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Research Progress on SOCS3 Regulation of Dairy Cow Lactation Signal Pathway

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Abstract: Suppressor of cytokine signaling 3 (SOCS3) is a cytokine-induced negative regulator of cytokine signaling. There is evidence that it inhibits the activation of signal transducers and activators of transcription 5 (STAT5), and the Janus kinase 2-signal transducer and activator of transcription 5 (JAK2-STAT5) signaling pathway plays a role in the transcriptional synthesis of milk proteins in dairy cows. And the expression of SOCS3 has an inhibitory effect o n the synthesis of SREBP-1c gene and fatty acids. Therefore, this paper reviews the effects of the structure and function of SOCS3 on the lactation signaling pathway of dairy cows, and aims to provide constructive suggestions for further increasing the milk protein content in milk through manual intervention.

Keywords: SOCS3; JAK2/STAT5; Milk Protein Transcription

Introduction

Milk is one of the ancient natural drinks and has the good reputation of “white blood”. With the improvement of people’s living standards, milk has long become an indispensable part of the public dining table. Milk is rich in nutrients, a large number of easily absorbed fats and proteins, and is also rich in calcium and phosphorus, immune substances, including complement, fat and immunoglobulin. Milk fat content accounts for about 3%~5% of milk, which is an important source of essential fatty acids and phospholipids for human body. It also contains many fat-soluble vitamins and is an important nutrient in milk. The most important lipid is triglyceride, followed by diglyceride, a small amount of cholesterol, phospholipid and Vitamins. Milk protein, as one of the most important components in milk, has always been the focus of research by researchers. It mainly includes casein (casein, CN) and whey protein (Whey protein). In addition, it also contains relatively small content. Milk fat globule membrane protein (MFGMP). Casein is the most abundant protein with the highest nutritional value in milk, of which Beta-casein accounts for 45%-48% of the total casein, which is a key indicator of milk protein content[1]. The synthesis of milk protein in cow mammary gland cells is mainly affected by JAK-STATs and mTOR signal pathways.

JAK-STATs is involved in the transcriptional regulation of milk protein. Under the action of prolactin, insulin and other lactation related hormones, JAK2 is activated and further STAT5 phosphorylates and enters nucleus to regulate the transcription of milk protein. Mammalian rapamycin target protein (mTOR) signaling pathway mainly plays a regulatory role in milk protein translation process, including upstream regulatory pathways phosphatidylinositol, 3 and kinase (PI3K).

The signal pathway of protein kinase B(AKT)-mTOR signal pathway and two downstream regulatory pathways are eukaryotic cell translation initiation factor 4E binding protein 1(4EBP1) pathway and ribosome S6 protein kinase (S6 kinase, S6K) pathway respectively. SOCS is JAK-STATs a negative regulator of signal transduction, which can be physically blocked by binding to phosphotyrosine on the receptor STATs binding to the receptor, or directly binding to

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JAKs specifically blocking its activity[2] As a member of SOCS family, SOCS3 not only plays an important role in the occurrence and development of virus infection, inflammatory diseases, tumors, obesity and other diseases, but also can participate in the physiological processes of breast growth and development, breast proliferation and lactation, and cell apoptosis regulation[3]. Current research shows that SOCS3 can affect lactation signal pathway in dairy cows during lactation degeneration and inflammation. Regulation of milk protein expression. Therefore, this article will discuss the research on SOCS3 and Lactation Synthesis of Dairy Cows "in recent years.

1. Signal pathway regulating milk protein aynthesis

JAK family has a total of 4 members, namely JAK1, JAK2, JAK3 and TYR2, JAKs are widely distributed, JAK1, JAK2, TYR2 are distributed in almost all tissues and cells, while JAK3 only exists in lymphatic system and bone marrow[4]. STAT and family have 7 and members, STAT1, STAT2, STAT3, STAT4, STAT5a, and STAT5b and STAT6, of which STAT5a and STAT5b are two homologs of STAT5, which can form phosphorylation complexes to play a role[5]. Prolactin (PRL)-mediated JAK2-STAT5 signaling pathway plays an important role in milk protein synthesis in breast tissues during lactation. Previous studies have proved that prolactin mediates JAK2/STAT5 transcriptional regulation of milk protein in mouse mammary epithelial cells. Loss of STAT5a gene leads to delayed breast development and decreased milk secretion in mice, while loss of STAT5b gene does not affect breast development[6]. Shi Linlin et al[7] on cow mammary gland cultured in vitro.

