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REVIEW

Cytokines and inflammation in adipogenesis: an updated review

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Abstract **The biological relevance of cytokines is known for more than 20 years. Evidence suggests that adipogenesis is one of the biological events involved in the regulation of cytokines, and pro-inflammatory cytokines (e.g., TNFα and IL-1β) inhibit adipogenesis through various pathways. This inhibitory effect can constrain the hyperplastic expandability of adipose tissues. Meanwhile, chronic low-grade inflammation is commonly observed in obese populations. In some individuals, the impaired ability of adipose tissues to recruit new adipocytes to adipose depots during overnutrition results in adipocyte hypertrophy, ectopic lipid accumulation, and insulin resistance. Intervention studies showed that pro-inflammatory cytokine antagonists improve metabolism in patients with metabolic syndrome. This review focuses on the cytokines currently known to regulate adipogenesis under physiological and pathophysiological circumstances. Recent studies on how inhibited adipogenesis leads to metabolic disorders were summarized. Although the interplay of cytokines and lipid metabolism is yet incompletely understood, cytokines represent a class of potential therapeutic targets in the treatment of metabolic disorders.**

Keywords cytokines; inflammation; adipogenesis; type 2 diabetes mellitus; metabolic disorder

Introduction

The adipose tissue has been recognized as a dynamic component of the endocrine system and plays an important role in the maintenance of energy balance and nutritional homeostasis [1]. Mature adipocytes are the most distinctive cell type of the adipose tissue and occupy more than 90% of its volume [2]. Meanwhile, leukocytes, macrophages, fibroblasts, endothelial cells, and preadipocytes are called stromal-vascular cells. Each gram of adipose tissue contains four to six million stromal–vascular cells, more than half of which are immune cells [3]. Thus, adipose tissues are known as a large source of macrophages and other immune cells [4].

Precursor cells become lipid-laden mature adipocytes via a two-step developmental process called adipogenesis. A mesenchymal cell differentiates into preadipocyte, which then undergoes terminal differentiation to become a lipid-filled adipocyte. The fate of adipogenesis is determined by cell–cell and cell–extracellular matrix (ECM) interactions within the adipose tissue. These interactions rely on numerous factors including peroxisome proliferator-activated receptor γ (PPARγ), CCAAT/enhancer-binding proteins (C/EBPs), Wingless and INT-1 proteins (Wnts), and cytokines. PPARγ and C/EBPs are considered essential factors in adipogenesis [1,5]. During the early stages of adipogenesis, multiple inducers activate PPARγ expression. PPARγ then activates C/EBPα expression, and these two factors act in cooperation to maintain adipogenesis [1].

Both adipocytes and immune cells participate in the secretion of cytokines, which play a pivotal role in adipogenesis. The secreted cytokines then affect appetite regulation, energy metabolism, and immunological interactions [3]. Table 1 summarizes the cytokines that regulate adipogenesis. This review focuses on how cytokines regulate adipogenesis and how dysregulated adipogenesis leads to complications associated with inflammation-mediated metabolic diseases, such as type 2 diabetes mellitus (T2DM), cardiovascular diseases, and nonalcoholic fatty liver disease (NAFLD).

Tumor necrosis factor α

Tumor necrosis factor α (TNFα) is primarily a pro-

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Table 1 Cytokines that regulate adipogenesis

Family of cytokines	Symbol	Cytokine name	Primary property	Receptor	Major sources of secretion in adipose tissue	Model	Effect on adipogenesis	References
	TNFα	Tumor necrosis factor α	Pro-inflammatory	TNFR-1, TNFR-2	Cells of the monocyte/macrophage lineage, including adipose tissue macrophages	Human abdominal subcutaneous preadipocytes, 3T3-L1 cells, 3T3-F442A cells	↓	[6–9]
IL-1 family	IL-1β	Interleukin-1β	Pro-inflammatory	IL-1R1, IL-1R2	Cells of the monocyte/macrophage lineage	Human abdominal subcutaneous preadipocytes	↓	[10]
	IL-18	Interleukin-18	Pro-inflammatory	IL-18R	Macrophages, DC, epithelial cells, endothelial cells		Unknown	
	IL-33	Interleukin-33	Pro-inflammatory	ST2	Necrotic cells, cells under stress	Wistar rat (pre)adipocytes, 3T3-L1 cells, C57BL/6 mouse (pre)-adipocytes, BALB/c mouse (pre)adipocytes	↓	[11,12]
	IL-1F6	Interleukin-1F6	Pro-inflammatory	IL-1Rrp2	Stromal vascular fraction	Human subcutaneous abdominal (pre)adipocytes, human SGBS cells	↓	[13]
	IL-1Ra	Interleukin-1Ra	Anti-inflammatory	IL-1R1	Stromal vascular fraction	C57BL/6J mouse epididymal (pre)adipocytes	↑	[14]
	IL-37	Interleukin	Anti-inflammatory	IL-18Rα	Mature adipocytes and vascular stromal cells	Human SGBS cells	↓	[15]
Gp130 cytokines	IL-6	Interleukin-6	Pro-inflammatory	IL-6Rα	Adipose tissue macrophages	Human subcutaneous (pre)adipocytes, 3T3-L1 cells, 3T3-F442A cells	↓	[16–18]
	IL-11	Interleukin-11	Pro-inflammatory	IL-11R	Stromal vascular cells	Human long term marrow cultures, 3T3-L1 cells	↓	[19,20]
	OSM	Oncostatin M	Pro-inflammatory	Type 1 OSM receptor, type 2 OSM receptor		3T3-L1 cells, mouse embryonic fibroblasts	↓	[21]
	NP	Neuropoietin	?	CNTFRα		3T3-L1 cells	↓	[22]
	IL-4	Interleukin-4	Pro-inflammatory/ anti-inflammatory	IL-4R	Lymphocytes, basophils and mast cells	3T3-L1 cells	↓	[23]
	IL-10	Interleukin-10	Anti-inflammatory	IL-10R	T helper cells, monocytes/macrophages, dendritic cells, B cells		Unknown	
	IL-15	Interleukin-15	Pro-inflammatory	IL-15Rα	Adipocytes and stromal vascular cells	3T3-L1 cells	↓	[24]
	IL-7	Interleukin-7	Pro-inflammatory	IL-7R	Stromal vascular cells	Mouse epididymal (pre)adipocytes	↑	[25]
	IL-17	Interleukin-17	Pro-inflammatory	IL-17R	T helper cells	3T3-L1 cells	↓	[26–28]
	IL-34	Interleukin-34	Pro-inflammatory	CSF-1 receptor	Adipocytes and stromal vascular cells	Human subcutaneous preadipocytes	↑	[29]
Interferons	IFN-α	Interferon-α	Pro-inflammatory	Type I interferon receptors	Fibroblasts and monocytes	3T3-L1 cells; human primary (pre)adipocytes	↓	[30]
	IFN-γ	Interferon-γ	Pro-inflammatory	Type II interferon receptors	T helper cells	Mouse mesenchymal stem cells, 3T3-L1 cells, primary mouse (pre)adipocytes, human visceral (pre)adipocytes	↓↑	[31,32]

