



# Cytokines and Abnormal Glucose and Lipid Metabolism

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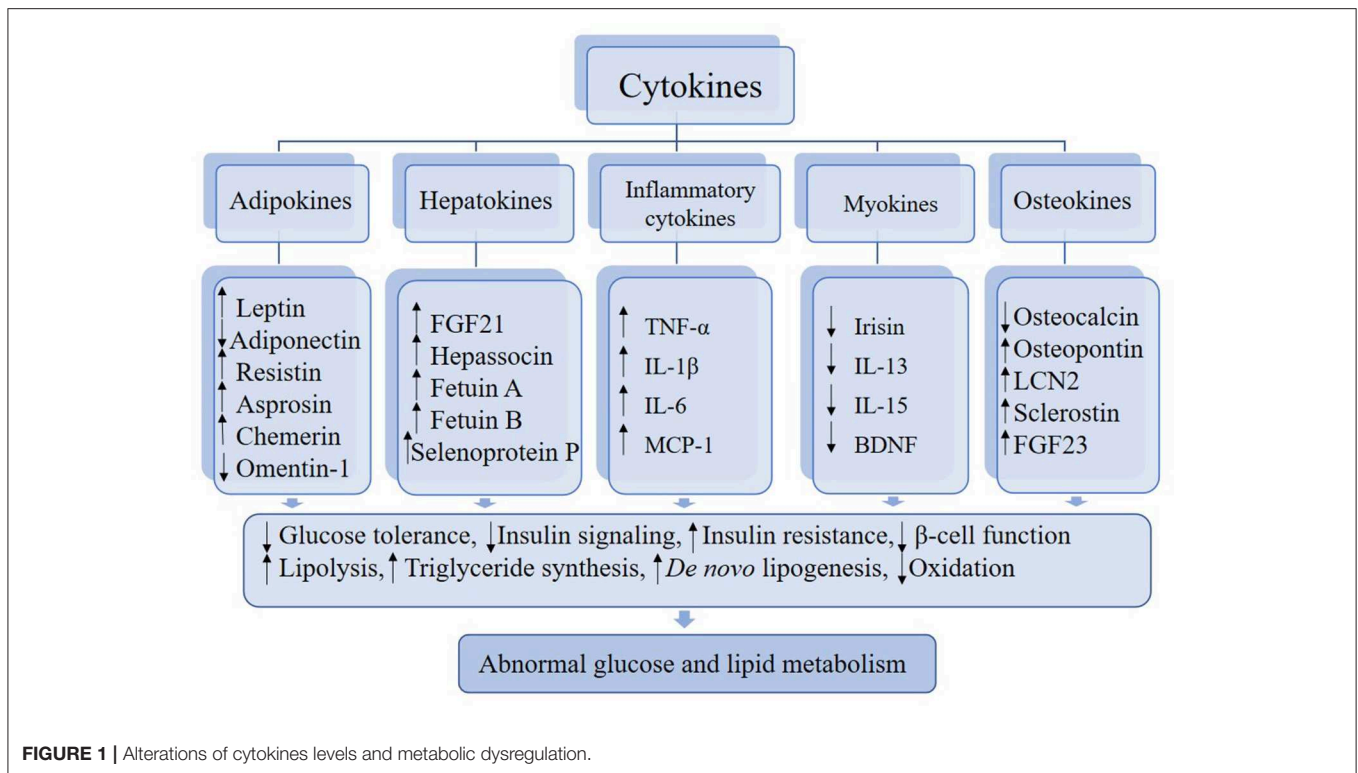
Clear evidence indicates that cytokines, for instance, adipokines, hepatokines, inflammatory cytokines, myokines, and osteokines, contribute substantially to the development of abnormal glucose and lipid metabolism. Some cytokines play a positive role in metabolism action, while others have a negative metabolic role linking to the induction of metabolic dysfunction. The mechanisms involved are not fully understood, but are associated with lipid accumulation in organs and tissues, especially in the adipose and liver tissue, changes in energy metabolism, and inflammatory signals derived from various cell types, including immune cells. In this review, we describe the roles of certain cytokines in the regulation of metabolism and inter-organ signaling in regard to the pathophysiological aspects. Given the disease-related changes in circulating levels of relevant cytokines, these factors may serve as biomarkers for the early detection of metabolic disorders. Moreover, based on preclinical studies, certain cytokines that can induce improvements in glucose and lipid metabolism and immune response may emerge as novel targets of broader and more efficacious treatments and prevention of metabolic disease.

**Keywords:** cytokine, glucose metabolism, lipid metabolism, insulin resistance, inflammation

## INTRODUCTION

Over the decades, overnutrition coupled with a sedentary lifestyle has led to a striking increase in metabolic diseases, such as type 2 diabetes (T2D) and non-alcoholic fatty liver disease (NAFLD). Some organs and tissues (e.g., adipose, liver, muscle, skeleton) secrete specific cytokines for inter-organ communication, and the production and secretion of these cytokines alter during nutritional stress and physical activity. Recent studies have shown that certain factors participate in glucose and lipid metabolism (1–4), and thus may associate with metabolic disorders.

In this review, we describe certain cytokines that are involved in abnormal glucose and lipid metabolism (**Figure 1**). Based on the most recent literature, we delve into the roles of these cytokines in the regulation of metabolism and inter-organ signaling (**Table 1**) with particular focus on the relation to pathophysiological aspects of metabolic disease. Finally, considering the emerging data supporting the contributions of various cytokines to metabolic disorders, we discuss the potential for these factors to emerge as biomarkers for the early detection of metabolic disorders and as novel approaches for therapy.



**FIGURE 1** | Alterations of cytokines levels and metabolic dysregulation.

## ADIPOKINES

The adipose tissue is not only an inert repository of excess energy but also a complex, highly active metabolic endocrine organ that secretes numerous cytokines, which are collectively termed adipokines (148). The endocrine functions of adipose tissue are induced by secreted proteins stimulated by metabolic effects and enzymes involved in the metabolism of steroid hormones (148). Most, but not all, adipokines are peptides or proteins with hormone-like properties that signal the functional status of adipose tissue to targets in the brain, liver, muscle, pancreas, immune system, and other tissues (149). A portion of the adipokines have been confirmed to directly or indirectly affect glucose and lipid metabolism, as well as insulin sensitivity through modulation of insulin signaling (148).

