Review

SOCS, inflammation and metabolism

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Abstract

Obesity is characterized by the development of low-grade chronic inflammation, which is a contributing factor in defective energy metabolism. A hallmark of metabolic dysregulation, obesity is a life-style disease that contributes to diabetes, hypertension, and dyslipidemia. Further, recent studies warn that obesity can be a risk factor for certain cancers and exacerbates infectious diseases. This association is called the "metabolic domino". Suppressor of cytokine signaling (SOCS) proteins are negative feedback regulators of cytokine and hormone signaling mediated by the JAK-STAT signaling pathway. SOCS proteins regulate cell-cell communication through JAK-STAT-dependent cytokines and signaling by Toll-like receptors (TLRs) and they may be influenced by dietary factors such as fatty acids and glucose. In this review, we focus on the role of the JAK-STAT-SOCS signaling cascade in metabolic disorder and obesity-related diseases.

Introduction

Human society has survived facing starvation, predation and infection. Advances in sciences including biology, medicine, agriculture, and engineering, have enriched lives. However, we now confront metabolic syndrome comprising disorders such as diabetes, cardiovascular disease, inflammation, and cancer. Obesity is the underlying cause of metabolic syndrome, which is a pandemic disease attributed to the changing global food system, wherein processed foods are heavily marketed, readily available, and affordable.

Because of their influence on metabolic syndrome, members of the suppressor of cytokine signaling (SOCS) family of proteins are the focus of intensive and numerous studies. Cytokine inducible SH2-protein (CIS)/SOCS proteins inhibit the activation of the JAK-STAT pathway and regulate signaling by interleukins (ILs), interferons (IFNs), members of the tumor necrosis factors (TNF) superfamily, growth factors, and hormones (Endo *et al.* 1997, Yoshimura *et al.* 2007). SOCS proteins regulate immune responses such as infection, inflammation and allergy, leukocyte homeostasis, and cell growth as well as metabolic processes such as glucose turnover (Howard & Flier 2006). Our literature search identified over 500 publications regarding the relationship between the SOCS family and metabolic syndrome (Figure 1, left). Among SOCS proteins, SOCS3 is potently involved in the progression of obesity and diabetes. These diseases are risk factor for cancers, infection, stroke, myocardial infraction, ulcers, infertility, and gallstones. Among a series of diseases, SOCS3 associates with obesity-related cancers (Figure 1, right). Recently, obesity has attracted great attention, because it is linked to the pathogenesis of certain cancers, including those of the colon, esophagus, breast, stomach, and pancreas (Wolin *et al.* 2010). Because patients with obesity-associated cancers experience higher mortality and are more resistant to chemotherapy, increased research efforts in this area are urgently required. In this review, our main focus is on the underlying mechanisms of metabolic dysregulation of the SOCS signaling pathway.

Structure and function of SOCS proteins

The genes that encode components of the JAK-STAT signaling pathway are transcriptionally regulated by its own SOCS family members (Inagaki-Ohara *et al.* 2013, Yasukawa *et al.* 2000). The structures of CIS/SOCS proteins are similar and include a central Src-homology 2 (SH2) domain that varies in length with limited homology in their N-terminal regions and a SOCS box motif in their C-terminal domains (Figure 2). The SOCS box interacts with Elongins B and C and

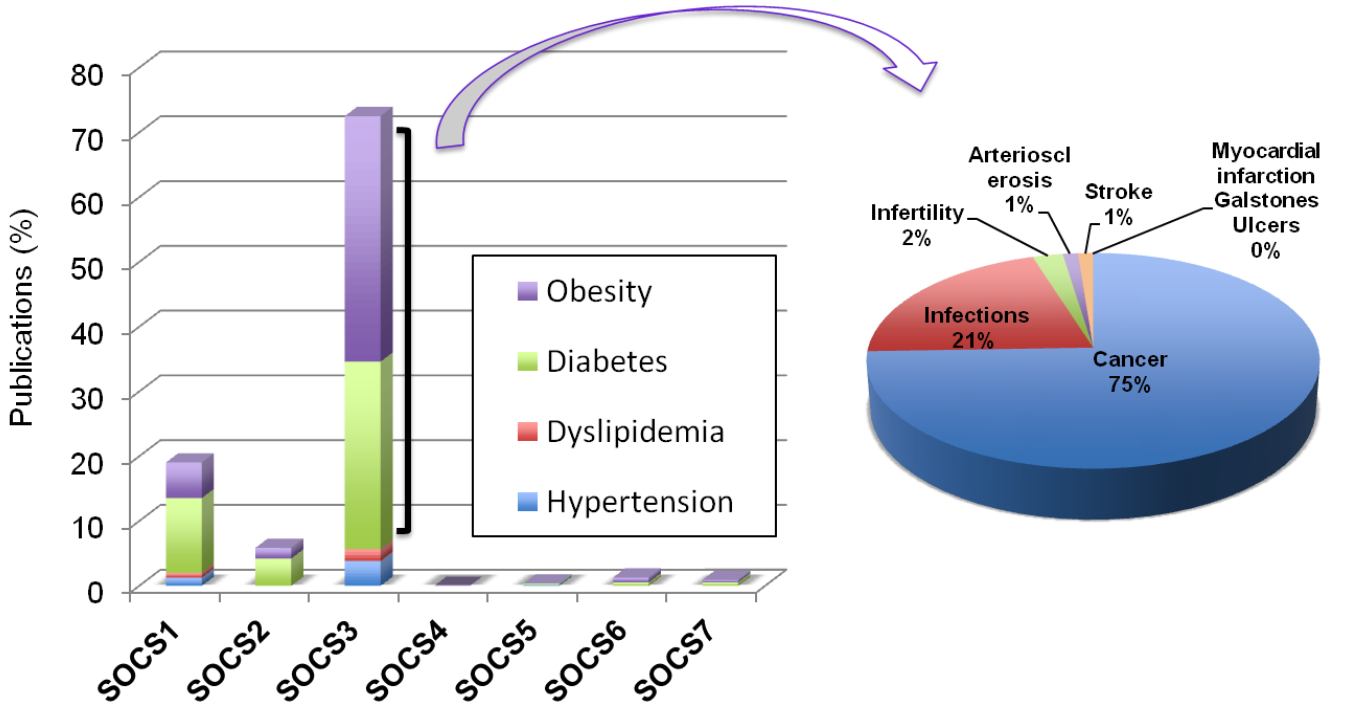

Figure 1. SOCS3 is a critical molecule in the development of metabolic syndrome and obesity-associated diseases. Each bar indicates the percentage of publications regarding metabolic syndrome on each SOCS family member according to a search of PubMed. 100 x (each SOCS)/(SOCS1-7) (left). Each pie chart shows the percentage of publications on obesity and diabetes-associated diseases involved in alteration of SOCS3 expression (right).

Cullin 5 to catalyze the ubiquitination of bound signaling protein, the RING-finger-domain-only protein RBX2 (which recruits E2 ubiquitin–transferase) (Figure 2) (Yoshimura *et al.* 2012). CIS/SOCS family proteins as well as other SOCS-box-containing molecules, likely act as E2 ubiquitin ligases. Because SOCS molecules bind to certain tyrosine-phosphorylated proteins, including Mal (toll-like receptor signaling) and IRS1/2 (insulin receptor substrate signaling) (Yoshimura *et al.* 2012), these targets may be ubiquitinated by SOCS. Unlike other SOCS proteins, SOCS1 and SOCS3 include a unique KIR domain, which is required for inhibition of JAK tyrosine kinase activity (Yasukawa *et al.* 1999) (Figure 2). The KIR domain of SOCS3 may function as a pseudosubstrate (Kershaw *et al.* 2013, Yasukawa *et al.* 1999) as well as a direct substrate of the ubiquitin-proteasome system (Piessevaux *et al.* 2008).

