Nutrigenomic Functions of PPARs in Obesogenic Environments

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Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors that mediate the effects of several nutrients or drugs through transcriptional regulation of their target genes in obesogenic environments. This review consists of three parts. First, we summarize current knowledge regarding the role of PPARs in governing the development of white and brown/beige adipocytes from uncommitted progenitor cells. Next, we discuss the interactions of dietary bioactive molecules, such as fatty acids and phytochemicals, with PPARs for the modulation of PPAR-dependent transcriptional activities and metabolic consequences. Lastly, the effects of PPAR polymorphism on obesity and metabolic outcomes are discussed. In this review, we aim to highlight the critical role of PPARs in the modulation of adiposity and subsequent metabolic adaptation in response to dietary challenges and genetic modifications. Understanding the changes in obesogenic environments as a consequence of PPARs/nutrient interactions may help expand the field of individualized nutrition to prevent obesity and obesity-associated metabolic comorbidities.

1. Introduction

In the past few decades, the prevalence of chronic diseases has been shown to be linked to nutrition deficiencies and overnutrition. Nutritional genomics/nutrigenomics, a unique approach for investigation of the genome-wide effects of nutrients at the molecular level, has contributed to the development of nutritional science and applications in medical and pharmacological research. Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors (TFs) that mediate the effects of several nutrients or drugs through transcriptional regulation of their target genes. PPAR isotypes of the NRI family, such as PPARα (nuclear receptor; NR1C1), PPARβ/δ (NR1C2), and PPARγ (NR1C3), can be distinguished based on their different biological roles and are the most relevant subtypes in the field of nutrition research. PPARs exert their biologically distinct functions in an isotype- and tissue-specific manner; however, the molecular details of tissue-dependent PPAR function remain unclear. PPARs are also able to repress transcription by interacting with other TFs and/or coactivators, thereby interfering with other signaling pathways to control physiology. Understanding the changes in the obesogenic environment as a consequence of PPAR/nutrient interactions may help expand the field of individualized nutrition to prevent obesity and its associated metabolic comorbidities.

In this review, we summarized current knowledge regarding (1) the role of PPARs in governing the development of white and brown/beige adipocytes from uncommitted progenitor cells, (2) interactions between dietary bioactive molecules and PPARs for the modulation of PPAR-dependent transcriptional activity and metabolic consequences, and (3) the effects of PPAR polymorphisms on obesity and metabolic outcomes.
2. Transcriptional Regulation of PPARs in White, Brown, and Beige Adipose Tissue

2.1. Functions of PPARs in White Adipose Tissue

2.1.1. Regulation of Adipogenesis. The process of adipogenesis is divided into two distinct stages: determination and terminal differentiation. Each stage is governed by the orchestrated regulation of TFs. TFs involved in the stage of adipocyte determination include CCAAT/enhancer-binding protein β and δ (C/EBPβ and C/EBPδ), glucocorticoid receptor (GR), signal transducer and activator of transcription 5A (STAT5A), and cAMP-response element-binding protein (CREB) [22, 23]. These TFs induce the transcriptional activation of target genes responsible for the second stage of adipogenesis. Regulators of early-stage adipogenesis, that is, C/EBPα and C/EBPδ, directly induce the expression of C/EBPα and PPARγ, which transcriptionally activate their own expression and the expression of other adipogenesis-related genes, for example, PPARγ coactivator 1 alpha (PGC-1α) and fatty acid synthase (FAS) [24–26].

PPARγ is known for its role in the regulation of adipogenic and lipogenic pathways [4, 27, 28]. Initial studies examining the role of PPARγ in adipogenesis showed that PPARγ-knockout mice had little adipose tissue [29]. PPARγ cooperatively acts with early adipogenic TFs, such as C/EBPs [30]. C/EBPβ and C/EBPδ induce PPARγ expression, and C/EBPα and PPARγ commutatively induce the expression of each other by facilitating chromatin binding [4, 31]. Some studies have suggested that the involvement of PPARs in adipogenesis is limited to the effects of PPARγ during later stages of adipogenesis and terminal differentiation of adipocytes. However, evidence has shown that PPARγ also plays a role in the early stages of adipogenesis. A subset of adipocyte progenitors is present within the WAT perivascular region in which PPARγ is expressed, suggesting that this protein may have a role in adipocyte self-renewal [32, 33]. The involvement of PPARγ in adipogenesis is more evident at the later stages of adipogenesis in mature adipocytes. Because the ablation of PPARγ is lethal, cell-specific knockout of PPARγ has been utilized in mature mouse adipocytes by applying the tamoxifen-dependent Cre-ER (T2) recombination system. A few days after ablation of the PPARγ gene, mature adipocytes and brown adipocytes died, and a subset of PPARγ-positive cells appeared [34], suggesting the involvement of PPARγ in maintaining mature adipocytes.

2.1.2. PPARs and Adipokines. PPARγ controls the expression of adipokines, including adiponectin, leptin, fibroblast growth factor 1 (FGF1), FGF21, resistin, and tumor necrosis factor-α (TNF-α). Adiponectin is a main adipokine that stimulates insulin sensitization by increasing glucose uptake and decreasing gluconeogenesis. Between the two adiponectin receptors (AdipoR1 and AdipoR2), AdipoR2 activates hepatic PPARα [35]. Hepatic PPARα activation by AdipoR2 decreases lipid accumulation and lipid peroxidation, contributing to improvements in hepatic steatosis and nonalcoholic steatohepatitis [35]. Adipose PPARα and PPARγ activation increases adipocyte uptake of glucose and free fatty acids and enhances insulin sensitivity by inducing the expression of Adipor1 and Adipor2 [36]. In contrast to adiponectin, PPARγ indirectly suppresses adipose leptin expression by inhibiting the binding of C/EBP to the leptin promoter region [37].

FGF1 is known to be selectively induced in adipose tissues by consumption of a high-fat diet through PPARγ, which acts on adipose tissue remodeling [38]. The phenotypes of FGF1-knockout mice depend on the conditions. FGF1-knockout mice do not show abnormal phenotypes under normal physiological conditions; however, the mice show disruption of fat expansion and subsequent development of diabetes in an obesogenic environment from high-fat feeding. FGF21 is expressed in the adipose tissue and liver and exerts tissue-specific effects. In adipose tissues, FGF21 increases energy expenditure and prevents weight gain in diet-induced obese and ob/ob mice [39]. Moreover, FGF21 also sensitizes cells to the effects of insulin by increasing adipose PPARγ activity [40]. The PPARγ agonist rosiglitazone induces FGF21 in the epididymal WAT of C57Bl/6 mice, and adipose FGF21 stimulates PPARγ, affecting adipogenesis and insulin sensitization. In the livers of these mice, FGF21 is induced by the PPARα agonist GW7647, and hepatic FGF21 acts as a hormone, regulating carbohydrate and lipid metabolism [40]. FGF21-knockout mice exhibited lipodystrophy with little adipose tissue owing to the low expression levels of PPARγ and its target genes.

