription factors to stimulate expression of target genes.

Curcumin treatment impairs both Wnt signaling and cell–cell adhesion pathways, resulting in cell cycle arrest at the G_2/M phase and induction of apoptosis in HCT-116 colon cancer cells.[110] Curcumin induces activation of caspase-3, which in turn mediates cleavage of β-catenin, resulting in transactivation of β-catenin/Tcf-Lef, decreased promoter DNA binding activity of the beta-catenin/Tcf-Lef complex, and decreased levels of c-Myc protein. Mahmoud and coworkers, while investigating the

efficacy of curcumin for prevention of tumors in C57BL/6J-Min/$^{+}$ (Min/$^{+}$) mice, found that curcumin decreased expression of the oncoprotein β-catenin in the enterocytes of the Min/$^{+}$ mouse, which led to its antitumor effect. These animals bear a germline mutation in the *Apc* gene and spontaneously develop numerous intestinal adenomas by 15 weeks of age. Curcumin decreased tumor formation in Min/$^{+}$ mice by over 60%. Tumor prevention by curcumin was associated with increased enterocyte apoptosis.[111]

Electrophile-Response Element. Transcription has been shown in several systems to be mediated through binding of transcription factor complexes to TPA response element (TRE) and electrophile-response elements (EpRE). Curcumin exposure has been shown to increase the enzymes responsible for glutathione synthesis (particularly glutamate-cysteine ligase) and metabolism as well as glutathione content, suggesting the eliciting of an adaptive response to stress. Studies have shown that curcumin caused an increase in binding of proteins to DNA sequences for both *cis* elements, more importantly, altered the composition and nuclear content of proteins in these complexes. Curcumin exposure increased JunD and c-Jun content in AP-1 complexes and increased JunD while decreasing MafG/MafK in EpRE complexes. Thus, the beneficial effects elicited by curcumin appear to be due to changes in the pool of transcription factors that compose EpRE and AP-1 complexes, affecting expression of genes for glutamate-cysteine ligase and other phase II enzymes.[112]

Nrf-2. The transcription factor Nrf-2 normally exists in an inactive state as a result of binding to a cytoskeleton-associated protein, Keap1. It can be activated by redox-dependent stimuli. Alteration of the Nrf-2-Keap1 interaction enables Nrf-2 to translocate to the nucleus, bind to the antioxidant-responsive element (ARE), and initiate the transcription of genes coding for detoxifying enzymes and cytoprotective proteins. The Nrf-2/ARE signaling pathway plays a key role in activating cellular antioxidants, including heme oxygenase-1 (HO-1), NADPH quinone oxidoreductase-1, and glutathione. This response is also triggered by a class of electrophilic compounds that includes curcumin.

Curcumin stimulates the expression of Nrf-2 in a concentration- and time-dependent manner in renal epithelial cells. This effect is associated with a significant increase in HO-1 protein expression and hemoxygenase activity. Curcumin stimulates *ho-1* gene activity by promoting inactivation of the Nrf-2–Keap1 complex, leading to increased Nrf-2 binding to the resident *ho-1* ARE.[113]

Rushworth and coworkers have shown that curcumin activates ARE-mediated gene expression in human monocytes via PKC delta, upstream of p38 and Nrf-2.[114] Gastrointestinal glutathione peroxidase has been suggested to act as barrier against hydrogen peroxide absorption and also has been implicated in the control of inflammation and malignant growth. Curcumin has been found to exert antiinflammatory and anticarcinogenic effects by up-regulating the selenoprotein gastrointestinal glutathione pyroxidase by activating the Nrf-2/Keap1 system.[115]

Tumor Suppressor Gene p53

p53 is a tumor suppressor and transcription factor. It is a critical regulator in many cellular processes, including cell signal transduction, cellular response to DNA damage, genomic stability, cell cycle control, and apoptosis. The protein activates transcription of downstream genes such as $p21^{WAF1}$ and *Bax* to induce the apoptotic process, inhibiting the growth of cells with damaged DNA or cancer cells.[116,117] Mutant p53 loses its ability to bind DNA effectively, and as a consequence, the p21 protein is not made available to regulate cell division. Thus, cells divide uncontrollably and form tumors. Subjects with only one functional copy of the *p53* gene are predisposed to cancer and usually develop several independent tumors in a variety of tissues in early adulthood. Curcumin has been shown to be a potent inhibitor of p53.[118]

Curcumin down-regulates the expression of p53 as well as the survival genes *egr-1*, *c-myc*, and *bcl-*X_L in B cells.[118] In a study on melanoma cells, curcumin induced apoptosis independent of the level of p53 expression. It induced apoptosis in four cell lines with wild-type and four cell lines with mutant p53 without inducing additional expression of p53[119]; in human breast cancer cells, however, curcumin induced apoptosis through p53-dependent Bax induction.[120,121] Curcumin also inhibited cell cycle progression of immortalized human umbilical vein endothelial cells by up-regulating the CDK inhibitors $p21^{WAF1/CIP1}$, $p27^{KIP1}$, and p53.[122] In neuroblastoma, curcumin up-regulated p53 expression and induced nuclear translocation of p53, followed by induction of $p21^{WAF-1/CIP-1}$ and Bax expression.[123]

TNF

TNF has been shown to mediate tumor initiation, promotion, and metastasis.[124] The pro-inflammatory effects of TNF are due primarily to its ability to activate NF-κB. Almost all cell types, when exposed to TNF, activate NF-κB, leading to expression of inflammatory genes

such as COX-2, LOX-2, cell adhesion molecules, inflammatory cytokines, chemokines, and inducible nitric oxide synthase. TNF is a growth factor for most tumor cells,[125] including ovarian cancer, cutaneous T-cell lymphoma,[63] glioblastoma,[126] acute myelogenous leukemia,[127] B-cell lymphoma,[128] breast carcinoma,[129] renal cell carcinoma,[130] multiple myeloma,[131] and Hodgkin's lymphoma.[132] Various fibroblasts, including normal human fibroblasts, scleroderma fibroblasts, synovial fibroblasts, and periodontal fibroblasts, proliferate in response to TNF.

Curcumin suppresses the expression of TNF at both the transcriptional and posttranscriptional levels. Studies in our laboratory have shown that both TNF mRNA and protein are constitutively expressed in mantle cell lymphoma cell lines.[59] The autocrine expression of TNF leads to constitutive expression of NF-κB and NF-κB-regulated gene products. Curcumin inhibits the expression of both *TNF* mRNA and TNF protein in mantle cell lymphoma cell lines. Suppression of TNF by curcumin led to inhibition of NF-κB and cell proliferation, as was the case when TNF secretion was neutralized using an anti-TNF antibody.[59]

Inflammatory Enzymes

Cyclooxygenase-2. Cyclooxygenases are forms of prostaglandin H synthase, which converts arachidonic acid released by membrane phospholipids into prostaglandins. COX-2 is regulated by mitogens, tumor promoters, cytokines, and growth factors. It is overexpressed in practically every premalignant and malignant condition involving the colon, liver, pancreas, breast, lung, bladder, skin, stomach, head and neck, and esophagus.[133] Depending on the stimulus and the cell type, several transcription factors, including AP-1, nuclear factor IL-6, and NF-κB, can stimulate COX-2 transcription.[133]

Curcumin exhibits significant COX-2-inhibiting activity through suppression of NF-κB. Preclinical studies have shown that curcumin suppresses COX-2 activity through suppression of the NF-κB-inducing kinase and IKK enzymes.[74] Several groups have shown that curcumin down-regulates expression of COX-2 protein in different tumor cells,[74,134] most likely through downregulation of NF-κB activation,[74] which is needed for COX-2 expression. Chun and coworkers reported that curcumin inhibited phorbol ester-induced expression of COX-2 in mouse skin through suppression of extracellular signal-regulated kinase activity and NF-κB activation. COX-2 has been implicated in the development of many human cancers.[135] We have demonstrated that curcumin inhibits cigarette smoke-induced COX-2 expression in lung cancer cell lines.[75]

Plummer and coworkers explored the inhibition of COX-2 activity as a systemic biomarker of drug efficacy, a biomarker of potential use in clinical trials of many chemopreventive drugs known to inhibit this enzyme. They measured COX-2 protein induction and prostaglandin E2 production in human blood after incubation with lipopolysaccharide (LPS). When 1 μM curcumin was added *in vitro* to blood from healthy volunteers, LPS-induced COX-2 protein levels and concomitant prostaglandin E2 production were reduced by 24% and 41%, respectively.[136]

Lipoxygenase Lipoxygenases (LOX) are the enzymes responsible for generating leukotrienes from arachidonic acid. There are three types of LOX isozymes, whose differences are based on the different cells and tissues they affect. 15-LOX synthesizes antiinflammatory 15-HETE; 12-LOX is involved in provoking inflammatory/allergic disorders; and 5-LOX produces 5-HETE and leukotrienes, which are potent chemoattractants that promote development of asthma. Aberrant arachidonic acid metabolism is involved in the inflammatory and carcinogenic processes.

Curcumin and its metabolite tetrahydrocurcumin effectively inhibited the release of arachidonic acid and its metabolites in LPS-stimulated RAW cells and A23187-stimulated HT-29 colon cancer cells. They potently inhibited the formation of prostaglandin E2 in LPS-stimulated RAW cells. Curcumin and tetrahydrocurcumin also inhibited the activity of human recombinant 5-LOX, with median inhibitory concentrations (IC_{50} values) of 0.7 and 3 μM, respectively. Curcumin affects arachidonic acid metabolism by blocking the phosphorylation of cytosolic phospholipase A2, decreasing the expression of COX-2, and inhibiting the catalytic activities of 5-LOX. These activities may contribute to the antiinflammatory and anticarcinogenic actions of curcumin and its analogs.[137]

Cyclin D1

Cyclin D1, a component subunit of Cdk4 and Cdk6, is a rate-limiting factor in progression of cells through the first gap (G_1) phase of the cell cycle.[138] The loss of this regulation is the hallmark of cancer.[139] Cyclin D1 is overexpressed in many cancers, including those of the breast, esophagus, head and neck, and prostate, and mantle cell lymphoma.[140-145] Targeted overexpression of cyclin D1 induced mammary adenocarcinoma,[146] and transgenic mice lacking both *cyclin D1* alleles failed to develop normal mammary glands.[147] Furthermore, cyclin D1 is required for transformation by activated HER2/neu.[148]

Curcumin down-regulates the expression of cyclin D1 at the transcriptional and posttranscriptional levels.[57,70,149] Choudhuri and coworkers

reported that curcumin reversibly inhibited normal mammary epithelial cell cycle progression by down-regulating cyclin D1 expression and blocking its association with Cdk4/Cdk6 as well as by inhibiting phosphorylation and inactivation of the retinoblastoma protein.[150] Cyclin D1 expression is regulated by NF-κB, and suppression of NF-κB activity by curcumin in multiple myeloma cells led to downregulation of cyclin D1.[70] Similarly, suppression of NF-κB in mantle cell lymphoma by curcumin led to suppression of cyclin D1.[59] This resulted in a decrease in formation of the cyclin D1-Cdk4 holoenzyme complex, suppressing proliferation and induction of apoptosis. In another study, curcumin induced G_0/G_1 and/or G_2/M phase cell cycle arrest, up-regulated cdk inhibitors such as $p21^{Cip1/waf1}$ and $p27^{Kip1}$, and down-regulated cyclin B1 and cdc2.[122]

Protein Kinases

EGFR/HER2/neu. *HER2/neu* (also known as *ErbB-2*, avian erythroblastosis oncogene B) is a member of the EGFR family and is notable for its role in the pathogenesis of breast cancer and as a target of treatment. It is a cell membrane surface-bound tyrosine kinase and is involved in the signal transduction pathways leading to cell growth and differentiation. Almost 30% of breast cancers have been shown to overexpress the *HER2/neu* protooncogene,[151] and both HER2 and EGF receptors stimulate proliferation of breast cancer cells. Overexpression of these two proteins correlates with progression of human breast cancer and poor patient prognosis.[151] Suppression of HER2/neu and EGFR activity represents one possible mechanism by which curcumin suppresses the growth of breast cancer cells.

