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# Mediators of Impaired Adipogenesis in Obesity-Associated Insulin Resistance and T2DM

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## Abstract

Obesity has become a global health issue due to its high prevalence and associated comorbidities including insulin resistance (IR) and type 2 diabetes mellitus (T2DM). Obesity is associated with the expansion of adipose tissues through hypertrophy of mature adipocytes and differentiation of local preadipocytes in a process known as adipogenesis to store excess triacylglycerols (TAGs). Impairment of adipogenesis leads to ectopic fat deposition in skeletal muscles, liver, and kidneys, triggering IR in these tissues and increased risk of T2DM. Many factors contribute to impaired adipogenesis including obesity-associated mild chronic inflammation, oxidative stress, and fatty acid signaling. This review summarizes recent literature covering mediators of impaired adipogenesis and underlying molecular pathways.

**Keywords:** adipogenesis, mediators, inflammation, oxidative stress, fatty acids

## 1. Obesity-associated metabolic disease

Rapidly changing lifestyle, accompanied by consumption of excess energy in the form of a calorie-rich high-fat diet, lower voluntary activity, and increased exposure to environmental pollutants, have led to an exponential rise in noncommunicable metabolic diseases [1]. A key component of chronic metabolic diseases is obesity that has become a global health problem associated with a range of comorbidities including insulin resistance and type 2 T2DM [2], coronary artery disease (CAD) [3], nonalcoholic fatty liver [4], cancers [5], and elevated risk of premature death [6, 7].

Adipose tissue is an endocrine organ that responds to obesity by secreting elevated quantities of free fatty acids, adipokines, and proinflammatory cytokines, triggering IR and risk of T2DM [8]. Obesity is also characterized by increased adiposity mediated by enlarged size of mature adipocytes (hypertrophy) and elevated number of newly recruited adipocytes (hyperplasia) [9–12]. Adipose tissue dysfunction is characterized by adipocyte hypertrophy, mild chronic inflammation, and oxidative stress, causing reduced ability to generate new adipocytes from the undifferentiated precursors (preadipocytes). The impaired adipogenesis increases risk of IR and T2DM by triggering ectopic fat deposition in nonadipose tissues

and proinflammatory environment characterized by impaired secretion of various adipose-derived adipokines [13].

Obesity also represents an imbalance between the primary site of storing energy (the white fat) and the site that is specialized in energy expenditure (the brown fat) [14]. White adipocytes store fat in the form of triacylglycerols as a single fat lipid droplet that gets readily hydrolyzed by lipases when energy is needed. The resulting fatty acids are mobilized to other tissues to undergo fatty acid oxidation as a source of energy [15]. The imbalance between lipolysis and lipogenesis plays a crucial role in progression of metabolic disease including T2DM and nonalcoholic fatty liver disease [16]. The brown fat, on the other hand, uses the energy derived from fatty acid oxidation for heat generation [17].

Adipocyte hypertrophy is associated with increased uptake of excess TAGs, which triggers fat accumulation within the larger subcutaneous adipose tissue (SAT) [18–20]. SAT therefore plays a buffering role as it prohibits progression of obesity-associated pathologies [21]. However, the buffering capacity becomes limited as impairment of SAT expansion causes IR [22–24] as the excess fat are deposited in the visceral adipose tissue (VAT) as well as ectopically in the skeletal muscle, liver, kidney, and heart tissues [25]. This is augmented by the infiltration of macrophages and activation of the innate immune cells [26], which triggers hyperinsulinemia that inhibits lipolysis and activates lipoprotein lipase (LPL). This causes further hyperinsulinemia, hypertriglyceridemia, increased IR in these tissues [27], and risk of T2DM [28].

Although obesity is generally associated with these comorbidities, some obese individuals seem to be protected as they maintain insulin sensitivity (IS) and show lower hypertension and proatherogenic and inflammatory profiles than their equally obese pathogenic counterparts [29–32]. Investigating the underlying causes for this protective phenotype could potentially help obesity-associated pathogenicity. Although still unknown, various potential mechanisms were proposed to contribute to metabolically healthy obese (MHO) phenotype. These include lower visceral and ectopic fat deposition than subcutaneous fat accumulation due to efficient SAT adipogenesis, reduced inflammatory component in the adipose tissue, healthy levels of secreted adipokines, and more active lifestyle [33]. A genetic component was also suggested to interact with various environmental factors, although not yet determined [34]. Interestingly, lean diabetics also exhibit larger adipocytes than healthy individuals, perhaps due to impaired differentiation of preadipocytes but not a result of different frequencies of stromal vascular cells, lipolysis, or levels of inflammatory mediators [35]. Current therapeutic strategies focus on treating obesity-associated diseases instead of preventing the underlying mechanisms. Therefore, understanding the molecular mediators underlying the protective phenotype in MHO individuals could provide critical information to help individuals suffering from pathological obesity (PO). In this review, we aimed to understand the role of adipogenesis in obesity-associated IR and T2DM by screening 2317 articles investigating adipogenesis and mediators of impaired adipogenesis in PubMed with the aid of Rayyan, a systematic review web application [36].

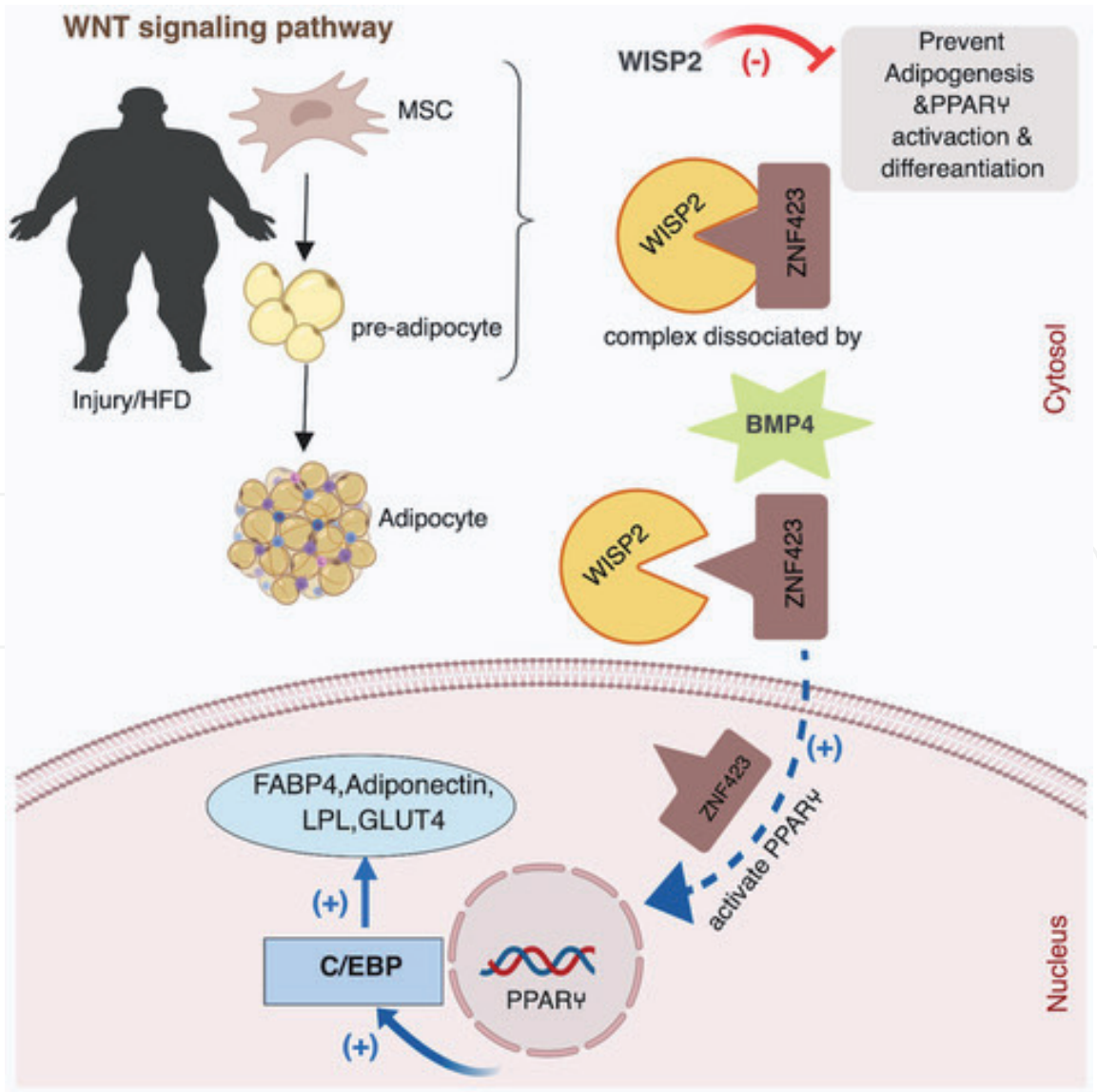
## **2. The role of adipogenesis in obesity-associated IR and T2DM**

The adipose tissue is a dynamic part of the endocrine system that plays a crucial role in maintaining energy balance and nutritional homeostasis [37]. Mature adipocytes constitute the most abundant distinctive cell type in the adipose tissue, occupying 90% of its volume [38]. Other components include leukocytes, macrophages, fibroblasts, endothelial cells, and preadipocytes, which constitute the

stromal vascular cells (4–6 million cells per gram of adipose tissue, half of which are immune cells) [39].

Obesity-induced adipocyte hypertrophy is associated with impaired recruitment and differentiation of preadipocytes. Despite their abundance, preadipocytes fail to undergo terminal differentiation into mature adipocytes via the activation of the canonical Wnt signaling [40]. Preadipocytes are produced by mesenchymal stem cells (MSCs) under the influence of different signaling molecules. The mature adipocytes secrete BMP4 that triggers preadipocyte differentiation by inducing the separation of Wnt1 inducible-signaling pathway protein 2 (WISP2) and zinc finger protein 423 (ZNF423), allowing ZNF423 to translocate into the nucleus and activate peroxisome proliferator-activated receptors (PPAR $\gamma$ ) and downstream cascade including CCAAT/enhancer-binding proteins  $\beta$  (C/EBP $\beta$ ),  $\delta$ , and  $\alpha$  [41, 42] (**Figure 1**).

BMP4 also plays an anti-inflammatory role by reducing tumor necrosis factor- $\alpha$  (TNF- $\alpha$ )-mediated proinflammatory cytokine induction in human adipocytes. Therefore, BMP4 plays a protective role against IR and T2DM [43]. Subsequently, PPAR $\gamma$  and C/EBP $\alpha$  activate preadipocyte differentiation and the expression of mature makers such as adiponectin, fatty acid-binding protein 4 (FABP4), glucose transporter type 4 (GLUT4), and LPL. The activation of PPAR $\gamma$ , therefore,



**Figure 1.**  
Schematic representation of the role of Wnt signaling in adipogenesis.



maintains IS and exhibits an anti-inflammatory function, whereas IR causes impaired adipogenesis and increased risk of T2DM [44, 45].