The role of SOCS proteins in leptin and insulin signaling

Obesity is characterized by chronic low-grade systemic and local inflammation. Infiltrating macrophages produce IL-1β and TNF-α, and T cells release IFN-γ as well as TNF-α. These pro-inflammatory cytokines are toxic for the pancreatic β-cells. Diabetes is caused when insulin production by β-cells is deficient (type 1 diabetes; T1D) or when cells that express the insulin receptor (IR) cannot respond to physiological concentrations of insulin (type 2 diabetes; T2D). Evidence indicates that genetic and environmental factors cause T1D (Bluestone *et al.* 2010). In contrast, T2D is caused by life-style (e.g. high-fat diet [HFD] and insufficient exercise) and accounts for more than 95% of patients with diabetes. T2D leads to alterations of glucose and lipid metabolism associated with insulin resistance (Lebrun & Van Obberghen 2008). Cytokines accelerate resistance to leptin and insulin in patients with T2D (Suchy *et al.* 2013). SOCS proteins regulate cytokine signaling and play important roles in pathophysiological processes leading to diabetes and obesity -associated diseases as well (Tanti *et al.* 2012).

Leptin Signaling

Leptin (product of ob gene), an adipocyte-derived hormone, binds to its receptor (ObR) in the hypothalamus to decrease food consumption and increase energy expenditure (Friedman & Halaas 1998). ObR is synthesized as multiple isoforms (ObRa–ObRf) as follows: four short isoforms with shortened intracellular tails (ObRa,c,d and f), one secreted (ObRe) and one long isoform (ObRb). Leptin belongs structurally to the long-chain helical cytokine family and activates the JAK-STAT signaling pathway and PI3K via ObRb, which is a type I cytokine receptor, similar to gp130

(Al-Qassab *et al.* 2009, La Cava & Matarese 2004). ObRb lacks intrinsic enzymatic activity and is activated by phosphorylation of its Cterminus by autophosphorylated JAK2, which is bound to the SH2 domain of STAT3 (Howard & Flier 2006). In the nucleus, STAT3 mediates gene transcription, including that of SOCS3. SOCS3 binds phosphorylated tyrosyl residue 985 (PY-985) of ObRb and to JAK2 to attenuate leptin receptor-mediated signaling. Phosphorylation of PY-985 of ObRb recruits the SH2 domain-containing protein-tyrosine phosphatase SHP-2 that functions upstream of extracellular-signal-regulated kinase (ERK) and c-fos transcription (Banks *et al.* 2000).

Leptin-stimulated signaling via STAT3 rapidly induces SOCS3, which inhibits signaling through the leptin receptor. Further studies of gene-targeted mice reveal that leptin's action specific to the central nervous system is sufficient to regulate body weight, food consumption, energy expenditure, glucose metabolism, and behavior (Gautron & Elmquist 2011). However, leptin's anorexigenic effects are suppressed in obese individuals and animals with HFD-induced obesity, despite elevated levels of serum leptin. This pathological condition is termed "leptin resistance" (Gautron & Elmquist 2011). These observations led to the proposal that SOCS3 is a potential mediator of leptin resistance. Further, peripheral administration of leptin to ob/ob mice specifically induces SOCS3 mRNA in regions of the hypothalamus that are important for regulating feeding behavior (Bjorbaek *et al.* 1998). Mice lacking SOCS3 from cells of the entire brain or only from proopiomelanocortin (POMC) neurons, which are leptin target neurons present in the arcuate nucleus of the hypothalamus, are resistant to HFD-induced obesity (Kievit *et al.* 2006, Mori *et al.* 2004). In addition, studies of SOCS3 transgenic mice show that overexpression of SOCS3 in POMC neuron but not in ObRb neurons is sufficient to impart leptin resistance and obesity mediated by antagonizing signaling through phosphorylated STAT3 and mTOR-S6K (Reed *et al.* 2010). In the periphery, leptin inhibits insulin secretion and expression of preproinsulin mRNA in the pancreatic β- cells. SOCS3 expressed by β-cells is involved in leptin-mediated inhibition of preproinsulin synthesis (Mori *et al.* 2007). Furthermore, leptin transactivates STAT3/STAT5b and the promoter of the preproinsulin 1 gene, and SOCS3 inhibits the activities of both promoters (Lebrun & Van Obberghen 2008), suggesting that SOCS3 inhibits directly the JAK-STAT signaling pathway as well as downstream signaling when the pathway is activated by leptin.

Insulin signaling

Insulin is secreted by the pancreas and stimulates the uptake of glucose and nutrients into peripheral target tissues. Like leptin, insulin reduces body weight and food intake, and regulates the expression of genes encoding neuropeptides as well as the activity of hypothalamic neurons. Similarly, signaling of the insulin receptor (IR) is mediated by phosphorylation of tyrosyl residues. Unlike ObRb, the IR has intrinsic tyrosine kinase activity that upon ligand binding, autophosphorylates the transmembrane domain of its β-subunit on tyrosyl residues Y1158, Y1162, and Y1163 to recruit downstream effector proteins, including IR substrates (IRS) 1 and 2. SOCS1 and SOCS3 bind to the IR. SOCS1 phosphorylated on its C-terminus (Y1158, Y1162 and Y1163), SOCS3, and protein-tyrosine phosphatase 1B (PTP-1B) suppress insulin and leptin signaling via different molecular mechanisms (Suchy *et al.* 2013) (Figure 3).

Increased expression of SOCS1 and SOCS3 induces insulin resistance in a variety models of obesity and diabetes via inhibition of JAK-STAT signal-

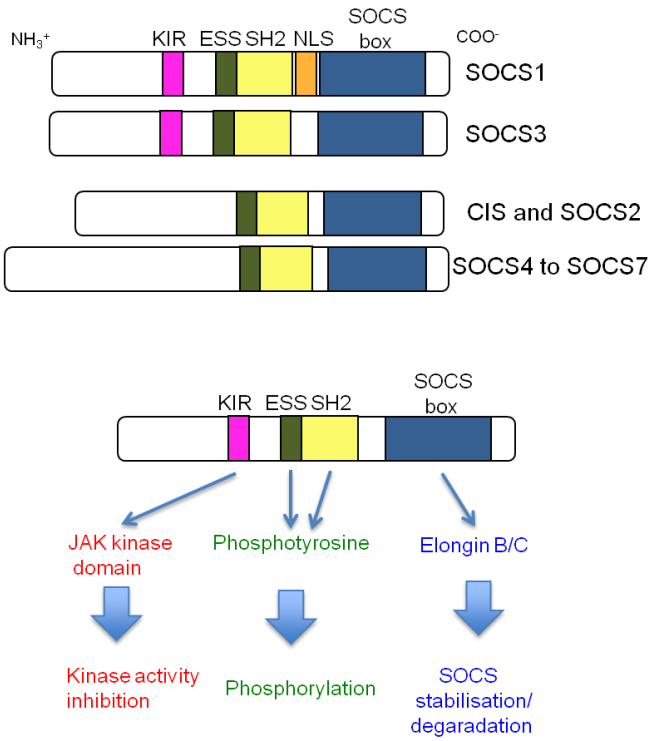

Figure 2. The structure and function of SOCS proteins. The SOCS family consists of eight members. All eight members share a central SH2 domain, extended SH2 domain (ESS), and a C-terminal SOCS box. In addition, SOCS1 and SOCS3 possess a kinase inhibitory region (KIR) that serves as a pseudo-substrate for JAKs that inhibits JAK function. Only SOCS1 contains a nuclear localization signal. A diagram of the extended interactions of SOCS with target proteins. The SOCS box interacts with several ubiquitinating machinery enzymes, i.e. Elongins B and C.