(*Continued*)

Family of cytokines	Symbol	Cytokine name	Primary property	Receptor	Major sources of secretion in adipose tissue	Model	Effect on adipogenesis	References
	MCP-1 (CCL-2)	Monocyte chemoattractant protein-1 (chemokine (C-C motif) ligand 2)	Pro-inflammatory	CCR2	Adipocytes, macrophages and endothelial cells	3T3-L1 cells, murine tissue engineering model	↑	[33,34]

inflammatory cytokine that plays a key role in the regulation of inflammatory response, cell differentiation, cell proliferation, and apoptosis [38,39]. TNFα binds to two distinct receptors, namely, TNFα receptors (TNFR) type 1 or 2 (Fig.1) [40]. Upon binding to either receptor, TNFα activates NF-κB and MAPK (JNK, ERK, and p38) signaling [41]. In adipose tissues, the majority of TNFα is produced by stromal–vascular cells and adipose tissue macrophages (ATMs) [4,42]. Furthermore, TNFα contributes to insulin resistance in obesity [43–46], and its circulating levels are elevated in individuals with obesity or T2DM [47,48]. TNFα treatment in 3T3-L1 cells and rats also induces insulin resistance [49,50]. Moreover, blockage of TNFα using null mutation of TNFα gene and its two receptors genes improves insulin sensitivity in *ob/ob* rodent model [51].

TNFα is a potent inhibitor of adipogenesis and blocks adipocyte differentiation mainly by activating TNFR1 [8], which stimulates the NF-κB, ERK1/2 and JNK signaling pathways [8,9,52]. The differentiation of 3T3-L1 cells is restored once NF-κB and JNK signaling are blocked by specific inhibitors [9]. TNFα inhibits adipogenesis through multiple mechanisms, including the activation of Wnt/β-catenin/TCF dependent pathway and inhibition of transcription factors, such as PPARγ and C/EBPs [53–55].

In 3T3-L1 cells and mouse models, the inhibition of PPARγ by TNFα involves thiazolidinediones, a class of PPARγ agonists that restore adipogenesis [53,54]. The TNFα-induced blockage of adipogenesis through PPARγ inhibition may act at the transcriptional [56,57] and post-translational levels. In 3T3-L1 adipocytes, treatment with TNFα enhances the activities of JNK1/2 and p38 SAP kinase. Activated JNK1/2 and p38 SAP kinase promotes the c-Jun and ATF2 activity, thereby increasing Map4k4 expression, which negatively regulates PPARγ expression and adipogenesis in 3T3-L1 cells [7,58]. TNFα may induce

