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Mechanisms of chronic JAK-STAT3-SOCS3 signaling in obesity

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Janus kinase (JAK)-signal transducers and activators of transcription (STAT) signaling pathways are critical for the maintenance of homeostatic and developmental processes; however, deregulation and chronic activation of JAK-STAT3 results in numerous diseases. Among others, obesity is currently being intensively studied. In obesity, chronic JAK-STAT3 is activated by the CNS by increased circulating leptin levels leading to the development of leptin resistance, whereas in the peripheral organs chronic IL-6-induced JAK-STAT3 impairs insulin action. We report the consequences of chronic JAK-STAT3 induced signaling as present under obese conditions in the main metabolic organs.

The evolutionary conserved Janus kinase (JAK)-signaling transducers and activators of transcription (STAT) signaling pathway is used by a variety of cytokines, hormones and growth factors to regulate numerous developmental and homeostatic processes, including hematopoiesis, immune cell development, stem cell maintenance and organismal growth.[1] However, chronic activation of JAK-STAT underlies various diseases or disorders, such as cancer or obesity.[2-4]

Upon binding of the ligand to its receptor, two or more receptor-associated JAKs are brought into close proximity through receptor oligomerization, which leads to their autophosphorylation and/or transphosphorylation by the opposing JAK. Specifically, JAKs possess two nearly identical phosphate transfer domains, one domain exhibits the kinase activity, and the second inhibits the kinase activity of the first. Four members of the JAK family have been identified to date, namely JAK1, 2, 3, and TYK2.[5-11] The activated JAKs phosphorylate signature tyrosine residues in the cytoplasmic region of the receptors to create docking sites for STATs. The mammalian STAT protein family comprises seven members, namely STAT 1, 2, 3, 4, 5A, 5B and 6, which bind to phosphorylated tyrosine residues with their Src homology 2 (SH2) domain.[12-18] Upon docking to the receptor, the JAKs phosphorylate conserved tyrosine residues within the STAT protein that are located between the SH3 domain and the C-terminal transactivation domain (TAD). This phosphorylation results in the formation of parallel STAT dimers, which are stabilized by reciprocal phosphotyrosine and SH2 domain interactions.[19,20] Dimerization of STATs induces their nuclear translocation, whereupon the STAT dimer or more complex STAT oligomers bind to specific palindromic enhancer sequences in their target genes, ultimately controlling the expression of these genes.[19-25]

The JAK-STAT signaling pathway transcriptionally regulates its own suppressor. Suppressors of cytokine signaling (SOCS) molecules act as a negative feedback signal by inhibiting JAK and STAT activation and phosphorylation.[26,27] The SOCS family includes eight family members, SOCS1–7 and cytokine-inducible SH2-containing protein (CIS).[28,29] Another known suppressor of JAK-STAT is the phosphotyrosine phosphatase 1B (PTP1B), which can directly inactivate JAK and STAT and/or prevent JAK interaction with the tyrosine residue of the receptors.[30,31] Moreover, the transcriptional activity of STAT in the nucleus can also be controlled by protein inhibitors of activated STAT (PIAS), which blocks the DNA-binding activity of STAT.[32]

This review focuses on the chronic JAK-STAT3-SOCS3 signaling that is induced by accelerated leptin and interleukin-6 (IL-6) as present in obesity.

Chronic JAK-STAT3-SOCS3 in the CNS Causes Leptin Resistance and Obesity

Obesity is a steadily increasing health burden that affects more than one-third of Western populations. This disorder develops either as a result of increased nutritional intake, of decreased physical activity or both. These processes of energy uptake and expenditure are tightly controlled via leptin and insulin, hormones that act on specific neuronal populations in the central nervous system (CNS).[33,34] Leptin is secreted from white adipocytes proportional to the amount of fat stored in the white adipose tissue and acts in the CNS under normal conditions to suppress food intake and increase energy expenditure.[35] Leptin binds to the leptin receptor (LepR), of which multiple isoforms exist. In mice, six isoforms of the *lepr* protein have been identified (LepRa–LepRf) that can be divided into three classes with distinct functions: four short isoforms with shortened intracellular tails, one secreted (LepRe) and one long isoform (LepRb).[36] The

