Inflammation, Vol. 42, No. 3, June 2019 (© 2019)
DOI: 10.1007/s10753-019-00959-6

REVIEW

Review: the Roles and Mechanisms of Glycoprotein 130 Cytokines in the Regulation of Adipocyte Biological Function

Dufang Ma,[1] Yong Wang,[1] Guofeng Zhou,[2] Yongcheng Wang,[2] and Xiao Li[1,3]

Abstract— Chronic low-grade inflammation is now widely accepted as one of the most important contributors to metabolic disorders. Glycoprotein 130 (gp130) cytokines are involved in the regulation of metabolic activity. Studies have shown that several gp130 cytokines, such as interleukin-6 (IL-6), leukemia inhibitory factor (LIF), oncostatin M (OSM), ciliary neurotrophic factor (CNTF), and cardiotrophin-1 (CT-1), have divergent effects on adipogenesis, lipolysis, and insulin sensitivity as well as food intake. In this review, we will summarize the present knowledge about gp130 cytokines, including IL-6, LIF, CNTF, CT-1, and OSM, in adipocyte biology and metabolic activities in conditions such as obesity, cachexia, and type 2 diabetes. It is valuable to explore the diverse actions of these gp130 cytokines on the regulation of the biological functions of adipocytes, which will provide potential therapeutic targets for the treatment of obesity and cachexia.

KEY WORDS: glycoprotein 130 cytokines; interleukin-6 cytokine; leukemia inhibitory factor; oncostatin M; ciliary neurotrophic factor; cardiotrophin-1; adipocyte biological function.

INTRODUCTION

To date, more than 10 cytokines in the interleukin-6 (IL-6) cytokine family, such as IL-6, leukemia inhibitory factor (LIF), oncostatin M (OSM), ciliary neurotrophic factor (CNTF), cardiotrophin-1 (CT-1), interleukin-11 (IL-11), and interleukin-27 (IL-27) have been discovered. All of these cytokines regulate a variety of complex biological processes, such as hematopoiesis, immune activity, inflammation, pregnancy, reproduction, the cardiovascular system, osteoclast formation, and neuronal survival [1]. Because all of these IL-6 family cytokines utilize glycoprotein 130 (gp130) as a common signaling pathway through their unique receptor system, they are commonly referred to as gp130 cytokines. Specifically, each IL-6 family cytokine binds to its specific receptor α-subunit, followed by the activation of the common receptor subunit gp130. The functional pleiotropy of these IL-6 family cytokines is partially attributed to their specific receptor α-subunit, and the redundancy among the cytokines is achieved by the common receptor subunit gp130 [2]. For example, IL-6 and IL-11 transduce signals *via* the induction of a gp130 homodimer after binding to IL-6 receptor α (IL-6α) and IL-11Rα, respectively. CNTF and CT-1 initially bind to their specific α receptors and then form a heterodimer with the signal-transducing gp130 receptor β (gp130 β) and LIF receptor β (LIF β) to transduce signals. LIF and OSM directly induce the formation of the gp130R β/LIF β and gp130R β/OSM receptor heterodimers, respectively [3].

In the past decade, numerous noteworthy studies have focused on adipose tissue physiology. Many of these studies have indicated that adipose tissue dysfunction is a key underlying mechanism that contributes to obesity and type 2 diabetes. Targeting the regulation of adipocyte biology

[1] Cardiology Department, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, China
[2] First Clinical Medical College, Shandong University of Traditional Chinese Medicine, Jinan, China
[3] To whom correspondence should be addressed at Cardiology Department, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, China. E-mail: lixiao617@hotmail.com

will provide a promising method for the treatment of obesity and type 2 diabetes [4]. Inflammatory cytokines regulate the proliferation and apoptosis of adipocytes and are involved in the modulation of lipolysis and lipid synthesis through autocrine and paracrine mechanisms [5]. In recent years, it has been revealed that gp130 cytokines exert a wide range of biological functions in the regulation of adipocyte biology, and they may provide promising anti-obesity therapeutic targets [6]. Therefore, it is valuable to provide insight into the various roles of gp130 cytokines in metabolic activities and to understand their contributions to metabolic disorders. The present review focuses on the role and potential mechanisms of gp130 cytokines, including IL-6, LIF, CNTF, CT-1, and OSM, in regulating adipocyte biology and metabolic activity.

INTERLEUKIN-6

IL-6 is a pleiotropic cytokine that is secreted by adipose tissue and various cell types. In healthy humans, IL-6 produced by adipose tissue accounts for 15–35% of the circulating levels [7]. Obese individuals have increased blood levels of IL-6 compared with healthy individuals [8]. However, until now, it has remained unclear whether the increased production of IL-6 plays a harmful role or a protective role in obesity. A growing number of publications from recent years have supported the pro-inflammatory effect of IL-6. These reports have revealed that an increased production of IL-6 is attributed to insulin resistance partly by upregulating SOCS3, a protein that binds and inhibits insulin receptors [9], while the neutralization of IL-6 selectively improves obesity-induced insulin resistance [10]. Notably, numerous studies have shown that IL-6 levels are greatly increased in obese humans, and the increased IL-6 is strongly correlated with increased body weight index and waist circumference [11–13]. In contrast to the conclusion that IL-6 is a negative factor in metabolic homeostasis, a study revealed that IL-6-deficient ($IL\text{-}6^{-/-}$) mice developed mature-onset obesity, insulin resistance, and increased liver inflammation in response to a high-fat diet (HFD) [14, 15]. In addition, based on an experiment in mice with a myeloid cell-specific deletion of the IL-6Rα chain, Mauer et al. [16] reported that the disruption of IL-6 receptor (IL-6R) signaling was associated with insulin resistance and metabolic disorders when the mice were fed an HFD. Furthermore, in mice that were fed an HFD, the absence of IL-6R signaling in macrophages increased their tendency towards developing a pro-inflammatory "M1 phenotype." Increased IL-6 levels potentiate the M2 activation of adipose tissue macrophages by upregulating the expression of IL-4Ra in the context of diet-induced obesity to attenuate inflammatory responses and metabolic disorders. In parallel, IL-6 may inhibit M1 activation by saturated fatty acids and other inflammatory cytokines. Thus, IL-6 regulates the activation of adipose tissue alternative macrophages to attenuate inflammatory responses, improving insulin resistance.

