Curcumin induces brown fat-like phenotype in 3T3-L1 and primary white adipocytes

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Abstract

Recent advances have been made in the understanding of pharmacological and dietary agents that contribute to browning of white adipose tissue in order to combat obesity by promoting energy expenditure. Here, we show that curcumin induces browning of 3T3-L1 and primary white adipocytes via enhanced expression of brown fat-specific genes. Curcumin-induced browning in white adipocytes was investigated by determining expression levels of brown adipocyte-specific genes/proteins by real-time reverse transcriptase polymerase chain reaction, immunoblot analysis and immunocytochemical staining. Curcumin increased mitochondrial biogenesis, as evidenced by transmission electronic microscopic detection and enhanced expression of proteins involved in fat oxidation. Curcumin also increased protein levels of hormone-sensitive lipase and p-acyl-CoA carboxylase, suggesting its possible role in augmentation of lipolysis and suppression of lipogenesis. Increased expression of UCP1 and other brown adipocyte-specific markers was possibly mediated by curcumin-induced activation of AMP-activated protein kinase (AMPK) based on the fact that inhibition of AMPK by dorsomorphin abolished expression of PRDM16, UCP1 and peroxisome proliferator-activated receptor gamma co-activator 1-alpha while the activator 5-Aminoimidazole-4-carboxamide ribonucleotide elevated expression of these brown marker proteins. Our findings suggest that curcumin plays a dual modulatory role in inhibition of adipogenesis as well as induction of the brown fat-like phenotype and thus may have potential therapeutic implications for treatment of obesity.

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Keywords: Anti-obesity; Curcumin; Adipocyte browning; Non-shivering thermogenesis; UCP1

1. Introduction

Obesity develops when energy intake exceeds energy expenditure [1] and is mainly characterized by excessive deposition of adipose tissues [2,3]. Restriction of caloric intake is considered to be first line defense against obesity, but this strategy does not help people with dysfunctional development of brown fat tissue, which dissipates surplus caloric intake into heat energy via a process known as non-shivering thermogenesis [4,5]. In this regard, browning of white adipocytes is considered as an alternative strategy against diet-induced obesity. After the recent finding of brown adipose tissue (BAT) in adult human subjects, strategies for combating obesity have shifted from preventing fat accumulation to promoting energy expenditure by activation of BAT and browning of white adipose tissue (WAT) [6,7]. In this sense, induction of white fat browning represents an attractive potential strategy for the treatment of obesity and related complications.

Although brown and white adipocytes originate from different cell lineages and each lineage has a different progenitor, they are readily interconvertible to each other [8]. Expression of UCP1 in multilocular cells with thermogenic capability to develop in white fat depots with some external stimuli is being characterized as beige or brile (brown in white) [9]. This UCP1-driven heat dissipation is known as adaptive thermogenesis [10]. UCP1 uncouples the electron transport chain from energy production, resulting in release of heat energy [11]. Cold exposure and pharmacological activation of β3-adrenergic receptors are key factors in the appearance of brite adipocytes in WAT via promotion of WAT remodeling by adipocyte progenitors [12,13]. Ectopic expression of hallmark proteins for brown adipocytes such as UCP1 and PGC-1α in white adipocytes induces acquisition of BAT features [14,15]. More recent studies identified novel brite-specific markers such as PRDM16 that have been targeted for identification of brown fat-stimulating agents [16,17].

Recent advances have been made in the understanding of pharmacological and dietary agents that contribute to browning of WAT, and a number of dietary compounds have been proposed as tools for increasing energy expenditure and decreasing fat accumulation in mammals [18,19], including capsaicin, berberine, orexin and irisin [19–22]. Here, we found that curcumin induces browning in both white adipocytes-derived 3T3-L1 cells and primary white adipocytes from rats.

Curcumin is a naturally occurring curcuminoid of turmeric, which is a member of the ginger family (Zingiberaceae) and perhaps one of...
the most studied medicinal herbs [23]. Curcumin has diverse beneficial effects ranging from anti-cancerous and anti-inflammatory activities to behavioral improvement in Alzheimer’s disease [24–28]. Dietary curcumin administration was reported to prevent weight gain in rodent animal models. For example, curcumin plays an anti-inflammatory role in obesity and obesity-related metabolic disorders [29] and directly interacts with WAT to suppress chronic inflammation [30]. Moreover, it was reported that curcumin administration can prevent HF-induced obesity and insulin resistance by arresting lipogenesis in the liver and the inflammatory pathway in adipocytes as well as reduce blood glucose levels by enhanced expression of glucose transporters in mice and humans [31,32]. Curcumin also inhibits adipocyte differentiation and adipogenesis in cultured adipocytes with concentration of 5–30 μM [33,34]. However, despite its demonstrated effects, the potential health benefits of curcumin have been limited due to its poor solubility, rapid metabolism and rapid systemic elimination [35]. However, various approaches have been undertaken to improve bioavailability of curcumin [37,38].

