http://www.pjbs.org

PJBS

ISSN 1028-8880

Pakistan Journal of Biological Sciences

ANSInet
Asian Network for Scientific Information
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan

OPEN ACCESS Pakistan Journal of Biological Sciences

ISSN 1028-8880
DOI: 10.3923/pjbs.2022.1100.1108

Review Article
Research Advances on Suppressor of Cytokine Signaling 3 (SOCS3) in Animal Carbohydrate and Lipid Metabolism Processes

[1,2]Wuyi Liu and [1]Xin Wang

[1]Department of Biological Science, School of Biological Science and Food Engineering, Fuyang Normal University, Fuyang, China
[2]Anti-Aging Chinese Herbal Medicine Anhui Province Engineering Technology Research Center, Fuyang Normal University, Fuyang, China

Abstract

The SOCS3 proteins played important roles in regulating the energy metabolism processes. They are crucial intracellular inhibitors related to animal obesity, immunity and inflammation. This makes SOCS3 genes very important in animal genetics and breeding. The research was conducted to investigate and explore the recent advance in the present studies on SOCS3 in animal energy and lipid metabolism processes. All the references were carefully retrieved from the PubMed database by searching key words "suppressor of cytokine signaling (SOCS)", "SOCS3 ", "animal carbohydrate metabolism", "animal lipid metabolism", "animal energy metabolism", "insulin resistance", "leptin", "obesity", "SOCS*" and "AMPK". All the related references retrieved were initially screened and fully reviewed for manual inspection. This effort intends to get a quick understanding and make insights into the mechanisms of Suppressor of Cytokine Signaling 3 (SOCS3) and their molecular interactions with the other cellular proteins. In this review, it was found that SOCS3 proteins could regulate cytokine receptors' signal transduction mainly through the JAK/STAT and GH/IGF-I and mTOR-STAT3-SOCS3 signaling pathways, whereas the genetic mutations or knockouts of SOCS3 genes had significant effects on animal energy metabolism. The review summarized all the relevant research reports on SOCS3 in the animal carbohydrate and lipid metabolism processes, which can provide practical reference for the genetic breeding of high-quality domestic animal breeds. It is also of great significance to further research on the genetic regulation mechanism of SOCS3 genes affecting energy metabolism and the well development of the animal breeding system.

Key words: Suppressors of cytokine signaling, SOCS3, insulin resistance, leptin, obesity

Citation: Liu, W. and X. Wang, 2022. Research advances on Suppressor of Cytokine Signaling 3 (SOCS3) in animal carbohydrate and lipid metabolism processes. Pak. J. Biol. Sci., 25: 1100-1108.

Corresponding Author: Wuyi Liu, Department of Biological Science, School of Biological Science and Food Engineering, Fuyang Normal University, Fuyang, China

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

In the modern animal breeding system, excessive pursuit of growth rate ("fast growth") and feed reward ("high output") has significantly improved the production performance of meat-typed domestic animals, but made livestock and poultry more sensitive to the external environment[1]. There are many stressors in the usual processes of intensive livestock and poultry breeding, such as damp heat, crowding, transportation, immune injection, immune reaction, etc. The stress reaction stimulated by stressors exists in the whole process of livestock and poultry production, including feeding, transportation and slaughter. Stress reaction not only reduces the production performance and carcass meat quality of livestock and poultry but also affects the health and welfare of livestock and poultry. It is conceivable that stress will ultimately increase the susceptibility of livestock and poultry to diseases[1]. In practice, there are great differences between fast large meat strains/breeds and indigenous small sized strains/breeds in the meat production animals of livestock and poultry. In particular, different animal strains in the same species have similar muscle development speeds and slaughter rates in the same feeding period, but their carbohydrate and lipid metabolism and immune regulation pathway are very different, which are closely related to the differentiation in meat quality of these two types of meat livestock and poultry. At the same time, fast and large meat animals are prone to many kinds of stressors which lead to huge economic losses and the internal genetic regulation mechanism within their stress reactions also needs to be explored in depth.

In recent years, researchers have found that the Suppressor of Cytokine Signaling 3 (SOCS3) activated/triggered by leptin signal plays important roles in the cellular energy metabolism, especially in the carbohydrate and lipid metabolism processes[2-18]. The SOCS3 is a heterologous multimer in its protein structure, which is composed of a SH2 region, an extended SH2 sub-domain (ESS), a SOCS box and the N-terminal KIP (i.e., kinase identity region) domain (Fig. 1). Among them, SH2 region is located in the inhibitor's center and it can bind to the substrate by recognizing the homologous phosphotyrosine in structure. The ESS sub-domain is the SH2 expansion region of the N-base terminal, whose function is mainly to interact with the substrate. The SOCS box is a functional domain fixed at the C-end, whereas, KIP is the N-terminal kinase inhibition region. The KIP region is an analogue binding region to JAK kinases of the JAK-STAT signaling pathway. It can competitively inhibit the activity of JAK kinase[2-4,19] (Fig. 1 and 2).

