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# JAK-STAT in lipid metabolism of adipocytes

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JAK-STAT signaling pathway plays an important role in the cells' development and homeostasis. Over the past decades, the studies have identified the role of the JAK-STAT pathway in cell proliferation and apoptosis. Here, we want to discuss that whether and how the JAK-STAT pathway affects the lipid metabolism of adipose tissue. A host of cytokines and hormones can regulate lipid metabolism through activating the JAK-STAT signaling pathway. Activated STATs can regulate lipid metabolism directly by influencing the expression of enzymes. We have summarized the relevant research and articles of JAK-STAT during the recent years. Within this review, we will introduce you the recent research and highlight the unresolved problems in understanding how JAK-STAT signaling pathway contribute to the lipid metabolism in mature adipocytes and preadipocytes. Dysregulation of the JAK-STAT pathway would lead to a multiple metabolism disorders and medicines for this signaling pathway maybe become a new idea for diseases such as metabolic syndrome, especially in children.

## Introduction

### JAK-STAT signaling pathway

The Janus kinase–signal transducers and activators of transcription (JAK-STAT) signaling pathway is a pleiotropic cascade used to transduce a multitude of signals for development and homeostasis in animals.[1] These cellular signals involve in immunity, cancerogenesis,[2] ontogenesis,[3] inflammation,[4,5] stem cell maintenance,[6] neuron function[7,8], and lipid metabolism.[9] The dysregulation of the JAK-STAT pathway would cause disease, such as immunodeficiency, cancer, allergy,[10] renal disease,[11] hepatic disease,[12,13] and so on.

To date, 4 members have been identified in JAK kinase family, including JAK1, JAK2, JAK3, and TYK2. JAK1 and JAK2 have been detected in adipocytes. They are critical to the role of JAK-STAT in fat tissue. JAK3 and TYK2 express in adipose tissue, but no evidence indicates that they are expressed in adipocytes.[14] Each JAKs contains 4 mainly domains, including kinase domain, non-catalytic kinase-like domain (a dual-specificity protein kinase that negatively regulates cytokine signaling), phosphotyrosine binding domain and receptor binding domain.[1,15,16] In humans, JAK1 maps to chromosome 1p32.3–p31.3; JAK2 maps to chromosome 9p24; JAK3 maps to chromosome 19p13.1 and TYK2 maps to chromosome 19p13.2.

The STAT proteins family contains 7 members (STATs 1, 2, 3, 4, 5A, 5B, and 6). STATs 1, 3, 5A, and 5B have been detected in adipocytes.[17] STAT6 may be involved in the differentiation of preadipocytes. So far, there is no evidence to support the presence of STATs 2 and 4 in fat cells. These STAT genes all have been identified in three chromosomal clusters. In mouse, STATs 1 and 4 map to a region of chromosome 1 (equivalent to human 2q12–q33); STATs 3, 5A, and 5B map to a region of chromosome 11 (human 12q13–q14.1); and STATs 2 and 6 map to a region of chromosome 10 (human 17q11.1–q22).[18] In contrast, another review shows that STATs 3, 5A, and 5B map to a region of chromosome 11 (human 17q11.2–q22); and STATs 2 and 6 map to a region of chromosome 10 (human 12 q13–q14.1).[19] All STATs contain 5 domains, including oligomerization domain, coiled coil (protein interaction), DNA binding domain, phosphotyrosine binding domain, and transcriptional activation domain.[1]

There are several forms of JAKs-STATs, including JAK1/3-STAT6, JAK1/2-STAT1/3/5, and so on.[20,21] The activated JAK-STAT pathway begins with the combination of cytokine and its receptor. The receptor activates the associated JAKs, which in turn phosphorylate the receptor cytoplasmic domain to allow recruitment of a STAT. Several STATs, such as STAT, may also be directly activated by the cytokine-receptors. The STAT is phosphorylated, dimerizes, and moves to the nucleus to bind specific sequences in the genome and activate gene expression.[22] There are 10 forms of STATs–STATs after phosphorylation. pSTATs 1, 2, 3, 4, 5 (5A and 5B interact in a manner as heterodimers), and 6 forms of 6 homodimers and 4 heterodimers. Few STAT2–STAT2 dimers form in the absence of STAT1 and bind target DNA sequence weakly as do STAT2:3. Other two heterodimers are STAT1:2(need p48) and STAT1:3 which is primarily involved in the cells' apoptosis and inflammation.[18] What we will review here is the homodimers of STATs-STATs. STATs could be posttranslationally modified by phosphorylation, methylation, acetylation, ubiquitylation, ISGylation, and SUMOylation. The tyrosine phosphorylation of STATs is necessary for its dimerization, nuclear translocation, and DNA binding.[15] STATs can also be serine phosphorylated by MAPKs (mitogen-activated protein kinases), such as p38. The serine phosphorylation of the 727-site of STAT1 and STAT3 has been widely studied. Ser727 is of particular interest as a potential MAPK site, thus bringing STATs and MAPK together and allowing "cross-talk" among different cytokines receptor systems.