Insulin and downstream Akt signaling also play important roles as modulators of adipose tissue growth and adipogenesis as insulin activates glucose and free fatty acid uptake, inhibits lipolysis, and de novo fatty acid synthesis in adipocytes, and induces adipogenesis [46]. The transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) has been shown to induce energy expenditure and reduce adipose tissue growth, leading to prevention of dietary obesity and lowering adipogenesis, inflammation, and IR [47]. The inhibition of inhibitor of nuclear factor kappa-B kinase subunit  $\beta$  (IKK $\beta$ ) in mice lowers high-fat diet-induced adipogenesis and inflammation and protects from diet-induced obesity and IR [48]. MicroRNAs (miRNAs) have been also shown to play an important role in adipogenesis, IR, and inflammation as previously reviewed [49]. Tonicity-responsive enhancer-binding protein (TonEBP), a key transcription factor involved in cellular adaptation to hypertonic stress, has been suggested to influence macrophage activity, adipogenesis, and IS by inhibiting the epigenetic transition of PPAR $\gamma$ 2 [50]. Protectin DX (PDX), a  $\omega$ -3 fatty acid-derived proresolution mediator, was reported to reduce inflammation and IR via an AMPK-dependent pathway and suppress adipogenesis and lipid accumulation during 3T3-L1 differentiation [51].

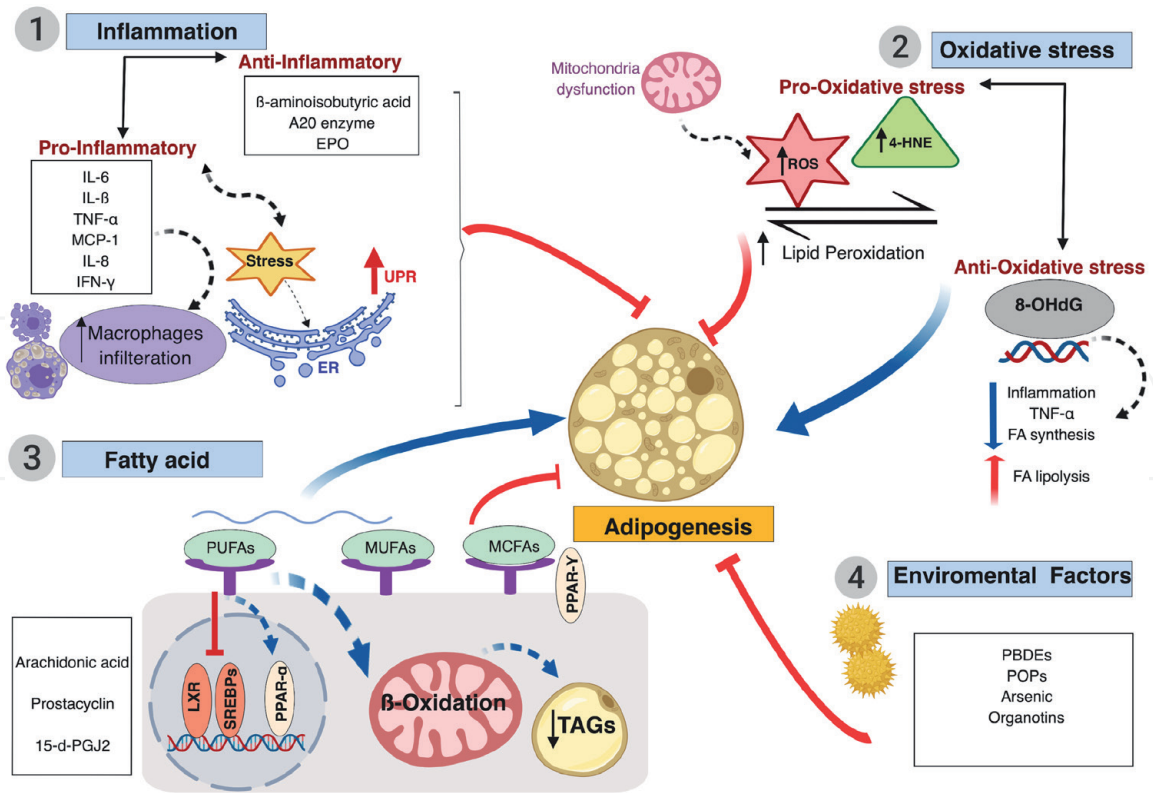
We have recently shown that higher adipogenic capacity of preadipocytes isolated from SAT and VAT from MHO individuals than PO counterparts may be one of the underlying mechanisms for MHO protection due to a greater ability to store TAGs in the SAT depot. This process was shown to be influenced by inflammatory mediators, oxidative stress, and fatty acid signaling [45, 52–55].

### 3. Mediators of impaired adipogenesis in IR and T2DM

#### 3.1 Inflammatory mediators

##### 3.1.1 Impaired adipogenesis in response to proinflammatory signals

Obesity-associated comorbidities are mediated by chronic mild inflammation (**Figure 2**). Lipid-laden adipocytes produce increased levels of cytokines such as Interleukin 6 (IL-6), IL- $\beta$ , TNF- $\alpha$ , monocyte chemoattractant protein-1 (MCP-1), and IL-8 [10, 56, 57] which can inhibit preadipocyte differentiation [21, 45]. The impaired adipogenesis is associated with stress of the endoplasmic reticulum (ER) and elevated expression of unfolded protein response (UPR), both can exacerbate the proinflammatory phenotype of preadipocytes and adipocytes [58]. The effect of proinflammatory phenotype varies among various fat depots. VAT is a more inflammatory tissue than SAT as it secretes higher levels of proinflammatory cytokines. Macrophage infiltration into adipose tissue is regulated through serum resistin and leptin in obese individuals with early metabolic dysfunction [59]. The presence of macrophages in VAT contributes significantly to this phenotype. The presence of macrophages in human SAT, on the other hand, is causally related to impaired preadipocyte differentiation, which in turn is associated with systemic IR [60, 61]. Adipocyte differentiation, therefore, was shown to be significantly lower in VAT than SAT. Macrophage depletion can reduce inflammatory cytokines and trigger adiponectin secretion from both SAT and VAT adipocytes, leading to the induction of preadipocyte differentiation in SAT, but not VAT. Additionally, a negative correlation between SAT adipogenesis, but not VAT, and systemic IR was observed [62]. Chronic systemic inflammation is also associated with elevated lipolysis in white adipose tissue and lipogenesis in nonadipose tissues, causing ectopic fat deposition



**Figure 2.** Mediators of impaired adipogenesis in IR and T2DM. Most proinflammatory cytokines as well as some anti-inflammatory mediators can impair adipogenesis (1). Similarly, various mediators of oxidative stress can impact adipogenesis both positively and negatively depending on their structure (2). Fatty acid signaling plays a key role in adipogenesis but at various degrees depending on the composition of the fatty acids (3). Finally, various environmental factors can impact adipogenesis mostly negatively (4).

in nonadipose tissues and imbalance in free fatty acid homeostasis and increased risk of IR [63].

Among the proinflammatory cytokines, IL-6 is produced by adipocytes, activated leukocytes, and endothelial cells [64] in obesity [65–68]. IL-6 shows a synergistic effect with other mediators of metabolic disease, collectively contributing to the progression of other obesity-associated comorbidities such as CAD and T2DM [64, 69]. IL-6 impairs the LPL function leading to increased levels of circulating fat [69, 70]. Moreover, obesity-associated increase in IL-6 is linked to reduced insulin-triggered glucose uptake [60, 61]. Previous reports have indicated that insulin treatment improves the glucose transport activity of adipocytes in T2DM [21] and lowers IL-6 and TNF- $\alpha$  levels [53]. Although the precise mechanisms of IL-6-associated IR is not well characterized, human adipocytes from IR individuals were shown to exhibit significantly higher IL-6 expression levels [45]. IL-6 impairs insulin action by inhibiting expression of insulin receptor, insulin receptor substrate-1 (IRS-1), and GLUT4 in human preadipocytes as well as 3T3-L1 adipocytes [45, 71]. Furthermore, IL-6 was shown to reduce IS through decrease in adiponectin expression and secretion [72] and via impairment of insulin signaling in hepatocytes [73].

Various other cytokines have been shown to impact adipogenesis [74]. The proinflammatory cytokines IL-1  $\beta$ , TNF- $\alpha$ , and MCP1 can also influence the hyperplastic expansion of adipose tissue and impair adipogenesis [59]. IL-1 $\beta$  triggers a proinflammatory response in human adipose tissues, particularly in VAT depot. IL-1 $\beta$  also inhibits insulin signal transduction, leading to impaired IS in adipose tissue [75]. IL-1 $\beta$  and cyclooxygenase-2 (COX-2) play a detrimental role in adipose tissue dysfunction in obesity [76]. With obesity, levels of MCP-1 and TNF- $\alpha$  increase in VAT before macrophage infiltration, suggesting a highly proinflammatory

phenotype of the visceral depot prior to infiltration of immune cells and macrophage phenotype switch [77]. Unlike IL-6, IL-1  $\beta$ , and TNF- $\alpha$ , MCP-1 and MCP-1-induced protein (MCPIP) were shown to induce adipogenesis. Treatment of reactive oxygen species (ROS) inhibitor, apocynin, reduced the MCPIP-triggered adipogenesis [78]. Other cytokines involved in adipogenesis include interferon- $\gamma$  (IFN- $\gamma$ ), a central mediator of macrophage function. Compared to obese wild-type control animals, obese IFN- $\gamma$  knockouts exhibit better IS, smaller adipocyte size, and lower cytokine expression [79].

### 3.1.2 Impaired adipogenesis in response to anti-inflammatory signals

Contrary to the notion that inflammation plays a negative role in metabolism, some studies suggest that proinflammatory signals in the adipocytes are actually needed for functional adipose tissue homeostasis (**Figure 2**). Indeed, adipose tissue inflammation was shown in various animal models of adipose tissue-specific reduction of proinflammatory potential to be required as an adaptive response, allowing proper storage of excess fat and filtering of gut-derived endotoxins [80]. Additionally, various molecules with anti-inflammatory properties were shown to influence adipogenesis and risk of IR. Myokines, for example, secreted by skeletal muscle cells during exercise such as  $\beta$ -aminoisobutyric acid, can impair adipogenesis via activating AMPK signaling pathway and reducing levels of proinflammatory cytokines such as TNF- $\alpha$  [81]. Another example is the ubiquitin-editing enzyme A20 that impairs IL-6 secretion from adipocytes, leading to modulation of differentiation of MSCs [82]. The overexpression of A20 was also shown to reduce lipogenesis and adipogenesis via lowering levels of sterol regulatory element binding protein-1c (SREBP-1c) and aP2, causing lower fat accumulation in differentiated 3T3-L1 cells [83]. A third example is the nonerythropoietic EPO-derived peptide that plays an anti-inflammatory and anti-adipogenic roles in high-fat diet mice with IR [84]. On the other hand, other anti-inflammatory molecules could rescue impaired adipogenesis. Glucose-dependent insulintropic polypeptide (GIP), for example, is a potent activator of adipogenesis through modulation of inflammation in adipose tissue [85]. Additionally, the expression of neuronatin (Nnat), a proteolipid involved in neuronal development, in response to inflammation and dietary excess, has been suggested to play an important role in adipogenesis through lowering oxidative stress and inflammation [86].

