Curcumin molecular targets in obesity and obesity-related cancers

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Obesity is characterized as an increased BMI, which is associated with the increased risk of several common cancers, including colorectal, breast, endometrial, renal, esophageal, gallbladder, melanoma, multiple myeloma, leukemia, lymphoma and prostate cancer. The increased risk of obesity-related cancers could be mediated by insulin resistance, adipokines, obesity-related inflammatory cytokines, sex hormones, transcription factors and oxidative stress, which disrupt the balance between cell proliferation and apoptosis. The yellowish compound, curcumin (diferuloylmethane), is known to possess multifaceted pharmacological effects. The molecular mechanisms linking obesity to cancer risk, and how curcumin mediates anticancer and obesity activities, have not yet been publicized. Curcumin modulates multiple molecular targets and reverses insulin resistance as well as other symptoms that are associated with obesity-related cancers. In this study, we show that ample evidence exists to support recommendations that curcumin mediates multiple molecular pathways, and is considered to be of therapeutic value in the treatment and prevention of obesity-related cancers.

Obesity is now recognized as a devastating burden to the healthcare system of our population and is the underlying basis for a broad number of cancers. The prevalence regarding obesity in most developed and developing countries has risen steadily over the past two decades [1]. It has been suggested that excess BMI is associated with the risk of several chronic diseases, including cancer, which reduce life expectancy, and have huge economic and collective social penalties [2]. The American Cancer Society's conclusion indicated that approximately 14–20% of cancer-related deaths in the USA are attributed to obesity related problems [101]. Similarly, a study conducted by the International Association for the Study of Obesity in European countries during 2007, reported that approximately 40–50% of men and 25–35% of women were overweight (BMI $\geq$ 25.0 and $\leq$ 30 kg/m^2, respectively), with an additional 15–25% of men and 15–25% of women being obese (BMI $\geq$ 30.0 kg/m^2) [102]. In addition, previously reported studies during 2002 and 2003, by the International Agency for Research on Cancer as part of the WHO, suggested that sufficient evidence exists for a link between obesity and increased risk of colon cancer, postmenopausal breast cancer, endometrial cancer, kidney cancer and esophageal cancer [103].

Around the turn of the 20th century, molecular links between obesity and different cancers have progressively emerged and a number of epidemiological studies have uncovered several mechanisms, including overexpression of proinflammatory molecules such as TNF-α, MCP-1, inducible nitric oxide synthase (iNOS) and plasminogen activator inhibitor-1), in adipose, liver and muscle tissues; and increased activation of inflammatory signaling pathways, such as the NF-κB and JNK systems in these tissues [3,4]. In support of the epidemiological studies, insulin activation triggers the intracellular signaling cascades in both the ERK and PI3K pathways, and thus, insulin signaling has the potential to lead to obesity and tumor progression. Furthermore, it is reported that the association of obesity with and the increased risk of developing cancer may be via the overexpression of inflammatory cytokines, adipokines and increased IGF-1 levels [5].

Curcumin (1,7-bis[4-hydroxy-3-methoxyphenyl]-1,6-heptadiene-3,5-dione), a turmeric polyphenol isolated from the dried ground rhizome of the perennial herb curcuma species (*Curcuma longa*), is known to exhibit potential activity against obesity and cancer through antioxidant and anti-inflammatory mechanisms. Curcumin inhibited MAPK (ERK, JNK and p38) phosphorylation, which was associated with the differentiation of 3T3-L1 cells into adipocytes [6]. Furthermore, adipokines, such as leptin, are strongly correlated with obesity. Leptin binds to its transmembrane receptor, ObR, which increases the expression

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of regulatory proteins that are involved in cell proliferation and angiogenesis. Curcumin reduces the phosphorylation level of the leptin receptor ObR and eliminates leptin signaling by attenuating oxidative stress and stimulating the expression of PPAR-γ activity [7].

The current paper focuses on the studies that describe the underlying molecular mechanisms involved in obesity and cancer. We summarize several *in vitro* and *in vivo* studies that suggested that curcumin mediates multiple molecular targets and has a great potential for the treatment of obesity-related cancers. Curcumin has been reviewed extensively during the last decade, but in spite of numerous recent studies on its biological effect and mechanism of action, no comprehensive review has yet appeared on this subject.

Mechanisms linking obesity to cancer risk

Many *in vitro* and *in vivo* models provide convincing evidence for insulin and IGF-1, which are considered the main players in obesity-related cancers. Insulin exerts its tumor-enhancing effects directly via the insulin receptor or indirectly via IGF-1, estrogen and adrenal hormones. The binding of insulin to the cell-surface receptor of premalignant cells activates the PI3K/AKT pathway, leading to the activation of mTOR, which is involved in cell growth and proliferation [8]. Insulin also increases IGF-1 levels by upregulating its synthesis and downregulating IGFBP-1 activation. Moreover, IGF-1 also increases the production of VEGF, an angiogenic factor that supports tumor growth [9]. Recently, the Endogenous Hormones and Breast Cancer Collaborative Group analyzed data from 17 prospective studies in 12 countries and observed a positive association between the circulating levels of IGF-1 and breast cancer risk [10]. In addition, the study of 150 adult patients from different parts of the world indicated that non-alcoholic fatty liver disease is associated with obesity and metabolic features, and hepatocellular carcinoma could arise in noncirrhotic livers, suggesting that metabolic abnormalities is the early risk factor for the hepatocellular carcinoma [11]. Several studies have shown the expression of leptin in obesity-related cancers, which binds to the extracellular domain of the transmembrane receptor ObR, which belongs to the class I cytokine receptor family [12]. Receptor binding induces the activation of different signaling pathways including JAK/STAT, MAPK, IRS1 and SOCS3 [13]. Furthermore, low levels of adiponectin in plasma have been considered to be high-risk and differentially affect gene expression in a variety of cancers [14]. It has been reported that adiponectin activates a caspase cascade consisting of caspase-8, -9 and -3, which significantly increases tumor cell apoptosis through decreased neovascularization, leading to cell death and impaired tumor growth [15]. In addition, circulating levels of adiponectin are inversely associated with obesity-related disorders and also possesses anti-inflammatory, antidiabetic and antiatherogenic activities [16].