Resistin is another adipokine that is upregulated in patients with type 2 diabetes and inflammation-related diseases [41]. Transcriptional regulation of resistin is governed by cooperative regulation of PPARγ and C/EBP in murine adipocytes, but not in human adipocytes. Additionally, PPARγ reduces the expression of proinflammatory cytokines in adipose tissue by acting on nuclear factor-kappa B (NF-κB) signaling. PPARγ inhibits NF-κB activity and induces its degradation by direct binding to NF-κB [42], leading to downregulation of the proinflammatory cytokines TNF-α, interleukin-6 (IL-6), and plasminogen activator inhibitor-1. As a transrepressive effect of PPARγ and NF-κB, NF-κB also inhibits PPARγ transcriptional activity by acting on histone deacetylase 3 [43].

2.1.3. Regulation of PPARs in Subcutaneous and Visceral WAT. Three subtypes of PPAR, that is, PPARα, PPARβ/δ, and PPARγ, have tissue-specific regulatory functions. The tissue-specificity of each PPAR isoform is due to differences in the tissue-specific expression and specific target genes of each PPAR isoform. The tissue distribution, target genes, and main functions of PPAR subtypes are summarized in Table 1. Among the three PPAR subtypes, PPARγ is highly expressed in adipose tissues and stimulates glucose uptake and adipokine secretion [1]. Through its interactions with adipokines, PPARγ is involved in adipogenesis, lipid metabolism, glucose homeostasis, adipose remodeling, and WAT browning in WAT [2]. PPARγ agonists have been used as oral hypoglycemic agents by sensitizing cells to insulin action; however, the application of these agents is often limited because of their effects on increasing body fat content [3]. The PPARγ agonist thiazolidinedione (TZD) selectively
induces the differentiation of immature preadipocytes in subcutaneous fat. Newly differentiated adipocytes are small and exhibit increased insulin sensitivity without altering the total weight of the WAT [44]. Interestingly, the opposite is true of visceral fat pads; TZD treatment decreases the numbers of large adipocytes in visceral fat by increasing apoptosis in large and relatively insulin-resistant visceral adipocytes [45]. Fat deposition in subcutaneous adipose tissue is relatively beneficial compared with increased visceral fat contents in terms of the risk of metabolic syndrome and cardiovascular diseases (CVDs). Lipoprotein lipase (LPL) has been suggested to be involved in PPARγ-dependent fat redistribution from visceral to subcutaneous tissues in PPARγ agonist-treated experimental models. The mass and catalytic activities of LPL are increased in subcutaneous fat, but not in visceral fat depots, accompanied by alterations in factors involved in the regulation of LPL activity, fatty acid transport, and lipogenesis [46, 47]. Nonetheless, in addition to increased subcutaneous fat, other side effects, including adverse cardiac outcomes, have been reported in patients receiving rosiglitazone, resulting in withdrawal of rosiglitazone from the market. Novel approaches have been applied for the use of PPARγ agonist as antidiabetic drugs, including development of new types of PPARγ agonists, dual PPARα and PPARγ agonists, and combination with agents that can suppress adipocyte differentiation and fat accumulation. In particular, dual PPARα and PPARγ agonists have been accepted to be promising for the treatment of type 2 diabetes with dyslipidemia. Administration of lobsiglitazone and saroglitazar was effective in lowering HbA1c and in improving glucose control and lipid profiles in subjects of type 2 diabetes [48–51]. It does not mean that these dual PPARα and PPARγ agonists have no side effects. For example, weight gain was still observed in lobsiglitazone-treated diabetic subjects [50]. Collectively, existing evidence suggests that the usage of dual PPARα and PPARγ agonists was relatively well tolerated and acceptable considering the balance between efficacy and side effects.

2.2. Regulation of PPARs in BAT

2.2.1. Cellular Origin of Brown and Beige Adipocytes. At least two metabolically distinct brown adipocytes are found in humans: "classical brown" and "beige" adipocytes [52–54]. Classical brown adipocytes possess molecular attributes similar to interscapular BAT (iBAT) of rodents based on constitutive uncoupling protein-1 (UCP1) expression, homogeneous multilocular morphology, and a myogenic origin (Myf5⁺) [55, 56]. Conversely, beige adipocytes are differentiated from nonmyogenic lineage progenitors (Myf5⁻) and possess low levels of UCP1 expression under unstimulated conditions. Although there is still some controversy regarding the cellular identity, anatomical location, and recruitment versus transdifferentiation of beige adipocytes [57, 58], the metabolic relevance of beige adipocytes in terms of energy expenditure [52, 59] has well been established in response to environmental stimuli, such as low temperature [60, 61], and to physical activity [62]. Because BAT activity is negatively associated with adiposity, insulin resistance (IR), and aging, therapeutics targeting BAT recruitment and activity have attracted attention as a potential novel treatment strategy. PPARγ regulates the general differentiation program and metabolic function of brown adipocytes as well as white adipocytes. Given the metabolic relevance of BAT in metabolism, we will summarize the role of the PPARs in regulating brown and beige fat development in this section. We also propose that reduced PPARγ activity may explain the compromised BAT activities in obesity and metabolic syndrome.