Curcumin has been shown to downregulate the activity of *EGFR*[152,153] and *HER2/neu*[152,153] and to deplete cells of HER2/neu protein.[154] Moreover, we recently found that curcumin can downregulate bcl-2 expression, which may contribute to its antiproliferative activity.[149] Like geldanamycin, curcumin provokes intracellular degradation of HER2.[155] *HER2* mutations, however, limit the capacity of geldanamycin to disrupt the tyrosine kinase activity of HER2. Thus, these *HER2* mutants are resistant to geldanamycin-induced degradation, but they maintain their sensitivity to curcumin through ErbB-2 degradation.

EGFR is expressed at high levels in colorectal cancer and prostate cancer. Curcumin inhibits the growth of human colon cancer-derived Moser cells by suppressing expression of the *cyclinD1* and *EGFR* genes.[109] Curcumin also down-regulates EGFR signaling in prostate cancer cells by down-regulating levels of EGFR protein, inhibiting the

intrinsic EGFR tyrosine kinase activity, and by inhibiting ligand-induced activation of EGFR.[156]

Mitogen-Activated Protein Kinases. Mitogen-activated protein kinase (MAPK) pathways serve as an important target molecule for cancer prevention and therapy. The MAPK cascades include extracellular signal-regulated protein kinases (ERK), c-Jun N-terminal kinases/stress-activated protein kinases (JNK/SAPK), and p38 kinases. ERK are believed to be strongly activated and to play a critical role in transmitting signals initiated by growth-inducing tumor promoters, including TPA, EGF, and PDGF.[157,158] On the other hand, stress-related tumor promoters, such as UV irradiation and arsenic, potently activate JNK/SAPK and p38 kinases.[159-161] The MAPK pathway consists of a cascade in which a MAP3K activates a MAP2K, which activates a MAPK (ERK, JNK, and p38), resulting in activation of NF-κB, cell growth, and cell survival.[162]

Kim and coworkers recently reported that curcumin inhibited LPS-induced MAPK activation and translocation of NF-κB p65 in dendritic cells.[163] The ability of curcumin to modulate the MAPK signaling pathway might contribute to the inhibition of inflammation by curcumin. Salh and coworkers reported that curcumin is able to attenuate experimental colitis through reduction in the activity of p38 MAPK.[164] Chen and coworkers found that curcumin inhibits JNK activation induced by various agonists, including phorbol myristate acetate plus ionomycin, anisomycin, UV-C, gamma-radiation, TNF, and sodium orthovanadate.[94] Although both JNK and ERK activation by PMA plus ionomycin was suppressed by curcumin, the JNK pathway was more sensitive.

Other Protein Kinases. Curcumin can mediate its effects through modulation of various other protein kinases involved in the biochemical pathways responsible for carcinogenesis. Our group showed that highly purified protein kinase A (PKA), protein kinase C (PKC), protamine kinase (cPK), phosphorylase kinase (PhK), autophosphorylation-activated protein kinase (AK), and pp60c-src tyrosine kinase were all inhibited by treatment with curcumin. PhK was completely inhibited at a low concentration of curcumin.[165] At a curcumin concentration of around 0.1 mmol/L, PhK, pp60c-src, PKC, PKA, AK, and cPK were inhibited by 98%, 40%, 15%, 10%, 1%, and 0.5%, respectively.

Other investigators have shown suppression of PMA-induced activation of cellular PKC by curcumin.[166] Treatment of cells with 15 or 20 μM curcumin inhibited TPA-induced PKC activity in the particulate fraction by 26% or 60%, respectively, and did not affect the level of PKC. Curcumin also inhibited PKC activity in both cytosolic and particulate

fractions *in vitro* by competing with phosphatidylserine. The inhibitory effect of curcumin was reduced, however, after preincubation with the thiol compounds. These findings suggest that suppression of PKC activity may contribute to the molecular mechanism of inhibition of TPA-induced tumor promotion by curcumin.

Besides *in vitro* suppression, curcumin also can inhibit PKC in cells.[167] Hasmeda and coworkers showed that curcumin inhibited calcium- and phospholipid-dependent PKC and the catalytic subunit of cyclic AMP-dependent protein kinase (cAK; IC_{50} values, 15 and 4.8 μM, respectively).[167] Curcumin inhibits plant calcium-dependent protein kinase (IC_{50}, 41 μM), but does not inhibit myosin light chain kinase or a high-affinity 3′,5′-cyclic AMP-binding phosphatase. It inhibits cAK, PKC, and calcium-dependent protein kinase in a fashion that is competitive with respect to both ATP and the synthetic peptide substrate employed. The IC_{50} values for inhibition of cAK by curcumin are very similar when measured with kemptide (in the presence or absence of ovalbumin) or with casein or histone III-S as a substrate. However, the presence of bovine serum albumin (0.8 mg/mL) largely overcomes inhibition of cAK by curcumin.

The ubiquitously expressed nonreceptor tyrosine kinase c-Abl regulates stress responses induced by oxidative agents such as ionizing radiation and hydrogen peroxide. Curcumin has been shown to activate c-Abl, which in turn mediates the cell death response, in part through activation of JNK. Inhibition of Abl by STI571 treatment or downregulation of Abl expression through Abl-specific ShRNA diminished cell death induction and JNK activation induced by curcumin. Highlighting the interdependent nature of the Abl and JNK signaling in the curcumin-induced cell death response were the findings that JNK inhibitor caused very little cell death inhibition in STI571-pretreated cells and in Abl ShRNA-expressing cells.[168]

Farnesyl Protein Transferase

Ras proteins must be isoprenylated at a conserved cysteine residue near the carboxyl terminus (Cys-186 in mammalian Ras p21 proteins) to extend their biological activity. Studies indicate that an intermediate in the mevalonate pathway, most likely farnesyl pyrophosphate, is the donor of this isoprenyl group, and that using inhibitors of the mevalonate pathway could block the transforming properties of the *ras* oncogene. Chen and coworkers examined the effects of curcumin on farnesyl protein transferase (FPTase).[169] They found that partially purified FPTase capable of catalyzing the farnesylation of unprocessed

Ras p21 proteins *in vitro* was inhibited by curcumin and its derivatives. This is another potential mechanism by which curcumin could suppress cellular growth.

Kang and coworkers examined the effects of methanolic extracts of several diarylheptanoids, including curcumin, demethoxycurcumin, bisdemethoxycurcumin, bisdimethoxymethylcurcumin, and 1,2-dihydrobis(de-O-methyl)curcumin on FPTase activity. They found that the diarylheptanoids suppress FPTase activity with an IC_{50} varying from 29 to 50 μM. These results demonstrate that the inhibitory activity on FPTase depends on the structure of the diarylheptanoid.[170]

Adhesion Molecules

Cell adhesion molecules are transmembrane proteins that are required for binding of cells to other cells or other extracellular molecules. Expression of various cell surface adhesion molecules, such as intercellular cell adhesion molecule-1, vascular cell adhesion molecule-1, and endothelial leukocyte adhesion molecule-1, on endothelial cells is absolutely critical for tumor metastasis.[171] The expression of these molecules is regulated in part by NF-κB.[172] Curcumin blocks the cell surface expression of adhesion molecules in endothelial cells, and this accompanies suppression of tumor cell adhesion to endothelial cells.[173] We have demonstrated that downregulation of these adhesion molecules is mediated through downregulation of NF-κB activation.[173]

Curcumin can modify cell receptor binding.[174] Curcumin-treated B16F10 melanoma cells formed eight-fold fewer lung metastases in C57BL6 mice than untreated cells. Curcumin inhibits the binding of fibronectin, vitronectin, and collagen IV to the extracellular matrix (ECM) proteins. It also suppresses the expression of $\alpha 5\beta 1$ and $\alpha 5\beta 3$ integrin receptors, pp125 focal adhesion kinase (FAK), tyrosine phosphorylation of a 120-kD protein, and collagenase activity. Curcumin enhances the expression of antimetastatic proteins, TIMP-2, nonmetastatic gene 23 (Nm23), and E-cadherin. Gupta and Ghosh reported that curcumin inhibits TNF-induced expression of adhesion molecules on human umbilical vein endothelial cells. Jaiswal and coworkers showed that treatment with curcumin causes p53- and p21-independent G_2/M phase arrest and apoptosis in colon cancer cell lines.[110] Their results suggest that curcumin treatment impairs both Wnt signaling and cell–cell adhesion pathways, resulting in G_2/M phase arrest and apoptosis in HCT-116 cells.

Antiproliferative Effects

Curcumin suppresses the growth and proliferation of a wide variety of tumor cell lines of different tissue origins. The antiproliferative effect of curcumin is dependent on the cell type, concentration of curcumin, and duration of treatment. Curcumin inhibits the proliferation of tumor cells by suppressing the cell cycle regulatory proteins. Several proteins are known to regulate the timing of the events in the cell cycle, and loss of this regulation is the hallmark of cancer. Major control switches of the cell cycle are the cyclins and the cyclin-dependent kinases. Cyclin D1, a component subunit of Cdk4 and Cdk6, is a rate-limiting factor in progression of cells through the first gap (G_1) phase of the cell cycle.[138] Dysregulation of the cell cycle checkpoints and overexpression of growth-promoting cell cycle factors such as cyclin D1 and CDK are associated with tumorigenesis.[139] Cyclin D1 is overexpressed in many cancers, including those of the breast, esophagus, head and neck, and prostate.[140-144] Curcumin has been shown to inhibit progression of the cell cycle by down-regulating the expression of cyclin D1 at the transcriptional and posttranscriptional levels.[57,70] Curcumin arrested the cell cycle by preventing expression of cyclin D1, Cdk1, and cdc25. It inhibited the growth of transplantable tumors in different animal models and increased the life span of tumor-harboring animals.