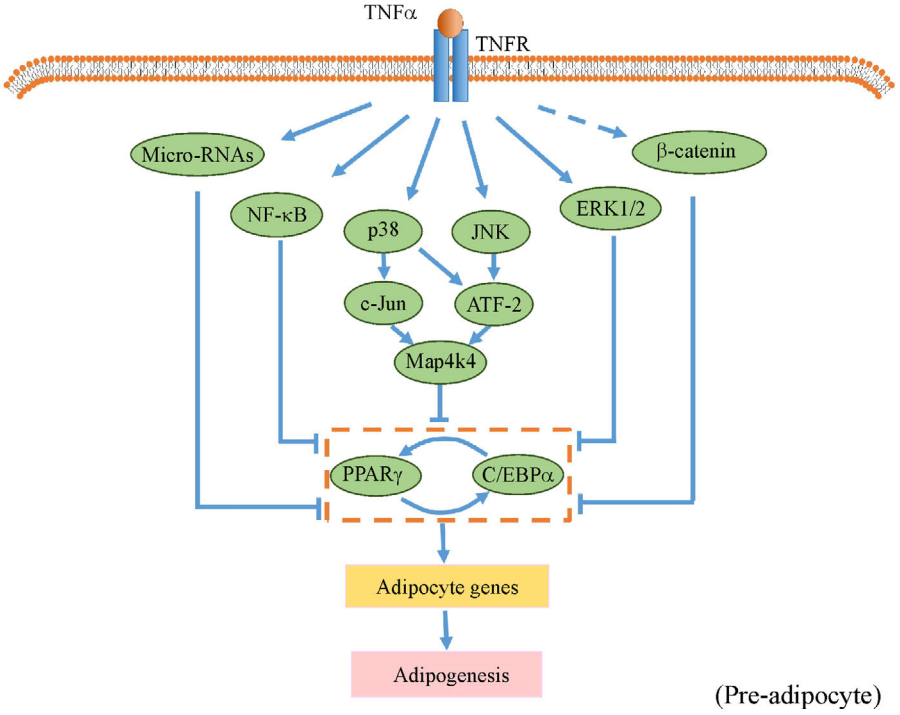

Fig. 1 TNFα signaling regulates adipogenesis. Signaling of TNFα through TNFR leads to activation of multiple pathways including NF-κB, p38, JNK, and ERK1/2. Wnt/β-catenin/TCF dependent pathway and numerous microRNAs are also activated. The activation of these pathways results in adipogenesis inhibition and suppression of PPARγ and C/EBPα expression and activity, which are important transcriptional regulators of adipogenesis.

cleavage of PPARγ by activating the caspase cascade, which disrupts the nuclear localization of PPARγ [59].

TNFα also inhibits adipogenesis by stimulating other negative physiological regulators, such as Wnt/β-catenin signaling. Wnt/β-catenin pathway downregulates PPARγ and C/EBPα expression and inhibits adipocyte differentiation [55]. In animal models, TNFα activates Wnt/β-catenin/T-cell factor 4 pathways by stimulating TNFR1-mediated death domain signals [6]. Meanwhile, TNFα deficiency downregulates Wnt10b and β-catenin, upregulates adipocyte-specific genes in epididymal white adipose tissues, and promotes significant body weight gain in chow diet mice [60].

Numerous microRNAs regulate biological processes in adipose tissues, especially adipogenesis [61] (Table 2). Recent studies have shown that microRNAs regulate adipogenesis in different stages and may act as downstream factors of TNFα. Price *et al.* found that the levels of microRNAs are altered in adipose tissues during the development of obesity and insulin resistance [62]. Certain microRNAs, including miR-221, miR-155, miR-103, miR-143, miR-335, miR-27, has-miR-26b and miR-378, in adipose tissues are regulated by TNFα [35–37,63–67]. In cultured human preadipocytes, miR-221 expression is suppressed by TNFα [35]. By contrast, human adipocytes transfected with miR-221 express increased level of proteins involved in lipid metabolism, including PPARγ [35]. Despite these facts, how TNFα, adipogenesis, and related microRNAs interact with one another remains unknown, although several mechanisms have been proposed *in vitro*. In 3T3-L1 cells, Liu *et al*. demonstrated that TNFα upregulates miR-155 and miR-27 by activating the NF-κB pathway [36]. miR-155 and miR-27 expression both inhibit early adipogenic transcription factors, such as C/EBPβ and cAMP-response element binding protein (CREB), by directly targeting their 3' untranslated regions (UTRs) [36,64]. TNFα downregulates miR-103 and miR-143, which accelerate adipogenesis [37]. These findings show that miRNAs act as mediators in the regulation of adipogenesis and insulin sensitivity via TNFα and give rise to the idea of using microRNA targeting as a novel therapeutic strategy for obesity and T2DM treatment.

In general, current studies show that TNFα inhibits adipogenesis through multiple mechanisms, but the importance of each mechanism is not fully understood. Integration of these mechanisms should be considered when investigating the regulation of adipogenesis by TNFα.

IL-1 family

The IL-1 family contains 11 members playing important roles in the regulation of immunity and inflammatory responses. Among these members, some are pro-inflammatory cytokines, such as IL-1β, IL-18, IL-1F6 (IL-36α), whereas others are anti-inflammatory cytokines, such as IL1Ra and IL-37 [68]. IL-1β is a well-known inhibitor of adipogenesis [69]. It is mainly produced by THP-1 macrophages in adipose tissues and, to a lesser extent, in adipocytes [70]. IL-1β binds to type 1 IL-1 receptor to activate intracellular signaling including NF-κB pathway, which inhibits adipogenesis (Fig.2) [71,72]. In obese mice models, IL-1β is upregulated in adipose tissue [70] and is found to inhibit adipocyte differentiation and fat accumulation [10] at the physiological concentration of 500 pg/mL [10]. Additionally, immunodepleting IL-1β does not affect the anti-adipogenic potential of macrophages [10], indicating that this cells synthesize other factors that also possess anti-adipogenic activity. Interestingly, previous studies showed that the knockout of IL-1Ra, the natural inhibitor of IL-1β, results in increased food intake, reduced body weight, and reduced adipogenesis in mice [14]. Additionally, IL-1Ra$^{-/-}$ mice showed decreased levels of leptin, IL-1β, IL-6, and TNFα. These results suggest that IL-1Ra and IL-1β, along with other unknown factors, form a network that regulates energy expenditure and adipogenesis.