**Abbreviations:** T2D, type 2 diabetes; NAFLD, non-alcoholic fatty liver disease; MetS, metabolic syndrome; CNS, central nervous system; FFA, free fatty acids; BMI, body mass index; HDL, high-density lipoprotein; VLDL, very low-density lipoprotein; HFD, high-fat diet; WAT, white adipose tissue; FGF21, fibroblast growth factor 21; IRS1, insulin receptor substrate 1; TNF- $\alpha$ , tumor necrosis factor  $\alpha$ ; IL, Interleukin; MCP-1, monocyte chemoattractant protein 1; NASH, non-alcoholic steatohepatitis; SREBP1C, sterol regulatory element-binding protein 1; ApoB, apolipoprotein B; BDNF, brain-derived neurotrophic factor; ucOC, undercarboxylated osteocalcin; LCN2, Lipocalin 2; PPAR, peroxisome proliferator-activated receptors; PKA, protein kinase A; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; GLUT, glucose transporter.

## LEPTIN

Leptin, the product of the obese gene (*ob*; also known as *Lep*), is an adipocyte-derived hormone, which is responsible for the regulation of feeding behavior and energy homeostasis through the central nervous system (CNS) (150, 151).

Leptin promotes the oxidation of fatty acids through its stimulation of Adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) phosphorylation and activation (5). It also enhances insulin sensitivity in the peripheral tissues, which is mediated by the central activation of the phosphoinositide 3-kinase (PI3K)/Akt pathway (6). Moreover, leptin stimulates the uptake of glucose and prevents the accumulation of lipids in non-adipose tissues, which can result in functional impairments known as "lipotoxicity" (7). The leptin deficient mice (*ob/ob* mice) exhibited hyperphagia, obesity and insulin resistance, while the administration of leptin in leptin lacking mice reverses these alterations (152).

In humans, the congenital leptin deficiency leads to significant hyperphagia, early-onset extreme obesity, and hormonal and metabolic disturbances (153). Consistent with mice studies, administration of recombinant leptin effectively improved metabolic disorders in patients with lipodystrophy or congenital leptin deficiency (154, 155). Notably, leptin concentrations are significantly increased in obesity and T2D (156), and positively correlated with adipose mass, indicating the occurrence of leptin resistance (157). Further investigations and experimentations need to be done to shed light on molecular mechanisms of leptin resistance.

Leptin exerts potent anti-diabetic actions, independent of its effects on body weight. Indeed, long-term leptin administration could significantly improve glycemic control, insulin sensitivity, and lipid metabolism in mice with T2D (8, 158). However, data from clinical trials failed to find that leptin can effectively improve insulin sensitivity in T2D people with severe obesity (9, 159). Nevertheless, due to the fact that not all T2D subjects are overly obese, an issue is: does administration of leptin improve insulin sensitivity in non-obese, leptin-sensitive, T2D individuals?

## ADIPONECTIN

Adiponectin is a peptide predominantly expressed in white adipose tissue (WAT), and also produced in hepatocytes during stress (10, 11). Contrary to other adipokines, adiponectin is negatively associated with fat mass (160).

The powerful insulin-sensitizing role of adipokines is due, in part, to its binding to cognate receptors, such as adiponectin receptor (AdipoR)1 and AdipoR2, subsequently leading to activation of AMPK and peroxisome proliferator-activated receptors (PPAR)- $\alpha$  signaling pathways (10). Moreover, adiponectin has an anti-steatotic effect on the hepatocytes, due to increases in free fatty acid (FFA) oxidation, and reduces FFA influx, *de novo* lipogenesis and gluconeogenesis (12). Notably, adiponectin protects hepatocytes from apoptosis, a hallmark of NAFLD, by inhibition of c-Jun NH2 terminal kinase (161). In addition, adiponectin exerts anti-inflammatory and anti-fibrotic action though acting on HSC, Kupffer, and possibly sinusoidal cells (162). In mice, administration of adiponectin exhibits glucose-lowering effects and improves insulin resistance, while adiponectin-deficient mice suffer from insulin resistance and diabetes (163). More recently, a study reported that AdipoR1 regulates healthy longevity through the activation of AMPK in skeletal muscle, which in turn activates SirT1 (13). Similarly, another study in *C. elegans* showed that the adiponectin receptor (PAQR-2) signaling acts as a key player linking low temperature with autophagy to extend lifespan (164).

High adiponectin levels were associated with a markedly reduced relative risk of T2D (14). Circulating adiponectin levels, as well as those of AdipoR1/R2 expression, are decreased in the conditions of obesity, T2D and NAFLD (15). Given that the US Food and Drugs Administration has not yet approved any therapies for the treatment of NAFLD and disease management is concentrated on treatment of common comorbidities, adiponectin may be a promising therapeutic target for NAFLD. Further experimental investigations are needed to estimate the efficacy and safety of adiponectin therapy in patients with NAFLD.

## RESISTIN

Resistin (named after “resistance to insulin”) is a member of the family of resistin-like molecules (RELms), also known as “found in inflammatory zone” (FIZZ) (162). In mice, resistin is synthesized mainly in adipocytes (16), whereas in humans, resistin is predominantly produced by macrophages infiltrating

adipose tissue and peripheral blood mononuclear cells, and it is not detectable in adipocytes (165).

Resistin has been shown to induce insulin resistance in mice (9). Cell-based studies revealed that resistin greatly increased hepatocyte very low-density lipoprotein (VLDL) apoB and lipid secretion through enhancing microsomal triglyceride transfer protein (MTP) activity, impairing intracellular insulin signaling and stimulating *de novo* lipogenesis via the sterol regulatory element-binding protein (SREBP)1 and SREBP2 pathways (166). Administration of recombinant resistin impairs glucose tolerance and insulin sensitivity in normal mice, whereas treatment of anti-resistin antibody improves these metabolic abnormalities (16). Mice lacking resistin have low post-fasting blood glucose levels via reduced hepatic glucose production (167). And resistin deficiency in ob/ob mice leads to increased obesity due the reduction in metabolic rate without an affect on food intake, but also leads to improved glucose tolerance and insulin sensitivity largely owing to enhancing insulin-mediated glucose disposal, as well as drastically attenuated hepatic steatosis (17, 18).

Resistin expression was increased in subjects with central obesity, T2D and NAFLD (19, 20). Although studies in animal models consistently show that resistin promotes insulin resistance, evidence for this effect in humans is unclear. Thus, further researches are required toward this direction.

