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Review Article

Theme: Natural Products as Therapeutic Modulators
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Curcumin and Cancer Cells: How Many Ways Can Curry Kill Tumor Cells Selectively?

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Abstract. Cancer is a hyperproliferative disorder that is usually treated by chemotherapeutic agents that are toxic not only to tumor cells but also to normal cells, so these agents produce major side effects. In addition, these agents are highly expensive and thus not affordable for most. Moreover, such agents cannot be used for cancer prevention. Traditional medicines are generally free of the deleterious side effects and usually inexpensive. Curcumin, a component of turmeric (*Curcuma longa*), is one such agent that is safe, affordable, and efficacious. How curcumin kills tumor cells is the focus of this review. We show that curcumin modulates growth of tumor cells through regulation of multiple cell signaling pathways including cell proliferation pathway (cyclin D1, c-myc), cell survival pathway (Bcl-2, Bcl-xL, cFLIP, XIAP, c-IAP1), caspase activation pathway (caspase-8, 3, 9), tumor suppressor pathway (p53, p21) death receptor pathway (DR4, DR5), mitochondrial pathways, and protein kinase pathway (JNK, Akt, and AMPK). How curcumin selectively kills tumor cells, and not normal cells, is also described in detail.

KEY WORDS: apoptosis; cancer; curcumin; molecular targets; signaling pathways.

INTRODUCTION

There are four types of cancers; (a) carcinoma: arise from the epithelial sheet that covers the surfaces, e.g., skin, colon, etc. Approximately 90% of all human cancers are carcinomas; (b) sarcoma: these include cancer of the connective tissues such as muscle, bone, cartilage, and fibrous tissue. Approximately 2% of all cancers are sarcomas; (c) leukemia and (d) lymphoma: they originate from blood forming cells and from cells of the immune system, respectively. Approx. 8% of all cancers are leukemia and lymphomas. Based on metastatic potential, there are two classifications of cancers; (a) benign tumors or adenomas: when neoplastic growth remains clustered as a single mass, (b) malignant tumor or adenocarcinoma: when tumor invades normal tissue and spreads throughout the body.

It is estimated that human body consists of 10–13 trillion cells. Almost all of these cells get turned over within approximately 100 days, thus suggesting an apoptosis/cell death rate of 100–130 billion cells each day. What is the mechanism of this mode of cell death in normal cells is unclear. Cancer cells are distinct from normal cells in six different ways and these characteristics are shared by all cancers; self sufficiency in growth signals, insensitivity to growth inhibitory signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, and tissue invasion, and metastasis (1). The ability of tumor cell populations to expand in number is determined not only by the rate of cell proliferation but also by the rate of cell death. Apoptosis is a major source of cell death, thus agents that trigger apoptosis/cell death, could be the most promising candidates as therapeutic for cancer.

Why certain types of cancers are more prevalent in some countries than others is not clear but lifestyle, including diet, is known to play major role (2). Among the potential dietary contributors to this disparity is turmeric (*Curcuma longa*), a spice that is consumed frequently by people from southeast Asia, a continent with low incidence of most cancers. Powder of turmeric is extensively used in Ayurveda, Unani, and Siddha medicine as a home remedy for various diseases. This powder, curcumin (diferuloylmethane) is a yellow-colored polyphenol, first isolated in 1815, crystallized in 1870, (3,4) and identified as 1,6-heptadiene-3,5- dione-1,7-bis(4-hydroxy-3-methoxyphenyl)-(1*E*,6*E*). Curcumin analoges which made by mother nature and man have been described (2). In addition, besides diferuloylmethane or curcumin, turmeric contains minor fractions such as demethoxycurcumin (curcumin II), bisdemethoxycurcumin (curcumin III), and the recently identified cyclocurcumin (5). All these analoges suggest that while hydroxyl groups in curcumin are required for its antioxidant activity, its methoxy groups are essential for its antiinflammatory and antiproliferative activity. Various molecular targets modulated by this agent include transcription

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factors, growth factors and their receptors, cytokines, enzymes, and genes regulating cell proliferation and apoptosis (6)

The anticarcinogenic properties of curcumin in animals have been demonstrated by its inhibition of tumor initiation (7) and tumor promotion (8,9). Studies of curcumin have shown that it influences structurally unrelated membrane proteins across several signaling pathways (10). A recent report suggests that curcumin inserts deep into the cellular membrane in a transbilayer orientation, anchored by hydrogen bonding to the phosphate group of lipids, thus inducing negative curvature in the bilayer (11). The promotion of negative curvature by curcumin may have a direct effect on apoptosis by increasing the permeabilizing activity of the apoptotic protein tBid (12). Curcumin has been shown to suppress multiple signaling pathways and inhibit cell proliferation, invasion, metastasis, and angiogenesis. The chemopreventive action of curcumin might be due to its ability to induce apoptosis by several pathways. Curcumin directly or indirectly controls different gene or gene products involved in cell death pathways as discussed here

MODES OF CELL DEATH

There are two major pathways of cell death, apoptosis (death by suicide) and necrosis (death by injury). Apoptosis is also known as programmed cell death and involves a series of biochemical events leading to characteristic cell morphology and death. Necrosis is caused by external factors, such as infection, toxins, or trauma. Additional cell death mechanisms, such as autophagy, entosis, paraptosis, and anoikis, have been defined more recently. A brief review of these modes of cell death will serve as background for our discussion of the modes and mediators of curcumin-induced cell death.

Apoptosis

Apoptosis is a normal physiological process that is required for the maintenance of cell homeostasis. The cellular changes involved in this process are both morphological and biochemical, including disintegration of the cytoskeleton and subsequent cell shrinkage, chromatin condensation, and activation of specific proteases, called caspases (13–15). Apoptosis can be initiated by a variety of internal and external stimuli, including receptor ligation and toxic insults. Apoptosis not only plays a crucial role in tissue development and homeostasis, but is also involved in a wide range of pathological conditions (16,17). Apoptotic cell death is accompanied by a series of complex biochemical events and definite morphologic changes, which include cell shrinkage, chromatin condensation, DNA fragmentation, membrane budding, and the appearance of membrane-associated apoptotic bodies (18). Failure to accurately undergo apoptosis can cause severe anomalies, ranging from autoimmune disease to cancer.