In skin cells, STAT5a and other genes were silenced by gene silencing technology, and the expression changes of related proteins and mRNA were detected, proving that STAT5a also plays an indispensable role in the transcription process of milk protein in dairy cows. at present STAT5a has become a marker transcription factor for the transcription level of reactive milk protein. When JAK2 is stimulated by PRL, its kinase activates and phosphorylates tyrosine residues in the receptor chain[8] to form corresponding STAT5 docking sites. subsequently, the raised STAT5 binds to the target receptor through SH2 domain, phosphorylates under the action of JAK2, and the activated STAT5 is separated from the receptor in shape.

Nucleation after Homologous or Heterologous Dimer Formation and Promoter Binding on Milk Protein Gene to Regulate Transcription. While regulating milk protein, STAT5 can also activate transcription of SOCS2 and SOCS2 can negatively inhibit STAT5, prevent its overexpression, regulate and control lactation stability[9].

When the transcription process of milk protein is completed, the signal pathways that play a role in the translation process are mainly PI3K-AKT-mTOR ,PI3K is an important signal molecule upstream of mTOR ,while AKT is located downstream of PI3K ,also known as protein kinase, B (PKB) When nutrients, growth hormone, insulin, etc. stimulate PI3K-AKT-mTOR signal pathway, firstly activate PI3K on cell membrane, and then make phosphatidylinositol diphosphate (PIP2) generate phosphatidylinositol triphosphate (PIP3)[10]. PIP3 acts as a second messenger to activate its downstream signal AKT. Then mTOR is activated, phosphorylated downstream target proteins 4EBP1 and S6K1, 4EBP1 and S6K1 are key regulatory factors in the protein translation process. unphosphorylated 4EBP1 binds to eukaryotic translation initiation factor 4E(eIF4E), preventing the formation of translation initiation complexes, and unphosphorylated S6K1 binds to eukaryotic initiation factor 3 (eIF3), in an inactivated state. Studies have found that mTOR can phosphorylate and dissociate 4EBP1 and eIF4E after phosphorylation.

EIF4E combines with milk protein translation initiation factor to form translation initiation complex, which promotes the initiation of mRNA translation[11,12]. In addition, phosphorylated mTOR complex can combine with eIF3, enabling S6K1 to be activated and released from eIF3. activated S6K1 phosphorylated its downstream substrates, such as RPS6 and so on, to enhance the ability of cells to synthesize proteins[13,14] to increase the amount of milk protein synthesis. PRL, STAT1, STAT3, STAT5 can be activated at the same time, JAK and kinase can be activated by different cytokines, STAT and STAT proteins are activated in various ways, so the composition and content of milk proteins change accordingly. " Except PRL and Insulin.

(INS) and growth hormone (GH) can all affect the synthesis of milk protein. INS can promote breast cells to absorb amino acids from blood and inhibit protein decomposition, regardless of whether PRL and INS exist or not, it can promote gene expression related to milk protein synthesis. Some glucocorticoids such as hydrocortisone can also activate JAK-STATs signaling pathway to regulate transcription of milk protein[16]. Studies have found that injection of

glucocorticoid into pregnant cows can induce lactation, greatly improving the yield of artificially induced lactation.[17]. These hormones related to lactation can activate JAK-STATs or mTOR signal pathway, synergy PRL mediated lactation pathway, but when PRL concentration is too high, it may be used as an inflammatory stimulus to activate inflammatory signal pathway NF-κ B[18] and affect milk protein expression.