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An increase in transcriptional activation upon phosphorylation of Ser727 of STATs has been predicted from the prevailing (cross-talk) model. However, in cell lines, mutation of Ser727 in STAT1 displays a repressed effect and results in only 20% of wild-type activity.[23] So, the effect of the serine phosphorylation remains to be clarified. It could promote or inhibit the tyrosine phospholyration.[23-26] And the unphosphorylated STATs also mediates non-canonical function, such as angiotensin II-induced cardiac hypertrophy.[27] In mitochondria, u-STAT3 participates in cellular respiration and mitosis.[28,29] So far, Studies by independent groups have revealed that STATs 1, 3, 5A, 5B, and 6 express in fat cells.[30]

**Lipid metabolism**

Adipocytes play critical roles in lipid storage, energy homeostasis, and whole body insulin sensitivity. Approximately 90% of the adipocyte volume is TAG (triglycerides) which is located in an only lipid droplet that dislocates the nucleus to the periphery, resulting in limited cytosolic space.[31] In normal individuals, the adipogenesis and lipolysis are in balance. And obesity results from an imbalance between energy intake and expenditure.[32] The newest data show that the average prevalence of overweight and obesity of adults in China is 21.0% and 2.5%.[33] With obesity, the individuals are in state of chronic inflammation and adipose tissue dysfunction.[9] The expandability of adipose tissue determines the onset of metabolic syndrome, such as insulin resistance and diabetes type 2.[34]

Fat cells have two types, white adipocytes and brown adipocytes. White adipose tissue (WAT) plays important roles in energy storage through lipid release and glucose uptake. Utilizing the CM (chylomicron), VLDL, and glucose, WAT could synthetize TAG. Excess accumulation of white adipose tissue causes obesity. It can also release hormones and cytokines which contribute whole-body metabolism and insulin resistance as an endocrine tissue.[35] Brown adipose tissue (BAT) contributes to energy expenditure because of its high content of mitochondria containing uncoupling protein-1 (UCP-1).[9] Evidences have been provided to support the presence of BAT in adult humans except newborns and rodents. One study shows that as little as 50 g of maximally stimulated brown adipose tissue could account for up to 20% of daily energy expenditure in an adult human.[36] Until recently, hormone-sensitive lipase (HSL) has been considered to be the key rate-limiting enzyme responsible for regulating TAG mobilization and a novel lipase named adipose triglyceride lipase/desnutrin (ATGL) has been identified as an important effector in the control of fat cell lipolysis.[37] During physical training, TAG is first mobilized and hydrolyzed by HSL, ATGL, and monoacylglycerol lipase (MGL), each of which possesses a distinct regulatory mechanism. Eventually, it becomes FFA (free fatty acid). A great deal of energy is released during the oxygenolysis of TG. The FFA could be delivered to and used by the function organs such as heart and muscle with the help of plasma albumin.[37] It is important to note that the developmental origin of white and brown fat is distinct and different precursor cells are involved in the generation of these different types of adipose tissue.[38] The classical pathway of lipolysis activation in adipose tissue is cAMP-dependent. The production of cAMP is modulated by G-protein-coupled receptors of the Gs/Gi family and cAMP degradation is regulated by phosphodiesterase. Several other pathways involved in the lipolysis such as MAPK, JAK-STAT have been identified in recent years.[39] As we know, leptin is a well-known hormone marker for obesity which can promote TAG hydrolysis. It has confirmed that leptin can upregulate ATGL mRNA expression but downregulate ATGL protein expression.[40] With specific inhibitors of JAK2 and p38-MAPK, the ATGL mRNA expression is decreased and ATGL protein expression is increased significantly. It demonstrates that leptin-mediated regulation of ATGL expression is regulated by the JAK-STAT and MAPK signaling pathways (**Fig. 1**).[40]