Necrosis

Necrosis typically occurs as a result of mechanical or toxic cell injury. Necrotic cells are distinguished from apoptotic cells in that they undergo stages such as cell swelling, plasma membrane rupture, organelle breakdown, and ultimately lysis, allowing release of the cytoplasmic contents and hence induction of an inflammatory response (14).

Autophagy

Autophagy or autophagocytosis is a cellular degradation process involving the degradation of a cell's own components through the lysosomal action (19). It is a tightly regulated cell-degradation mechanism that plays a normal part in cell growth, development, and homeostasis, helping to maintain a balance between the cellular products. This process involves dynamic membrane rearrangements under a range of physiological conditions. It plays a role in cellular maintenance and development, and has been implicated in a number of genetic diseases (20).

Entosis

Entosis is a nonapoptotic cell death process that occurs in human tumors and that is provoked by loss of attachment to matrix. This cell death mechanism is initiated by an unusual process involving the invasion of one live cell into another, followed by the degradation of internalized cells by lysosomal enzymes (21). This cell death process and apoptosis can both result in the internalization of one cell inside of another; the mechanisms responsible for cell internalization are highly distinguishable. Unlike the phagocytic ingestion of apoptotic cells, cell internalization in suspension is not associated with caspase activation nor driven by phosphatidylserine exposure (22).

Paraptosis

Paraptosis, an alternative, nonapoptotic cell death program that may be induced by the insulin-like growth factor I receptor (among other inducers), is mediated by mitogen-activated protein kinases (MAPKs). Caspases are not activated in this process, nor are caspase inhibitors effective in blocking cell death (23). It is reported that TAJ/TROY, a member of the tumor necrosis factor receptor superfamily that induces nonapoptotic cell death by paraptosis, is accompanied by phosphatidylserine externalization and loss of the mitochondrial transmembrane potential and is independent of caspase activation (24).

Anoikis

One form of detachment-induced death is an apoptotic program termed anoikis that has been characterized in suspension cell cultures (25,26). Cell death induced by detachment from extracellular matrix functions as a luminal clearing mechanism during development (27) and also may function as a barrier to the development of carcinomas, which display luminal filling as a hallmark.

MECHANISMS OF CELL DEATH BY CURCUMIN

Curcumin has a diverse range of molecular targets, supporting the concept that it acts upon numerous biochem-

ical and molecular cascades. Curcumin physically binds to as many as 33 different proteins, including thioredoxin reductase, cyclooxygenase-2, (COX2), protein kinase C, 5-lipoxygenase (5-LOX), and tubulin. Various molecular targets modulated by this agent include transcription factors, growth factors and their receptors, cytokines, enzymes, and genes regulating cell proliferation, and apoptosis (6). Curcumin has been shown to inhibit the proliferation and survival of almost all types of tumor cells. Accumulating evidence suggests that the mode of curcumin-induced cell death is mediated both by the activation of cell death pathways and by the inhibition of growth/proliferation pathways (Table I; Refs. 28–173). Many studies indicate the selective role of curcumin towards cancer cells than normal cells (Table II). We could identify more than 40 biomolecules that are involved in cell death induced by curcumin (Fig. 1). The mechanistic relationship among different signal transduction pathways, whether acting alone or together, leading to apoptosis is described. Because curcumin mediates its effect through multiple cell signaling pathways, the likelihood of developing resistance to it is less. How these interrelated pathways are activated is explained below.

Table I. A List of Apoptotic and Growth Inhibitory Pathways Activated by Curcumin in Tumor Cells

Pathways	References
Apoptotic pathways	
Caspase activation	(28–43)
Caspase-independent pathway	(28,42,44–46)
Induction of death receptors	(47–49)
Fas receptor aggregation	(41,50)
Induction of p53/p21 pathway	(51–60),
Release of apoptosis-releasing factor	(28,48,49,61–64)
Induction of DNA fragmentation	(65–76),
Suppression of Antiapoptotic proteins	(53,61,70,78–94)
Mitochondrial Activation	(28,29,31,32,35,45, 47,51,53,61,65,67, 69,71,83,88,95–117)
Autophagy	(118,119)
Induction of BIM	(46)
Activation of c-Jun kinase	(72,100,107,120–124)
Inhibition of IL6/STAT3 activation	(79,111,125)
Inhibition of NF-κB	(126–129)
Inhibition of Wnt/beta-catenin signaling	(130,131)
Growth inhibitory pathways	
Cell cycle regulation	(52,56,97,132,133)
Inhibition of PI3K-AKT activation	(134)
Inhibition of mTOR	(118,135,136)
Down-regulation of androgen receptors	(51,53,62,137–140),
Inhibition of growth factors and their receptors	(2,141,142)
Inhibition of AMP-activated protein kinase	(136,145)
Inhibition of COX2 and 5 LOX	(61,70,85,89,112, 126–128,146–150)
Inhibition of Ornithine decarboxylase	(98,151)
Inhibition of Acidic Sphingomyelinase	(152,153)
Inhibition of phospholipase D	(134,152,154)
Activation of Thioredoxin reductase	(155–157)
Inhibition of p300-HAT	(158,159)
Intracellular [Ca(2+)](i) depletion	(117,160–162)
Binding and Inhibition of Glyoxylase	(163,164)
Binding to Microtubules	(165,166)
Proteasome activation	(167–169)
Prooxidant/antioxidant mechanism	(42,85,96,149, 170–173)

IL-6 Interleukin-6, *STAT-3* signal transducer and activator of transcription 3, *mTOR* mammalian target of rapamycin, *NF-κB* nuclear factor-kappa B, *COX-2* cyclooxygenase-2, *5-LOX* 5-lipoxygenase, *PI3K* phosphoinositide 3-kinase, *HAT* histone acetyltransferase