Many proinflammatory cytokine factors such as TGF-β, IFN-γ, interleukins, including IL-1, IL-6, IL-10 and IL-8, MCP-1 and plasminogen activator inhibitor-1, and fibrinogen are produced from activated macrophages, which may also be important in the development of obesity-related cancers. Additionally, adipose-secreted factors such as leptin and visfatin also have a major role in obesity and cancer [17]. Another important source that have role in obesity-related cancers are steroid hormones such as adrenal steroids, estrogens, androgens and progesterone. Adipose tissue is the major site of estrogen synthesis in men and postmenopausal women, with high levels of aromatase (which promotes the formation of estrogens from androgenic precursors), and circulating levels of estrogen and estradiol, which have a strong relation to BMI [18]. Insulin and IGF-1 both inhibit the synthesis of sex hormone-binding globulin, which is responsible for testosterone and estradiol transportation in the plasma, and may increase the amount of unbound sex steroids available for biological activity [19]. Furthermore, glucocorticoid hormones have long been known to inhibit tumor promotion, possibly through the induction of p27, and thus, impair cell-cycle machinery. Studies have also observed that corticosterone can inhibit protein kinase C and MAPK signaling, including reduced ERK signaling and AP-1 DNA binding [20]. The close association of obesity with cancers has attracted a significant amount of attention, and understanding the exact molecular mechanisms linking obesity and cancer may be of vital importance to the treatment of this pathology.

Curcumin chemistry

There is strong evidence that, chemically, curcumin is a bis-α, β-unsaturated β-diketone that exists in equilibrium with its enol tautomer and two oxy-substituted aryl moieties, which are linked together through a seven-carbon chain. Various turmeric analogs and curcumin derivatives have been reported that include curcumin, demethoxycurcumin, bisdemethoxycurcumin, cyclocurcumin and dihydrocurcumin,

tetrahydrocurcumin, hexahydrocurcumin, hydrocurcuminol, curcumin glucuronide, and curcumin sulfate (Figure 1). A difference exists between curcuminoids in physicochemical properties and physiological activities because of methoxy substitution. Methoxy substitution on the aromatic ring can extensively organize the interactions of curcuminoids with nucleophiles via the 'Michael reaction'. The hydrogen bonding interaction between the phenolic OH and the ortho-methoxy groups which affects the O–H bond energy and H-atom abstraction by free radicals makes curcumin more antioxidant [21]. Therefore, the ortho-methoxy group and the structure–activity relationship in curcumin are important for the antioxidant activity. There is no relation that correlates the molecular mechanisms of curcumin or its analogs with their pharmacological effects. Different analogs have different bioactivities and differential efficacy of these analogs is cell-, tissue- and organism-specific [22].

Curcumin molecular targets in obesity-related cancers

Curcumin has been used as a home remedy in ancient Chinese and traditional Indian medicine for the treatment of different ailments. In the

