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# Mechanisms underlying the metabolic beneficial effect of curcumin intervention: Beyond anti-inflammation and anti-oxidative stress

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ABSTRACT

Obesity is often associated with the development of insulin resistance. Dietary intervention with plant polyphenols, such as curcumin, has been shown to attenuate body weight gain in high fat diet fed animal models, associated with the improvement on glucose disposal and insulin sensitivity. For about two decades, mechanistic explorations on such metabolic beneficial effects of dietary polyphenols were mainly focused on the anti-inflammation as well as anti-oxidative stress features of these compounds, including curcumin. During the past a few years, several lines of investigations have indicated that the insulin signaling improvement effect of curcumin intervention can be dissociated from its anti-inflammation functions. Importantly, studies have advanced our knowledge on how curcumin attenuate white adipose tissue inflammation and adipogenesis. Furthermore, this dietary polyphenol increases energy expenditure in mouse models, either by facilitating white adipose tissue "browning", or by stimulating brown adipocyte UCP1 expression. Finally, curcumin intervention was shown to regulate both the production and the sensitivity of the hepatic hormone fibroblast growth factor 21 (FGF21). Here I have reviewed the literature on those investigations and presented my view that these advancements have brought us a novel perspective on dietary polyphenol study, especially for their obesity treatment and prevention features.

Obesity is defined as a medical condition in which excess body fat mess has been accumulated to certain extent which may bring negative effects on the health. For decades, high fat diet (HFD) induced obese mouse or other rodent models have been broadly utilized for the exploration of mechanisms that leads to the development of obesity and its associated metabolic disorders. The occurrence of obese in those models, as well as in a large portion of obese human subjects, is tightly associated with the development and progression of insulin resistance, including the resistance detected at the molecular level in the liver and in the adipose tissues. In 1993, Spiegelman and colleagues published a milestone research, showing the induction of tumor necrosis factor-α (TNF-α) in the white adipose tissue from four different rodent models of obesity and diabetes, while the neutralization of TNF-α in obese fa/fa rats led to a significant improvement on insulin signaling, as the peripheral glucose uptake was increased in response to insulin treatment (Hotamisligil et al., 1993). These observations as well as intensive follow up studies have led to the establishment of the theory that chronic inflammation causes insulin resistance and its associated medical disorders, including obesity. Thus, targeting inflammation in adipose tissues and elsewhere becomes the novel therapeutic strategy for obesity, insulin resistance, and related metabolic disorders (Deisl et al., 2013).

It is well known that insulin signaling can be influenced by nutrient sensing while dietary intervention with various phytochemicals including polyphenols can attenuate HFD induced body weight gain, associated with the improvement on glucose disposal, the reduction of plasma lipid level, and the attenuation of insulin resistance. With the influence of the "chronic inflammation" theory (Hotamisligil et al., 1993; Hotamisligil, 2006), investigations conducted during the past two decades on mechanistic exploration of the metabolic beneficial effects of dietary polyphenols have been mainly focused on their anti-inflammation and anti-oxidative features. For example, Weisburg and colleagues kkhave systematically assessed the effect of curcumin intervention in HFD-induced obese and leptin-deficient ob/ob mouse models. For the mechanistic exploration, they have attributed the metabolic improvement on glucose and insulin tolerance mainly to

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reduced white adipose tissue macrophage infiltration, increased adipose tissue adiponectin production, and decreased hepatic nuclear factor-kappa B activity (Weisberg et al., 2008). Our team and others have also verified the stimulatory effect of curcumin or other dietary compounds on the nuclear factor erythroid 2-like 2 (Nrf2) mediated anti-oxidative stress signaling cascade (Yu et al., 2011; Shao et al., 2012).

The compensatory features of inflammation in obesity and insulin resistance during metabolic disease development and progression have been suggested by scholars (Ye and McGuinness, 2013; Wang and Ye, 2015; Crewe et al., 2017; Nolan et al., 2015). Scientists in metabolism and other fields have hence started paying attention to the exploration of anti-inflammation and anti-oxidative stress independent beneficial effects of curcumin or other dietary polyphenols. I will briefly summarize the following three lines of studies on curcumin function in the adipose tissue and in the liver, conducted by my team and by our colleagues, which are related to obesity and metabolic disease treatment and prevention.

