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Identification of STAT target genes in adipocytes

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Adipocytes play important roles in lipid storage, energy homeostasis and whole body insulin sensitivity. Studies in the last two decades have identified the hormones and cytokines that activate specific STATs in adipocytes in vitro and in vivo. Five of the seven STAT family members are expressed in adipocyte (STATs 1, 3, 5A, 5B and 6). Many transcription factors, including STATs, have been shown to play an important role in adipose tissue development and function. This review will summarize the importance of adipocytes, indicate the cytokines and hormones that utilize the JAK-STAT signaling pathway in fat cells and focus on the identification of STAT target genes in mature adipocytes. To date, specific target genes have been identified for STATs, 1, 5A and 5B, but not for STATs 3 and 6.

Adipocytes

Adipocytes, or fat cells, are highly specialized cells that play a major role in energy homeostasis in vertebrates. Obesity is the primary disease of fat cells and the most common metabolic disorder in the industrial world. Obesity affects > 30% of the adult population in the United States and is a major risk factor for the development of Type 2 diabetes mellitus, cardiovascular disease and hypertension. Adipocytes have three primary functions: they are insulin-sensitive, they store lipid and they secrete hormones that act in distant tissues. The disruption of any one of these functions results in an unhealthy metabolic disease state. Recent studies suggest that obesity and its related disorders may be linked to a breakdown in the regulatory mechanisms that control the expression of a variety of genes in adipocytes. Significant advances toward an understanding of these regulatory processes have been made by studying the function of transcription factors, which regulate the differentiation of fat cells and are involved in the modulation of adipocyte gene expression. It is well recognized that several transcription factors are induced during adipocyte differentiation, play a critical role in the regulation of adipocyte gene expression and are altered in conditions of obesity and/or insulin resistance.[1,2] Several laboratories have investigated the role of STATs (signal transducers and activators of transcription) in adipocyte development and function.

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Signal Transducers and Activators of Transcriptions: STATs

There are seven signal transducers and activators of transcription (STAT) proteins that are designated STATs 1, 2, 3, 4, 5A, 5B and 6 that exhibit unique tissue distributions and regulate the expression of tissue specific genes.[3] The expression and modulation of gene expression modulated by STATs can be cell specific, and transgenic knockout studies have shown critical roles for every member of the STAT family.[3] STATs are primarily activated by cytokines and hormones. Ligand binding initiates a cascade that results in STAT tyrosine phosphorylation, dimerization and translocation to the nucleus where STATs modulate transcription.[3,4] In addition to the canonical activation by tyrosine phosphorylation, STATs can undergo several other posttranslational modifications, including serine phosphorylation, acetylation, methylation and sumoylation.[5] Of note, there is also substantial evidence that STATs can function in non-canonical mechanisms to modulate transcriptional activity and they can also function in chromatin organization and mitochondrial respiration in ways that appear to be independent of transcriptional regulation.[5,6]

STATs and Adipocytes

Studies by independent groups have revealed that STATs 1, 3, 5A, 5B and 6 are expressed in fat cells. As shown in **Figure 1**, STATs 1, 5A and 5B are substantially induced during 3T3-L1 adipocyte differentiation.[7] Similar induction patterns of STATs 5A and 5B occur in human subcutaneous preadipocytes.[8] The expression and activation of STAT6 is not changed during adipocyte development. Studies in both mouse and human cells have revealed a similar induction of STATs 3, 5A and 5B, but there was a difference in STAT1 induction in mouse and human cells. However, it is unlikely that STAT1 plays a critical role in adipocyte development because STAT1 knockout mice do not have any apparent body weight abnormalities.[9] The significance of the differential expression of STAT1 during the adipogenic program remains unclear. However, there are numerous studies that establish a role of STATs 3, 5A and 5B in human and murine adipogenesis. STAT3 expression does increase during the proliferative phase that occurs during the adipogenesis of the murine 3T3-L1 cells.[10] STAT3 expression is tightly regulated by PIAS3, protein inhibitor of activated STAT3.[11] Inhibition of adipogenesis has also been observed with AG490, a JAK2 inhibitor, and STAT3 siRNAs.[12] Furthermore, the ectopic expression of a dominant negative STAT3 suppresses adipocyte differentiation.[13] Mice lacking STAT3 in adipose tissue were generated using the