ing, competition for the binding of the IRS1 or targeting the degradation of IRS1 (Howard & Flier 2006, Yoshimura *et al.* 2007). However, SOCS1/RAG2-deficient mice, which survive to adulthood and gain body weight similar to wild-type mice, exhibit inflammation of adipose tissue, accompanied by elevated levels of leptin, TNF-α, and CD68 (a macrophage marker) in adipose tissue (Emanuelli *et al.* 2008). They also exhibit increased transcription of lipogenic genes in the liver, such as Srebp1c and Fas (Emanuelli *et al.* 2008). Furthermore, SOCS1 over-expression alone is insufficient to block total IFN-γ activity in pancreatic islets (Zaitseva *et al.* 2009). Interestingly, SOCS1-deficient neonatal mice exhibit drastic hypoglycemia and hypoinsulinemia, develop multiorgan inflammatory disease, and die before weaning (Jamieson *et al.* 2005). In contrast, SOCS3 haplo-deficient mice and mice with SOCS3-deficiency in the brain are resistant to HFD-induced obesity and are insulin resistance (Howard *et al.* 2004, Mori *et al.* 2004).

Inhibition of the expression of SOCS3 alone or together with SOCS1 and SOCS3, using antisense oli-

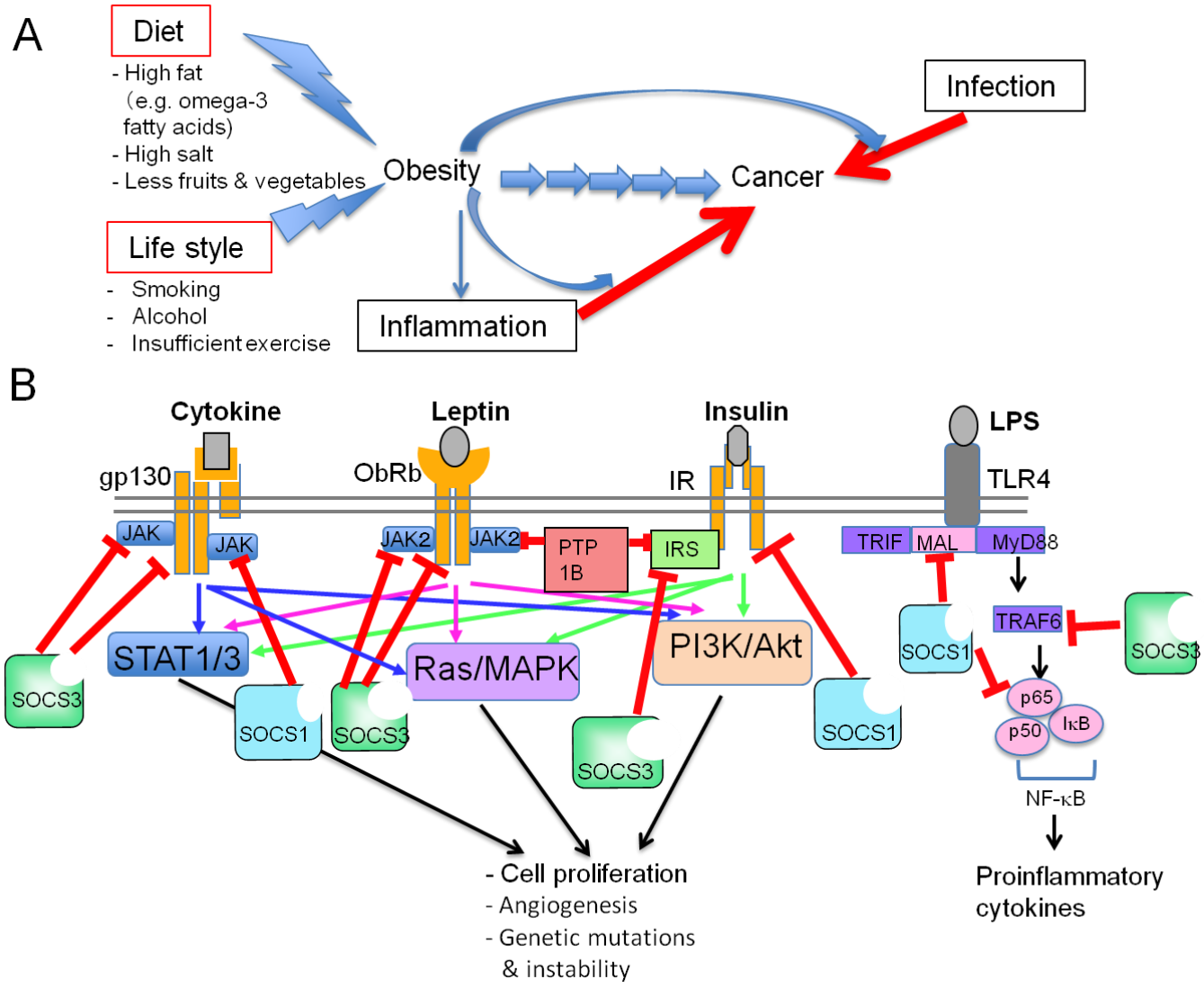

Figure 3. Multiple signaling pathways activated in obesity-associated diseases. A) Diet and lifestyle are critical factors for the development and regulation of obesity. Obesity is characterized by chronic low-grade systemic and local inflammation. Further, obesity accelerates inflammation- and infection-associated cancers through the receptors for cytokines, leptin, insulin, and bacterial components such as LPS via multiple signaling pathways including JAK-STAT, Ras-MAPK, PI3KAkt, and TLR. ObRb, which is analogous to gp130, lacks intrinsic kinase activity as illustrated in B). B) Binding of leptin to ObRb induces autophosphorylation and activation of noncovalently associated JAK2, which in turn, leads to phosphorylation of highly conserved tyrosyl residues in the intracellular domain of ObRb that recruit STAT3. STAT3 activation induces SOCS3 expression. Unlike gp130 and ObRb, IR possesses intrinsic tyrosine kinase activity that recruits and phosphorylates effector IRS molecules that, in turn, recruit adaptor molecules and mediate downstream signaling through PI3K and ERK. PTP1B inhibits leptin and insulin signaling by dephosphorylating JAK2 and IR, respectively.

gonucleotides in the livers of db/db mice, suppresses the expression of lipogenic genes (Ueki *et al.* 2004). Hepatic SOCS3 mediates insulin resistance; however, aged hepatocyte-specific SOCS3-deficient mice exhibit reduced insulin signaling in muscle, although insulin sensitivity in the liver is enhanced (Torisu *et al.* 2007). These studies suggest that lack of SOCS3 in the liver promotes systemic insulin resistance mediated by STAT3 activation induced by inflammatory factors produced from the liver. SOCS1-deficiency alone does not prevent HFD-induced obesity and insulin resistance. Considering the role of SOCS3 as a suppressor of IL-1β, IFN-γ, and TNF-α signaling in pancreatic β-cells, the SOCS3 pathway may prevent the onset of T2D as well as T1D (Bruun *et al.* 2009).

Several factors, such as IL-6, leptin, TNF-α, and infection with hepatitis C virus (HCV) regulate SOCS3 expression. For example, insulin increases the rate of SOCS3 expression in adipose tissue, liver, and muscle tissues (Emanuelli *et al.* 2001). Double deletions of the gene encoding SOCS3 and PTP-1B in the brain cells, compared with deleting them individually, improves sensitivity to insulin in an additive manner; however, the SOCS3 deletion contributes more significantly, which accounts for the low level of insulinemia detected in the double mutants (Briancon *et al.* 2010). This strategy is considered an important example of targeted therapy of T2D and obesity.