Table II. Modulation of Proliferation and Apoptosis of Tumor Cells by Curcumin

Cell types	References
Tumor cells	
Hematological cancers	
Leukemia	
ALL	(174)
ATL	(108,125,175,176)
AML	(177)
Promyelocytic leukemia	(32,43,98,178–180)
Erythromyeloblastoid leukemia	(181)
Lymphoma	
Burkitt's Lymphoma	(47,50)
Hodgkin's lymphoma	(50,79)
Non-Hodgkin's lymphoma	(59,150,182)
Follicular lymphoma	(183)
Primary effusion lymphoma	(111)
Multiple myeloma	(84,184,185)
Gastrointestinal cancers	
Esophagus	(186)
Intestine	(187)
Liver	(97,102,114,172,188–191)
Pancreas	(146,148)
Colorectal	(31,39,54,63,78,92,95,120,131, 152,167,192–198)
Genitourinary cancer	
Bladder	(199,200)
Kidney	(191)
Prostrate	(2,53,70,76,91,124,137–139,201–204)
Brain tumors	(34,35,52,57,68,71,88,106,110, 119,205–209)
Breast cancer	(58,65,121,123,143,172,180,210–212)
Gyneoncologic cancers	
Cervix	(191)
Ovary	(191,213)
Thoracic/H&N cancers	
Lung	(29,147,188,191,211,214,215)
Melanoma	(36,41,133,160,216,217)
Normal cells	
Endothelial cells	(38,218)
Lymphocytes	(59,219,220),
Hepatocytes	(96,163,172)
Fibroblasts	(78,83,147,221–223)
Thymocytes	(173)
Mammary epithelial cells	(224)

ALL Acute lymphoblastic leukemia, *ATL* Acute T cell leukemia, *AML* acute myelogenous leukemia

Caspase Activation

Caspases, or cysteine-aspartic acid proteases, are a family of cysteine proteases that play essential roles in apoptosis, necrosis, and inflammation. There are numerous reports that suggests the involvement of caspases in curcumin-induced apoptosis (28,30–35). Curcumin causes DNA

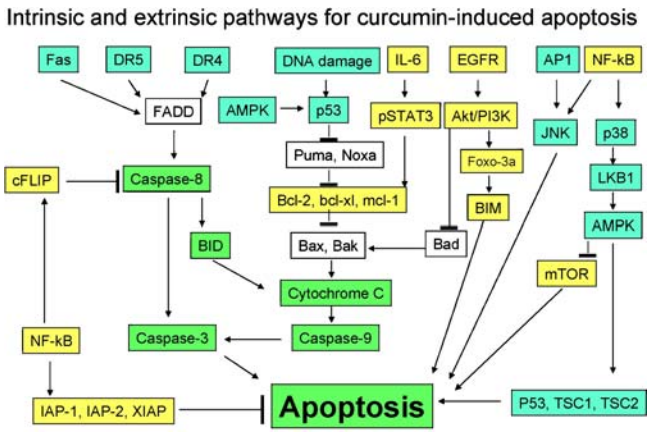

Fig. 1. Modulation of various cell death pathways by curcumin. Targets up-regulated by curcumin are in a *blue box*, those down-regulated are in a *yellow box*, and those unaffected are in a *white box*. *AP-1* activator protein-1, *AMPK* 5' adenosine monophosphate-activated protein kinase, *BID* BH3 interacting domain death agonist, *BIM* BCL2-like 11 (apoptosis facilitator), *cFLIP* cellular FLICE-like inhibitory protein, *FADD* Fas-associated protein with Death Domain, *DR4* death receptor 4, *DR5* death receptor 5, *EGFR* epithelial growth factor receptor, *IAP* inhibitor of apoptosis protein, *IL-6* interleukin-6, *JNK* c-Jun N-terminal kinase, *mTOR* mammalian target of rapamycin, *NF-kB* nuclear factor-kB, *PI3K* phosphoinositide 3-kinase, *STAT3* signal transducer and activator of transcription 3, *XIAP* X-linked IAP

damage and endoplasmic reticulum (ER) stress and mitochondrial-dependent-induced apoptosis through the activation of caspase-3 (29). Combined curcumin and TRAIL treatment enhanced accumulation of hypo-diploid U87MG cells in sub G1 cell cycle phase and induced the cleavage of procaspases-3, -8, -9, and release of cytochrome *c* from mitochondria (35). Earlier reports suggest that curcumin activates caspases-3 and -8 but not caspase-9, supporting the rationale that apoptosis occurs via a membrane-mediated mechanism. Both a caspase-8 and broad-based caspase inhibitor, but not a caspase-9 specific inhibitor, suppressed curcumin-induced cell death (41). Curcumin induces apoptosis through mitochondrial pathway involving caspase-8, BID cleavage, cytochrome *c* release, and caspase-3 activation in HL-60 cells (225).

Induction of Death Receptors

Death receptors are cell surface receptors that transmit apoptotic signals initiated by specific ligands such as Fas ligand, TNF-α, and TRAIL. These receptors play a crucial role in apoptosis and can activate a caspase cascade within seconds of ligand binding. Induction of apoptosis via this mechanism is therefore very rapid.

Studies showed that curcumin inhibited the expression of Bcl-2, Bcl-xL, survivin, and XIAP, and induced the expressions Bax, Bak, PUMA, Bim, and Noxa and death receptors (TRAIL-R1/DR4 and TRAIL-R2/DR5). Curcumin is a potent enhancer of TRAIL-induced apoptosis through upregulation of DR5 expression. Both treatment with DR5/Fc chimeric protein and silencing of DR5 expression using small interfering RNA (siRNA) attenuated curcumin plus TRAIL-induced apoptosis, showing that DR5 plays a critical role in this mode of cell death. Curcumin also induced the expression of a potential proapoptotic gene, C/EBP homologous protein (CHOP), both at its mRNA and protein levels (47,48). It has also been reported that curcumin significantly induces death receptor 5 (DR5) expression both at the mRNA and protein levels, accompanying the generation of the reactive oxygen species (ROS) (49).

Fas Receptor Aggregation

Fas receptor is the ligand for Fas-activated apoptosis. Binding of the ligand promotes receptor clustering, DISC formation and the activation of the caspase cascade. In addition, the Fas receptor is generally thought only to activate apoptosis and does not play an important role in other aspects of cell signaling like the TNF receptor. Curcumin induces Fas receptor aggregation in a FasL-independent manner, and low-temperature incubation, previously shown to inhibit receptor aggregation, prevented curcumin-induced cell death (41). Apoptosis in nasopharyngeal carcinoma cell line NCE induced by curcumin was found to up-regulate the Fas receptor gene as well as the protein in a dose-dependent manner (73). Curcumin is able to inhibit the proliferation of CA46 cells and induce apoptosis by down-regulating the expression of c-myc, Bcl-2, and mutant-type p53, and up-regulating the expression of Fas (50). Curcumin induced the modulation of cell cycle and apoptosis in gastric and colon cancer cells and stimulated the activity of caspase-8, which initiates Fas signaling pathway of apoptosis (197).