## ASPROSIN

Asprosin, the C-terminal cleavage product of profibrillin (encoded by *FBN1*), is a new fasting-induced glucogenic protein hormone produced by WAT and associated with hepatic glucose release (168). Asprosin accelerates hepatic glucose production by activating the G protein-cAMP-protein kinase A (PKA) pathway (169). It also acts as an orexigenic hormone, that activates AgRP neurons to increase food consumption and body weight (170). In mice, a single injection of asprosin caused a swift rise in blood glucose and insulin levels, while a reduction in asprosin and treatment with an asprosin-specific monoclonal antibody improved insulin sensitivity and reduced appetite and body weight (168, 169).

In humans, asprosin-deficient patients showed a reduction in subcutaneous WAT and a unique pattern of metabolic disorders, including partial lipodystrophy, along with decreased plasma insulin while maintaining euglycemia (169). Asprosin concentrations are increased in conditions of obesity and T2D, and are independently associated with levels of fasting glucose and triglycerides (171). It remains unclear whether the asprosin inhibition could be effective management for obesity and T2D. It has not yet been determined that the receptor for asprosin is involved, and the factors regulating its secretion are not clear. Further research is needed to fill these gaps.

## CHEMERIN

Chemerin is an adipokine secreted in an inactive form (prochemerin) and activated through C-terminal cleavage by inflammatory and coagulation serine proteases (172), acting through its receptor, such as the chemerin receptor (ChemR)

**TABLE 1** | Cytokines that involved in glucose and lipid metabolism.

Cytokines	Metabolic actions	Circulating levels	References
<b>Adipokines</b>			
<sup>a</sup> Leptin	Promotes the oxidation of fatty acids, enhances insulin sensitivity, stimulates the uptake of glucose, controls feeding	↑obesity,↑T2D	(5–7)
<sup>a</sup> Adiponectin	Enhances insulin sensitivity, anti-steatotic, anti-inflammatory, anti-fibrotic, regulates healthy longevity	↓T2D,↓NAFLD	(8–12)
<sup>b</sup> Resistin	Induces insulin resistance, increases lipid secretion	↑T2D	(9, 13–16)
<sup>b</sup> Asprosin	Accelerates hepatic glucose production, increases food consumption and body weight	↑obesity,↑T2D	(17–20)
<sup>b</sup> Chemerin	Exacerbates glucose intolerance, impairs insulin signaling and vascular dysfunction	↑T2D,↑NAFLD	(21–28)
<sup>a</sup> Omentin-1	Promotes glucose uptake, improves insulin sensitivity, anti-atherosclerotic	↓T2D, ↓MetS	(29–33)
<b>Hepatokines</b>			
<sup>a</sup> FGF21	Ameliorates pancreatic β-cell function and survival, increases glucose uptake, maintains glucose homeostasis, inhibits lipolysis	↑obesity,↑T2D	(34–40)
<sup>b</sup> Hepassocin	Blocks insulin signaling, induces insulin resistance, exacerbates lipid accumulation	↑NAFLD, ↑T2D	(41–43)
<sup>b</sup> Fetuin A	Causes insulin resistance, pro-inflammatory	↑T2D	(44–53)
<sup>b</sup> Fetuin B	Induces glucose intolerance and insulin resistance	↑NAFLD,↑T2D	(54, 55)
<sup>b</sup> Selenoprotein P	Impairs insulin signaling and glucose homeostasis, increases glucose output	↑NAFLD,↑T2D	(56–59)
<b>Inflammatory cytokines</b>			
<sup>b</sup> TNF-α	Mediates insulin resistance, stimulates of lipolysis, pro-inflammatory	↑T2D	(60–67)
<sup>b</sup> IL-1β	Stimulates triglycerides, cholesterol accumulation, and lipid droplet formation; reduces insulin-stimulated glucose uptake and lipogenesis	↑obesity,↑T2D, ↑NAFLD	(68–80)
IL-6	Has a dual role in modulating insulin action	↑T2D	(62, 81–89)
<sup>b</sup> MCP-1	Induces insulin resistance, elevates hepatic triglyceride content	↑T2D	(90–95)
<b>Myokines</b>			
<sup>a</sup> Irisin	Induces glucose and fatty acid uptake, ameliorates hepatic steatosis, improves insulin resistance, anti-inflammatory, loses weight	↓obesity,↓T2D	(96–103)
<sup>a</sup> IL-13	Increases skeletal muscle glucose uptake, oxidation, and glycogen synthesis	↓T2D	(104, 105)
<sup>a</sup> IL-15	Enhances insulin sensitivity and action, reduces fat mass and adipogenesis, decreases circulating triglycerides and VLDL	↓obesity	(106–110)
<sup>a</sup> BDNF	Enhances insulin signal transduction and fat oxidation	↓T2D	(111–116)
<b>Osteokines</b>			
<sup>a</sup> Osteocalcin	Promotes β-cell proliferation and insulin expression and secretion, favors glucose uptake and utilization in muscle, favors fatty acid uptake and utilization in muscle	↓T2D, ↓MetS	(4, 117–124)
<sup>b</sup> Osteopontin	Induces steatosis, inflammation, insulin resistance, and gluconeogenesis	↑NAFLD	(125–130)
<sup>a</sup> LCN2	Improves insulin sensitivity, decreases body weight and fat mass	↑obesity,↑T2D	(131–135)
<sup>b</sup> Sclerostin	Enhances <i>de novo</i> lipid synthesis and reduces fatty acid oxidation	↑T2D	(136–139)
<sup>b</sup> FGF23	Mediates insulin resistance, stimulates lipolysis	↑T2D	(140–147)

<sup>a</sup>Cytokines that induce positive metabolic effects.

<sup>b</sup>Cytokines that induce negative metabolic effects.

↑Increased circulating levels.

↓Decreased circulating levels.

23 (21). Although chemerin and its receptors exist throughout the human body, the adipose tissue and hepatocytes are major sources of chemerin (22, 23).

Plasma chemerin levels were found to be increased in diet-induced obese mice, and in another study of obese diabetic db/db mice, the chemerin was found to exacerbate glucose intolerance, lower serum insulin levels, and decrease tissue glucose uptake (24, 25). Importantly, ChemR23 knockout mice presented with reduced adiposity and body mass, and the chemerin levels were shown to be reduced by weight loss and fat reduction (26). In addition, antagonism of the chemerin/ChemR23 system in a T2D animal model was found to ameliorate vascular dysfunction and normalize insulin signaling via redox-sensitive and Akt-dependent pathways (27). However,

a study reported that isolated islets and perfused pancreas from chemerin-deficient mice revealed impaired glucose-dependent insulin secretion, and conversely, chemerin transgenic mice revealed enhanced insulin secretion and improved glucose tolerance (28).