Curcumin has antiproliferative effects in different types of cell lines *in vitro*. One of the initial reported descriptions of curcumin cytotoxicity occurred in Dalton's lymphoma ascites cells, in which curcumin at a concentration of 4 μg/mL produced 50% cytotoxicity. Curcumin also inhibited the growth of Chinese hamster ovary cells and human leukemic lymphocytes in culture.[175] At a concentration of 20 μg/mL, curcumin produced 50% growth arrest in K-562 human chronic myelogenous leukemia cells.[176]

One of the main mechanisms through which curcumin arrests cell growth is by inducing apoptosis. Curcumin also down-regulates expression of the Wilms' tumor-1 (*WT-1*) gene, which is highly overexpressed in leukemic blast cells of myeloid and lymphoid origin and serves as a marker for leukemic detection.[177] Moreover, expression of MEK-1, c-jun, and P210 bcr/abl were decreased by curcumin, ultimately retarding the *ras*-mediated signal transduction cascade and thus affecting the process of cell proliferation.[178] Curcumin suppressed the growth of several T-cell leukemia cell lines.[179] Its reduction of the expression of cyclin D1, cdk1, cdc-25, and survivin provided a way for the apoptotic machinery to act.[180] The survival

pathway mediated by the Akt-PI3K cascade was also inhibited by curcumin.[179]

Curcumin is highly cytotoxic toward several colon cancer cell lines. Curcumin blocked entry to the cell cycle from G_2 to M by inhibiting expression of cdc2/cyclin B.[110] The proapoptotic members of the Bcl-2 family, such as Bax, were activated, and antiapoptotic genes such as *Bcl-XL* were inhibited by curcumin.[181] Curcumin also triggers caspase-3-mediated cell death. It activated GADD153, which in turn acts as an activator of apoptosis.[182] Curcumin mediated the degradation of β-catenin, thus affecting the Wnt signaling pathway. The cell–cell adhesion pathway mediated by E-cadherin was also blocked by curcumin.[183] Thus, curcumin exerts its effects in colon cancer cell lines by induction of caspases, impairment of Wnt signaling events, inhibition of cell–cell adhesion, and blocking transition of the cell cycle from G_2 to M.

In the human hepatoma G2 cell line, the antiproliferative action of curcumin is mediated by suppression of the hepatocyte growth factor (HGF) and its receptor c-met.[184] In a dose- and time-dependent manner, curcumin induced p53-mediated apoptotic death in basal cell carcinoma cell lines.[185] Curcumin inhibited the growth of human head and neck squamous cell carcinoma cell lines by suppressing the expression of cyclin D1 and arresting the cell cycle in the G_1/S phase.[69] In human melanoma A375 cells, curcumin induced cell growth arrest in a time- and concentration-dependent manner by inhibiting the activity of the anti-apoptotic gene *XIAP* and elevated the levels of p53, p21, p27 (KIP1), and checkpoint kinase 2.[186]

Expression of cyclin D1 is regulated by NF-κB, and suppression of NF-κB activity by curcumin resulted in downregulation of cyclin D1 in multiple myeloma cells.[70] This led to a decrease in formation of the cyclin D1-Cdk4 holoenzyme complex, resulting in suppression of proliferation and induction of apoptosis. In another study, curcumin induced G_0/G_1 and/or G_2/M phase cell cycle arrest, up-regulated CDK inhibitors such as p21/Cip1/waf1 and p27Kip1, and down-regulated cyclin B1 and cdc2.[122] Choudhuri and coworkers reported that curcumin reversibly inhibited normal mammary epithelial cell cycle progression by down-regulating cyclin D1 expression and blocking its association with Cdk4/Cdk6 as well as by inhibiting phosphorylation and inactivation of the retinoblastoma protein.[150]

Apoptotic Effects

Apoptosis helps to establish a natural balance between cell death and cell renewal in mature animals by destroying excess, damaged, or

abnormal cells. The balance between survival and apoptosis, however, often tips toward the former in cancer cells. The major mechanism by which curcumin induces cytotoxicity in tumor cells is induction of apoptosis. Curcumin decreases the expression of antiapoptotic members of the Bcl-2 family and elevates the expression of p53, Bax, and procaspases-3, -8, and -9. Several NF-κB–regulated genes, including *Bcl-2*, *Bcl-XL*, *cIAP*, *survivin*, *TRAF1*, and *TRAF2*, have been reported to function primarily by blocking the apoptosis pathway.[187] Curcumin has been shown to suppress activation of NF-κB and the antiapoptotic genes regulated by NF-κB. It induces apoptosis through a mitochondrial pathway involving caspase-8, Bid cleavage, cytochrome C release, and caspase-3 activation. Our findings suggest that curcumin suppresses the constitutive expression of Bcl-2 and Bcl-XL in mantle cell lymphoma[59] and multiple myeloma[70] cell lines. Curcumin also activates caspase-7 and caspase-9 and induces PARP cleavage in both cell lines.

The serine/threonine protein kinase Akt/PKB has been considered an attractive target for cancer prevention and treatment. It is the cellular homologue of the viral oncogene *v-Akt* and is activated by various growth and survival factors. Akt plays critical roles in mammalian cell survival signaling and is active in various cancers.[188,189] Activated Akt promotes cell survival by activating the NF-κB signaling pathway[190,191] and by inhibiting apoptosis through inactivation of several proapoptotic factors, including Bad, Forkhead transcription factors, and caspase-9.[192-194] We have found that curcuminoids downregulate expression of cell proliferation and antiapoptotic and metastatic gene products through suppression of IKK and Akt activation.[195] Several reports by other investigators also suggest that curcumin has molecular targets within the Akt signaling pathways, and that inhibition of Akt activity may facilitate inhibition of proliferation and induction of apoptosis in cancer cells.[196,197] Curcumin completely inhibited Akt activation in the human prostate cancer cell lines LNCaP and PC-3 cells, suggesting that curcumin may inhibit prostate cancer growth via inhibition of Akt.[150]

Curcumin also suppressed the growth of several T-cell leukemia cell lines in a dose-dependent manner.[179] Curcumin was found to be highly cytotoxic toward several malignant colon cancer cell lines.[198] Curcumin activates GADD153, which in turn acts as an activator of apoptosis.[182] In the human hepatoma G2 cell line, the cytotoxic action of curcumin is mainly through inducing DNA damage of both the nuclear and the mitochondrial genome. Curcumin induced p53-mediated apoptotic death in a dose- and time-dependent fashion in basal cell carcinoma lines.[185] In several types of human melanoma cells, curcumin induces apoptosis

through the Fas receptor/caspase-8 pathway independent of p53 and suppresses the antiapoptotic gene *XIAP*.[119]

In some other cell lines, curcumin mediates its cytotoxic action by generating reactive oxygen species (ROS). Although curcumin is a potent scavenger of free radicals, there are reports describing its potential for generating free radicals.[199] In human submandibular gland carcinoma cell line HSG, curcumin at a very low concentration (>15 μM) generated ROS that caused damage to mitochondria, as evinced by decrease in the mitochondrial membrane potential and externalization of phosphatydyl serine, and the whole process eventually ended up in the initiation of apoptosis.[200] In human gingival fibroblasts, moreover, treatment with curcumin produced dose-dependent generation of ROS, to which its cytotoxic activity was attributed.[200] The growth-suppressive effect of curcumin on follicular lymphoma cells also was mediated by generation of ROS. Flow cytometry and western blotting analysis revealed that curcumin shifted the equilibrium of Bcl-2 family members toward apoptosis and initiated caspase-mediated cell death in these cell lines.[201]

Curcumin has been shown to sensitize TNF-related apoptosis-inducing ligand (TRAIL)-mediated apoptosis through up-regulation of death receptor 5 (DR5). DR5 is an apoptosis-inducing membrane receptor for TRAIL. Both treatment with DR5/Fc chimeric protein and silencing of DR5 expression using small-interfering RNA attenuated curcumin plus TRAIL-induced apoptosis, showing the critical role of DR5 in apoptosis. Curcumin also induced expression of a potential proapoptotic gene,

C/EBP homologous protein (*CHOP*), at both mRNA and protein levels. Suppression of *CHOP* expression by small-interfering RNA did not, however, abrogate the curcumin-mediated induction of DR5 and the cell death induced by curcumin plus TRAIL, demonstrating that CHOP is not involved in curcumin-induced DR5 up-regulation.[202] In a previous report, these investigators had shown that curcumin sensitized TRAIL-induced apoptosis through ROS-mediated up-regulation of DR5.[203]

Chemokines and Metastasis

Chemokines are small, chemotactic cytokines that direct migration of leukocytes, activate inflammatory responses, and participate in regulation of tumor growth. Most chemokines are expressed in response to a stimulus, but some are constitutively expressed in a tissue-specific manner. Chemokines exert their migration-inducing properties on leukocytes through binding to chemokine receptors. IL-8 (CXCL8) was the first chemokine discovered to stimulate endothelial cell chemotaxis, prolifer-

ation, and *in vivo* angiogenesis.[204] Elevated levels of the angiogenic CXC chemokine IL-8 have been detected in a variety of tumors.

