Review Article
Curcumin and Obesity

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Abstract

Turmeric has been long recognized for its anti-inflammatory and health-promoting properties. Curcumin is one of the principal anti-inflammatory and healthful components of turmeric comprising 2–8% of most turmeric preparations. Experimental evidence supports the activity of curcumin in promoting weight loss and reducing the incidence of obesity-related diseases. With the discovery that obesity is characterized by chronic low-grade metabolic inflammation, phytochemicals like curcumin which have anti-inflammatory activity are being intensely investigated. Recent scientific research reveals that curcumin directly interacts with white adipose tissue to suppress chronic inflammation. In adipose tissue, curcumin inhibits macrophage infiltration and nuclear factor κB (NF-κB) activation induced by inflammatory agents. Curcumin reduces the expression of the potent proinflammatory adipokines tumor necrosis factor-α (TNFα), monocyte chemoattractant protein-1 (MCP-1), and plasminogen activator inhibitor type-1 (PAI-1), and it induces the expression of adiponectin, the principal anti-inflammatory agent secreted by adipocytes. Curcumin also has effects to inhibit adipocyte differentiation and to promote antioxidant activities. Through these diverse mechanisms curcumin reduces obesity and curtails the adverse health effects of obesity. © 2013 BioFactors, 39(1):78–87, 2013

Keywords: *curcumin; obesity; inflammation; turmeric; adipocyte*

Turmeric rice

Five-Star Recipe with Golden Color and Healthful Outcomes [1]

- 2 tablespoons butter
- 1/2 chopped onions
- 1 minced garlic cloves
- 1 cup basmati rice
- 1 tablespoon fresh grated turmeric
- 1 1/2 cups vegetable broth
- 1 bay leaf
- 1 drop thyme
- salt and pepper

1. Introduction

Obesity is recognized as a worldwide health crisis and represents an area of increasing concern because of its predominant effects on worldwide morbidity, mortality, and economics [2]. Obesity is a health concern as it is a risk factor for many common chronic diseases including heart disease and stroke, diabetes mellitus, osteoarthritis (OA), hypertension, and others. Obesity is characterized by chronic low-grade metabolic inflammation and may be regulated by the control of preadipocyte differentiation. Thus, dietary factors like curcumin which have anti-inflammatory activities and which may have effects on preadipocyte differentiation and cellular oxidation are of great therapeutic importance.

Scientific evidence indicates that accompanying the expansion of white adipose tissue (WAT) in obesity there are marked changes in the cellular make-up of adipose tissue and the factors secreted. With obesity, adipose tissue M1 macrophages become more abundant and activated, recognizing danger associated molecular patterns and elaborating inflammatory mediators. The pattern of cytokine secretion from these activated macrophages as well as from the accompanying adipocytes within the adipose tissue changes with enhanced production of proinflammatory mediators at the expense of normally protective anti-inflammatory factors such as adiponectin. Overall, these changes contribute to the pathological outcomes associated with obesity such as type 2 diabetes and others.

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Curcumin is among the spices and other nutraceuticals that are now recognized to protect against the pathologic effects of obesity and related metabolic disorders [3]. Curcumin has direct effects on WAT to reduce inflammatory macrophage infiltration, to curb inflammatory adipokine synthesis, and to increase adipocyte adiponectin production. Curcumin may also directly retard preadipocyte differentiation and promote ultimate antioxidant expression. As curcumin has favorable effects in combating obesity-related disorders, it is important to understand how curcumin affects adipose tissue with among the goals the development of additional therapeutics to treat the common chronic metabolic disorders that are a consequence of obesity.

2. Prevalence of Obesity

The World Health Organization defines obesity as abnormal or excessive fat accumulation that presents a risk to health [4]. Persons with a body mass index (BMI) of 25 or more are generally considered overweight and those with a BMI of 30 or more are defined as obese. In 2008, 1.4 billion adults worldwide were overweight and one-half billion were classified as obese. The results of the National Health and Nutrition Examination Survey (NHANES) from 2009 to 2010 regarding the population prevalence of obesity in the United States showed that 69.2% of all adults aged $\geq$ 20 were overweight or obese [5]. This grouping included 74.1% of men and 64.5% of women. In the same NHANES study, the prevalence of obesity (BMI $>$ 30) in the United States was 35.5% among adult men and 36.3% among adult women. In 2012, the American Medical Association, the largest physician group in the United States, adopted policy H-150.953 to address obesity as a major public health program.