Induction of p53/p21 Pathway

The transcription factor p53 has been reported to play a very important role in apoptosis (226,227). As a tumor suppressor, p53 is responsible for protecting cells from tumorigenic alterations (227,228). Mutational inactivation of p53 is frequently observed in various human cancers (229). Studies on cell death on p21(+/+) and p21(−/−) HCT-116 cells treated with curcumin showed an associated reduction in procaspase-3 and PARP-1 cleavage, which are indicative of apoptosis, and concluded that curcumin-induced apoptosis in HCT-116 colon cancer cells does not depend on p21 status (78). The inhibition of p21 WAF1/CIP1 by siRNA blocks curcumin-induced apoptosis, thus establishing a link between cell cycle and apoptosis (51). Results of Liu *et al.* (52) demonstrated that ING4 expression was almost undetectable in U251 cells, but significantly up-regulated during cell cycle arrest induced by curcumin, and p53 expression was up-regulated followed by induction of p21 WAF1/CIP1 and ING4. Experiments using p53-null as well as dominant-negative and wild-type p53-transfected cells have established that curcumin induces apoptosis in carcinoma cells via a p53-dependent pathway. The studies showed that curcumin selectively increases p53 expression at G2 phase of carcinoma cells and releases cytochrome *c* from mitochondria, which is an essential requirement for apoptosis (56).

Release of Apoptosis-Inducing Factor

Apoptosis-inducing factor (AIF) is a mitochondrial apoptogenic protease that up on an apoptotic stimulus

translocates from mitochondria to cytosol and further to the nucleus, where it triggers chromatin condensation and large-scale DNA fragmentation (230). Curcumin-mediated apoptosis in HeLa, SiHa, and Ca Ski cells appears to be due to upregulation of proapoptotic Bax, AIF, release of cytochrome *c* and down-regulation of antiapoptotic Bcl-2, Bcl-xL (61). It was shown for the first time by Thayyullathil *et al*. that curcumin-induced rapid reactive oxygen species (ROS) generation causes the release of AIF from the mitochondria to the cytosol and nucleus, hence, leading to caspase 3-independent apoptosis (28). It is also reported that curcumin-induced release of cytochrome *c*, a second mitochondria-derived activator of caspase (Smac) and AIF, was also blocked in Bax−/− cells (63).

Cell Cycle Regulation

The cell cycle is set of events, resulting in cell growth and division into two daughter cells. The stages are G1-S-G2-M. The G1 stage is "GAP 1". The S stage is "Synthesis", this is the stage when DNA replication occurs. The G2 stage is "GAP 2". The M stage is "mitosis", and is when nuclear and cytoplasmic division occurs. Curcumin was found to induce G0/G1 and/or G2/M phase cell cycle arrest, up-regulate CDKIs, p21WAF1/CIP1, p27KIP1, and p53, and slightly down-regulate cyclin B1 and cdc2 in ECV304 cells (231). The cyclin D1 proto-oncogene is an important regulator of G1 to S phase transition in numerous cell types from diverse tissues. A study has demonstrated that curcumin induces apoptosis in the G2 phase of the cell cycle in deregulated cyclin D1-expressing mammary epithelial carcinoma cells, leaving its normal cells unaffected (56). Curcumin induced the expression of cyclin-dependent kinase (CDK) inhibitors p16(/INK4a), p21 WAF1/CIP1, and p27(/KIP1), and inhibited the expression of cyclin E and cyclin D1, and hyperphosphorylation of retinoblastoma (Rb) protein (51). Curcumin induces the degradation of cyclin E expression through the ubiquitin-dependent pathway and up-regulates cyclin-dependent kinase inhibitors p21 and p27 in multiple human tumor cell lines (6). In human mantle cell lymphoma, curcumin causes cell cycle arrest at the G1/S phase of the cell cycle and induces apoptosis (150). Curcumin enhances the expression of tumor cyclin-dependent kinase (CDK) inhibitors p21 and p27 as well as tumor suppressor protein p53 but suppressed the expression of retinoblastoma protein and also induced the accumulation of cells in G1 phase of the cell cycle in multiple human tumor cell lines (232). A recent report shows the activation of ATM/Chk1 by curcumin leads to G2/M cell cycle arrest and apoptosis in pancreatic cancer cells (233)

Inhibition of PI3K-AKT Activation

Akt (protein kinase B), a serine/threonine kinase, is a critical enzyme in signal transduction pathways involved in cell proliferation, apoptosis and angiogenesis. Studies showed that curcumin concentration- and time-dependently inhibited the phosphorylation of Akt, mTOR, and their downstream substrates in human prostate cancer PC-3 cells, and this inhibitory effect acts downstream of phosphatidylinositol 3-kinase and phosphatidylinositol-dependent kinase 1(234). Curcumin causes dose-dependent apoptosis and DNA fragmentation of Caki cells, which is preceded by the sequential dephosphorylation of Akt, down-regulation of the antiapoptotic Bcl-2, Bcl-xL, and IAP proteins, release of cytochrome *c* and activation of caspase 3 (134). Curcumin-induced effects have been shown to be associated with the suppression of NF-κB and IKK activities but independent of the B-Raf/MEK/ERK and Akt pathways in melanoma cell lines (235).

Inhibition of mTOR

mTOR is a large (>250 kDa) class IV PI-3 kinase family member with protein kinase activity. mTOR forms a complex with the 12-kDa cytosolic protein, FKBP-12, and rapamycin and functions to arrest the cell cycle in the G_1 phase. mTOR regulates Akt activity, a crucial downstream effector in the PI-3K–PTEN pathway, which controls cell proliferation and survival. Targeting this function of mTOR may also have therapeutic potential. For example, curcumin was shown to inhibit the Akt/mammalian target of rapamycin/p70 ribosomal protein S6 kinase pathway and activate the extracellular-signal-regulated kinases (ERK) 1/2, thereby inducing autophagy (118).