Curcumin inhibits production of proinflammatory chemokines, including IL-8, by tumor cells. Curcumin inhibited both IL-8 production and signal transduction through IL-8 receptors. It suppressed constitutive production of IL-8 in human pancreatic carcinoma cell lines and enhanced the expression of two IL-8 receptors, CXCR1 and CXCR2.[205] Curcumin down-regulated the expression of monocyte chemoattractant protein 1 (MCP-1)[206] and interferon-inducible protein-10kD (IP-10) in a mouse bone marrow stromal cell line by down-regulating the levels of *MCP-1* and *IP-10* mRNA expression induced by TNF, IL-1, and LPS. The suppressive effects of curcumin on both these chemokine mRNAs were reversible; the cells recovered complete from this suppression within 24 hours after removal of curcumin.[207]

Metastasis is the process by which cancer cells migrate from the tissue of origin to other distant sites through the blood circulation to form new malignant lesions in other organs. Curcumin is highly antimetastatic in nature. Curcumin inhibited the formation of lung nodules induced by B16F-10 melanoma cells by 89.3% and increased the life span of C57BL/6 mice implanted with these cells by 143.9%. The invasive property of B16F-10 melanoma cells across the collagen matrix was inhibited by curcumin, as shown by the Boyden chamber assay. Zymographic analysis showed that curcumin inhibited the activities of MMP-2 and MMP-9.[208,209] Curcumin also down-regulated the activities of membrane type 1 MMP (MT1-MMP) and FAK (which plays a role in the integrin-mediated signal transduction cascade) in B16F-10 melanoma cells.[210] Curcumin-treated B16F-10 cells showed a marked reduction in the expression of alpha5 beta1 and alpha5 beta3 integrin receptors. Curcumin also enhanced the expression of antimetastatic proteins TIMP-2, Nm23, and E-cadherin, which reduced the metastatic tendency of the melanoma cells.[174]

Curcumin was highly antimetastatic against DU145 prostate cancer cells both *in vitro* and *in vivo*. It reduced the metastatic activity of DU145 in a xenograft tumor model. Administration of curcumin produced a marked decrease in tumor volume and levels of MMP-2 and MMP-9.[211] In a human breast cancer xenograft model, administration of curcumin markedly decreased metastasis to lung and suppressed expression of NF-κB, MMP-9, COX-2, VEGF, and intercellular adhesion molecule-1.[76]

TPA induces profound expression of COX-2 and MMP-9 in human breast epithelial MCF10A cells, thereby elevating the levels of prostaglandins and the invasive and metastatic tendencies of the cells. Treat-

ment of the cells with curcumin inhibited the expression of COX-2 and MMP-9, which in turn altered the invasive and metastatic properties of the cells.[212]

Osteopontin, a type of ECM protein, has been found to be overexpressed in various types of cancer. Osteopontin increases the ability of tumor cells to survive and metastasize to other distant organs. It stimulates expression of pro-MMP-2 and MT1-MMP through an NF-κB-mediated pathway in murine B16F-10 melanoma cells. The osteopontin-mediated expression of NF-κB, proMMP-2, and MT1-MMP were suppressed by curcumin in a nude mouse model.[213]

Curcumin reduced the metastasis of tumors in Long Evans Cinnamon rats, which develop tumors in the kidney and the liver because of an aberrant copper transporting ATPase gene. These rats accumulate copper in their body. Although treatment with curcumin failed to prevent induction of primary tumors in the kidney and the liver, it did reduce metastasis of tumors to other sites.[214]

Angiogenesis

Tumor angiogenesis is the proliferation of a network of blood vessels that penetrates into a cancerous growth, supplying nutrients and oxygen and removing waste products. For most solid tumors, angiogenesis is essential for tumor growth and metastasis.[215] Tumor angiogenesis actually starts with cancerous tumor cells releasing molecules that send signals to surrounding normal host tissue. More than a dozen different proteins (eg, bFGF, EGF, granulocyte colony-stimulating factor, IL-8, PDGF, TGF-α, TNF, VEGF), as well as several smaller molecules (eg, adenosine, prostaglandin E), have been identified as angiogenic factors released by tumors as signals for angiogenesis. Among these molecules, VEGF and bFGF appear to be the most important for sustaining tumor growth. VEGF and bFGF are produced by many kinds of cancer cells (and by certain types of normal cells).

The precise mechanism that leads to angiogenesis is not fully understood, but growth factors that cause proliferation of endothelial cells have been shown to play a critical role in this process. Curcumin has been shown to suppress the proliferation of human vascular endothelial cells *in vitro*[216] and to abrogate the FGF-2-induced angiogenic response *in vivo*,[217] suggesting that curcumin is also an antiangiogenic factor. The effect of curcumin on endothelial cell migration, attachment and tube formation on Matrigel was studied by Thaloor and coworkers Curcumin had no effect on endothelial cell migration or attachment to either plastic or Matrigel, but caused a dose-dependent inhibition of tube formation

when the cells were treated before plating or at the time of plating on Matrigel. Curcumin treatment inhibited angiogenesis in a subcutaneous Matrigel plug model in mice and caused the preformed tubes to break down.[218]

CD13/aminopeptidase N (APN) is a membrane-bound, zinc-dependent metalloproteinase that plays a key role in tumor invasion and angiogenesis. Shim and coworkers observed that curcumin binds to APN and irreversibly inhibits its activity.[219] Curcumin has been shown to suppress angiogenesis *in vivo*.[220] Dorai and coworkers reported that curcumin inhibited angiogenesis of LNCaP prostate cancer cells *in vivo*.[221]

To elucidate possible mechanisms of antiangiogenic activity by curcumin, Park and coworkers performed cDNA microarray analysis and found that curcumin modulated cell cycle-related gene expression.[122] Specifically, curcumin induced G_0/G_1 and/or G_2/M cell cycle arrest, up-regulated CDK inhibitors p21WAF1/CIP1, p27KIP1, and p53, and slightly down-regulated cyclin B1 and cdc2 in ECV304 cells. The up-regulation of CDK inhibitors by curcumin played a critical role in regulation of cell cycle distribution in these cells, which may underlie the antiangiogenic activity of curcumin.

Curcumin also inhibits MMP-2, which is implicated in the formation of loose and primitive-looking meshwork formed by aggressive cancers such as melanoma and prostate cancers. Gelatinase A (MMP-2) and gelatinase B (MMP-9) are metalloproteinases that cause the formation of new capillaries by activating growth factors, and curcumin has been shown to inhibit the gelatinolytic activities of secreted 53- and 72-kDa MMP and to suppress expression and transcription of the 72-kDa MMP, indicating its inhibitory effects at both the transcriptional and posttranscriptional levels. Gelatinase B expression is induced by the transcription factor AP-1, which in turn is regulated by FGF-2, and this expression is inhibited by curcuminoids.[173,222] In studies using corneal implantation pellets, FGF-2 pellets were inhibited by coimplantation of a curcuminoid pellet, and this correlated with inhibition of endogenous gelatinase B expression. These results provide evidence that curcuminoids inhibit expression of gelatinase B and target the FGF-2 angiogenic signaling pathway and also that curcumin acts as an angiogenesis inhibitor by modulating matrix metalloproteinases.

This plasticity of the cancer cells mimicking the endothelial cells is mainly brought about by the capacity of the cancer cells to express endothelium-associated genes, such as *VE-Cadherin*, *Src*, *FAK*, and PI-3 kinases, all of which are good targets for curcumin. Most notably, curcumin also can interfere with the expression of VEGF by processes

other than hypoxia, such as TGF-β release, COX-2 overexpression, hydrogen peroxide release from bone cells, constitutive and aberrant EGFR and Src signaling and, most importantly, aberrant NF-κB signaling in established cancers.[223]

Curcumin's antiangiogenic property is due in part to its inhibitory action on the serine proteinase family urokinase plasminogen activator system (uPA). uPA interacts with a specific receptor via the EGF-like domain in the urokinase amino-terminal fragment.[224] Its angiogenic effect is due to its effect on the migration of endothelial cells and through activation and/or release of several angiogenic factors, such as FGF, TGF, TNF, HGF, and VEGF. In mouse keratinocytes, uPA expression and secretion is increased by TGF-β1. Curcumin decreases the uPA levels induced by TGF-β1 in transformed keratinocytes; inhibits the TGF-β-induced synthesis of fibronectin, an early response gene to the growth factor; and reduces TGF-β-stimulated cell migration and invasiveness.[225] It modulates EGF-stimulated uPA production, which involves activation of the extracellular signal-regulated kinases 1/2 and JNK signaling pathways and also inhibits phosphorylation of the EGFR.[226] In a study by Parra and coworkers,[227] uPA induced by N-methyl-N′-nitro-N-nitrosoguanidine was inhibited by curcumin. Curcumin blocked binding of AP-1 to the uPA enhancer element to abrogate uPA secretion.[227]

Chemosensitizing Effects

Chemosensitivity is the susceptibility of tumor cells to the cell-killing effects of anticancer drugs. Most of the chemotherapeutic agents frequently induce drug resistance. HER2, a growth factor receptor overexpressed in breast cancer, has been implicated in paclitaxel-induced resistance, probably through activation of NF-κB. Acquired resistance to chemotherapetic agents is most likely mediated through a number of mechanisms, including the multidrug resistance (MDR) protein. Multidrug resistance is a phenomenon often associated with decreased intracellular drug accumulation in the tumor cells of a patient, resulting from enhanced drug efflux. It is often related to overexpression of P-glycoprotein on the surface of tumor cells, thereby reducing drug cytotoxicity. Curcumin has been shown to augment the cytotoxic effects of chemotherapeutic drugs, including doxorubicin,[228] tamoxifen,[229] cisplatin and camptothecin, daunorubicin, vincristine, and melphalan.[70] Paclitaxel has a major disadvantage in that its dose is limited by toxicity. Bava and coworkers reported that combination of paclitaxel with curcumin yields greater anticancer effects than paclitaxel alone. At the cellular level, this combination augments activation of caspases and cytochrome C re-

lease.[230] Similarly, the combination of curcumin with cisplatin resulted in synergistic antitumor activity in the hepatic cancer HA22T/VGH cell line, which constitutively expresses activated NF-κB. Combination of curcumin with cisplatin led to additive decreases in the expression of c-myc, Bcl-X_L, c-IAP-2, and XIAP.[231]

Curcumin is cytotoxic to doxorubicin-resistant B16-R murine melanoma cells, either cultivated as monolayers or grown in three-dimensional cultures (i.e., spheroids). The combination of a prophylactic immune preparation of soluble proteins from B16-R cells and treatment with curcumin on tumor appearance resulted in substantial inhibition of growth of B16-R cells, whereas either treatment by itself showed little effect. Moreover, animals receiving the combination therapy exhibited enhancement of their humoral antisoluble B16-R protein immune response and a significant increase in median survival time.[232]

NF-κB has been implicated in the development of drug resistance in cancer cells. The basal level of NF-κB activity is heterogeneous in various cancer cells and roughly correlates with drug resistance. Curcumin has been shown to downregulate doxorubicin-induced NF-κB activation.[233] MDR is a major cause of chemotherapy failure in cancer patients. One of the resistance mechanisms is overexpression of drug efflux pumps such as P-glycoprotein and multidrug resistance protein 1 (MRP1, ABCC1). On treatment with etoposide in the presence of 10 μM curcuminoids, the sensitivity of etoposide was increased severalfold in MRP1-expressing HEK 293 cells.[234] Curcumin also decreased P-glycoprotein function and expression and promotion of caspase-3 activation in MDR gastric cancer cells. Treatment of these cells with curcumin decreased the IC_{50} value of vincristine and promoted vincristine-mediated apoptosis in a dose-dependent manner. Moreover, curcumin reversed the MDR of the human gastric carcinoma SGC7901/VCR cell line.[235] Curcumin decreased P-glycoprotein expression in a concentration-dependent manner and had the same effect on *MDR1* mRNA levels.[236,237]