## 3.2 Oxidative stress

Obesity leads to the accumulation of ROS, the hallmark of oxidative stress, in the adipose tissue causing impaired adipogenesis and increased risk of IR and T2DM. The balance between ROS generation and activation of endogenous antioxidants is crucial for cells undergoing adipogenesis [87] (**Figure 2**). The oxidative damage and changes in the expression of antioxidant enzymes with age are similar between SAT and VAT. However, preadipocytes from SAT are significantly more resistant than VAT-derived cells to cell death caused by oxidative stress [88]. Interestingly, within SAT and VAT depots, preadipocytes from insulin-sensitive obese subjects were more prone to oxidative damage than preadipocytes from equally obese insulin-resistant individuals [52, 53]. The depletion of ROS from adipose tissue in mice models of oxidative stress was associated with increased adipose tissue mass, lower ectopic fat deposition, and enhanced IS. Similarly, ROS accumulation limited the expansion of adipose tissue, leading to elevated ectopic fat accumulation and increased risk of IR [89]. Elevated ROS within the adipose tissue triggers lipid peroxidation [45] and accumulation of reactive aldehydes including the bioactive



lipid peroxidation product 4-hydroxynonenal (4-HNE) [90]. Elevated 4-HNE causes damage of cell structure and function through the formation of the stable adducts 4-hydroxyalkenals with proteins, phospholipids, and DNA [91, 92]. Increased 4-HNE levels have been associated with impaired adipogenesis and IR [53, 93–96]. Another marker of oxidative damage is 8-hydroxy-2-deoxyguanosine (8-OHdG) which was recently shown to exert anti-inflammatory effects, by reducing TNF- $\alpha$ -induced IR in vitro. It was also shown to reduce adipose tissue mass in vivo through activation of adipose triglyceride lipase and lowering the expression of fatty acid synthase [97]. Levels of cholesterol oxidation-derived oxysterols increase in adipose tissues of T2DM patients and act as inhibitors of adipogenesis through activation of Wnt pathway [98]. Heme oxygenase (HO), a major cytoprotective enzyme, functions upstream of Wnt signaling and lowers lipogenesis and adipogenesis, decreasing lipid accumulation and levels of proinflammatory cytokines [99].

Conversely, ROS was also shown to enhance adipogenesis by lowering sirtuin 1 (Sirt1) expression [100, 101]. Heme-induced oxidative stress was shown to inhibit Sirt1, leading to increased adipogenesis [102]. The expression of deleted in bladder cancer protein 1 (DBC1), another inhibitor of the Sirt1, is reduced with obesity, leading to lower adipogenesis and VAT dysfunction [103]. Sirt3 plays a crucial role in mitochondrial function. Silencing of Sirt3 can cause adipocyte dysfunction which impairs adipogenesis and causes IR [104]. Nonselenocysteine-containing phospholipid hydroperoxide glutathione peroxidase (NPGPx) is a sensor of oxidative stress. Lack of NPGPx causes elevation in ROS and promotion of adipogenesis through ROS-dependent dimerization of protein kinase A regulatory subunits and activation of C/EBP $\beta$  [105]. Additional evidence suggesting ROS involvement in promotion of adipogenesis comes from antioxidant supplementation experiments where lower levels of ROS resulting from antioxidants contribute to adipose tissue dysfunction and IR [106]. Indeed, antioxidant supplementation exhibited a negative impact when used before induction of oxidative stress as a result of lowering physiological ROS levels because ROS plays a role as second messengers in adipogenesis, lipid metabolism, and insulin signaling [107]. For example, the supplementation with N-acetylcysteine, a known antioxidant and precursor of glutathione, was shown to reduce fat deposition during adipogenic differentiation of mouse fibroblasts [108]. Activation of beta-3 adrenergic receptor ( $\beta$ 3-AR) enhances ROS accumulation in cultured adipocytes. Antioxidants enhance  $\beta$ 3-AR-triggered mitochondrial ROS production, suggesting that chronic supplementation of antioxidants could indeed generate an elevation in oxidative stress associated with mitochondrial dysfunction in adipocyte [109]. On the other hand, glutathione depletion was shown to inhibit adipogenesis as the result of lowering cell proliferation during the initial mitotic clonal expansion of the adipocyte differentiation process [110].

### 3.3 Fatty acid signaling

The main role of adipocytes is TAG storage. Although TAGs do not function as signaling molecules per se, the lipid intermediates generated during lipogenesis and lipolysis influence intracellular insulin signaling and participate in progression of IR. These include free fatty acids, diacylglycerols (DAGs), and ceramides [111].

Lipolysis-driven efflux of fatty acids triggers TAG synthesis and causes stress of the ER and activation of Jun kinase pathway in the adipose tissues [112, 113]. This leads to an elevation in the levels of both DAGs and ceramides and progression of IR in adipocytes [114]. Ceramides were shown to influence lipid-mediated IR in muscles. Delta 4-desaturase, sphingolipid 1 (DEGS1) is a desaturase that mediates ceramide biosynthetic pathway. Ablation of DEGS1 in preadipocytes prevented



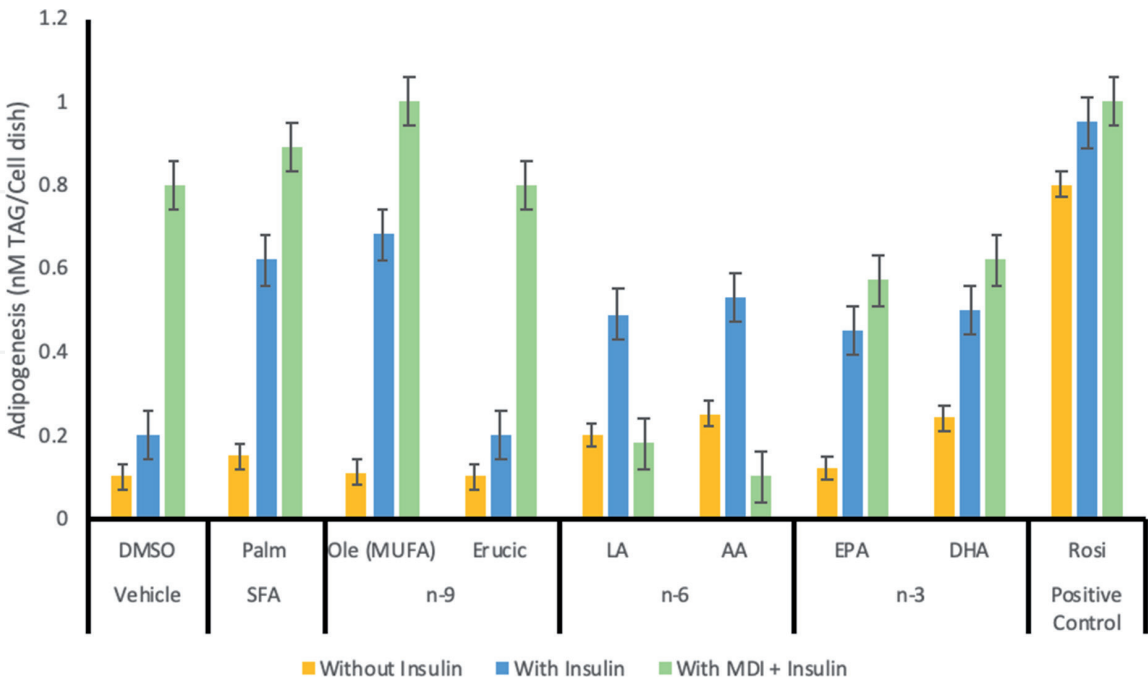
adipogenesis and decreased lipid accumulation [115]. There are essential enzymes responsible for TAG hydrolysis including hormone-sensitive lipase (HSL), adipose triglyceride lipase (ATGL), and monoglyceride lipase (MGL) [116]. ATGL regulates lipolysis by transcription factor specificity protein 1 (Sp1). Insulin-mediated transcription of Sp1 is critical for this regulation. In mature adipocytes, PPAR $\gamma$  reverses transcriptional repression by Sp1 at the ATGL promoter, leading to stimulation of ATGL mRNA expression. During obesity and IR, the transcription of ATGL becomes downregulated. The extent of the downregulation depends on interactions between Sp1 and PPAR $\gamma$  [117].

A number of factors influence the function of fatty acids in regulating adipogenesis. The number of carbons and the position and number of double bonds are crucial determinants of properties of the fatty acids. Changes in fatty acids including elongation, desaturation,  $\beta$ -oxidation, peroxidation, and incorporation into phospho- and complex lipids can play an essential role in their metabolic function. Fatty acids and their metabolites can control protein expression involved in lipid and energy metabolism by influencing gene transcription, mRNA processing, and posttranslational modifications [118–121]. Most fatty acids activate all three members of the PPAR family [122–125]. Polyunsaturated fatty acids (PUFAs), except for erucic acid, are more potent stimulators of PPAR $\gamma$  than monounsaturated fatty acids (MUFAs) and saturated fatty acids [122–126] (**Figure 2**). The optimal binding affinity is reached with 16–20 carbon-containing compounds. DHA too was shown to stimulate PPARs [124]. Various studies have reported the beneficial effects of PUFAs on lipid-related human disorders [127–131], which largely depend on the structure of the fatty acids and their metabolic properties. PUFAs can inhibit lipogenic gene transcription by downregulating the expression SREBPs [132–135] and act as antagonists of liver X receptors (LXR) [136, 137] and as agonists for PPARs [122–124, 138, 139]. PUFAs, but not saturated or MUFAs, inhibit lipogenic genes by downregulating SREBP-1c. PPAR  $\alpha$  plays an important role in metabolic adaptation to fasting by enhancing mitochondrial and peroxisomal fatty acid oxidation and ketogenesis [140]. Dietary PUFAs were also shown to stimulate expression of PPAR $\alpha$  target genes, induce  $\beta$ -oxidation, and lower plasma TAGs [141–149]. Fatty acids can also play a role as modulators of kinase signaling pathways [150–155].