2.2.2. Transcriptional Regulation of PPARγ in Brown and Beige Adipocytes. PPARγ is the single most important TF that governs white adipocyte differentiation. However, PPARγ alone is insufficient to drive the entire brown adipogenic transcriptional program, and its transcriptional partner, PR domain-containing protein 16 (PRDM16), is also required. Nonetheless, PPARγ activity is essential for the development of both classical brown and beige adipocytes. Using a brown preadipocyte cell line, researchers have shown that PPARγ...
binding to the PPAR response element of UCP1 is required for the transcriptional activity of UCP1 [63]. Inhibition of PPARγ activity using a dominant-negative mutant promotes the whitening of interscapular brown fat [64]. In addition, genome-wide binding analyses have demonstrated that PPARγ binds to many other genes unique to brown adipocytes, suggesting that PPARγ binding to PPRE response elements in brown target genes confers lineage specificity during brown fat differentiation [65, 66]. In addition to promoting classical brown adipocyte differentiation, PPARγ has also been implicated in white-to-beige conversion. Lack of functional PPARγ activity leads to defective beige fat recruitment, suggesting that beige fat development is dependent on PPAR function [64]. Conversely, synthetic PPARγ ligands, particularly those in the TZD class, are potent regulators of mitochondrial biogenesis and cause significant increases in brown-specific phenotypes in white adipocytes, including UCP1 upregulation and uncoupled respiration [67–73]. In later studies, Ohno et al. showed that the white-to-beige conversion by PPARγ agonism could be explained by stabilization of PRDM16 protein, the master transcriptional regulator of brown adipocytes [74]. Interestingly, energy expenditure is not increased in TZD-treated animals. This could be due to the observation that TZD-mediated systemic lipogenesis overshadows the improved mitochondrial function and suppresses β3-adrenergic receptor- (ADRB3-) mediated activation in vivo [75–77]. Another important mechanism through which PPARγ agonism enhances BAT activity involves the activation of SIRT1, a Sirt2 homolog and NAD-dependent deacetylase [78]. Moreover, activation of SIRT1 and deacetylation of PPARγ by resveratrol increase the recruitment of PRDM16, resulting in implementation of the transcriptional cascade for brown signature genes [74]. In addition to PPARγ, PPARα plays a role in brown adipocyte formation. Because PPARα is a primary regulator of mitochondrial β-oxidation, it is not surprising that PPARα expression levels are higher in brown adipocytes than in white adipocytes. Although PPARα expression is often regarded as a downstream brown marker gene, other studies have demonstrated that PPARα functions simultaneously with PPARγ to increase the brown-specific expression of PRDM16, PGC1α, and UCP1 [79, 80]. PPARβ/δ is ubiquitous, showing highest expression in the gut, but is now thought to be important in exercise-induced white-to-beige conversion and thermogenesis [81]. In conclusion, the plasticity of adipocytes in response to different environmental stimuli is likely regulated by the dynamic associations among TFs (e.g., PPARs and PRDM16) and their coregulators (e.g., PGC1α and SIRT1). These interactions between environmental and transcriptional regulators determine the lineage commitment of adipogenic progenitor cells, that is, white, brown, and beige adipocytes, and the metabolic fate of existing adipocytes, that is, browning or its reversal, whitening.

2.2.3. Compromised Activities of PPARs in Obese and Metabolically Unhealthy BAT. Chronic activation of ADRB3 is a key signaling event enhancing BAT activity and/or mass. In healthy humans, at least three distinct metabolic responses occur concurrently in response to ADRB3 signaling: (1) an increase in BAT activity in preexisting classical brown adipocytes, (2) metabolic switch of some, if not all, existing white adipocytes to beige adipocytes in subcutaneous fat, and (3) new beige adipocyte formation from adipogenic progenitor cells [82, 83]. Emerging evidence has revealed that these metabolic adaptations of BAT are preceded by cellular remodeling of WAT via type 2 innate immune responses, that is, IL-4 and IL-13 secretion [84, 85], M2 macrophage polarization [86], and local catecholamine production from macrophages and eosinophils [86, 87]. Unfortunately, BAT activity in humans is inversely correlated with body fat mass [88, 89], age, and blood glucose levels [90, 91]. Compromised BAT activation in conditions of obesity and metabolic vulnerability is associated with impairment of immunological remodeling in WAT upon ADRB3 activation. Given the critical role of PPARs in BAT regulation, the molecular mechanisms through which these defective immune responses affect the transcriptional regulation of PPARs/PRDM16 and the recruitment of these proteins to brown-specific target genes need to be defined. One of the most plausible and reasonable mechanisms for defective BAT activation in obesity involves the inverse regulation of NF-κB and PPARγ transactivation [92–95]. Toll-like receptor 4- (TLR4-) mediated NF-κB activation in obesity severely impairs cold-induced type 2 immune responses [85], downregulates PPARγ and PPARα expression, and markedly reduces beige fat development [96]. Similarly, Goto et al. showed that IL-1β, which causes systemic IR, strongly reduces PPARγ expression and blocks BAT development upon cold exposure [97]. Hence, pharmaceutical or nutritional strategies to restore PPAR activities by NF-κB suppression should be revisited as a new approach to reinstate type 2 immune responses and PPAR/PRDM16 recruitment for beige fat development.

3. Effects of Nutrition on the Modulation of PPARs

3.1. Fatty Acids (FAs) and Their Derivatives. Food components that act as ligands for PPARs can show multiple effects, including antidiabetic, antiadipogenic, and anti-inflammatory effects [98–100]. A wide range of PPAR agonists have been identified; synthetic PPAR agonists, such as fibrates and TZD, as well as natural PPAR ligands, such as dietary FAs and their derivatives, have been shown to bind to and activate PPARs [101–103]. Indeed, fibrates and TZD are already used to treat hyperlipidemia and diabetes mellitus, respectively. Ligand-activated PPARs play a critical role in regulating metabolic activities associated with lipid metabolism, glucose metabolism, and the inflammatory state [99]. As shown in various ligand-binding assays, PPARs generally prefer to bind to polyunsaturated FAs, whereas saturated FAs are poor PPAR ligands. Thus, the activity of PPARs can be modulated by FAs derived from the diet; however, the capacity of FAs to activate PPAR-dependent gene transcription varies according to the type of FA [101, 104]. A variety of FAs and their derivatives as PPAR ligands are shown in Table 2.
Table 2: FAs and their derivatives as PPARs ligands.

<table>
<thead>
<tr>
<th>Receptor</th>
<th>PPARα</th>
<th>PPARβ/δ</th>
<th>PPARγ</th>
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<tbody>
<tr>
<td>Saturated FAs (weaker)</td>
<td>Unsaturated FAs</td>
<td>Unsaturated FAs (LA, LNA, CLA, DHA, EPA)</td>
<td></td>
</tr>
<tr>
<td>Unsaturated FAs (LA, LNA, PUFAs, including AA, EPA, phytanic acid)</td>
<td>Saturated FAs (much weaker)</td>
<td>15-d-PGJ2</td>
<td></td>
</tr>
<tr>
<td>Leukotriene B4</td>
<td>Prostacyclin</td>
<td>15-HETE</td>
<td></td>
</tr>
<tr>
<td>8-HETE</td>
<td>4-HNE</td>
<td>9-HODE</td>
<td></td>
</tr>
<tr>
<td>8,9-Epoxeyicosatrienoic acids</td>
<td>4-HDDE</td>
<td>13-HODE</td>
<td></td>
</tr>
<tr>
<td>II,12-Epoxeyicosatrienoic acids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OEA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEA</td>
<td></td>
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</tr>
</tbody>
</table>

AA, arachidonic acid; CLA, conjugated linoleic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; 15-d-PGJ2, 15-deoxy-Δ12,14 prostaglandin J2; LA, linoleic acid; LNA, α-linolenic acid; OEA, oleoylethanolamide; PEA, palmitoylethanolamide; 4-HDDE, 4-hydroxydeca-(2E,6Z)-dienal; 4-HNE, 4-hydroxy-2-nonenal; 15-HETE, 15(S)-hydroxyeicosatetraenoic acid; HODE, hydroxoyoctadecadienoic acid.