The effect of curcumin on apoptosis in MDR cell lines has been reported. Piwocka and coworkers demonstrated that curcumin induced cell death in MDR CEM(P-gp4) and LoVo(P-gp4) cells and that this effect was independent of caspase-3.[238] Mehta and coworkers also examined the antiproliferative effects of curcumin against MDR cell lines, which were found to be highly sensitive to curcumin. The growth-inhibitory effect of curcumin was time- and dose-dependent, and correlated with its inhibition of ornithine decarboxylase activity. Curcumin preferentially arrested cells in the G_2/S phase of the cell cycle.[239]

Subtoxic concentrations of curcumin sensitize human renal cancer cells

to TRAIL-mediated apoptosis. Apoptosis induced by the combination of curcumin and TRAIL is not interrupted by Bcl-2 overexpression. Treatment with curcumin significantly induced DR5 expression accompanying generation of ROS.[203] Curcumin causes cell death in melanoma cell lines with mutant p53. Such cells are strongly resistant to conventional chemotherapy, but curcumin overcomes the chemoresistance of these cells and provides potential new avenues for treatment.[119]

Radiosensitizing Effects

Radiotherapy plays an important role in the management of cancers. Radiotherapy helps in achieving local control of tumors following surgery in patients with early stage cancer, but radiotherapy alone fails to suppress the tumors that recur and become radioresistant. The factors governing radioresistance in patients whose cancer recurs are still not clear. Several studies have shown that curcumin sensitizes tumor cells to radiation therapy.

Chendil and coworkers investigated the radiosensitizing effects of curcumin in p53-mutant prostate cancer cell line PC-3.[240] Compared with cells that were only irradiated, cells treated with curcumin at 2 and 4 μM concentrations in combination with radiation showed significant enhancement of radiation-induced clonogenic inhibition and apoptosis. Radiation up-regulated TNF-α protein in these cells, leading to an increase in NF-κB activity and induction of Bcl-2 protein. Curcumin, in combination with radiation, inhibited TNF-α-mediated NF-κB activity, resulting in bcl-2 protein downregulation. These results suggest that curcumin is a potent radiosensitizer, and it acts by overcoming the effects of radiation-induced prosurvival gene expression in prostate cancer.

Khafif and coworkers investigated whether curcumin can sensitize squamous cell carcinoma cells to the ionizing effects of irradiation. Incubation with curcumin only (3.75 μM) for 48 hours did not decrease the number of cells or the ability to form colonies in the absence of radiation. In plates that were exposed to 1 to 5 Gy of radiation, however, cell counts dropped significantly if pretreated with curcumin; the maximal effect was at 2.5 Gy. The colonogenic assay revealed a significant decrease in the ability to form colonies following pretreatment with curcumin at all radiation doses.[241] Thus, curcumin may serve as an adjuvant in radiotherapy.

Another study examined the effect of turmeric and curcumin on the frequencies of chromosome aberrations in Chinese hamster ovary cells exposed to 2.5 Gy of gamma-radiation. Treatment of these cells with 100, 250, or 500 mg/mL turmeric or 2.5, 5, or 10 mg/mL curcumin, before

exposure to 2.5 Gy of gamma-radiation during different phases of the cell cycle, increased the frequencies of chromosome aberrations. Turmeric at 500 mg/mL elevated the frequency of chromosome aberrations during G_2/S phase, whereas curcumin at 10 mg/mL increased these frequencies during S and G_2/S phases of the cell cycle. The results clearly indicate the exacerbated effect of turmeric and curcumin on radiation-induced clastogenicity, suggesting that these antioxidants are also potentiating agents depending on the experimental conditions. Turmeric was not clastogenic by itself, whereas curcumin at 10 mg/mL increased the chromosomal damage frequency.[242]

Radioprotective Effects

Findings of several studies suggest that curcumin is radioprotective. Oral administration of curcumin at doses of 5, 10, or 20 mg/kg of body weight significantly reduced the frequencies of micronucleated polychromatic erythrocytes in mice that underwent whole-body exposure to 1.15 Gy or 0.05 Gy/s of gamma-radiation at 24, 30, or 48 hours postirradiation. This effect was observed after a single administration of curcumin either 2 hours before or immediately after irradiation.[243] Thresiamma and coworkers showed that curcumin protects from radiation-induced toxicity. In their study, whole-body irradiation of rats (10 Gy in five fractions) produced lung fibrosis within 2 months as seen from increased lung collagen hydroxyproline and histopathologic examination. Oral administration of curcumin (200 μmole/kg of body weight) significantly reduced the lung collagen hydroxyproline. In serum and liver, lipid peroxidation increased by irradiation was reduced significantly by curcumin treatment. The activity of superoxide dismutase and glutathione peroxidase in the liver, increased by radiation, was reduced significantly by curcumin. This study also corroborated the findings of Abraham and coworkers, in that curcumin again significantly reduced the increased frequency of micronucleated polychromatic erythrocytes in mice induced by whole-body irradiation.[244] In another study, Thresiamma and coworkers investigated the protective effect of curcumin on radiation-induced genotoxicity. They showed that induction of micronuclei and chromosomal aberrations produced by whole-body exposure to γ-radiation (1.5-3.0 Gy) in mice was significantly inhibited by oral administration of curcumin (400 μmoles/kg body weight); curcumin also inhibited micronucleated polychromatic and normochromatic erythrocytes, significantly reduced the number of bone marrow cells with chromosomal aberrations

and chromosomal fragments, and inhibited radiation-induced DNA strand breaks in lymphocytes as seen from DNA unwinding studies.[245]

Inano and Onoda investigated the radioprotective action of curcumin on formation of urinary 8-hydroxy-2′-deoxyguanosine, tumorigenesis, and death induced by gamma-radiation.[246] Evaluation of the protective action of dietary curcumin (1%, w/w) against the long-term effects of gamma radiation revealed that curcumin significantly decreased the incidence of mammary and pituitary tumors. Curcumin did not prolong survival, however, when administered for 3 days before and/or 3 days after irradiation (9.6 Gy). These findings demonstrate that curcumin is an effective radioprotective agent, inhibiting acute and chronic effects, but not death, after irradiation.

Exactly how curcumin provides radioprotection is not fully understood. There are studies that indicate, however, that curcumin can inhibit the radiation-induced damage of specific proteins.[247] Varadkar and coworkers examined the effect of curcumin on radiation-induced PKC activity isolated from the liver cytosol and the particulate fraction of unirradiated mice and mice irradiated at 5 Gy. Following irradiation, the PKC activity was increased in both cytosolic and particulate fractions. Curcumin inhibited the activated cytosolic and particulate PKC at very low concentrations.[248] Since activation of PKC is one of the means of conferring radioresistance on a tumor cell, suppression of PKC activity by curcumin may be a method of preventing development of radioresistance following radiotherapy.

Another potential mechanism of radioprotection involves suppression of radiation-induced gene expression. Oguro and Yoshida examined the effect of curcumin on UV-A-induced ornithine decarboxylase (*ODC*) and metallothionein (*MT*) gene expression in mouse skin.[249] They showed that UV-A induced *MT* mRNA in mouse skin, and that 1,4-diazabicylo-[2,2,2]-octan, a singlet oxygen scavenger, reduced UV-A–mediated induction of *MT* mRNA (by 40%). UV-A slightly enhanced TPA-mediated *ODC* mRNA induction, while it enhanced ODC enzyme activity by 70%. UV-A additively intensified TPA-mediated *MT* mRNA induction. Curcumin dramatically inhibited both TPA^{-} and TPA^{+} UV-A-induced expression of the *ODC* and *MT* genes.

Curcumin up-regulates enzymes such as catalase, glutathione transferase, glutathione peroxidase, and superoxide dismutase, and their mRNAs. It has been reported to scavenge free radicals, increase antioxidant status, inhibit lipid peroxidation, and elevate levels of glutathione and sulfhydryl groups.[248,250-256] All these mechanisms may account, in part, for the radioprotective effects of curcumin.

In Vivo Studies

Several animal models have been employed to investigate the antitumor and anticarcinogenic effects of curcumin. The mechanisms by which curcumin suppresses carcinogenesis have been investigated in several animal tumor systems, including skin, colon, lung, duodenum, stomach, esophagus, and oral cavity.

Kuttan and coworkers[175] examined the anticancer potential of curcumin *in vivo* by using Dalton's lymphoma cells grown as ascites in mice. Initial experiments indicated that curcumin reduced the development of animal tumors. Curcumin was encapsulated (5 mg/mL) into neutral and unilamellar liposomes prepared by sonication of phosphatidylcholine and cholesterol. An aliquot of liposomes (50 mg/kg) was administered intraperitoneally to mice the day after instillation of the Dalton's lymphoma cells, and this treatment was continued daily for 10 days. Surviving animals were counted 30 days and 60 days after completion of treatment. All animals treated with liposomal curcumin survived 30 days, and only two of the animals developed tumors and died before 60 days.

The effects of curcumin on several skin carcinogenesis models have been investigated. Topical application of curcumin together with tumor promoter TPA, twice weekly for 20 weeks to female CD-1 mice previously initiated with dimethylbenzanthracene (DMBA), strongly inhibited TPA-induced papilloma formation.[257,258] In a related study, topical application of relatively low doses of curcumin (20 or 100 nmol) markedly abrogated TPA-induced tumor promotion.[259] In other studies, dietary administration of 2% turmeric significantly inhibited DMBA plus TPA-induced skin tumor formation in female Swiss mice.[260] In a benzo[*a*]pyrene-initiated and TPA-promoted two-stage skin tumorigenesis model, curcumin reduced the number of tumors per mouse and decreased the number of tumor-bearing mice.