It has been suggested that the pro-inflammatory effects of IL-6 signaling appear to be mediated by the "trans-signaling" (the binding of an IL-6 and soluble IL-6Ra complex to cell surface gp130), while the anti-inflammatory effect is mediated by classic signaling through IL-6Ra and gp130 [17, 18]. A soluble form of gp130 is the natural decoy receptor for the IL-6/soluble IL-6R complex and can therefore limit trans-signaling [19]. Mice with a selective blockade of IL-6 trans-signaling, as a result of the genetic overexpression of soluble gp130 (sgp130Fc), exhibited increased adipogenesis in response to an HFD [20]. Moreover, unlike mice with complete ablation of IL-6 signaling ($IL\text{-}6^{-/-}$mice) that exhibited hyperlipidemia, increased hepatosteatosis and liver inflammation when fed an HFD [14], the selective blockade of IL-6 trans-signaling did not exacerbate HFD-induced hyperlipidemia, hepatosteatosis, or liver inflammation. In addition, the inflammation and fibrosis induced by macrophage accumulation has been revealed as a major mechanism of adipose tissue dysfunction in obesity [21–23], while the selective blockade of IL-6 trans-signaling induced by the overexpression of sgp130Fc has been shown to prevent macrophage accumulation and fibrosis in the white adipose tissue of mice fed an HFD [20]. This study suggested that it is possible that the selective blocking of IL-6 trans-signaling in adipose tissue may prevent adipose tissue dysfunction in obese conditions. Similarly, a study of the central nervous system indicated that a central application of IL-6 in mice suppressed feeding and improved glucose tolerance; however, blocking IL-6 trans-signaling in the brain abrogated the ability of IL-6 to suppress feeding, indicating that IL-6 trans-signaling is essential for the appetite suppression associated with IL-6 in the central nervous system [24].

Excessive lipolytic activity and impaired lipogenic capacities in adipocytes are some of the main causes of metabolic disorders [25]. A high dose of IL-6 can stimulate lipolysis and fat oxidation in human or mouse adipocytes *in vivo* and *in vitro* [26, 27]. Additionally, in the condition of cachexia, IL-6 promoted a switch from white to brown fat by increasing UCP-1 expression, which leads to increased lipid mobilization and energy expenditure [28]. However, although IL-6-mediated lipolysis that is mainly

restrained to visceral adipose tissue could reduce lipid stores by promoting the release of free fatty acids, it increases ectopic fat accumulation, which leads to increased hepatic and cardiac fat levels and insulin resistance [29–32]. In contrast to its effect on visceral adipocytes [32, 33], IL-6 activation in subcutaneous adipose tissue induced leptin-mediated intestinal glucagon-like peptide 1 (GLP-1) release, which could enhance insulin secretion and thereby counteract insulin resistance in obesity [34, 35]. Collectively, these studies have indicated that the controversy related to the favorable and unfavorable effects of IL-6 in metabolic homeostasis may be related to its complicated signaling biology and depot-dependent action.

LEUKEMIA INHIBITORY FACTOR

The earliest studies evaluating LIF in animals were aimed at assessing its effect on hematopoiesis [36]. Later, LIF was found to regulate the growth and differentiation of a wide variety of cell types and to be involved in processes such as inflammation, neural development, and fertilization [37]. In adipocytes, LIF promoted preadipose cells to express the early adipogenic transcription factors C/EBPβ and C/EBP δ *via* the mitogen-activated protein kinase cascade (MAPK), which induced adipocyte differentiation [38]. However, other findings have shown that LIF prevented adipogenesis in bone marrow stromal cells [39]. Furthermore, in 3T3-L1 cells, studies have indicated that LIF did not modulate adipogenesis [40, 41]. These inconsistent results may be related to the different developmental stages of the cells and tissues.

LIF promotes fat loss and decreases fat stores in the body. An earlier study reported that LIF secreted by a melanoma cell line contributed to cancer cachexia [42]. When recombinant murine LIF was injected into mice, it caused significant weight loss [43]. Therefore, it has been proposed that LIF might induce weight loss through its catabolic effects. However, the in-depth mechanism of LIF in controlling lipolysis has not been studied. In cultured adipocytes, Maurren K et al. [44] found that LIF promoted lipolysis by decreasing lipoprotein lipase (LPL) activity. Most recently, Gurpreet K et al. [45] showed that LIF-induced lipolysis was dependent on its receptors, LIFR-α and gp130, which stimulated the signal transducer and activator of transcription (STAT)1 and STAT3 pathway and ultimately activated adipose triglyceride lipase (ATGL)-mediated lipolysis. These results suggested that LIF has a direct contribution to peripheral fat loss by promoting adipocyte lipolysis. In addition to the effect of LIF on peripheral lipolysis, a previous study performed by Elena et al. [46] also revealed that intracerebroventricular injection of a recombinant adeno-associated viral vector encoding LIF (rAAV-LIF) resulted in a dose-dependent reduction in serum leptin levels. Notably, this reduction in leptin was accompanied by suppressed food intake and loss of fat instead of increased food intake. Similar results were also obtained by Gurpreet K et al. [45], who showed that the injection of recombinant LIF into leptin-deficient (ob/ob) mice, which is a murine model of hyperphagia, resulted in a persistent decrease in food intake and loss of fat mass and body weight, suggesting that LIF might directly induce hypophagia independent of signaling *via* the leptin receptor. This effect of LIF on the inhibition of food intake was directly mediated by the pro-opiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus. This study showed that arcuate POMC neurons express the LIF receptor and that LIF stimulates the release of the anorexigenic peptide α-MSH in POMC neurons, which is partly similar to leptin. Transgenic mice lacking gp130 in their POMC neurons failed to respond to LIF [47, 48]. Collectively, targeting LIF may provide a potential therapeutic treatment against both obesity and cachexia by regulating lipolysis balance and food intake.

CILIARY NEUROTROPHIC FACTOR

The ciliary neurotrophic factor (CNTF) was identified as a neurotrophic factor and was evaluated as a therapeutic tool for patients with motor neuron diseases [49]. Interestingly, during the trials that investigated CNTF, CNTF administration resulted in unexpected weight loss [50]. Furthermore, treatment with CNTFAx15, a second-generation CNTF analog, caused weight loss in obese C57BL/6J mice [51]. Studies have demonstrated that, in brown adipocytes, CNTF enhanced β3-adrenergic expression; activated metabolic signaling pathways such as MAPK, PI3K, Akt, and p70 S6 kinase; and upregulated the expression of PGC-1α, PPARα, and UCP-1 [52, 53]. All these changes promote energy consumption. In white adipocyte tissue, CNTF treatment promoted mitochondrial biogenesis, enhancing fatty acid oxidation and reducing lipogenic capacity, thereby reducing triglyceride stores in white adipocytes [53]. In addition, Matthew et al. [54] found that CNTF induced insulin sensitization in skeletal muscle and liver, preventing acute lipid-induced insulin resistance. Additionally, they also found that CNTF, through the CNTFRα-IL-6-gp130β receptor complex, increased skeletal muscle fatty acid oxidation and reduced

insulin resistance by activating AMP-activated protein kinase (AMPK) [55]. These results indicate that CNTF exerts direct peripheral anti-obesogenic effects by promoting energy consumption and improving insulin resistance.