2. Regulation of lactation in degeneration stage of mammary gland

SOCS3 belongs to SOCS and family members. The currently identified SOCS members include CIS and SOCS1-SOCS7.Its structure includes a SH2 domain responsible for phosphotyrosine residues and a short and small C terminal with only about 40 and amino acid domains, called SOCS cassette. SOCS1, and SOCS3 are the most studied molecules in the family, which are different from other SOCS members, SOCS1, and SOCS3 containing short n, terminal kinase inhibitory region (kir), 19, similar to JAK, substrate. KIR is a segment SH2 upstream of domain 12 amino acid residue sequence, which inhibits JAK by partially blocking the substrate binding groove on the kinase surface, which allows SOCS3 to inhibit signal transduction 3 by directly inhibiting the catalytic activity of JAK. In view of the sequence similarity between KIR and JAK activation ringst0 it has been suggested that KIR can also be used as a false substrate for JAK1 and JAK2, thus inhibiting their activity[20]. However, subsequent studies show that SOCS3 is not used as a false substrate, but as a non-competitive inhibitor for ATP binding to substrate[21], and directly inhibits JAK1, JAK2 and TYK2 by binding to conservative glycine. SOCS3 cannot inhibit JAK3 due to lack of glutamine -methionine (GQM) motif in JAK3. The motif is only found in JAK1, JAK2 and TYK2, and has been highly conserved in vertebrate evolution, and has never been found in JAK3[22]. When SOCS3 KIR binds to JAK, it does not affect the classical phosphotyrosine binding groove on SH2 domain. It can still bind to gp130, a common receptor and signal transduction subunit of IL-6 family. SOCS3 uses two opposite surfaces to simultaneously bind JAK2 and gp130[23] to inhibit the activation and expression of STAT3 and STAT5.

SOCS3 plays a role in physiological processes such as cell apoptosis, immune regulation and inflammatory response while participating in the growth and development of mammary gland and proliferation and lactation. 19,20 and therefore, SOCS3 have different expressions in different periods. It plays different roles in different periods. It was found in the mammary gland research of mice that the expression of SOCS3 was highly expressed in the early ten days of pregnancy, the early lactation period and the mammary gland degeneration period, but hardly expressed in the middle and late pregnancy and the lactation peak period[21] At the same time, in vitro experiments of mice found that SOCS3 can inhibit PRL induced milk protein gene expression and STAT5 activation 24 In the study of human breast cells, it is found that the growth and development of breast is regulated not only by hormones such as GH, PRL, but also by SOCS and proteins. STAT3 and potential STAT5 can stimulate SOCS3 gene transcription, and have negative regulatory effects on JAK signal transduction[25]. Wall *et al.* found that during the dry milk stage of dairy cow lactation degeneration, short sunshine can reduce the expression of SOCS and further enhance the signal transmission of prolactin to breast[26]. The above contents suggest that SOCS may play a role in the stage of breast degeneration.

In rodents, mammary gland degeneration is mainly divided into two stages. The first stage starts immediately after weaning and is mainly an acute reaction stage characterized by a decrease in milk protein synthesis, which generally lasts for 48 hours and is related to cell apoptosis and shedding.

The segment is generally reversible; The second stage starts at 48 hours and is characterized by significant changes in breast structure, including atrophy of lung lobules and alveolar structures and proliferation of adipocytes[27]. The degeneration of breast in this stage is irreversible. The degeneration process is slower in bovine mammary glands than in mice, and more alveolar structures are retained, which makes the degeneration of bovine mammary glands have a longer reversible period. Experiments prove that the degeneration process is still in a reversible period 192 hours after the cows stop milking[28]. Mammary gland degeneration is usually associated with increased activation of NF-κB, and STAT3. In the first stage of degeneration, it has been shown that milk stasis induces expression and secretion of proinflammatory cytokine leukemia inhibitory factor (LIF)[29], LIF can bind with heterodimers formed by LIF receptors and gp130 so that JAK2 is activated by trans autophosphorylation[30] and further phosphorylates STAT3. However, the activation of STAT3 is not enough to induce mammary gland degeneration, and nuclear transcription factor κ B (NF-κ B) is also needed. In breast tissue, activation of NF-κB increases during pregnancy, decreases during lactation, and then increases again