Busquets and coworkers showed that systemic administration of curcumin for 6 consecutive days to rats bearing the highly cachectic Yoshida AH-130 ascites hepatoma resulted in inhibition of tumor growth.[261] Interestingly, curcumin was also able to reduce *in vitro* tumor cell content by 24% at concentrations as low as 0.5 μM without promoting any apoptotic events. Although systemic administration of curcumin has been shown to facilitate muscle regeneration, administration of the compound to tumor-bearing rats did not result in any changes in muscle wasting, when compared with the untreated tumor-bearing animals. Curcumin attenuated the *N*-nitrosodiethylamine (DENA)-initiated and phenobarbital-promoted formation of hepatic hyperplastic nodules, body weight loss,

and hypoproteinemia in Wistar rats.[262] The chemopreventive effect of curcumin was also demonstrated in a murine hepatocarcinogenesis model. Five-week-old C3H/HeN mice were injected intraperitoneally with DENA. One group of the mice was fed a 0.2% curcumin-containing diet, starting 4 days before DENA injection and until termination of the experiment. At the age of 42 weeks, the curcumin group had 81% less multiplicity and 62% fewer hepatocarcinomas than the no-curcumin group.[263]

Menon and coworkers reported curcumin-induced inhibition of B16F10 melanoma lung metastasis in mice.[208] Oral administration of curcumin reduced the number of lung tumor nodules by 80%. The life span of the animals treated with curcumin was increased by 143.85%.[208] Moreover, lung collagen hydroxyproline and serum sialic acid levels were significantly lower in treated animals than in the untreated controls. Curcumin treatment significantly inhibited the invasion of B16F-10 melanoma cells across the collagen matrix of a Boyden chamber. Curcumin treatment did not inhibit the motility of B16F-10 melanoma cells across a polycarbonate filter *in vitro*. These findings suggest that curcumin inhibits the invasion of B16F-10 melanoma cells by inhibition of MMP, thereby inhibiting lung metastasis.

Curcumin decreases the proliferative potential and increases the apoptotic potential of both androgen-dependent and androgen-independent prostate cancer cells *in vitro*, largely by modulating the apoptosis suppressor proteins and by interfering with the growth factor receptor signaling pathways as exemplified by the EGFR. To extend these observations, Dorai and coworkers investigated the anticancer potential of curcumin in a nude mouse prostate cancer model.[221] The androgen-dependent LNCaP prostate cancer cells were grown, mixed with Matrigel, and injected subcutaneously. The experimental group received a synthetic diet containing 2% curcumin for up to 6 weeks. At the endpoint, mice were killed, and sections taken from the excised tumors were evaluated for pathology, cell proliferation, apoptosis, and vascularity. Results showed that curcumin induced a marked decrease in the extent of cell proliferation as measured by the BrdU incorporation assay and a significant increase in the extent of apoptosis as measured by an in situ cell death assay. Moreover, microvessel density as measured by CD31 antigen staining decreased significantly. The investigators concluded that curcumin is a potentially therapeutic anticancer agent, as it significantly inhibited prostate cancer growth, as exemplified by LNCaP *in vivo*, and that curcumin has the potential to prevent progression of this cancer to its hormone-refractory state. Aggarwal and coworkers recently reported that

curcumin inhibits growth and survival of human head and neck squamous cell carcinoma cells via modulation of NF-κB signaling.[69]

The chemopreventive activity of curcumin was observed when it was administered before, during, and after carcinogen treatment as well as when it was given only during the promotion/progression phase of colon carcinogenesis.[264] Collett and coworkers investigated the effects of curcumin on apoptosis and tumorigenesis in male apc (min) mice treated with the human dietary carcinogen 2-amino-1-methyl-6-phenylimidazo-[4,5-b]pyridine (PhIP).[265] Curcumin enhanced PhIP-induced apoptosis and inhibited PhIP-induced tumorigenesis in the proximal small intestine of Apc (min) mice. Mahmoud and coworkers investigated the effect of curcumin for the prevention of tumors in Min/$^{+}$ mice, which bear a germline mutation in the *apc* gene and spontaneously develop numerous intestinal adenomas by 15 weeks of age.[111] A dietary level of 0.15% curcumin decreased tumor formation in Min$^{-/-}$ mice by 63%. Examination of intestinal tissue from the treated animals showed the tumor prevention by curcumin was associated with increased enterocyte apoptosis and proliferation. Curcumin also decreased expression of the oncoprotein β-catenin in the erythrocytes of the Min/$^{+}$ mouse, an observation previously associated with an antitumor effect.

Perkins and coworkers also examined the preventive effect of curcumin on the development of adenomas in the intestinal tract of the Min/$^{+}$ mouse, a model of human familial adenomatous polyposis.[266] These investigators explored the link between the chemopreventive potency of curcumin in the Min/$^{+}$ mouse and levels of drug and metabolites in target tissue and plasma. Mice received dietary curcumin for 15 weeks, after which adenomas were enumerated. Whereas curcumin at 0.1% in the diet was without effect, at 0.2% and 0.5% it reduced adenoma multiplicity by 39% and 40%, respectively.

Male F344 rats fed a diet containing curcumin at a dose of 0.5 g/kg during the initiation and postinitiation stages exhibited 91% reduction in the frequency of 4-nitroquinoline-1-oxide-induced tongue carcinoma.[267] The incidence of oral preneoplasia was also decreased by curcumin administration. Likewise, dietary curcumin significantly inhibited *N*-nitrosomethylbenzylamine-induced esophageal carcinogenesis in rats when given during the postinitiation as well as the initiation phases.[268] In Syrian golden hamsters, curcumin treatment protected against DMBA-induced or methyl-(acetoxymethyl)-nitrosamine-induced oral mucosal tumorigenesis.[269,270]

Odot and coworkers showed that curcumin was cytotoxic to B16-R melanoma cells resistant to doxorubicin and demonstrated that the

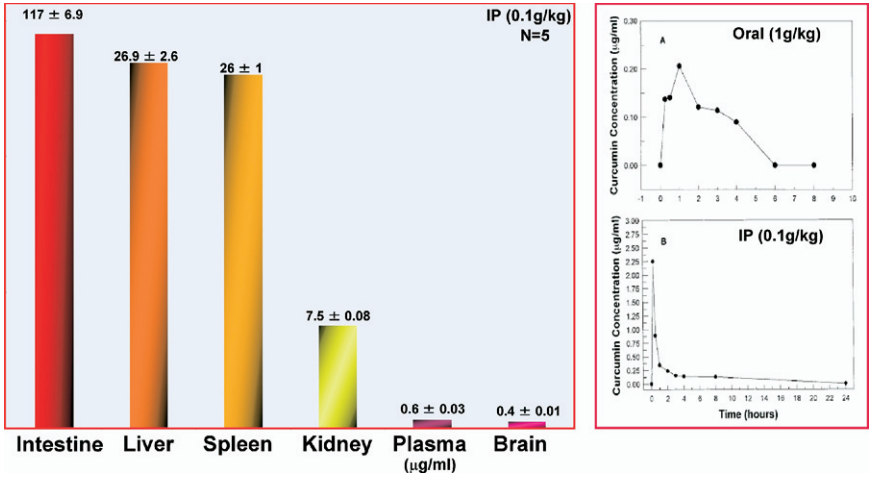

FIG 2. Plasma and tissue distribution of curcumin.[271] (Color version of figure is available online.)

observed cytotoxic effect was due to induction of programmed cell death.[232] They examined the effectiveness of a prophylactic immune preparation of soluble proteins from B16-R cells, or a treatment with curcumin as soon as tumoral appearance, alone or in combination on B16-R melanomas in mice. The combination treatment resulted in substantial inhibition of growth of B16-R melanomas, whereas each treatment by itself showed little effect. Moreover, animals receiving the combination therapy exhibited enhancement of their humoral antisoluble B16-R protein immune response and a significant increase in their median survival time (>82.8% versus 48.6% and 45.7%, respectively, for the immunized only group and the curcumin only group).

Pan and coworkers[271] investigated the pharmacokinetic properties of curcumin in mice (Fig 2). After intra peritoneal administration of curcumin (0.1 g/kg) to mice, about 2.25 μg/mL of curcumin appeared in the plasma in the first 15 minute. One hour after administration, the levels of curcumin in the intestine, spleen, liver, and kidney were 177.04, 26.06, 26.90, and 7.51 μg/g, respectively. Only traces (0.41 μg/g) were observed in the brain at 1 hour. Treatment of the plasma with beta-glucuronidase resulted in a decrease in the concentrations of these two putative conjugates and the concomitant appearance of tetrahydrocurcumin and curcumin. Ryu and coworkers[272] examined the biodistribution of fluoropropyl-substituted curcumin in mice. They found that curcumin was

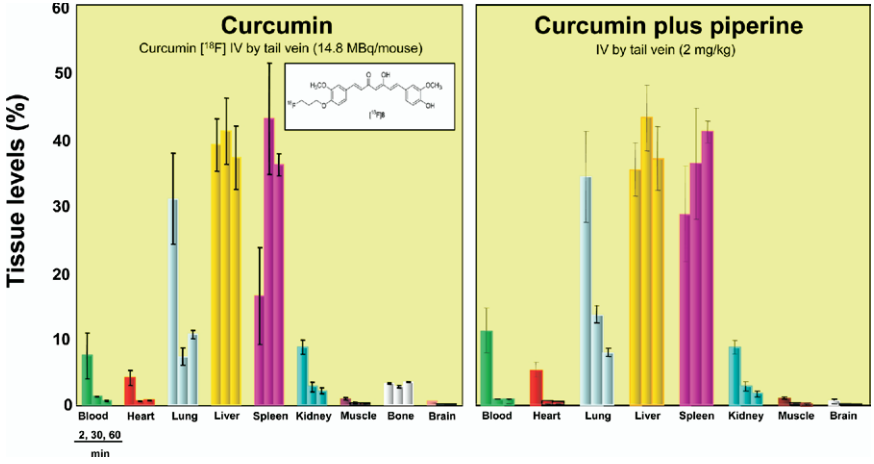

FIG 3. Tissue distribution of curcumin in mice.[272] (Color version of figure is available online.)

available in blood, heart, lung, liver, spleen, kidney, bone, and brain (Fig 3).

Clinical Trials with Curcumin

Several pilot clinical trials have been reported using curcumin (Table 1). There are additional phase II clinical trials for various diseases with curcumin that are ongoing (Table 2). Despite its proven safety over centuries of use in south Asian countries, over a dozen clinical studies evaluating the safety and efficacy of curcumin in humans have already been reported. Phase I study of curcumin in humans was reported by Cheng and coworkers in 2001. These investigators examined the toxicology, pharmacokinetics, and biologically effective dose of curcumin in humans.[273] This prospective phase I study evaluated curcumin in patients with the premalignant high-risk conditions, such as recently resected urinary bladder cancer, arsenic Bowen's disease of the skin, uterine cervical intraepithelial neoplasm, oral leukoplakia, and intestinal metaplasia of the stomach. The study subjects took curcumin at doses of 500, 1000, 2000, 4000, or 8000 mg daily for 3 months. The dose was escalated to the next level when less than one-third of three to six patients at certain dose level experienced toxicity greater than grade 1 during the 3-month treatment period. A total of 25 patients were enrolled in this study. The results revealed no treatment-related toxicity at doses up to 8000 mg/d for 3 months. Further escalation of curcumin dose was prohibited, however, because of the bulky volume of curcumin tablets.