In addition to the direct effects of CNTF on peripheral adipose and muscle tissue, studies have shown that CNTF plays an important central role in regulating metabolism homeostasis. Like the central action of leptin, intracerebroventricular injection of CNTF promoted adipose tissue apoptosis and reduced peripheral fat mass [56]. Additionally, central administration of CNTF induced cell proliferation in feeding centers of the murine hypothalamus; moreover, many of the new cells expressed neuronal markers and showed functional phenotypes relevant to energy-balance control. This result suggested that the sustained central effects of CNTF on energy balance are linked to its promotion of hypothalamic neurogenesis [57]. Later, Gregory R et al. [54] found that intraperitoneal injection of $CNTF_{AX15}$ reduced food intake by inhibiting hypothalamic AMPK activity. Importantly, the effects of $CNTF_{AX15}$ persisted in the context of diet-induced obesity, whereas the effects of leptin on AMPK signaling were reduced. Therefore, both the peripheral and central effects of CNTF highlight its potential role in the therapeutic treatment of obesity.

CARDIOTROPHIN

CT-1 has been shown to support cardiomyocyte survival and hypertrophy *in vitro* and to increase heart weight and ventricular weight *in vivo* [58]. Similar to other gp130 cytokines, CT-1 is partly derived from adipose tissue and participates in the control of adipocyte physiology and energy metabolism. An early *in vitro* study revealed that chronic CT-1 treatment resulted in decreased fatty acid synthase and insulin receptor substrate-1 protein expression in 3T3-L1 adipocytes; moreover, chronic CT-1 treatment resulted in decreased insulin sensitivity as demonstrated by decreased insulin-stimulated glucose uptake [59]. Furthermore, the effects of CT-1 were mediated by the JAK/STAT and MAPK signaling pathways in fat cells *in vitro* and *in vivo* [59]. In contrast, a study performed by Moreno-Aliaga et al. [60] showed that CT-1 null mice ($CT^{-/-}$ mice) developed decreased energy expenditure, mature-onset obesity, insulin resistance, and hypercholesterolemia despite reduced food intake. Acute treatment with recombinant CT-1 decreased blood glucose in an insulin-dependent manner and promoted fatty acid oxidation. Similarly, chronic administration of CT-1 reduced food intake, enhanced energy expenditure, and upregulated genes implicated in the control of lipolysis, fatty acid oxidation, and mitochondrial biogenesis in the white adipocyte tissue and genes typifying the brown fat phenotype. Similarly, in adipose tissue, CT-1 has been shown to promote lipolytic activity by promoting the PKA-mediated phosphorylation of perilipin and hormone-sensitive lipase (HSL) and increasing ATGL content [61]. Additionally, this study also found that CT-1 was capable of regulating the secretory pattern of adipokines by adipocytes; decreasing the production of pro-inflammatory adipokines, including leptin, resistin, and visfatin; and stimulating the secretion of apelin [62], which elevates insulin sensitivity and glucose utilization in adipose and muscle tissues [63]. These studies strongly support the idea that CT-1 is a promising therapy for obesity since it promotes energy utilization, improves insulin sensitivity, and inhibits the appetite and inflammatory reactions.

Although experimental research has implicated the favorable effects of CT-1 in regulating metabolic homeostasis, inconsistent results have been obtained from human studies regarding the relationship between CT-1 and obesity. Studies performed in patients with diabetes, hypertension, or metabolic syndrome have found that obese patients showed lower levels of CT-1 than non-obese patients; moreover, serum levels of CT-1 were inversely correlated with body mass index (BMI) [64, 65]. These results have also been found in non-diabetic obese subjects [66]. Conversely, in a population of 137 apparently healthy subjects, obese patients had increased serum levels of CT-1 compared with the serum levels of the normal weight subjects [67]. A study performed in overweight/obese children demonstrated that weight loss accompanied decreased serum levels of CT-1; moreover, decreased CT-1 levels were strongly associated with a reduction in cholesterol levels and metabolic syndrome risk [68]. These discrepant results may be due to the different study populations and lack of adjustment for possible confounding factors of CT-1.

ONCOSTATIN M

OSM is a gp130 cytokine that shares substantial sequence homology with LIF [69, 70]. OSM exhibits a variety of biological effects, depending on the target cells, by binding to a heterodimeric membrane receptor comprising the OSM-specific β subunit (OSMR β) [71]. OSM is synthesized by various inflammatory cells, such as activated T cells, neutrophils, eosinophils, and macrophages. In adipose tissue, OSM is not produced from adipocytes but is derived from cells in the stromovascular fraction, including macrophages. OSMR β is expressed in adipocytes [72].

Tadasuke [73, 74] and colleagues revealed that OSM receptor β subunit-deficient (OSMR $\beta^{-/-}$) mice exhibited mature-onset obesity, severe hepatic steatosis and insulin resistance; moreover, the occurrence of insulin resistance preceded obesity in the OSMR $\beta^{-/-}$ mice. Additionally, these OSMR $\beta^{-/-}$ mice exhibited more M1 phenotypes of adipose tissue macrophages with augmented adipose tissue inflammation. Treatment with OSM improved obesity, adipose tissue inflammation, insulin resistance, and hepatic steatosis in both diet-induced obese and *ob/ob* mice. Functionally, OSM directly changed the phenotype of adipose tissue macrophages from the M1 type to the M2 type, which inhibited inflammation in the adipose tissue. In the liver, OSM directly induced lipolysis and suppressed lipogenesis, promoting fatty acid oxidation. In addition, OSM increased the expression of active GLP-1 in the intestines and thereby suppressed food intake [72, 75]. In contrast to these studies, David et al. [72] demonstrated that OSM expression is elevated in rodents and humans with obesity/type 2 diabetes. Moreover, in humans, OSM levels in the subcutaneous fat positively correlated with body weight and insulin levels and had an inverse correlation with glucose disposal rates. In contrast to the effects of other gp130 cytokines, adding OSM to cultured adipocytes increased the secretion of plasminogen activator inhibitor 1 (PAI-1), which is known to have profound effects on tissue fibrosis and results in adipose tissue dysfunction. These results indicated that increased adipose tissue-derived OSM promotes a metabolically unfavorable phenotype, which contrasted with the studies performed by Tadasuke et al. [73, 74].