Recently, many studies have found that the inflammatory factors mediate the specific signal transduction of inflammatory response in cells[2-15], which leads to the phosphorylation of Insulin Receptor Substrate 1 (IRS-l) serine in insulin (INS) sensitive cells (INSSC), such as hepatocytes and adipocytes, through the intracellular inhibitors IL-6 and SOCS3. Subsequently, the signal transduction of inflammatory response inhibits the tyrosine phosphorylation of IRS-l and simultaneously blocks the insulin signal transduction, which induces insulin resistance (IR)[3-15]. Actually, SOCS3 is a potential inhibitor protein related to obesity, immunity and inflammation. It is involved in the negative feedback regulation of insulin (INS) signal factors[15] (Fig. 2). Cell transfection experiments showed that SOCS3 might prevent STAT3 and STATS-mediated transcriptional activation of islet cells, thereby inhibiting cell proliferation and insulin production caused by the growth hormone (GH) signal pathway[15]. Bjørbæk *et al.*[7-9] reported that SOCS3 could inhibit the binding of leptin and its receptor LEPR (leptin receptor) in feedback, resulting in the pathway blockages in the signal transduction of leptin, INS and GH signals, which ultimately affected the obesity of mice. Since then, SOCS3 genes become hot spots in animal genetics and breeding research[10-37]. The article was designed to investigate and review the recent advance in the present studies on SOCS3 in animal energy and lipid metabolism processes. All the references were carefully retrieved from the PubMed database by searching key words "suppressor of cytokine signaling (SOCS)", "SOCS3", "animal carbohydrate metabolism", "animal lipid metabolism", "animal energy metabolism", "insulin resistance", "leptin", "obesity", "SOCS*" and "AMPK". All the related references retrieved were initially screened and fully reviewed for manual inspection. This article was also aimed to review the recent advance in research on SOCS3 in the carbohydrate and lipid metabolism processes of animals, especially domestic animals.

SOCS genes in animals: Suppressors of cytokine signaling (SOCS) are a group of suppressive proteins or intracellular regulators emerging in human and animal physiological activities (Fig. 3), such as extracellular stimulus and cytokine response[16]. The SOCS is also a protein family of intracellular inhibitors suppressing the signal transduction of Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway, i.e., JAK/STAT pathway, which plays a critical role in the signaling of a wide array of cytokines and growth factors. The SOCS proteins were first reported in 1997[26-28]. It is previously reported that there were a total of eight types of SOCS proteins or SOCS family members that negatively regulate the JAK/STAT pathway[29] (Fig. 2 and 4). The SOCS

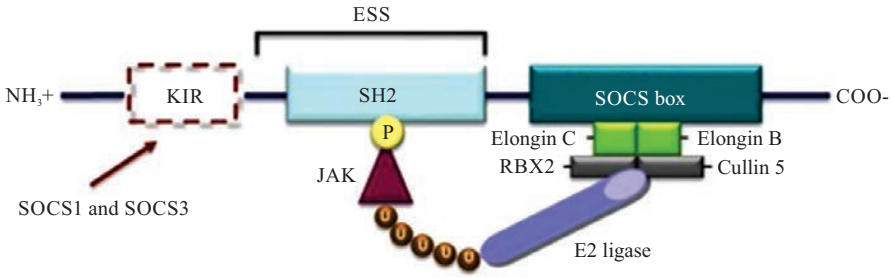

Fig. 1: Schematic diagram of the protein structures of SOCS1 and SOCS3

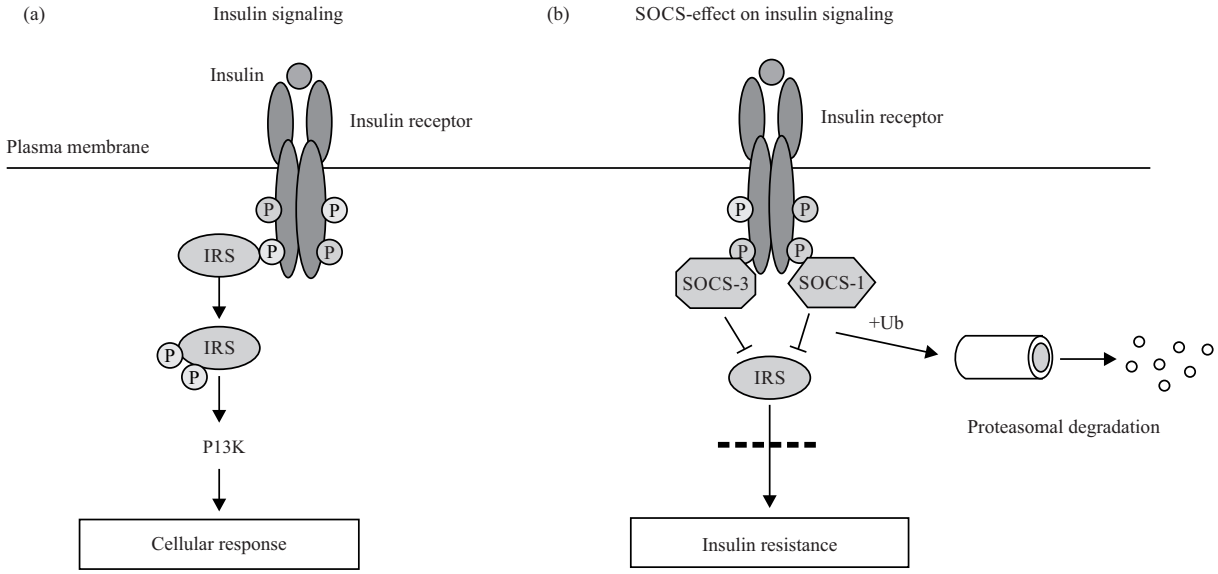

Fig. 2: Negative regulation mechanism inhibiting the insulin signal pathway of SOCS1 and SOCS3 proteins[14]