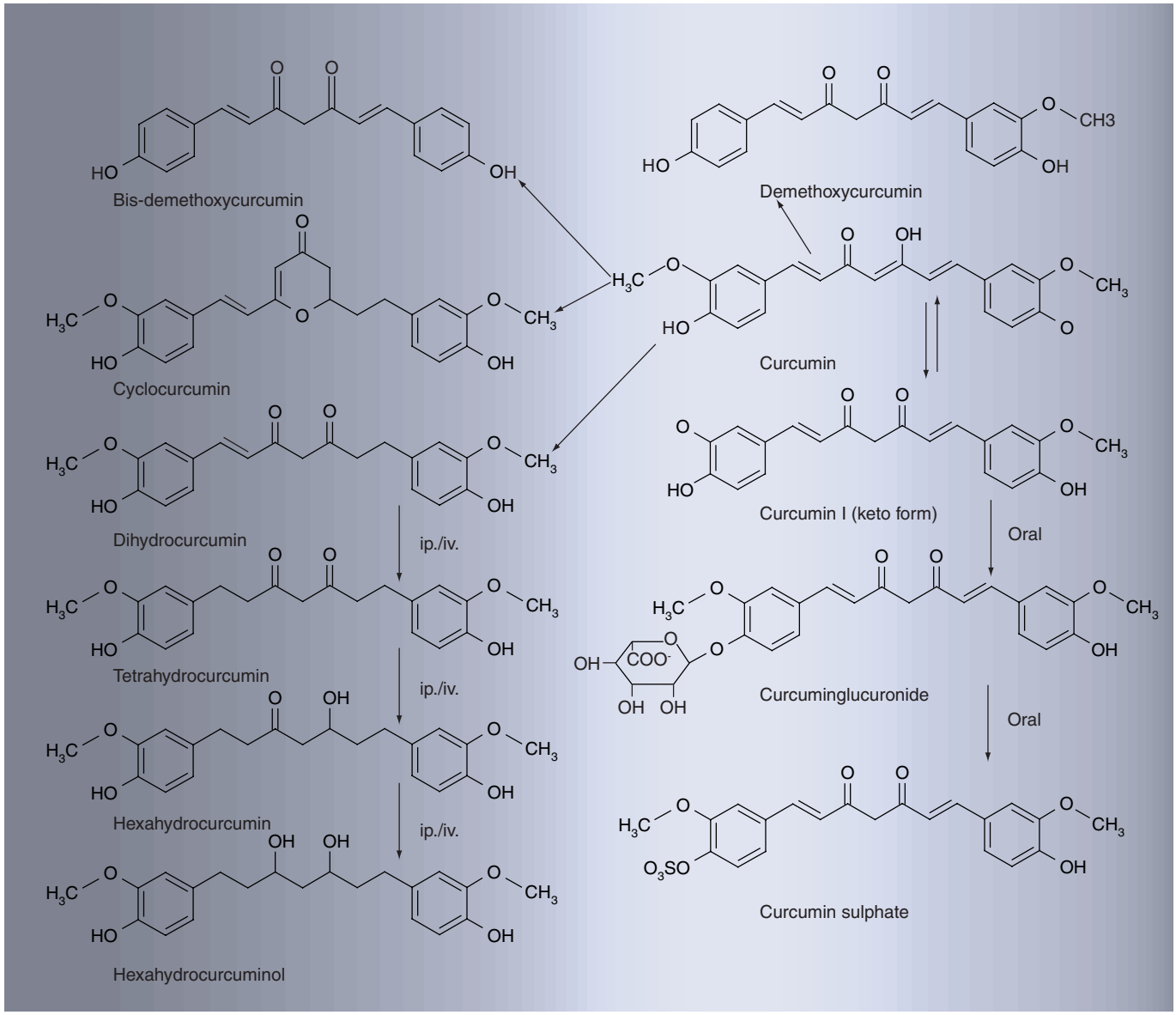

Figure 1. Natural turmeric analogs and curcumin metabolites in rodents and humans. Curcumin, when administered orally, undergoes glucuronidation and sulfation, while when administered via iv. or ip. routes, it undergoes reduction that leads to the formation of tetrahydrocurcumin, hexahydrocurcumin and hexahydrocurcuminol.
ip.: Intraperitoneal; iv.: Intravenous.

last decade, research has focused on drugs that have the ability to diminish obesity and cancer together [23]. Curcumin disrupted the signaling pathways and molecular targets that are involved in obesity and obesity-related cancer progression (Figure 2). The following are the different molecular targets that establish the basic biologic and scientific rationale for the potential role of curcumin in controlling obesity-related cancers.

Insulin & IGF

The IGF system, including IGFs (IGF-1 and IGF-2), the IGF membrane receptor type 1 (IGF-1R) and IGFBPs, has been implicated to play a critical role in the progression of various cancers. The cellular effects of IGF-1 are mediated by IGF-1R. Curcumin decreased the secretion of IGF-1 and suppressed *IGF-1R* gene expression at the transcriptional level with a simultaneous increase of IGFBP-3 in a dose-dependent manner, as well as inhibited IGF-1-stimulated IGF-1R tyrosine kinase activation in a human breast carcinoma cell line [24]. In addition, IGFBP-5 and CCAAT/enhancer-binding protein (C/EBP) are suppressors of head and neck carcinogenesis. Curcumin increased nuclear *C/EBP* and *IGFBP-5* expression through the activation of p38. It was concluded that curcumin activates p38, which, in turn, activates the C/EBP transactivator by interacting with binding elements in the IGFBP-5 promoter [25]. In another study, IGF-2 was extensively more