3. Health Risks of Obesity

Obesity presents a major risk to health. The WHO estimated in May 2012 that being overweight or obese leads directly to the death of at least 2.8 million adults each year worldwide [4]. NHANES data from 2000 were analyzed with regard to the number of excess deaths associated with given BMI among American adults [6]. Relative to normal weight, obesity was associated with nearly 112,000 excess deaths in the US. Grade I obesity (BMI 30 to $<$35) was associated with almost 30,000 of these excess deaths and grades II and III obesity (BMI $\geq$ 35) were associated with $>$ 82,000 of the excess deaths. Independent results from pooled analysis of a large number of prospective studies including over 1.4 million adults showed that overweight and obesity were associated with an increased risk of all-cause mortality [7]. Significantly, there is also a long-term health impact of obesity in childhood and adolescence. A body of consistent evidence supports the association of child and adolescent obesity with increased risk of both premature mortality and adult cardiometabolic morbidity [8].

TABLE 1 ***Obesity (BMI $>$ 30 kg/m^2) and the estimated relative risk of disease***

Disease	*Men*	*Women*
	Relative risk	
All-cause mortality	1.55	1.50
Ischemic heart disease	2.00	2.00
Stroke	1.50	1.55
Diabetes	5.50	7.00
COPD	1.00	1.00
Cancer—Breast	1.00	1.25 ($>$age 50)
Cancer—Colorectal	1.40	1.10
Cancer—Gallbladder	1.25	1.85
Cancer—Endometrial	–	2.50
Cancer—Esophageal (Adenocarcinoma)	2.45	2.15

Risk Relative to normal BMI (20–24.9). Source: [9].

Obesity raises the risk factors for specific common chronic diseases including cardiovascular diseases such as heart disease and stroke, diabetes mellitus, musculoskeletal disorders especially OA, and some cancers including endometrial, breast, and colon cancers [9–11] (Table 1).

Obesity confers a significant relative risk for cardiovascular diseases. Major risk factors for cardiovascular diseases are categorized as traditional and nontraditional or novel. Traditional risk factors are often modifiable and include hypertension, cigarette smoking, hypercholesterolemia, diabetes mellitus, elevated systolic blood pressure, and obesity. Thus, obesity is recognized as one of the basic traditional risk factors for cardiovascular disease in all people, both children and adults [12,13]. In addition to traditional risk factors, there is an expanding list of nontraditional or novel risk factors for cardiovascular diseases [14]. This class of risk factors includes elevated inflammatory and prothrombotic factors such as C-reactive protein (CRP), fibrinogen, interleukin-6 (IL-6), factor VIII, and lipoprotein (a). Significantly, these risk factors are all oxidative, proinflammatory, and elevated in obesity [15]. It is these oxidative and proinflammatory influences that appear to be positively affected by curcumin and thus one means by which curcumin counters some of the adverse health effects of obesity.

Mechanistically, elevated levels of nontraditional novel risk factors in obesity can be explained in part by the prominent effects of macrophage infiltration into the expanded adipose tissue in the obese [16]. Adipose tissue macrophages elaborate high levels of inflammatory signals and secrete proinflammatory cytokines such as TNF-α and IL-6. TNF-α promotes systemic inflammation and its levels correlate both with the

degree of adiposity and with the prevalence of associated insulin resistance [17]. Among its activities, IL-6 stimulates the liver to produce copious amounts of high-sensitivity CRP and this increased level of high-sensitivity CRP is particularly associated with abdominal obesity [18].

Obesity is also a significant risk factor for diabetes mellitus. Within the last decades, the numbers of clinical cases of obesity and type 2 diabetes have paralleled one another [19,20]. Excess accumulation of abdominal fat is regarded as an independent risk factor for developing diabetes and it worsens insulin resistance [20]. As the capacity of these adipocytes to store fats becomes saturated, lipids overflow into other tissues, especially the liver and muscle [21]. The Insulin Resistance Atherosclerosis Study of over 1,400 Hispanics and African-Americans concluded that high levels of visceral and subcutaneous fat are strongly and independently associated with insulin resistance [22]. The reduction of obesity-associated tissue inflammation by curcumin or other means improves insulin resistance and reduces the overall metabolic derangement in prediabetes and in type 2 diabetes [3].

Obesity also impacts the incidence of OA. Obesity is a risk factor for OA not only because of the increased weight-bearing on joints but because of the inflammatory component of OA [23]. Proinflammatory factors are secreted by inflamed synovial membranes of the articular capsules under excess weight-bearing, resulting in cartilage damage and breakdown [24,25]. Adipocytes within the infrapatellar fat pad of OA patients secrete inflammatory cytokines, interleukins, and adipokines that negatively influence cartilage by up-regulating the production of matrix metalloproteinases (MMPs) and by inhibiting the production of cartilage matrix proteins [26]. The inflammatory adipokines leptin and resistin have been shown to be elevated within the synovial fluid of patients with OA [26–28]. Thus, direct and indirect anti-inflammatory effects of curcumin would result in changes in adipokine secretion from these adipocytes. Analyses of *in vitro* and *in vivo* studies suggest that curcumin may be a beneficial complementary treatment for OA [29]. Although data are limited, curcumin and curcumoids have beneficial effects in reducing inflammatory mediator production by human chondrocytes and cartilage explants and in acting either directly or indirectly as an antioxidant [29].