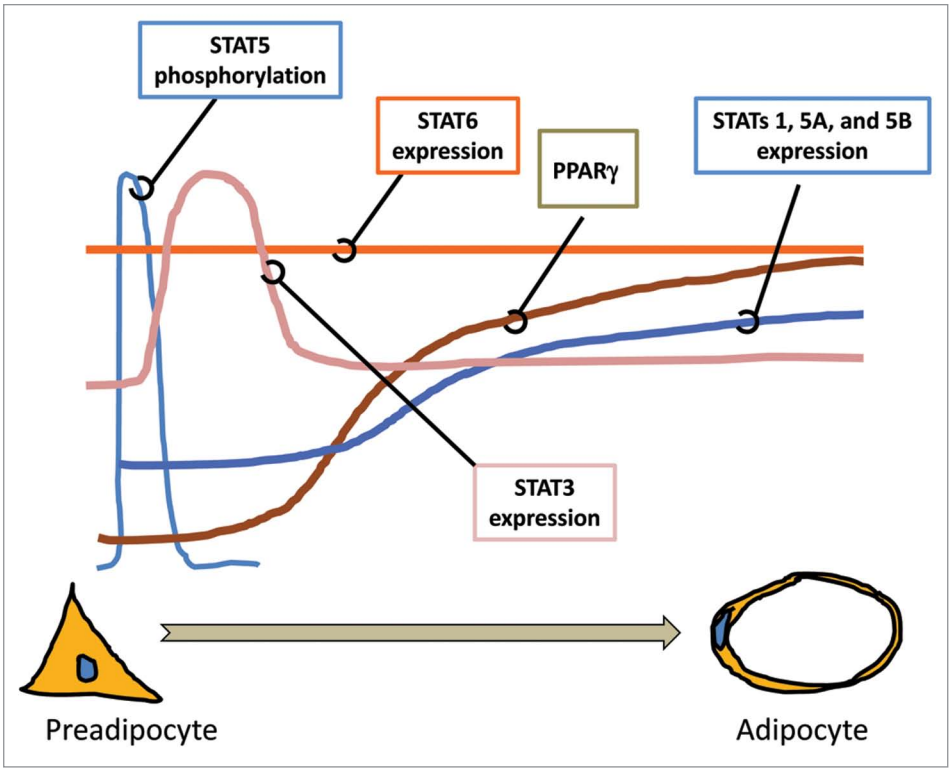

Figure 1. The expression and activation of STATs during adipocyte differentiation. Many studies have examined the expression and activation of STATs during the development of adipocytes from preadipocytes. As shown above, STAT5 proteins are tyrosine phosphorylated at the initiation of adipocyte differentiation. This activation precedes the increase in expression of STATs 1, 3, 5A and 5B, which is observed. STAT3 expression is increased during clonal expansion. The induction of the transcription factor PPARγ, a necessary factor for adipocyte development, precedes the increased expression of STATs, 1, 5A and 5B. The expression of STAT6 does not change during adipocyte development. Although the expression of several STATs is changed during adipocyte development, only STAT5 proteins have been shown to play a critical role in adipocyte development in vitro and in vivo.

aP2 promoter and these mice exhibited higher body weights and increased adipocyte size compared with wild-type littermates.[14] Collectively, these studies suggest a possible role for STAT3 in adipogenesis and body weight homeostasis. Nevertheless, additional studies are necessary to further clarify the contribution of STAT3 in adipocyte development and physiology.