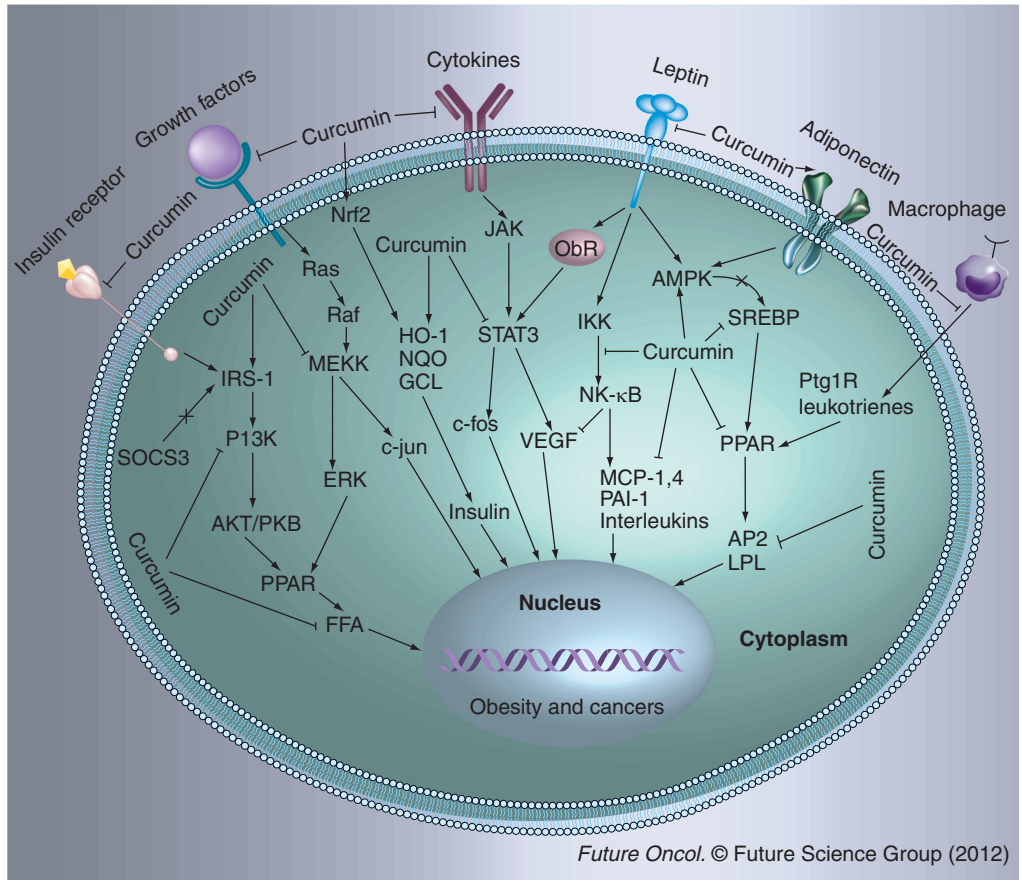

Figure 2. Multiple molecular targets of curcumin for obesity and cancer. Curcumin inhibits the insulin receptor, extracellur growth factors, inflammatory cytokines and leptin, and reduces macrophage infiltration, while increasing the production of adiponectin and AMPK, which results in the downregulation of NF-κB, SREBP, MCP-1–4, interleukins and PAI-1. Curcumin induces Nrf2 and increases the secretion of HO-1, which decreases insulin resistance. Curcumin blocks ObR and inhibits STAT, VEGF, ERK and Ptg1R binding with PPAR-γ. Curcumin inhibits EGF-stimulated phosphorylation of IRS-1 and PI3K, and decreases the level of PPAR and FFA. Curcumin enhances apoptotic death and inhibits deregulated cellular proliferation, differentiation and progression by altering multiple signaling molecules. Blunt-head lines indicate that these molecules can be downregulated by curcumin, whereas arrowhead lines show upregulation and crossed lines indicate inhibition in signaling pathways.
AMPK: AMP-activated protein kinase; FFA: Free fatty acid; HO-1: Heme oxygenase 1; Nrf2: Nuclear factor E2-related factor 2; PAI-1: Plasminogen activator inhibitor-1.

effective than progastrin in reversing proapoptotic effects of curcumin in the presence of p38 MAPK. The proapoptotic effects of curcumin was restored by treatment with the p38 inhibitors, suggesting that concomitant administration of curcumin would be required for reducing hyperproliferative or tumorigenic response of intestinal epithelia cells to endocrine and autocrine IGFs [26]. The effect of curcumin in concomitant treatment with 5-fluorouracil plus oxaliplatin has been investigated for 'chemosurviving' cells. Curcumin reverses chemotherapy resistance and cell-cycle arrest through the inhibition of IGF-1R, EGFR, HER-2 and AKT as well as the expression of COX-2 and cyclin-D1. However, curcumin alone was found to be more effective than both gefitinib and *IGF-1R* siRNA-mediated growth inhibition of chemotherapy-surviving HCT-116 cells, and addition of FOLFOX to curcumin did not increase the growth inhibitory effect of curcumin [27]. Curcumin is a well-known inhibitor of NF-κB and its upstream products, such as TNF-α, and downstream products, including IL-6 and COX-2, in adipocytes. Curcumin inhibited TNF-α activated NF-κB signaling, and reduced cytokines and *COX-2* gene expression [28]. In addition, PGC-2 is a SCAN domain-containing coactivator, specific for the AF-1 transcriptional activity of PPAR-γ and is thought to have a specific role in regulating adipogenesis [29]. Curcumin significantly inhibited uterine leiomyoma (ELT-3) cell proliferation, possibly through the activation of PPAR-γ, which is expressed in ELT-3 cells, where curcumin acted as a PPAR-γ ligand. This inhibitory effect of curcumin was attenuated by the treatment of cells with PPAR-γ as an antagonist. These observations suggested curcumin can be used as an alternative therapy for various benign gynecological tumors [30]. Recently, it has been observed that curcumin suppresses lipid accumulation and decreases the expression of fatty acid synthase (FAS), downregulating the mRNA levels of *PPAR-γ* and *CD36* during adipocyte differentiation [31].

Adipokines

Adipokines are adipocyte-secreted hormones that have been observed for their remarkable effects in the pathogenesis of obesity-related cancers. The importance of leptin and adiponectin, which act in an endocrine and paracrine fashion, and are considered to have a potential role in obesity-related cancers, has been highlighted here (Figure 3).

Leptin

Leptin is a 16-kDa protein, primarily produced in adipose tissue. Circulating leptin levels are directly correlated with the amount of body fat, which ranges from 5 to 10 ng/ml in normal healthy individuals and up to 40–100 ng/ml in obese individuals [32]. Leptin binds to its transmembrane receptor, ObR, and activates various signaling pathways that are involved in cell proliferation, including JAK/STAT, MAPK, IRS1 and SOCS3, as well as upregulating the expression of angiogenic factors such as VEGF [15]. Curcumin reduced serum insulin and leptin levels in fructose-induced hypertriglyceridemia and liver steatosis rats. Suppression of curcumin on leptin signaling resulted in phosphorylation of the long structure of the leptin receptor and STAT3, which downregulated the hepatic protein PTB in the liver of fructose-fed rats [33]. Furthermore, curcumin reduced leptin signaling by stimulating PPAR-γ activity as well as attenuating leptin-induced oxidative stress and prevented liver fibrogenesis associated with hyperleptinemia in NASH patients [7]. Recently, it has been shown that curcumin increased AMP-activated protein kinase (AMPK) activity, and prevented leptin from raising glucose levels in hepatic stellate cells by blocking the translocation of glucose transporter-4 and increasing glucokinase (Figure 3) [34,35].