4. Metabolic Effects of Obesity

WAT is a complex endocrine organ consisting of multiple cell types including adipocytes as the predominant type, and also stem cells, mesenchymal precursor cells, preadipocytes, fibroblasts, vascular components, and significant numbers of tissue macrophages and lymphocytes [30]. WAT secretes energy-controlling factors as well as a multitude of proteinaceous cytokines, collectively called adipokines. It is estimated that 20–30% of the expressed genes of WAT encode secreted adipokines. Extensive proteomic profiling of the secretome of adipocytes derived from human subcutaneous WAT identified 263 distinct secreted proteins, including previously-recognized as well as novel factors [31]. Adipokines greatly affect host health by exerting chronic regulatory actions on metabolism, immune function, vascular homeostasis and, specific to the present discussion, inflammation [32]. Table 2 lists several classic adipokines and significant proinflammatory adipokines.

Obesity promotes serious metabolic consequences including insulin-resistance [35]. Increased fat mass during obesity is associated with adipocyte hypertrophy, low grade inflammation due to macrophage infiltration, and altered adipose adipokine secretion reflected with an overall increase in circulating levels of pro-inflammatory cytokines and a reduction in the anti-inflammatory adiponectin. The altered secretion of fatty acids and adipokines by adipose tissue promotes lipotoxicity, mitochondrial dysfunction, and insulin resistance in peripheral tissues [35].

Chronic low-grade inflammation may underlie much of the pathology contributing to the health risks associated with obesity [36–38]. Low-grade inflammation is nearly universal in the obese state. Early observations showed that in disease states associated with obesity such as type 2 diabetes, there were significant increases in the levels of acute phase reactants and inflammatory mediators including adipose tissue-derived inflammatory cytokines [39]. Hotamisligil et al. made a hallmark observation implicating inflammatory cytokines in obesity-associated disease when it was shown that the proinflammatory cytokine TNF-α produced by adipose tissue in obesity was able to induce insulin resistance [40]. Adipose tissue-derived TNF-α has been observed to be overproduced in obese humans as well as in rodent models of obesity [41,42].

Another important observation associating low-grade inflammation and obesity was that of the inverse relationship between plasma fibrinolytic activity and obesity [43]. Measurements of plasma fibrinolytic activity, inhibitors of fibrinolysis, and fibrinogen were made in subjects of varying obesity states and it was concluded that the low blood fibrinolytic activity found in obesity was due to decreased activity of plasminogen activator. The reduced fibrinolytic activity and decreased plasminogen activator activity in obesity was shown in turn to be associated with increased levels of plasminogen activator inhibitor type-1 (PAI-1). The enhanced production of PAI-1 in the obese decreases fibrinolysis and promotes a significant increase in the risk of thromboembolism. The increased PAI-1 is most likely caused by characteristic patterns of inflammatory cytokine release, including TNF-α in adipose tissue [44].

5. Adipokines and Inflammation

The central observation linking obesity and inflammation was the identification of the overexpression of proinflammatory adipokines by adipose tissue in obesity and their contribution to systemic metabolic dysfunction in obesity [33,40]. With

TABLE 2 ***White adipose tissue adipokines***

Adipokine	*Effects of obesity*	*Role in inflammation*
Adiponectin	Decreased in obesity	Down-regulates inflammatory responses
Leptin	Increased in obesity	Proinflammatory effects on T-cells, impairs NK cell function
Apelin	Apelin inhibits food intake	Positively correlated with BMI
Omentin	Decreased in obesity	Inhibits TNF-α induced inflammation
Visfatin	Circulating levels increased, associated with insulin resistance	Elevated in both acute and chronic inflammation
Proinflammatory Adipokines		
TNF-α	Increased expression and secretion by WAT	Increased systemic inflammation
IL-6	Increased in obesity	Promotes hepatic CRP
IL-18	Elevated in visceral WAT	Proinflammatory cytokine
Plasminogen activator inhibitor-1 (PAI-1)	Increased in obesity	Upregulated by TNF-α, IL-1
Monocyte chemoattractant protein-1 or CCL2	Enhanced monocyte extravasation	Enhanced monocyte recruitment and extravasation

Sources: [33,34].