Vascular endothelial growth factor (VEGF) is involved in promoting angiogenesis [76]. It has been demonstrated that OSM induced increased VEGF production and vessel density in both subcutaneous and visceral adipose tissue by activating the JAK/STAT pathway [77], and this increased VEGF expression and vessel density might support angiogenesis in adipose tissue. Conversely, a previous study showed that OSM inhibited the adipogenesis of 3T3-L1 cells and mouse embryonic fibroblasts (MEFs) through the Ras/extracellular signal-regulated kinase (ERK) and STAT 5 signaling pathways [41, 78]. Therefore, it is necessary to further determine the overall function of OSM in the regulation of adipose physiology in obese conditions.

CONCLUSION

Although the functions and mechanisms underlying the action of gp130 cytokines in adipose tissue have not been fully elucidated, gp130 cytokines have divergent

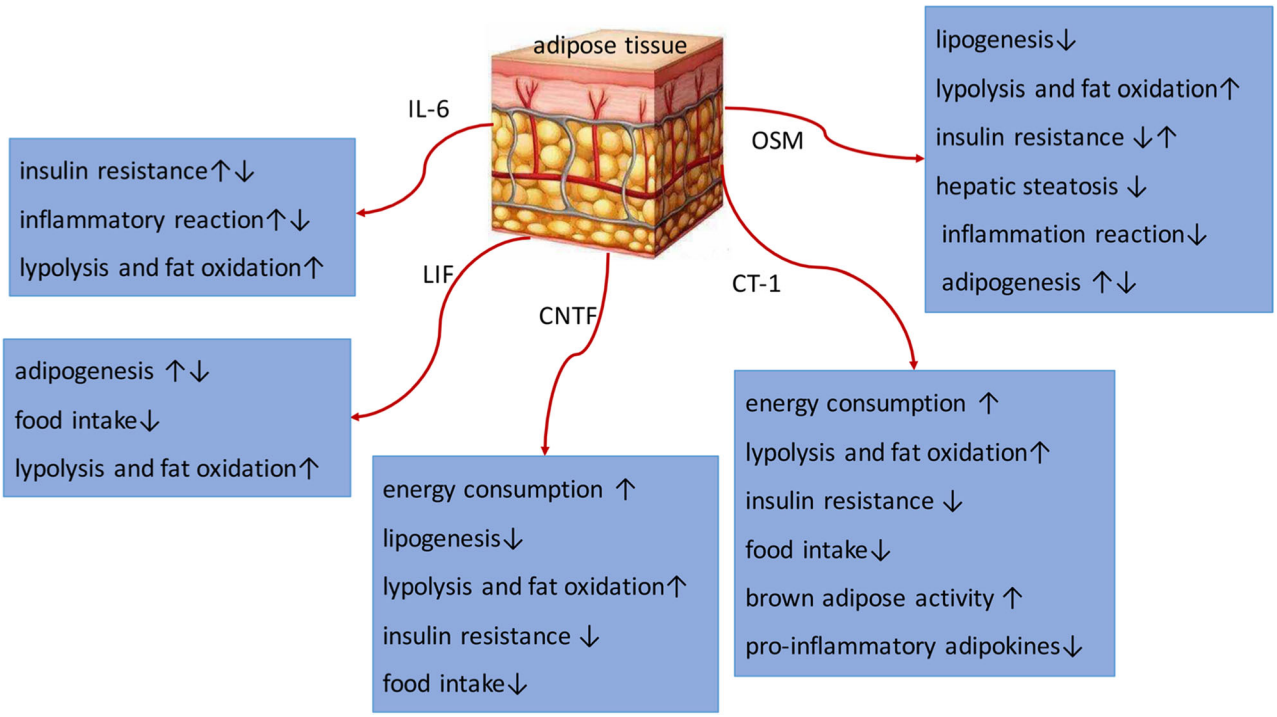

Fig. 1. Effects of IL-6, LIF, CNTF, CT-1, and OMS on the regulation of adipocyte biological processes and energy metabolism activities.

regulatory effects on food intake, insulin sensitivity, lipolysis, lipogenesis, and inflammatory activity in adipose tissue (summarized in Fig. 1). Additionally, these cytokines share gp130 as a common signal transducer in their receptor complex and activate common signaling pathways, including JAK/STAT and MAPK (ERK1 and 2) [79]. Analysis of gp130 signaling revealed that these gp130 cytokines exerted differential crosstalk signaling capabilities in both cultured adipocytes *in vitro* and adipose tissue *in vivo* [6]. Therefore, further research is needed to explore the changes in gp130 cytokine expression in the adipose tissue of obese individuals and the overall and mutual effects of these gp130 cytokines on the regulation of energy metabolism. A more in-depth study of these diverse actions of gp130 cytokines in regulating the biological process of adipose tissue is essential to develop new therapeutic strategies for the treatment of obesity and cachexia.

FUNDING INFORMATION

This work was supported by the Chinese National Natural Science Foundation (No. 81673970 and No. 81874449).

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest. The authors declare that they have no conflict of interest.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