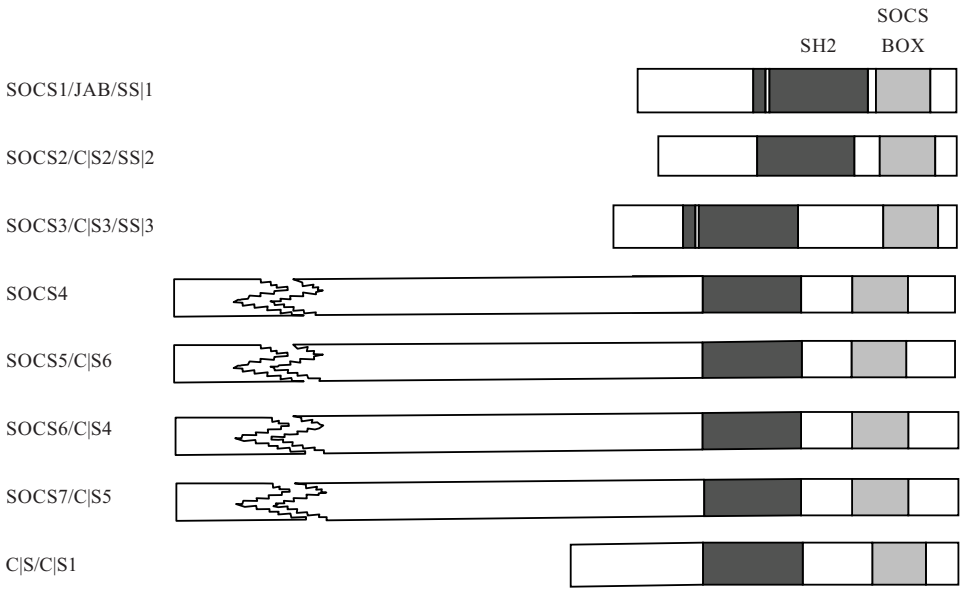

Fig. 3: Protein domains of SOCS gene family[4]

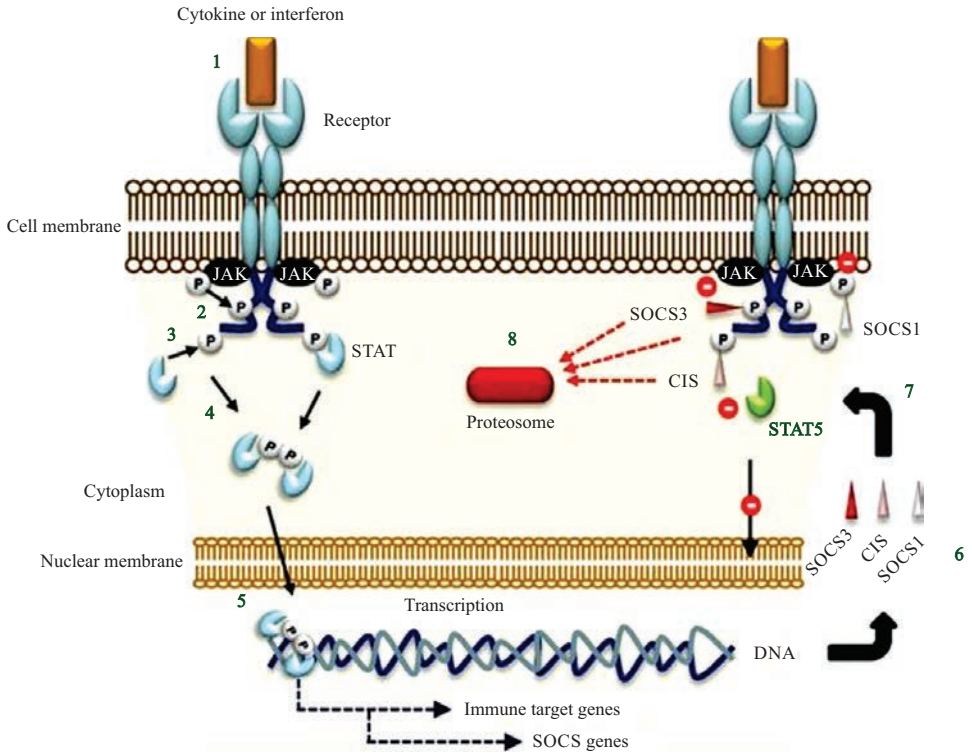

Fig. 4: Negative regulation mechanism inhibiting cell signal pathway of SOCS3 proteins[19]

proteins are well known for regulating the physiological activities of mankind and animals[16,29] with different N-terminal lengths and sequences (Fig. 3). They are basically composed of a consistent central region SH2 (Src Holog 2 and SH2) and a conservative C-terminal domain SOCS box[16,29], among which the SH2 domain binds to the phosphorylated tyrosine residues and mediate the bindings and interactions between SOCS proteins and other signal transduction molecules (Fig. 3). The SH sites of different SOCS proteins are essential elements for activating the complex of tyrosine phosphorylation receptors and they are key structural motifs for the inhibition of SOCS proteins[2-6]. However, the SH site itself is not enough to inhibit the signal transduction of the JAK-STAT signaling pathway, which requires the involvement of pre-SH sites of the N-terminal regions that are called the kinase inhibition regions[5,6]. The SH site binds to the phosphorylated tyrosine residue on the JAK protein, while the N-terminal regions of SOCS proteins are variable in a length of 50-380 amino acids[5,6].