## JAK-STAT and Lipid Metabolism

**In mature adipocytes**

*STAT1*

IFN-γ has been identified as an activator of STAT1. IFNγ induces robust STAT1 phosphorylation and SOCS1 mRNA expression, with modest, transient STAT3 phosphorylation and SOCS3 induction. Specific inhibition of JAK2 or JAK3 failed to block the effects of IFN-γ, suggesting a predominant role for JAK1–STAT1.[41] The activated STAT1 proteins bind to the promoter of PPAR-γ2 (peroxisome proliferator-activated receptor-gamma 2) and lipoprotein lipase (LPL). It induces a repress action on the expression of PPAR-γ2 and LPL. PPAR-γ2 is an activator of adipogenesis[42] while LPL is the rate-limiting enzyme that catalyzes the hydrolysis of serum triglycerides from lipoproteins into free fatty acids for uptake and storage in adipose tissue. Therefore, it indicates that STAT1 possibly promotes adipogenesis and inhibits lipolysis in mature fat cells.[30] The other identified activators include LIF, OSM, CT-1, GH, and IL-11.[14]

*STAT3*

Many cytokines can generate their signal via the STAT3 signaling pathway which mediates a potent anti-inflammation response dependent on its target gene, suppressor of cytokine signaling-3 (SOCS3).[43-45] STAT3 is involved in distinct functions in different cells.[46] The ASKO mice which was created with an adipocyte-specific disruption of the STAT3 gene, had a higher weight and more adipose tissue mass than their littermate controls, associated with adipocyte hypertrophy but without adipocyte hyperplasia, hyperphagia, or reduced energy expenditure.[47] This observation indicates that STAT3 promotes lipolysis and inhibits adipogenesis. As described previously, with the inhibitor of JAK2, JAK2's downstream target, STAT3 is inhibited as a result. So, STAT3 maybe contribute to the expression of ATGL.[40,48] Likewise, the ability of STAT3 inhibitor, STATTIC, to attenuate lipolysis and ATGL protein abundance in bovine adipocytes indicates leptin induced lipolysis may be regulated by a STAT3 mediated increasing in ATGL protein abundance.[49] Whereas JAK-STAT has no effect on the HSL expression.[50] But the STAT3-induced promotion of lipolysis is inconsistent with the fact that STAT3 inhibits inflammation which promotes lipolysis and reduces lipid storage.[51,52] TNF-α, a factor of inflammation, induces the lipolysis and inhibits