In humans, the circulating chemerin concentration is significantly elevated among individuals with obesity and/or T2D (173) and NAFLD (29), and the levels of chemerin correlate with levels of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-6 (30, 31). Targeting chemerin/ChemR23 may be a potential therapeutic strategy to improve insulin resistance and vascular function in obesity-associated diabetes.

## OMENTIN

Omentin-1, also known as intelectin-1, is a novel adipokines mainly expressed in visceral adipose tissue and is the major circulating form of omentin (32). The levels of omentin-1 is downregulated by glucose and insulin, and upregulated by fibroblast growth factor-21 and dexamethasone (33).

Omentin-1 is known to have key roles in the maintenance of body metabolism and insulin sensitivity, and has anti-inflammatory, anti-atherosclerotic, and cardiovascular-protective effects via AMP-activated protein kinase/Akt/NF- $\kappa$ B/mitogen-activated protein kinase (ERK, JNK, and p. 38) signaling (33). In cultured human vascular cells, exogenous omentin promoted glucose uptake, and improved the insulin activity and anti-inflammatory response (174).

In humans, serum omentin-1 levels are significantly decreased in patients with obesity (54), T2D (175), and metabolic syndrome (MetS) (34). And plasma omentin-1 levels were inversely correlated with body mass index (BMI), waist circumference, leptin levels, and insulin resistance, and positively correlated with adiponectin and high-density lipoprotein (HDL) levels (54). Thus, circulating omentin-1 levels may serve as a biomarker of related metabolic disorders.

## HEPATOKINES

It is well-established that the liver is a crucial organ in energy stores, including systemic glucose and lipid metabolism (35). Hepatic fat content is an excellent marker of the metabolic abnormalities, and hepatic steatosis has a causal role in the induction of a series of metabolic disease, such as NAFLD, MetS, and T2D (1).

Hepatokines are proteins either uniquely or predominantly produced by the hepatocytes; upon secretion, certain hepatokines influence metabolic processes via autocrine, paracrine, and endocrine signaling pathways in the liver and in non-hepatic tissues (1). Under some circumstances, especially the condition of liver steatosis, the hepatokine production and secretion profile can be altered (36). These factors show positive or negative metabolic effects, with some improving metabolic variables, while others lead to metabolic dysfunction and inflammation (37).

## FIBROBLAST GROWTH FACTOR (FGF)21

FGF21, a member of the FGF superfamily, is a secreted protein expressed mainly in the liver (38). In general, it serves as a metabolic regulator and is known to induce positive metabolic functions that regulate insulin sensitivity and lipid and energy metabolism (39).

In adipose tissue, FGF21 inhibits lipolysis (40) and increases insulin-dependent glucose uptake via up-regulated expression of glucose transporter 1(39). FGF21 preserves pancreatic  $\beta$ -cell function and survival by activation of the extracellular signal-regulated kinase (ERK) 1/2 and Akt signaling pathways (152). Moreover, FGF21 induces fasting gluconeogenesis via the brain-liver axis, to maintain glucose homeostasis during prolonged fasting (176). FGF21 knockout mice showed severe

hypoglycemia and defective hepatic gluconeogenesis, and these impairments reversed after injection of FGF21 (176). In obese mice, administration of recombinant FGF21 has been shown to alleviate hepatic steatosis, induce browning of WAT, increase energy expenditure, improve insulin sensitivity, and restore glucose tolerance (39, 177).

Circulating FGF21 levels are elevated in subjects with obesity, T2D (37), and MetS (41), and positively correlate with triglycerides, fasting insulin, and insulin resistance (41). Serum levels of FGF21 is a sensitive marker of the degree of steatosis (42). Consistent with the mice studies, the administration of FGF21 analog shows good performance in patients with obesity and T2D (43, 44). Hence, the favorable metabolic action of FGF21 treatment appears to be in contrast with the elevated levels of FGF21 detected in obese and T2D subjects. It remains unclear whether these conflicting findings suggest that high levels of FGF21 are produced in these cases to compensate for underlying metabolic stress, or whether FGF21 resistance is present in the context of high levels of FGF21 associated with obesity and T2D.

## HEPASSOCIN

Hepassocin, also called fibrinogen-like protein 1 and hepatocyte-derived fibrinogen-related protein 1 (HFREP1), is a liver-specific growth factor that has been found to participate in the regulation of proliferation of hepatocytes and regeneration of the liver (45). High glucose regulates the expression of hepassocin, and the fasting glucose concentrations is an independently associated factor for the plasma hepassocin levels (46).

Cell-based studies in HepG2 hepatocellular carcinoma cells revealed that hepassocin can block insulin signaling and induce insulin resistance through an ERK1/2-dependent signaling pathway (46). In mice, both the hepatic over-expression of hepassocin and administration of recombinant hepassocin lead to exacerbated hepatic lipid accumulation and induction of insulin resistance in both liver and skeletal muscle tissues (46). Conversely, knockdown of hepassocin in HFD-fed mice led to improved glucose utility and insulin sensitivity, and ameliorated impaired insulin signaling both in liver and skeletal muscle (46).

In humans, circulating levels of hepassocin are increased in prediabetes, T2D, and NAFLD, owing to its association with impaired fasting glucose, glucose intolerance, and insulin resistance (46, 47). Consequently, high hepassocin levels are risk factors for insulin resistance and diabetes, and hepassocin may be a promising biomarker for the detection of prediabetic status.

## FETUIN A

Fetuin A is a glycoprotein expressed predominantly in the liver and has been identified as an endogenous inhibitor of insulin receptors (48). This glycoprotein is an independent risk factor for the development of T2D (49).

Fetuin A impairs insulin action working through its binding to the insulin receptor tyrosine kinase in liver and skeletal muscle, and resulting in decreased rates of autophosphorylation

and downstream insulin signaling cascades (48). Fetuin A also stimulates the production of pro-inflammatory cytokines in adipocytes and macrophages (50). The process involves Fetuin A serving as an endogenous ligand for the Toll-like receptor (TLR) 4, which then enables free fatty acids to activate TLR4 signaling to induce insulin resistance (51). Besides, liver expression of the gene encoding fetuin A positively associates with the expression of key enzymes in glucose and lipid metabolism (52). Mice that knocked out the gene encoding Fetuin A (*Ahsg* gene) were insulin sensitive (53) and resistant to weight gain when fed a HFD (178). Whereas, injection of recombinant fetuin A into mice reduced insulin sensitivity (179).