## 1. The inhibition of adipogenesis

Adipogenesis is a cell differentiation process by which pre-adipocyte becomes mature adipocyte. This process is known to be inhibited by the canonical Wnt signaling cascade, in which β-catenin/TCF functions as the key effector (Ross et al., 2000; Jin, 2016). The body weight lowering effect of curcumin intervention triggered the assessment on its effect on adipogenesis. A study by Kim and colleagues showed that curcumin possesses an anti-adipogenic function both in the 3T3-L1 murine cell model and in human primary preadipocytes, determined by the intracellular lipid accumulation assay (Kim et al., 2011). They then found that curcumin inhibited the mitotic clonal expansion process during the early stage of adipocyte differentiation, involving the inhibition of genes that encode the early adipogenic transcription factors, including Krüppel-like factor 5 (KLF5), CCAAT/enhancer binding proteinα (C/EBPα) and peroxisome proliferator-activated receptorγ (PPARγ) (Kim et al., 2011). Utilizing the same 3T3-L1 cell model, Ahn et al. demonstrated that during the differentiation process, curcumin treatment enhanced nuclear translocation of β-catenin. In addition, they found that curcumin reduced CK1α, GSK-3β, and Axin, components of the destruction complex of free β-catenin. Thus, curcumin may suppress 3T3-L1 adipogenesis via stimulating the canonical Wnt signaling cascade (Ahn et al., 2010). It is very difficult to recapture such observations, such as the stimulation of β-catenin nuclear translocation and function *in vivo* in the experimental mice (Shao et al., 2012). We have, however, conducted further mechanistic exploration with the 3T3-L1 cell model. We found that another Wnt pathway effector molecule, Tcf7l2, is the target of the microRNA miR-17-5p. miR-17-5p is a member of the miR-17/92 cluster, which was shown to accelerate 3T3-L1 adipogenic differentiation (Wang et al., 2008). TCF7L2 over-expression and its functional knockdown generated repressive and stimulatory effect on 3T3-L1 cell adipogenesis, respectively. Importantly, curcumin treatment attenuated miR-17-5p expression and stimulated Tcf7l2 expression in the 3T3-L1 cell model (Tian et al., 2017). Questions remain to be investigated include whether curcumin intervention also represses adipogenesis *in vivo* and whether the *in vivo* repression plays a role on reducing body weight gain. In addition, it remains to be determined how other members of the miR-17/92 cluster are involved in adipogenesis (Wang et al., 2008), in the presence and absence of curcumin intervention.

## 2. The enhancement of thermogenesis

To increase energy expenditure can reduce energy deposition and hence inhibit adipose tissue expansion. Intensive investigations for more than a decade have defined the role of the uncoupling protein 1 (UCP1), mainly located within the mitochondria inner membrane, that mediates thermogenesis in response to cold exposure or other environmental changes (Jin, 2016; da Silva Xavier et al., 2012). In 2015, Wang et al. found that after C57BL/6 mice on regular low fat chow diet with 50-day daily curcumin gavage (50–100 mg/kg body weight per day), their white adipose tissue (WAT) showed the emergence of beige adipocytes, associated with elevated thermogenic gene expression and mitochondrial biogenesis (Wang et al., 2015). This team has also demonstrated that curcumin promoted β3AR gene expression in the inguinal WAT and elevated the levels of plasma norepinephrine, a hormone that can induce WAT browning (Wang et al., 2015). Recently, our team has demonstrated that in HFD fed C57BL/6 mice, 12 week curcumin dietary intervention not only reduced WAT macrophage infiltration, but also altered macrophage functional polarity in WAT (increased the ratio of M2-like versus M1-like macrophages) (Song et al., 2018). The intervention also increased energy expenditure and body temperature in response to cold challenge, associated with increased UCP1 expression in the brown adipose tissue (BAT) (Song et al., 2018). In our experimental settings, the “browning effect” on WAT, however, was not observed (Song et al., 2018). It is necessary to mention that the stimulatory effect on UCP1 expression or WAT browning has been reported for many other dietary polyphenols or phytochemicals, including piperine (the alkaloid extracted from black pepper), diet that contains resveratrol and quercetin, or with raspberry supplementation, or grape pomace extract (Kim et al., 2017; Xing et al., 2018; Arias et al., 2017; Rodriguez Lanzi et al., 2018). Thus, further investigations are needed to identify the existence of a common pathway that mediates the effect of dietary polyphenols on WAT browning and BAT UCP1 expression. It is also desirable to establish the *in vitro* system for testing the “browning” effect of curcumin and other dietary polyphenols.