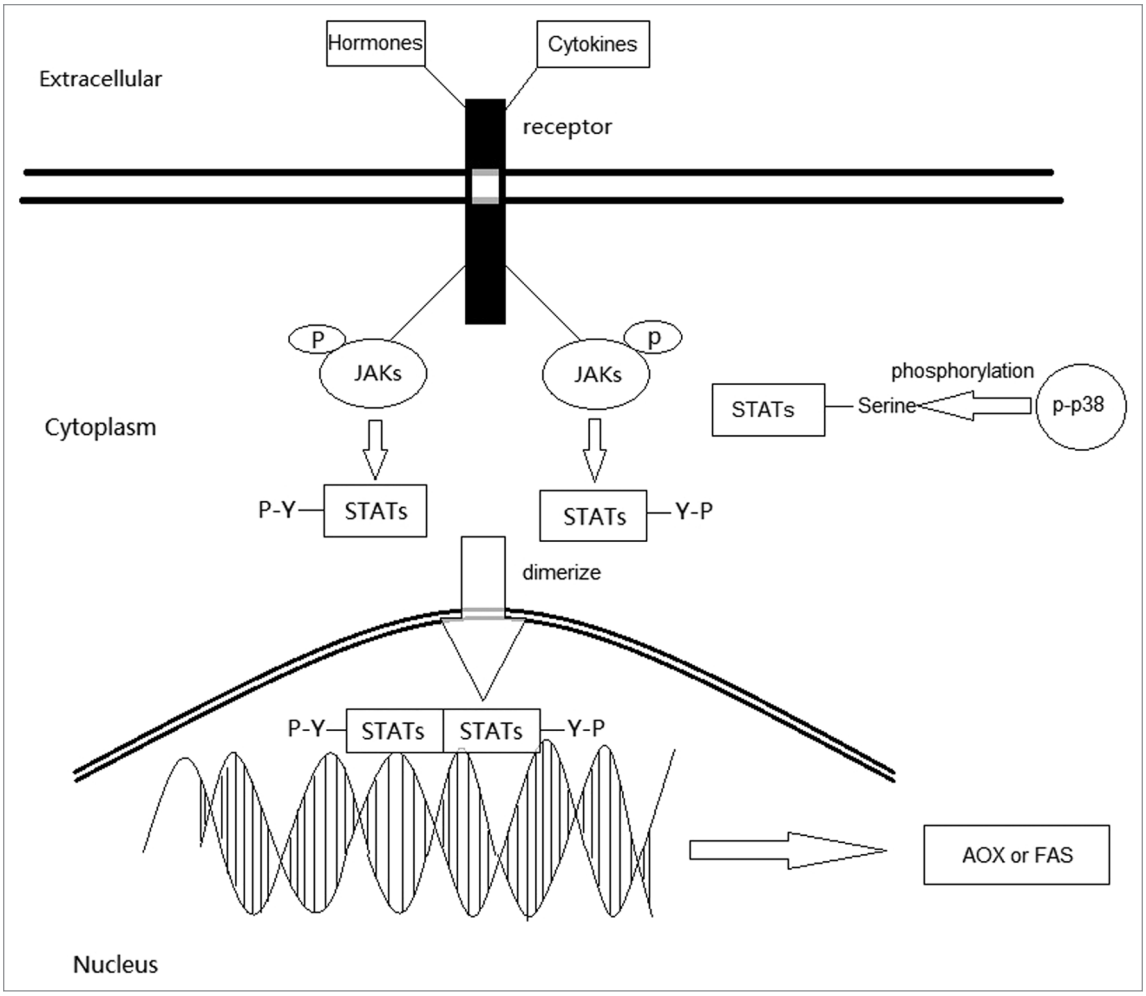


**Figure 1.** The signaling pathway of JAK-STAT.

adipogenesis in WAT.[53] Numerous of studies have indicated that pSTAT3 activated by cytokines, such as IL-10, can inhibit the LPS-induced expression of TNF-α.[54,55] Moreover, in hepatocyte, forced expression of STAT3 reduces abundance of mRNAs for fatty acid synthase and acetyl-CoA carboxylase. And the amount of mRNA for acyl-CoA oxidase (AOX), which contributes to β-oxidation, is also decreased by overexpression of STAT3.[12] The activators include LIF, OSM, CNTF, CT-1, IFN-γ, NP, GH, Leptin, IL-6, IL-10, and IL-11.[56-59]

*STAT5*

In adipocytes, AOX and fatty acid synthase (FAS) are identified to be the target genes of STAT5.[60,61] A STAT5A binding site in FAS and AOX promoter mediates the repression of FAS expression while promotes the expression of AOX.[9,30] Therefore STAT5 possibly induces an effect on the lipid metabolism like STAT3. Studies have shown that the adiogenic effect of GH could be suppressed by overexpression of STAT5A mutant (STAT5A–Y694F) with the reduction of PPARγ2 expression. In this research, STAT5A/5B stimulated C/EBPβ (C/AAAT enhancer binding protein β)- and C/EBPδ-induced adipogenesis with enhancement of PPARγ2 expression. In addition, STAT5A/5B enhanced the transcriptional activity of C/EBPβ/δ in the PPARγ gene promoter. Furthermore, STAT5A/5B stimulated PPARγ-induced adipogenesis and enhanced the transcriptional activity of PPARγ. These results suggest that the STAT5A/5B signaling pathway could stimulate adipogenesis cooperated with C/EBPβ/δ and PPARγ in the GH-induced lipid metabolism.[62] STAT5 may be involved in the expression of ATGL like STAT3.[39,48] And they may play a dual role in the lipid metabolism according to the activator. The activators of STAT5 (STAT5A and STAT5B) include GH and PRL.[14]

*STAT6*

Studies have indicated that only IL-4 can activate STAT6, and it has been shown to activate this transcription factor in 3T3-L1 preadipocytes but not in adipocytes.[63]

**In preadipocytes**

*STAT1*

On one hand, STATs tend to promote lipolysis in mature adipocyte. On the other hand, STATs tend to induce proliferation and promote adipogenesis of preadipocytes. But in cultured murine and human adipocytes, the protein level of STAT1 is downregulated during differentiation. It indicates that STAT1 may not promote adipogenesis during the differentiation of adipocytes.[14] Consistently, another study shows that IFN-γ

may suppress differentiation in human adipocytes via JAK-STAT1.[64] Treatment with IFNγ could block differentiation of pre-adipocytes to the mature phenotype.[41] Therefore, STAT1 in preadipocytes tends to promote lipolysis and repress adipogenesis.