TABLE 1. Clinical studies with curcumin

No.	Study	Subjects	Dose	Comments	Reference
1	Double blind crossover study	18 patients (22-48 years)	1200 mg/day 2 weeks	Antirheumatic	Deodhar et al., 1980[28]
2	Double blind crossover study	46 male patients (15-68 years)	400 mg; 3×/day 5 days	Inguinal hernia	Satoskar et al., 1986[281]
4	Double blind crossover study	10 volunteers	500 mg/day 7 days	Serum cholesterol, LPO	Soni and Kuttan, 1992[285]
3	Double blind crossover study	62 patients (40-85 years)	Topical	HNSCC, breast, vulva, skin	Kuttan et al., 1987[286]
5	Double blind crossover study	40 patients	625 mg; 4×/day 8 weeks	Well tolerated	James, 1994[287]
6	Double blind crossover study	53 patients	375 mg; 3×/day 12 weeks	Chronic anterior uveitis	Lal et al., 1999[279]
7	Double blind crossover study	8 patients	375 mg; 3×/day 6-22 months	Idiopathic inflammation, Orbital pseudotumors	Lal et al., 2000[280]
8	Prospective Phase I trial	25 patients	500-1200 mg/day 3 months	Head and Neck cancers	Cheng et al., 2001[273]
9	Prospective Phase I trial	15 patients	36-180 mg 4 months	Colorectal cancers, serum GST down	Sharma et al., 2001[274]
10	Prospective Phase I trial	24 healthy volunteers	500-12,000 mg single oral dose	Prevention of colon cancer, Maximum tolerated dose not reached	Lao et al., 2006[276]
11	Phase II clinical trial	17 patients with advanced pancreatic cancer	8000mg/daily orally for 2 months	Well tolerated with biologic activity in Pancreatic cancer	Dhillon et al., 2006[289]

TABLE 2. Ongoing clinical studies with curcumin

No.	Name and Trial	Disease	Institution	Status
1	Pilot Study	Multiple Myeloma	M.D. Anderson Cancer Center, USA	Suspended May 2006
2	Interventional Pharmacokinetics	Oral Bioavailability of Curcumin in Normal Healthy Volunteers	Massachusetts General Hospital, USA	Recruiting patients September 2006
3	Interventional Gemcitabine	Pancreatic Cancer	Rambam Health Care Campus, Israel	Recruiting patients September 2005
4	Interventional The Efficacy of Coenzyme Q10 And Curcumin	Anemia, Blood and Blood Disorders, Bone Marrow Diseases, Cancer.	Hadassah Medical Organization, Israel	Patient recruitment September 2006
5	Mild to Moderate Alzheimer's Disease	Alzheimer's Disease	Institute for the Study of Aging (ISOA), USA	Recruiting patients November 2006
6	Phase III Trial of Gemcitabine, Curcumin and Celebrex	Colorectal Cancer	Tel-Aviv Sourasky Medical Center, Israel	Patient recruitment February 2006
7	Trial of Curcumin in Advanced Pancreatic Cancer	Pancreatic Cancer	M.D. Anderson Cancer Center, USA	Recruiting patients June 2006
8	Curcumin in Preventing Colon Cancer in Smokers With Aberrant Crypt Foci	Colorectal Cancer, Drug Abuse	National Cancer Institute (NCI), USA	Recruiting patients October 2006
9	Curcumin in Preventing Colon Cancer in Smokers With Aberrant Crypt Foci	Colorectal Cancer	National Cancer Institute (NCI), USA	Recruiting patients October 2006
10	A Pilot Study of Curcumin and Ginkgo for Treating Alzheimer's Disease	Alzheimer disease	Chinese University of Hong Kong	No longer recruiting patients
11	Sulindac and Plant Compounds in Preventing Colon Cancer	Colorectal Cancer	Rockefeller University, USA	Suspended May 2004
12	Curcumin for the Chemoprevention of Colorectal Cancer	Colorectal Cancer	University of Pennsylvania, USA	Recruiting patients November 2006
13	Curcuminoids for the Treatment of Chronic Psoriasis vulgaris	Psoriasis	University of Pennsylvania, USA	Recruiting patients October 2005

TABLE 2. (Continued) Ongoing clinical studies with curcumin

No.	Name and Trial	Disease	Institution	Status
14	The Effects of Curcuminoids on Aberrant Crypt Foci in the Human Colon	Colon Cancer	University of Medicine and Dentistry New Jersey, USA	Recruiting patients September 2005
15	Colorectal polyps	Colon Cancer	New York City Health and Hospital, USA	Recruiting
16	Cystic Fibrosis	Cystic Fibrosis	University of Albuquerque, USA	Recruiting
17	Oral Cancer	Oral Cancer	Oral Cancer Consortium, India (AIIMS, New Delhi; CRI, TMH, Mumbai; RCC, Thiruvananthapuram, HI, Amrita, Kochi, Kerala)	Recruiting
18	Cervical Cancer	Cervical cancer	Cervical Cancer Consortium, India (AIIMS, New Delhi; CRI, TMH, Mumbai)	Recruiting
19	Leukoplakia	Oral Cancer	Amrita, Kochi, Kerala; CRI, TMH, Mumbai; RCC, Thiruvananthapuram, India	Recruiting

Source: http://clinicaltrials.gov/ct/action/GetStudy

Sharma and colleagues conducted two phase I studies of curcumin with different formulations in patients with colorectal cancer refractory to conventional chemotherapeutic agents.[274,275] In the first study, a novel standardized Curcuma extract in proprietary capsule form was given at doses between 440 and 2200 mg/d, containing 36 to 180 mg of curcumin. Fifteen patients with advanced colorectal cancer refractory to standard chemotherapies received Curcuma extract daily for up to 4 months. Oral Curcuma extract was well tolerated, and dose-limiting toxicity was not observed. Neither curcumin nor its metabolites were detected in blood or urine, but curcumin was recovered from feces. Curcumin sulfate was identified in the feces of 1 patient. Radiologically stable disease was demonstrated in 5 patients for the 2- to 4-month treatment period. The results suggested that: 1) Curcuma extract can be administered safely to patients at doses of up to 2.2 g daily, equivalent to 180 mg of curcumin; 2) curcumin has low oral bioavailability in humans and may undergo intestinal metabolism; and 3) larger clinical trials of curcuma extract are

TABLE 3. Sources of curcumin

Company	Formulation	Web Site
Sabinsa Corporation	Research grade, C3 complex, 500 mg capsules	http://www.sabinsa.com/products/circumin_book.htm
Kalsec	Coloring agent	http://www.kalsec.com/products/turmeric_over.cfm
Turmeric Curcumin	95% curcumin, 500 mg capsules	http://www.turmeric-curcumin.com/
Iherb	500 mg capsules of 95% curcumin with bioperine and bromelain	http://www.iherb.com/curcumin1.html
Club Natural	Various combinations	http://www.clubnatural.com/curex9550180.html
American Nutrition	Various combinations	www.AmericanNutrition.com
Herbal Fields	Curmax, Curcumin (95%, 200 mg) with Boswellia (100 mg)	http://www.herbalfields.com/curcumin.html
NOW Food	700mg of Standardized Turmeric Root Extract 95.0% Curcuminoids	http://herbal-remedies-usa.stores.yahoo.net/antioxidant.html
Sanjivani Phytopharma Pvt Ltd	Curcumin (95%) 300 mg tablets (Turmeric extract 300 mg)	http://www.alibaba.com/catalog/11577384/Curcumin_95_Tablets_Turmeric_Extract_Tablets.html
Doctor's Best	95% total curcuminoids, 500 mg	http://www.loweringcholesterol.net/supplement-facts/curcumin-500
Jarrow	Curcumin 380 mg, 95% concentrate of turmeric antioxidants	http://www.global-nutrition-inc.com/jr-021.html
Life extension	Turmeric root extract 800 mg, 95% (760 mg) curcuminoids	http://www.lef.org/newshop/items/item00912.htm
Nature's way	Turmeric extract standardized to 95% curcuminoids, 500 mg	http://herbal-remedies-usa.stores.yahoo.net/63100.html
Bazaar of India	Turmeric capsules, 510 mg	http://herbal-remedies-usa.stores.yahoo.net/tumeric-capsules.html
Alternative Health & Herbs Remedies	Turmeric Tincture, 100% Organic	http://herbal-remedies-usa.stores.yahoo.net/turtin2oz.html
Natural Factors	Turmeric and Bromelain, 450 mg	http://www.naturalpharmacy.com/supplement-facts/Turmeric-Bromelain-NF
Ageless Cures	500 or 1000 mg per capsule of 95% curcuminoids	http://www.agelesscures.com/?gclid=CJO0kbyLz4gCFRE9FQod1irO4A
Source Naturals	Turmeric extract, 95% curcumin	http://www.vitadigest.com/sn-turmeric-100.html

TABLE 3. (Continued) Sources of curcumin

Company	Formulation	Web Site
Physician Formulas	Curcumin and turmeric, 500 mg	http://www.physicianformulas.com/store/Scripts/prodview.asp?idproduct=49&name=Curcumin
Tattva's Herbs	Turmeric Plus	
Arjuna Natural	Bio-Curcumax, 500 mg capsules	http://www.arjunanatural.com
Biochem Pharmaceutical Industries Ltd.	Biocumin (Curcumin 500 mg, Piperine 5 mg)	http://www.biochemgroup.com
Ashian Herbex Ltd.	Cancure, Kurcuma	http://www.ashianherbex.com
Konark Herbals Ltd.	Curcuma longa powder extract	http://www.konarkgroup.com/t-herbalhome.aspx
Synthite Indus Chem, Kerala, India	NatXtra Curcumin	http://www.synthite.com
Indo World, India	Turmeric oleoresin, 95% curcumin	http://www.indo-world.com
The Really Healthy Company	Alpha-Guard antioxidant complex, 40 mg curcumin capsules	http://healthy.co.uk/products/alpha-guard.html
Sigma-Aldrich	Research grade	http://www.sigmaaldrich.com/cgibin/hsrun/Distributed/HahtShop/HAHTpage/HS_CatalogSearch
Calbiochem	Research grade	http://www.calbiochem.com/Products/ProductDetail_CBCB.asp?catNO=239802
LKT laboratories	Research grade	http://www.lktlabs.com

merited. In the subsequent phase I study, Sharma and colleagues evaluated another formulation, a 500-mg curcuminoid capsule containing 450 mg curcumin, 40 mg demethoxycurcumin, and 10 mg bisdemethoxycurcumin. The dose levels of curcumin were 450, 900, 1800, or 3600 mg per day for up to 4 months. A total of 15 patients with refractory colorectal cancer were enrolled. Again, the drug was well tolerated, except three patients experienced minor gastrointestinal adverse events, including grade 1 diarrhea and grade 2 nausea. Furthermore, minor elevations of serum alkaline phosphatase and serum lactate dehydrogenase levels (compatible with grade 1-2 toxicity) were observed in 4 and 3 patients, respectively.