REFERENCES

1. White, U.A., and J.M. Stephens. 2011. The gp130 receptor cytokine family: Regulators of adipocyte development and function. *Current Pharmaceutical Design* 17 (4): 340–346.
2. Fujio, Y., M. Maeda, T. Mohri, M. Obana, T. Iwakura, A. Hayama, T. Yamashita, H. Nakayama, and J. Azuma. 2011. Glycoprotein 130 cytokine signal as a therapeutic target against cardiovascular diseases. *Journal of Pharmacological Sciences* 117 (4): 213–222.
3. Ernst, M., and B.J. Jenkins. 2004. Acquiring signalling specificity from the cytokine receptor gp130. *Trends in Genetics* 20 (1): 23–32. https://doi.org/10.1016/j.tig.2003.11.003.
4. Kajimura, S. 2017. Adipose tissue in 2016: advances in the understanding of adipose tissue biology. *Nature Reviews. Endocrinology* 13 (2): 69–70. https://doi.org/10.1038/nrendo.2016.211.
5. Murakami, S. 2017. The physiological and pathophysiological roles of taurine in adipose tissue in relation to obesity. *Life Sciences* 186: 80–86. https://doi.org/10.1016/j.lfs.2017.08.008.
6. White, U.A., W.C. Stewart, and J.M. Stephens. 2011. Gp130 cytokines exert differential patterns of crosstalk in adipocytes both in vitro and in vivo. *Obesity (Silver Spring)* 19 (5): 903–910. https://doi.org/10.1038/oby.2010.293.
7. Fruhbeck, G., J. Gomez-Ambrosi, F.J. Muruzabal, and M.A. Burrell. 2001. The adipocyte: a model for integration of endocrine and metabolic signaling in energy metabolism regulation. *American Journal of Physiology. Endocrinology and Metabolism* 280 (6): E827–E847. https://doi.org/10.1152/ajpendo.2001.280.6.E827.
8. Mohamed-Ali, V., S. Goodrick, A. Rawesh, D.R. Katz, J.M. Miles, J.S. Yudkin, S. Klein, and S.W. Coppack. 1997. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. *The Journal of Clinical Endocrinology and Metabolism* 82 (12): 4196–4200. https://doi.org/10.1210/jcem.82.12.4450.
9. Lazar, M.A. 2005. How obesity causes diabetes: not a tall tale. *Science* 307 (5708): 373–375. https://doi.org/10.1126/science.1104342.
10. Sabio, G., M. Das, A. Mora, Z. Zhang, J.Y. Jun, H.J. Ko, T. Barrett, J.K. Kim, and R.J. Davis. 2008. A stress signaling pathway in adipose tissue regulates hepatic insulin resistance. *Science* 322 (5907): 1539–1543. https://doi.org/10.1126/science.1160794.
11. Klover, P.J., T.A. Zimmers, L.G. Koniaris, and R.A. Mooney. 2003. Chronic exposure to interleukin-6 causes hepatic insulin resistance in mice. *Diabetes* 52 (11): 2784–2789.
12. Khaodhiar, L., P.R. Ling, G.L. Blackburn, and B.R. Bistrian. 2004. Serum levels of interleukin-6 and C-reactive protein correlate with body mass index across the broad range of obesity. *JPEN Journal of Parenteral and Enteral Nutrition* 28 (6): 410–415. https://doi.org/10.1177/0148607104028006410.
13. Bastard, J.P., C. Jardel, E. Bruckert, P. Blondy, J. Capeau, M. Laville, H. Vidal, and B. Hainque. 2000. Elevated levels of interleukin 6 are reduced in serum and subcutaneous adipose tissue of obese women after weight loss. *The Journal of Clinical Endocrinology and Metabolism* 85 (9): 3338–3342. https://doi.org/10.1210/jcem.85.9.6839.
14. Matthews, V.B., T.L. Allen, S. Risis, M.H. Chan, D.C. Henstridge, N. Watson, L.A. Zaffino, et al. 2010. Interleukin-6-deficient mice develop hepatic inflammation and systemic insulin resistance. *Diabetologia* 53 (11): 2431–2441. https://doi.org/10.1007/s00125-010-1865-y.
15. Wallenius, V., K. Wallenius, B. Ahren, M. Rudling, H. Carlsten, S.L. Dickson, C. Ohlsson, and J.O. Jansson. 2002. Interleukin-6-deficient mice develop mature-onset obesity. *Nature Medicine* 8 (1): 75–79. https://doi.org/10.1038/nm0102-75.
16. Mauer, J., B. Chaurasia, J. Goldau, M.C. Vogt, J. Ruud, K.D. Nguyen, S. Theurich, A.C. Hausen, J. Schmitz, H.S. Brönneke, E. Estevez, T.L. Allen, A. Mesaros, L. Partridge, M.A. Febbraio, A. Chawla, F.T. Wunderlich, and J.C. Brüning. 2014. Signaling by IL-6 promotes alternative activation of macrophages to limit endotoxemia and obesity-associated resistance to insulin. *Nature Immunology* 15 (5): 423–430. https://doi.org/10.1038/ni.2865.
17. Scheller, J., A. Chalaris, D. Schmidt-Arras, and S. Rose-John. 2011. The pro- and anti-inflammatory properties of the cytokine interleukin-6. *Biochimica et Biophysica Acta* 1813 (5): 878–888. https://doi.org/10.1016/j.bbamcr.2011.01.034.
18. Kraakman, M.J., T.L. Allen, M. Whitham, P. Iliades, H.L. Kammoun, E. Estevez, G.I. Lancaster, and M.A. Febbraio. 2013. Targeting gp130 to prevent inflammation and promote insulin action. *Diabetes, Obesity & Metabolism* 15 (Suppl 3): 170–175. https://doi.org/10.1111/dom.12170.
19. Jostock, T., J. Mullberg, S. Ozbek, R. Atreya, G. Blinn, N. Voltz, M. Fischer, M.F. Neurath, and S. Rose-John. 2001. Soluble gp130 is the natural inhibitor of soluble interleukin-6 receptor transsignaling responses. *European Journal of Biochemistry* 268 (1): 160–167.