To date, the browning effect of curcumin in white adipocytes with respect to obesity has not been reported. The present study therefore investigated the effect of curcumin on induction of beige phenotype in cultured white adipocytes. To this end, we used two different white adipocyte cell models, 3T3-L1 and primary white adipocytes isolated from inguinal WAT of rats.

2. Materials and methods

2.1. Cell culture and differentiation

Dulbecco’s Modified Eagle’s Medium (DMEM: Thermo, Waltam, MA, USA) supplemented with 10% fetal bovine serum (PBS; PAA Laboratories, Pasching, Austria) and 100 μg/ml of penicillin-streptomycin (Invitrogen, Carlsbad, CA, USA) was used to culture 3T3-L1 preadipocytes (ATCC, Manassas, VA, USA) at 37°C in a 5% CO2 incubator. 100 μM rosiglitazone (Sigma-Aldrich) was used to culture 3T3-L1 preadipocytes (ATCC, Manassas, VA, USA) at 37°C in a 5% CO2 incubator. Cells grown on poly-L-lysine-pretreated coverslips were washed four times with deionized water, and images were captured under a microscope.

Isopropanol) and water in a 6:4 ratio was layered onto cells for 20 min, followed by fixation with 10% formalin for 1 h at room temperature, and washing again three times with phosphate-buffered saline (PBS). Adipocytes were incubated in Dulbecco’s modified Eagle’s medium (DMEM) supplemented with 10% PBS and 100 U/ml of penicillin-streptomycin (Sigma-Aldrich) under a 5% CO2 atmosphere at 37°C. After confluence (Day 1), cells were initiated for adipocyte differentiation by incubation with differentiation induction medium. For treatment of browning cocktail and culture, differentiation induction medium was supplemented with 50 μM tridodecy- onine, and maturation medium was supplemented with 50 μM tridodecylamine with 1 μM rosiglitazone. To test the effects of 5-Aminois德zole-4-carboxamide ribonucleotide [AICAR] and dornorphin, AICAR (1 mM) or dornorphin (5 μM) was added to the differentiation induction and maturation media until cells were harvested.

2.2. Oil Red O staining

Control and curcumin-treated cells were matured for 4–8 days, followed by washing with PBS, fixation with 10% formalin for 1 h at room temperature, and washing again three times with diized water. A mixture of Oil Red O solution (0.05 Oil Red O dye in isopropanol) and water in a 6:4 ratio was layered onto cells for 20 min, followed by washing four times with deionized water, and images were captured under a microscope.

2.3. Immunofluorescence

Cells grown on poly-l-lysine-pretreated coverslips were fixed with 4% paraformaldehyde followed by washing with PBS and then subjected to permeabilization with 0.2% Triton X-100 (Sigma). Cells were washed with PBS three times, blocked with 1% BSA in PBS-T for 1 h and incubated with polyclonal anti-UCP1 antibody (1:200 dilution) (Santa Cruz Biotechnology, Santa Cruz, CA, USA) overnight at 4°C, followed by three washes with PBS.

Cells were then incubated with FITC-conjugated anti-goat secondary antibody (1:400 dilutions), DAPI (Invitrogen) was used to stain nuclei of cells. Fluorescence images were captured using a confocal laser scanning microscope LSM700 (Carl Zeiss, Oberkochen Germany). Analysis of images (control and curcumin-treated) was performed by software Zen 2009 (Carl Zeiss). For staining of mitochondria, Mitotracker Red (1 μM, Cell Signaling Technology, Beverly, MA, USA) was directly added to the growing media at a concentration of 20–25 μM, and cells were kept for 30–40 min at 37°C. After incubation, cells were fixed in 4% formaldehyde, followed by a single wash with PBS and immunostaining.

2.4. Quantitative real-time reverse transcriptase polymerase chain reaction

Total RNA was isolated from matured cells (4–8 days) using a total RNA isolation kit (RNA-spin, INRON Biotechnology, Seongnam, Korea). RNA (1 μg) was converted to cDNA using Maxima RT premix (INRON Biotechnology). Power SYBR green (Roche Diagnostics GmbH, Mannheim, Germany) was employed to quantitatively determine transcript levels of genes with reverse transcriptase polymerase chain reaction (RT-PCR) [Stratagene 2400 mix 3000 qPCR System, Agilent Technologies, Santa Clara, CA, USA]. PCR reactions were run in duplicate for each sample, and transcript levels of every gene were normalized to the level of β-actin. Sequences of primer sets used in this study are listed in Table 1.