developing obesity, fat tissue changes significantly [36]. Both observational and experimental models of obesity show that various proinflammatory mediators are selectively synthesized and secreted by adipose tissue of the obese. The recruitment of macrophages as well as T cells into adipose tissue in the obese state contributes to enhanced proinflammatory mediator synthesis [45]. In obesity, macrophages are recruited to adipose tissue and converted from tissue remodeling, anti-inflammatory M2 types to classically activated, tissue destructive M1 types [46]. This infiltration and type conversion of macrophages of adipose tissue in obesity precedes the development of insulin resistance in animal models, suggesting the crucial role of obesity-related adipose tissue inflammation in associated diseases such as type 2 diabetes [47]. T cell recruitment into adipose tissue in obesity has been shown to promote the production of unique proinflammatory mediators from adipose tissue including eotaxin, CCL5/RANTES, and G-CSF [45,48]. In addition, adipose tissue contains secretory preadipocytes, fibroblasts, and vascular components [49]. Macrophages, adipocytes, as well as many of these other cell types contribute to the proinflammatory state associated with obesity.

TNF-α was the first proinflammatory cytokine identified as being hypersecreted by adipose tissue in obesity [40]. Most WAT-derived TNF-α is secreted by stromal vascular cells which include macrophages and the nonfat cells present in adipose tissue [50]. Studies with subcutaneous adipose-tissue specimens showed a strong, positive correlation between TNF-α secretion and BMI, total body fat, and adipocyte volume [51]. In obesity, the synthesis and secretion of proinflammatory adipokines are specifically up-regulated whereas the production of the major anti-inflammatory adipokine adiponectin is specifically down-regulated (Table 2) [33,52,53]. In addition to TNF-α, among the more-widely studied inflammatory adipokines are leptin, IL-1β, IL-6, IL-8, IL-10, and IL-15, resistin, lipocalin-2, plasminogen activator inhibitor-1 (PAI-1), leukemia inhibitory factor, hepatocyte growth factor, SAA3, macrophage migration inhibitory factor, haptoglobin, complement factors B, D, C3, and prostaglandin E2 [33,54].

The molecular mechanisms driving the chronic low-grade metabolic inflammation in obesity is uncertain, but recent research has led to the elaboration of interesting hypotheses [55]. With the identification of the NLRP3 inflammasome in adipose tissue, it was suggested that the NLRP3 inflammasome may regulate obesity-associated inflammation and insulin sensitivity by functioning as a sensor for danger-associated molecular patterns [56,57]. The NLRP3 inflammasome is a cytosolic molecular complex of the NOD-like family consisting of the regulatory subunit NLRP3, the adapter ASC, and the effector subunit procaspase-1. Its expression in adipose tissue correlates directly with body weight [45,58]. When activated by diverse environmental or endogenous danger signals, the NLRP3 inflammasome complex assembles with subsequent recruitment and activation of procaspase-1 leading to the cleavage of IL-1β and IL-18 into biologically active proinflammatory cytokines [56]. There are multiple primary danger-associated molecular patterns or lipotoxicity-associated signals that trigger the NLRP3 inflammasome in adipose tissue. Studies suggest that the accumulation of fatty acids and increased

production of ceramide in obese adipose tissue may be among these danger signals [45,55].

Elevated caspase-1 activity in adipose tissue with obesity leads to increased processing of IL-1β and IL-18 and the promotion of a proinflammatory environment that drives adipose tissue dysfunction [59]. Studies of adipose tissue biopsies from obese men suggest that NLRP3 inflammasome activation and the accompanying TH1 shift of T cells are related to insulin resistance [60]. In obese mice, ablation of the NLRP3 regulatory subunit prevents obesity-induced inflammasome activation within fat depots, promotes increases in the number of anti-inflammatory M2 macrophages, and improves overall insulin signaling [45].

Dietary curcumin and curcumoids may reduce the production or sensing of danger-associated molecular patterns in the adipose tissue and through this means protect against the pathologic chronic inflammation associated with long-term obesity. Curcumin and other phytochemicals have been demonstrated to inhibit pattern recognition receptor pro-inflammation signals, particularly signals resulting from NOD2 dimerization and NOD2 signaling to NF-κB [61]. Although direct effects of dietary curcumin on NLRP3 inflammasome activation have not been demonstrated, extensive studies of NOD-like receptor effector domain interactions show that NOD2, as affected by curcosome, specifically and directly interacts with NLRP3. Thus, by interfering with NOD2 signaling curcumin may reduce NLRP3 inflammasome activity [62].