## 3. Hepatic function on lipogenesis related gene expression

The liver is the major organ for lipogenesis and for conveying the function of insulin in metabolic homeostasis. It has been well documented that HFD induced plasma lipid elevation can be prevented or attenuated by dietary intervention with polyphenols including curcumin, resveratrol and others. Such beneficial effects were also demonstrated in recent clinical trials (Rahmani et al., 2016; Faghihzadeh et al., 2015; Chen et al., 2015). Whether such attenuation is absolutely secondary to the anti-inflammation effect of these polyphenols on improving insulin signaling remained unclear. In order to test our working hypothesis for the existence of anti-inflammation-independent insulin sensitizing effect of curcumin, we assessed the effect of “6-day” curcumin gavage in a dexamethasone induced insulin resistance mouse model (i.e. without enhanced inflammation and body weight change) and observed an improvement on insulin tolerance (Tian et al., 2015). We then observed that the improvement was associated with the increase in hepatic expression of the metabolic hormone fibroblast growth factor 21 (FGF21), which triggered a further investigation by our team (Zeng et al., 2017).

FGF21 is mainly produced in the liver and released during fasting (Badman et al., 2007; Inagaki et al., 2007; Kharitonenkov and DiMarchi, 2015; Markan et al., 2014; Potthoff et al., 2012), functioning as a “starvation” hormone (Inagaki et al., 2007; Kharitonenkov et al., 2005; Kharitonenkov, 2009). Intensive studies have revealed that FGF21 induction after fasting occurs via the activation of the nuclear receptor peroxisome proliferator-activated receptor α (PPARα) (Badman et al., 2007; Inagaki et al., 2007; Vernia et al., 2014; Lundasen et al., 2007; Kharitonenkov et al., 2007). During the adaptive starvation response period, the PPARα/FGF21/peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) axis facilitates fatty acid oxidation, tri-carboxylic acid cycle flux and gluconeogenesis. The insulin sensitizing effect of FGF21 has been documented, and this hormone and its homologues have been intensively studied in pre-clinical studies and in clinical trials (Kharitonenkov et al., 2005; Coskun et al.,

2008; Shao et al., 2015; Woo et al., 2013; Bozic et al., 2016; Gariani et al., 2013; Xu et al., 2009). Murine and human subjects with obesity, however, were found to have elevated serum FGF21 levels, indicating that obesity represents the FGF21 resistant status (Bozic et al., 2016; Fisher et al., 2010; Chavez et al., 2009; Chen et al., 2011; Zhang et al., 2008; Berti et al., 2015; Rusli et al., 2016). In normal C57BL/6 mice with low fat diet (LFD) feeding or in mouse or human hepatocytes, we found that short term (4 or 8 days) curcumin gavage or direct *in vitro* curcumin treatment stimulated *Fgf*21 mRNA expression, hepatic FGF21 hormone production, or plasma FGF21 level elevation. In HFD-fed C57BL/6 mice, however, 12-wk curcumin intervention was shown to attenuate HFD-induced plasma and hepatic FGF21 elevation. Such attenuation by curcumin intervention was recently reproduced in a female rat study in mitigating the development of nonalcoholic fatty liver disease (NASH) (Cunningham et al., 2018). More importantly, the attenuation was associated with partial restoration of hepatic expression of genes that encode the FGF21 receptor FGFR1 and the co-receptor βKlotho, and the expression of the lipolysis genes (Zeng et al., 2017). Furthermore, hepatocytes in mice on HFD for 4 weeks showed attenuated response to ex vivo recombinant FGF21 treatment which was abolished by concomitant dietary curcumin intervention. We hence claimed that curcumin intervention can improve FGF21 sensitivity in mice with HFD challenge (Zeng et al., 2017). It is necessary to point out that FGF21 expression can also be stimulated by resveratrol (Li et al., 2014), or another category of the dietary polyphenol anthocyanin (our unpublished data), and dietary betaine supplementation (Ejaz et al., 2016). It remains to be determined whether the insulin signaling sensitization effect of curcumin intervention is secondary to the restoration or maintenance of FGF21 sensitivity.