According to previous reports [4-16], SOCS firstly binds to the phosphorylated tyrosine residues of JAKs or cytokine receptor subunits through the SH2 region in the inhibitor center and then the C-terminal of SOCS will interact with ubiquitin junction structure components and intermediary proteins. Thus, the functional circulations of SOCS proteins are formed and they will play a crucial physiological role[4-16,20]. The N-terminal of SOCS3 and SOCS1 contains another kinase inhibition region (KIP), which acts as a false binding region for JAKs binding to competitively inhibit the activity of JAK kinase[19]. Many studies have shown that there is a complex crystal loop structure between the mouse SOCS3 protein and the JAK2 kinase binding region, so the kinase inhibition region of SOCS3 can block the substrate binding tank of JAK2[20-22]. Furthermore, molecular biochemical results also show that the kinase inhibition region of SOCS3 protein can block the binding of JAK2 with the substrate[19,22]. Through these negative cellular effects, SOCS3 proteins/inhibitors can weaken the signal transduction reaction of cytokines and growth factors in target cells[19,22] (Fig. 4).

Compared with those in mammalian genomes, there are similar energy metabolism regulation pathways in the chicken genome, such as carbohydrate metabolism and lipid metabolism. In particular, chicken SOCS3 is highly related to the inhibition of leptin signal transduction and insulin resistance[17-22]. The SOCS3 gene and protein sequences in the chicken genome were initially recorded in the NCBI database in 2001, with the registered numbers NP_989,931.1 and Q90X67, respectively. Chicken SOCS3 protein is composed of 209 amino acids, which has a high homology with mammal SOCS3 proteins. According to previous research reports, there were many studies on SOCS3 proteins in mammals (especially

pigs and mice) and fish, but there are few cases of chicken and poultry SOCS3 inhibitors. It is found that there are merely a few sporadic reports on the expression level and immune function of the SOCS3 gene in chicken leptin signal transduction and GH/IGF-I signaling pathways[17-22]. In addition, SOCS3 proteins are also active inhibitors in feedback in the energy metabolism of stressed animals[34-36]. Relevant research shows that, when animals are stressed, the activated AMPK kinase in animal skeletal muscle can change the lipid and sugar metabolisms[36]. Thus, the body can inhibit ATP consumption and promote ATP production and then cell energy can be rapidly restored[36]. However, in obese individuals, SOCS3 released from the hypothalamus can inhibit the activation of leptin-related AMPK kinase in skeletal muscle and suppress fatty acid metabolism to regulate systemic obesity and insulin sensitivity in rodents[28-30]. Conversely, the activations of cytokines like AMPK and adiponectin will prevent SOCS3 inhibitors and reduce the leucine-induced hepatic insulin resistance by suppressing the signal transduction of the mTOR-STAT3-SOCS3 signaling pathway and reducing IRS-1 serine phosphorylation[29-32]. Therefore, the intracellular resistance of skeletal muscle to key metabolic hormones like leptin and insulin is actually an early physiological defect of animal obesity. Under heat stress, the inflammatory factors and secretions expressed in skeletal muscle, such as IFN-γ, IFN-α, IL-2, IL-10, IL-6 and IL-12, can induce high expressions of CIS, SOCS1, SOCS2, SOCS3 and other SOCS family members in the cells and animal body[33], thereby initiating the physiological feedback inhibition. Therefore, SOCS3 proteins/inhibitors also play an important role in the regulation of normal carbohydrate and lipid metabolisms in animals[29-33].

The SOCS3 proteins/inhibitors can indirectly regulate energy metabolism by regulating the body's resistance the key metabolic hormones like leptin and insulin and inhibit the activity of AMPK kinase in feedback, reducing the rate of carbohydrate and lipid metabolisms[36]. The SOCS3 regulates cytokine receptors' signal transduction mainly through the following pathways. First, SOCS3 can directly interfere with the phosphorylation of kinase JAKs and inhibit the activation of JAKs[34-41]. Research shows that KIP is an additional peptide structure composed of 24 amino acids in the front of the SH2 region[34], which can be employed as a substrate to competitively bind to the catalytic site of JAKs, to prevent the catalytic action of JAKs and to block the binding of STAT and kinase[34-41]. Second, SOCS3 can bind to the phosphotyrosine residues of the receptor and completely block the aggregation of STAT. For instance, the mechanism analysis of SOCS3 inhibiting the Growth Hormone Receptor (GHR) signal showed that SOCS3 bound to the phosphotyrosine residues in the near end region of GHR and linked to the STAT receptor region through the KIP region of SOCS3, thus preventing the receptor from binding with other cellular signals[34-36]. Finally, SOCS3 can inhibit the generation and transduction of the downstream signals through the reported leucosome pathway by inactivating corresponding receptors or related membrane proteins[37-41]. For instance, in the inhibiting process of Leptin Receptor (LEPR) signals, SOCS3 could competitively bind to LEPR with Protein Tyrosine Phosphatase-2 (SHP-2) to a certain extent, resulting in the inhibition of SHP-2-regulated Extracellular Signal-Regulated Kinase (ERK) activation[37]. Consequently, SOCS3 plays a role in signal transduction inhibition and regulation. Therefore, SOCS3 is overall involved in regulating the metabolisms of animal lipids and sugar (especially the glycolysis metabolism) in the body, which is of great significance to the production of domestic livestock and poultry meat products.