2.5. Immunoblot analysis

Cell lysates were prepared using RIPA buffer (Sigma) by homogenization and centrifugation at 14,000 × g for 20 min. Cell extract was diluted in 5× sample buffer [50 mM Tris at pH 6.8, 2% sodium dodecyl sulfate (SDS), 10% glycerol, 5% [mercaptoethanol and 0.1% bromphenol blue] and heated for 5 min at 95°C before 10 or 12% SDS-polyacrylamide gel electrophoresis. After electrophoresis, samples were transferred to a polyvinylidene difluoride membrane (Santa Cruz Biotechnology) and then blocked for 1 h with TBS-T (10 mM Tris–HCl, 150 mM NaCl, and 0.1% Tween 20) containing 5% skim milk. The membrane was rinsed three times consecutively with TBS-T buffer, followed by incubation for 1 h with horseradish peroxidase-conjugated-anti-goat IgG or anti-rabbit IgG secondary antibody (1:1000, Santa Cruz Biotechnology) in TBS-T buffer containing 1% skim milk. Development was carried out using enhanced chemiluminescence (West-ZOL, INRON Biotechnology). Quantification of band intensities was performed by using ImageJ software (NIH).

2.6. Transmission electron microscopy

3T3-L1 and primary adipocytes were washed with 0.1 M phosphate buffer and fixed in 2.5% (w/v) glutaraldehyde solution overnight at 4°C. Then, cells were post-fixed in 1% (w/v) osmium tetroxide, dehydrated in ascending gradations of ethanol, and embedded in fresh epoxy resin. Ultra-thin sections (70 nm) were cut and stained with 1% (w/v) uranyl acetate and lead citrate before being examined under a transmission electron microscope H-7600 (Hitachi, Tokyo, Japan).

2.7. Statistical analysis

All data were expressed as the mean±S.D., and comparison was made by using One-way ANOVA using the Statistical Package of Social Science (SPSS, version 17.0; SPSS, Chicago, IL, USA) program, followed by Tukey’s post hoc tests. Statistical significances between control, cocktail and curcumin-treated groups were indicated as either *P<0.05 or **P<0.01.

Table 1

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<th>Gene</th>
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The primary sequence used for real-time quantitative PCR.

Gene Forward Reverse

3T3-L1 Cidea GCGGAATAGCGACGACTCACC TGTCACTGGGATGTCATTGAGG
Fgt21 GCTTTGTGCTTGCATTCTGA TCTACATCAGCTGAGGCTCTG
Ppar GCTTTGTGCTTGCATTCTGA CTGCTTTGTGCTTGCATTCTGA
Tmec2 GCTTTGTGCTTGCATTCTGA CAGACCGGCTCCCTCTCTCTCT
Tbx1 GCTTTGTGCTTGCATTCTGA CAGACCGGCTCCCTCTCTCTCT
Fgt21 GCTTTGTGCTTGCATTCTGA CAGACCGGCTCCCTCTCTCTCT
Prdm16 GCTTTGTGCTTGCATTCTGA CAGACCGGCTCCCTCTCTCTCT
Tmec2 GCTTTGTGCTTGCATTCTGA CAGACCGGCTCCCTCTCTCTCT
Ucp1 GCTTTGTGCTTGCATTCTGA CAGACCGGCTCCCTCTCTCTCT

2.8. Western blot analysis

To determine the role of curcumin on induction of beige phenotype in cultured white adipocytes, cell lysates were prepared using RIPA (G T C C T G C G G A C C G A C T C A C C )...
3. Results

3.1. Curcumin induces browning of 3T3-L1 and primary white adipocytes

To investigate the browning effect of curcumin, 3T3-L1 and primary inguinal adipocytes from rats were used as cellular models and treated with different concentrations of curcumin (1–20 μM). Curcumin significantly increased brown fat markers (PGC-1α, PPARγ and UCP1) in both adipocytes in a dose-dependent manner (Fig. 1). Next, both adipocytes were treated with a browning cocktail (rosiglitazone and triidothyronine) with and without curcumin, after which expression levels of brown fat-specific genes were determined. As shown in Fig. 2, curcumin treatment in both adipocytes resulted in rapid up-regulation of brown fat-specific genes against vehicle and positive control (cocktail group). The enhanced expression of brown fat markers, including UCP1, PGC-1α, PRDM16 and C/EBPβ as well as Timem26, Cidea, Fgf21 and Cited1, suggests possible conversion of white adipocytes into beige cells. Increased expression of key brown cell marker proteins (C/EBPβ, PGC-1α, PRDM16 and UCP1) was further confirmed by Western blot analysis (Fig. 2B). In addition, enhanced expression of UCP1 upon curcumin treatment was confirmed at the cellular level by immunostaining (Fig. 3).