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LepRb consists of 1,162 amino acids and is the only isoform with a clearly demonstrated signaling capacity.[37] LepRb belongs to the family of class 1 cytokine receptors, which contain an extracellular ligand-binding, a transmembrane spanning and a cytoplasmic signaling domain.[37] Similar to other cytokine receptors, LepRb does not possess intrinsic enzymatic activity. Instead this receptor signals via JAK2, a non-covalently associated tyrosine kinase of the JAK family.[38-40] The autophosphorylation of JAK2 results in its activation and further phosphorylation of the tail of LepRb, which is then bound by the SH2 domain of STAT3.[41] In this way, LepRb-induced gene expression mediates the effects of leptin on energy homeostasis and neuroendocrine function.

The absence of LepRb in *db/db* mice results in obesity, impaired growth, infertility and diabetes mellitus.[37] These mice display a phenotype that is indistinguishable from that of *db3J/db3J* mice, which lack all three LepR isoforms, and comparable to that of leptin-deficient *ob/ob* animals.[41] Leptin administration to leptin-deficient *ob/ob* mice reduces the development of obesity and results in normal and lean mice.[42] Pioneering studies using the Cre-loxP system revealed that leptin exerts its physiological effects in neurons of the CNS, given that mice carrying a specific LepR inactivation in Nestin-expressing neurons developed obesity comparable to that of *ob/ob* and *db/db* mice.[43] Furthermore, complementation of LepRb expression specifically in the CNS of *db/db* mice resulted in lean mouse mutants, further underlining leptin's function in the CNS.[44] In line with these experiments, intracerebroventricular leptin administration reduces food intake in lean and *ob/ob* mice.[45] Interestingly, conditional inactivation of STAT3 in neurons of the CNS phenocopied the obese phenotype of LepR-deficient mice, which indicates that LepR-induced signaling is mediated through downstream activation of STAT3.[46]

LepR expression is widely distributed throughout the brain, and identification of neuronal populations that mediate leptin's effects on energy expenditure and caloric intake is important to understand the physiological relevance of leptin action. Early dissectional studies have demonstrated that specific areas of the hypothalamus, such as the arcuate nucleus, are crucial for the central control of energy expenditure and food ingestion. In line with this notion, experiments with conditional LepR mice demonstrated that neurons which express the anorexigenic pro-opiomelanocortin (POMC) and those expressing orexigenic agouti-related peptide (AgRP) and neuropeptide Y (NPY)—two neuronal populations in the arcuate nucleus—are primary sites within the brain that control the aforementioned processes through further regulation of second-order neurons.[47] Specifically, LepR-induced signal transduction via STAT3 directly activates POMC expression, which is post-translationally processed into the active peptide α melanocyte-stimulating hormone (MSH).[48] The secreted α-MSH activates second-order neurons that express the receptors for α-MSH namely melanocortin 3 and 4 receptors (MC3R and MC4R).[35] On the other hand, leptin reduces AgRP expression, which inhibits MC3R and MC4R induced signaling.[49] In line with this evidence, defined inactivation of either LepR or STAT3 in POMC neurons reduced POMC expression and energy expenditure and increased food intake, thereby causing mild obesity in the knockout animals; however, the obesity was less severe compared with that of *db/db* mice, which implies that leptin targets neuronal populations other than POMC neurons in the arcuate nucleus.[47,48]

The importance of these knockout studies for our current understanding of the molecular mechanisms of leptin action in specific neuronal populations of the CNS is invaluable; however, exogenous leptin administration shows no therapeutic effect in most patients with obesity or diet-induced obese mice. This fact arises owing to the development of leptin resistance, a phenomenon that underlies the majority of obesity cases rather than the rare described mutations in the genes encoding leptin or LepR. In obese individuals with leptin resistance, leptin levels are high due to the drastically elevated fat load and expansion of the white adipose tissue; the protein is, however, unable to convey its biological effects. Two mechanisms have been proposed that might account for the development of leptin resistance: (1) the saturation of leptin transport across the blood-brain barrier in obesity or (2) the chronic leptin signal transduction caused by high leptin levels increases expression of negative feedback regulators, thereby making LepR-expressing neurons resistant to leptin. Although the first assumption has been addressed by some reports,[50] the current scientific view favors the second argument.