Adiponectin

Adiponectin is a 30-kDa protein secreted exclusively by white and brown adipocytes [36]. Adiponectin is highly abundant in the circulatory system, with plasma concentrations of 3–30 μg/ml in healthy individuals. Adiponectin is a well-known insulin-sensitizing hormone, and it inhibits cancer progression and invasion through its receptors (adipoR1 and adipoR2). The expression of adiponectin receptors in the lung tissue was apparent only in the cancerous lung tissue (64.2% adipoR1 and 61.9% adipoR2) while adiponectin receptors were not expressed in the noncancerous tissues [37]. Adiponectin modulates several intracellular signaling pathways through its receptors and stimulates AMPK, PPAR-γ and MAPK in classical insulin target organs, such as the liver and skeletal muscles (Figure 2). Thus, obese individuals with low levels of adiponectin could be at a higher risk of developing tumors (Figure 3) [38]. Curcumin has been screened for an antiatherosclerosis effect through the increased expression of adiponectin [39]. Curcumin, in concomitant

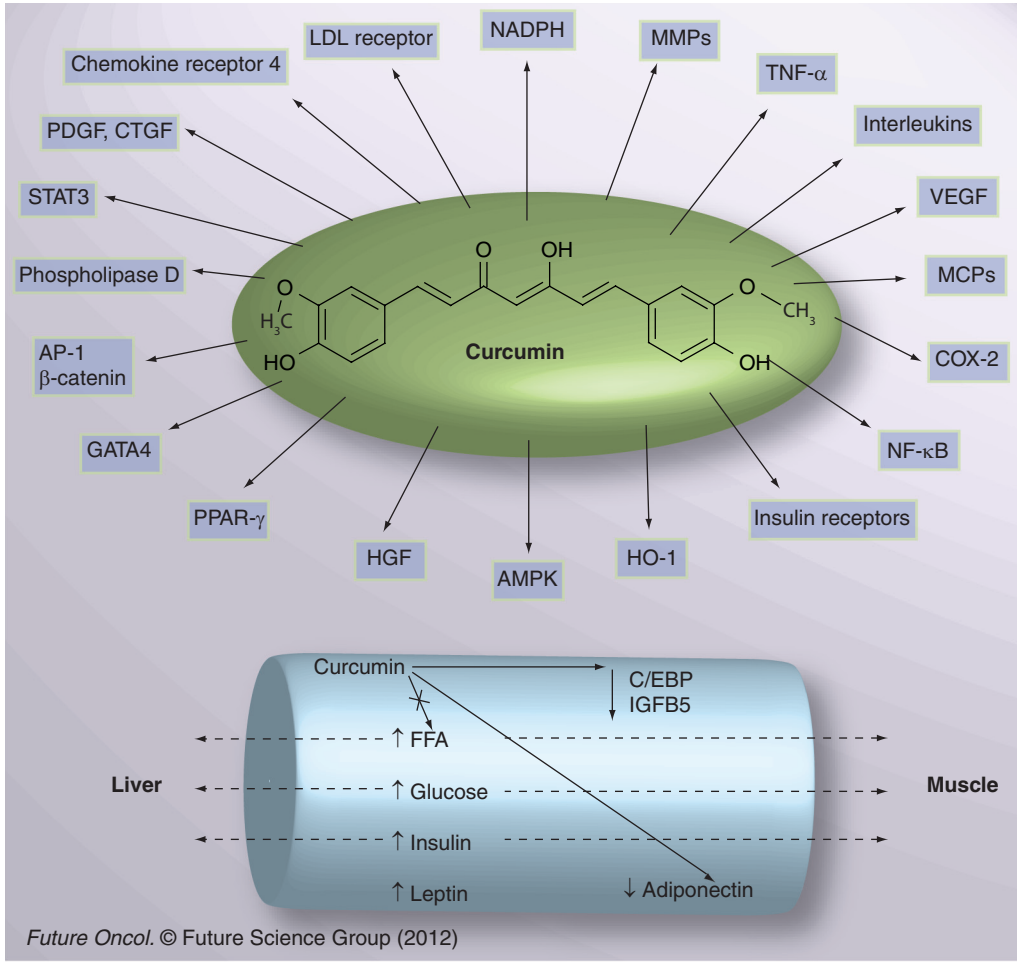

Figure 3. Curcumin can modulate several transcription factors (NF-κB, nuclear factor E2-related factor 2, AP-1, STAT proteins, PPAR and β-catenin), adipokines (TNF, interleukins, leptin, adiponectin and MCP) growth factors (VEGF, CTGF and TGF-β) and enzymes (COX-2, inducible nitric oxide synthase and NADPH oxidase). Curcumin increases nuclear C/EBP and IGFBP-5 expression as well as activated adiponectin, which are downregulated in obesity-related cancers. Curcumin inhibits the leptin and insulin from raising glucose levels and decreases FFA. Crossed lines indicate that these molecules can be inhibited or downregulated by curcumin, whereas arrowhead lines from curcumin show upregulation.
AMPK: AMP-activated protein kinase; C/EBP: CCAAT/enhancer-binding protein; FFA: Free fatty acids; HO-1: Heme oxygenase 1; LDL: Low-density lipoprotein; MMP: Matrix metalloprotease.

administration with docosahexaenoic acid, increased the endogenous production of adiponectin in mouse and human preadipocytes [40]. The insufficient adiponectin production and elevated levels of thioredoxin and thioredoxin reductase (TrxR1) promoted mammary tumor development. Adiponectin, in the presence of curcumin, resulted in the reactivation of phosphatase and tensin homolog in these mouse tumor cells, and could inhibit *TrxR1* promoter-mediated transcription and restore the mRNA expression of TrxR1 [41]. In addition, the effect of different concentrations (10–100 μg/ml) of curcumin on adiponectin secretion and IL-6 has been investigated *in vitro* in human adipose tissues. Compared with the untreated control group after a 6 h culture, the content of adiponectin in the adipose tissue culture medium increased by 100 μg/ml of curcumin ($p < 0.05$) and the content of IL-6 was significantly decreased by 100 μg/ml [42].