IL-18 is member of the IL-1 family and is a pro-inflammatory cytokine. In human adipose tissues, stromal–vascular cells are the main sources of IL-18 [73], with higher levels of IL-18 in visceral adipose tissue compared with subcutaneous adipose tissue [75]. The circulating levels of IL-18 are elevated in obese subjects [73], although these levels are restored to normal after bariatric surgery [74]. Paradoxically, IL-18 knockout mice show increased body weight and insulin resistance, whereas

Table 2 Regulatory effect of microRNAs on adipogenesis

Name	Effect on adipogenesis	Targets	The impact of TNFα on microRNAs	References
miR-221	↑	PPARγ	↓	[35]
miR-155	↓	C/EBPβ, CREB	↑	[36]
miR-27	↓	C/EBPβ, CREB	↑	[36]
miR-103	↑	–	↓	[37]
miR-143	↑	–	↓	[37]
has-miR-26b	↑	PTEN	↓	[37]
miR-378	↑	–	↑	[37]

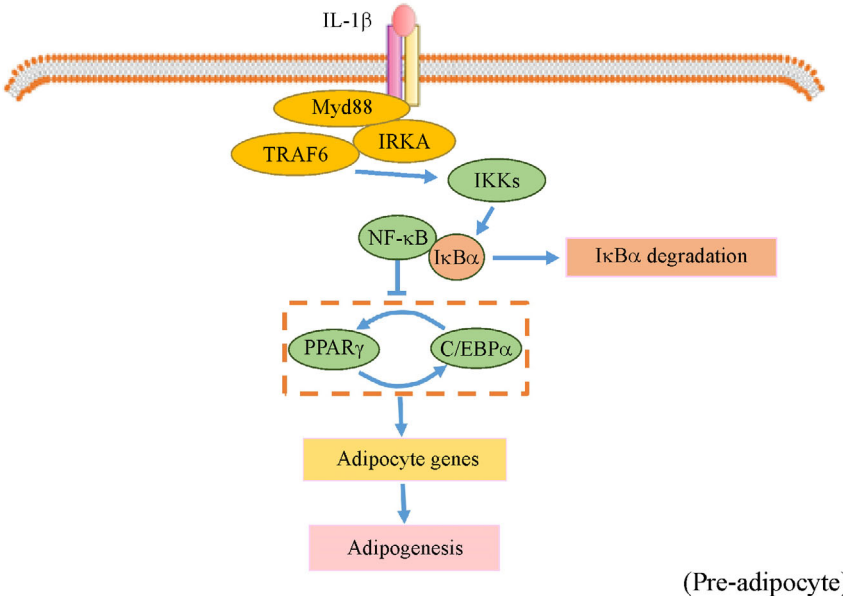

Fig. 2 IL-1β signaling affects adipogenesis. IL-1β is mainly produced by macrophages in adipose tissue, with small amounts being synthesized by adipocytes. It binds to type 1 IL-1 receptor to activate intracellular signaling including NF-κB pathway, which inhibits adipogenesis.

administration of recombinant IL-18 reduces food intake and body weight gain in wild type mice [76,77]. IL-18 also increases insulin sensitivity in mice and 3T3 cells [76,78] (reviewed in [79]). *Nlrp1* knockout mice, which are IL-18 deficient, shows increased adipose tissue mass, adipocyte size, and lipid deposition in their livers [80]. IL-18 signals through STAT3 and activates AMPK in muscles [81], which elicit positive metabolic effects by enhancing fatty acid oxidation and reducing obesity [81]. The effect of IL-18 on adipogenesis and lipid metabolism must be further investigated.

Meanwhile, IL-33 provides protection against obesity-induced inflammation and insulin resistance in mouse models and humans [70,82]. IL-33 is abundant in human adipose tissues, including adipocytes, endothelial cells, and fibroblast-like reticular cells [83–85]. It potently induces type 2 immunity and inflammation, which are mediated by IL-4, IL-5, IL-9, and IL-13. Hence, IL-33 inhibits the infiltration of pro-inflammatory immune cells into the adipose tissue by maintaining the number and functions of $ST2^+$ cells and M2 macrophages [12,86]. ST2 is the receptor for IL-33 and is highly expressed in group 2 innate lymphoid cells (ILC2s) and T helper 2 (Th2) cells [11]. In rodent models, IL-33 or ST2 deficiency causes aggravated obesity and insulin resistance and decreased ILC2s, eosinophils, Tregs, and M2 polarized macrophages in white adipose tissue [87]. In contrast, administration of recombinant IL-33 into diabetic (ob/ob) mice ameliorates obesity and diabetes mellitus [12]. Moreover, IL-33 may influence adipogenesis by targeting adipocyte precursors. An *in vitro* study shows that IL-33 treatment reduces expression of adipogenic genes and inhibits aldosterone-induced adipose differentiation and inflammation [11]. Further studies are needed to elucidate the pathway by which IL-33 influences differentiation of adipocyte precursors.

IL-37 acts as an anti-inflammatory cytokine. In humans, elevated IL-37 mRNA levels in adipose tissues are positively correlated with increased insulin sensitivity and decreased inflammatory levels [15]. Moreover, IL-37 directly activates AMPK signaling that reduces adipocyte differentiation in SGBS cells [15]. These results indicate that IL-37 affects adipogenesis and insulin sensitivity by regulating the inflammatory response and by directly targeting preadipocytes.

Gp130 cytokines

The IL-6 family or gp130 cytokines, contains multiple members, including IL-6, IL-11, IL-27, ciliary neurotrophic factor (CNTF), cardiotrophin-1 (CT-1), cardiotrophin-like cytokine (CLC), leukemia inhibitory factor (LIF), oncostatin M (OSM), and neuropoietin (NP) [88]. All members of gp130 cytokines form homodimers or heterodimers with gp130 receptors to facilitate signaling transduction. Most gp130 cytokines bind to their specific α-receptors (IL-6Rα); this induces dimerization of β-receptors before intracellular signaling [88].