Leptin-induced signaling via STAT3 rapidly activates the negative feedback regulator SOCS3, which inhibits leptin-induced signal transduction. It is tempting to speculate that, under obese conditions, increased basal circulating leptin might increase the basal activity of LepRb/STAT3 signaling in neurons of the CNS. This process would in turn elevate the otherwise silent SOCS3 expression levels, thus further impairing LepRb sensitivity. Leptin resistance therefore manifests mainly as the inability of acute leptin action to suppress food intake and increase energy expenditure.[51] A function of central SOCS3 in limiting LepRb action has been implicated by the finding of largely accelerated SOCS3 expression in numerous animal models of obesity.[52] Moreover, mice lacking one allele of SOCS3 are protected from the development of diet-induced obesity and maintain central leptin sensitivity.[53] Of note, the complete inactivation of SOCS3 is embryonically lethal owing to the fact that SOCS3 limits signaling of numerous cytokine receptors during development and physiology.[54,55] Whereas mice with a CNS-specific inactivation of SOCS3 still retain sensitivity to leptin under obese conditions,[56] in mice with inactivation of SOCS3 in POMC neurons leptin sensitivity is only maintained in this neuron population; these animals are thus only mildly protected against diet-induced leptin resistance.[57] Evidently, these experiments demonstrate a critical role of SOCS3 as a negative regulator of LepRb-induced signaling in the CNS.

Gamber and colleagues demonstrated increased expression of the LepRb in the hypothalamus of obese mice, especially in POMC neurons. To investigate the relevance of this finding in the development of obesity, the authors generated mice overexpressing LepRb in POMC neurons.[51] Overexpression of LepRb specifically in POMC neurons had no effect on adiposity or SOCS3 expression under normal conditions; however, diet-induced obesity associated with elevated circulating leptin levels increased SOCS3 expression in POMC neurons and

accelerated caloric intake and subsequently elevated body weight of these mice. These results indicate that an over-reactivity of LepR-induced signaling in POMC neurons—as present in obesity—increases SOCS3 expression, which in turn leads to the development of leptin resistance.[51] In line with these experiments, we could demonstrate that expression of a constitutively active variant of STAT3 specifically in POMC neurons increases SOCS3 expression independent of leptin action under normal conditions. This expression translated into increased food intake and adiposity as a result of the development of leptin resistance.[58] When exposed to diet-induced obesity, these mutant mice developed obesity as severe as that of control mice; both cohorts showed comparable leptin-resistant states and similarly activated STAT3 and elevated SOCS3 levels.[58] Taken together, these data suggest that high leptin in obesity increases basal LepRb-induced STAT3-mediated downstream signaling, particularly in POMC neurons, which eventually increases SOCS3 expression, thereby impairing acute leptin-activated signaling, namely by developing a resistance to leptin. However, while the role of leptin resistance in POMC neurons seems to meet the current model, the function of elevated leptin-induced STAT3 activation specifically in AgRP neurons resulted in a different outcome. Mice with overactivated STAT3 in AgRP neurons show a relative resistance to diet-induced obesity owing to increased locomotor activity.[59] Though STAT3 activation was supposed to alter AgRP and SOCS3 expression in this neuronal subpopulation, expression of those genes was unaltered in these mice. Thus, these experiments demonstrate that mechanisms of leptin resistance in AgRP neurons and POMC neurons might follow a different path. Nevertheless, signals other than leptin might well increase central SOCS3 expression under obese conditions that lead to leptin resistance.

Noteworthy, while numerous studies report the CNS as major site for leptin-induced STAT3 activity, also peripheral actions of leptin have been described. Of note, an unanticipated role for leptin-induced JAK-STAT3 in cardioprotection has been discovered.[60] Here, STAT3 activation by leptin reduced infarct size, a function that has been previously demonstrated for TNFα-induced STAT3 action.[61] Collectively, these studies reveal that leptin not only exerts central actions but can also have beneficial effects in peripheral organs. However, though such peripheral functions of leptin exist, chronic JAK-STAT3-SOCS3 action in obesity is mainly derived from other signals that vice versa not only act in the periphery but can also have substantial role in the CNS. Among these signals, not only inflammatory cytokines, such as IL-6 and tumor necrosis factor α, but also free fatty acids and other lipids.