Function of SOCS proteins in Toll-like receptor (TLR) signaling

The SOCS proteins, in particular SOCS1 and SOCS3, inhibit TLR signaling as well as the JAK-STAT signaling pathway. Chronic inflammatory signaling is a key factor in the development of obesity, causes peripheral insulin, and accelerates leptin resistance. TLRs are a class of receptors that have key roles within the innate immune system by activating proinflammatory signaling cascades upon recognition of microbial and viral products (Medzhitov 2001). In particular, TLR4 contributes to the development of insulin resistance through its activation by an increased number of exogenous ligands, such as dietary fatty acids and lipopolysaccharide (LPS). Activation of the TLR4 signaling cascade induces the production of proinflammatory cytokines, chemokines, and reactive oxygen species (ROS), which are all effectors of innate immunity. TLR4 is expressed by many cells in insulin target tissues, including pancreatic β-cells as well as liver, skeletal muscle (Kim & Sears 2010). Therefore, TLR4 activation may suppress insulin action through proinflammatory cytokine signaling, ROS generation, and producing insulin-desensitizing factors.

The daily diet plays an important role in the development of obesity and diabetes, and the types and caloric content of meals are significant contributors to the inflammatory response. For example, consumption of foods high in carbohydrates and fat induce inflammation and increase in the LPS concentration in the plasma. Consumption of these foods, but not those with high-fiber content, elevates SOCS3 expression in circulating mononuclear cells (Ghanim *et al.* 2009). Long-chain polyunsaturated omega-3 fatty acids such as DHA and EPA antagonize TLR4 activation by saturated fatty acids and LPS (Lee *et al.* 2001, 2003, Shi *et al.* 2006). Consumption of sweets and cream increase the levels of TNF-α, IL-1β, and SOCS3 but not those of SOCS1 (Deopurkar *et al.* 2010). Further, cream enhances the post-meal spike in the concentration of circulating LPS concentration in contrast to drinking a beverage containing sugar. Moreover, SOCS3 signaling and NF-κB activation in circulating mononuclear cells are remarkably elevated when cream and soft drinks are consumed. These results suggest that the level of SOCS1 and SOCS3 induced by consuming certain kinds of food may differ, although SOCS proteins modulate insulin resistance.

Obesity-related diseases

Obesity-induced inflammation is an important contributor to the development of pathologies such as T2D, atherosclerosis, liver disease, infections, and some types of cancer (Gregor & Hotamisligil 2011, Wolin *et al.* 2010). In particular, cancer and infection are highly associated with the regulation of SOCS protein expression in obesity-associated diseases (Figure 1, right).

Cancer

Persistent inflammation increases cancer risk, which is driven by genetic alterations that cause inflammation and neoplasia. STATs and NF-κB are key coordinators of innate immunity and inflammation and are executors of tumor promoters (Inagaki-Ohara *et al.* 2013). Twenty percent of cancers can be attributed to obesity (Wolin *et al.* 2010), and increased cancer-related mortality (Reeves *et al.* 2007) attracts great attention as a global health problem. The number of people with diabetes has increased and is predicted to rise to 552 million by 2030 (Wild *et al.* 2004), suggesting that cancer risk will rise proportionately.

White adipose tissue (WAT) performs multiple functions other than to store lipids. The increase in the mass of WAT during the progression of obesity elevates the production of adipokines such as leptin, IL - 6, TNF-α, causing chronic mild inflammation. Dia-

betic patients are at significantly higher risk for common cancers including those of the breast, gastrointestinal (GI) (esophageal, colorectal) tract, liver, pancreas, urinary tract, and female reproductive tissues (Xu *et al.* 2014).

Breast cancer

Approximately 60% of breast cancers are hormone-dependent. The hormonal changes that occur postmenopause are attributed to a specific metabolic state that represents a greater risk for breast cancer. These changes are considered indispensable for a more effective therapy (Maccio & Madeddu 2011). Among adipokines, leptin is the most intensively studied regarding its metabolism and role in obesityrelated carcinogenesis, because leptin induces physiological responses in peripheral tissues other than those involved in neuronal activity. Increased expression of leptin and ObRb in human grade-III invasive breast tumors is associated with shorter time to tumor recurrence and mortality (Garofalo *et al.* 2006, Maccio *et al.* 2010).

Tumor cells derived from MMTV-Wnt1 mice, a widely used model of mammary tumors, show decreased growth in ob/ob mice (leptin-deficient) compared with diet-induced obese mice with an intact leptin signaling pathway (Zheng *et al.* 2011). This result suggests that leptin signaling plays an essential role in the growth and survival of tumors induced by MMTV-Wnt1. Tumor initiating stem cells express high levels of ObR to promote tumorigenesis caused by STAT3 activation and by inducing pluripotencyassociated transcription factors such as Oct4 and Sox2 (Feldman *et al.* 2012). In patients with obesity-related breast cancer, the JAK2-STAT3 pathway is activated and SOCS3 is down-regulated (Santillan-Benitez *et al.* 2014). These effects of leptin are mediated through a set of responses of ObRb-positive tumor cells, including a cancer stem cell population that expresses the ObRb. These findings suggest that leptin affects tumor initiation and progression through STAT3 activation.

Gastrointestinal (GI) cancer

The relative risk of GI cancer in obese individuals is highly prevalent among patients with obesityassociated Barrett's esophagus and colon cancer (Wolin *et al.* 2010). The combination of adenomatous polyposis coli (Apc) and db/db mice enhances Apc-driven tumorigenesis of the small intestine and induces gastric and colonic tumors. In contrast, db/db mice do not develop GI neoplasia (Gravaghi *et al.* 2008). Recently, gastric cancer has emerged as an obesity-associated cancer. Normal stomach tissues spontaneously express leptin and ObRb, and their expression levels increase during carcinogenesis (Bado *et al.* 1998, Inagaki-Ohara *et al.* 2014), and induce autocrine signaling (Hoda *et al.* 2007), suggesting that the stomach is more susceptible to ObR signaling than other tissues. Approximately 90% of gastric cancers are gastric adenocarcinomas (GCA), which are further categorized as distal or non-cardia GCA and proximal or cardia GCA. Interestingly, cardia GCA is associated with obesity (Cho *et al.* 2012, O'Doherty *et al.* 2012), suggesting that the unique localization of the leptin-ObR signaling pathway to cells of the GI tract functions predominantly in the early phase of human GC and serves as a biomarker. Therefore, targeting this pathway may be invaluable for treatment.

Hepatic cancer

Leptin's oncogenic role, including its capability to enhance tumor invasiveness and migration of hepatocellular carcinoma (HCC) cells, may be antagonized by adiponectin in HCC through suppression of STAT3 and Akt phosphorylation when SOCS3 is up-regulated (Sharma *et al.* 2010). Studies conducted in vitro reveal that the SOCS3 binding site is essential for the interaction with IRS1 and IRS2, whereas the affinity of SOCS1 for a domain within the catalytic loop is crucial for IRS2 (Ueki *et al.* 2004). SOCS1 and SOCS3 bind to the IR in cells, and their overexpression impairs the phosphorylation of IRS1 and IRS2 stimulated by insulin. Insulin resistance is caused by IL-6 due to suppression of tyrosine phosphorylation of IRS-1 through the induction of SOCS3 in murine primary hepatocytes and human hepatocarcinoma cells (Wunderlich *et al.* 2013). Indeed, IL-6-deficient mice are resistant to diethylnitrosamine (DEN)-induced carcinogenesis when fed a HFD (Park *et al.* 2010). Recently, Shimizu *et al.* (2011) showed that several signaling pathways including insulin/IGF-1/PI3K/Akt, ERK, JNK, and STAT3 are important in DEN-induced liver carcinogenesis in db/db mice. SOCS3 expression is reduced in the levers of HCC patients, which is supported by findings that mice with hepatocyte-specific deletion of SOCS3 are resistant to concanavalin A-induced hepatocarcinogenesis (Ogata *et al.* 2006).