Binding of IL-6 to IL-6Rα leads to the generation of a

receptor complex and signal transmission into cells. The intracellular signaling process is initiated by the recruitment and activation of Janus-activated kinase/signal transducer and activator of transcription factor (JAK/STAT) molecules, which then activate the transcription factors of various genes [89]. Meanwhile, soluble IL-6Rα (sIL-6Rα) exists apart from membrane-bound IL-6Rα [90]. IL-6 can bind to sIL-6Rα to form a ligand/receptor complex [90]. The complex transduces signals in cells with membrane-bound gp130Rβ without the need of a transmembrane IL-6Rα [90]. This process is known as "trans-signaling." IL-6 is pro-inflammatory when it trans-signals but has beneficial effects on energy metabolism when it signals via the transmembrane IL-6Rα [90]. IL-6 is recognized as an important cytokine in the chronic inflammatory state of obesity. During obesity, IL-6 production in adipose tissues is consistently elevated, especially in insulin resistance populations [16,91]. This condition is associated with reduced subcutaneous adipogenesis capacity, decreased PPARγ and C/EBPα expression, and increased GATA3 transcription [16]. Accordingly, treatment with 20 ng/mL IL-6 causes diminished rate of adipogenesis in preadipocytes from insulin-sensitive and insulin-resistant subjects [16]. Drugs, such as chito-oligosaccharide and D-dopachrome tautomerase inhibit adipogenesis by inducing IL-6 expression in preadipocytes [18,92].

The effect of IL-6 on insulin sensitivity is still debatable. In 3T3-F442A and 3T3-L1 cells, long-term (8 days) treatment with IL-6 reduces insulin-induced lipogenesis and glucose transportation [17]. Moreover, Carey *et al.* reported that IL-6 reduces obesity-induced insulin resistance in muscle cells by activating AMPK [93]. In insulin resistant, obese IL-$6^{-/-}$ mice [94,95], intracerebroventricular, but not intraperitoneal IL-6 treatment increases energy expenditure [94]. These results suggest that IL-6 has different effects on energy metabolism in different body compartments, with centrally acting IL-6 exerting anti-obesity effects in rodents [94]. Different IL-6 dosage, cell types or animal models may have contributed to the inconsistent results [90].

The effects of other Gp130 cytokines on adipogenesis and insulin resistance are not fully elucidated. In earlier studies, IL-11 was found to inhibit preadipocyte differentiation and lipid accumulation in human long-term bone marrow cultures [19]. Though CNTF shows positive effects on adipocyte metabolism [96], there is no direct evidence for the influence of CNTF on adipogenesis. NP and CNTF have nearly similar structures and functions [97]. In cultured 3T3-L1 pre-adipocytes, NP inhibits adipogenesis by reducing the expression of PPARγ and adiponectin [22]. Moreover, NP increases insulin resistance by inhibiting insulin signaling proteins such as IRS-1 and Akt [22]. In general, the effects of IL-11, CNTF, and NP on adipogenesis only draw minimal attention. Future studies will be needed to assess the effects of gp130 cytokines on adipogenesis and metabolic disorders.

IL-15, IL-4, and IL-10

IL-15 is a member of a widely expressed immunoregulatory cytokine family [98] and mainly acts as a pro-inflammatory cytokine [98]. IL-15 can activate multiple immune cells, including NK cells, and promote the release of pro-inflammatory cytokines [98]. IL-15 KO mice show decreased expression of pro-inflammatory mediators, such as TNFα, IL-6, and Ccl-5 in their adipose tissues [99]. The administration of IL-15 in animal models reduces body weight and amount of white adipose tissues [100–102]. These reductions are partially due to decreased lipogenesis and VLDL triacylglycerol uptake [100]. In 3T3-L1 cells, IL-15 inhibits adipogenesis by upregulating α-calcineurin expression, a calcium-dependent serine/threonine phosphatase, and mediates the calcium-dependent inhibition of adipocyte differentiation [24,103]. IL-15 KO mice show decreased accumulation of fat in the white adipose tissues and increased lipid utilization via adaptive thermogenesis [99]. In humans, subcutaneous adipose tissue of obese individuals contains more IL-15 than that of lean individuals. There is also a significant positive correlation between IL-15 and resting lipolysis in subcutaneous adipose tissue [104]. This result indicates that IL-15 partially enhances lipolysis of subcutaneous fat. More studies are needed to fully illustrate the effect of IL-15 on adipose tissue metabolism.

IL-4 can be secreted by lymphocytes, basophils, and mast cells [105]. As a Th2 cytokine, IL-4 plays an important role in the pathogenesis of asthma [106]. However, in mice and human psoriasis, IL-4 attenuates TH17 cell-mediated inflammation by selectively suppressing IL-23 production in antigen-presenting cells [107]. It also acts as an anti-inflammatory cytokine in systemic sclerosis [108]. Therefore IL-4 can act as either a pro-inflammatory or an anti-inflammatory cytokine in various diseases. IL-4 inhibits adipogenesis by downregulating PPARγ and C/EBPα expression in 3T3-L1 cells [23]. It also inhibits adipogenesis at the early phase of 3T3-L1 cell differentiation. This effect is not observed in STAT6 knockouts, indicating that the anti-adipogenesis effect of IL-4 is achieved through the STAT6 pathway [23].