Arachidonic acid (AA), a polyunsaturated omega-6 fatty acid, is the major PUFA that has been implicated in the regulation of adipogenesis. Short exposure of 3T3-L1 mouse preadipocytes to AA triggers adipocyte differentiation, associated with increase in (FABP4/aP2). Calcium, protein kinase C, and ERK play critical role in this pathway through which AA induces the expression of adipocyte protein 2 (aP2) [156]. AA binds to PPAR- $\gamma$ 2 to stimulate GLUT4 expression in HepG2 cell line, exhibiting an alternative insulin-independent activation of GLUT4 [157]. AA cascade is then controlled by cyclooxygenases enzymes, lipoxygenases, and P450 epoxygenases. When AA is generated from plasma membrane via phospholipases and then metabolized by prostaglandin G/H synthase, different prostaglandins are produced, causing opposing effects on adipocyte differentiation. The proadipogenic effect of AA is mediated by prostaglandin product (prostacyclin) and is thus cyclooxygenase dependent [158–160]. Among prostaglandin classes, 15-deoxy- $\Delta$ 12,14-prostaglandin J2 (15-d-PGJ2) was shown to be proadipogenic [161, 162]. On the other hand, prostaglandin F2 $\alpha$  (PGF2 $\alpha$ ) was shown to exert anti-adipogenic effects in primary preadipocytes [163–165], 1246 cells [164], and 3T3-L1 cells [166–168]. The anti-adipogenic effect of PGF2 $\alpha$  is mediated through prostaglandin F receptor-mediated elevation in intracellular calcium and DNA synthesis [168] and activation of MAPK, causing reduction in PPAR $\gamma$  phosphorylation [169]. The role of prostaglandin E2 (PGE2), the third main prostaglandin, in adipogenesis is controversial as PGE2 exhibits antilipolytic effect in mature adipocytes but shows

no effect on preadipocytes [170]. However, it was recently demonstrated that PGE2 inhibited adipogenesis of 3T3-L1 cells [171, 172]. Epoxyeicosatrienoic acids (EETs), AA metabolites, and AA-derived cytochrome P450 (CYP) epoxygenase metabolites exert anti-inflammatory effects in the vasculature. The expression of CYP2J, a member of P450 subfamily with a role in the bioactivation of AA in extrahepatic tissues, inhibits NF- $\kappa$ B and MAPK signaling pathways and activates of PPAR $\gamma$ , thus reducing IR and diabetic phenotype [173]. n-3 PUFAs, on the other hand, reduce adipose growth and play a role in adipogenesis in various rodent studies [174–183].

Medium-chain fatty acids (MCFAs) (C8–C10) bind the PPAR $\gamma$  ligand binding domain in vitro, causing full inhibition of phosphorylation of PPAR $\gamma$  by cyclin-dependent kinase 5 (cdk5) and reversal of IR in adipose tissue. MCFAs that bind PPAR $\gamma$  also inhibit thiazolidinedione-dependent adipogenesis in vitro [184]. On the other hand, MUFAs were shown to induce adipogenesis and enhance TAG accumulation in 3T3-L1 mouse preadipocytes. Levels of TAGs were greater in cells treated with c-22:1 than c18:1 and c-20:1. Among the c-22:1 fatty acids, c9–22:1 treatment showed higher fat accumulation, associated with increased expression of adipogenic and lipogenic transcription factors, such as PPAR $\gamma$  and C/EBP $\alpha$  and SREBP-1. However, c-20:1 FAs exhibited less effect than c-18:1 and c-22:1 [185]. Alpha-lipoic acid (ALA) activates insulin signaling pathway and exerts insulin-like properties in adipose and muscle cells. However, 3T3-L1 preadipocytes treated with LA exhibit lower insulin-induced differentiation by modulating activity and/or expression of various anti-adipogenic transcription factors mainly through activating the MAPK pathways that negatively regulate PPAR $\gamma$  and C/EBP $\alpha$  [141]. 10-oxo-12(Z)-octadecenoic acid, a linoleic acid metabolite, triggered adipocyte differentiation through PPAR $\gamma$  activation and elevated adiponectin secretion and insulin-triggered glucose uptake [142]. Dietary n-3 fatty acids showed more effective activation of PPAR $\alpha$  in the liver of rodents [143–145] than n-6 fatty acids [146]. **Figure 3** summarizes the



**Figure 3.** Adipogenic capacity of various fatty acids in 3T3L-1 cells in the absence or presence of 1  $\mu$ g/ml insulin in differentiation medium (MDI) containing 0.5 mM isobutyl-1-methylxanthine and 1  $\mu$ M dexamethasone in DMEM and 10% FBS. 100  $\mu$ M palmitic acid (palm), oleic acid (ole), erucic acid, linoleic acid (LA), arachidonic acid (AA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), or 1  $\mu$ M rosiglitazone (rosi) dissolved in DMSO were added when differentiation was induced at day 0 and were present throughout the differentiation period (adapted from Madsen et al.) [147].

effect of various fatty acid species on the proadipogenic capacity of 3T3L-1 cells in the presence or absence of insulin (Madsen et al.) [147].

Lipidomics studies were performed to investigate differences between SAT and VAT depots. These studies have shown evidence of depot-specific enrichment of certain species of TAGs, glycerophospholipids, and sphingolipids and specific correlations between certain lipid species and body mass index, inflammation, and IS [148, 149]. We have recently shown in human SAT and omental (OM) adipose tissue biopsies from 64 obese individuals a number of TAGs that changed with increased risk IR and T2DM including C46:4, C48:5, C48:4, C38:1, C50:3, C40:2, C56:3, C56:4, C56:7, and C58:7. Enrichment analysis showed C12:0 fatty acid to be associated with TAGs that are least abundant in T2DM. Our data also indicated that C18:3 was present in both depleted and enriched TAGs in T2DM [55]. Secretion of interleukin IL-6 was found to be significantly lower after treatment with C18:2, C22:6, and C16:0 through blocking NF-κB and activating PPARγ [186]. Our data also showed positive correlations between C56:4 and C57:4, both containing C18:2 and C16:0, with SC adipogenic capacity. OM adipogenic capacity was associated with C49:1, C38:0, and C56:2, containing C16:0, C18:1, and C14:0 [55]. **Table 1** summarizes a list of

Metabolic trait	R <sup>2</sup>	Importance	TAG	MW	Fatty acid composition	Fatty acid identities
SC adipogenic	0.9	0.16	C58:10	926.8	C18:2, C18:2, C22:6	Linoleic acid, linoleic acid, docosaheaxaenoic acid
		0.16	C56:4	910.8	C18:1, C18:2, C20:1	Oleic acid, linoleic acid, gadoleic acid
		0.14	C57:4	924.7	C22:0, C19:4, C16:0	Behenic acid, C19:4, palmitic acid
		0.09	C40:1	692.7	C18:1, C16:0, C6:0	Oleic acid, palmitic acid, caproic acid
		0.08	C60:1	970.8	C24:0, C24:0, C18:1	Lignoceric acid, oleic acid
		0.22	C38:1	664.7	C18:1, C16:0, C4:0	Oleic acid, palmitic acid, butyric acid
OM adipogenic	1	0.18	C48:1	804.8	C18:0, C16:1, C14:0	Stearic acid, palmitoleic acid, myristic acid
		0.14	C49:1	818.7	C18:1, C17:0, C14:0	Oleic acid, heptadecanoic acid, myristic acid
		0.11	C56:1	916.8	C18:0, C18:0, C20:1	Stearic acid, stearic acid, gadoleic
		0.09	C54:0	890.8	C18:0, C18:0, C18:0	Stearic acid, stearic acid
		0.06	C38:0	666.7	C10:0, C14:0, C14:0	Capric acid, myristic acid
		0.05	C56:2	914.8	C18:1, C18:1, C20:0	Oleic acid, oleic acid, arachidic acid
		0.04	C51:1	846.7	C18:1, C15:0, C18:0	Oleic acid, pentadecanoic acid, stearic acid

**Table 1.**  
List of TAGs associated with IR, SC, and OM adipogenic capacity.

TAGs associated with SAT and OM adipogenic capacity. These fatty acids were reported to stimulate adipogenesis in rodents [187–191] and potentially in human preadipocytes.

#### **4. Environmental factors**

Various types of environmental factors were shown to influence adipogenesis. These include environmental pollutants. Among the environmental pollutants, polybrominated diphenyl ethers (PBDEs) represent a widely used type of flame retardants in commercial products and a main source of environmental contaminants. PBDEs accumulate in adipose tissue, potentially changing its endocrine function causing elevation in the risk of IR. We have previously shown that specific congeners of PBDEs (28, 47, 99, and 153) were predominant in VAT from obese individuals and that PBDEs 99, 28, and 47 were elevated in obese IR compared to obese IS. Treatment of human VAT-derived preadipocytes from obese IS individuals with PBDE28 inhibited insulin signaling and reduced adipogenesis [54]. In addition to PBDEs, evidence linking accumulation of other persistent organic pollutants (POPs) and risk of IR and T2DM was previously described [54, 192]. Additionally, the association between inorganic arsenic exposure and the risk of T2DM and obesity was previously reported [193]. Arsenic-induced T2DM is suggested to be mediated by inflammation, oxidative stress, and apoptosis, playing a significant role in the pathogenesis of obesity. Arsenic inhibits adipogenesis and enhances lipolysis, leading to obesity. Other reports have suggested that arsenic may induce lipodystrophy [193]. Another evidence suggests that uremic toxin-treated 3T3-L1 cells and MSC-derived adipocytes exhibit impaired adipogenesis and apoptosis through activation of the Na/K-ATPase/ROS amplification cycle [194]. Other types of environmental pollutants include organotins, widely used antifouling biocides for ships and fishing nets, play a role as endocrine disruptors as they bind to PPAR $\gamma$ /RXR $\alpha$ , induce adipogenesis, and repress inflammatory genes in different mammalian cells [195].

#### **5. Conclusion**

The pathology of obesity-associated IR and T2DM involves ectopic fat deposition in response to elevated energy intake and poor fat storage. The latter is due to impaired adipogenesis as newly recruited preadipocytes become unable to differentiate into fully functional adipocytes. This review presents several factors that influence adipogenesis in pathological obesity including inflammatory mediators, oxidative stress, fatty acid signaling, and other environmental factors. Most proinflammatory cytokines such as IL-6, IL-1 $\beta$ , TNF- $\alpha$ , IL-8, and IFN $\gamma$  as well as some anti-inflammatory mediators including  $\beta$ -aminoisobutyric acid, A20 enzyme, and EPO have been shown to impair adipogenesis, leading to adipocyte hypertrophy, ectopic fat accumulation, and increased risk of IR and T2DM. However, basal level of adipose tissue inflammation has been shown to be required for normal adipogenesis and functional adipose tissue homeostasis. Similarly, various mediators of oxidative stress were shown to impact adipogenesis positively such as lipid peroxidation product 4-HNE and negatively such as the marker of oxidative damage 8-OHdG. Targeting lipid peroxidation products was shown to reverse impairment of adipogenesis and sustain IS. However, complete depletion of oxidative stress could also lead to impairment of adipogenesis as basal oxidative stress was shown to be required for normal adipogenesis. Fatty acid signaling also plays a very



important role in adipogenesis as various fatty acid species such as PUFAs, MUFAs, and MCFAs were shown to regulate preadipocyte differentiation at various degrees depending on their composition. Finally, various environmental factors were suggested to impact adipogenesis, mainly through triggering inflammation and oxidative stress, leading to impairment of adipogenesis and increased risk of IR.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

All authors participated in reviewing the literature and preparing and approving the manuscript. MAE is responsible for the integrity of the work as a whole.