Collectively, these studies reveal that leptin exerts its actions centrally and provides beneficial effects to peripheral organs. However, although such peripheral functions of leptin exist, chronic JAK-STAT3- SOCS3 pathway activity in obesity is mainly derived from other signals that, in contrast, act in the periphery as well as the CNS. Further, crosstalk between leptin and IGF-1 significantly increases the proliferation as well as invasion and migration of breast cancer cells, suggesting that the cooperation of several signaling pathways is required to induce obesity-associated carcinogenesis.

Infection

Hepatitis C virus

Overwhelming epidemiological evidence indicates that persistent infection with HCV and HBV is a major risk factor for the development of HCC (Koike *et al.* 2008). In transgenic mice carrying the gene encoding the HCV core protein (PA28 gamma (+/+) Core Tg), the HCV core protein induces hyperexpression of TNF-α (Miyamoto *et al.* 2007), and HCV infection causes insulin resistance and T2D, which is sufficient to impair insulin signaling in vitro through the SOCS protein activation and the consequent decrease in IRS- 1 expression (Pascarella *et al.* 2011).

Chronic HCV infection of humans is treated with a combination of Peginterferon (a long acting IFN) and Ribavirin (guanosine analog that inhibits RNA synthesis). These drugs contribute to decreased sensitivity to interferon, which is inhibited by SOCS3 (del Campo *et al.* 2010). Interestingly, SOCS1-deficient mice show hyperglycemia but die before reaching three weeks of age due to enhanced IFN-γ signaling (Starr *et al.* 1998). Human embryonic stem cell-derived hepatocytes (hESC-Heps) are capable of supporting the full HCV life cycle and viral infection to a lesser extent compared with the HUh 7 hepatocarcinoma cell line that produces IL-29, a type III IFN, upon stimulation by HCV infection (Zhou *et al.* 2014). Considering that the level of viral infection and replication in hESC-Heps is increased by addition of JAK inhibitor I that modulates signaling through the JAK-STAT pathway as well as the downstream response to IFN, "tunable" hESC-Heps may serve as a platform for the development of anti- HCV drugs.

Influenza

The association between obesity and influenza was first reported during the 2009 influenza A (H1N1) pandemic (Louie *et al.* 2011, Morgan *et al.* 2010). Obese volunteers infected with influenza A (H1N1) show a reduced ability to produce type I IFN in response to the TLR3 ligand, delayed proinflammatory responses, and increased basal expression of SOCS3 but not SOCS1 (Teran-Cabanillas *et al.* 2014). Dietinduced obese mice exhibit similar responses. In these mice, the number of influenza virus-specific CD8+- memory T cells in the lung, an important cell population for protection against the subsequent virus exposure is decreased, but expression of SOCS1 and SOCS3 is increased (Karlsson *et al.* 2010). These results suggest that new vaccine strategies are required for obese individuals, because the standard vaccine that induces the proliferation of memory T cells may be less effective in an obese population.

Intestinal microbiota

It is important to understand that the output of signaling pathways that are activated by certain bacteria may protect against intestinal inflammation or obesity. Members of the phyla Bacteroidetes and Firmicutes dominate the gut microbiome, and an increased ratio of Firmicutes to Bacteroidetes is implicated in the development of adult obesity (Eckburg *et al.* 2005, Ley *et al.* 2006, Turnbaugh *et al.* 2006). Obesity is characterized by chronic low-grade inflammation with reduced GI barrier function involving a variety factors and inflammatory mediators (Chakraborty *et al.* 2010). "Metabolic endotoxemia" can initiate obesity and insulin resistance through gastrointestinal bacteria- triggered SOCS3 signaling. High-fat and high-fructose diets alter the composition of the gut microbiota and the permeability of the gut, which increase the proliferation of enterobacterial species and the levels of circulating LPS (Cani & Delzenne 2009, Kim & Sears 2010). Germ-free mice or mice treated with antibiotics specific for gram-negative bacteria do not exhibit HFD -induced insulin resistance or other metabolic abnormalities associated with obesity (Backhed *et al.* 2007, Cani *et al.* 2008). The presence of body fat-inducing gut microbiota may be associated with hypothalamic signs of SOCS3-mediated leptin resistance (Schele *et al.* 2013). Further, the strong correlation between increased LPS concentrations and HFD-induced endotoxemia, an important component of obesity-associated inflammation in obese patients, is consistent with enhanced expression of TLR4 and NF-κB in circulating mononuclear cells (Cani *et al.* 2008, Ghanim *et al.* 2009). Deletion of Tlr4 from the myeloid cells protects mice against HFD-induced inflammation, adipose macrophage infiltration, and insulin resistance (Saberi *et al.* 2009). TLR5 binds to bacterial flagellin, and mice lacking this receptor display hyperphagia and develop the characteristic features of metabolic syndrome, including hyperlipidemia and insulin resistance (Vijay-Kumar *et al.* 2010). These metabolic changes correlate with changes in the composition of the gut microbiota, and transfer of the gut microbiota from TLR5-deficient mice to wild-type germ-free mice confers many features of metabolic syndrome to the latter.

Emerging evidence suggest that the GI tract is the origin of inflammation in HFD-induced obesity as well as adipose tissue. A HFD promotes inflammation in the GI tract, which is considered a potential source of inflammation associated with HFD-induced obesity. Adult germ-free (GF) mice have less body fat and do not become obese when they are fed a HFD, and replacing the microbiota of adult GF mice with the microbiota harvested from conventional mice increases in body fat (Backhed *et al.* 2004, Backhed *et al.* 2007).

These results indicate that nonpathogenic enteric bacteria in healthy individuals may play a key role in diet-induced obesity.

Mice devoid of PTP1B are resistant to diet-induced obesity (Bence *et al.* 2006, Elchebly *et al.* 1999, Owen *et al.* 2012). Furthermore, knockdown of PTP1B expression in the RAW264.7 macrophage cell line increases the production of IL-6, TNF-α, and IFN-β in response to a variety of TLR ligands, indicating that PTP1B can act as a negative regulator of TLR4-signaling in macrophages (Xu *et al.* 2008). Myeloid cell-specific PTP1B knockout (LysM-PTP1B) mice resist LPS-induced endotoxemia and hepatic damage associated with decreased TNF-α expression and show an increase in basal and LPS-induced IL-10 production associated with enhanced STAT3 activation (Grant *et al.* 2014). These findings suggest that myeloid PTP1B is a previously unrecognized inhibitor of STAT3/IL-10 mediated signaling and may serve as a target for treating inflammation and diabetes in obese patients.

Concluding remarks

Over the past decade, SOCS proteins have been clearly shown to inhibit the leptin and insulin signaling pathways in vitro and in vivo and to influence energy balance and glucose homeostasis. These discoveries highlight the importance of SOCS for regulating the mechanisms of onset and development of diseases involved in metabolic dysfunction in central and peripheral tissues through the JAK-STAT signaling cascade as well as through crosstalk with other mediators (Figure 3). In the future, SOCS proteins will likely provide therapeutic targets for T2D and obesity-associated cancer, although investigations should take into account the induction of SOCS proteins by diverse cytokines and cell types.