IL-10 is secreted by multiple cell types including T-helper cells (THs), monocytes/macrophages, dendritic cells, and B cells. IL-10 suppresses inflammation through various mechanisms. The effect of IL-10 on lipid and glucose metabolism is not well studied. In adipose tissue

environments, stable overexpression of IL-10 in the macrophage cell line promotes a macrophage phenotypic switch from M1 to M2 phenotype [109]. This result indicates that IL-10 may improve insulin resistance and metabolic syndrome by suppressing inflammation.

IL-7, IL-17, and IL-34t

IL-17 is a pro-inflammatory cytokine that plays a key role in anti-microbial host defense response and autoimmune diseases [110]. IL-17 signals through a multimeric receptor complex composed of IL-17RA and IL-17RC [26]. In adipose tissue, IL-17 is predominantly produced by γδ T cells [28]. Obesity induces the proliferation of IL-17 that produces adipogenesis-inhibiting Th17 cells [26]. IL-17 and IL-17RA-deficient mice exhibit increased body weight, and young IL-17 knockout mice show enhanced glucose tolerance and insulin sensitivity [28]. 3T3-L1 preadipocytes show inhibited adipogenesis after IL-17A or IL-17F treatment [111]. A mechanistic study revealed that IL-17 alters adipogenesis by regulating the expression of Krüppel-like family (KLF) members, such as KLF15, KLF2, and KLF3, and blocking PPARγ and C/EBPα [27]. Furthermore, IL-17A induces COX-2 production, which then activates prostaglandin E2 (PGE2) expression in mesenchymal stem cells derived from human bone marrow (hBM-MSCs) [112]. This process inhibits adipocyte differentiation [112].

IL-7 is a pro-inflammatory cytokine associated with the survival, proliferation, and maturation of B lymphocytes and T lymphocytes [113]. Elevated IL-7 expression is observed in obese populations [114]. IL-7-receptor-deficient (IL-7r KO) mice exhibit decreased body weight, reduced visceral fat, and decreased levels of PPARγ2 and C/EBPα [25], and IL-7r KO mice show reduced pro-inflammatory cytokine production and macrophage infiltration in white adipose tissue and has improved glucose tolerance and insulin sensitivity [25].

IL-34 acts as an alternative ligand for colony-stimulating factor-1 (CSF-1) receptor [115]. IL-34 and CSF-1 are important regulatory factors of monocyte differentiation, proliferation, and survival [115–117]. IL-34 levels in adipose tissues are significantly elevated in obese people with expression levels being markedly elevated during adipogenesis [29]. Recombinant human (rh) IL-34 promotes lipid accumulation and improves insulin sensitivity at 100 ng/mg in human isolated adipocytes [29].

Interferons

Interferons (IFNs) represent a family of multifunctional immunoregulatory cytokines which is widely used in the treatment of cancer and virus infection [118,119]. Its mode of action usually involves binding receptors and activating STAT signaling complexes [120]. IFNs influence insulin sensitivity, glucose tolerance, and lipid metabolism [121].

IFN-γ knockout mice exhibit systemic inflammation, decreased size of VAT adipocytes, and enhanced insulin sensitivity, despite the fact that IFN-γ is a pro-inflammatory cytokine [122]. Previous studies on MSCs and 3T3-L1 cells demonstrated that IFN-γ treatment considerably reduces the rates of adipocyte differentiation and lipid deposition [31,123]. The adipogenic marker, PPARγ, is downregulated in MSCs subjected to IFN-γ treatment [31]. JAK/STAT signaling pathways mediate the inhibitory effect of interferons [30,124]. In another study, it was found that IFN-γ reduces adipogenesis in 3T3-L1 cells by directly inhibiting the activation of hedgehog signaling [32]. In adipocytes, IFN-α inhibits PPARγ, C/EBPβ, and C/EBPα [30] and induces apoptosis in adipose tissue cells [125]. Nevertheless, the importance of JAK/STAT signaling and hedgehog signaling pathways that mediate IFN must be further studied.

Monocyte chemotactic protein-1

Monocyte chemotactic protein-1 (MCP-1) is a member of the CC chemokine family and a potent chemotactic factor for monocytes. It is expressed by various cell types, including adipocytes, macrophages, and endothelial cells [126]. CC chemokine receptors 2 (CCR2) is the receptor for MCP-1. In severely obese subjects, MCP-1 protein levels are higher in abdominal fat than in subcutaneous fat and the rate of macrophage infiltration into abdominal adipose tissue increases [127]. In human primary adipocytes, chronic treatment of hypoxic adipocytes with TNFα resulted in a higher secretion of the chemokines, MCP-1 and IL-8, while attenuated TNFα-induced signaling caused by reduced expression of TNFR1 or Tacrolimus (FK506, an immunosuppressor) results in reduced MCP1 secretion [128,129].

MCP-1 has multiple effects on adipose tissue inflammation, energy metabolism, and obesity. In mice modela, treatment with MCP-1 results in insulin resistance [130]. In mice fed with a high-fat diet, *Ccr2* deficiency or treatment with CCR2 antagonist reduces macrophage accumulation and inflammation in adipose tissues and improves insulin sensitivity [131]. In 3T3-L1 cells, the administration of MCP-1 promotes the expression of the C/EBP family and PPARγ. The adipogenic potential of MCP-1 is not associated with PPARγ expression [33]. MCP-1 treatment also increases adipose tissue mass *in vivo* in a murine tissue engineering model [34]. The effect of MCP-1 occur via the induction of MCP-1 induced protein (MCPIP), which promotes adipogenesis via oxidative stress, endoplasmic reticulum (ER) stress, and autophagy [132].