## Abbreviations

COX-2	cyclooxygenase-2
15-d-PGJ2	15-deoxy- $\Delta$ 12,14-prostaglandin J2
4-HNE	4-hydroxynonenal
8-OHdG	8-hydroxy-2-deoxyguanosine
AA	arachidonic acid
ATGL	adipose triglyceride lipase
BMP4	bone morphogenetic protein 4
C/EBP	CCAAT/enhancer-binding protein
CAD	Coronary artery disease
cdk5	cyclin-dependent kinase 5
DAGs	diacylglycerols
DBC1	deleted in bladder cancer protein 1
DHA	docosahexaenoic acid
DMEM	dexamethasone
DMSO	dimethyl sulfoxide
EETs	epoxyeicosatrienoic acids
EPA	eicosapentaenoic acid
EPO	nonerythropoietic derived peptide
ER	endoplasmic reticulum
FABP4	fatty acid-binding protein 4
GIP	glucose-dependent insulinotropic polypeptide
HSL	hormone-sensitive lipase
IFN- $\gamma$	interferon- $\gamma$
IKK $\beta$	inhibitor of nuclear factor kappa-B kinase subunit $\beta$
IL-6	interleukin 6
IR	insulin resistance
IS	insulin sensitive
LA	linoleic acid
LPL	lipoprotein lipase
LXR	liver X receptors
MCFAs	medium chain fatty acids
MCP-1	monocyte chemoattractant protein-1
MCPIP	Mcp-1-induced protein

MDI	insulin in differentiation medium
MGL	monoglyceride lipase
MHO	metabolically healthy obese
miRNAs	microRNAs
MUFAs	monounsaturated fatty acids
NF-kappa-B	nuclear factor kappa-light-chain enhancer of activated B cells
Nnat	neurentin
NPGPx	nonselenocysteine-containing phospholipid hydroperoxide glutathione peroxidase
Ole	oleic acid
OM	omental adipose tissue
Palm	palmitic acid
PBDEs	diphenyl ethers
PDX	protectin DX
PGE2	prostaglandin E2
PGF2 $\alpha$	prostaglandin F2 $\alpha$
PO	pathological obesity
POPs	organic pollutants
PPAR	peroxisome proliferator-activated receptors
PUFAs	polyunsaturated fatty acids
ROS	reactive oxygen species
Rosi	rosiglitazone
SAT	subcutaneous adipose tissue
Sirt1	sirtuin 1
Sp1	transcription factor specificity protein 1
SREBP-1c	sterol regulatory element binding protein 1C
T2DM	type 2 diabetes
TAGs	triacylglycerols
TonEBP	tonicity-responsive enhancer-binding protein
UPR	unfolded protein response
VAT	visceral adipose tissue
WISP2	inducible-signaling pathway protein 2
ZNF423	zinc finger protein 423
$\beta$ 3-AR	beta-3 adrenergic receptor
MSCs	mesenchymal stem cells
Ap2	adipocyte protein 2
CYP	cytochrome P450
ALA	alpha-lipoic acid

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## References

- [1] Maire B et al. Nutritional transition and non-communicable diet-related chronic diseases in developing countries. *Santé*. 2002;**12**(1):45-55
- [2] Kodama S et al. Quantitative relationship between body weight gain in adulthood and incident type 2 diabetes: A meta-analysis. *Obesity Reviews*. 2014;**15**(3):202-214
- [3] Bogers RP et al. Association of overweight with increased risk of coronary heart disease partly independent of blood pressure and cholesterol levels: A meta-analysis of 21 cohort studies including more than 300 000 persons. *Archives of Internal Medicine*. 2007;**167**(16):1720-1728
- [4] Tsuneto A et al. Fatty liver incidence and predictive variables. *Hypertension Research*. 2010;**33**(6):638-643
- [5] Eliassen AH et al. Adult weight change and risk of postmenopausal breast cancer. *Journal of the American Medical Association*. 2006;**296**(2):193-201
- [6] McGee DL, Diverse Populations C. Body mass index and mortality: A meta-analysis based on person-level data from twenty-six observational studies. *Annals of Epidemiology*. 2005;**15**(2):87-97
- [7] Adams KF et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. *The New England Journal of Medicine*. 2006;**355**(8):763-778
- [8] Makki K, Froguel P, Wolowczuk I. Adipose tissue in obesity-related inflammation and insulin resistance: Cells, cytokines, and chemokines. *ISRN Inflammation*. 2013;**2013**:139239
- [9] Jo J et al. Hypertrophy and/or hyperplasia: Dynamics of adipose tissue growth. *PLoS Computational Biology*. 2009;**5**(3):e1000324
- [10] Bjorntorp P. Effects of age, sex, and clinical conditions on adipose tissue cellularity in man. *Metabolism*. 1974;**23**(11):1091-1102
- [11] Spalding KL et al. Dynamics of fat cell turnover in humans. *Nature*. 2008;**453**(7196):783-787
- [12] Rutkowski JM, Stern JH, Scherer PE. The cell biology of fat expansion. *The Journal of Cell Biology*. 2015;**208**(5):501-512
- [13] Murdolo G et al. Oxidative stress and lipid peroxidation by-products at the crossroad between adipose organ dysregulation and obesity-linked insulin resistance. *Biochimie*. 2013;**95**(3):585-594
- [14] Elattar S, Satyanarayana A. Can brown fat win the battle against white fat? *Journal of Cellular Physiology*. 2015;**230**(10):2311-2317
- [15] Ahmadian M, Wang Y, Sul HS. Lipolysis in adipocytes. *The International Journal of Biochemistry and Cell Biology*. 2010;**42**(5):555-559
- [16] Saponaro C et al. The subtle balance between lipolysis and lipogenesis: A critical point in metabolic homeostasis. *Nutrients*. 2015;**7**(11):9453-9474
- [17] Rosen ED, Spiegelman BM. Adipocytes as regulators of energy balance and glucose homeostasis. *Nature*. 2006;**444**(7121):847-853
- [18] Okuno A et al. Troglitazone increases the number of small adipocytes without the change of white adipose tissue mass in obese Zucker rats. *The Journal of Clinical Investigation*. 1998;**101**(6):1354-1361
- [19] Tontonoz P, Hu E, Spiegelman BM. Stimulation of adipogenesis in



fibroblasts by PPAR gamma 2, a lipid-activated transcription factor. *Cell*. 1994;**79**(7):1147-1156

[20] Cinti S et al. Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. *Journal of Lipid Research*. 2005;**46**(11):2347-2355

[21] Radcke S, Dillon JF, Murray AL. A systematic review of the prevalence of mildly abnormal liver function tests and associated health outcomes. *European Journal of Gastroenterology and Hepatology*. 2015;**27**(1):1-7

[22] Vigouroux C et al. Molecular mechanisms of human lipodystrophies: From adipocyte lipid droplet to oxidative stress and lipotoxicity. *The International Journal of Biochemistry and Cell Biology*. 2011;**43**(6):862-876

[23] Virtue S, Vidal-Puig A. Adipose tissue expandability, lipotoxicity and the metabolic syndrome—An allostatic perspective. *Biochimica et Biophysica Acta*. 2010;**1801**(3):338-349

[24] Xue P et al. Adipose deficiency of Nrf2 in Ob/Ob mice results in severe metabolic syndrome. *Diabetes*. 2013;**62**(3):845-854

[25] Hocking S et al. Adiposity and insulin resistance in humans: The role of the different tissue and cellular lipid depots. *Endocrine Reviews*. 2013;**34**(4):463-500

[26] Kursawe R et al. A role of the inflammasome in the low storage capacity of the abdominal subcutaneous adipose tissue in obese adolescents. *Diabetes*. 2016;**65**(3):610-618

[27] Snel M et al. Ectopic fat and insulin resistance: Pathophysiology and effect of diet and lifestyle interventions. *International Journal of Endocrinology*. 2012;**2012**:983814

[28] Guilherme A et al. Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. *Nature Reviews. Molecular Cell Biology*. 2008;**9**(5):367-377

[29] Bogardus C et al. Relationship between degree of obesity and in vivo insulin action in man. *The American Journal of Physiology*. 1985;**248**(3 Pt 1):E286-E291

[30] Samocha-Bonet D et al. Insulin-sensitive obesity in humans—A ‘favorable fat’ phenotype? *Trends in Endocrinology and Metabolism*. 2012;**23**(3):116-124

[31] Karelis AD et al. The metabolically healthy but obese individual presents a favorable inflammation profile. *The Journal of Clinical Endocrinology and Metabolism*. 2005;**90**(7):4145-4150

[32] Stefan N et al. Identification and characterization of metabolically benign obesity in humans. *Archives of Internal Medicine*. 2008;**168**(15):1609-1616

[33] Stefan N et al. Metabolically healthy obesity: Epidemiology, mechanisms, and clinical implications. *The Lancet Diabetes and Endocrinology*. 2013;**1**(2):152-162

[34] Jung CH, Lee WJ, Song KH. Metabolically healthy obesity: A friend or foe? *The Korean Journal of Internal Medicine*. 2017;**32**(4):611-621

[35] Acosta JR et al. Increased fat cell size: A major phenotype of subcutaneous white adipose tissue in non-obese individuals with type 2 diabetes. *Diabetologia*. 2016;**59**(3):560-570

[36] Ouzzani M et al. Rayyan-a web and mobile app for systematic reviews. *Systematic Reviews*. 2016;**5**(1):210

[37] Coelho M, Oliveira T, Fernandes R. Biochemistry of adipose tissue: An

endocrine organ. *Archives of Medical Science*. 2013;**9**(2):191-200

[38] Yuan Y, Gao J, Ogawa R. Mechanobiology and mechanotherapy of adipose tissue-effect of mechanical force on fat tissue engineering. *Plastic and Reconstructive Surgery*. Global Open. 2015;**3**(12):e578

[39] Han S et al. Adipose-derived stromal vascular fraction cells: Update on clinical utility and efficacy. *Critical Reviews in Eukaryotic Gene Expression*. 2015;**25**(2):145-152

[40] Gustafson B et al. Restricted adipogenesis in hypertrophic obesity: The role of WISP2, WNT, and BMP4. *Diabetes*. 2013;**62**(9):2997-3004

[41] Hammarstedt A et al. WISP2 regulates preadipocyte commitment and PPAR gamma activation by BMP4. *Proceedings of the National Academy of Sciences of the United States of America*. 2013;**110**(7):2563-2568

[42] Gupta RK et al. Transcriptional control of preadipocyte determination by Zfp423. *Nature*. 2010;**464**(7288):619-623

[43] Baraban E et al. Anti-inflammatory properties of bone morphogenetic protein 4 in human adipocytes. *International Journal of Obesity (2005)*. 2016;**40**(2):319-327