20. Kraakman, M.J., H.L. Kammoun, T.L. Allen, V. Deswaerte, D.C. Henstridge, E. Estevez, V.B. Matthews, B. Neill, D.A. White, A.J. Murphy, L. Peijs, C. Yang, S. Risis, C.R. Bruce, X.J. du, A. Bobik, R.S. Lee-Young, B.A. Kingwell, A. Vasanthakumar, W. Shi, A. Kallies, G.I. Lancaster, S. Rose-John, and M.A. Febbraio. 2015. Blocking IL-6 trans-signaling prevents high-fat diet-induced adipose tissue macrophage recruitment but does not improve insulin resistance. *Cell Metabolism* 21 (3): 403–416. https://doi.org/10.1016/j.cmet.2015.02.006.
21. Sun, K., J. Tordjman, K. Clement, and P.E. Scherer. 2013. Fibrosis and adipose tissue dysfunction. *Cell Metabolism* 18 (4): 470–477. https://doi.org/10.1016/j.cmet.2013.06.016.
22. Sun, K., J. Park, O.T. Gupta, W.L. Holland, P. Auerbach, N. Zhang, R. Goncalves Marangoni, S.M. Nicoloro, M.P. Czech, J. Varga, T. Ploug, Z. An, and P.E. Scherer. 2014. Endotrophin triggers adipose tissue fibrosis and metabolic dysfunction. *Nature Communications* 5: 3485. https://doi.org/10.1038/ncomms4485.
23. Sun, K., N. Halberg, M. Khan, U.J. Magalang, and P.E. Scherer. 2013. Selective inhibition of hypoxia-inducible factor 1alpha ameliorates adipose tissue dysfunction. *Molecular and Cellular Biology* 33 (5): 904–917. https://doi.org/10.1128/mcb.00951-12.
24. Timper, K., J.L. Denson, S.M. Steculorum, C. Heilinger, L. Engstrom-Ruud, C.M. Wunderlich, S. Rose-John, F.T. Wunderlich, and J.C. Bruning. 2017. IL-6 Improves Energy and Glucose Homeostasis in Obesity via Enhanced Central IL-6 trans-Signaling. *Cell Reports* 19 (2): 267–280. https://doi.org/10.1016/j.celrep.2017.03.043.
25. Moreno-Indias, I., and F.J. Tinahones. 2015. Impaired adipose tissue expandability and lipogenic capacities as ones of the main causes of metabolic disorders. *Journal Diabetes Research* 2015: 970375. https://doi.org/10.1155/2015/970375.
26. Yang, Y., D. Ju, M. Zhang, and G. Yang. 2008. Interleukin-6 stimulates lipolysis in porcine adipocytes. *Endocrine* 33 (3): 261–269. https://doi.org/10.1007/s12020-008-9085-7.
27. Petersen, E.W., A.L. Carey, M. Sacchetti, G.R. Steinberg, S.L. Macaulay, M.A. Febbraio, and B.K. Pedersen. 2005. Acute IL-6 treatment increases fatty acid turnover in elderly humans in vivo and in tissue culture in vitro. *American Journal of Physiology. Endocrinology and Metabolism* 288 (1): E155–E162. https://doi.org/10.1152/ajpendo.00257.2004.
28. Petruzzelli, M., M. Schweiger, R. Schreiber, R. Campos-Olivas, M. Tsoli, J. Allen, M. Swarbrick, S. Rose-John, M. Rincon, G. Robertson, R. Zechner, and E.F. Wagner. 2014. A switch from white to brown fat increases energy expenditure in cancer-associated cachexia. *Cell Metabolism* 20 (3): 433–447. https://doi.org/10.1016/j.cmet.2014.06.011.
29. Morelli, M., M. Gaggini, G. Daniele, P. Marraccini, R. Sicari, and A. Gastaldelli. 2013. Ectopic fat: the true culprit linking obesity and cardiovascular disease? *Thrombosis and Haemostasis* 110 (4): 651–660. https://doi.org/10.1160/th13-04-0285.
30. Gaggini, M., C. Saponaro, and A. Gastaldelli. 2015. Not all fats are created equal: adipose vs. ectopic fat, implication in cardiometabolic diseases. *Horm Mol Biol Clin Investig* 22 (1): 7–18. https://doi.org/10.1515/hmbci-2015-0006.
31. Abdullahi, A., and M.G. Jeschke. 2016. White Adipose Tissue Browning: A Double-edged Sword. *Trends in Endocrinology and Metabolism* 27 (8): 542–552. https://doi.org/10.1016/j.tem.2016.06.006.
32. Wueest, S., F. Item, F.C. Lucchini, T.D. Challa, W. Muller, M. Bluher, and D. Konrad. 2016. Mesenteric Fat Lipolysis Mediates Obesity-Associated Hepatic Steatosis and Insulin Resistance. *Diabetes* 65 (1): 140–148. https://doi.org/10.2337/db15-0941.
33. Perry, R.J., J.G. Camporez, R. Kursawe, P.M. Titchenell, D. Zhang, C.J. Perry, M.J. Jurczak, et al. 2015. Hepatic acetyl CoA links adipose tissue inflammation to hepatic insulin resistance and type 2 diabetes. *Cell* 160 (4): 745–758. https://doi.org/10.1016/j.cell.2015.01.012.
34. Wueest, S., C.I. Laesser, M. Boni-Schnetzler, F. Item, F.C. Lucchini, M. Borsigova, W. Muller, M.Y. Donath, and D. Konrad. 2018. IL-6-Type Cytokine Signaling in Adipocytes Induces Intestinal GLP-1 Secretion. *Diabetes* 67 (1): 36–45. https://doi.org/10.2337/db17-0637.
35. Wueest, S., and D. Konrad. 2018. The role of adipocyte-specific IL-6-type cytokine signaling in FFA and leptin release. *Adipocyte* 7 (3): 226–228. https://doi.org/10.1080/21623945.2018.1493901.
36. Akiyama, Y., N. Kajimura, J. Matsuzaki, Y. Kikuchi, N. Imai, M. Tanigawa, and K. Yamaguchi. 1997. In vivo effect of recombinant human leukemia inhibitory factor in primates. *Japanese Journal of Cancer Research* 88 (6): 578–583.
37. Nicola, N.A., and J.J. Babon. 2015. Leukemia inhibitory factor (LIF). *Cytokine & Growth Factor Reviews* 26 (5): 533–544. https://doi.org/10.1016/j.cytogfr.2015.07.001.
38. Aubert, J., S. Dessolin, N. Belmonte, M. Li, F.R. McKenzie, L. Staccini, P. Villageois, B. Barhanin, A. Vernallis, A.G. Smith, G. Ailhaud, and C. Dani. 1999. Leukemia inhibitory factor and its receptor promote adipocyte differentiation via the mitogen-activated protein kinase cascade. *The Journal of Biological Chemistry* 274 (35): 24965–24972.
39. Gimble, J.M., F. Wanker, C.S. Wang, H. Bass, X. Wu, K. Kelly, G.D. Yancopoulos, and M.R. Hill. 1994. Regulation of bone marrow stromal cell differentiation by cytokines whose receptors share the gp130 protein. *Journal of Cellular Biochemistry* 54 (1): 122–133. https://doi.org/10.1002/jcb.240540113.
40. Hogan, J.C., and J.M. Stephens. 2005. Effects of leukemia inhibitory factor on 3T3-L1 adipocytes. *The Journal of Endocrinology* 185 (3): 485–496. https://doi.org/10.1677/joe.1.05980.
41. White, U.A., W.C. Stewart, R.L. Mynatt, and J.M. Stephens. 2008. Neuropoietin attenuates adipogenesis and induces insulin resistance in adipocytes. *The Journal of Biological Chemistry* 283 (33): 22505–22512. https://doi.org/10.1074/jbc.M710462200.
42. Mori, M., K. Yamaguchi, and K. Abe. 1989. Purification of a lipoprotein lipase-inhibiting protein produced by a melanoma cell line associated with cancer cachexia. *Biochemical and Biophysical Research Communications* 160 (3): 1085–1092.
43. Metcalf, D., N.A. Nicola, and D.P. Gearing. 1990. Effects of injected leukemia inhibitory factor on hematopoietic and other tissues in mice. *Blood* 76 (1): 50–56.
44. Marshall, M.K., W. Doerrler, K.R. Feingold, and C. Grunfeld. 1994. Leukemia inhibitory factor induces changes in lipid metabolism in cultured adipocytes. *Endocrinology* 135 (1): 141–147. https://doi.org/10.1210/endo.135.1.8013346.
45. Arora, G.K., A. Gupta, S. Narayanan, T. Guo, P. Iyengar, and R.E. Infante. 2018. Cachexia-associated adipose loss induced by tumor-secreted leukemia inhibitory factor is counterbalanced by decreased leptin. *JCI Insight* 3 (14). https://doi.org/10.1172/jci.insight.121221.
46. Beretta, E., H. Dhillon, P.S. Kalra, and S.P. Kalra. 2002. Central LIF gene therapy suppresses food intake, body weight, serum leptin and insulin for extended periods. *Peptides* 23 (5): 975–984.
47. Grossberg, A.J., J.M. Scarlett, X. Zhu, D.D. Bowe, A.K. Batra, T.P. Braun, and D.L. Marks. 2010. Arcuate nucleus proopiomelanocortin neurons mediate the acute anorectic actions of leukemia inhibitory factor via gp130. *Endocrinology* 151 (2): 606–616. https://doi.org/10.1210/en.2009-1135.
48. Lee, S., J. Lee, G.M. Kang, and M.S. Kim. 2018. Leptin directly regulate intrinsic neuronal excitability in hypothalamic POMC neurons but not in AgRP neurons in food restricted mice. *Neuroscience Letters* 681: 105–109. https://doi.org/10.1016/j.neulet.2018.05.041.