3.2. Curcumin induces mitochondrial biogenesis

To judge whether curcumin increases mitochondrial biogenesis, which is a marked feature of fat browning, transmission electronic microscopic study was conducted. As shown in Fig. 4A, density of mitochondria was markedly elevated in both curcumin-treated adipocytes, and this was further confirmed by a Mito® Tracker Red that specifically binds to mitochondria (Fig. 3). The increased mRNA and protein levels of PGC-1α, a key player in mitochondrial biogenesis, also support these results (Fig. 2). Taken together, curcumin drives thermogenic programming, thereby increasing the brown fat phenotype along with mitochondrial biogenesis.

3.3. Curcumin regulates lipid metabolism in adipocytes

We investigated whether curcumin increases lipolysis and fat oxidation in both adipocytes. Our data demonstrate that curcumin treatment led to significant elevation of mitochondrial CPT1 and Cytochrome C protein levels, suggesting enhanced fat oxidation upon curcumin treatment (Fig. 4B). Moreover, increased expression levels of HSL and p-ACC reflect augmented lipolysis and suppressed fatty acid synthesis, respectively (Fig. 4B). In addition, small lipid droplet numbers, as visualized by Oil Red O staining, increased upon curcumin treatment (Fig. 4C).

3.4. Curcumin induces brown fat phenotype via AMPK-mediated pathway

To identify the possible mechanism underlying the browning effect of curcumin, we determined expression levels of AMPK, a metabolic master switch regulating fatty acid utilization and energy homeostasis. Curcumin treatment significantly increased expression levels of
both total AMPK and phosphorylated AMPK (p-AMPK) as well as the ratio of p-AMPK to AMPK (Fig. 5). These results drove us to hypothesize that curcumin induces the brown fat phenotype via the AMPK-mediated pathway. To test this hypothesis, we treated both adipocytes with AICAR (1 mM) or dorsomorphin (5 μM), which are a potent activator and inhibitor of AMPK, respectively. Inhibition of AMPK by dorsomorphin abolished expression of UCP1, PRDM16 and PGC-1α while the activator AICAR elevated expression of these brown genes.

Fig. 3. Curcumin treatment induces expression of UCP1 protein. 3T3-L1 and primary white adipocytes after curcumin treatment were fixed with p-formaldehyde, subjected to staining for Mito® Tracker Red, and then ICC staining for UCP1. The immunofluorescent images were captured at 400× and 800× magnifications.
Fig. 4. Curcumin treatment results in mitochondrial biogenesis. Representative transmission electronic microscopic images from and 3T3-L1 and primary white adipocytes treated with curcumin [A]. Protein expression levels of CPT, HSL, p-ACC and Cytochrome C in 3T3-L1 and primary white adipocytes treated with curcumin [B]. Expression levels were measured by densitometric analysis, and protein levels were normalized with β-Actin. Oil Red O staining was performed to depict maturation of both 3T3-L1 and primary white adipocytes. Curcumin treatment increases number of small lipid droplets [C]. All data are presented as the mean±S.D., and differences between groups were determined by One-way Analysis of Variance (ANOVA) using the Statistical Package of Social Science (SPSS, version 17.0; SPSS, Chicago, IL, USA) program, followed by Tukey’s post hoc tests. Statistical significance between control and curcumin-treatment groups was shown as *p<.05 and **p<.01; between cocktail and curcumin-treated groups was depicted as †p<.05; between control and cocktail was noted as ##p<.01.
marker proteins (Fig. 6). These expression patterns suggest that curcumin increases expression of hallmark proteins for brown adipocytes in both adipocytes via a mechanism involving AMPK and PGC-1α (Fig. 7).

### 4. Discussion

Strategies that manipulate WAT to acquire BAT-like characteristics are a promising approach to help, prevent and manage obesity [40]. The present study provides insights into the role of dietary curcumin in inducing the brown fat phenotype in 3T3-L1 and primary white adipocytes. We successfully demonstrated that curcumin along with a browning cocktail could synergistically induce the brite phenotype and drive the BAT thermogenic program through significant elevation of brown fat-specific genes such as Fgf21, Cidea, Tmem26 and Tbx1 as well as proteins such as UCP1, PGC-1α and PRDM16. It was demonstrated that Tmem26 and Tbx1 are brown fat-specific markers, and brite cells are highly enriched in these two markers [41]. Our results show that curcumin significantly elevated expression of both genes, suggesting a possible role for curcumin in inducing the brite phenotype. Our data also strongly demonstrate that curcumin significantly up-regulated UCP1, a hallmark protein of brown adipocytes, at both mRNA and protein levels. Enhanced protein levels of UCP1 was accompanied by elevated expression of PRDM16, a master regulator of BAT development [42].