Association between SOCS3 gene, leptin signal transduction and obesity: It is well known that OB and OB-R gene loci are the most important to obesity. Most obese people show hyper-leptinemia, a mass formed by blood stasis in obesity. The OB gene loci encode leptin and the OB-R gene loci encode Leptin Receptor (LEPR). Leptin is a hormone substance mainly secreted by adipocytes. It can regulate human and animal food intakes, corresponding energy consumption and the neuroendocrine system with the hypothalamus to reduce body weight. Leptin is similar to the cytokines in structure and it can bind to its receptor to play a role by activating the signal transduction of the JAK/STAT pathway. An animal study showed that, after injection of recombinant leptin into the OB/OB genotype mice or Wister rats, the expression of the SOCS3 gene in the hypothalamus increased rapidly, while the expressions of other SOCS family members like CIS and SOCS2 did not change significantly[12]. This showed that leptin specifically induced the expression of the SOCS3 gene[12], although multiple cytokines might simultaneously induce the expression of multiple SOCS family members. After the mRNA transfection of the OB-R gene into CHO cells, the expression of the SOCS3 gene increased significantly compared with the basic cellular levels of SOCS3 proteins[8]. On the other hand, leptin pretreatment inhibited the signal transduction of newly added leptin levels on the basis of increasing the expression of the SOCS3 gene in cells[8]. The genetic experiment on another cell strain transfected with SOCS3 mRNA showed that SOCS3 inhibited the tyrosine kinase activity of JAK2 by binding with JAK2, thereby inhibiting the signal transduction of JAK/STAT pathway after the leptin receptor[9]. Subsequently,

more and more studies found that SOCS3 inhibits the signal transduction of OB-R protein by combining with phosphorylated Tyr985 of the intracellular segment of OB-R protein[9-20]. For instance, an adenovirus vector was used to carry out mRNA transfection of the ob gene to induce animal hyper-leptinemia in OB/OB genotype mice[18]. It was found that the detected levels of blood leptin were similarly upregulated in experimental animals, but those of the daily food intake, body weight and body fat loss were very low[18]. After the gene transfection, the measured levels of SOCS3 mRNA increased three times in ob/ob genotype mice and the increased levels of SOCS3 protein also had significant statistical significance[18]. With the adenovirus vector, gene transfections of ob and SOCS3 genes into the islet cells of normal rats showed that blood levels of lipids were upregulated in animal metabolism[19-21]. Especially, after the transfected stimulation of the ob gene, there was an expressed leptin level of 20 μg L^{-1} and the content of glycerol trioxide decreased by 85% in the transfected cells[20]. Whereas the content of glycerol trioxide in cells transfected with the SOCS3 gene only decreased by 22%[20]. However, after leptin stimulation, the mRNA levels of fatty acid oxidase (ACO) and the Carnitine Palmitate Phthaloyl Transferase 1 (CPT-1) genes in the control cells increased significantly, while those in the cells overexpressing SOCS3 did not[16-20]. Later, cellular studies confirmed that SOCS3 was a negative feedback regulator of leptin signal transduction, suggesting that SOCS3 might mediate central and peripheral leptin resistance[12-15]. Compared with the wild-type mice, mice of SOCS3 heterozygous deletion were more sensitive to leptin levels and their hypothalamic leptin receptors were more responsive to exogenous leptin signals[13-15]. These mice could resist high-fat food-induced obesity and the generation of related metabolic syndrome[13-15]. Therefore, inhibiting the expression of SOCS3 in the hypothalamus may effectively treat obesity caused by leptin resistance[13-15]. Particularly, Mori *et al.*[14] built a neuron-specific model of SOCS3 knockout mice to deeply analyze and explore the relationship between SOCS3 and energy metabolism balance in neurons. In the neuron cell experiment of SOCS3 genetic hybrid and SOCS3 gene knockout mice, the overall weights of mice in both models were reduced[13-15]. Furthermore, the LEPR signal in the hypothalamus was enhanced during the leptin regulation reaction, showing these experimental mice had a stronger leptin sensitivity compared with the wild-type mice[13-15]. These experimental mice showed a higher leptin sensitivity, prevented the diet induced obesity, improved blood glucose levels, decreased leptin levels and increased the signal activity of JAK2/STAT3/SOCS3 pathway[13-15]. However, the above two model experimental mice are not easy to develop into diet induced obesity[13-15]. In addition, leptin sensitivity in the corticotropin proneurons of SOCS3 knockout mice was increased, which stopped the development into fatty liver of animals and promoted the blood glucose balance in the body[37]. The other studies found that SOCS3 bound to LEPR tyrosine-985 and participated in mediating the signal inhibition of JAK STAT pathway[37-40]. Therefore, SOCS3 could play an inhibitory role in LEPR signaling[37-40]. Combined with the research results of SOCS3 knockout mice, SOCS3 may participate in the regulation of energy metabolism balance as a potential leptin resistance regulator.