49. Miller, R.G., J.H. Petajan, W.W. Bryan, C. Armon, R.J. Barohn, J.C. Goodpasture, R.J. Hoagland, G.J. Parry, M.A. Ross, and S.C. Stromatt. 1996. A placebo-controlled trial of recombinant human ciliary neurotrophic (rhCNTF) factor in amyotrophic lateral sclerosis rhCNTF ALS Study Group. *Ann Neurol* 39 (2): 256–260. https://doi.org/10.1002/ana.410390215.
50. A double-blind placebo-controlled clinical trial of subcutaneous recombinant human ciliary neurotrophic factor (rHCNTF) in amyotrophic lateral sclerosis. ALS CNTF Treatment Study Group. 1996. *Neurology* 46 (5): 1244–1249.
51. Bluher, S., S. Moschos, J. Bullen Jr., E. Kokkotou, E. Maratos-Flier, S.J. Wiegand, M.W. Sleeman, and C.S. Mantzoros. 2004. Ciliary neurotrophic factorAx15 alters energy homeostasis, decreases body weight, and improves metabolic control in diet-induced obese and UCP1-DTA mice. *Diabetes* 53 (11): 2787–2796.
52. Ott, V., M. Fasshauer, A. Dalski, H.H. Klein, and J. Klein. 2002. Direct effects of ciliary neurotrophic factor on brown adipocytes: evidence for a role in peripheral regulation of energy homeostasis. *The Journal of Endocrinology* 173 (2): R1–R8.
53. Liu, Q.S., M. Gao, S.Y. Zhu, S.J. Li, L. Zhang, Q.J. Wang, and G.H. Du. 2007. The novel mechanism of recombinant human ciliary neurotrophic factor on the anti-diabetes activity. *Basic & Clinical Pharmacology & Toxicology* 101 (2): 78–84. https://doi.org/10.1111/j.1742-7843.2007.00092.x.
54. Watt, M.J., A. Hevener, G.I. Lancaster, and M.A. Febbraio. 2006. Ciliary neurotrophic factor prevents acute lipid-induced insulin resistance by attenuating ceramide accumulation and phosphorylation of c-Jun N-terminal kinase in peripheral tissues. *Endocrinology* 147 (5): 2077–2085. https://doi.org/10.1210/en.2005-1074.
55. Watt, M.J., N. Dzamko, W.G. Thomas, S. Rose-John, M. Ernst, D. Carling, B.E. Kemp, M.A. Febbraio, and G.R. Steinberg. 2006. CNTF reverses obesity-induced insulin resistance by activating skeletal muscle AMPK. *Nature Medicine* 12 (5): 541–548. https://doi.org/10.1038/nm1383.
56. Duff, E., C.L. Li, D.L. Hartzell, Y.H. Choi, M.A. Della-Fera, and C.A. Baile. 2004. Ciliary neurotrophic factor injected icv induces adipose tissue apoptosis in rats. *Apoptosis* 9 (5): 629–634. https://doi.org/10.1023/B:APPT.0000038042.31683.7b.
57. Kokoeva, M.V., H. Yin, and J.S. Flier. 2005. Neurogenesis in the hypothalamus of adult mice: potential role in energy balance. *Science* 310 (5748): 679–683. https://doi.org/10.1126/science.1115360.
58. Jin, H., R. Yang, G.A. Keller, A. Ryan, A. Ko, D. Finkle, T.A. Swanson, W. Li, D. Pennica, W.I. Wood, and N.F. Paoni. 1996. In vivo effects of cardiotrophin-1. *Cytokine* 8 (12): 920–926. https://doi.org/10.1006/cyto.1996.0123.
59. Zvonic, S., J.C. Hogan, P. Arbour-Reily, R.L. Mynatt, and J.M. Stephens. 2004. Effects of cardiotrophin on adipocytes. *The Journal of Biological Chemistry* 279 (46): 47572–47579. https://doi.org/10.1074/jbc.M403998200.
60. Moreno-Aliaga, M.J., N. Perez-Echarri, B. Marcos-Gomez, E. Larequi, F.J. Gil-Bea, B. Viollet, I. Gimenez, J.A. Martinez, J. Prieto, and M. Bustos. 2011. Cardiotrophin-1 is a key regulator of glucose and lipid metabolism. *Cell Metabolism* 14 (2): 242–253. https://doi.org/10.1016/j.cmet.2011.05.013.
61. Lopez-Yoldi, M., M. Fernandez-Galilea, L.M. Laiglesia, E. Larequi, J. Prieto, J.A. Martinez, M. Bustos, and M.J. Moreno-Aliaga. 2014. Cardiotrophin-1 stimulates lipolysis through the regulation of main adipose tissue lipases. *Journal of Lipid Research* 55 (12): 2634–2643. https://doi.org/10.1194/jlr.M055335.
62. Lopez-Yoldi, M., B. Marcos-Gomez, M.A. Romero-Lozano, N. Sainz, J. Prieto, J.A. Martinez, M. Bustos, and M.J. Moreno-Aliaga. 2017. Cardiotrophin-1 Regulates Adipokine Production in 3T3-L1 Adipocytes and Adipose Tissue From Obese Mice. *Journal of Cellular Physiology* 232 (9): 2469–2477. https://doi.org/10.1002/jcp.25590.
63. Zhu, S., F. Sun, W. Li, Y. Cao, C. Wang, Y. Wang, D. Liang, R. Zhang, S. Zhang, H. Wang, and F. Cao. 2011. Apelin stimulates glucose uptake through the PI3K/Akt pathway and improves insulin resistance in 3T3-L1 adipocytes. *Molecular and Cellular Biochemistry* 353 (1–2): 305–313. https://doi.org/10.1007/s11010-011-0799-0.
64. Vespasiani-Gentilucci, U., A. De Vincentis, J. Argemi, G. Galati, E. Anso, G. Patti, and A. Picardi. 2013. Cardiotrophin-1 is not associated with carotid or coronary disease and is inversely associated with obesity in patients undergoing coronary angiography. *Archives of Medical Science* 9 (4): 635–639. https://doi.org/10.5114/aoms.2013.37272.
65. Hung, H.C., F.H. Lu, H.Y. Ou, H.T. Wu, J.S. Wu, Y.C. Yang, and C.J. Chang. 2013. Increased cardiotrophin-1 in subjects with impaired glucose tolerance and newly diagnosed diabetes. *International Journal of Cardiology* 169 (3): e33–e34. https://doi.org/10.1016/j.ijcard.2013.08.112.
66. Hung, H.C., F.H. Lu, H.T. Wu, H.Y. Ou, Y.C. Yang, J.S. Wu, and C.J. Chang. 2015. Cardiotrophin-1 is inversely associated with obesity in non-diabetic individuals. *Scientific Reports* 5: 17438. https://doi.org/10.1038/srep17438.
67. Natal, C., M.A. Fortuno, P. Restituto, A. Bazan, I. Colina, J. Diez, and N. Varo. 2008. Cardiotrophin-1 is expressed in adipose tissue and upregulated in the metabolic syndrome. *American Journal of Physiology. Endocrinology and Metabolism* 294 (1): E52–E60. https://doi.org/10.1152/ajpendo.00506.2007.
68. Rendo-Urteaga, T., S. Garcia-Calzon, E. Martinez-Anso, M. Chueca, M. Oyarzabal, M.C. Azcona-Sanjulian, M. Bustos, M.J. Moreno-Aliaga, J.A. Martinez, and A. Marti. 2013. Decreased cardiotrophin-1 levels are associated with a lower risk of developing the metabolic syndrome in overweight/obese children after a weight loss program. *Metabolism* 62 (10): 1429–1436. https://doi.org/10.1016/j.metabol.2013.05.011.
69. Rose, T.M., and A.G. Bruce. 1991. Oncostatin M is a member of a cytokine family that includes leukemia-inhibitory factor, granulocyte colony-stimulating factor, and interleukin 6. *Proceedings of the National Academy of Sciences of the United States of America* 88 (19): 8641–8645.
70. Rose, T.M., M.J. Lagrou, I. Fransson, B. Werelius, O. Delattre, G. Thomas, P.J. de Jong, G.J. Todaro, and J.P. Dumanski. 1993. The genes for oncostatin M (OSM) and leukemia inhibitory factor (LIF) are tightly linked on human chromosome 22. *Genomics* 17 (1): 136–140. https://doi.org/10.1006/geno.1993.1294.
71. Tanaka, M., T. Hara, N.G. Copeland, D.J. Gilbert, N.A. Jenkins, and A. Miyajima. 1999. Reconstitution of the functional mouse oncostatin M (OSM) receptor: molecular cloning of the mouse OSM receptor beta subunit. *Blood* 93 (3): 804–815.
72. Sanchez-Infantes, D., U.A. White, C.M. Elks, R.F. Morrison, J.M. Gimble, R.V. Considine, A.W. Ferrante, E. Ravussin, and J.M. Stephens. 2014. Oncostatin m is produced in adipose tissue and is regulated in conditions of obesity and type 2 diabetes. *The Journal of Clinical Endocrinology and Metabolism* 99 (2): E217–E225. https://doi.org/10.1210/jc.2013-3555.
73. Komori, T., M. Tanaka, E. Senba, A. Miyajima, and Y. Morikawa. 2013. Lack of oncostatin M receptor beta leads to adipose tissue inflammation and insulin resistance by switching macrophage phenotype. *The Journal of Biological Chemistry* 288 (30): 21861–21875. https://doi.org/10.1074/jbc.M113.461905.
74. Komori, T., M. Tanaka, E. Senba, A. Miyajima, and Y. Morikawa. 2014. Deficiency of oncostatin M receptor beta (OSMRbeta) exacerbates high-fat diet-induced obesity and related metabolic disorders in mice. *The Journal of Biological Chemistry* 289 (20): 13821–13837. https://doi.org/10.1074/jbc.M113.542399.