[44] Gustafson B et al. Insulin resistance and impaired adipogenesis. *Trends in Endocrinology and Metabolism*. 2015;**26**(4):193-200

[45] Almuraikhy S et al. Interleukin-6 induces impairment in human subcutaneous adipogenesis in obesity-associated insulin resistance. *Diabetologia*. 2016;**59**(11):2406-2416

[46] Peng X et al. Thioredoxin reductase 1 suppresses adipocyte differentiation and insulin responsiveness. *Scientific Reports*. 2016;**6**:28080

[47] Tang T et al. Uncoupling of inflammation and insulin resistance by NF-kappaB in transgenic mice through elevated energy expenditure. *The Journal of Biological Chemistry*. 2010;**285**(7):4637-4644

[48] Helsley RN et al. Targeting IκB kinase β in adipocyte lineage cells for treatment of obesity and metabolic dysfunctions. *Stem Cells (Dayton, Ohio)*. 2016;**34**(7):1883-1895

[49] Hilton C, Neville MJ, Karpe F. MicroRNAs in adipose tissue: Their role in adipogenesis and obesity. *International Journal of Obesity (2005)*. 2013;**37**(3):325-332

[50] Lee JH et al. TonEBP suppresses adipogenesis and insulin sensitivity by blocking epigenetic transition of PPARγ2. *Scientific Reports*. 2015;**5**:10937

[51] Jung TW et al. Protectin DX attenuates LPS-induced inflammation and insulin resistance in adipocytes via AMPK-mediated suppression of the NF-κB pathway. *American Journal of Physiology. Endocrinology and Metabolism*. 2018;**315**(4):E543-E551

[52] Elrayess MA et al. 4-hydroxynonenal causes impairment of human subcutaneous adipogenesis and induction of adipocyte insulin resistance. *Free Radical Biology and Medicine*. 2017;**104**:129-137

[53] Jaganjac M et al. Combined metformin and insulin treatment reverses metabolically impaired omental adipogenesis and accumulation of 4-hydroxynonenal in obese diabetic patients. *Redox Biology*. 2017;**12**:483-490

[54] Helaleh M et al. Association of polybrominated diphenyl ethers in two fat compartments with increased risk of insulin resistance in obese individuals. *Chemosphere*. 2018;**209**:268-276

- [55] Al-Sulaiti H et al. Triglyceride profiling in adipose tissues from obese insulin sensitive, insulin resistant and type 2 diabetes mellitus individuals. *Journal of Translational Medicine*. 2018;**16**(1):175
- [56] Acosta JR et al. Increased fat cell size: A major phenotype of subcutaneous white adipose tissue in non-obese individuals with type 2 diabetes. *Diabetologia*. 2016;**59**(3):560-570
- [57] Flower L et al. Stimulation of interleukin-6 release by interleukin-1beta from isolated human adipocytes. *Cytokine*. 2003;**21**(1):32-37
- [58] Longo M et al. Pathologic endoplasmic reticulum stress induced by glucotoxic insults inhibits adipocyte differentiation and induces an inflammatory phenotype. *Biochimica et Biophysica Acta*. 2016;**1863**(6 Pt A): 1146-1156
- [59] Kang YE et al. The roles of adipokines, proinflammatory cytokines, and adipose tissue macrophages in obesity-associated insulin resistance in modest obesity and early metabolic dysfunction. *PLoS One*. 2016;**11**(4):e0154003
- [60] Kern PA et al. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. *American Journal of Physiology. Endocrinology and Metabolism*. 2001;**280**(5):E745-E751
- [61] Fasshauer M et al. Interleukin (IL)-6 mRNA expression is stimulated by insulin, isoproterenol, tumour necrosis factor alpha, growth hormone, and IL-6 in 3T3-L1 adipocytes. *Hormone and Metabolic Research*. 2003;**35**(3):147-152
- [62] Liu LF et al. Adipose tissue macrophages impair preadipocyte differentiation in humans. *PLoS One*. 2017;**12**(2):e0170728
- [63] Mei M et al. Inflammatory stress exacerbates ectopic lipid deposition in C57BL/6J mice. *Lipids in Health and Disease*. 2011;**10**:110
- [64] Pradhan AD et al. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *Journal of the American Medical Association*. 2001;**286**(3):327-334
- [65] Kopp HP et al. Impact of weight loss on inflammatory proteins and their association with the insulin resistance syndrome in morbidly obese patients. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2003;**23**(6):1042-1047
- [66] Roytblat L et al. Raised interleukin-6 levels in obese patients. *Obesity Research*. 2000;**8**(9):673-675
- [67] Laimer M et al. Markers of chronic inflammation and obesity: A prospective study on the reversibility of this association in middle-aged women undergoing weight loss by surgical intervention. *International Journal of Obesity and Related Metabolic Disorders*. 2002;**26**(5):659-662
- [68] Bastard JP et al. Elevated levels of interleukin 6 are reduced in serum and subcutaneous adipose tissue of obese women after weight loss. *The Journal of Clinical Endocrinology and Metabolism*. 2000;**85**(9):3338-3342
- [69] Yudkin JS et al. Inflammation, obesity, stress and coronary heart disease: Is interleukin-6 the link? *Atherosclerosis*. 2000;**148**(2):209-214
- [70] Pepys MB, Hirschfield GM. C-reactive protein: A critical update. *The Journal of Clinical Investigation*. 2003;**111**(12):1805-1812
- [71] Rotter V, Nagaev I, Smith U. Interleukin-6 (IL-6) induces insulin resistance in 3T3-L1 adipocytes and is, like IL-8 and tumor necrosis factor-alpha, overexpressed in human fat



cells from insulin-resistant subjects. *The Journal of Biological Chemistry*. 2003;**278**(46):45777-45784

[72] Fasshauer M et al. Adiponectin gene expression and secretion is inhibited by interleukin-6 in 3T3-L1 adipocytes. *Biochemical and Biophysical Research Communications*. 2003;**301**(4):1045-1050

[73] Senn JJ et al. Interleukin-6 induces cellular insulin resistance in hepatocytes. *Diabetes*. 2002;**51**(12):3391-3399

[74] Gustafson B, Smith U. Cytokines promote Wnt signaling and inflammation and impair the normal differentiation and lipid accumulation in 3T3-L1 preadipocytes. *The Journal of Biological Chemistry*. 2006;**281**(14):9507-9516

[75] Bing C. Is interleukin-1 $\beta$  a culprit in macrophage-adipocyte crosstalk in obesity? *Adipocytes*. 2015;**4**(2):149-152

[76] Labrecque J et al. Interleukin-1 $\beta$  and prostaglandin-synthesizing enzymes as modulators of human omental and subcutaneous adipose tissue function. *Prostaglandins, Leukotrienes, and Essential Fatty Acids*. 2019;**141**:9-16

[77] Bruun JM et al. Monocyte chemoattractant protein-1 release is higher in visceral than subcutaneous human adipose tissue (AT): Implication of macrophages resident in the AT. *The Journal of Clinical Endocrinology and Metabolism*. 2005;**90**(4):2282-2289

[78] Younce C, Kolattukudy P. MCP-1 induced protein promotes adipogenesis via oxidative stress, endoplasmic reticulum stress and autophagy. *Cellular Physiology and Biochemistry: International Journal of Experimental Cellular Physiology, Biochemistry, and Pharmacology*. 2012;**30**(2):307-320

[79] O'Rourke RW et al. Systemic inflammation and insulin sensitivity

in obese IFN- $\gamma$  knockout mice. *Metabolism: Clinical and Experimental*. 2012;**61**(8):1152-1161

[80] Harkins JM et al. Expression of interleukin-6 is greater in preadipocytes than in adipocytes of 3T3-L1 cells and C57BL/6J and Ob/Ob mice. *The Journal of Nutrition*. 2004;**134**(10):2673-2677

[81] Jung TW et al.  $\beta$ -Aminoisobutyric acid attenuates LPS-induced inflammation and insulin resistance in adipocytes through AMPK-mediated pathway. *Journal of Biomedical Science*. 2018;**25**(1):27

[82] Dang R-J et al. A20 plays a critical role in the immunoregulatory function of mesenchymal stem cells. *Journal of Cellular and Molecular Medicine*. 2016;**20**(8):1550-1560

[83] Ai L et al. A20 reduces lipid storage and inflammation in hypertrophic adipocytes via p38 and Akt signaling. *Molecular and Cellular Biochemistry*. 2016;**420**(1):73-83

[84] Liu Y et al. Nonerythropoietic erythropoietin-derived peptide suppresses adipogenesis, inflammation, obesity and insulin resistance. *Scientific Reports*. 2015;**5**:15134

[85] Ahlqvist E et al. Link between GIP and osteopontin in adipose tissue and insulin resistance. *Diabetes*. 2013;**62**(6):2088-2094

[86] Li X et al. Bio-informatics analysis of a gene co-expression module in adipose tissue containing the diet-responsive gene Nnat. *BMC Systems Biology*. 2010;**4**:175

[87] Higuchi M et al. Differentiation of human adipose-derived stem cells into fat involves reactive oxygen species and Forkhead box O1 mediated upregulation of antioxidant enzymes. *Stem Cells and Development*. 2013;**22**(6):878-888