6. Curcumin Effects on Obesity-Associated Inflammation

Beneficial and anti-inflammatory effects of curcumin and curcuminoids in the obese state are produced through regulation of a diverse range of molecular targets (Fig. 1) [3,63–65]. In adipose tissue macrophages and several other cells and tissues, curcumin down-regulates the DNA-binding and transcriptional activities of the inflammatory transcription factors NF-κB and AP-1, scavenges reactive oxygen species, and suppresses mitogen-activated protein kinases generated by inflammatory stimuli [66–69].

Curcumin inhibits inflammatory cytokine secretion in experimental systems. The secretion of the TNF-α and monocyte chemoattractant protein-1 (MCP-1) from mouse Raw 264.7 macrophages was shown to be stimulated after treatment with conditioned medium from mesenteric adipose tissue isolated from obese mice [70]. Pretreatment with curcumin inhibited in a dose-dependent manner this secretion of inflammatory cytokines. This conditioned medium from adipose tissue also stimulated the release of MCP-1 from 3T3-L1 adipocytes, and this too was inhibited by curcumin pretreatment [70]. Using the same mouse Raw 264.7 macrophage cell line, pretreatment with curcumin or with either of two curcumin analogs also inhibited in a dose-dependent manner the LPS-stimulated

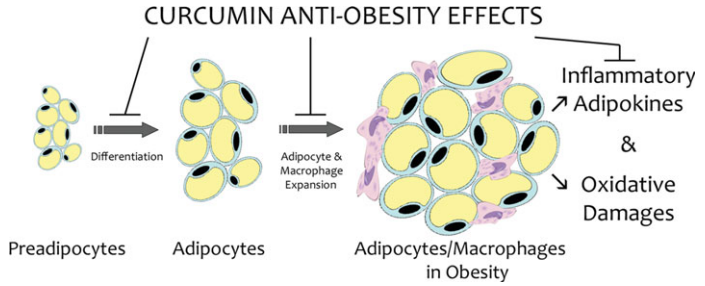

FIG 1

Curcumin effects on adipose tissue in obesity. The figure shows the differentiation, expansion, and macrophage infiltration of WAT with increasing obesity. Curcumin has experimentally reported diverse effects to inhibit preadipocyte differentiation, to inhibit macrophage expansion and infiltration in WAT, to suppress inflammatory adipokine secretion from WAT, and to promote cytoprotective antioxidant expression.

mRNA and secretory protein levels of TNF-α, IL-1β, and IL-6 [71]. In parallel, curcumin and its analogs inhibited LPS-stimulated NF-κB nuclear translocation and DNA binding, all supportive of direct stimulation of anti-inflammatory mechanisms by curcumin.

The effects of a dietary curcumin admixture were studied by Weisberg in genetically obese *ob/ob* mice and obese mice consuming high-fat diets (HFD) [63]. Remarkably, the curcumin supplementation ameliorated symptoms of diabetes and insulin-resistance in these obese mice. The animals fed curcumin also showed significantly reduced macrophage infiltration of WAT, consistent with a local reduction in low-grade inflammation. Also observed in curcumin-fed animals were an increased production of the anti-inflammatory adiponectin by adipose tissue, overall increased adiponectin in circulation, and decreased hepatic NF-κB activity. Overall, the curcumin-fed animals showed diminished inflammation and improved glycemic status as determined by blood glucose levels, HbA1c, and insulin tolerance tests [63].

To improve delivery, curcumin-containing liposomes, termed curcusome nanoparticles, were injected intraperitoneally in *ob/ob* mice and effects on TNFα-producing hepatic dendritic cells and adipose tissue macrophages were determined [68]. Animals receiving injections of curcusome nanoparticles exhibited reduced TNF-α production from both hepatic dendritic cells and adipose tissue macrophages and this was associated with an improvement of insulin resistance. The isolated adipose tissue inflammatory dendritic cells from the control *ob/ob* mice showed enhanced activation of classical NF-κB signaling. However, in animals treated with curcusome nanoparticles, classic NF-κB activation was reduced as was NF-κB-dependent IL-6 secretion [68]. Overall, the results confirm Weisberg's initial studies that dietary curcumin improves obesity-associated inflammation and metabolic dysfunction [63].

A more recent study utilized an interesting and relevant model: longer-term 28-week HFD feeding of C57BL/6J mice and curcumin supplementation only two days per week [65]. This study was designed to more closely mimic the natural development of insulin resistance in humans as well as to utilize more intermittent curcumin consumption that might be more typical. In this model, body weight increased after 16 weeks of HFD and from that point on until the end of the study, the inclusion of dietary curcumin slowed body weight gain and improved whole body glucose disposal both by enhancing insulin sensitivity and by inhibiting hepatic gluconeogenesis. Dietary curcumin reduced the effect of HFD on macrophage infiltration in WAT, improved insulin stimulated PKB phosphorylation in adipose tissue and liver, and repressed the expression of NF-κB and JNK activity in epididymal fat pads. All observations are supportive of an anti-inflammatory effect of dietary curcumin [65]. Interestingly and in contrast to other studies as reported below, further study of the epididymal fat pads from these animals showed no stimulatory effect of dietary curcumin on Wnt pathway components or Wnt target gene expression.