In humans, circulating levels of fetuin A are elevated in patients with hepatic steatosis (55) and T2D (52); moreover, this increase is correlated strongly and negatively with insulin sensitivity (180). In view of the interaction between increasing plasma concentrations of both FFA and fetuin A resulting in insulin resistance (56), disruption of the fetuin A-TLR4 association may serve as a potential therapeutic strategy for T2D.

## FETUIN B

Fetuin B is the second member of the fetuin family, an endogenous inhibitor of the insulin receptor tyrosine kinase, and is produced primarily in liver tissue (57). Cell-based studies have demonstrated that fetuin B can lead to insulin resistance in myotubes and hepatocytes (36), and *in vivo* studies have shown that administration of fetuin B to lean mice causes glucose intolerance but not insulin resistance (36). Moreover, partial silencing of fetuin B in obese mice improved glucose tolerance, independent of weight loss (36).

In humans, plasma fetuin B levels are increased in obese individuals with hepatic steatosis (36) and T2D, and associated positively with intrahepatic triglyceride and insulin resistance (36, 58). However, the mechanism underlying its role in these pathogenesis remains unclear. Further researches are necessary to shed light on how fetuin B exerts its metabolic effect.

## SELENOPROTEIN P

Selenoprotein P, encoded by the *Sepp1* gene, is a secretory protein produced and secreted primarily by the liver. It is responsible for transporting selenium from the liver to extrahepatic tissues (59). A recent study reported that selenoprotein P regulates insulin action and systemic energy metabolism in rodents and humans (181).

Cell-based studies revealed that administration of purified selenoprotein P resulted in impaired insulin signaling through reduced insulin-stimulated phosphorylation of the insulin receptor and AKT in mouse primary hepatocytes and immortalized myocytes *in vitro*, and increased phosphorylation of insulin receptor substrate 1 (IRS1) at Ser307 (182). In mice, the administration of selenoprotein P induced hepatic and peripheral insulin resistance, whereas both genetic deletion and RNA interference-mediated knockdown of selenoprotein P ameliorated insulin signaling and improved glucose tolerance

(182). Additionally, high circulating levels of adiponectin were observed in *Sepp1* knockout mice, revealing the occurrence of crosstalk between the hepatokine selenoprotein P and the adipokine adiponectin (183).

In humans, selenoprotein P is increased in patients with T2D (182) and NAFLD (181), and is positively correlated with triglycerides, glucose, and insulin resistance (184). However, most of current data comes from small sample clinical studies, thus further prospective large-scale studies are warranted.

## INFLAMMATORY CYTOKINES

The immune system is closely linked to metabolic changes, and components are changed in obesity and T2D (68). The detection of immune cells in metabolic tissues and organs, such as macrophages, has highlighted a dynamic, ongoing crosstalk that exists between immune and metabolism regulatory systems (185). Their interactions are termed “immunometabolism.” Inflammation has emerged as an important pathophysiological factor of T2D, with inflammatory cytokines playing a pivotal role. Inflammatory cytokines characterize an inflammatory state (recently named as “metaflammation”), which is defined by a chronic low-grade inflammation initiated by metabolic and inflammatory cells in response to an excessive energetic nutrient load (186). Some pro-inflammatory cytokines, such TNF- $\alpha$  and IL-1 $\beta$ , take part in disrupting the insulin and lipid signaling pathways, thereby influencing insulin sensitivity and lipid metabolism (60). Promisingly, some treatments targeting pro-inflammatory cytokines displayed improved glucose metabolism and insulin secretion and sensitivity in T2D (61).

### TNF- $\alpha$

TNF- $\alpha$ , a member of TNF family, is a potent pro-inflammatory cytokine and immuno-modulator produced mainly by macrophages and monocytes (62). TNF- $\alpha$  is involved with multiple functions and plays a variety of roles in metabolic disorders (63).

TNF- $\alpha$  is a mediator of insulin resistance through its ability to block the action of insulin (64). The TNF- $\alpha$ -mediated insulin resistance is partially through the down-regulation of key genes (i.e., Glut4), which are necessary for normal insulin action, direct influences on insulin signaling, induction of elevated free fatty acids by stimulation of lipolysis, and negative regulation of peroxisome PPAR- $\gamma$ , a vital insulin-sensitizing nuclear receptor (65, 66). In mice, administration of exogenous TNF- $\alpha$  could lead to insulin resistance, conversely neutralization of TNF- $\alpha$  improved insulin sensitivity (67). Furthermore, TNF- $\alpha$  deficiency has been shown to significantly improve insulin sensitivity, and lower circulating levels of free fatty acids (187).

In humans, the circulating concentration of TNF- $\alpha$  are elevated in T2D, and this alteration is strongly associated with impaired glucose tolerance and enhanced insulin resistance, islet dysfunction, and increased T2D risk (109–111). Some studies have shown that a statistically significant reduction in the risk of developing T2D in treatment with TNF inhibition, and

the improvement in insulin sensitivity in during prolonged treatment with the anti-TNF- $\alpha$  antibody infliximab in insulin resistant subjects (61). However, most of these studies were not prospective and it is unclear whether these improvements are direct or indirect influences. Further study is necessary to determine whether TNF- $\alpha$  inhibition can help in the management of human metabolic disease.

## IL-1 $\beta$

IL-1 $\beta$ , a member of the IL-1 family, plays an important role in endocrinology and the regulation of responses correlated with inflammatory stress (72). IL-1 $\beta$  is considered to mediate inflammation, steatosis, and fibrosis in liver (68).

In  $\beta$ -cells, IL-1 $\beta$  activates the JNK pathway (73), which is involved in cytokine-mediated apoptosis (74) and mediates oxidative stress-induced suppression of insulin gene transcription (75). Moreover, IL-1 $\beta$  decreases expression of the insulin receptor substrate IRS-1, inhibits glucose transporter (GLUT)4 translocation to the plasma membrane, and reduces insulin-stimulated glucose uptake and lipogenesis (76). In mice, IL-1 $\beta$  was found to promote hepatic steatosis by stimulating triglycerides, cholesterol accumulation, and lipid droplet formation and to regulate inflammation, hepatic insulin resistance, and fibrosis (77). In contrast, inhibition of IL-1 $\beta$  was found to attenuate steatosis and liver injury (78), improve atherosclerosis (79), and lower glycemia (80). Furthermore, the IL-1 $\beta$  deficiency mice exhibited less hepatic steatosis and intact insulin sensitivity (188).