after weaning. activated STAT3 can up-regulate SOCS3 expression, phosphorylated SOCS3 can combine with nuclear transcription factor kappa b inhibitory protein (ikappa b) to prevent its degradation or inhibit nf-kappa b activation[33] by combining with upstream TNF receptor-related factor 6 (TRAF6) to block traf6 functions. At the same time SOCS3 inhibits the phosphorylation of STAT3 and STAT5 by inhibiting the activation of JAK2 and STAT5 and STAT5 cannot enter nucleus to regulate transcription and reduce the synthesis of milk protein. STAT3 Inactivation Causes SOCS3 Expression to Decrease Gradually, Forming a Negative Regulation Mechanism to Ensure Physiological Controllability of Cell Apoptosis in Degeneration Process[29] This negative regulation of SOCS3 may be the key mechanism of the balance between STAT3, STAT5 and STAT3 and STAT5 signal conduction in the process of breast degeneration.

3. Regulation of SOCS3 on milk protein synthesis in subclinical mastitis

Staphylococcus aureus can induce chronic infection of cow mammary gland, which is the main factor leading to cow recessive mastitis[34]. When staphylococcus aureus invades breast tissue, its cell wall intrinsic component lipoteichoic acid (LTA-sa), as a major surface antigen, can be captured by Toll-like receptor 2(TLR2) and Toll-like receptor 4(TLR4), thus activating nuclear transcription factor inhibitory protein (IκB). The production of IL-1β, IL-6 and tumor necrosis factor α(TNFα) was induced by myeloid differentiation factor 88(MyD88)-dependent signal transduction pathway[35], which also showed a significant increase of these three inflammatory factors in human subclinical mastitis[36]. IL-1β and so on can also activate IκB and up-regulate the expression of NF-κB and at the same time activate the apoptosis signal pathway STAT3 through gp130 pathway to promote the apoptosis of cow mammary gland cells and the degeneration of mammary gland. Highly expressed, STAT3, and, NF-κB, Activating Its Negative Regulatory Factor, SOCS3, Further Inhibiting, STAT5, Entering Nucleus to Regulate Milk Protein Expression and Reduce Milk Yield. In vitro experiments prove that IL-1β can induce the inactivation of signal transduction of STAT5 and glucocorticoid receptor (GR), and activate STAT3 and NF-κ B[37,38] in cow mammary epithelial cells at the same time. By adding IL-1β to cow mammary epithelial cells and stimulating them at different times, phosphorylation STAT5 decrease and phosphorylation STAT3 increase with time were observed by nuclear localization immunostaining. Continuous activation of STAT3 is necessary for anti-inflammatory effect, while its instantaneous activation can promote the occurrence of inflammation[29]. The activation of IL-1β can also increase the expression of IL-6 and TNFα[37], further promoting the development of inflammatory process. The interaction between signal paths is shown in Figure 1 and Figure 2.

Previous studies have shown that in human and mouse mammary gland cells, SOCS3 and STAT5 are directly related to [39,40]. After overexpression of the SOCS3 and SOCS 3 genes in cow mammary gland epithelial cells, the amounts of intracellular phosphorylation, STAT5a, and β casein have decreased. Moreover, overexpressed SOCS3 is mainly concentrated in the nucleus, and after inhibiting SOCS3, phosphorylation in the nucleus, STAT5a, increased expression, 41, which indicates that SOCS3 has negative regulation on STAT5, and inhibits β and casein gene expression. Although more and more evidences show the expression of SOCS3, negative regulation, STAT5 ,there is no research pointing out that SOCS3 directly acts on STAT5 and inhibits its expression. More research tends to SOCS3 reduce the transcription level of milk protein by inhibiting JAK2, indirect inhibition and STAT5. However, in human breast cancer cells SOCS3 can induce the production of mutant promoters (pSRE) that bind to STAT5), and similar reports [42,43] have been reported in mouse cells.There may be a binding site for STAT5 on SOCS3 in dairy cows. This has yet to be further demonstrated.