Lao and coworkers studied the safety of curcumin in 24 healthy volunteers.[276] Subjects were given a single oral administration of curcumin C3 complex (Sabinsa Corporation) (Table 3) with doses escalating from 500 to 12,000 mg. Safety was assessed for 72 hours following

curcumin administration. Seven of the 24 developed adverse effects, including diarrhea, headache, rash, and yellowish stool. All of the toxic effects were grade 1 and not dose related. The maximal tolerated dose of curcumin was not reached because doses greater than 12,000 mg were unacceptable to patients owing to the bulky volume of the tablets.

Two additional studies were conducted to understand the distribution of curcumin and its metabolites in intestinal tissues and liver.[277,278] The investigators examined whether oral administration of curcumin results in concentrations of the agent in normal and malignant human liver tissue that are sufficient to elicit pharmacological activity. In total, 12 patients with hepatic metastases from colorectal cancer received 450 to 3600 mg of curcumin daily for 1 week before surgery. Curcumin was poorly available following oral administration; levels of the parent compound and its glucuronide and sulfate conjugates in the peripheral or portal circulation were in the low nanomolar range. The results suggest that doses of curcumin required to furnish hepatic levels sufficient to exert pharmacological activity are probably not feasible in humans.[277] In the second study, Garcea and coworkers tested the hypothesis that pharmacologically active levels of curcumin can be achieved in the colon and rectum of humans as measured by effects on levels of M(1)G and COX-2 proteins. Patients with colorectal cancer ingested curcumin capsules (3600, 1800, or 450 mg daily) for 7 days. Curcumin was detected in normal mucosa and malignant colorectal tissues in patients receiving 1800 mg or 3600 mg of curcumin daily.[278] Curcumin sulfate and curcumin glucuronide also were identified in the intestinal tissues. Curcumin and its metabolites were not found in bile or in normal or malignant liver tissues in any patient.[277] However, trace amounts of hexahydrocurcumin and hexahydrocurcuminol were detected in the normal liver tissue of one patient receiving 3600 mg of curcumin daily.

In conclusion, these phase I clinical studies confirmed the safety of curcumin in humans for periods of up to 4 months of continuous treatment. In patients with premalignant lesions or advanced colorectal cancers treated with curcumin at doses as high as 3600 mg to 8000 mg daily for up to 4 months, only a few had toxic effects, and those were relatively mild nausea and diarrhea. The maximal tolerated dose, a traditional endpoint for anticancer chemotherapy, was not reached in these studies. The findings of these studies indicate that curcumin has a low bioavailability following oral application. However, oral intake of curcumin at doses as high as 3600 to 12,000 mg result in detectable levels of curcumin and its metabolites in plasma and urine, indicating that active absorption and metabolism of curcumin do occur. The important finding

is that pharmacologically active levels of curcumin could be achieved in colorectal tissue in patients taking curcumin orally.

A number of clinical studies, most of which were single-arm phase II design, have suggested that curcumin might be beneficial in diseases such as chronic inflammatory disorders, malignancies, and premalignant lesions. Deodhar and coworkers performed a short-term, double-blind, crossover study in 18 patients to compare the antirheumatic activity of curcumin and phenylbutazone.[28] The patients were administered 1200 mg curcumin/d or 300 mg phenylbutazone/d for 2 weeks. These investigators reported that curcumin was well tolerated, had no apparent side effects, and showed comparable antirheumatic activity.

Lal and coworkers administered curcumin orally to patients suffering from chronic anterior uveitis at a dose of 375 mg 3 times a day for 12 weeks.[279] Of 53 patients enrolled, 32 completed the 12-week study.[280] They were divided into two groups: one group of 18 patients received curcumin alone, whereas the other group of 14 patients, who had a strong purified protein derivative reaction, also received antitubercular treatment. In both groups, the uveitis started improving after 2 weeks of treatment. All the patients who received curcumin alone experienced improvement, whereas the group receiving antitubercular therapy along with curcumin had a response rate of 86%. Follow-up monitoring of all the patients for the next 3 years indicated a recurrence rate of 55% in the first group and 36% in the second group. Four of 18 (22%) patients in the first group and 3 of 14 patients (21%) in the second group lost their vision in the follow-up period because of various complications (eg, vitritis, macular edema, central venous block, cataract formation, glaucomatous optic nerve damage). None of the patients reported any side effects. In efficacy and number of recurrences following treatment, curcumin was comparable to corticosteroid therapy, which is at present is considered the only available standard treatment for this disease. The lack of side effects with curcumin is its greatest advantage compared with corticosteroids.

Satoskar and coworkers[281] evaluated the antiinflammatory properties of curcumin in patients with postoperative inflammation. They studied 46 male patients (aged 15 to 68 years) who underwent surgery for inguinal hernia and/or hydrocoele. Patients received curcumin (400 mg), phenylbutazone (100 mg), or placebo (250 mg lactose) 3 times a day for a period of 5 days from the first postoperative day. After surgery, the spermatic cord was evaluated for edema and tenderness. Phenylbutazone and curcumin both produced a better antiinflammatory response than placebo, and curcumin was considered safe.[281]

Holt and coworkers reported the use of curcumin in the treatment of

inflammatory bowel disease.[282] Five patients with ulcerative proctitis were treated with curcumin, 550 mg twice daily for 1 month followed by 550 mg 3 times daily for another month. All patients experienced clinical improvement. Another five patients with Crohn's disease were treated with curcumin, 360 mg three times daily for 1 month followed by 360 mg 4 times daily for another 2 months. Four of the patients experienced improvement, as evinced by improvements of the surrogate end points, Crohn's Disease Activity Index, and erythrocyte sedimentation rate. Five familial adenomatous polyposis patients with prior colectomy received curcumin (480 mg) and quercetin (20 mg) orally three times a day and the number and size of polyps were assessed at baseline and after therapy.[283] All 5 patients had a decreased polyp number and size from baseline after a mean of 6 months of treatment with curcumin and quercetin. No laboratory abnormalities and minimal adverse side effects were noted.[283]

Durgaprasad and colleagues reported the efficacy of curcumin in patients with nonalcoholic chronic pancreatitis of the tropics.[284] A total of 20 patients were randomized to receive either placebo or curcumin (a mixture of 500 mg pure extract of curcumin and 5 mg of piperine) 3 times daily for 6 weeks. Only 15 patients (75%) returned for evaluation following 6 weeks of treatment. There was no improvement in pain as assessed by visual analog score. Nevertheless, the curcumin-treated group had a significant reduction in the serum erythrocyte malonyldialdehyde level and an increase in the serum glutathione level, suggesting a reversion of excessive lipid peroxidation.

Lal and coworkers[280] described for the first time the clinical efficacy of curcumin in the treatment of patients suffering from idiopathic inflammatory orbital pseudotumors.[280] Curcumin was administered orally to eight patients at a dose of 375 mg/3 times a day for a period of 6 to 22 months. The patients were monitored for a period of 2 years at 3-month intervals. Five patients completed the study, of which four recovered completely. In the remaining patient the swelling regressed completely but some limitation of movement persisted. No side effect was noted in any patient, and there was no recurrence. Thus curcumin could be used as a safe and effective drug in the treatment of idiopathic inflammatory orbital pseudotumors.

Soni and coworkers examined the effect of curcumin on serum levels of cholesterol and lipid peroxides in 10 healthy human volunteers. A dose of 500 mg of curcumin per day for 7 days significantly decreased the level of serum lipid peroxides (33%), increased high-density lipoprotein cholesterol (29%), and decreased total serum cholesterol (11.63%). The results suggest that curcumin could be an effective chemopreventive

agent against arterial diseases.[285] An ethanol extract of turmeric as well as an ointment of curcumin were found to produce remarkable symptomatic relief in patients with external cancerous lesions. Reduction in smell were noted in 90% of the cases and reduction in itching in almost all cases. 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 1 of the 62 patients evaluated.[286]

James led a New England clinical trial of curcumin's effectiveness as an antiviral agent in 40 participants.[287] Two dropped out; 23 were randomized to the high-dose group (4 capasules 4 times a day) and 15 to the lose-dose group (3 capsules 3 times a day) for 8 weeks. Although it had no antiviral effects, curcumin was well tolerated, and most participants liked taking curcumin and felt better. Rasyid and coworkers performed a randomized, single-blind, three-phase, crossover-designed examination on 12 healthy volunteers to determine the dose of curcumin capable of producing a 50% contraction of the gall bladder and to find out whether there is a linear relationship between doubling the curcumin dosage and the doubling of gall bladder contraction. Their study showed that 40 mg curcumin was capable of producing a 50% contraction of the gall bladder and there was no linear relationship between doubling curcumin dosage and the doubling of gall bladder contraction.[288]

A phase II trial of curcumin in patients with advanced pancreatic cancer evaluated the toxicity and activity of curcumin, as well as its impact on survival and biologic correlates. Patients were treated with 8 g of curcumin (Sabinsa C3 complex) daily by mouth for two months and evaluated. Of the 17 patients that were enrolled as of the date of analysis, 11 patients were evaluable for response and 15 were evaluable for toxicity. The results suggest that curcumin is well tolerated and demonstrates a biologic activity in pancreatic cancer.[289] Several other studies are underway to determine the therapeutic effectiveness of curcumin in diseases.

Conclusion

The exhaustive research and numerous investigations carried over the last few decades suggest that curcumin has great potential in the prevention and cure of cancer. Curcumin modulates several biochemical pathways and numerous targets involved in carcinogenesis. Phase I clinical trials have revealed that up to 8 g of curcumin per day for 3 months is well tolerated in humans, although the optimum dose that can be administered for therapy is still unclear. Orally administered curcumin

has poor bioavailability and tissue accumulation, yet it has been found to be effective. The low levels of curcumin in the serum and tissue may account for its safety, but leave a question mark on the dose that should be administered to bring out the therapeutic effect. Several other agents such as piperine and ginger are known to improve the bioavailability of drugs by suppressing glucuronidation in the liver, but whether that affects the safety of the drugs has not been determined. These findings lead us to two conclusions: first, structural analogs of curcumin that are more bioavailable and effective than current forms should be designed, and second, large and well-controlled clinical trials are required to determine the potential of curcumin for prevention and therapy of disease. Nevertheless, it is clear that curcumin, a component of turmeric, exhibits anticancer and other health benefits. It is cost-effective and has been used for centuries without known side effects.

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