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Author Contributions

K. I-O. wrote the manuscript and A. Y. provided comments.

Conflicts of Interest

The authors declare no conflicts of interest.

References

Al-Qassab H, Smith MA, Irvine EE, Guillermet-Guibert J, Claret M, Choudhury AI, Selman C, Piipari K, Clements M, Lingard S, Chandarana K, Bell JD, Barsh GS, Smith AJ, Batterham RL, Ashford ML, Vanhaesebroeck B & Withers DJ 2009 Dominant role of the p110beta isoform of PI3K over p110alpha in energy homeostasis regulation by POMC and AgRP neurons. *Cell Metab* **10** 343-354

Bäckhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, Semenkovich CF & Gordon JI 2004 The gut microbiota as an environmental factor that regulates fat storage. *Proc Natl Acad Sci U S A* **101** 15718-15723

Backhed F, Manchester JK, Semenkovich CF & Gordon JI 2007 Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. *Proc Natl Acad Sci U S A,* **104** 979-984

Bado A, Levasseur S, Attoub S, Kermorgant S, Laigneau JP, Bortoluzzi MN, Moizo L, Lehy T, Guerre-Millo M, Le Marchand-Brustel Y & Lewin MJ 1998 The stomach is a source of leptin. *Nature* **394** 790-793

Banks AS, Davis SM, Bates SH & Myers MG Jr 2000 Activation of downstream signals by the long form of the leptin receptor. *J Biol Chem* **275** 14563-14572

Bence KK, Delibegovic M, Xue B, Gorgun CZ, Hotamisligil GS, Neel BG & Kahn BB 2006 Neuronal PTP1B regulates body weight, adiposity and leptin action. *Nat Med* **12** 917-924

Bjorbaek C, Elmquist JK, Frantz JD, Shoelson SE & Flier JS 1998. Identification of SOCS-3 as a potential mediator of central leptin resistance. *Mol Cell* **1** 619-625

Bluestone JA, Herold K & Eisenbarth G 2010 Genetics, pathogenesis and clinical interventions in type 1 diabetes. *Nature* **464** 1293-1300

Briancon N, McNay DE, Maratos-Flier E & Flier JS 2010 Combined neural inactivation of suppressor of cytokine signaling-3 and protein-tyrosine phosphatase-1B reveals additive, synergistic, and factor specific roles in the regulation of body energy balance. *Diabetes* **59** 3074-3084

Bruun C, Heding PE, Rønn SG, Frobøse H, Rhodes CJ, Mandrup-Poulsen T & Billestrup N 2009 Suppressor of cytokine signalling-3 inhibits Tumor necrosis factor-alpha induced apoptosis and signalling in beta cells. *Mol Cell Endocrinol* **311** 32-38

Cani PD, Bibiloni R, Knauf C, Waget A, Neyrinck AM, Delzenne NM & Burcelin R 2008 Changes in gut

microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. *Diabetes* **57** 1470-1481

Cani PD & Delzenne NM 2009 The role of the gut microbiota in energy metabolism and metabolic disease. *Curr Pharm Des* **15** 1546-1558

Chakraborty S, Zawieja S, Wang W, Zawieja DC & Muthuchamy M 2010. Lymphatic system: a vital link between metabolic syndrome and inflammation. *Ann N Y Acad Sci* **1207** E94-102

Cho Y, Lee DH, Oh HS, Seo JY, Lee DH, Kim N, Jeong SH, Kim JW, Hwang JH, Park YS, Lee SH, Shin CM, Jo HJ, Jung HC, Yoon YB & Song IS 2012 Higher prevalence of obesity in gastric cardia adenocarcinoma compared to gastric noncardia adenocarcinoma. *Dig Dis Sci* **57** 2687-2692

del Campo JA, Lopez RA & Romero-Gomez M 2010 Insulin resistance and response to antiviral therapy in chronic hepatitis C: mechanisms and management. *Dig Dis* **28** 285-293

Deopurkar R, Ghanim H, Friedman J, Abuaysheh S, Sia CL, Mohanty P, Viswanathan P, Chaudhuri A & Dandona P 2010 Differential effects of cream, glucose, and orange juice on inflammation, endotoxin, and the expression of Toll-like receptor-4 and suppressor of cytokine signaling-3. *Diabetes Care* **33** 991-997

Eckburg PB1, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, Gill SR, Nelson KE & Relman DA 2005 Diversity of the human intestinal microbial flora *Science* **308** 1635-1638

Elchebly M, Payette P, Michaliszyn E, Cromlish W, Collins S, Loy AL, Normandin D, Cheng A, Himms-Hagen J, Chan CC, Ramachandran C, Gresser MJ, Tremblay ML & Kennedy BP 1999 Increased insulin sensitivity and obesity resistance in mice lacking the protein tyrosine phosphatase-1B gene. *Science* **283** 1544-1548

Emanuelli B, Macotela Y, Boucher J & Ronald Kahn C 2008 SOCS-1 deficiency does not prevent diet-induced insulin resistance. *Biochem Biophys Res Commun* **377** 447-452

Emanuelli B, Peraldi P, Filloux C, Chavey C, Freidinger K, Hilton DJ, Hotamisligil GS & Van Obberghen E 2001 SOCS-3 inhibits insulin signaling and is up-regulated in response to tumor necrosis factor-alpha in the adipose tissue of obese mice. *J Biol Chem* **276** 47944-47949

Endo TA, Masuhara M, Yokouchi M, Suzuki R, Sakamoto H, Mitsui K, Matsumoto A, Tanimura S, Ohtsubo M, Misawa H, Miyazaki T, Leonor N, Taniguchi T, Fujita T, Kanakura Y, Komiya S & Yoshimura A 1997 A new protein containing an SH2 domain that inhibits JAK kinases. *Nature* **387** 921-924

Feldman DE, Chen C, Punj V, Tsukamoto H & Machida K 2012 Pluripotency factor-mediated expression of the leptin receptor (OB-R) links obesity to oncogenesis through tumor-initiating stem cells. *Proc Natl Acad Sci U S A* **109** 829-834

Friedman JM & Halaas JL 1998 Leptin and the regulation of body weight in mammals. *Nature* **395** 763-770

Garofalo C, Koda M, Cascio S, Sulkowska M, Kanczuga-Koda L, Golaszewska J, Russo A, Sulkowski S & Surmacz E 2006 Increased expression of leptin and the leptin receptor as a marker of breast cancer progression: possible role of obesity-related stimuli. *Clin Cancer Res* **12** 1447-1453

Gautron L & Elmquist JK 2011 Sixteen years and counting: an update on leptin in energy balance. *J Clin Invest* **121** 2087-2093

Ghanim H, Abuaysheh S, Sia CL, Korzeniewski K, Chaudhuri A, Fernandez-Real JM & Dandona P 2009 Increase in plasma endotoxin concentrations and the expression of Toll-like receptors and suppressor of cytokine signaling-3 in mononuclear cells after a high-fat, high-carbohydrate meal: implications for insulin resistance. *Diabetes Care* **32** 2281-2287

Grant L, Shearer KD, Czopek A, Lees EK, Owen C, Agouni A, Workman J, Martin-Granados C, Forrester JV, Wilson HM, Mody N & Delibegovic M 2014 Myeloid-cell protein tyrosine phosphatase-1B deficiency in mice protects against high fat diet and lipopolysaccharide-induced inflammation, hyperinsulinemia, and endotoxemia through an IL-10 STAT3-dependent mechanism. *Diabetes* **63** 456-470