7. Curcumin Effects on Adipocyte Differentiation

Curcumin may suppress preadipocyte differentiation and thus reduce the number of adipocytes and fat content of adipose tissue [3,72,73]. In experimental systems, the cocktail of isobutylmethylxanthine (IBMX), insulin, and dexamethasone promotes the differentiation of primary human preadipocytes and murine 3T3-L1 preadipocytes [74]. Curcumin treatment (5–20 μM) produced a dose-dependent inhibition of adipocyte differentiation as assessed by both oil red O staining and adipocyte specific gene expression (peroxisome proliferator-activated receptor γ (PPARγ), CCAAT enhancer binding protein α (C/EBPβ) leptin, adiponectin, and resistin) [74]. This inhibitory action of curcumin was largely limited to the early stage of adipocyte differentiation, a stage typified by mitotic clonal expansion, rather than post-mitotic terminal stages of differentiation.

Other studies confirmed these cell culture outcomes and extended them with *in vivo* analyses using mice fed HFD [75]. In these studies, dietary curcumin did not affect food intake but reduced body weight gain, adiposity, and microvessel density in subcutaneous adipose tissue. In the adipose tissue of curcumin-fed mice, the expression of adipocytic transcription factors (C/EBPα, PPARγ) was reduced as was the activity of glycerol-3-phosphate acyl transferase-1 [75]. Twelve weeks of dietary curcumin in HFD-fed mice increased the level of phospho-AMPK in subcutaneous adipose tissues, augmented fatty acid oxidation, and attenuated the synthesis of glycerol lipids [75]. In 3T3-L1 adipocytes, curcumin stimulated AMPK activity and down-regulated PPARγ [76]. Thus, curcumin-dependent activation of AMPK may also contribute to the mechanism of curcumin-induced inhibition of adipocyte differentiation.

8. Curcumin Effects on Wnt/β-Catenin Signaling

Part of the effect of curcumin on inhibition of preadipocyte differentiation has been proposed to be through modulation of the canonical Wnt signaling pathway in preadipocytes [72]. The presence or absence of Wnt signaling controls the fate of mesenchymal stem cells including the growth arrest of preadipocytes and their terminal differentiation into mature adipocytes [77–81]. The canonical Wnt signaling system serves as an adipogenic switch: the initiation of adipogenesis requires inactivation of canonical Wnt signaling. When Wnt signaling is off, preadipocyte differentiation occurs and adipocyte conversion proceeds; when Wnt signaling is on, preadipocyte differentiation is inhibited.

Active Wnt signaling reduces glycogen synthase kinase 3 (GSK3) activity and this loss of GSK3 activity allows cytosolic underphosphorylated β-catenin to accumulate and to translocate to the nucleus. In preadipocytes, nuclear β-catenin promotes Tcf/LEF-1-mediated transcription of cyclin D1 and c-Myc, which in turn function to inactivate transcription factors essential for adipogenesis, including C/EBPα and PPARγ [82]. Overexpression of Wnt10b in preadipocytes activates canonical Wnt signaling, stabilizes free cytosolic β-catenin, and blocks adipocyte differentiation [77]. In preadipocytes, Wnt10b binds to cell surface Frizzled family receptors (FZD1, 2, and 5) and low-density lipoprotein receptor related protein coreceptors (LRP5, 6) to activate nuclear β-catenin signaling and inhibit differentiation into mature adipocytes. Conversely, disruption of canonical Wnt signaling leads to the GSK3 phosphorylation-dependent ubiquination and proteasomal clearance of β-catenin, which in turn drives preadipocyte differentiation [77–81].

The direct role of Wnt/β-catenin signaling in the anti-adipogenic activity of curcumin was examined using mouse 3T3-L1 preadipocyte cells [72]. In these experiments, 10–25 μM curcumin inhibited adipocyte differentiation driven by the differentiation cocktail of IBMX, insulin, and dexamethasone. Associated with this effect in inhibiting differentiation, curcumin treatment increased Wnt10b gene expression, inhibited MAPK phosphorylation, and restored the nuclear translocation of β-catenin in a dose-dependent manner [72]. In parallel, curcumin reduced the expression of GSK3α, casein kinase 1α, and axin, all components of the destruction complex targeting β-catenin, and curcumin enhanced the expression of c-Myc and cyclin D1, downstream targets of β-catenin. All of these activities driven by curcumin were associated with suppressed adipogenesis in 3T3-L1 cells. The exact mechanisms of these actions of curcumin in blocking adipocyte differentiation are not clear. However, as Wnt10b gene expression was increased markedly within 48 h of curcumin exposure and as overexpressed Wnt10b stabilized β-catenin and blocked differentiation, Wnt10b expression may be the central target of curcumin action in the 3T3-L1 preadipocytes [72].