75. Komori, T., M. Tanaka, H. Furuta, T. Akamizu, A. Miyajima, and Y. Morikawa. 2015. Oncostatin M is a potential agent for the treatment of obesity and related metabolic disorders: a study in mice. *Diabetologia* 58 (8): 1868–1876. https://doi.org/10.1007/s00125-015-3613-9.
76. Hattori, K., T. Sumi, T. Yasui, M. Morimura, H. Nobeyama, E. Okamoto, M. Noriyuki, K. Honda, H. Kiyama, and O. Ishiko. 2004. VEGF mRNA in adipocytes increase with rebound weight-gain after diet-restriction. *International Journal of Molecular Medicine* 13 (3): 395–399.
77. Rega, G., C. Kaun, S. Demyanets, S. Pfaffenberger, K. Rychli, P.J. Hohensinner, S.P. Kastl, W.S. Speidl, T.W. Weiss, J.M. Breuss, A. Furnkranz, P. Uhrin, J. Zaujec, V. Zilberfarb, M. Frey, R. Roehle, G. Maurer, K. Huber, and J. Wojta. 2007. Vascular endothelial growth factor is induced by the inflammatory cytokines interleukin-6 and oncostatin m in human adipose tissue in vitro and in murine adipose tissue in vivo. *Arteriosclerosis, Thrombosis, and Vascular Biology* 27 (7): 1587–1595. https://doi.org/10.1161/atvbaha.107.143081.
78. Miyaoka, Y., M. Tanaka, T. Naiki, and A. Miyajima. 2006. Oncostatin M inhibits adipogenesis through the RAS/ERK and STAT5 signaling pathways. *The Journal of Biological Chemistry* 281 (49): 37913–37920. https://doi.org/10.1074/jbc.M606089200.
79. Heinrich, P.C., I. Behrmann, S. Haan, H.M. Hermanns, G. Muller-Newen, and F. Schaper. 2003. Principles of interleukin (IL)-6-type cytokine signalling and its regulation. *The Biochemical Journal* 374 (Pt 1): 1–20. https://doi.org/10.1042/bj20030407.