Down-Regulation of Androgen Receptors

Various studies evaluated the role of curcumin in cell growth and activation of signal transduction pathways in both androgen-dependent and -independent prostate cancer cell lines (35,53,62,138,139). The results showed that curcumin down-regulated transactivation and expression of AR, AP-1, NF-κB, and CBP. These studies showed that curcumin has enormous potential as an anticancer agent against prostate cancer (140). Curcumin enhanced the apoptosis-inducing potential of TRAIL in androgen-unresponsive PC-3 cells and sensitized androgen-responsive TRAIL-resistant LNCaP cells (62).

Inhibition of Growth Factors and their Receptors

Growth factors play a critical role in the proliferation of tumor cells. EGF, HER2, FGF, VEGF, PDGF, insulin growth factor (IGF)-1, and others have been associated with cell proliferation. The suppression of these growth factors or their receptors results in suppression of tumor growth. For example, the inhibition of EGFR expression and decreased ERK1/2 activity decreased survival and enhanced induction of apoptosis in lung and pancreatic adenocarcinoma cells (148). Curcumin inhibited EGF-stimulated phosphorylation of EGFR in MDA-MB-468 cells and phosphorylation of ERK 1 and -2, as well as ERK activity and levels of nuclear c-fos in MDA-MB-468 and HBL100 cells (143). Recently it was reported that curcumin inhibits 253JB-V and KU7 bladder cancer cell growth, which could be attributed to induction of apoptosis and decreased expression of the proapoptotic protein survivin and VEGF and VEGFR1 (144)

Inhibition of AMP-Activated Protein Kinase (AMPK)

AMP-activated protein kinase is a heterotrimeric serine/threonine protein kinase comprising a catalytic subunit (α)

and two regulatory subunits (β and γ). Curcumin strongly activates AMPK in a p38-dependent manner in CaOV3 ovarian cancer cells, thus inducing cell death (145). Stimulation of AMPK by curcumin down-regulated peroxisome proliferator-activated receptor-gamma (PPAR-γ) in 3T3-L1 adipocytes and decreased COX2 expression in MCF-7 cells, which in turn affects the proliferation rate.

Inhibition of COX2 and 5 LOX

Cyclooxygenase-2 (COX), also known as prostaglandin (PG) H2 synthase, is the rate-limiting enzyme in the conversion of arachidonic acid into PGs. The two known forms of COX are referred to as COX1 and COX2. Overexpression of COX2 has been frequently observed in colon tumors, and COX2 plays a major role in colon carcinogenesis Curcumin was found to modulate both the expression and the activity of these enzymes. A number of studies were carried out to establish the role of curcumin in mediating COX2 and 5 LOX (61,70,85,89,112,126–128,146–150). In human colon epithelial cells, curcumin inhibits COX2 induction by the colon tumor promoters tumor necrosis factor alpha and fecapentaene-12, thus inhibiting proliferation and inducing apoptosis (236). Curcumin has been shown to regulate the eicosanoid pathway involving COX and LOX. The details of how 5LOX and COX2 are regulated by curcumin are not fully established; however, we do know that curcumin regulates LOX and COX2 predominately at the transcriptional level and, to a certain extent, the posttranslational level (237). There is a report that the inhibition of COX2 and Wnt/EGFR/NF-κB-signaling pathways induces apoptosis in colon cancer cells (238).

Inhibition of Ornithine Decarboxylase

A recent study has shown that a chemopreventive effect of curcumin could be due to the hyperproduction of ROS, which would in turn induce apoptosis in tumor cells. The study found that enzyme activity and protein expression of ornithine decarboxylase (ODC) were reduced during curcumin treatment. Overexpression of ODC in human promyelocytic leukemia HL-60 parental cells could reduce curcumin-induced apoptosis, which would lead to loss of mitochondrial membrane potential, through reducing intracellular ROS. Moreover, ODC over expression prevented cytochrome *c* release and the activation of caspase-9 and caspase-3 following curcumin treatment (98). An earlier study showed the effects of curcumin on renal carcinoma. In the study, Fe-NTA, a known complete renal carcinogen, which generates ROS *in vivo*, was given intraperitoneally to mice, and curcumin was tested for its ability to inhibit oxidative stress and the ODC activity and histopathological changes in the kidney. ODC activity in the kidney was significantly increased but remained at normal levels in curcumin-pretreated mice (239).

Inhibition of Acidic Sphingomyelinase

Curcumin's apoptosis-inducing effects in colon cancer cell lines are accompanied by ceramide generation. This increase occurs through *de novo* synthesis, as much as the increase in ceramide could be attenuated by pre-incubation of the cells with myriocin, and no changes were observed in sphingomyelin levels or in either acidic or neutral sphingomyelinase activities. However, the inhibition of ROS using *N*-acetylcysteine led to an inhibition of JNK activation. Hence, the study concluded that curcumin induces apoptosis via a ROS-associated mechanism that converges on JNK activation, and to a lesser extent via a parallel ceramide-associated pathway (153). Curcumin reduced the hydrolytic capacity of the cells against choline-labeled sphingomyelin, associated with a mild increase in cellular sphingomyelin in the cells. Curcumin also inhibited acid sphingomyelinase an effect that may account for its antiproliferative effects against colon cancer cells (152).

Inhibition of Phospholipase D

The enzymatic activity of phospholipase D (PLD) is known to be essential for cell survival and protection from apoptosis. During apoptosis, a small fraction of PLD1 is cleaved by caspases in a p53-independent manner and NF-PLD1 amplifies apoptotic signaling through inhibition of the remaining PLD1 activity (217). In a cell-free system, curcumin inhibited several types of phospholipases, most effectively PLD. It also inhibited 12-*O*-tetradecanoylphorbol-13-acetate-induced PLD activation in intact J774.1 cells in a dose-dependent manner (154).