In humans, serum levels of IL-1 $\beta$  are increased in obesity, NAFLD (189), T2D (190), and MetS (81), but decrease significantly after extensive weight loss (82). Emerging clinical studies showed that IL-1 receptor antagonist (anakinra) and IL-1 $\beta$ -specific antibody (gevokizumab, canakinumab, LY2189102) treatment improved glucose metabolism and insulin secretion in patients with T2D (61, 83). Moreover, IL-1 antagonism was well-tolerated with no evidence of drug-related adverse events, apart from reactions at the anakinra injection site (61).

## IL-6

IL-6 is a multifunctional cytokine with complex roles and is expressed in numerous cells, including immune cells, skeletal muscle cells, and islet  $\beta$ -cells (84). It has a dual role in modulating insulin sensitivity, acting as both an enhancer and inhibitor of insulin action (62).

To exert its biological effects, IL-6 utilizes two pathways: classic and trans-signaling. While it is generally believed that the classic signaling is participated in the anti-inflammatory and regenerative activities of IL-6, the trans-signaling is involved in the pro-inflammatory responses induced by this cytokine (85, 86). Moreover, IL-6 is responsible for macrophage recruitment to adipose tissue in obesity, leading to the development of inflammation, insulin resistance, and T2D (87). In addition, IL-6 has been shown to exert long-term inhibitory effects on the gene transcription of IRS-1, GLUT4, and PPAR, along with a

marked reduction in IRS-1, and on insulin-stimulated tyrosine phosphorylation and insulin-stimulated glucose transport, which result in impaired insulin signaling and action (88). It is worth noting that the central application of IL-6 suppresses feeding and improves glucose tolerance via enhanced trans-signaling in the CNS of obese mice, even under conditions of leptin resistance (89). Studies have also shown that short- and long-term administration of adipocytes with IL-6 produces different influences on insulin signaling. Short-term treatment with IL-6 has been found not to impair the effect of insulin in the adipose tissue of rats (191), but increased glucose uptake in adipocytes (90). In contrast, chronic administration of IL-6 has been found to induce insulin resistance, suppress glucose transport, and reduce insulin-induced lipogenesis (88, 91). In humans, circulating levels of IL-6 are elevated in T2D, and this cytokine is an independent predictor of T2D (92).

## MONOCYTE CHEMOTACTIC PROTEIN 1 (MCP-1)

MCP-1, a member of the chemokine (chemotactic cytokine) family, is a powerful monocyte agonist that plays a crucial role in the recruitment of macrophages (93). MCP-1 is mediated by NF- $\kappa$ B activation and oxidative stress (94), and up-regulated by oxidized lipids, endoplasmic reticulum stress (95), and high glucose concentrations (192). Additionally, MCP-1 links obesity to insulin resistance and hepatic steatosis (96).

Mice that were engineered to express the MCP-1 transgene showed macrophage infiltration into adipose tissue, elevated hepatic triglyceride content, and insulin resistance (96). MCP-1 induces hepatic steatosis and insulin resistance via up-regulating the expression of *SREBP-1c*, a transcription factor that regulates the expression of genes important in lipid synthesis, and glucose-6-phosphatase (G6Pase), an enzyme involved in hepatic glucose production (96). In contrast, MCP-1 knockout mice and inhibition of MCP-1 activity exhibited improvements in insulin resistance and hepatic steatosis (96, 97). Consistent with the findings in mice, humans show increased plasma levels of MCP-1 in T2D (98).

## MYOKINES

Skeletal muscle is considered to be the largest organ in the body of non-obese subjects and is now recognized as an active endocrine organ due to its function in releasing numerous myokines (3). Myokines are part of a complex communication network within the body which connects skeletal muscle with other organs, such as adipose tissue, liver, and pancreas (3). Recent studies have indicated that myokines, such as irisin, interleukin (IL)-13, and IL-15, are deeply involved in glucose and lipid metabolism via autocrine, paracrine and endocrine activities (99). It is speculated that the contractile activity influences skeletal muscle secretory functions, which may link physical activity to the health-promoting effects of exercise [5].

## IRISIN

Irisin, encoded by the *Fndc5* gene, is the cleaved and secreted product of the fibronectin type III domain-containing protein 5 (FNDC5). This myokine is a transmembrane protein expressed principally in skeletal muscle (100), but is also expressed in WAT to a lower extent (101).

Irisin participates in energy expenditure via stimulation of the browning of WAT (100), direct induction of glucose and fatty acid uptake, and regulation of gene expression of metabolic enzymes in human muscle via AMPK activation (102). Cell-based studies revealed that the treatment of recombinant irisin greatly increased uptake of glucose and fatty acids, as well as expression of genes involved in glucose transport and lipid metabolism; however, the expression of genes involved in glycogenolysis or gluconeogenesis was suppressed (102). Furthermore, exogenously administered irisin, adenovirus-over-expressed irisin and irisin transgenic mice exhibited improved glucose homeostasis, ameliorated hepatic steatosis, improved insulin resistance, reduced inflammatory cytokine production, and weight loss (100, 103, 104, 193). *FNDC5* gene deficiency aggravated fat accumulation, obesity, insulin resistance, and inflammation accompanied with enhanced AMPK inhibition, macrophages recruitment, and M1 polarization (103).

In humans, irisin levels, and *FNDC5* gene expression are decreased in obese and T2D individuals (105). A previous study reported that irisin increases immediately after exercise and is positively correlated with exercise intensity (102). The positive role of irisin in metabolism supports the idea that moderate exercise is good for health. However, there are some conflicting findings in the literature (194). To date, the role of irisin in T2D is still not entirely clear. Further research is required to determine the links between irisin and T2D.

## IL-13

IL-13 is well-known as an anti-inflammatory cytokine by inhibiting the secretion of some inflammatory cytokines derived from macrophages and monocytes (106). Recently, however, IL-13 was determined to also serve as a novel myokine that is synthesized and released by human myotubes under the conditions of accelerated glucose uptake and metabolism through autocrine pathway (173).