Inflammatory markers

Numerous proinflammatory cytokines and growth factors that are synthesized and released by adipose tissue, such as IL-6, TNF and macrophage migration inhibitory factor, are believed to have direct protumorigenic properties in the development of cancer [43]. Curcumin decreased cholangiocarcinogenesis in hamsters by suppressing inflammation-mediated signaling pathways, such as suppression of the

transcription factors including NF-κB, AP-1 and STAT-3, and reduction in the expression of proinflammatory proteins such as COX-2 and iNOS (Figure 2). In addition, curcumin suppressed the expression of cell survival proteins, such as bcl-2 and bcl-xL, proliferation (cyclin D1 and c-myc), tumor invasion (matrix metalloprotease-9 and ICAM-1), angiogenesis (VEGF) and microvessel density [44]. Curcumin has been shown to suppress obesity-induced inflammatory responses by suppressing adipose tissue macrophage accumulation or activation, and inhibiting TNF-α, iNOS and MCP-1 release from adipocytes [45]. Curcumin eliminated the hyperglycemia-induced hepatic stellate cell activation and abrogated the membrane translocation of glucose transporter 2 through the p38 MAPK signaling pathway by stimulating the activity of PPAR-γ and *de novo* synthesis of glutathione [46]. Furthermore, curcumin suppressed the expression of PPAR-γ-regulated genes such as α1 collagen, α-smooth muscle actin, CTGF, and receptors for TGF-β, PDGF-β and EGF [47]. Curcumin reduced β-catenin–TCF signaling through the inhibition of GSK-3β, ERK1/2, JNK and p38, which have major roles in angiogenesis and differentiation of cells and, thus, prevent obesity-related cancer. Curcumin inhibited C/EBPα, PPAR-γ, SREBP-1 and FAS in adipocytes. Curcumin suppression of adipogenic differentiation is accompanied by the Wnt signaling component, β-catenin, and the reduced differentiation stimulated expression of CK1α, GSK-3β and axin, which degrade β-catenin [48]. Curcumin reduced macrophage infiltration of white adipose tissue and inhibited hepatic inflammation markers such as TNF-α, IL-1β, SOCS3, MCP-1 and CC motif receptor-2. It has been observed that curcumin supplementation lowers the production of inflammatory cytokines, including TNF-α, IL-6, IL-8 and MCP-1, from monocytes induced by high amounts of glucose. In addition, curcumin lowers the blood levels of TNF-α, IL-6 and MCP-1, as well as decreasing glucose and glycosylated hemoglobin in diabetic rats that are fed on a curcumin diet [49]. It is also confirmed that the curcumin regulation of AMPK and its downstream targets, such as PPAR-γ, MAPK and COX-2 have important roles in controlling obesity-related cancer [50].

Metabolic effects

Epidemiological studies have provided a substantial amount of evidence that metabolic syndromes are associated with increased risk of many abnormalities such as raised blood pressure, elevated glucose level and lowered high-density lipoprotein (HDL) cholesterol. These disorders are associated with energy balance and increase many cancer-promoting factors, including insulin, IGF-1, inflammatory cytokines, adipokines and reactive oxygen species [51]. Numerous studies have indicated that curcumin reduces serum cholesterol concentrations by increasing the expression of hepatic low-density lipoprotein (LDL) receptors, blocking oxidation of LDL, increasing bile acid secretion and metabolic excretion of cholesterol, and repressing the expression of genes involved in cholesterol biosynthesis [52]. Curcumin decreased TNF-α and plasma free fatty acid levels in high-fat diet (HFD) male Sprague Dawley rats, where it showed an antihyperglycemic effect and improved insulin sensitivity [53]. The hypocholesterolemic effect of curcumin has been correlated with decreased triglyceride (27%), total cholesterol (33.8%), and LDL-cholesterol (56%), and significantly lowered the atherogenic index by 48% as compared with the control group. The curcumin diet upregulated hepatic *CYP7A1* mRNA levels and hepatic triglyceride levels were significantly reduced by 41% in rats fed with curcumin-supplemented diets in comparison with the control group [54]. Curcumin treatment also increased LDL-receptor mRNA and expression of SREBP genes, whereas mRNAs of the PPAR-γ target genes, CD36/fatty acid and fatty acid-binding protein 1 were downregulated in human hepatoma cell line HepG2 [55]. The possible hypolipidemic effect of curcumin was investigated in rats fed a high-cholesterol diet; however, curcumin diet supplement (0.5% weight/weight) decreased serum total cholesterol by approximately 21%, LDL by 42.5% and elevated HDL by 50% [56]. Moreover, curcumin abrogated the PDGRβ receptor (PDGF-βR) and the EGF receptor, and induced PPAR-γ as observed through the decreased level of PI3K (PI3K/AKT), ERK and JNK [57]. All these studies indicate that curcumin mediates its metabolic effects through multiple mechanisms and might be useful in controlling the progression of obesity-related cancers.