As stated above, not all investigations of curcumin in fat tissue, adipocytes, or other tissues have shown effects of curcumin on Wnt pathway components or Wnt target gene expression [65]. Indeed, in colon and prostate cancers, curcumin impairs Wnt/ β-catenin signaling, an activity that may be part of the antitumorigenic effects of curcumin in these tissues [83,84]. As there are estimated to be 19 Wnt family members in the human genome, differences in response to curcumin among types is expected [85]. In regards to human obesity, canonical Wnt10b expression is high in preadipocytes and declines rapidly after induction of differentiation. However, in human obesity associated with high adipocyte differentiation, serum levels of the proinflammatory, non-canonical Wnt5a are elevated [77,78,86].

9. Curcumin Effects on the NRF2/KEAP1 Pathway

Curcumin affects the NFE2-related factor 2 (Nrf2). Nrf2 has been extensively studied for its protective role in suppressing oxidative stress and inhibiting carcinogenesis [87]. Nrf2 is a transcription factor and master regulator of antioxidant responses, affecting the expression of hundreds of cytoprotective genes controlling antioxidant enzymes, immune responses, and inflammation. Under quiescent conditions, Nrf2 is sequestered in the cytoplasm through tight binding to the negative regulator protein Keap1. Upon activation, conformational change of the Keap1 protein reduces its binding affinity for Nrf2 which as a result escapes proteosomal degradation and allows subsequently translocation to the nucleus. In the nucleus, Nrf2 dimerizes and binds to antioxidant response elements in target genes, regulating their expression.

Low doses of curcumin promote the nuclear translocation of Nrf2 in hepatocytes [88]. Curcumin activates Nrf2 presumably through modification of Keap1, allowing for dissociation, nuclear translocation, and promotion of antioxidant expression, particularly the ultimate antioxidants NADPH-quinone oxidoreductase 1 (NQO1) and heme oxygenase-1 (HO-1) [3,89]. Thus, curcumin may activate protective antioxidant systems.

However, the selective deficiency by targeted knockout of Nrf2 in human subcutaneous preadipocytes and murine 3T3-L1 cells was observed to impair adipocyte differentiation [90]. In C57BL6 mice, the loss of Nrf2 resulted in decreased adipose tissue mass and resistance to diet-induced obesity in the absence of any obvious changes in food intake or intestinal fat absorption [90]. With this model, an activation of Nrf2 by curcumin would be predicted to stabilize C/EBPα and PPARγ and promote adipocyte differentiation which would be inconsistent with an effect of curcumin to inhibit preadipocyte differentiation.

10. Curcumin and Epigenetics

Obesity may be strongly influenced by epigenetics in which specific adverse environmental exposures directly affect the genome and ultimately lead to the promotion of increased susceptibility to obesity and consequent diseases such as type II diabetes and cardiovascular disease [91]. Although mainly studied in the potential role of curcumin in cancer therapy, curcumin may promote epigenetic modulations that affect target genes in obesity. These actions include global DNA hypomethylation, histone modifications, micro RNA metabolism, and specific inhibition of p300/CBP histone acetyltransferase [92].

Curcumin has been extensively studied for its effects on DNA hypomethylation, specifically CpGs demethylation in gene promoters [93]. Curcumin through effects resulting from DNA hypomethylation, restores expression of Nrf2 and subsequently induces Nrf2-mediated anti-oxidative actions and activation of cellular stress defense pathways [93]. Thus, curcumin affects Nrf2, a master regulator of cellular antioxidant systems, not only through coactivation of Nrf2-mediated transcription, but also by inducing Nrf2 gene expression through epigenetic pathways.

11. Curcumin Effects on SIRT1 in Adipose Tissue

Sirtuin1 (SIRT1), an NAD-dependent protein deacetylase, regulates gene transcription and affects multiple signaling pathways including inflammation [94]. SIRT1 is expressed in WAT where it represses the transcriptional activity of the nuclear receptor PPARγ, the ligand-activated transcription factor which functions as the master regulator of adipocyte differentiation [95]. Under normal feeding conditions, SIRT1 protects against inflammation in adipose tissue and against overall obesity. SIRT1 also slows the progression to metabolic dysfunction under dietary stress. In studies with human subjects, SIRT1 level in adipose tissue is inversely related to BMI and adipose tissue macrophage infiltration [96].