*STAT3*

In preadipocytes, the target genes of STAT3 has been identified as C/EBPβ. Studies have showed that JAK2–STAT3 pathway is involved in the early stage of 3T3-L1 adipocyte differentiation though regulating the C/EBPβ transcription.[65] pSTAT3 binds to its target gene, C/EBPβ, and promote the proteins level which in turn promote adipogenesis.[14] C/EBP transcription factors (including C/EBP α, β, and δ) are the first family of transcription factors shown to play a critical role in the differentiation of fat cells in vitro. Mice lacking both C/EBPβ and δ or α alone exhibits a defective differentiation.[66] With the inhibiting factors of STAT3, such as AG490, dimethylfumarate and STAT3 siRNA, adipocyte differentiation would be suppressed. And PPAR-γ agonist may abolish the inhibitor-STAT3-induced suppression of adipogenesis, suggesting that STAT3 regulates adipocyte differentiation through PPAR-γ.[67,68] Additional researches support that STAT3 promote the differentiation of preadipocytes. They have shown that pSTAT3 may promote fat cell differentiation via modulating the progress of mitotic clonal expansion, a proliferative phase that occurs immediately following induction of adipogenesis.[69]

*STAT5*

In preadipocytes, the target genes of STAT5 have been identified as C/EBPα and PPAR-γ. STAT5 induces adipogenesis of preadipocytes. STAT5, especially STAT5A, may bind to the promoter of C/EBPα and PPARγ3 and promote the expression of C/EBPα and PPARγ, which in turn induce adipogenesis of preadipocytes during its differentiation. STAT5B may enhance the STAT5A-induced preadipocytes differentiation.[9] $STAT5A^{-/-}$ or $STAT5B^{-/-}$ or $STAT5^{-/-}$ mice exhibits reduced fat pad sizes compared with wild-type mice.[66] And the athymic mice injected with Swiss 3T3 cells expressing STAT5A may result in fat pad formation at the site of injection.[70] Another research also showed that virus-mediated gene transfer of the constitutively active form of both STAT5A and STAT5B resulted in enhanced adipocyte differentiation in the absence of fetal bovine serum, which was judged by the expression of proadipogenic factors as well as accumulation of fat droplets in the cell line.[71] STAT5 may also modulate the proteins level of adiponectin which contributes to the lipid metabolism of adipocytes.

*STAT6*

STAT6 can be activated by IL-4, but its expression is not regulated during fat cell development and is uniform in preadipocytes.[14] So the effect of STAT6 in lipid metabolism remains to be clarified.

## Conclusion and Outlook

In conclusion, adipose tissue is the only tissue capable of hydrolyzing its stores of TAG and of mobilizing fatty acids and glycerol in the bloodstream so that they can be used by other tissues, such as heart and muscle. Disorder of lipid metabolism may result in metabolic syndrome including obesity, fatty liver, and insulin resistance and so on. Many agents and pathways involved in the regulation of lipolysis and adipogenesis in adipose tissue have been clarified. A host of cytokines and hormones can regulate lipid metabolism through activating the JAK-STAT signaling pathway. Modulation of the JAKs–STATs pathway can regulate lipid metabolism in adipocyte. Activated STATs can regulate lipid metabolism directly by influencing the expression of enzymes, such as AOX and FAS. Meanwhile, STATs also play roles in inflammation and anti-inflammation, which could impact on the lipid metabolism. But a host of problems remain to be resolved. Further studies are necessary to identify the other target genes of STATs in adipocyte and to determine how modifications such as serine phosphorylation, acetylation, methylation and sumoylation impact on STATs. How JAKs-STATs impact on the expression of ATGL? Whether JAKs–STATs participate in the HSL or MGL-induced lipolysis? And the JAKs-STATs pathway in BAT remains to be elucidated. Although the roles of different JAKs-STATs in the lipid metabolism of adipocytes and preadipocytes have been studied with cell lines and animal models as reviewed, it will be important to continue to explore the roles and mechanisms of JAKs-STATs in human adipose tissue because of the impact of species variation. The dysregulation of JAKs-STATs pathway would lead to a multiple metabolism disorders and medicines aimed at this signaling pathway maybe become a new idea for metabolic syndrome.[72]

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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