### 3.1. Summary

With curcumin as an example, I present here a glance of our recent knowledge advancement on mechanistic insight of functions of dietary polyphenols, focusing on their metabolic beneficial effect.

Fig. 1 illustrates our current understanding on the function of curcumin in adipose tissues. Firstly, curcumin inhibits adipogenesis via stimulating the canonical Wnt signaling cascade. This effect is at least partially mediated by down-regulating the expression of microRNAs including miR-17-5p, resulting in elevated TCF7L2 expression, as well as the stimulation of β-cat nuclear translocation. Secondly, in WAT, curcumin not only inhibits macrophage infiltration, but also alters macrophage functional polarity. This is achieved by inhibiting pro-inflammatory cytokines in both adipocytes and in macrophages, as well as by stimulating anti-inflammatory cytokines mainly produced in adipocytes (Song et al., 2018). Finally, in BAT, curcumin up-regulates UCP1 expression and hence increases energy expenditure. It is likely that in certain conditions, curcumin can exert the “browning effect” in WAT, which deserves further investigation.

In the liver, curcumin is known to improve insulin signaling via attenuating chronic inflammation and stimulating the anti-oxidative signaling cascade. This dietary polyphenol can also regulate both FGF21 production and its sensitivity, dependent on the needs, as illustrated in Fig. 2. We suggest that the stimulatory effect of curcumin on FGF21 expression is not secondary to its anti-inflammation effect, as we have demonstrated this effect *in vitro* in both mouse and human hepatocytes, as well as *in vivo* in a mouse model without enhanced inflammation and body weight change (Tian et al., 2015). Some of the above findings on curcumin research apply to other dietary polyphenols while certain functions with curcumin intervention might be unique for this chemical compound. These novel findings bring us a novel perspective on dietary polyphenol research, especially for their obesity treatment and prevention features.

As my colleagues and I have commented very recently (Jin, 2018; Jin et al., 2018), further mechanistic explorations on functions of curcumin and other dietary polyphenols have encountered the challenges, mainly due to their multiple targets feature and the absence of defined receptors. For example, although we are aware of the function of curcumin in regulating multiple signaling cascades presented above and elsewhere (Liu et al., 2005), exact mechanisms underlying the triggering of multiple signaling cascades in temporal and special manners are far away from clear. A related issue is that the extremely low absorption rate of curcumin and other dietary polyphenols in the gut made us to wonder what the true functional chemical entities of curcumin that exert the *in vivo* function. This concern also applies to many other dietary polyphenols or other phytochemicals, facilitating us to explore the contribution of their interactions with the gut microbiota, which has been commented elsewhere (Anhe et al., 2015; Breton et al., 2016; Cote et al., 2015; Battiprolu et al., 2012; Plovier et al., 2017; Anhe and Marette, 2017).