Activation of Thioredoxin Reductase

The thioredoxin reductase (TrxR) isoenzymes, TrxR1 in cytosol or nucleus and TrxR2 in mitochondria, are essential mammalian selenocysteine (Sec)-containing flavoenzymes with a -Gly-Cys-Sec-Gly active site. TrxRs are the only enzymes catalyzing the NADPH-dependent reduction of the active site disulfide in thioredoxins (Trxs), which play essential roles in substrate reductions, defense against oxidative stress, and redox regulation by thiol redox control. Trx can scavenge reactive oxygen species (ROS) and directly inhibits proapoptotic proteins such as apoptosis signal-regulating kinase 1 (ASK1). There are a number of inhibitors with chemotherapy applications that target either Trx or TrxR to induce apoptosis in cancer cells. A study has shown that rat TrxR1 activity in Trx-dependent disulfide reduction was inhibited by curcumin (156). Different curcumin analogs were also investigated for their inhibitory effects on thioredoxin reductase (TrxR). Most of them were more potent TrxR inhibitors than natural curcumin (157).

Inhibition of STAT3 Activation

Signal transducers and activators of transcription (STATs) play important roles in numerous cellular events, including differentiation, inflammation, and the immune response. Furthermore, constitutive STAT activation can be observed in a high number of tumors. Curcumin is incorporated into H-RS cells and inhibits both NF-κB and STAT3 activation, leading to decreased expression of proteins involved in cell proliferation and apoptosis, e.g., Bcl-2, Bcl-xL, cFLIP, XIAP, c-IAP1, survivin, c-myc, and cyclin D1 (79). Curcumin treatment induced a decrease of nuclear STAT3, -

5a, and -5b, without affecting either STAT1 or the phosphorylation state of STAT1, -3 or -5 in the K562 cell line. Most interestingly, the decrease of nuclear STAT5a and -5b after curcumin treatment was accompanied by an increase of truncated STAT5 isoforms, indicating that curcumin is able to induce the cleavage of STAT5 into its dominant-negative variants lacking the STAT5 C-terminal region (240). The constitutive phosphorylation of STAT3 found in certain multiple myeloma cells was abrogated by treatment with curcumin (241), and inhibition of STAT3 by curcumin leads to the induction of apoptosis (185)

Activation of c-Jun Kinase

In vitro experiments indicated that inhibition of c-Jun/AP-1 binding to its cognate motif by curcumin may be responsible for the inhibition of c-Jun/AP-1-mediated gene expression (242). Curcumin, a natural inhibitor of JNK signaling, protected the HT22 cells from glutamate-induced death at nanomolar concentrations (243). Curcumin time- and dose-dependent induction of apoptosis was accompanied by sustained phosphorylation and activation of c-jun N-terminal kinase (JNK) and p38 MAPK as well as inhibition of constitutive NF-κB transcriptional activity (195).

Induction of DNA Fragmentation

Curcumin inhibits activation of Vgamma9Vdelta2 T cells by phosphoantigens and induces apoptosis involving apoptosis-inducing factor and large-scale DNA fragmentation. This cytotoxicity was associated with increased annexin V reactivity, nuclear expression of active caspase-3, cleavage of poly (ADP-ribose) polymerase, translocation of apoptosis-inducing factor to the nucleus, and morphological evidence of nuclear disintegration (244). Curcumin activates the apoptotic pathway in human renal Caki cells. Treatment of Caki cells with 50μM curcumin resulted in the activation of caspase 3, cleavage of phospholipase C-γ1, and DNA fragmentation (134). Curcumin treatment protected cells from UVC-induced oligonucleosomal DNA degradation. Experiments using recombinant DFF activated with caspase-3 showed that curcumin inhibits plasmid DNA and chromatin degradation although it does not prevent activation of DFF40/CAD endonuclease after its release from the inhibitor (33). Curcumin-treated Jurkat cells exhibited DNA splitting into high- but not low-molecular-weight fragments. These cells retained their high mitochondrial Delta psi, and the content of Ca2+ in endoplasmic reticulum stores remained at the level typical for untreated cells (45).

Direct DNA Damage

Drug- or radiation-induced injury to DNA may produce deviations in DNA's normal double helical conformation. These changes include structural distortions that interfere with replication and transcription, as well as point mutations that disrupt base pairing and exert damaging effects on future generations through changes in DNA sequence. If the damage is minor, it can often be repaired (DNA repair). If the damage is extensive, it can induce apoptosis. Curcumin induces such DNA damage to both the mitochondrial and nuclear genomes in human hepatoma G2 cells. The study demonstrated dose-dependent damage in both the mitochondrial and nuclear genomes and the greater extent of the mitochondrial damage. The mechanism underlies the elevation in ROS and lipid peroxidation generated by curcumin (245). Studies with mouse–rat hybrid retina ganglion cell line N18 cells showed a dose- and time-dependent increase in DNA damage with curcumin treatment, which was confirmed by comet assay as well as agarose gel electrophoresis (246).

Intracellular [Ca (2±)](i) Depletion

Curcumin induced a marked depletion of [Ca(2+)](i) in Caki cells bathed with both Ca(2+)-containing and -free solutions. This indicates that curcumin acts as a stimulator of intracellular Ca(2+) uptake into mitochondria via uniporter pathway and may involve the execution of apoptosis (162). Reports suggest that curcumin may induce the expression of the HSP70 gene through the initial depletion of intracellular Ca(+2), followed by the suppression of p53 gene function in the target cells (247).

Mitochondrial Activation

Mitochondria play a pivotal role in the process of apoptosis. The intrinsic pathway of apoptosis involves the activation of proapoptotic members of the Bcl-2 family that exert their function through mitochondria. Role of mitochondria is well established in a curcumin-induced apoptosis (28,31,32,47,53,61,65,67,69,88,95,97–118). Curcumin induces the release of cytochrome *c* from mitochondria, causing activation of caspase 3 and concomitant PARP cleavage, which is the hallmark of caspase-dependent apoptosis (28). Curcumin-induced rapid ROS generation causes the release of AIF from the mitochondria to the cytosol and nucleus, hence leading to caspase 3-independent apoptosis (69). HepG2 cells exposed to curcumin for 1 h showed a transient elevation of mitochondrial membrane potential (MMP), followed by cytochrome c release into the cytosol and disruption of MMP after 6 h exposure to curcumin. These results suggest that mitochondrial hyperpolarization is a prerequisite for curcumin-induced apoptosis and that mtDNA damage is the initial event triggering a chain of events leading to apoptosis in HepG2 cells (102). A study on curcumin protection of PC12 cells against MPP (+)-induced apoptosis suggested that the cytoprotective effects of curcumin might be mediated by the Bcl-2-mitochondria-ROS-iNOS pathway (108). Curcumin induced an increase in rat liver mitochondrial membrane permeability, resulting in swelling, loss of membrane potential and inhibition of ATP synthesis. These effects were mediated by the opening of the permeability transition pore (117). Curcumin targets proliferative cells more efficiently than differentiated cells and induces apoptosis via mitochondrial pathways. Addition of curcumin to neuro 2a cells induces a rapid decrease in mitochondrial membrane potential and the release of cytochrome *c* into cytosol, followed by activation of caspase-9 and caspase-3 (116).