It has been demonstrated that IL-13 is a master regulator of glucose metabolism, working via suppression of hepatic glucose production and directly inhibiting the transcription of hepatic genes that encode key gluconeogenic enzymes, such as *PEPCK* and *G6P* (107). In cultured human myotubes, the levels of IL-13 were found to be significantly decreased (~75%) in those from T2D individuals compared to myotubes from healthy subjects (108). IL-13 exposure increases skeletal muscle glucose uptake, oxidation, and glycogen synthesis via an Akt-dependent mechanism (108). On the contrary, genetic deletion of IL-13 in mice resulted in hyperglycemia, which progressed to hepatic insulin resistance and systemic metabolic disturbances (107). And basal glycogen synthesis was found to be reduced

in cultured myotubes upon exposure to an IL-13-neutralizing antibody (108).

However, the molecular mechanisms underlying the regulation of IL-13 expression and release by exercise are, as yet, unclear. Further research should be undertaken to explore how exercise affects IL-13 expression and secretion.

## IL-15

IL-15, a member of IL-2 superfamily, is a myokine that is highly expressed in skeletal muscle and released by myotubes; it is also produced by a wide variety of other cells and tissues (109).

The IL-15 secreted from skeletal muscle communicates with the adipose tissue to stimulate a reduction in fat mass and adipogenesis, and to decrease triglycerides and VLDL in blood (110), primarily through the UCPs and PPAR- $\delta$  signaling pathways (195). Moreover, in skeletal muscle and liver, IL-15 may enhance insulin sensitivity (196) and subsequent glucose transport and utilization, thereby improving glucose homeostasis through the activation of GLUT4 via Jak3/STAT3 (197). It has been demonstrated in animal models and human that IL-15: improves lipid and glucose metabolism, and insulin sensitivity; enhances mitochondrial activity; reduces WAT inflammation; and alleviates endoplasmic reticulum stress (197). Genetic research reported that IL-15 transgenic mice exhibited lean body condition, whereas IL-15 gene knockout mice showed significant increase in weight gain without changes in appetite (111).

In humans, plasma IL-15 is significantly decreased in obesity (111) and negatively associated with fat mass (112). Therefore, IL-15 may be a feasible therapeutic target for prevention and treatment in obesity and T2D.

## BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF)

BDNF, a member of the neurotrophic factor family, is a protein produced in skeletal muscle cells that is increased by contraction (113). BDNF regulates neuronal differentiation and synaptic plasticity, and its reduced levels are involved in the pathogenesis of Alzheimer's disease and other disorders (114).

It is reported that BDNF increases phosphorylation of AMPK and acetyl CoA carboxylase, enhances fat oxidation (115), regulates glucose metabolism, and ameliorates insulin sensitivity (116). In obese diabetic mice, BDNF reduces food intake and lowers blood glucose levels (131). In another study, the administration of BDNF enhanced insulin-triggered tyrosine phosphorylation of the insulin receptor in the liver (116) and insulin-stimulated phosphatidylinositol-3 kinase (PI3K)/Akt activity, which demonstrated that BDNF can enhance insulin signal transduction (116). Moreover, in db/db mice, the hypoglycemic effect induced by the administration of BDNF was found to last for several weeks after treatment cessation and was independent of food reduction (131). Conversely, BDNF-deficient mice displayed hyperphagia, obesity, hyperleptinemia, and hyperinsulinemia (198).



In humans, plasma BDNF is decreased in individuals with both obesity and T2D, and is inversely correlated with serum levels of free fatty acids and insulin resistance (199). Moreover, lower BDNF levels are involved with obesity and diabetic complications (200).

## OSTEOKINES

Recently, bone has emerged as an unexpected pleiotropic endocrine organ according to the finding of its secretion of molecules, which act in autocrine/paracrine manners to modulate skeletal homeostasis as well as some extra-skeletal systems (201). Bone is not only metabolically active, with glucose as the major energy source, but also actively takes part in systemic energy metabolism (4). First, osteoblasts can uptake glucose (a process primarily mediated by GLUT1) for utilization through aerobic glycolysis (202). Interestingly, the total uptake of glucose by bone exceeds that of traditional glucose-utilizing organs, including muscle, WAT, and the liver (203). Second, numerous key enzymes associated with the glycolytic pathway in carbohydrate metabolism are also present in osteoblasts (204) and osteoclasts (136). Moreover, osteoblasts express both the insulin receptor (205) and GLUT (117), which provides the basis for bone-mediated regulation of glucose metabolism. In addition, several osteokines (bone-derived cytokines), such as osteocalcin (118), lipocalin 2(201) and sclerostin (119) link bone and glucose metabolism, with involvement in modulation of glucose homeostasis, appetite, and browning of adipose tissue.

## OSTEOCALCIN

Osteocalcin, also known as bone  $\gamma$ -carboxyglutamic acid protein, is one of the osteoblast-specific proteins that is an established biomarker of bone turnover, and it is reported to be associated with glucose and fat metabolism (118, 120). Circulating levels of undercarboxylated and bioactive osteocalcin double during aerobic exercise at the time levels of insulin decrease (121).

The endocrine functions of osteocalcin are fulfilled by its undercarboxylated form, termed undercarboxylated osteocalcin (ucOC) (4). Osteocalcin receptors are present in both central nervous system (122) and peripheral tissues, for instance, in the pancreas (123), adipocytes (124), and muscle (121), thereby facilitating its physiological functions. There is a growing body of experimental evidence suggesting that ucOC promotes pancreatic  $\beta$ -cell proliferation and insulin expression and secretion (118, 123), induces up-regulation of adiponectin in adipocytes to ameliorate insulin resistance (124), promotes release of glucagon-like peptide-1 to indirectly stimulate insulin secretion (206), and favors glucose and fatty acid uptake and utilization in muscle during exercise (121). Mice lacking osteocalcin manifested decreased  $\beta$ -cell proliferation, glucose intolerance, and insulin resistance (118). In contrast, the metabolic abnormalities

in these mice were improved by infusion of exogenous ucOC (125).

In humans, serum osteocalcin levels are significantly lower in subjects with T2D (126) and MetS (120). However, the results regarding incident T2D are controversial. In several longitudinal studies, the serum osteocalcin level was found to not associate with the development of T2D (127).

## OSTEOPONTIN

Osteopontin, a member of small integrin-binding ligand N-linked glycoproteins (SIBLINGs) family, is a major non-collagenous bone matrix protein which participates in normal and pathological calcification (128). This glycoprotein is expressed in a variety of cells, including osteoblasts, osteoclasts, macrophages, as well as T-lymphocytes (128). Osteopontin acts as a mediator of obesity-related hepatic alterations including steatosis, inflammation, insulin resistance, and excess gluconeogenesis (129).