FAs are ubiquitous biological molecules that act as metabolic fuels and essential components of cellular functions [101]. Although FAs are essential biological components, elevated levels of circulating FAs are closely related to most common metabolic disorders, such as CVD, hyperlipidemia, obesity, and IR [105]. Not all fats are created equal; high consumption of foods enriched in saturated FAs has been shown to be associated with the development of common diseases, such as coronary artery disease, obesity, diabetes, and cancer, whereas consumption of a diet high in polyunsaturated FAs (PUFAs), such as fish oil, appears to have protective effects against atherosclerosis and heart disease [106, 107]. As FA sensors, PPARs should also be considered when evaluating the distinctly different physiological effects of different FAs owing to small structural variations in FAs and their derivatives [99, 108].

PUFAs are classified as n-3 and n-6 FAs that have opposing effects in the modulation of receptor signaling and gene expression; n-6 (i.e., arachidonic acid [AA])-derived eicosanoids are mostly proactive, whereas n-3 (i.e., eicosapentaenoic acid [EPA])-derived eicosanoids are inhibitory [109]. After the essential FAs linoleic acid (LA, n-6) and α-linolenic acid (LNA, n-3) are consumed, they are further metabolized by various desaturases and elongases to generate long-chain FAs including AA, EPA, and docosahexaenoic acid (DHA; n-3) [110]. AA, EPA, and DHA are then further metabolized by cyclooxygenases, lipoxygenases, and/or epoxygenases to various FA-derived eicosanoids, some of which are listed in Table 2 as PPAR ligands [111]. FAs bind directly to PPARα at physiologically relevant levels and induce transcriptional activation. In fact, unsaturated FAs and PUFAs bind to PPARα in the μM range, which can be achieved by dietary intake [108]. With regard to activation potency, the n-3 FAs EPA and DHA are more potent as in vivo activators of PPARα than n-6 FAs [112–114]. Moreover, various eicosanoids can activate PPARα with a stronger affinity than their PUFA precursors [103, 115, 116]. Recent findings have shown that acylethanolamides (AEs), such as anandamide (AEA), palmitoylethanolamide (PEA), and oleoylethanolamide (OEA), which are biosynthesized in the gastrointestinal tract, also act as PPARα activators [117]. PPARα activation by OEA results in appetite suppression and lipolysis, whereas activation of PPARα by PEA results in anti-inflammatory effects [118]. Known PPARβ/δ ligands are similar to those for PPARα with much lower levels of activation [108]. PPARγ ligands include unsaturated FAs, such as LA, LNA, CLA, DHA, and EPA, as well as FA derivatives in the physiologically relevant range [119]. Additionally, PPARγ agonists can have systemic anti-inflammatory effects [100]. For example, the prevention of high-fat or high-energy diet-induced adipose tissue inflammation and remodeling by long-chain n-3 PUFAs is reported to involve PPARγ activation [120, 121]. Collectively, various FAs and their derivatives are natural ligands for PPARs, with a fair amount of overlap among the three PPAR subtypes, and these molecules act as metabolic regulators by controlling the PPAR activity. Although many studies have helped to elucidate the role of PPARs in FA-mediated activation, more research is needed to determine the tissue distribution of PPAR subtypes in humans and evaluate the concentration and availability of FAs and their derivatives in human tissues.

3.2. Conjugated Linoleic Acids (CLAs). CLAs are FAs that are mainly found in foods derived from ruminant animals [122]. CLAs are geometrical and positional isomers (cis or trans-double bond positioning at 7, 9, 8, 10, 9, 11, 10, 12, or 11, 13) of the parent molecule LA (cis-9, cis-12-18:2, n-6). The cis-9, trans-11 (9Z, 11E-octadecenoic acid, C18:2) isomer, also known as rumenic acid, is generated through bihydrogenation of dietary LAs by ruminant microflora and is the most abundant natural CLA isomer (over 75–80% of total CLAs). Due to their multiple health benefits, CLAs are currently being used as dietary supplements for altering body composition in humans and livestock [123, 124]; however, little is known regarding the mechanisms of these beneficial properties of CLAs.

CLA isomers are ligands for PPARα, PPARβ/δ, and PPARγ [125, 126], exhibiting differences in health benefits and PPAR activation [124, 127]. For example, 9Z, 11E-CLA is a potent PPARα ligand in the low nM range and exerts...
potent anticancer effects [125, 128]. In contrast, 10E, 12Z-CLA causes adipocyte delipidation, IR, and inflammation by acting as a PPARγ antagonist [129]. In addition, a mixture of CLA isomers as well as 9Z, 11Z-CLA and 9Z, 11E-CLA isomers can significantly activate PPARβ/δ in preadipocytes [108]. Thus, there are important cellular mechanisms that are able to differentiate subtle structural changes in various CLA isomers to allow tissue- and species-specific responses [130, 131]. Taken together, these findings support that CLA affects the production of eicosanoids either directly or indirectly, enhances PPARγ activation, attenuates the NF-κB pathway, and directly decreases proinflammatory cytokines to have beneficial effects on inflammation, ultimately influencing metabolic syndrome-related conditions, including obesity, IR, and atherosclerosis [132]. Thus, CLAs can directly exert anti-inflammatory effects by regulating the expression of inflammatory mediators, potentially through NF-κB-dependent and/or PPARγ-dependent pathways [133, 134].