Binding and Inhibition of Glyoxalase

Glyoxalases (Glo1 and Glo2) are involved in the glycolytic pathway by detoxifying the reactive methylglyoxal (MGO) into D-lactate in a two-step reaction using glutathione (GSH) as cofactor. Inhibitors of glyoxalases are considered antiinflammatory and anti-tumor agents. Curcumin inhibits Glo1, resulting in non-tolerable levels of MGO and GSH. As a result, various metabolic pathways are disturbed, so that for example, cellular ATP and GSH content are depleted (163). The depletion of cellular ATP and GSH may in turn decrease cell survival.

Suppression of Antiapoptotic Proteins

The inhibitors of apoptosis (IAP) proteins are a recently discovered class of caspase inhibitors that selectively bind and inhibit caspase-3, -7, and -9; these inhibitors have great potential in the treatment of malignancy (248). Curcumin is reported to inhibit the expression of these caspases inhibitors both *in vitro* and *in vivo* (89). Other antiapoptotic proteins that are inhibited by curcumin include Bcl-2, Bcl-xL, X-linked inhibitors of apoptosis (XIAP), and survivin (61,77–94,127). Curcumin sensitizes prostate cancer cells to TRAIL by inhibiting Akt-regulated NF-κB and NF-kappaB-dependent antiapoptotic Bcl-2, Bcl-xL, and XIAP (91). Curcumin-induced apoptosis in human androgen-independent (DU145) and -dependent (LNCaP) prostate cancer cell lines (124) and HL-60 cells (225), which correlated with down-regulation of the expression of Bcl-2 and Bcl-xL

Binding to Microtubules

Curcumin may inhibit cancer cell proliferation by perturbing microtubule assembly dynamics. At higher inhibitory concentrations (>10μM), curcumin induced significant depolymerization of interphase microtubules and mitotic spindle microtubules of HeLa and MCF-7 cells. However, at low inhibitory concentrations there were minimal effects on cellular microtubules. It disrupted microtubule assembly *in vitro*, reduced GTPase activity, and induced tubulin aggregation (165). In one study, curcumin-down-regulated Taxol induced phosphorylation of the serine/threonine kinase Akt, a survival signal which in many instances is regulated by NF-kappaB, but tubulin polymerization and cyclin-dependent kinase Cdc2 activation induced by Taxol was not affected by curcumin (249).

Proteasome Activation

It has been reported that curcumin-induced apoptosis is mediated through the impairment of ubiquitin proteasome system (UPS). Curcumin disrupts UPS function by directly inhibiting the enzyme activity of the proteasome's 20S core catalytic component. The direct inhibition of proteasome activity also causes an increase in half-life of IκBα that ultimately leads to the down-regulation of NF-κB activation (169), thus activating the apoptotic pathway. Exposure of mouse neuro 2a cells to curcumin causes a dose-dependent decrease in proteasome activity and an increase in ubiquitinated proteins. Curcumin targets proliferative cells more efficiently than differentiated cells and induces apoptosis via mitochondrial pathways (116).

Pro- and Antioxidant Mechanisms

Studies have shown that curcumin mediates its apoptotic and antiinflammatory activities through modulation of the redox status of the cell (42,149,169). TNF-mediated NF-κB activation was inhibited by curcumin; and glutathione reversed the inhibition. Glutathione also counteracted the inhibitory effects of curcumin on TNF-induced NF-κB-regulated antiapoptotic (Bcl-2, Bcl-xL, IAP1), proliferative (cyclin D1), and proinflammatory (COX2, iNOS, and MMP-9) gene products (85). Reports suggest that curcumin modifies TrxR by shifting the enzyme from an antioxidant to a prooxidant (156). Low concentrations of curcumin may protect hepatocytes by reducing lipid peroxidation and cytochrome c release. Conversely, higher concentrations provoke glutathione depletion, caspase-3 activation, and hepatocytotoxicity (96). Curcumin pretreatment significantly decreased ROS and resulted in survival of copper-injured BRL cells, possibly by anti-oxidation and inhibition of p-JNK expression (170). Curcumin induces apoptosis via ROS generation in malignant cells, but not in normal cells (172). In Jurkat cells, curcumin prevents glutathione decrease, thus protecting cells against caspase-3 activation and oligonucleosomal DNA fragmentation (42). In normal cells, curcumin induces apoptosis in a glutathione-independent pathway (173).

Autophagy

Autophagy is a response of cancer cells to various anticancer therapies. It is designated programmed cell death type II and characterized by the formation of autophagic vacuoles in the cytoplasm. In one study, curcumin induced G2/M arrest and nonapoptotic autophagic cell death in U87-MG and U373-MG malignant glioma cells. It inhibited the Akt/mTOR/p70S6K pathway and activated the ERK1/2 pathway, resulting in induction of autophagy. In the subcutaneous xenograft model of U87-MG cells, curcumin inhibited tumor growth significantly ($P<0.05$) and induced autophagy (119). It inhibited the Akt/mammalian target of rapamycin/p70 ribosomal protein S6 kinase pathway and activated the extracellular-signal-regulated kinases and induced autophagy (118).

Inhibition of NF-κB

The transcription factor NF-κB is constitutively expressed in almost all cancer types and suppresses apoptosis in a wide variety of tumors. The constitutive expression of NF-κB has been reported in human cancer cell lines in culture, carcinogen-induced mouse mammary tumors, and biopsies from cancer patients. There are various reports that curcumin inhibits the activation of NF-κB by inducers such as TNF, H_2O_2. phorbol ester, cigarette smoke condensate, interleukin (IL)-1, 12-*O*-tetradecanoylphorbol-13-acetate (TPA), and anticancer drugs (6) . Curcumin inhibits the activation of NF-κB and the expression of various oncogenes regulated by NF-κB, including c-jun, c-fos, c-myc, NIK, MAPKs, ERK, ELK, PI3K, Akt, CDKs, and iNOS (250).