- [88] Liu R et al. Dynamic differences in oxidative stress and the regulation of metabolism with age in visceral versus subcutaneous adipose. *Redox Biology*. 2015;**6**:401-408
- [89] Okuno Y et al. Oxidative stress inhibits healthy adipose expansion through suppression of SREBF1-mediated lipogenic pathway. *Diabetes*. 2018;**67**(6):1113-1127
- [90] Tchkonina T et al. Fat tissue, aging, and cellular senescence. *Aging Cell*. 2010;**9**(5):667-684
- [91] Furukawa S et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. *The Journal of Clinical Investigation*. 2004;**114**(12):1752-1761
- [92] Gueraud F et al. Chemistry and biochemistry of lipid peroxidation products. *Free Radical Research*. 2010;**44**(10):1098-1124
- [93] Salans LB, Knittle JL, Hirsch J. The role of adipose cell size and adipose tissue insulin sensitivity in the carbohydrate intolerance of human obesity. *The Journal of Clinical Investigation*. 1968;**47**(1):153-165
- [94] Higdon A et al. Cell signalling by reactive lipid species: New concepts and molecular mechanisms. *The Biochemical Journal*. 2012;**442**(3):453-464
- [95] Bauer G, Zarkovic N. Revealing mechanisms of selective, concentration-dependent potentials of 4-hydroxy-2-nonenal to induce apoptosis in cancer cells through inactivation of membrane-associated catalase. *Free Radical Biology and Medicine*. 2015;**81**:128-144
- [96] Chen ZH, Niki E. 4-hydroxynonenal (4-HNE) has been widely accepted as an inducer of oxidative stress. Is this the whole truth about it or can 4-HNE also exert protective effects? *IUBMB Life*. 2006;**58**(5-6):372-373
- [97] Huh JY et al. 8-Hydroxy-2-deoxyguanosine ameliorates high-fat diet-induced insulin resistance and adipocyte dysfunction in mice. *Biochemical and Biophysical Research Communications*. 2017;**491**(4):890-896
- [98] Murdolo G et al. Free radical-derived oxysterols: Novel adipokines modulating adipogenic differentiation of adipose precursor cells. *The Journal of Clinical Endocrinology and Metabolism*. 2016;**101**(12):4974-4983
- [99] Vanella L et al. Increased heme-oxygenase 1 expression in mesenchymal stem cell-derived adipocytes decreases differentiation and lipid accumulation via upregulation of the canonical Wnt signaling cascade. *Stem Cell Research and Therapy*. 2013;**4**(2):28
- [100] Lin C-H et al. Oxidative stress induces imbalance of adipogenic/osteoblastic lineage commitment in mesenchymal stem cells through decreasing SIRT1 functions. *Journal of Cellular and Molecular Medicine*. 2018;**22**(2):786-796
- [101] Denu RA, Hematti P. Effects of oxidative stress on mesenchymal stem cell biology. *Oxidative Medicine and Cellular Longevity*. 2016;**2016**:2989076
- [102] Puri N et al. Heme induced oxidative stress attenuates sirtuin1 and enhances adipogenesis in mesenchymal stem cells and mouse pre-adipocytes. *Journal of Cellular Biochemistry*. 2012;**113**(6):1926-1935
- [103] Moreno-Navarrete JM et al. Deleted in breast cancer 1 plays a functional role in adipocyte differentiation. *American Journal of Physiology. Endocrinology and Metabolism*. 2015;**308**(7):E554-E561
- [104] Wu Y-T et al. Depletion of Sirt3 leads to the impairment of adipogenic differentiation and insulin resistance via interfering mitochondrial function of

adipose-derived human mesenchymal stem cells. *Free Radical Research*. 2018;**52**(11):1398-1415

[105] Chang Y-C et al. Deficiency of NPGPx, an oxidative stress sensor, leads to obesity in mice and human. *EMBO Molecular Medicine*. 2013;**5**(8):1165-1179

[106] Castro JP, Grune T, Speckmann B. The two faces of reactive oxygen species (ROS) in adipocyte function and dysfunction. *Biological Chemistry*. 2016;**397**(8):709-724

[107] Alcala M et al. Short-term vitamin E treatment impairs reactive oxygen species signaling required for adipose tissue expansion, resulting in fatty liver and insulin resistance in obese mice. *PLoS One*. 2017;**12**(10):e0186579

[108] Pieralisi A et al. N-acetylcysteine inhibits lipid accumulation in mouse embryonic adipocytes. *Redox Biology*. 2016;**9**:39-44

[109] Peris E et al. Antioxidant treatment induces reductive stress associated with mitochondrial dysfunction in adipocytes. *The Journal of Biological Chemistry*. 2019;**294**(7):2340-2352

[110] Findeisen HM et al. Oxidative stress accumulates in adipose tissue during aging and inhibits adipogenesis. *PLoS One*. 2011;**6**(4):e18532

[111] Zhang C, Klett EL, Coleman RA. Lipid signals and insulin resistance. *Journal of Clinical Lipidology*. 2013;**8**(6):659-667

[112] Jiao P et al. FFA-induced adipocyte inflammation and insulin resistance: Involvement of ER stress and IKKbeta pathways. *Obesity (Silver Spring)*. 2011;**19**(3):483-491

[113] Furuhashi M, Hotamisligil GS. Fatty acid-binding proteins: Role in metabolic diseases and potential as

drug targets. *Nature Reviews. Drug Discovery*. 2008;**7**(6):489-503

[114] Summers SA. Ceramides in insulin resistance and lipotoxicity. *Progress in Lipid Research*. 2006;**45**(1):42-72

[115] Barbarroja N et al. Increased dihydroceramide/ceramide ratio mediated by defective expression of degs1 impairs adipocyte differentiation and function. *Diabetes*. 2015;**64**(4):1180-1192

[116] Papackova Z, Cahova M. Fatty acid signaling: The new function of intracellular lipases. *International Journal of Molecular Sciences*. 2015;**16**(2):3831-3855

[117] Roy D et al. Coordinated transcriptional control of adipocyte triglyceride lipase (Atgl) by transcription factors Sp1 and peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) during adipocyte differentiation. *The Journal of Biological Chemistry*. 2017;**292**(36):14827-14835

[118] Clarke SD. Polyunsaturated fatty acid regulation of gene transcription: A molecular mechanism to improve the metabolic syndrome. *The Journal of Nutrition*. 2001;**131**(4):1129-1132

[119] Clarke SD. The multi-dimensional regulation of gene expression by fatty acids: Polyunsaturated fats as nutrient sensors. *Current Opinion in Lipidology*. 2004;**15**(1):13-18

[120] Kersten S. Effects of fatty acids on gene expression: Role of peroxisome proliferator-activated receptor alpha, liver X receptor alpha and sterol regulatory element-binding protein-1c. *The Proceedings of the Nutrition Society*. 2002;**61**(3):371-374

[121] Wahle KW, Rotondo D, Heys SD. Polyunsaturated fatty acids and gene expression in mammalian systems. *The Proceedings of the Nutrition Society*. 2003;**62**(2):349-360

- [122] Forman BM, Chen J, Evans RM. Hypolipidemic drugs, polyunsaturated fatty acids, and eicosanoids are ligands for peroxisome proliferator-activated receptors alpha and delta. *Proceedings of the National Academy of Sciences of the United States of America*. 1997;**94**(9):4312-4317
- [123] Johnson TE et al. Structural requirements and cell-type specificity for ligand activation of peroxisome proliferator-activated receptors. *The Journal of Steroid Biochemistry and Molecular Biology*. 1997;**63**(1):1-8
- [124] Yu K et al. Differential activation of peroxisome proliferator-activated receptors by eicosanoids. *Journal of Biological Chemistry*. 1995;**270**(41):23975-23983
- [125] Kliewer SA et al. Fatty acids and eicosanoids regulate gene expression through direct interactions with peroxisome proliferator-activated receptors alpha and gamma. *Proceedings of the National Academy of Sciences of the United States of America*. 1997;**94**(9):4318-4323
- [126] Keller H et al. Fatty acids and retinoids control lipid metabolism through activation of peroxisome proliferator-activated receptor-retinoid X receptor heterodimers. *Proceedings of the National Academy of Sciences of the United States of America*. 1993;**90**(6):2160-2164
- [127] Roynette CE et al. n-3 polyunsaturated fatty acids and colon cancer prevention. *Clinical Nutrition*. 2004;**23**(2):139-151
- [128] Hirafuji M et al. Cardiovascular protective effects of n-3 polyunsaturated fatty acids with special emphasis on docosahexaenoic acid. *Journal of Pharmacological Sciences*. 2003;**92**(4):308-316
- [129] Abeywardena MY, Head RJ. Long-chain n-3 polyunsaturated fatty acids and blood vessel function. *Cardiovascular Research*. 2001;**52**(3):361-371
- [130] Bucher HC et al. N-3 polyunsaturated fatty acids in coronary heart disease: A meta-analysis of randomized controlled trials. *The American Journal of Medicine*. 2002;**112**(4):298-304
- [131] Larsson SC et al. Dietary long-chain n-3 fatty acids for the prevention of cancer: A review of potential mechanisms. *The American Journal of Clinical Nutrition*. 2004;**79**(6):935-945
- [132] Worgall TS et al. Polyunsaturated fatty acids decrease expression of promoters with sterol regulatory elements by decreasing levels of mature sterol regulatory element-binding protein. *The Journal of Biological Chemistry*. 1998;**273**(40):25537-25540
- [133] Hannah VC et al. Unsaturated fatty acids down-regulate srebp isoforms 1a and 1c by two mechanisms in HEK-293 cells. *Journal of Biological Chemistry*. 2001;**276**(6):4365-4372
- [134] Mater MK et al. Sterol response element-binding protein 1c (SREBP1c) is involved in the polyunsaturated fatty acid suppression of hepatic S14 gene transcription. *Journal of Biological Chemistry*. 1999;**274**(46):32725-32732
- [135] Xu J et al. Sterol regulatory element binding protein-1 expression is suppressed by dietary polyunsaturated fatty acids. A mechanism for the coordinate suppression of lipogenic genes by polyunsaturated fats. *Journal of Biological Chemistry*. 1999;**274**(33):23577-23583
- [136] Ou J et al. Unsaturated fatty acids inhibit transcription of the sterol regulatory element-binding protein-1c (SREBP-1c) gene by antagonizing ligand-dependent activation of the LXR. *Proceedings*



of the National Academy of Sciences.  
 2001;**98**(11):6027-6032

The Journal of Biological Chemistry.  
 1997;**272**(43):26827-26832

[137] Yoshikawa T et al. Polyunsaturated fatty acids suppress sterol regulatory element-binding protein 1c promoter activity by inhibition of liver X receptor (LXR) binding to LXR response elements. *The Journal of Biological Chemistry*. 2002;**277**(3):1705-1711

[138] Barak Y et al. PPAR gamma is required for placental, cardiac, and adipose tissue development. *Molecular Cell*. 1999;**4**(4):585-595

[139] Göttlicher M et al. Structural and metabolic requirements for activators of the peroxisome proliferator-activated receptor. *Biochemical Pharmacology*. 1993;**46**(12):2177-2184

[140] Nakamura MT et al. Mechanisms of regulation of gene expression by fatty acids. *Lipids*. 2004;**39**(11):1077-1083

[141] Cho K-J et al. Alpha-lipoic acid inhibits adipocyte differentiation by regulating pro-adipogenic transcription factors via mitogen-activated protein kinase pathways. *The Journal of Biological Chemistry*. 2003;**278**(37):34823-34833

[142] Goto T et al. 10-oxo-12(Z)-octadecenoic acid, a linoleic acid metabolite produced by gut lactic acid bacteria, potently activates PPAR $\gamma$  and stimulates adipogenesis. *Biochemical and Biophysical Research Communications*. 2015;**459**(4):597-603

[143] Wong SH et al. The adaptive effects of dietary fish and safflower oil on lipid and lipoprotein metabolism in perfused rat liver. *Biochimica et Biophysica Acta*. 1984;**792**(2):103-109

[144] Ren B et al. Polyunsaturated fatty acid suppression of hepatic fatty acid synthase and S14 gene expression does not require peroxisome proliferator-activated receptor alpha.