Different adipogenesis processes in humans and mice

Owing to the limitations of human clinical trials, mouse models are frequently used in the investigation of adipogenesis. Previous studies have shown that PPARγ and C/EBPα are key transcriptional regulators of both human and mouse adipogenesis [133]. Genome wide study of the binding sites of these two regulators shows that the overall regulatory regime of PPARγ and C/EBPα between human and mouse adipocytes is highly conserved, including their potential direct cooperativity by binding to adjacent sites [133]. Although the functional targets of the transcription factors important in adipogenesis are conserved, most binding sites and regulators are species-specific [133–135]. LIM domain only 3 (LMO3) is a human visceral-fat-specific and glucocorticoids-dependent positive regulator of adipogenesis [135]. These findings may partially explain the difference between the results from mouse models and human trials. The mechanisms by which cytokines influence the species-specific regulators of adipogenesis remain unknown and whether this influence occur requires further investigation.

Crosstalk between cytokines and other pathways important for metabolism

Cytokines are associated with other essential molecules for metabolism, particularly leptin, resistin, and adiponectin. On the one hand, cytokines influence the secretion of these molecules, thereby influencing metabolism. On the other hand, these molecules can either promote or inhibit the secretion of other cytokines, therefore regulating the inflammatory states of the human body.

Leptin is the product of the obese (ob) gene. Several leptin receptor (LEPR) isoforms are present in humans [136]. Leptin binds to the long form of LEPR and activates the JAK/STAT signaling pathway [136]. Ob/ob mice that lack leptin exhibit hyperphagia, obesity, and insulin resistance [137]. In patients with lipodystrophy, leptin improves glycemic control and decreases triglyceride levels [138]. Previous studies regarding the expression of leptin within the inflammatory models of human-cultured adipocytes produced different results. In 3T3-L1 cells, human bone marrow adipocytes, adipocytes from subcutaneous white adipose tissue, and omental adipocytes from morbidly obese people, TNFα significantly decreases leptin expression [139–143]. However, a study shows that TNFα stimulates leptin expression in adipocytes from human omental adipose tissue. An *in vivo* study showed that TNFα also induces leptin expression in Syrian hamsters and C57BL/6 mice [144,145]. These different results may be explained by the use of different cell models, locality of adipose tissue, and duration and dose of exposure to the cytokines [139]. The different results from *in vitro* and *in vivo* studies also indicate that pro-inflammatory cytokines may regulate leptin secretion through other means apart from directly binding to the receptors of target cells.

In discrete mouse colon cells, leptin upregulates pro-inflammatory cytokines, such as IL-6 and IL-1β [146] and promotes the activation and proliferation of circulating monocytes, thereby inducing IL-1, TNFα, and IL-6 production [136]. Furthermore, leptin enhances IL-18 secretion in cultured human THP-1 monocytes through caspase-1 activation [147]. It also polarizes T helper cell subsets towards the TH1 phenotype that secretes IFN-γ [136].

Adiponectin is an adipocyte-specific secretory protein [148]. Adiponectin signals through adiponectin receptors (AdipoRs). Adiponectin stimulates adipogenesis, attenuates inflammation, and regulates rates of lipolysis and fatty acid oxidation [148]. There are opposing effects of adiponectin with TNFα on lipid metabolism and inflammation (reviewed in [149,150]). Adiponectin is negatively regulated by TNFα and IL-6 [149]. In turn, TNFα production is negatively regulated by adiponectin [151]. Adiponectin also induces the production of anti-inflammatory cytokines like IL-10 and IL-Ra [149].

Resistin is also an adipokine and has been associated with inflammatory response. Resistin gets its name from its resistance to insulin function. In adipose tissues, resistin is predominantly expressed in the macrophages [152]. In rat pancreatic acinar AR42J cells, it stimulates TNFα and IL-6 production through NF-κB activation [152].

Adipogenesis, inflammation, and metabolic disorder

Adipose tissue expansion can be accomplished by increasing the volume of each adipocyte (hypertrophy) or recruiting new adipocytes from precursors (hyperplasia) [2]. In adults, adipose tissue expands mainly by hypertrophy in spite of only ~10% adipocyte turnover annually [153]. Although obesity is closely related to T2DM, approximately 30% of the obese population do not show insulin resistance and are considered as metabolic healthy obese [154]. The metabolic consequences of obesity are influenced by the depots of fat and mode of adipose tissue expansion (reviewed in [2]). The storage of excess energy through lipid accumulation in subcutaneous adipose tissues is beneficial to metabolic health [155]. Preadipocytes from subcutaneous adipose depots exhibit greater potential for proliferation and adipogenesis than those

from visceral depots [156–158]. Moreover, TNFα and IL-6 levels in subcutaneous fat are much lower than those in visceral fat [155].

Low grade chronic inflammatory state commonly exists in obese populations. Compared with normal adipocytes, hypertrophic adipocytes secrete more free fatty acids (FFAs) and adipokines (for example, MCP-1, TNFα, IL-1β, and IL-6), and recruit more pro-inflammatory M1-like macrophages and other immune cells [157,159]. This effect is caused by multiple factors, including hypoxia, ER stress in adipocytes, activation of Toll-like receptors (TLRs) by FFAs, and cell apoptosis [160–163].