Gravaghi C, Bo J, Laperle KM, Quimby F, Kucherlapati R, Edelmann W & Lamprecht SA 2008 Obesity enhances gastrointestinal tumorigenesis in Apc-mutant mice. *Int J Obes (Lond)* **32** 1716-1719

Gregor MF & Hotamisligil GS 2011 Inflammatory mechanisms in obesity. *Annu Rev Immunol* **29** 415-445

Hoda MR, Keely SJ, Bertelsen LS, Junger WG, Dharmasena D & Barrett KE 2007 Leptin acts as a mitogenic and antiapoptotic factor for colonic cancer cells. *Br J Surg* **94** 346-354

Howard JK, Cave BJ, Oksanen LJ, Tzameli I, Bjorbaek C & Flier JS 2004 Enhanced leptin sensitivity and attenuation of diet-induced obesity in mice with haploinsufficiency of Socs3. *Nat Med* **10** 734-738

Howard JK & Flier JS 2006 Attenuation of leptin and insulin signaling by SOCS proteins. *Trends Endocrinol Metab* **17** 365-371

Inagaki-Ohara K, Kondo T, Ito M & Yoshimura A 2013 SOCS, inflammation, and cancer. *JAKSTAT* **2** e24053

Inagaki-Ohara K, Mayuzumi H, Kato S, Minokoshi Y, Otsubo T, Kawamura YI, Dohi T, Matsuzaki G & Yoshimura A 2014 Enhancement of leptin receptor sig-

naling by SOCS3 deficiency induces development of gastric tumors in mice. *Oncogene* **33** 74-84
Jamieson E, Chong MM, Steinberg GR, Jovanovska V, Fam BC, Bullen DV, Chen Y, Kemp BE, Proietto J, Kay TW & Andrikopoulos S 2005 Socs1 deficiency enhances hepatic insulin signaling. *J Biol Chem* **280** 31516-31521
Karlsson EA, Sheridan PA & Beck MA 2010 Diet-induced obesity in mice reduces the maintenance of influenza-specific CD8+ memory T cells. *J Nutr* **140** 1691-1697
Kershaw NJ, Murphy JM, Liau NP, Varghese LN, Laktyushin A, Whitlock EL, Lucet IS, Nicola NA & Babon JJ 2013 SOCS3 binds specific receptor-JAK complexes to control cytokine signaling by direct kinase inhibition. *Nat Struct Mol Biol* **20** 469-476
Kievit P, Howard JK, Badman MK, Balthasar N, Coppari R, Mori H, Lee CE, Elmquist JK, Yoshimura A & Flier JS 2006 Enhanced leptin sensitivity and improved glucose homeostasis in mice lacking suppressor of cytokine signaling-3 in POMC-expressing cells. *Cell Metab* **4** 123-132
Kim JJ & Sears DD 2010 TLR4 and Insulin Resistance. *Gastroenterol Res Pract* 212563
Koike K, Tsutsumi T, Miyoshi H, Shinzawa S, Shintani Y, Fujie H, Yotsuyanagi H & Moriya K 2008 Molecular basis for the synergy between alcohol and hepatitis C virus in hepatocarcinogenesis. *J Gastroenterol Hepatol* **23** S87-91
La Cava A & Matarese G 2004. The weight of leptin in immunity *Nat Rev Immunol* **4** 371-379
Lebrun P & Van Obberghen E 2008 SOCS proteins causing trouble in insulin action. *Acta Physiol (Oxf)* **192** 29-36
Lee JY, Plakidas A, Lee WH, Heikkinen A, Chanmugam P, Bray G & Hwang DH 2003 Differential modulation of Toll-like receptors by fatty acids: preferential inhibition by n-3 polyunsaturated fatty acids. *J Lipid Res* **44** 479-486
Lee JY, Sohn KH, Rhee SH & Hwang D 2001 Saturated fatty acids, but not unsaturated fatty acids, induce the expression of cyclooxygenase-2 mediated through Toll-like receptor 4. *J Biol Chem* **276** 16683-16689
Ley RE, Turnbaugh PJ, Klein S & Gordon JI 2006 Microbial ecology: human gut microbes associated with obesity. *Nature* **444** 1022-1023
Louie JK, Acosta M, Samuel MC, Schechter R, Vugia DJ, Harriman K, Matyas BT & California Pandemic (H1N1) Working Group 2011 A novel risk factor for a novel virus: obesity and 2009 pandemic influenza A (H1N1). *Clin Infect Dis* **52** 301-312
Maccio A & Madeddu C 2011 Obesity, inflammation, and postmenopausal breast cancer: therapeutic implications. *ScientificWorldJournal* **11** 2020-2036
Macciò A, Madeddu C, Gramignano G, Mulas C, Floris C, Massa D, Astara G, Chessa P & Mantovani G 2010 Correlation of body mass index and leptin with tumor size and stage of disease in hormone-dependent postmenopausal breast cancer: preliminary results and therapeutic implications. *J Mol Med (Berl)* **88** 677-686
Medzhitov R 2001 Toll-like receptors and innate immunity. *Nat Rev Immunol* **1** 135-145
Miyamoto H, Moriishi K, Moriya K, Murata S, Tanaka K, Suzuki T, Miyamura T, Koike K & Matsuura Y 2007. Involvement of the PA28gamma-dependent pathway in insulin resistance induced by hepatitis C virus core protein. *J Virol* **81** 1727-1735
Morgan OW, Bramley A, Fowlkes A, Freedman DS, Taylor TH, Gargiullo P, Belay B, Jain S, Cox C, Kamimoto L, Fiore A, Finelli L, Olsen SJ & Fry AM 2010 Morbid obesity as a risk factor for hospitalization and death due to 2009 pandemic influenza A(H1N1) disease. *PLoS One* **5** e9694
Mori H, Hanada R, Hanada T, Aki D, Mashima R, Nishinakamura H, Torisu T, Chien KR, Yasukawa H & Yoshimura A 2004 Socs3 deficiency in the brain elevates leptin sensitivity and confers resistance to dietinduced obesity. *Nat Med* **10** 739-743
Mori H, Shichita T, Yu Q, Yoshida R, Hashimoto M, Okamoto F, Torisu T, Nakaya M, Kobayashi T, Takaesu G & Yoshimura A 2007 Suppression of SOCS3 expression in the pancreatic beta-cell leads to resistance to type 1 diabetes. *Biochem Biophys Res Commun* **359** 952-958
O'Doherty MG, Freedman ND, Hollenbeck AR, Schatzkin A & Abnet CC 2012 A prospective cohort study of obesity and risk of oesophageal and gastric adenocarcinoma in the NIH-AARP Diet and Health Study. *Gut* **61** 1261-1268
Ogata H, Kobayashi T, Chinen T, Takaki H, Sanada T, Minoda Y, Koga K, Takaesu G, Maehara Y, Iida M & Yoshimura A 2006. Deletion of the SOCS3 gene in liver parenchymal cells promotes hepatitis-induced hepatocarcinogenesis. *Gastroenterology* **131** 179-193
Owen C, Czopek A, Agouni A, Grant L, Judson R, Lees EK, Mcilroy GD, Göransson O, Welch A, Bence KK, Kahn BB, Neel BG, Mody N & Delibegović M 2012. Adipocyte-specific protein tyrosine phosphatase 1B deletion increases lipogenesis, adipocyte cell size and is a minor regulator of glucose homeostasis. *PLoS One* **7** e32700
Park EJ, Lee JH, Yu GY, He G, Ali SR, Holzer RG, Osterreicher CH, Takahashi H & Karin M 2010 Dietary and genetic obesity promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF expression. *Cell* **140** 197-208
Pascarella S, Clement S, Guilloux K, Conzelmann S, Penin F & Negro F 2011. Effects of hepatitis C virus

on suppressor of cytokine signaling mRNA levels: comparison between different genotypes and core protein sequence analysis. *J Med Virol* **83** 1005-1015