Chronic JAK-STAT3-SOCS3 in Peripheral Organs Causes Insulin Resistance

As recently shown in obesity elevated circulating levels of cytokines impair insulin signaling in peripheral organs and even in the brain.[62,63] Several studies have demonstrated a link between insulin resistance and obesity as a chronic inflammatory state. In obese mice and humans numerous inflammatory cytokines are released in excess by the white adipose tissue derived from adipocytes as well as from recruited inflammatory cells such as macrophages.[64-66] Among the most prominent cytokines that are over-represented in the bloodstream of obese individuals with obesity are TNFα and IL-6; however only IL-6-induced signaling is mediated via JAK and STAT3.[42] In detail, IL-6 binds to its receptor, comprising the IL-6Rα chain (which confers specificity) and the GP130 signaling chain (which is common to other IL-6 type cytokine receptors).[42] The IL-6-bound receptor complex activates intracellular JAK2 subsequently leading to STAT3 activation, which in turn modulates gene expression, for example elevating SOCS3 expression. Of note, although certainly the IL-6Rα chain is expressed mainly by hepatocytes and immune cells, other cell types can also respond to IL-6 through a mechanism called IL-6 trans-signaling. In this process, the α chain is cleaved from the cell surface and in this soluble form jointly with IL-6 can bind to ubiquitously expressed GP130 to induce JAK-STAT3-mediated downstream signaling events.[67,68]

IL-6 derived from the muscle during intense exercise has been shown to exert beneficial effects on glucose homeostasis; however, increased basal IL-6 level in obese individuals impair insulin signaling presumably owing to its chronic nature. Clinical studies link elevated IL-6 serum levels with obesity, severity of insulin resistance and the risk of developing type 2 diabetes mellitus.[69-72] Accordingly, obese women exhibited a reduction in IL-6 serum levels and increased insulin sensitivity after weight loss.[73]

However, inactivation of IL-6 in mice has produced conflicting results and the expected increased insulin-sensitive phenotype could not be shown by two independent studies using the same IL-6 knockout mice.[74,75] However, Wallenius et al. demonstrated mature-onset obesity and decreased glucose tolerance in IL-6-deficient mice,[74] whereas by contrast, Di Gregorio and colleagues could not detect any obvious phenotype related to maturity-onset obesity and diabetes.[75]

The mechanism through which chronically raised IL-6 levels in obesity may cause insulin resistance is not yet defined, but may involve basal increases of SOCS protein levels in peripheral organs, similarly to the findings described for basal leptin-derived signal transduction in the CNS. Elevated IL-6 signaling in obesity leads to increased SOCS1 and SOCS3 protein levels in the three major insulin sensitive peripheral tissues, white adipose tissue, liver and muscle.[76] On the molecular level, SOCS1 and SOCS3 impair insulin action by binding to insulin receptor substrates (IRS)-1 and IRS-2, which leads to IRS-1 and IRS-2 ubiquitination and degradation.[77-79] Interestingly, SOCS1 whole body knockout mice demonstrate hyperglycemia but die before reaching 3 weeks of age due to enhanced interferon γ signaling.[80] As mentioned previously, SOCS3 whole-body knockout mice are embryonically lethal due to inappropriate leukemia inhibitory factor signaling.[54,55] SOCS3 heterozygous knockout mice are, however, protected against the development of obesity-associated insulin resistance.[53] On the other hand, overexpression of SOCS1 and SOCS3 leads to the development of insulin resistance by reducing tyrosine phosphorylation of IRS-1 and IRS-2, which is required for further insulin signal transduction.[77] These experiments point to a peripheral role of chronic IL-6-evoked

JAK-STAT3 induced SOCS3 expression in the development of insulin resistance under obese conditions. As follows, we summarize the effects of chronic JAK-STAT3-SOCS3 signaling on the development of obesity-induced insulin resistance in the main peripheral metabolic organs.