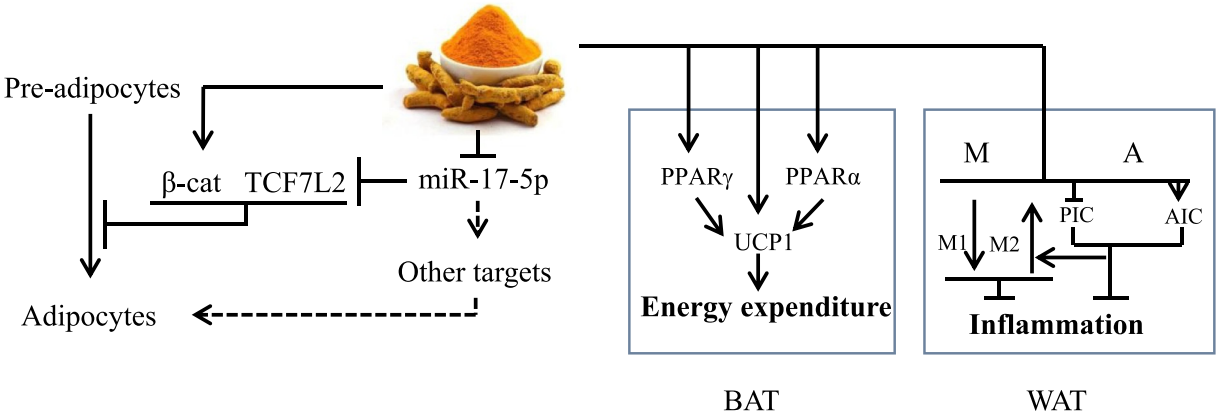


**Fig. 1. Illustration of functions of curcumin in adipose tissues**. Curcumin inhibits adipogenesis. This can be achieved by stimulating both β-catenin (β-cat) nuclear translocation and the expression of TCF7L2, resulting in the activation of the canonical Wnt signaling cascade. The stimulation on TCF7L2 expression is likely mediated by repressing the microRNA miR-17-5p. It remains to be further determined whether other downstream targets of miR-17-5p are also involved in regulating adipogenesis (indicated by the dotted arrow). In white adipose tissue (WAT), curcumin acts on both macrophages (M) and adipocytes (A). It increases the ratio of M2-like macrophages versus M1-like macrophages within WAT. It also possesses the stimulatory effect on expression of anti-inflammation cytokines (AIC) and the inhibitory effect on expression of pro-inflammatory cytokines (PIC). These effects collectively contribute to the inhibition of inflammation. In BAT, curcumin stimulates the expression of UCP1 via PPAR (both PPARα and PPARγ) dependent and independent mechanisms. Curcumin may also affect WAT browning, which is not shown in the diagram.

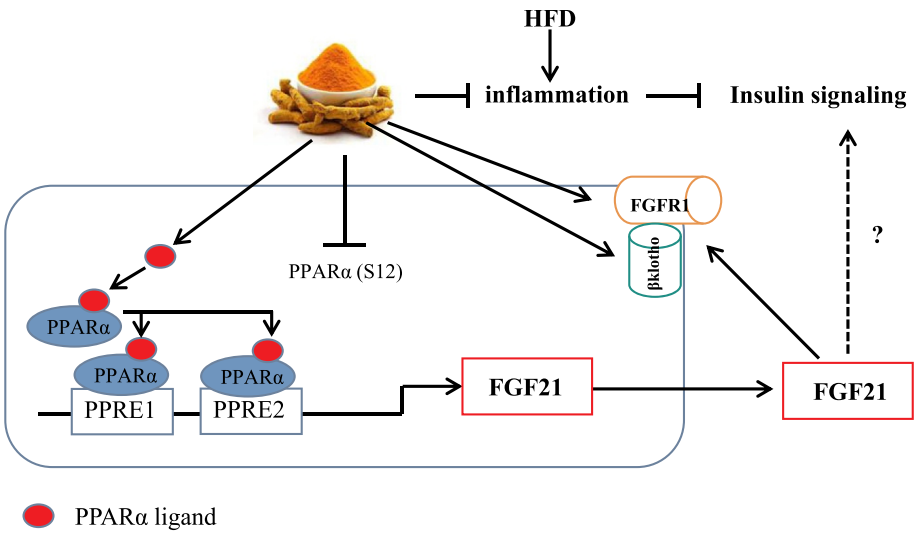


**Fig. 2. Illustration of the stimulatory effect of curcumin on hepatic FGF21 expression and its sensitivity restoration in response to HFD challenge.** Curcumin treatment increases hepatic *Fgf21* gene transcription. This is likely mediated by the enhancement of binding of the nuclear factor PPARα on the *Fgf21* gene promoter. PPRE1 and PPRE2, two conserved PPAR response elements or PPAR binding motifs, located on the *Fgf21* gene promoter. Curcumin or its metabolites may increase the levels or the activities of the PPARα ligands. Curcumin or its metabolites may also block PPARα S12 phosphorylation, an event that is negatively related to its activity. In response to HFD challenge, curcumin upregulates the expression of FGFR1 and βKlotho, maintaining or restoring FGF21 sensitivity. The restoration of FGF21 sensitivity may play a role in improving insulin sensitivity (indicated by the dotter arrow).

## Conflict of interest

The author has no conflict interest to claim.

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