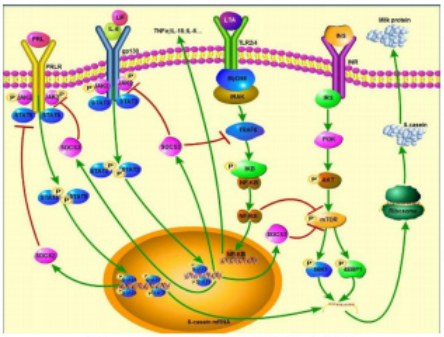

Figure 1. SOCS3 affects breast lactation signaling pathway.

It is an indisputable fact that mTOR signal pathway participates in the regulation of milk protein translation process.After the receptor activates PKB, PKB acts on mTOR, enhancing the activity of its downstream target genes S6K1 and 4EBP1 and promoting the translation and synthesis of milk protein. Milk fat, as another important nutrient substance in milk, is mainly regulated by peroxisome proliferator-activated receptor, γ, PPARγ, and sterol regulatory element binding protein, 1, SREBP1. PPAR γ regulates fat synthesis by regulating the differentiation of fat fine cells and gene expression, while SR EBP 1 regulates fat synthesis accordingly by affecting transcription of genes related to lipid metabolism. Recent studies have found that in bovine mammary epithelial cells, SOCS3 inhibits the expression of mTOR, interferes with SOCS3 and can improve the expression of SREBP1 and 41. The specific mechanism is still unclear. In breast development and cancer research, it has been found that JAK2 can activate PI3K upstream of mTOR through insulin receptor substrate (IRS) and prolactin receptor substrate (PRLR), thus promoting mTOR expression[44-45]. However, SOCS3 with high expression can inhibit the activation of JAK2. Therefore, it is speculated that SOCS3 and mTOR may be inhibited by similar mechanisms in milk synthesis. It has been reported that there are binding sites of SREBP1c on SOCS1 and promoter of mice, while SOCS and family structure are highly conservative, SOCS1 and SOCS3 are highly similar in structure. It is speculated that there may be the same binding site on SOCS3 which affects the synthesis of milk fat.

4. Conclusion

In conclusion, SOCS3 can affect lactation-related signaling pathways to regulate milk protein expression. During normal lactation, SOCS3 will not affect lactation. When lactation ends, mammary glands begin to degenerate to dry milk stage. At this time, SOCS3 is activated by STAT3 and then activated by JAK2 and STAT5. And inhibit the expression and phosphorylation of mTOR, thus reducing the transcription and synthesis of milk egg white, and reducing the milk protein content in milk. Similarly, in recessive mastitis, the inflammatory signal pathway is activated, resulting in the up-regulation of SOCS3 expression, leading to the weakening of breast lactation function and breast degeneration. Meanwhile, rt can inhibit SREBP1 expression and affect the synthesis of milk fat.

SOCS as a key target regulates the specific process of lactation through JAK-STAT, mTOR and other signaling pathways in milk secretion, dry milk and inflammation of dairy cows. Meanwhile, the relationship between SOCS3 and inflammatory signaling pathway NF-κB in mastitis will be the next research target. " At present, the research on the interaction between SOCS3, STAT3 and milk cow mammary gland cells has gradually become clear, but the mechanism of action between SOCS 3, STAT5 and mTOR still needs further research.

Moreover, it is still unclear how SOCS3 regulates SREBP1. Therefore, an in-depth study of SOCS3 and the influence of SOCS 3 on the signal transduction mechanism of breast milk secretion will help us to better understand milk synthesis, regulate milk secretion at the gene level, improve milk yield, control breast diseases, improve the nutritional quality of milk, and provide a strong guarantee for the sustainable and healthy development of China's milk industry.

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