3.3. Flavonoids. Flavonoids are a class of polyphenolic compounds that are secondary plant products [135]. The structure of flavonoids is based on C6-C3-C6, which involves two aromatic rings (A and B) linked to a heterocyclic ring (C) containing one oxygen and three carbons. Flavonoids are classified as flavanols, flavones, flavonols, flavanones, isoflavones, and anthocyanidins according to structural differences in the C ring. Many studies have reported the functionalities of flavonoids. One of the main functionalities of flavonoids is their antioxidant effects, for example, metal chelating activity [136], reactive oxygen species (ROS) scavenging [137, 138], antioxidant enzyme activation [139], and α-tocopherol reduction [140], which collectively result in inhibition of ROS-mediated cellular aging [141], inhibition of mutations [142], anticancer effects [143], inhibition of LDL oxidation and CVDs [144–146], and reduction of ischemic damage [147]. Moreover, many studies have examined the antiobesity effects of flavonoids with regard to energy expenditure and lipid metabolism [148–151]. However, additional studies are needed because the antiobesity effects of flavonoids are still unclear. Thus, in this review, we discuss the effects of flavonoids on PPARγ-mediated obesity based on the role of PPARγ as a master regulator of adipogenesis. Abundant evidence has shown that PPARγ influences the adipogenic transcriptional cascade as a master regulator of adipogenesis [26, 152]. PPARγ is also involved in glucose and cholesterol metabolism. Regulation of PPARγ activation is a primary focus in studies of the control of obesity and type 2 diabetes. TZD, a synthetic ligand for PPARγ activation, is used in the treatment of type 2 diabetes. However, because TZD has major side effects, such as edema, weight gain, and heart failure, many researchers have attempted to identify natural PPARγ activators [153–155]; indeed, identification of effective therapeutic modulators of PPARγ without side effects or with reduced side effects has become a major research focus. Many studies have investigated the therapeutic effects of natural substances owing to the potential or practical negative effects of synthetic medications. Natural substances originating from plants and fruits are traditionally used for the treatment of various diseases. Additionally, the value of natural substances as sources for new drug discovery is increasing because natural substances can be used as a therapeutic strategy to avoid side effects of synthetic drugs [156]. Taken together, these findings highlight the role of natural substances in PPARγ-mediated mechanisms. In this review, we discuss recent reports of the effects of flavonoids on PPAR activity based on an antiobesity perspective.

Recent findings have suggested that dietary flavonoids inhibit adipogenesis during differentiation of preadipocytes and prevent obesity by downregulation of PPARγ expression. Catechin significantly suppresses body fat accumulation and downregulates PPARγ in visceral WAT [5]. Quercetin also downregulates PPARγ in WAT but does not alter the amount of body fat [18]. Notably, most evidence has been reported from in vitro studies rather than in vivo studies. Several flavonoids, including hesperetin [12], isoflavones [13], licochalcone A [15], luteolin [16], quercetin [19], and tangeretin [21], have been shown to have inhibitory effects on adipogenesis during differentiation of preadipocytes into adipocytes, accompanied by downregulation of PPARγ. Activation of PPARγ induces upregulation of various downstream target genes involved in lipogenesis and FA synthesis. Although it is unclear whether the inhibition of adipocyte differentiation occurs directly through PPARγ activity, it is feasible that flavonoids may effectively inhibit the transcriptional activity of PPARγ by inhibiting adipocyte differentiation via downregulation of PPARγ [13].

Recently, numerous natural substances have been reported to potentially modulate PPARγ activity as a source of PPARγ ligands; the natural compounds involved in mediating these effects have been identified as flavonoids, lignans, and stilbenes [157]. In particular, the role of flavonoids in the regulation of PPARγ activity has been extensively studied owing to the agonist potential of these molecules. Moreover, several studies have reported and highlighted the role of flavonoids as latent PPARγ agonists against GW9662 or T0070907 (PPARγ antagonists) [6–8]. The agonistic effects of flavonoids on PPARγ-mediated obesity, however, vary according to the chemical characteristics of the flavonoids. Some flavonoids selectively modulate PPARγ activity and suppress adipogenesis or obesity [5, 12, 13, 15, 16, 18, 19, 21]. In contrast, other flavonoids promote adipogenesis by activation of PPARγ [6–11, 14, 17, 20], as shown in Table 3. Inhibition of the transcriptional activation of PPARγ by flavonoids is closely related to suppression of adipogenesis [13, 158]. Accordingly, PPARγ activity can be altered through various pathways, including posttranslational modification, ligand type, or ligand-binding domain. For example, inhibition of PPARγ phosphorylation at serine 273 by PPARγ ligands leads to antiobesity effects with fewer side effects because serine 273 phosphorylation prevents the transcription of antiobesity genes [156, 159]. Although flavonoids are known to show agonistic effects toward PPARγ, the detailed molecular mechanisms of their antiobesity effects have not been fully elucidated. Taken together, these findings support the importance of identifying novel flavonoids that modulate PPARγ activity through posttranslational modification, for example, through phosphorylation, in order to improve
Table 3: Summary of recent publications on the effects of flavonoids: adipogenesis and PPAR\(\gamma\) activity.

<table>
<thead>
<tr>
<th>Flavonoid</th>
<th>Model</th>
<th>Effect</th>
<th>PPAR(\gamma) activity</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catechin</td>
<td>Adipocyte differentiation in human bone marrow mesenchymal stem cells</td>
<td>Adipogenesis ↑</td>
<td>Activity ↑</td>
<td>[5, 6]</td>
</tr>
<tr>
<td>Daidzein</td>
<td>3T3-L1 preadipocyte differentiation</td>
<td>Adipogenesis ↑</td>
<td>Activity ↑</td>
<td>[7]</td>
</tr>
<tr>
<td>Equol</td>
<td>3T3-L1 preadipocyte differentiation</td>
<td>Adipogenesis ↑</td>
<td>Activity ↑</td>
<td>[8]</td>
</tr>
<tr>
<td>EGCG</td>
<td>AML-1 human preadipocyte differentiation</td>
<td>Adipogenesis ↑</td>
<td>Not measured</td>
<td>[9]</td>
</tr>
<tr>
<td>Fisetin</td>
<td>3T3-L1 preadipocyte differentiation</td>
<td>Adipogenesis ↑</td>
<td>Activity ↑</td>
<td>[10]</td>
</tr>
<tr>
<td>Flavanone</td>
<td>3T3-L1 preadipocyte differentiation</td>
<td>Adipogenesis ↑</td>
<td>Activity ↑</td>
<td>[11]</td>
</tr>
<tr>
<td>Hesperetin gluconides</td>
<td>3T3-L1 preadipocyte differentiation</td>
<td>Adipogenesis ↓</td>
<td>Not changed</td>
<td>[12]</td>
</tr>
<tr>
<td>Isoflavonoids</td>
<td>3T3-L1 preadipocyte differentiation</td>
<td>Adipogenesis ↓</td>
<td>Activity ↑</td>
<td>[13]</td>
</tr>
<tr>
<td>Kaempferol</td>
<td>3T3-L1 preadipocyte differentiation</td>
<td>Adipogenesis ↓</td>
<td>Activity ↑</td>
<td>[14]</td>
</tr>
<tr>
<td>Licochalcone A</td>
<td>3T3-L1 preadipocyte differentiation</td>
<td>Adipogenesis ↓</td>
<td>Not measured</td>
<td>[15]</td>
</tr>
<tr>
<td>Luteolin</td>
<td>3T3-L1 preadipocyte differentiation</td>
<td>Adipogenesis ↓</td>
<td>Not changed</td>
<td>[16]</td>
</tr>
<tr>
<td>Pentamethoxyquercetin</td>
<td>3T3-L1 preadipocyte differentiation</td>
<td>Adipogenesis ↓</td>
<td>Not measured</td>
<td>[17]</td>
</tr>
<tr>
<td>Quercetin</td>
<td>HFD-induced obese Wistar rats</td>
<td>Plasma TG ↓</td>
<td>Not changed</td>
<td>[18]</td>
</tr>
<tr>
<td>Quercetin-3-O-(6''-Feruloyl)-(\beta)-d-galactopyranoside</td>
<td>3T3-L1 preadipocyte differentiation</td>
<td>Adipogenesis ↓</td>
<td>Not measured</td>
<td>[19]</td>
</tr>
<tr>
<td>Sakuranetin</td>
<td>3T3-L1 preadipocyte differentiation</td>
<td>Adipogenesis ↓</td>
<td>Not changed</td>
<td>[20]</td>
</tr>
<tr>
<td>Tangeritin</td>
<td>3T3-L1 preadipocyte differentiation</td>
<td>Adipogenesis ↓</td>
<td>Not measured</td>
<td>[21]</td>
</tr>
</tbody>
</table>