White adipose tissue. Under basal conditions, up to 35% of systemic IL-6 is produced by the adipose tissue, predominantly by visceral fat depots.[81] The secretion from the visceral fat via the portal vein specifically affects the liver, given that almost 80% of total liver blood is derived from there.[81] Interestingly, increased diet-induced IL-6 release from the white adipose tissue was shown to crosstalk to the liver which displayed accelerated hepatic SOCS3 expression in turn impairing insulin action.[82] Nevertheless, locally, IL-6 induces the expression of SOCS3 in 3T3-L1 adipocytes[83,84] whereas overexpression of SOCS3 in adipocytes reduces IRS-1 protein levels as well as insulin-stimulated IRS-1 and IRS-2 phosphorylation and binding of p85 to IRS-1.[79,85] This action impairs insulin signaling and reduces glucose uptake in adipocytes and lipogenesis. However, mice which overexpress SOCS3 in adipocytes failed to develop diet-induced obesity owing to the fact that the insulin resistance occurred only locally in the white adipose tissue rather than systemically; this finding highlights the limited contribution of adipose tissue in whole-body glucose disposal.[85] Palanivel and colleagues investigated mice with white adipose tissue-specific SOCS3 deficiency, which showed only a mild protection against the development of obesity-associated insulin resistance.[86] Thus, although chronic JAK-STAT3-induced SOCS3 expression in white adipose tissue in obesity impairs local insulin sensitivity, systemic insulin action is unaltered. This phenomenon points to an important role of elevated SOCS3 levels in organs other than white adipose tissue to mitigate whole-body insulin sensitivity. However, in obesity, white adipose tissue is the predominant organ to release IL-6 into the circulation, which in turn inhibits insulin action in other organs.

Liver. The liver plays a key part in the regulation of whole-body energy homeostasis by controlling blood glucose levels during fasting and by storing excessive glucose as glycogen in the fed state. Studies in murine primary hepatocytes and human hepatocarcinoma cells revealed that IL-6 causes insulin resistance by suppressing tyrosine phosphorylation of IRS-1 through induction of SOCS3.[87] Moreover, SOCS1 and SOCS3 are elevated in the liver of obese mice[76] and the adenoviral-mediated gene transfer of SOCS1 or SOCS3 to the liver leads to glucose intolerance and insulin resistance.[77,78] In contrast treatment of genetically obese *db*/*db* mice with antisense oligonucleotides against SOCS1 and SOCS3 improves the development of insulin resistance and hepatic steatosis in these mice.[78] Accordingly, the hepatocyte-specific disruption of SOCS3 first improves insulin sensitivity in chow-fed animals by ameliorating IRS-1 tyrosine phosphorylation,[88,89] but with age these hepatocyte-specific SOCS3 knockout mice developed obesity and systemic insulin resistance owing to the hyperactivity of STAT3, which increases acute-phase proteins and inflammation.[88] The investigators conclude, that SOCS3 is a mediator of insulin resistance in the liver, but the lack of SOCS3 in the liver promotes systemic insulin resistance by mimicking chronic inflammation. In accordance with this study, Sachithanandan et al. demonstrate that diet-induced obesity in hepatocyte-specific SOCS3-deficient mice accelerates hepatic inflammation which leads to more pronounced development of systemic insulin resistance, hepatic steatosis and lipogenesis.[89] These data are also in line with our experiments which reveal a critical role of hepatic IL-6Rα-induced downstream signaling in the prevention of inflammatory cytokine expression derived from liver-resident Kupffer cells that impairs insulin action in the whole body.[90] Nevertheless, IL-6-induced STAT3 activation in hepatocytes is required for the proper suppression of hepatic glucose production during fasting, which is impaired under obesity conditions.[91] Taken together, hepatic IL-6-induced JAK-STAT3-SOCS3 signaling exerts a dual role on whole-body glucose homeostasis by preventing accelerated inflammation and inhibiting local insulin action.