Oxidative stress

Oxidative stress is characterized by an increase in BMI, and obesity decreases the body's protective antioxidants and enhances oxidative stress, normally relevant in obesity-related cancer

development. It has been hypothesized that lipid peroxidation plays a central role in the relationships between dietary factors and breast cancer. Curcumin significantly lowered lipid peroxide levels, levels of hepatic fatty acid and cholesterol biosynthesis in a high-fat obese model. In accordance with this, curcumin inhibited HIF-α1 and HIF-α2 protein levels in Hep3B hepatoma and MCF-7 breast carcinoma cells (Figure 3). Curcumin protected against cardiac oxidative and endoplasmic reticulum stress mediated by acute myocarditis. Curcumin significantly suppressed the expression of iNOS and the catalytic subunit of NADP-reduced NADPH oxidase [58]. Curcumin mediates a hypolipidemic effect by increasing plasma paraoxonase activity, HDL-cholesterol to total-cholesterol ratios, ratios of apoA-I to apoB, and hepatic fatty acid oxidation activity, as well as inhibition of hepatic fatty acid and cholesterol biosynthesis in hamsters on a HFD [59]. Curcumin protected against the induced oxidation of LPL, iron-induced hepatotoxicity and inflammation, as well as increasing antioxidant vitamin levels, which are depleted due to the oxidative stress induced by the HFD [60]. Curcumin reduced both hepatic and nonhepatic fat distribution through lowering the fatty acid synthesis and oxidation ratio. Curcumin activated a fatty acid-oxidizing enzyme, acyl-CoA oxidase, a deficiency of which can lead to hepatic steatosis [61]. Recently, it has been reported that the inhibition of FAS also reduced food intake and body weight. Curcumin is competitively bound in the malonyl/acetyl transferase domain of FAS because acetyl-CoA and malonyl-CoA were the two substrates of this domain. Curcumin prevented the differentiation of 3T3–L1 cells and repressed lipid accumulation through decreased expression of FAS, *PPAR*-γ mRNA level and CD36 [62]. Furthermore, the activities of serum antioxidant enzymes, such as glutathione transferase and glutathione peroxidase, were increased with curcumin treatment in rats on a HFD. Curcumin also diminished oxidative stress by reducing peroxide formation and enhancing antioxidant enzyme activity [60]. Curcumin induced nuclear factor E2-related factor 2 (Nrf2) protein expression with upregulation of glutamylcysteine ligase mRNA and increased the cellular antioxidant, glutathione, in human bile duct cancer. In addition, curcumin activated heme oxygenase-1, a redox-sensitive inducible protein, via inactivation of the Nrf2–Keap1 complex, leading to increased Nrf2 binding to the resident heme oxygenase-1 and antioxidant-responsive element [63,64]. The elevated level of these antioxidant systems plays a major role in preventing obesity and promoting the anticarcinogenic activities of curcumin.

Steroid hormones

The exact mechanism underpinning the association between steroid hormones and obesity–cancer risk has not been uncovered, but it may result from an increase in the serum concentration of bioavailable estradiol, which is caused by elevated levels of estrogens and aromatase in the adipose tissue, and a decrease in the serum concentration of sex hormone-binding globulin [18]. Curcumin inhibited the expression of estrogen receptor downstream genes, including *pS2* and *TGF*-β in estrogen receptor-positive MCF-7 cells and this inhibition is also dependent on the presence of estrogen. Curcumin also decreases estrogen responsive element-chloramphenicol acetyltransferase (CAT) activity induced by 17-β estradiol. These anti-invasive effects appear to be mediated through the downregulation of matrix metalloprotease-2 and the upregulation of tissue inhibitors of TIMP-1, as well as inhibition of VEGF and bFGF [65]. Recently, it has been shown that curcumin counteracted the proliferative effect of estradiol and induces apoptosis in cervical cancer cells through modulation of telomerase, viral oncoproteins E6 and E7, proliferating cell nuclear antigen, p16 and cyclin D1 [66]. Additionally, curcumin inhibited methyltrienolone and IL-6-mediated prostate-specific antigen gene expression in human androgen-sensitive prostatic carcinoma cells (LNCaP cells) through the downregulation of the expression and activity of androgen receptors. The effects of curcumin appear to be mediated via the androgen response element of the *PSA* gene [67]. Curcumin treatment blocked NF-κB binding and inflammatory cytokine (IL-6, TNF-α and MCP-1) secretion under high-glucose conditions in human monocyte (THP-1) cells accompanied by reduced histone acetylase activity, and decreased the level of p300 and acetylated *CBP*/*p300* gene expression [68]. Moreover, studies have shown that curcumin regulates chromatin remodeling through the modulation of histone deacetylase (HDAC) activity. It is believed that glucocorticoids engage HDAC2 and inhibit inflammatory responses through the glucocorticoid receptor. It is known that HDAC2 is a typical component of the corticosteroid anti-inflammatory action, which is impaired in chronic obstructive

pulmonary disease. Hence, curcumin induced expression of HDAC2 at post-transcription level and reverses corticosteroid resistance in reactive oxygen species-stressed monocytes, and is considered to have therapeutic potential in chronic obstructive pulmonary disease [69].