Curcumin prevents the entry of NF-κB into the nucleus, thereby decreasing the expression of cell cycle regulatory proteins and survival factors such as Bcl-2 and survivin. Curcumin arrested the cell cycle by preventing the expression of cyclin D1, cdk-1, and cdc-25 (126). In hepatic cancer HA22T/VGH cell line, curcumin inhibited constitutively activated NF-κB and NF-κB regulated gene products such as apoptosis proteins (IAPs) and other target genes (128). It inhibits TNF-induced NF-κB-regulated gene products involved in cellular proliferation (COX2, cyclin D1, and c-myc), antiapoptosis (IAP1, IAP2, XIAP, Bcl-2, and Bcl-xL; 127). Curcumin could prevent tumor-induced thymic atrophy by restoring the activity of NF-κB. Further investigations suggest that neutralization of tumor-induced oxidative stress and restoration of NF-κB activity along with the reduction of the TNF-α signaling pathway can be the mechanism behind curcumin-mediated thymic protection (251). Curcumin down-regulated NF-κB in human multiple myeloma cells, leading to the suppression of proliferation and induction of apoptosis (184)

Inhibition of Wnt/beta-catenin Signaling

The Wnt/beta-catenin signaling pathway plays a major role in development, tissue homeostasis, and regeneration. The deregulation of this pathway is found in various human cancers. Numerous reports suggest that curcumin is a good inhibitor of b-catenin/Tcf signaling in gastric, colon, and intestinal cancer cells (131,231). It has been reported that inhibition of Wnt-2 had synergistic effects on suppressing Wnt signaling and inducing apoptosis, suggesting that aberrant canonical Wnt/beta-catenin signaling in colorectal cancer can be regulated at multiple levels (252). Thus, the pro-apoptotic effects of curcumin could be mediated through this pathway

Activation of Nrf2

Nuclear erythroid 2 p45-related factor 2 (Nrf2) is a redox-sensitive basic leucine zipper transcription factor that is involved in the transcriptional regulation of many antioxidant genes. The Nrf2/antioxidant response element (ARE) signaling pathway plays a key role in activating cellular antioxidants, including heme oxygenase-1 (HO-1), NADPH quinone oxidoreductase-1 (NQO1), and glutathione. Curcumin treatment results in ROS generation, activation of Nrf2 and MAP kinases and the inhibition of phosphatase activity in hepatocytes, and when curcumin is not administered in toxic doses, these multiple pathways converge to induce HO-1 (253). Another study further suggests that curcumin has the ability to induce HO-1 expression, presumably through Nrf2-dependent ARE activation in rat vascular smooth muscle cells and human aortic smooth muscle cells, and provide evidence that the antiproliferative effect of curcumin is considerably linked to its ability to induce HO-1 expression (254).

Inhibition of hTERT

Another possible activity of curcumin able to induce cell death processes is the inhibition of hTERT, the active subunit of telomerase. Increasing concentrations of curcumin caused a decrease in the level of hTERT mRNA in MCF-7 cells. hTERT is activated in cancer cells and prevents telomere shortening and thus the activation of apoptotic processes. The inhibition of hTERT is an additional mechanism by which curcumin can induce cell death in cancer cells (255)

EFFECT OF CURCUMIN ON NORMAL CELLS

Curcumin has been shown to have differential effects on normal cells such as endothelial cells, lymphocytes, hepatocytes, fibroblasts, thymocytes, and mammary epithelial cells (78,96,110–115,163,172,173,224). Why curcumin kills tumor cells and not normal cells is not fully understood, but several reasons have been suggested. First, absorption and fluorescence spectroscopic methods showed that cellular uptake of curcumin is higher in tumor cells than in normal cells (256). The studies also showed that curcumin was maximally distributed in the cell membrane and the nucleus. Second, the glutathione levels in tumor cells tend to be lower than normal cells, thus enhancing the sensitivity of tumor cells to curcumin (172). Third, most tumor cells, but not normal cells, express constitutively active NF-κB and mediate their survival (150). Curcumin can suppress the survival and proliferation of tumor cells by suppressing NF-κB-regulated gene products. Apart from this, human epidermal keratinocytes have been shown to undergo apoptosis when exposed to curcumin through the inhibition of AP-1 (104). Low concentrations of curcumin may protect hepatocytes by reducing lipid peroxidation and cytochrome *c* release. Conversely, higher concentrations provoke glutathione depletion, caspase-3 activation, and hepatocytotoxicity (96). Interestingly, curcumin had no effect on normal rat hepatocytes, which showed no superoxide generation and therefore no cell death (172). Primary cultures of human dermal fibroblasts were less sensitive to lower doses of curcumin (78). Studies have shown that curcumin causes fibroblast apoptosis and that this could be inhibited by co-administration of antioxidants *N*-acetyl-L-cysteine , biliverdin or bilirubin, suggesting that ROS are involved (221). In endothelial cells, curcumin inhibited MAP kinase activity and enhanced TNF-induced apoptosis (218). Studies suggests that curcumin induces the apoptosis in human retinal endothelial cells by the regulation of intracellular ROS generation, VEGF expression and release, and VEGF-mediated PKC-beta II translocation (257). Curcumin can induce cell death in both quiescent and proliferating normal human lymphocytes, without oligonucleosomal DNA degradation, which is considered a main hallmark of apoptotic cell death (258). Curcumin induces cell death in lymphocytes that can be classified as apoptosis-like cell death (220).

CONCLUSION

Overall, our review shows that curcumin can kill a wide variety of tumor cell types through diverse mechanisms. Because of numerous mechanisms of cell death employed by curcumin, it is possible that cells may not develop resistance to curcumin-induced cell death. Furthermore, its ability to kill tumor cells and not normal cells makes curcumin an attractive candidate for drug development. Although numerous animal studies and clinical trials have

been done, additional studies are needed to gain the full benefit from curcumin.

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