TG, triglyceride; HFD, high-fat diet.

our understanding of the interactions of flavonoids with PPAR\(\gamma\); such studies are expected to enhance the therapeutic potential of flavonoids. Furthermore, additional studies of the PPAR-dependent effects of flavonoids on tissue-specific events, for example, in the WAT and BAT, are needed. Based on the importance of the tissue-specific roles of PPAR, as demonstrated in this review, future studies may focus on tissue-specific PPAR regulation by flavonoids.

4. Nutrigenetics and PPAR\(\gamma\) Polymorphisms

4.1. PPAR\(\gamma\) Gene and Polymorphism. PPAR\(\alpha\) is located on chromosome 22q13.3 and spans 93.15 kb. Single nucleotide polymorphisms (SNPs) in PPAR\(\alpha\), that is, L162V, V227A, and intron 7G>C, are associated with metabolic features, such as dyslipidemia, CVD, and type II diabetes [160]. In this review, we have focused on PPAR\(\gamma\) SNPs associated with the obesogenic environment because of the limited availability of information regarding the clinical/biological effects of genetic variants in PPAR\(\alpha\) and PPAR\(\beta/\delta\).

The PPAR\(\gamma\) gene, which encodes a TF belonging to the same family of NRs as steroid hormone receptors, is a master regulator of the relationships between nutrients (such as FAs), prostanoids, insulin-sensitizing agents, susceptibility to obesity, control of peptides released from adipocytes, and insulin sensitivity [161]. In macrophages, PPAR\(\gamma\) has been shown to regulate the suppression of inflammatory cytokine production and improvement of insulin sensitivity [162]. Alternative promoter regions within the PPAR\(\gamma\) gene allow the formation of three PPAR\(\gamma\) subtypes: PPAR\(\gamma\)1, PPAR\(\gamma\)2, and PPAR\(\gamma\)3. Although PPAR\(\gamma\)1 mRNA has been identified in many tissues, including the heart, liver, skeletal muscle, and adipose tissue, PPAR\(\gamma\)2 mRNA is abundantly expressed in adipose tissue, whereas PPAR\(\gamma\)3 mRNA is expressed in macrophages, epithelial tissue, and adipose tissue [163]. The PPAR\(\gamma\) gene extends over 100 kb and includes nine exons, which give rise to three different PPAR\(\gamma\) transcripts with differential promoter usage and differential splicing (PPAR\(\gamma\)1, PPAR\(\gamma\)2, and PPAR\(\gamma\)3). The PPAR\(\gamma\)1 and PPAR\(\gamma\)2 expressed during the differentiation of 3T3-L1 into adipocytes are derived from two alternative transcripts which share six identical C-terminal exons. Although PPAR\(\gamma\) is well known for its role in adipogenesis, it also plays a crucial role in maintaining normal physiology, including insulin sensitization.

This role of PPAR is consistent with many human genetic studies of various single amino acid mutations, such as Pro12Ala, Pro115Gln, Cys114Arg, C34G, Val290Met, Pro388Leu, Arg425Cyc, Pro467Leu, Cys162Trp, Pro12Ala, Pro115Gln, Cys114Arg, Cys131Tyr, and Pro467Leu, which are located in several domains [164]. Of these identified mutations in the PPAR\(\gamma\) gene, a common polymorphism occurs in the 3T3-L1 specific exon B. The Pro12Ala polymorphism rs1801282 (C34G) and the silent C1431T mutation (His449His, CAC478CAT) are frequently observed in PPAR\(\gamma\)2. Many mutations in the PPAR\(\gamma\) gene are associated with obesity and diabetes-related phenotypes [165]. For example, the Pro115Gln mutation is associated with obesity.
but not IR, and the mutations Val290Met and Pro467Leu are related to severe IR but not obesity [164]. The CCA-to-GCA missense mutation in codon 12 of exon B of the PPARγ gene encodes an NH2-terminal residue that defines the adipocyte-specific PPARγ2 isoform [166]. Obesity is a multifactorial disorder involving the regulation of food intake and energy expenditure, and ethnicity-dependent-genetic factors play significant pathogenic roles. PPARγ genes independently or dependently regulate the transcription of target genes involved in obesity-related processes, such as adipogenesis, IR, angiogenesis, and inflammation, in a tissue-dependent manner. Therefore, PPARγ2 gene polymorphisms influence obesity in a complex manner, likely involving ethnicity-dependent variations in obesity-related phenotypes.