Curcumin safety & toxicity

Clinical trials (Phase I and II) dealing with curcumin safety have shown that curcumin is safe and well tolerated. The curcumin doses (500–1200 mg/day) were administered in capsule form to 24 patients and safety was assessed for 72 h following curcumin administration. Only seven patients developed adverse effects, including diarrhea, headache, skin rashes and yellowish stool, which are grade 1 and not dose-related [70]. Curcumin administered at a dose of 3600–8000 mg/day for up to 4 months in patients with advanced colorectal cancers only resulted in minor gastrointestinal side effects, including nausea and diarrhea [71]. A 25-subject trial of cancer lesions was conducted in Taiwan, in which curcumin was administered at 4, 6, 8 and 12 g/day for 3 months. After curcumin treatment, no noticeable adverse effects were detected in patients. However, dosing above 8 g/day was unacceptable to the patients owing to the bulky nature of the drug [72]. Furthermore, different formulations have been reported in the literature for increasing the efficacy of curcumin, including adjuvant, nanocurcumin, liposomes, micelles and phospholipids. The polymeric nanoparticle that encapsulated curcumin, namely 'nanocurcumin', which is less than 100 nM in size, was synthesized from copolymers of *N*-iso-propylacrylamide, with *N*-vinyl-2-pyrrolidone and poly-(ethylene glycol) monoacrylate. In many cancer research centers, the BCM-95 (biocurcumax™) Phase II clinical study for oral premalignant lesions/cervical cancer is performed to assess the efficacy and safety of BCM-95. Another curcumin analog is dimethoxycurcumin, which possesses increased bioavailability in mice compared with parent curcumin and greater apoptotic properties in colorectal cancer [73]. However, only one study has pointed out that curcumin at doses of 4 g/day, 1 g/day or placebo in a 6-month, randomized, double-blind trial did not have any effect on triacylglycerols, or total LDL and HDL cholesterol over 1 month or 6 months [74].

Regarding curcumin toxicity, several *in vitro* and *in vivo* studies have found that curcumin induced DNA damage and chromosomal aberrations at concentrations similar to those reported in the literature for its beneficial effect. Furthermore, in the concentrations of 2.5–5 μg/ml curcumin was shown to induce DNA damage to both the mitochondrial and nuclear genomes in HepG2 cells [75]. Curcumin has also been reported to inhibit the activity of drug-metabolizing enzymes such as cytochrome P450, glutathione-*S*-transferase and UDP-glucuronosyltransferase [76]. The major obstacle for the clinical development of curcumin is its poor absorption, rapid excretion and low systemic bioavailability, which suggests that the therapeutic potential of oral curcumin is limited, although different methods have been adopted to enhance curcumin bioavailability such as nano-curcumin, phytosomes, liposomes, micelles and phospholipids.

Future perspective

The aforementioned literature clearly narrates the potential role of curcumin in the prevention and treatment of obesity-related cancer. The pleiotropic effect of curcumin is mediated through the regulation of transcription factors (NF-κB, Nrf2, activated protein 1, STAT proteins, PPAR and β-catenin), adipokines (TNF, interleukins, leptin, adiponectin, MCP), growth factors (VEGF, CTGF, TGF-β) and enzymes (COX-2, iNOS, NADPH). The modulation of several cellular transduction pathways by curcumin has recently been extended to elucidate the molecular basis for obesity-related cancers. The potential complementary effect of curcumin may occur through suppression of insulin resistance, uptake of glucose, inhibition of angiogenesis in adipose tissues and reduction of chronic inflammation associated with obesity-related cancer. However, the exact mechanism underpinning this effect of curcumin as well as the enhancing effects of curcumin through strutuctral modification is still under investigation.

Whilst the discovery of new formulations is promising, as demonstrated in several *in vitro* studies it will take a long time for the evaluation of safety, toxicity and efficacy, as well as translation to the clinic for early treatment. The molecular targets, bioavailability and animal studies of these formulations are not clear at present. Most human studies have been conducted as pilot studies with small numbers of patients. Future trials should include suitably planned pharmacokinetic and pharmacodynamic studies; such results might provide insights into curcumin's mechanisms of action at the clinical level, as well as those of new formulations. Furthermore, clinically, it is worth exploring the potential role that curcumin may play as part of chemotherapeutic combinations with clinically available anticancer

drugs. Thousands of studies have shown the potential role of curcumin in cancer management but no study is ready to advocate it unambiguously. All this will be possible after the completion of rationally designed Phase I/II/III clinical trials regarding obesity-related cancers. The evidence presented here suggests that curcumin should be assessed in such clinical settings. It is a realistic prospect that, in a few years time curcumin, and perhaps some new formulations, will play a significant role in the treatment and prevention of obesity-related cancers.

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Executive summary

Obesity & cancer

- Obesity is a complex pathophysiology that is considered a risk for the progression of cancers. Molecular mechanisms regarding obesity-related cancers are under investigation.

Mechanisms linking obesity to cancer risk

- Insulin, growth factors, transcription factors, adipocytokines, oxidative stress and metabolic syndromes are the main contributors to this mechanistic system.
- Numerous proinflammatory cytokines such as IL-6, TNF and macrophage infiltration also have a role in the development of cancer.

Curcumin molecular mechanisms in obesity-related cancer

- Curcumin abrogates the cross-linking signaling between obesity and cancers by inhibiting inflammatory cytokines, leptin and activated adiponectin.
- Curcumin suppresses lipid accumulation and decreases the expression of fatty acid synthase.
- Curcumin reduces serum cholesterol concentrations by increasing the expression of low-density lipoprotein receptors, blocking oxidation of low-density lipoprotein, and increasing bile acid secretion and metabolic excretion of cholesterol.

Curcumin safety & toxicity

- Curcumin is safe and well tolerated, even at very high doses, such as 12 g/day, and no major adverse effects have been reported so far.

Conclusion

- Obesity is a devastating burden to the health system.
- Obesity increases the risk of cancers through insulin resistance, adipokines, obesity-related inflammatory cytokines, steroid hormones, transcription factors and oxidative stress.
- Curcumin mediates multiple molecular targets and disrupts the signaling pathways leading to obesity-related cancer risk.

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