Skeletal muscle. Skeletal muscle, which uses glucose and fatty acids as fuel, is a primary target tissue for the development of insulin resistance. Forty percent of the body mass in non-obese subjects consists of skeletal muscle and 30% of the resting metabolic rate can be traced back to the skeletal muscle. Numerous studies have revealed, that skeletal muscle-specific defects in insulin signaling contribute to systemic metabolic phenotypes.[92] However, IL-6 released from the muscle during intense exercise exerts beneficial effects on whole-body glucose metabolism, whereby the chronically IL-6 levels in the obese state impair insulin action.[93] Nevertheless, IL-6 increases SOCS3 as well a PTP1B mRNA in skeletal muscle, thus inhibiting local and systemic insulin sensitivity[94] and SOCS3 mRNA is increased in murine muscle in diet-induced and genetic obesity.[76,95] A recent study from Yang et al. demonstrates that overexpressing SOCS3 in the murine muscle leads to the development of both skeletal muscle-specific and systemic insulin resistance by antagonizing IRS-1 phosphorylation.[95] However, in a similar approach, Lebrun et al. demonstrate that muscle-specific SOCS3 overexpression animals are overweight as a result of decreased locomotor activity rather than through the development of skeletal muscle specific insulin resistance.[96] Nevertheless, muscle-specific SOCS3 knockout mice exposed to diet-induced obesity are protected against hyperinsulinemia and insulin resistance as these animals exhibit enhanced skeletal muscle IRS-1 and AKT phosphorylation resulting in increased glucose uptake in the muscle.[97] Collectively, these studies reveal that chronic JAK-STAT3-SOCS3 in skeletal muscle impairs whole-body insulin sensitivity.

Conclusion

Chronic JAK-STAT3-SOCS3 during the course of obesity impairs proper leptin and insulin action and generates a futile cycle that further promotes weight gain. Recent advances in genetic mouse models combined with dietary composition have shed light on the underlying molecular mechanisms. Here, we report the mechanisms of chronic JAK-STAT3-SOCS3 signaling in obesity induced in the CNS via excessive leptin and in the periphery via elevations of IL-6 (**Fig. 1**) although vice versa

functions for both signals have been reported. We are aware of the existence of other signal transducers and crosstalk of the aforementioned mediators that regulate chronicity of JAK-STAT3-SOCS3 in the development of obesity, but are unable to address those in this framework. Moreover, numerous other high profile manuscripts exist that support our discussion, but have not been mentioned in this review. More effort has to be put forth to clarify the cell type-specific mechanisms of the JAK-STAT3-SOCS3 axis on the development of obesity-associated disorders such as leptin resistance and insulin resistance to approach suitable strategies in the therapeutic combat of this epidemiological disease. The discrepancy of acute vs. chronic effects of JAK-STAT3-SOCS3 complicates this task, the investigation of which has clear potential for further research.

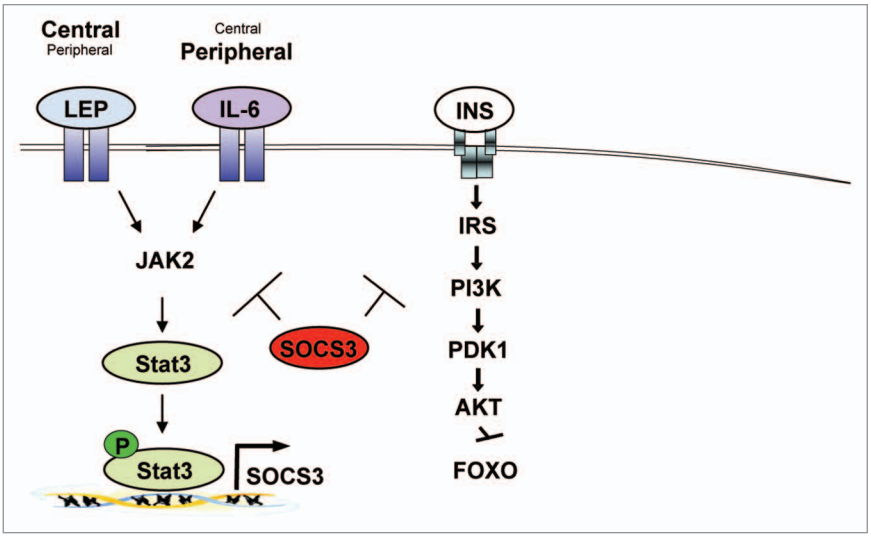

Figure 1. Chronic JAK-STAT3-SOCS3 signaling in obesity. Obesity increases circulating levels of leptin and IL-6 that in turn chronically activate intracellular JAK-STAT3 signaling. While Leptin (Lep) acts predominantly in the central nervous system, IL-6 has been reported to mainly function in peripheral organs, though both factors can also act vice versa. Chronic JAK-STAT3 signaling induced by leptin and IL-6 lead to the increased expression of the negative regulator SOCS3. SOCS3 in turn not only negatively regulates leptin and IL-6 signaling but also impairs insulin (INS) action eventually leading to obesity and insulin resistance.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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