Elevation of mitochondrial numbers is a characteristic feature of fat browning [17]. Current data demonstrate that curcumin increased mitochondrial biogenesis, as evidenced by transmission electronic microscopic detection as well as elevated expression of PGC-1α, a master regulator of mitochondrial biogenesis and function. Ectopic expression of PGC-1α in white adipocytes induces acquisition of BAT features, including expression of thermogenic markers. Our data also support an increased number of mitochondria and elevated expression of PGC-1α, which also acts as a cold inducible protein governing the adaptive thermogenic process [43].

In addition, curcumin treatment led to increased expression of important mitochondrial proteins such as CPT1 and Cytochrome C. It is well recognized that CPT1 increases mitochondrial activity and enhances fatty acid oxidation in brown adipocytes [44]. Cytochrome C also plays a key role in mitochondrial oxidative phosphorylation and is considered to be highly enriched in brown fat cells [45,46]. Therefore, enhanced expression of these two proteins is likely to reflect the stimulatory action of curcumin with regard to fat oxidation. Curcumin also appears to stimulate lipolysis and suppress lipogenesis, as it increased expression levels of HSL and p-ACC [47]. HSL is the key enzyme of lipolysis [48], whereas phosphorylation of ACC (p-ACC) results in reduction of ACC enzyme, which is the rate-limiting enzyme in fatty acid synthesis [49]. Moreover, our data show that curcumin-treated adipocytes contained a greater number of small lipid droplets, which provide a greater surface area for the actions of water-soluble lipolytic enzymes [40].

Activation of the AMPK-mediated pathway is pivotal in maintaining energy homeostasis [50]. Our data show that curcumin significantly increased expression of AMPK and its activated form (p-AMPK), and its effect was totally abolished upon inhibition of AMPK. The role of AMPK in browning of white adipocytes has been very controversial. For example, some studies have reported that browning of white adipocytes is accompanied with increased expression of AMPK and its phosphorylation [51,52]. In contrast, it was demonstrated that only activation of AMPK takes places but total AMPK level remains constant.
during the process of browning event [53]. Hutchinson et al. have reported that AMPK level increases in fully differentiated primary brown adipocytes [54]. To identify its role in the curcumin-induced browning pathway, we treated adipocytes with AICAR, a potent activator of AMPK, as well as dorsomorphin, a selective inhibitor of AMPK. Curcumin treatment resulted in higher expression of activated AMPK, which indicates that the effects of curcumin are mediated via AMPK. Arrest of brown fat expression marker proteins upon AMPK inhibition reinforces our conclusion that curcumin induces browning via the AMPK-mediated pathway. Shan et al. [50] indicated that the AMPK-PGC1α-Fndc5 pathway drives browning of WAT. Similarly, other natural compounds such as berberine and resveratrol were

**Fig. 6.** Effect of AICAR and dorsomorphin on expression of browning marker proteins. AICAR (1 mM) and dorsomorphin (5 μM) were treated to adipocytes, and protein expression levels were determined by Western blotting.

**Fig. 7.** Suggested pathway for curcumin-induced fat browning via AMPK-mediated pathway: (†) stimulatory, (┴) inhibitory action, (↑) up-regulation.

![Diagram of suggested pathway](image-url)
found to induce browning of white adipocytes through AMPK activation [20, 22]. Taken together, the AMPK-mediated pathway plays a pivotal role in induction of browning and stimulation of the thermogenic program in adipocytes [47]. Although AMPK is a key regulator in browning event, the accurate molecular mechanisms by which AMPK is activated during browning of white adipocytes remain to be demonstrated. It should be mentioned that current dose of curcumin show very low plasma levels [33]. Hence, new formulation strategy may be required to increase absorption of curcumin.

In conclusion, our findings suggest that curcumin plays a dual modulatory role in inhibition of lipogenesis as well as induction of the brown-like phenotype, thereby displaying potential therapeutic implications for the treatment of obesity. Although our in vitro data obtained from both 3T3-L1 and primary white adipocytes suggest that curcumin significantly induces fat browning, an in vivo study is required to solidify its role.

Conflicting interests

The authors declared no conflicts of interest.

Acknowledgements

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References


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