Cell-based experiments have shown that osteopontin impaired differentiation and insulin sensitivity of primary adipocytes as determined by inhibition PPAR- $\gamma$ , adiponectin gene expression and insulin-stimulated glucose uptake (130). Mice deficient in osteopontin have improved glucose tolerance and lower fasting plasma glucose, insulin, triglycerides, and proinflammatory cytokines after high fat diet regime compared to wild-type mice (129) and antibody-mediated neutralization of osteopontin action reduces obesity-induced inflammation and insulin resistance (207).

In humans, serum osteopontin may reflect up-regulated gene expression during liver fibrosis in NAFLD and may serve as a test for advanced hepatic fibrosis in NAFLD (208). Moreover, osteopontin is involved in the development of diabetic vascular complications (132, 209).

## LIPOCALIN (LCN)2

LCN2, a small secreted transport protein, was initially recognized for its role in innate immunity (133) and was then identified as an adipokine capable of inducing insulin resistance (134). More recently, a new insight on LCN2 was gained with the discovery of Lcn2 expression in mice being at least 10-fold higher in bone than that in WAT (201).

Mechanistically, osteoblast-derived LCN2 has been shown to cross the blood-brain barrier and suppress appetite after binding to the melanocortin 4 receptor (or MC4R) in the hypothalamus by activating an MC4R-dependent anorexigenic (appetite-suppressing) pathway, thereby decreasing body weight and fat mass and improving insulin sensitivity (201). Mice lacking *Lcn2* specifically in osteoblasts, rather than in adipocytes, showed increased food intake, fat mass, and body weight, along with decrease in glucose tolerance, insulin sensitivity, and serum insulin levels after glucose or arginine load (201). Meanwhile, islet number and size,  $\beta$ -cell mass and proliferation, and insulin secretion were also decreased in the LCN lacking mice (201). Conversely, chronic administration of exogenous

LCN2 to lean and obese mice produced similar effects, with food intake, fat mass and body weight gain becoming reduced and glucose metabolism and energy expenditure becoming heightened (201).

In humans, postprandial serum levels of LCN2 become significantly increased in normal-weight individuals after high-fat meals, and this effect is accompanied by enhanced total energy expenditure; the effect is opposite (decreased LCN2) in obese subjects (135). Intriguingly, LCN2 expression and serum levels are higher in obesity (210), T2D (137), and NAFLD (138). In addition, LCN2 levels were positively correlated with adiposity, hypertriglyceridemia, hyperglycemia, and insulin resistance index but negatively correlated with HDL cholesterol (139). As such, there may be a compensatory mechanism at the early stage of this disease.

## SCLEROSTIN

Sclerostin is a secreted protein predominantly expressed in osteocytes and is inhibited by osteoblast differentiation and bone formation (211). In general, sclerostin is considered a local inhibitor of bone acquisition that antagonizes deep bone metabolism via Wnt/ $\beta$ -catenin signaling (119).

Sclerostin exerts profound control over skeletal and whole-body metabolism by regulating the Wnt/ $\beta$ -catenin signaling pathway (119). Serum sclerostin levels were increased in mice models of disturbed metabolism, while sclerostin-deficient mice and those treated with a sclerostin-neutralizing antibody exhibited a reduction in the accumulation of WAT, along with corresponding enhancements in glucose and fatty acid metabolism, and increased insulin sensitivity (119). In contrast, recombinant sclerostin treatment was found to enhance *de novo* lipid synthesis and reduce both fatty acid oxidation and the expression of genes associated with fatty acid catabolism (119).

In humans, circulating levels of sclerostin are increased in T2D (140) and positively associated with BMI and fat mass (141). Moreover, the serum sclerostin levels exhibit a positive correlation with fasting glucose and result in insulin resistance; but negatively correlated with whole-body glucose disposal and insulin clearance rate (142).

## FGF23

FGF23, a unique member of the FGF family, is derived from bone that acts as a hormone and regulates renal phosphate and vitamin D metabolism (143). A growing body of epidemiological and experimental evidence suggests that FGF23 may regulate lipid and glucose metabolism as well as insulin action (144), but the underlying mechanisms are unclear. Furthermore, FGF23 involvement has been implicated in the onset and progression of atherosclerosis via its effects on endothelial cell function (145).

FGF23 knockout mice presented with reduced fat mass, developed hypoglycemia and increased peripheral insulin sensitivity, and showed improved subcutaneous glucose tolerance (146), suggesting a link between FGF23 and insulin resistance. However, another study in FGF23 lacking mice demonstrated no influence on aging, glucose homeostasis, or lipid metabolism with a non-functioning vitamin D receptor (147), suggesting that FGF23 may exert its effects depend on functioning vitamin D receptor.

In humans, serum FGF23 levels are elevated in individuals with obesity (212), MetS (144), prediabetes (213), and T2D (214). Moreover, FGF23 is associated positively with triglycerides, BMI, waist circumference, and fat mass, and negatively correlated with HDL and apolipoprotein A1 (144). However, another cross-sectional study of small sample did not show differences in circulating FGF23 levels between diabetic and non-diabetic patients, but reported that circulating FGF23 is associated with bone mineral density and preclinical vascular disease in T2D patients (215). Further experimental studies are needed to shed more light on the underlying mechanisms between FGF23 and glucose and lipid metabolism, and prospective studies of large scale are needed to determine the association between FGF23 and metabolic disease, such as T2D.

## CONCLUSION

Overnutrition and physical activity alter cytokines secretion, thereby influencing metabolic and immune regulatory pathways that caused or promoted metabolic disorders. These cytokines are part of a complex network that mediates communication between multiple organs and tissues (e.g., adipose, liver, muscle, skeleton). The emerging data support the contributions of certain cytokines to metabolic disorders. Given the disease-related changes in levels of relevant cytokines (for instance, leptin, adiponectin, resistin, FGF21, Fetuin A, TNF- $\alpha$ , IL-6, MCP-1), these factors may serve as biomarkers for the early detection of metabolic disorders. Moreover, based on preclinical studies, certain cytokines (FGF21, leptin, adiponectin, irisin) that can induce improvements in glucose and lipid metabolism and may emerge as novel targets of broader and more efficacious treatments and prevention of metabolic disease.

## AUTHOR CONTRIBUTIONS

ZY, QS, and JF contributed conception of the paper. JS wrote the manuscript. ZY and QS revised the manuscript.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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