Although acute inflammatory response promotes ECM-remodeling and angiogenesis, which benefits adipogenesis [164], the chronic inflammation of adipose tissue has been considered closely associated with insulin resistance and inhibition of adipogenesis [165]. During the development of obesity, the adipogenesis of subcutaneous adipose tissues can be inhibited by pro-inflammatory cytokines, such as TNFα, IL-1β, and IL-6. These pro-inflammatory cytokines are produced by stromal vascular cells, including adipose tissue macrophages and adipocytes [4,70]. As a result, adipocyte turnover and adipose tissue expansion are blocked by these pro-inflammatory cytokines [165]. The abdominal subcutaneous tissue of obese individuals is characterized by decreased number of pre-adipocytes, enlarged mature adipocytes, and elevated MAP4K4 levels [7,166]. MAP4K4, which inhibits adipogenesis, can be induced by TNFα [7,166]. When the hyperplastic expandability of subcutaneous adipose tissues is constrained by chronic inflammation, excess energy is stored by the hypertrophy of adipocytes and accumulation of triglyceride, which occur in the liver, muscles, myocardium, and perivisceral depots and will induce insulin resistance and cardiovascular diseases [158,167]. Excess visceral/intra-abdominal fat is considered as an important marker of ectopic storage of fat [168,169]. Moreover, increased abdominal fat is positively associated with increased risk of T2DM and cardiovascular disease [170]. Inflammation, constrain of subcutaneous fat hyperplastic expandability, hypertrophy of adipocytes, accumulation of visceral fat, and ectopic fat storage are closely associated, and their combined effects exacerbate the comorbidities of obesity [171,172].

Convergent evidence supports that pro-inflammatory cytokine antagonists improve glucose and lipid metabolism in T2DM patients. The inhibitory effect of TNFα on lipid accumulation in adipocytes is blocked by the inhibitors of NF-κB and IκBα [173]. In clinical studies focused on rheumatoid arthritis (RA) and psoriasis patients, treatment with TNFα antagonists, such as etanercept, infliximab, and adalimumab, improves response to insulin [174–176]. A retrospective cohort study published in 2011 showed that TNF inhibitor or hydroxychloroquine treatment significantly reduces the risk of DM in patients with RA and psoriasis compared with using other non-biological disease modifying anti-rheumatic drugs (DMARDs) [177]. In Crohn's disease (CD) patients, infliximab maintenance therapy has no adverse effect on lipid metabolism and is accompanied by a decrease in blood glucose and HbA1c concentrations [178]. Nevertheless, the effects of anti-TNFα therapy on patients with inflammatory diseases and patients with metabolic syndrome but without overt inflammatory disease must be determined. A mechanism study reveals that processing of IL-1β requires cleavage of pro IL-1β by caspase-1, which is regulated by nucleotide-binding oligomerization domain-like receptor, pyrin domain-containing (NLRP3) inflammasome [179]. Caspase-1 deficiency results in increased insulin sensitivity in mice and increases the production of metabolically active adipocytes; furthermore, treatment with caspase-1 inhibitors significantly improves the insulin sensitivity of obese mice [180]. According to a review by Donath, several IL-1β inhibitors, such as IL-1 receptor antagonists (anakinra) and IL-1β-specific antibodies (canakinumab), improve T2DM status with good tolerance and no severe adverse effect [181]. Canakinumab, an IL-1β-specific monoclonal antibody, is the first and only drug that selectively targets inflammation and significantly reduces cardiovascular risk in patients with CVA history. Canakinumab, in combination with standard of care therapy, reduces cardiovascular risk in people with CVA history and inflammatory atherosclerosis (hsCRP level $\geqslant$ 2 mg/L) during the 3.8 years of median follow-up time (Phase III Canakinumab Anti-inflammatory Thrombosis Outcomes Study-NCT01327846. https://www.novartis.com/news/media-releases/Novartis-phase-iii-study-shows-acz885-canakinumab-reduces-cardiovascular-risk). Although lipid and lipid-associated cardiovascular risk markers improve after treatment with TNFα antagonists (adalimumab) and IL-6 antagonists (tocilizumab), the clinical significance is still unclear and needs further study [182].

For T2DM patients, hyperlipidemia is the highest risk factor for atherosclerosis [183,184]. Moreover, given that more than 60% of T2DM patients die of cardiovascular complications [185] and 70% suffer from NAFLD [186,187], the management of lipid metabolism can be a prior consideration. As complications of T2DM such as atherosclerosis and NASH progress with time, reducing blood glucose per se may not reverse these diseases, and drugs targeting lipid metabolism may be more effective in managing T2DM complications. T2DM patients can benefit from statins, which can significantly reduce the risk of ASCVD [188]. However, statins increases insulin resistance and diabetes risks by inhibiting the secretion of insulin and interfering with the insulin signaling pathway (reviewed in [188]). Therefore, risk–benefit assessment and patient preference should be considered prior to the administration of statin for ASCVD therapy [189].

Conclusions

We summarized the cytokines that influence adipogenesis. Low grade chronic inflammation commonly exists in obese populations. In T2DM, obesity and insulin resistance result in the persistent production of pro-inflammatory cytokines, such as TNFα, IL-1β, and IL-6, which typically inhibit adipogenesis. During overnutrition, the restricted recruitment of new adipocytes may result in adipocyte hypertrophy, ectopic fat accumulation, and insulin resistance, which in turn may lead to atherosclerosis and NAFLD. Moreover, pro-inflammatory cytokine antagonists, such as infliximab and etanercept, improve glucose and lipid metabolism in T2DM patients [174–176]. Future investigations on the relationship between cytokines and adipogenesis are expected to lead to the improvement of management strategies for T2DM and other comorbidities of obesity.

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Compliance with ethics guidelines

Ning Jiang, Yao Li, Ting Shu, and Jing Wang declare that they have no conflicts of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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