Association between SOCS3 gene, insulin resistance and obesity: Insulin resistance (IR) is mainly manifested by the relative decrease of insulin sensitivity and the body is not sensitive to insulin, while there are decreased utilization rates of glucose in peripheral tissues, especially muscle and adipose tissue. Research reports found that specific inflammatory factors mediated the signal transduction of cellular inflammation reactions, which led to the serine phosphorylation of insulin receptor substrate 1 (IRS-1) in insulin-sensitive cells (i.e., hepatocytes and adipocytes)[17-19]. Furthermore, the inflammatory reactions subsequently inhibited the receptor's tyrosine phosphorylation of IRS-1, blocking insulin signal transduction and inducing insulin resistance (IR)[17,18,21]. Thus, SOCS3 is a potential factor related to obesity, immune and inflammatory reactions which is involved in the negative feedback regulation of insulin signals[17,18,21]. Cellular transfection experiment showed that SOCS3 could prevent the STAT3 and STATS-mediated transcriptional activation in islet cells and thereby inhibited cell proliferation and insulin production induced by GH signals[17]. Animal experiments also confirmed that the mRNA levels of the SOCS3 gene in adipose tissues of diabetic mice were significantly higher than those of the control group of normal animals[21]. It might be that the increased expression of SOCS3 inhibited the further transmission of insulin signals by suppressing the phosphorylation of insulin receptor substrate protein IRS1 and promoting the ubiquitination degradation of IRS1 and IRS2[17,18,21]. This process weakened the synthesis of liver glycogen and activated the glucose uptake of adipocytes[21]. Epidemiological evidence also showed that the 920th point of SOCS3 promoter were homozygotes of glandular heiyin in normal people or patients with type H diabetes who showed higher insulin sensitivity than those people with heterozygotes of SOCS3 promoter[28]. In fact, the expression levels of the SOCS3 gene are usually mediated and modulated by the signal transduction regulations of

inflammatory factors like interleukin and NF-κB and Estrogen-ERαp66[28,40-44]. The expression of the SOCS3 gene in obese mice increased, whereas *in vitro* experiments confirmed that SOCS3 directly acted on insulin receptors and inhibited the tyrosine phosphorylation of IRS-1, leading to IR and leptin resistance[21,28,40-44]. The detailed mechanism of SOCS3 leading to insulin resistance may be due to the competitive inhibition of IRS-1 tyrosine phosphorylation[21,28,40-44]. Recent studies found that SOSC3 could accelerate the degradation of IRS-1/IRS-2 through the ubiquitin-mediated degradation pathway[37-47]. Another result in mice showed that the anti-inflammatory astaxanthin (ASTA) had a strong protective effect on LPS-induced acute lung injury in mice[47]. Actually, the protective mechanism of astaxanthin was achieved through activating the SOCS3/JAK2/STAT3 signaling pathway to promote the differentiation of Treg cell (T regulatory cell) and reduce inflammatory reactions and cell differentiation of Th17 (T helper cell 17 and Th17)[47].

CONCLUSION

It is well known that SOCS3 proteins played important roles in regulating the body's energy metabolism of animals. SOCS3 proteins are crucial intracellular inhibitors related to animal obesity, immune and inflammation. It was found that SOCS3 proteins regulated cytokine receptors' signal transduction mainly through the JAK/STAT and GH/IGF-I and mTOR-STAT3-SOCS3 signaling pathways. Some genetic mutations or knockouts of SOCS3 genes had significant effects on animal energy metabolism, especially on the carbohydrate and lipid metabolism processes. This makes SOCS3 genes very important in animal genetics and breeding. However, there are presently only a few reports on the mutation of the SOCS3 gene and its genetic effects on carbohydrate and lipid metabolism in domestic animals, i.e., livestock and poultry. The review summarized the latest research progress of the SOCS3 gene in animals and livestock and poultry, which can provide a practical reference for the genetic breeding of high-quality domestic animal breeds, especially broilers and other poultry. It is of great significance to further research on the genetic regulation mechanism of SOCS3 genes affecting energy metabolism and the well development of animal breeding systems.

SIGNIFICANCE STATEMENT

The present review was conducted to investigate and explore the recent advance in the studies on SOCS3 in animal energy and lipid metabolism processes. The review summarized all the relevant research reports on SOCS3 in the animal carbohydrate and lipid metabolism processes, which can provide a practical reference for the genetic breeding of high-quality domestic animal breeds. The research was conducted to investigate and explore the recent advance in the studies on SOCS3 in animal energy and lipid metabolism processes. In this review, it was found that SOCS3 proteins could regulate cytokine receptors' signal transduction mainly through the JAK/STAT, GH/IGF-I and mTOR-STAT3-SOCS3 signaling pathways, whereas the genetic mutations or knockouts of SOCS3 genes significantly affected animal metabolism.

ACKNOWLEDGMENTS

The authors are grateful to the referees for their constructive comments. The projects of the Anhui Provincial Educational Commission and Anhui Provincial Committee of Science & Technology are acknowledged for financial support (No. KJ2019ZD36, No. 201806a02020028), the domestic visit and advanced study project of outstanding young backbone talents in Anhui universities (gxgnfx2022033), and the national training project of undergraduate innovation and entrepreneurship program (202210371025)".

REFERENCES

1. Nafikov, R.A. and D.C. Beitz, 2007. Carbohydrate and lipid metabolism in farm animals. J. Nutr., 137: 702-705.
2. Wang, B., E. Wangkahart, C.J. Secombes and T. Wang, 2019. Insights into the evolution of the suppressors of cytokine signaling (SOCS) gene family in vertebrates. Mol. Biol. Evol., 36: 393-411.
3. Xia, T., L. Zhang, G. Sun, X. Yang and H. Zhang, 2021. Genomic evidence of adaptive evolution in the reptilian SOCS gene family. PeerJ, Vol. 9. 10.7717/peerj.11677.
4. Jin, H.J., J.Z. Shao, L.X. Xiang, H. Wang and L.L. Sun, 2008. Global identification and comparative analysis of SOCS genes in fish: Insights into the molecular evolution of SOCS family. Mol. Immunol., 45: 1258-1268.
5. Krebs, D.L. and D.J. Hilton, 2001. SOCS proteins: Negative regulators of cytokine signaling. Stem Cells, 19: 378-387.
6. Krebs, D.L. and D.J. Hilton, 2000. SOCS: Physiological suppressors of cytokine signaling. J. Cell Sci., 113: 2813-2819.
7. Bjørbæk, C., J.K. Elmquist, J.D. Frantz, S.E. Shoelson and J.S. Flier, 1998. Identification of SOCS-3 as a potential mediator of central leptin resistance. Mol. Cell, 1: 619-625.
8. Bjørbæk, C., K. El-Haschimi, J.D. Frantz and J.S. Flier, 1999. The role of SOCS-3 in leptin signaling and leptin resistance. J. Biol. Chem., 274: 30059-30065.