[145] Rustan AC, Christiansen EN, Drevon CA. Serum lipids, hepatic glycerolipid metabolism and peroxisomal fatty acid oxidation in rats fed omega-3 and omega-6 fatty acids. *The Biochemical Journal*. 1992;**283**(Pt 2):333-339

[146] Takeuchi H et al. Comparative effects of dietary fat types on hepatic enzyme activities related to the synthesis and oxidation of fatty acid and to lipogenesis in rats. *Bioscience, Biotechnology, and Biochemistry*. 2001;**65**(8):1748-1754

[147] Madsen L, Petersen RK, Kristiansen K. Regulation of adipocyte differentiation and function by polyunsaturated fatty acids. *Biochimica et Biophysica Acta*. 2005;**1740**(2):266-286

[148] Jove M et al. Human omental and subcutaneous adipose tissue exhibit specific lipidomic signatures. *The FASEB Journal*. 2014;**28**(3):1071-1081

[149] Hodson L, Skeaff CM, Fielding BA. Fatty acid composition of adipose tissue and blood in humans and its use as a biomarker of dietary intake. *Progress in Lipid Research*. 2008;**47**(5):348-380

[150] Denys A, Hichami A, Khan NA. Eicosapentaenoic acid and docosahexaenoic acid modulate MAP kinase enzyme activity in human T-cells. *Molecular and Cellular Biochemistry*. 2002;**232**(1-2):143-148

[151] Fan X et al. Arachidonic acid and related methyl ester mediate protein kinase C activation in intact platelets through the arachidonate metabolism pathways. *Biochemical and Biophysical Research Communications*. 1990;**169**(3):933-940

[152] Jiang YH et al. Dietary fat and fiber differentially alter intracellular second



messengers during tumor development in rat colon. *Carcinogenesis*. 1996;**17**(6):1227-1233

[153] Kawaguchi T et al. Mechanism for fatty acid “sparing” effect on glucose-induced transcription: Regulation of carbohydrate-responsive element-binding protein by AMP-activated protein kinase. *The Journal of Biological Chemistry*. 2002;**277**(6):3829-3835

[154] Murata M et al. Dual action of eicosapentaenoic acid in hepatoma cells: Up-regulation of metabolic action of insulin and inhibition of cell proliferation. *The Journal of Biological Chemistry*. 2001;**276**(33):31422-31428

[155] Madani S et al. Diacylglycerols containing omega 3 and omega 6 fatty acids bind to RasGRP and modulate MAP kinase activation. *The Journal of Biological Chemistry*. 2004;**279**(2):1176-1183

[156] Nikolopoulou E et al. Arachidonic acid-dependent gene regulation during preadipocyte differentiation controls adipocyte potential. *Journal of Lipid Research*. 2014;**55**(12):2479-2490

[157] Moreno-Santos I et al. The antagonist effect of arachidonic acid on GLUT4 gene expression by nuclear receptor type II regulation. *International Journal of Molecular Sciences*. 2019;**20**(4):963

[158] Catalioto RM et al. Autocrine control of adipose cell differentiation by prostacyclin and PGF2 alpha. *Biochimica et Biophysica Acta*. 1991;**1091**(3):364-369

[159] Gaillard D et al. Requirement and role of arachidonic acid in the differentiation of pre-adipose cells. *The Biochemical Journal*. 1989;**257**(2):389-397

[160] Negrel R, Gaillard D, Ailhaud G. Prostacyclin as a potent effector

of adipose-cell differentiation. *The Biochemical Journal*. 1989;**257**(2):399-405

[161] Forman BM et al. 15-Deoxy-delta 12, 14-prostaglandin J2 is a ligand for the adipocyte determination factor PPAR gamma. *Cell*. 1995;**83**(5):803-812

[162] Kliewer SA et al. A prostaglandin J2 metabolite binds peroxisome proliferator-activated receptor gamma and promotes adipocyte differentiation. *Cell*. 1995;**83**(5):813-819

[163] Serrero G, Lepak NM. Prostaglandin F2alpha receptor (FP receptor) agonists are potent adipose differentiation inhibitors for primary culture of adipocyte precursors in defined medium. *Biochemical and Biophysical Research Communications*. 1997;**233**(1):200-202

[164] Serrero G, Lepak NM, Goodrich SP. Paracrine regulation of adipose differentiation by arachidonate metabolites: Prostaglandin F2 alpha inhibits early and late markers of differentiation in the adipogenic cell line 1246. *Endocrinology*. 1992;**131**(6):2545-2551

[165] Serrero G, Lepak NM, Goodrich SP. Prostaglandin F2 alpha inhibits the differentiation of adipocyte precursors in primary culture. *Biochemical and Biophysical Research Communications*. 1992;**183**(2):438-442

[166] Casimir DA, Miller CW, Ntambi JM. Preadipocyte differentiation blocked by prostaglandin stimulation of prostanoid FP2 receptor in murine 3T3-L1 cells. *Differentiation*. 1996;**60**(4):203-210

[167] Kamon J et al. Prostaglandin F(2)alpha enhances glucose consumption through neither adipocyte differentiation nor GLUT1 expression in 3T3-L1 cells. *Cellular Signalling*. 2001;**13**(2):105-109

- [168] Miller CW, Casimir DA, Ntambi JM. The mechanism of inhibition of 3T3-L1 preadipocyte differentiation by prostaglandin F2alpha. *Endocrinology*. 1996;**137**(12):5641-5650
- [169] Reginato MJ et al. Prostaglandins promote and block adipogenesis through opposing effects on peroxisome proliferator-activated receptor gamma. *The Journal of Biological Chemistry*. 1998;**273**(4):1855-1858
- [170] Vassaux G et al. Differential response of preadipocytes and adipocytes to prostacyclin and prostaglandin E2: Physiological implications. *Endocrinology*. 1992;**131**(5):2393-2398
- [171] Sugimoto Y et al. Microarray evaluation of EP4 receptor-mediated prostaglandin E2 suppression of 3T3-L1 adipocyte differentiation. *Biochemical and Biophysical Research Communications*. 2004;**322**(3):911-917
- [172] Tsuboi H et al. Prostanoid EP4 receptor is involved in suppression of 3T3-L1 adipocyte differentiation. *Biochemical and Biophysical Research Communications*. 2004;**322**(3):1066-1072
- [173] Li R et al. CYP2J2 attenuates metabolic dysfunction in diabetic mice by reducing hepatic inflammation via the PPAR $\gamma$ . *American Journal of Physiology. Endocrinology and Metabolism*. 2015;**308**(4):E270-E282
- [174] Suzuki M, Tamura T, Shimomura Y. Less body fat accumulation in rats fed a safflower oil diet than in rats fed a beef tallow diet. *The Journal of Nutrition*. 1990;**120**(11):1291-1296
- [175] Wang H, Storlien LH, Huang X-F. Effects of dietary fat types on body fatness, leptin, and ARC leptin receptor, NPY, and AgRP mRNA expression. *American Journal of Physiology-Endocrinology and Metabolism*. 2002;**282**(6):E1352-E1359
- [176] Minami A et al. Effect of eicosapentaenoic acid ethyl ester v. oleic acid-rich safflower oil on insulin resistance in type 2 diabetic model rats with hypertriacylglycerolaemia. *The British Journal of Nutrition*. 2002;**87**(2):157-162
- [177] Cha SH et al. Chronic docosahexaenoic acid intake enhances expression of the gene for uncoupling protein 3 and affects pleiotropic mRNA levels in skeletal muscle of aged C57BL/6Njcl mice. *The Journal of Nutrition*. 2001;**131**(10):2636-2642
- [178] Takahashi Y, Ide T. Dietary n-3 fatty acids affect mRNA level of brown adipose tissue uncoupling protein 1, and white adipose tissue leptin and glucose transporter 4 in the rat. *The British Journal of Nutrition*. 2000;**84**(2):175-184
- [179] Okuno M et al. Perilla oil prevents the excessive growth of visceral adipose tissue in rats by down-regulating adipocyte differentiation. *The Journal of Nutrition*. 1997;**127**(9):1752-1757
- [180] Jang IS et al. Role of dietary fat type in the development of adiposity from dietary obesity-susceptible Sprague-Dawley rats. *The British Journal of Nutrition*. 2003;**89**(3):429-438
- [181] Nakatani T et al. A low fish oil inhibits SREBP-1 proteolytic cascade, while a high-fish-oil feeding decreases SREBP-1 mRNA in mice liver: Relationship to anti-obesity. *Journal of Lipid Research*. 2003;**44**(2):369-379
- [182] Ukropec J et al. The hypotriglyceridemic effect of dietary n-3 FA is associated with increased beta-oxidation and reduced leptin expression. *Lipids*. 2003;**38**(10):1023-1029

- [183] Pellizzon M et al. Effects of dietary fatty acids and exercise on body-weight regulation and metabolism in rats. *Obesity Research*. 2002;**10**(9):947-955
- [184] Liberato MV et al. Medium chain fatty acids are selective peroxisome proliferator activated receptor (PPAR)  $\gamma$  activators and pan-PPAR partial agonists. *PLoS One*. 2012;**7**(5):e36297
- [185] Senarath S et al. Comparison of the effects of long-chain monounsaturated fatty acid positional isomers on lipid metabolism in 3T3-L1 cells. *Journal of Oleo Science*. 2019
- [186] Zhao G et al. Anti-inflammatory effects of polyunsaturated fatty acids in THP-1 cells. *Biochemical and Biophysical Research Communications*. 2005;**336**(3):909-917
- [187] Amri EZ, Ailhaud G, Grimaldi PA. Fatty acids as signal transducing molecules: Involvement in the differentiation of preadipose to adipose cells. *Journal of Lipid Research*. 1994;**35**(5):930-937
- [188] Davies JD et al. Adipocytic differentiation and liver x receptor pathways regulate the accumulation of triacylglycerols in human vascular smooth muscle cells. *The Journal of Biological Chemistry*. 2005;**280**(5):3911-3919
- [189] Ding S, Mersmann HJ. Fatty acids modulate porcine adipocyte differentiation and transcripts for transcription factors and adipocyte-characteristic proteins\*. *The Journal of Nutritional Biochemistry*. 2001;**12**(2):101-108
- [190] McNeel RL, Mersmann HJ. Effects of isomers of conjugated linoleic acid on porcine adipocyte growth and differentiation. *The Journal of Nutritional Biochemistry*. 2003;**14**(5):266-274
- [191] Wolins NE et al. S3-12, Adipophilin, and TIP47 package lipid in adipocytes. *The Journal of Biological Chemistry*. 2005;**280**(19):19146-19155
- [192] Magliano DJ et al. Persistent organic pollutants and diabetes: A review of the epidemiological evidence. *Diabetes and Metabolism*. 2014;**40**(1):1-14
- [193] Farkhondeh T, Samarghandian S, Azimi-Nezhad M. The role of arsenic in obesity and diabetes. *Journal of Cellular Physiology*. 2019 Aug;**234**(8):12516-12529
- [194] Bartlett DE et al. Uremic toxins activates Na/K-ATPase oxidant amplification loop causing phenotypic changes in adipocytes in In vitro models. *International Journal of Molecular Sciences*. 2018;**19**(9):2685
- [195] Milton FA et al. Dibutyltin compounds effects on PPAR $\gamma$ /RXR $\alpha$  activity, adipogenesis, and inflammation in mammals cells. *Frontiers in Pharmacology*. 2017;**8**:507