4.2. The Common Pro115Ala Polymorphism in PPARγ and Obesity. The Pro12Ala polymorphism in PPARγ was first identified in 1997, and a point mutation found in the B exon of the NH2-terminal of PPARγ at position 12 (rs1801282) was shown to cause a moderate decrease in the transcription activity and adipogenic potential of this protein [162]. The rare allele frequencies are high in Caucasians (12%) and relatively low in Asians (4% of Japanese and 1% of Chinese) and African Americans (3%) [167]. The Ala allele generated by the Pro12Ala polymorphism is associated with obesity and confers a 25% reduction in the risk of type II diabetes, IR, and CVD in Caucasians [167]. However, although PPARγ is associated with IR and type II diabetes, the 12Ala allele does not reduce the risk of diabetes in South Asians, Chinese, and Malaysians [168, 169]. The 12Pro-161Th haplotype is associated with lower body mass index (BMI) and lower fasting serum triglycerides (TGs) in Koreans but not in Iranians [170, 171]. In a meta-analysis of BMI subgroups, the Ala allele was shown to be associated with an increase in 0.96 units for BMIs of 35 or more, and this association was observed in individuals with BMIs of 37 to less than 35 or with BMIs of 35 or more when the meta-analysis was restricted to Caucasians [172]; this pattern was not found in Asians. Further analysis suggested that this discrepancy may be explained by differences in body weight distributions and lifestyles of these ethnic groups [173]. In Italian population, carriers of the PPARγ2 Ala allele were found to have higher BMIs and fat-mass levels than carriers of the wild-type allele, although a metabolically healthy profile was associated with the PPARγ2 Ala allele due to the more favorable distribution of adipose tissue. Researchers also found that there was a genetic interaction between Pro12Ala and ACE I/D with regard to BMI and fat mass [174]. According to a gene-diet interaction analysis of the PPARγ Pro12Ala polymorphism, there is an inverse association between the PUFA to saturated FA (SFA) ratio (P:S) and BMI/insulin levels in Ala carriers. Because the mean P:S ratio varies by more than 10-fold, for example, from 0.11 in Hungary to 1.2 in Portugal, this ratio may be a more effective stimulator of adipogenesis in Pro carriers than in Ala carriers [175]. This study suggested that when the dietary P:S ratio is low, the BMI in Ala carriers is greater than that in Pro homozygotes. Moreover, although consumption of a PUFA-containing diet does not affect PPARγ2 mRNA expression, individuals with the Pro12Pro genotype are more likely to benefit from consumption of a PUFA-containing diet [176]. Similarly, intake of monounsaturated FAs has been shown to have this effect in Ala12 allele carriers. A study in Québec, Canada, showed that total fat and saturated fat intake are positively correlated with body mass change in Pro12 homozygotes, whereas Ala12 allele carriers are protected from this change [177]. Moreover, the Ala12Ala genotype also associated with higher expression of PPARγ2, LPIN1, and sterol regulatory element-binding protein-1c mRNA compared with that in participants harboring the Pro12Pro genotype. Thus, it is possible that different dietary patterns between ethnic groups could modulate the relationship between BMI and this particular SNP.

Adiponectin, an adipocyte-derived hormone, is encoded by the adipocyte Clq and collagen domain-containing (ACDC) gene located in chromosome 3q27. Many studies have shown that adiponectin is reciprocally associated with central and peripheral fat distribution, IR, inflammation, and atherogenic lipid metabolites [178]. In a Danish study, several ACDC polymorphisms were found to be associated with body fat distribution, whereas Pro12Ala was found to be associated with body fat accumulation (overall adiposity). Additionally, the CC genotype of SNP-11377, an SNP in the promoter of the ACDC gene, was shown to interact with the homozygous Ala12Ala genotype to mediate BMI [179]. Cooperative interactions between the ACDC and PPARγ genes in the modulation of insulin sensitivity have also been demonstrated in a recent family-based association study, revealing significant interactions between SNP+457T/G of the ACDC gene and the Ala12 allele in a Taiwanese population; however, there was no evidence for this associated in the Italian population [180].

Among the SNPs rs10865710 (C-681G), rs7649970 (C-689T), and rs1801282 (C34G, Pro12Ala), the G allele of rs10865710 in the PPARγ gene is frequently observed and has been shown to be associated with increased susceptibility to nonalcoholic fatty liver disease (NAFLD) [181]. Despite ethnic differences in the prevalence of NAFLD, the incidence of NAFLD is known to primarily depend on lifestyle, dietary habits, and hepatic metabolic syndrome. Many genetic variations related to the obesogenic environment, including oxidative stress, inflammation, fibrogenic mediators, dyslipidemia, and IR, are involved in the pathogenesis of NAFLD [182]. The A12 allele is associated with lower fasting plasma glucose but does not affect blood pressure, BMI, or other metabolic parameters in Palestinian individuals. However, in obese patients, the 12A allele was associated with elevated total plasma cholesterol levels and a tendency toward increased low-density lipoprotein (LDL) cholesterol [183]. The PPARγ Pro12Ala polymorphism is associated with a reduced risk of myocardial infarction (MI) according to the Physician’s Health Study but confers an increased risk of MI or cardiac death according to the Health Professionals Follow-Up Study [184]. Additionally, we found that the 12AAla variant of PPARγ2 may influence CVD risk by affecting lipid metabolism in obese Palestinian individuals with type II diabetes [184]. Therefore, additional studies of the PPARγ Pro12Ala polymorphism are necessary to further elucidate the role of PPAR genetics in obesity independent of CVD,
particularly with regard to available pharmacological PPAR-targeted agents.