9. Bjorbaek, C., R.M. Buchholz, S.M. Davis, S.H. Bates and D.D. Pierroz *et al*., 2001. Divergent roles of SHP-2 in ERK activation by leptin receptors. J. Biol. Chem., 276: 4747-4755.
10. Nillni, E.A., C. Vaslet, M. Harris, A. Hollenberg, C. Bjørbak and J.S. Flier, 2000. Leptin regulates prothyrotropin-releasing hormone biosynthesis. J. Biol. Chem., 275: 36124-36133.
11. Peiser, C., G.P. McGregor and R.E. Lang, 2000. Leptin receptor expression and suppressor of cytokine signaling transcript levels in high-fat-fed rats. Life Sci., 67: 2971-2981.
12. Howard, J.K., B.J. Cave, L.J. Oksanen, I. Tzameli, C. Bjorbak and J.S. Flier, 2004. Enhanced leptin sensitivity and attenuation of diet-induced obesity in mice with haploinsufficiency of Socs3. Nat. Med., 10: 734-738.
13. Balthasar, N., R. Coppari, J. McMinn, S.M. Liu and C.E. Lee *et al*., 2004. Leptin receptor signaling in POMC neurons is required for normal body weight homeostasis. Neuron, 42: 983-991.
14. Mori, H., R. Hanada, T. Hanada, D. Aki and R. Mashima *et al*., 2004. Socs3 deficiency in the brain elevates leptin sensitivity and confers resistance to diet-induced obesity. Nat. Med., 10: 739-743.
15. Rønn, S.G., J.A. Hansen, K. Lindberg, A.E. Karlsen and N. Billestrup, 2002. The effect of suppressor of cytokine signaling 3 on GH signaling in β-cells. Mol. Endocrinol., 16: 2124-2134.
16. Alexander, W.S., 2002. Suppressors of cytokine signalling (SOCS) in the immune system. Nat. Rev. Immunol., 2: 410-416.
17. Wang, Z., Y.T. Zhou, T. Kakuma, Y. Lee and S.P. Kalra *et al*., 2000. Leptin resistance of adipocytes in obesity: Role of suppressors of cytokine signaling. Biochem. Biophys. Res. Commun., 277: 20-26.
18. Ueki, K., T. Kondo and C.R. Kahn, 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.
19. Yin, Y., W. Liu and Y. Dai, 2015. SOCS3 and its role in associated diseases. Hum. Immunol., 76: 775-780.
20. Babon, J.J., J.K. Sabo, A. Soetopo, S. Yao and M.F. Bailey *et al*., 2008. The SOCS box domain of SOCS3: Structure and interaction with the elongin-BC-cullin5 ubiquitin ligase. J. Mol. Biol., 381: 928-940.
21. Wang, Z.W., W.T. Pan, Y. Lee, T. Kakuma, Y.T. Zhou and R.H. Unger, 2001. The role of leptin resistance in the lipid abnormalities of aging. FASEB J., 15: 108-114.
22. Kershaw, N.J., J.M. Murphy, N.P.D. Liau, L.N. Varghese and A. Laktyushin *et al*., 2013. SOCS3 binds specific receptor-JAK complexes to control cytokine signaling by direct kinase inhibition. Nat. Struct. Mol. Biol., 20: 469-476.
23. Huang, G., M. Yuan, J. Zhang, J. Li and D. Gong, *et al*., 2016. IL-6 mediates differentiation disorder during spermatogenesis in obesity-associated inflammation by affecting the expression of Zfp637 through the SOCS3/STAT3 pathway. Sci. Rep., Vol. 6. 10.1038/srep28012.
24. Vida, M., A.L. Gavito, F.J. Pavón, D. Bautista and A. Serrano *et al*., 2015. Chronic administration of recombinant IL-6 upregulates lipogenic enzyme expression and aggravates high fat diet-induced steatosis in IL-6 deficient mice. Dis. Model Mech., 8: 721-731.
25. Senn, J.J., P.J. Klover, I.A. Nowak, T.A. Zimmers, L.G. Koniaris, R.W. Furlanetto and R.A. Mooney, 2003. Suppressor of cytokine signaling-3 (SOCS-3), A potential mediator of iterleukin-6-dependent insulin resistance in hepatocytes. J. Biol. Chem., 278: 13740-13746.
26. Starr, R., T.A. Willson, E.M. Viney, L.J. Murray and J.R. Rayner *et al*., 1997. A family of cytokine-inducible inhibitors of signaling. Nature, 387: 917-921.
27. Aman, M.J. and W.J. Leonard, 1997. Cytokine signaling: Cytokine-inducible signaling inhibitors. Curr. Biol., 7: R784-R788.
28. Yang, Z., M. Hulver, R.P. McMillan, L. Cai and E.E. Kershaw *et al*., 2012. Regulation of insulin and leptin signaling by muscle suppressor of cytokine signaling 3 (SOCS3). PLoS ONE, Vol. 7. 10.1371/journal.pone.0047493.
29. Shaw, E.J., E.E. Smith, J. Whittingham-Dowd, M.D. Hodges, K.J. Else and R.J. Rigby, 2017. Intestinal epithelial suppressor of cytokine signaling 3 (SOCS3) impacts on mucosal homeostasis in a model of chronic inflammation. Immun. Inflammation Dis., 5: 336-345.
30. Steinberg, G.R., A.J. McAinch, M.B. Chen, P.E. O'Brien, J.B. Dixon, D. Cameron-Smith and B.E. Kemp, 2006. The suppressor of cytokine signaling 3 inhibits leptin activation of AMP-kinase in cultured skeletal muscle of obese humans. J. Clin. Endocrinol. Metab., 91: 3592-3597.
31. Ll, H., 2010. Activation of AMPK Prevents Leucine Induced Hepatic Insulin Resistance by Suppressing mTOR-STAT3-SOCS3 Signaling and Reducing IRS-1 Serine Phosphorylation. 70th Scientific Sessions, 2010 .
32. Handy, J.A., N.K. Saxena, P. Fu, S. Lin, J.E. Mells, N.A. Gupta and F.A. Anania, 2010. Adiponectin activation of AMPK disrupts leptin-mediated hepatic fibrosis via suppressors of cytokine signaling (SOCS-3). J. Cell. Biochem., 110: 1195-1207.
33. Fujimoto, M. and T. Naka, 2003. Regulation of cytokine signaling by SOCS family molecules. Trends Immunol., 24: 659-666.
34. Yan, C., J. Cao, M. Wu, W. Zhang, T. Jiang, A. Yoshimura and H. Gao, 2010. Suppressor of cytokine signaling 3 inhibits LPS-induced IL-6 expression in osteoblasts by suppressing CCAAT/enhancer-binding protein β activity. J. Biol. Chem., 285: 37227-37239.
35. Barclay, J.L., S.T. Anderson, M.J. Waters and J.D. Curlewis, 2007. Regulation of suppressor of cytokine signaling 3 (SOC3) by growth hormone in pro-B cells. Mol. Endocrinol., 21: 2503-2515.
36. Hardie, D.G. and S.A. Hawley, 2001. AMP-activated protein kinase: The energy charge hypothesis revisited. BioEssays, 23: 1112-1119.