Piessevaux J, Lavens D, Peelman F & Tavernier J 2008 The many faces of the SOCS box. *Cytokine Growth Factor Rev* **19** 371-381

Reed AS, Unger EK, Olofsson LE, Piper ML, Myers MG Jr & Xu AW 2010 Functional role of suppressor of cytokine signaling 3 upregulation in hypothalamic leptin resistance and long-term energy homeostasis. *Diabetes* **59** 894-906

Reeves GK, Pirie K, Beral V, Green J, Spencer E, Bull D & Million Women Study Collaboration 2007 Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *BMJ* **335** 1134

Saberi M, Woods NB, de Luca C, Schenk S, Lu JC, Bandyopadhyay G, Verma IM & Olefsky JM 2009 Hematopoietic cell-specific deletion of toll-like receptor 4 ameliorates hepatic and adipose tissue insulin resistance in high-fat-fed mice. *Cell Metab* **10** 419-429

Santillan-Benitez JG, Mendieta-Zeron H, Gomez-Olivan LM, Ordonez Quiroz A, Torres-Juarez JJ & Gonzalez-Banales JM 2014 JAK2, STAT3 and SOCS3 gene expression in women with and without breast cancer. *Gene* **547** 70-76

Schele E, Grahnemo, L, Anesten, F, Hallen, A, Backhed F & Jansson JO 2013 The gut microbiota reduces leptin sensitivity and the expression of the obesity-suppressing neuropeptides proglucagon (Gcg) and brain-derived neurotrophic factor (Bdnf) in the central nervous system. *Endocrinology* **154** 3643-3651

Sharma D, Wang J, Fu PP, Sharma S, Nagalingam A, Mells J, Handy J, Page AJ, Cohen C, Anania FA & Saxena NK 2010 Adiponectin antagonizes the oncogenic actions of leptin in hepatocellular carcinogenesis. *Hepatology* **52** 1713-1722

Shi H, Kokoeva MV, Inouye K, Tzameli I, Yin H & Flier JS 2006 TLR4 links innate immunity and fatty acid-induced insulin resistance. *J Clin Invest* **116** 3015 -3025

Shimizu M, Sakai H, Shirakami Y, Yasuda Y, Kubota M, Terakura D, Baba A, Ohno T, Hara Y, Tanaka T & Moriwaki H 2011 Preventive effects of (-)-epigallocatechin gallate on diethylnitrosamine-induced liver tumorigenesis in obese and diabetic C57BL/KsJ-db/db Mice. *Cancer Prev Res (Phila)* **4** 396-403

Starr R, Metcalf D, Elefanty AG, Brysha M, Willson TA, Nicola NA, Hilton DJ & Alexander WS 1998 Liver degeneration and lymphoid deficiencies in mice lacking suppressor of cytokine signaling-1. *Proc Natl Acad Sci U S A* **95** 14395-14399

Suchy D, Labuzek K, Machnik G, Kozlowski M & Okopien B 2013 SOCS and diabetes--ups and downs of a turbulent relationship. *Cell Biochem Funct* **31** 181 -195.

Tanti JF, Ceppo F, Jager J & Berthou F 2012 Implication of inflammatory signaling pathways in obesity induced insulin resistance. *Front Endocrinol (Lausanne)* **3** 181

Teran-Cabanillas E, Montalvo-Corral M, Silva-Campa E, Caire-Juvera G, Moya-Camarena SY & Hernandez J 2014 Production of interferon alpha and beta, pro-inflammatory cytokines and the expression of suppressor of cytokine signaling (SOCS) in obese subjects infected with influenza A/H1N1. *Clin Nutr* **33** 922-926

Torisu T, Sato N, Yoshiga D, Kobayashi T, Yoshioka T, Mori H, Iida M & Yoshimura A 2007 The dual function of hepatic SOCS3 in insulin resistance in vivo. *Genes Cells* **12** 143-154

Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER & Gordon JI 2006 An obesity associated gut microbiome with increased capacity for energy harvest. *Nature* **444** 1027-1031

Ueki K, Kondo T & Kahn CR 2004 Suppressor of cytokine signaling 1 (SOCS-1) and SOCS-3 cause insulin resistance through inhibition of tyrosine phosphorylation of insulin receptor substrate proteins by discrete mechanisms. *Mol Cell Biol* **24** 5434-5446

Ueki K, Kondo T, Tseng YH & Kahn CR 2004 Central role of suppressors of cytokine signaling proteins in hepatic steatosis, insulin resistance, and the metabolic syndrome in the mouse. *Proc Natl Acad Sci U S A* **101** 10422-10427

Vijay-Kumar M, Aitken JD, Carvalho FA, Cullender TC, Mwangi S, Srinivasan S, Sitaraman SV, Knight R, Ley RE & Gewirtz AT 2010 Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. *Science* **328** 228-231

Wild S, Roglic G, Green A, Sicree R & King H 2004 Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* **27** 1047 -1053

Wolin KY, Carson K & Colditz GA 2010 Obesity and cancer. *Oncologist* **15** 556-565

Wunderlich CM, Hovelmeyer N & Wunderlich FT 2013 Mechanisms of chronic JAK-STAT3-SOCS3 signaling in obesity. *JAKSTAT* **2** e23878

Xu CX, Zhu HH & Zhu YM 2014 Diabetes and cancer: Associations, mechanisms, and implications for medical practice. *World J Diabetes* **5** 372-380

Xu H, An H, Hou J, Han C, Wang P, Yu Y & Cao X 2008 Phosphatase PTP1B negatively regulates MyD88 - and TRIF-dependent proinflammatory cytokine and type I interferon production in TLR-triggered macrophages. *Mol Immunol* **45** 3545-3552

Yasukawa H, Misawa H, Sakamoto H, Masuhara M, Sasaki A, Wakioka T, Ohtsuka S, Imaizumi T, Ma-

tsuda T, Ihle JN & Yoshimura A 1999 The JAK-binding protein JAB inhibits Janus tyrosine kinase activity through binding in the activation loop. *EMBO J* **18** 1309-1320

Yasukawa H, Sasaki A & Yoshimura A 2000 Negative regulation of cytokine signaling pathways. *Annu Rev Immunol* **18** 143-164

Yoshimura A, Naka T & Kubo M 2007 SOCS proteins, cytokine signalling and immune regulation. *Nat Rev Immunol* **7** 454-465

Yoshimura A, Suzuki M, Sakaguchi R, Hanada T & Yasukawa H 2012 SOCS, Inflammation, and Autoimmunity. *Front Immunol* **3** 20

Zaitseva II, Hultcrantz M, Sharoyko V, Flodstrom-Tullberg M, Zaitsev SV & Berggren PO 2009 Suppressor of cytokine signaling-1 inhibits caspase activation and protects from cytokine-induced beta cell death. *Cell Mol Life Sci* **66** 3787-3795

Zheng Q, Dunlap SM, Zhu J, Downs-Kelly E, Rich J, Hursting SD, Berger NA & Reizes O 2011 Leptin deficiency suppresses MMTV-Wnt-1 mammary tumor growth in obese mice and abrogates tumor initiating cell survival. *Endocr Relat Cancer* **18** 491-503

Zhou X, Sun P, Lucendo-Villarin B, Angus AG, Szkolnicka D, Cameron K, Farnworth SL, Patel AH & Hay DC 2014 Modulating innate immunity improves hepatitis C virus infection and replication in stem cell-derived hepatocytes. *Stem Cell Reports* **3** 204-214