4.3. The Common C1431T Polymorphism in PPARγ and Obesity. The C1431T polymorphism, also referred to as His447His, His447His, C16IT, or CAC478CAT, is a silent mutation located in exon 6 of PPARγ and is considered a better predictor of fasting insulin levels and IR than Pro12Ala. The polymorphism C1431T has been shown to be associated with susceptibility to CV diseases, diabetes, abnormal leptin concentrations, obesity, and metabolic syndrome and is associated with BMI [185, 186]. Although the C1431T polymorphism has not been extensively studied, the rare T allele has also been inconsistently linked to increases in weight. Because the Pro12Ala and C1431T polymorphisms are in linkage disequilibrium, both rare alleles are associated with increased body weight, and the overall effect is additive when these alleles occur together [187]. In Chinese patients with diabetes, the Pro12Ala and C1431T polymorphisms may not be major etiological factors for type 2 diabetes; however, the C1431T polymorphism is associated with overweightness or obesity, despite the observation that there are no differences in the frequencies of C1431T, Pro12Ala, and their haplotypes between patients with type 2 diabetes and control subjects [188]. Notably, the Ala12 allele is consistently associated with a lower BMI, whereas the T1431 allele is consistently associated with higher BMI in the Scottish nondiabetic population [186]. In contrast, the heterogenous and Ala homogenous type of PPARγ Pro12Ala are significantly associated with higher risk of obesity, whereas the C1431T polymorphism is not significantly associated in individuals from northern India. None of the haplotypes are associated with morbid obesity [189]. In the Korean population, the Pro12Ala and C1431T SNPs have been shown to be associated with some parameters of metabolic syndrome in women [190]. In the EDEN mother-child cohort study, mothers homozygous for the T allele of C1431T were also more obese (24% versus 9%, resp.; \( P = 0.035 \)), and three times more mothers had gestational diabetes (18% versus 6%, resp.; \( P = 0.044 \)). Moreover, the Pro-T haplotype conferred the highest risk of gestational diabetes (odds ratio = 1.89, 95% confidence interval [CI] = 1.05–3.40), whereas the Ala-C haplotype was associated with the lowest risk of gestational diabetes (odds ratio = 0.12, 95% CI = 0.52–1.70) [191]. Additionally, one study showed that both the Pro12Ala and C1431T variants of PPARγ are not associated with metabolic syndrome or obesity in a population from southern India [192]. However, in UK and Chinese individuals with coronary artery disease (CAD), the PPARγ C1431T polymorphism is significantly associated with CVD risk factors, such as fasting serum lipid profiles, in the context of variant genotypes (CT + TT) [193, 194]. Angiogram-positive patients carrying the T allele have significantly higher TGs, serum C-reactive protein, and fasting blood glucose levels, and obese patients harboring at least one CAT478 allele have higher leptin levels than other obese patients with similar BMIs, suggesting that the PPARγ gene may influence the levels of plasma leptin in obese individuals [195]. Finnish women with both Ala and 478CAT alleles have significantly more fat mass than women with other alleles. Thus, the CAC478CAT polymorphism is not associated with BMI or other variables related to obesity in different ethnic populations. Previous studies on isoflavones have shown their potential antiobesity effects, although the mechanisms are not clear; accordingly, foods containing high levels of isoflavones, such as Korean fermented soy food (Doenjang), have been used as functional foods for the treatment or prevention of obesity in Korea [196]. In a clinical study of Doenjang, visceral fat area was significantly decreased by Doenjang supplementation in individuals with a mutant T allele of PPARγ2 compared with those harboring a C allele [197], suggesting that Doenjang interacted with mutant alleles of PPARγ2 to exert antiobesity and antioxidative effects in obese individuals.

4.4. Rare PPARγ Polymorphisms and Obesity. The Pro115Gln polymorphism, a very rare gain-of-function mutation in PPARγ, is associated with obesity but not IR. Because fibroblasts containing the Pro115Gln mutation accumulate 2.5 times more TGs than the corresponding wild-type cell line, we expected individuals with the Pro115Gln mutation would tend to be obese in field studies. A variant of rare Pro115Gln has been shown to be associated with increased BMI among obese individuals, an effect attributed to constitutive activation of the PPARγ protein, which results in accelerated cell differentiation. Dominant-negative PPARγ mutations are associated with severe IR, hypertension, and alterations in lipid profiles (low high-density lipoprotein [HDL], high TGs) [198]. These studies implied that the Pro115Gln polymorphism has pathophysiological relevance in obesity; however, in the nationwide German Epidemiological Field Study, the Pro115Gln polymorphism was shown to have no relevant impact on morbid obesity [199]. The Val290Met and Pro467Leu polymorphisms are the best-characterized dominant-negative mutations of PPARγ2 and have been shown to dramatically reduce the transcriptional activity of PPARγ2 in vitro, resulting in severe IR with increasing fat accumulation, hypertension, and reduced adiponectin levels [165].

Based on these interesting findings from previous studies, we plan to investigate the association of rare or unknown polymorphisms in the PPARγ2 gene with BMI, obesity, and basal metabolic rates in obese individuals in the future.

5. Conclusion

The modulation of the PPAR activities poses significant impacts on metabolism, irrespective of the modifications that originated from external factors, such as hormones, temperature, excess nutrition, and PPAR-targeted drugs, or from genetic alternations such as polymorphism. Too much activation and too little activation of PPARs are both associated with improper fatty acid handling and maldistribution of fat, which leads to pathogenesis of metabolic diseases. In this review, we intend to provide an integrative view of PPAR regulation by summarizing the recent updates in PPAR regulation in white and brown fat, dietary ligands of PPARs and by incorporating common and rare PPAR polymorphism. We would like to emphasize that PPARs'
PPARs have a unique function of depositing extra energy into white adipose tissue and burning out fats in brown/beige adipose tissue and muscle should be balanced for maintaining metabolic health. To reach this goal, wise and prudent usage of natural PPAR ligands through diet could be an option. Also, keen understanding in tissue- and subtype-specific regulation of PPARs is perquisite for the development of drugs to treat metabolic syndrome utilizing PPAR biology. With the advent of “omics era,” our knowledge in individual variation in metabolic susceptibility has been tremendously progressed. Therefore, the individual genetic modification of PPARs should be taken into consideration with their environmental modifiers for an innovative approach to prevent obesity such as precision or personalized medicine.

**Abbreviations**

AA: Arachidonic acid  
ACDC: Adipocyte C1q and collagen domain containing  
ADRB3: β3-Adrenergic receptor  
AE: Acylethanolamide  
AEA: Anandamide  
APC: Adipogenic progenitor cell  
BAT: Brown adipose tissue  
BMI: Body mass index  
C/EBP: CCAAT/enhancer-binding protein  
CLA: Conjugated linoleic acid  
CREB: cAMP response element-binding protein  
CVD: Cardiovascular disease  
DHA: Docosahexaenoic acid  
EPA: Eicosapentaenoic acid  
FA: Fatty acid  
FAS: Fatty acid synthase  
FGF: Fibroblast growth factor  
GR: Glucocorticoid receptor  
IR: Insulin resistance  
IL: Interleukin  
LA: Linoleic acid  
LDL: Low-density lipoprotein  
LNA: Linolenic acid  
LPL: Lipoprotein lipase  
MI: Myocardial infarction  
NAD: Nicotinamide adenine dinucleotide  
NAFLD: Nonalcoholic fatty liver disease  
NF-κB: Nuclear factor-kappa B  
NR: Nuclear receptor  
OEA: Oleylethanolamide  
PEA: Palmitoylethanolamide  
PGC-1α: Peroxisome proliferator-activated receptor  
PPAR: Peroxisome proliferator-activated receptor  
PRDM16: PR domain-containing protein 16  
PUFA: Polyunsaturated fatty acids  
ROS: Reactive oxygen species  
SFA: Saturated fatty acid  
SIRT: Sir2 homolog  
SNP: Single nucleotide polymorphism  
STAT5A: Signal transducer and activator of transcription 5A  
TF: Transcription factor  
TNF-α: Tumor necrosis factor-α  
TZD: Thiazolidinedione  
UCP1: Uncoupling protein-1  
VFA: Visceral fat area  
WAT: White adipose tissue.

**Competing Interests**

The authors declare no conflict of interests.

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