Genetic ablation of *SIRT1* specifically in adipose tissue increases adiposity and predisposes animals to metabolic dysfunction [97]. Accompanying these metabolic effects are gene expression changes that highly overlap those seen induced by high-fat diets in wild-type mice, including gene categories related to inflammation [97]. In diet-induced obese mice, SIRT1 protein levels in perigonadal adipose tissue were found to be significantly lower compared to normal weight mice [63]. Thus, maintained expression and function of SIRT1 in adipose tissue protects from inflammation and forestalls the progression to metabolic dysfunction [97].

It would be predicted that activators of SIRT1 in adipose tissue would reduce macrophage infiltration, decrease inflammatory adipokine secretion, and improve insulin sensitivity. Studies with the polyphenol resveratrol as well as other more potent molecules identified through a novel screening program for SIRT1 activators showed that these dietary SIRT1 activators improved insulin sensitivity of liver, muscle, and fat in genetic and diet-induced obese mice [98]. Investigative study

of SIRT1-activating compounds suggests that these small molecules interact directly with the enzyme and affect enzyme activity by an allosteric mechanism [96]. However, more recent studies on the activity of resveratrol suggest that its activation of SIRT1 may be indirect and rather a consequence of AMPK activation [99].

Does curcumin affects SIRT1 expression in adipose tissue? It is an attractive mechanism to explain the some of the beneficial effects of curcumin on obesity-induced adipose tissue inflammation; however, it was not identified as a potent direct SIRT1-activating compound in high-throughput screens. Despite this, in mouse models of obesity curcumin treatment reduced endoplasmic reticulum stress in adipose tissue and this was accompanied by significant increases in the expression of SIRT1 [63].

Indeed indirect mechanisms of SIRT1 activation by curcumin may explain its activity. Like resveratrol, the effect of curcumin on SIRT1 may be indirect through its activation of AMPK [99–101]. Curcumin up-regulates the expression of phosphorylated AMP-activated protein kinase (AMPK), perhaps via LKB1, and this activated AMPK in turn can function as a SIRT1 activator [102].

12. Conclusions

Curcumin is one of the hundreds of components isolated from the ancient spice turmeric and it is being studied intensively today for its potential therapeutic activity in the treatment of obesity and obesity-related metabolic disorders [3]. Curcumin regulates local and systemic targets to suppress inflammation, to inhibit preadipocyte differentiation, and to activate potent cellular antioxidants. Obesity promotes a chronic low-grade inflammation, contributing to the development of metabolic dysfunction and the worsening of insulin resistance and symptoms of type 2 diabetes. Curcumin directly interacts with adipose tissue to suppress inflammation. In adipose tissue, curcumin inhibits macrophage infiltration, inhibits NF-κB activation induced by proinflammatory agents, down-regulates the expression of inflammatory adipokines including TNFα, MCP-1, and PAI-1, and induces the expression of adiponectin, the most anti-inflammatory agent secreted by adipocytes. There are multiple mechanism by which curcumin affects these anti-inflammatory processes. Diverse molecular targets of curcumin include transcription factors (NF-κB, AP-1), growth and differentiation factors (Wnt10b), inflammatory cytokines (TNF-α, IL-1β, and IL-6), mitogen-activated and AMP-activated protein kinases, and other complex regulatory systems.

Curcumin also retards preadipocyte differentiation, preventing the generation of larger numbers of mature adipocytes. The underlying cellular mechanism of this action may be the preservation of active canonical Wnt signaling within WAT with β-catenin-dependent suppression of C/EBPα and PPARγ, transcription factors essential for adipogenesis. In other tissues, curcumin induces the nuclear translocation and activation of Nrf2, a master regulatory transcription factor essential for the expression of multiple cytoprotective antioxidants. However, the effects of curcumin on Nrf2 activity in preadipocytes may be more complex. Curcumin also functions to blunt the sensing of danger-associated molecular patterns in adipose tissue and the subsequent activation of the NLRP3 inflammasome. Curcumin may also influence the longevity of the intracellular regulator of energy metabolism SIRT1 in adipose tissue. SIRT1 functions in adipose tissue to protect from inflammation.

In summary, curcumin affects WAT in obesity. Curcumin inhibits obesity-driven inflammatory pathways at the cellular and biochemical level and improves overall systemic inflammation, hyperglycemia, and insulin resistance. The efficacy of curcumin in regulating multiple targets culminates in overall impaired adipogenesis, suppression of chronic low grade inflammation, and enhancement of cellular antioxidant defenses.

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