37. Piao, L., J. Park, Y. Li, S. Shin and S. Shin *et al*., 2014. SOCS3 and SOCS6 are required for the risperidone-mediated inhibition of insulin and leptin signaling in neuroblastoma cells. Int. J. Mol. Med., 33: 1364-1370.
38. Kievit, P., J.K. Howard, M.K. Badman, N. Balthasar and R. Coppari *et al*., 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.
39. Olofsson, L.E., E.K. Unger, C.C. Cheung and A.W. Xu, 2013. Modulation of AgRP-neuronal function by SOCS3 as an initiating event in diet-induced hypothalamic leptin resistance. Proc. Natl. Acad. Sci., 110: E697-E706.
40. Martino, N., R.B. Ramos, D. Chuy, L. Tomaszek and A.P. Adam, 2022. SOCS3 limits TNF and endotoxin-induced endothelial dysfunction by blocking a required autocrine interleukin-6 signal in human endothelial cells. Am. J. Physiol. Cell Physiol., 323: C556-C569.
41. Sooryanarain, H., C.L. Heffron, H.M. Mahsoub, A.M. Hassebroek and B. Wang *et al*., 2022. Modulation of SOCS3 levels via STAT3 and estrogen-ERαp66 signaling during hepatitis E virus replication in hepatocellular carcinoma cells. J. Virol., Vol. 96. 10.1128/jvi.01008-22.
42. Gylvin, T., R. Nolsøe, T. Hansen, E.M.D. Nielsen and R. Bergholdt *et al*., 2004. Mutation analysis of suppressor of cytokine signalling 3, a candidate gene in type 1 diabetes and insulin sensitivity. Diabetologia, 47: 1273-1277.
43. Savage, D.B., K.F. Petersen and G.I. Shulman, 2005. Mechanisms of insulin resistance in humans and possible links with inflammation. Hypertension, 45: 828-833.
44. Shi, H., I. Tzameli, C. Bjørbæk and J.S. Flier, 2004. Suppressor of cytokine signaling 3 is a physiological regulator of adipocyte insulin signaling. J. Biol. Chem., 279: 34733-34740.
45. Vieira, E.E.S., I.C. Pereira, A.F. Braz, M.V. Nascimento-Ferreira and L.R. de Oliveira Torres *et al*., 2020. Food consumption of branched chain amino acids and insulin resistance: A systematic review of observational studies in humans. Clin. Nutr. ESPEN, 40: 277-281.
46. Schlosser, P., Y. Li, P. Sekula, J. Raffler and F. Grundner-Culemann *et al*., 2020. Genetic studies of urinary metabolites illuminate mechanisms of detoxification and excretion in humans. Nat. Genet., 52: 167-176.
47. Zhu, L., H. Wu, Z. Ma, D. Dong, Z. Yang and J. Tian, 2022. Astaxanthin ameliorates lipopolysaccharide-induced acute lung injury *via* inhibition of inflammatory reactions and modulation of the SOCS3/JAK2/STAT3 signaling pathways in mice. Food Funct., 13: 11638-11651.