The involvement of STAT5 in adipogenesis has been widely investigated. The ectopic expression of C/EBP transcription factors in non-precursor cells can induce adipogenesis[15] in a mechanism that is accompanied by a substantial increase in STAT5A and STAT5B expression.[16] PPARγ, a transcription factor critical for adipocyte development, has also been shown to increase the expression of both STATs 5A and 5B during adipocyte development.[17] In preadipocytes, the control that growth hormone exerts on adipogenesis is inhibited by STAT5 antisense oligonucleotides.[18] Also, constitutively active STAT5 can drive adipogenesis in preadipocytes.[19] A variety of methods including transgenic knockout mice and ectopic expression studies have confirmed the physiological relevance of STAT5 proteins in adipogenesis. Ectopic expression of STAT5A induces adipogenesis in 3T3-L1 preadipocytes,[20] and in several non-precursor cell lines.[21] Unlike STAT5A, STAT5B does not display pro-adipogenic properties in non-precursor cells.[21] Growth hormone activated STAT5 proteins have been shown to induce PPARγ expression in 3T3-L1 cells and C3H10T1/2 cells,[22] suggesting a mechanism by which STAT5 proteins are able to promote adipocyte differentiation. Interestingly, transgenic knockout experiments have shown that disruption in either STAT5A or STAT5B or both genes resulted in abnormal adipose tissue and mice lacking both STAT5 proteins had fat pads one-fifth the normal size.[23] To date, there are no studies on tissue-specific knockouts of STAT5 genes in adipocytes and the phenotype of the STAT5 null mice could be attributed to developmental effects of STAT5 that are independent of direct effects on preadipocyte differentiation. However, new studies have shown that ectopic STAT5A expression can confer adipogenesis in fibroblasts in vivo.[24] In addition to demonstrating a direct role of STAT5A in preadipocyte differentiation in vivo, these studies also revealed the usefulness of athymic mice in studying the role of transcription factors in adipose tissue development. In summary, the importance of the STAT5 proteins in adipogenesis has been demonstrated in vitro and in the whole animal.

Activators of STATs in Adipocytes

Studies by a variety of groups over the past 20 years have shown that adipocytes are responsive to several JAK-STAT activating cytokines and hormones including LIF, OSM, CT-1, interleukin (IL)-6, CNTF, NP, GH, PRL and IFNγ (**Table 1**). Most of these observations are based on vitro studies performed in cultured murine or human adipocytes. However, there is also sufficient and compelling evidence to show that adipose tissue in vivo is responsive to these JAK-STAT activators.[25-27] As shown in **Figure 2**, adipocytes contain receptors for these ligands, most of which are present in circulation. An important function of adipocytes is the production of a variety of endocrine mediators. Of note, there are four JAK-STAT activating hormones which have been shown to be produced from adipocytes (**Fig. 2**). One of these STAT activators is leptin, an important endocrine hormone that serves as an adiposity signal and can affect food intake and energy expenditure. Of note, the majority of leptin is produced and secreted from adipocytes and the primary target tissue is the arcuate nucleus in the hypothalamus. Leptin binding to its receptor within this feeding center in the hypothalamus results in JAK2, STAT3 and STAT5 activation. In leptin receptor-deficient

mice, analysis of mutant leptin receptor knock-in has revealed distinct roles of STAT3 and STAT5 in leptin action.[28-31] Besides leptin, other JAK-STAT activating hormones have also been shown to be produced from adipocytes (refer to **Fig. 2**) including IL-6,[32,33] CT-1[34] and PRL.[35-38]

Adipose tissue is largely comprised of adipocytes, but like other tissues contains endothelial cells, connective tissue and other types of stromal cells. The presence of infiltrating immune cells, such as macrophages and T cells is well documented and studies in the last decade suggest that these cells are modulated in conditions of obesity and Type 2 diabetes. IFNγ is produced from both natural killer (NK) cells[39] and T cells[40-43] present in adipose tissue. IFNγ can inhibit the differentiation of preadipocytes,[44,45] induce insulin resistance in mature adipocytes[46,47] and decrease PPARγ expression in adipocytes.[48] It is highly likely that the production of IFNγ from infiltrated immune cells acts in a paracrine fashion on adjacent adipocytes to result in insulin resistance. As clearly indicated in **Figure 2**, the JAK-STAT signaling pathways play an important role in the majority of cell types that are found in adipose tissue. Although endothelial cells have endocrine functions, there is no evidence of JAK-STAT producing hormones from these cells. However, it is probable that the production of JAK-STAT ligands from adipocytes and infiltrating immune cells likely impacts the functions of endothelial cells that reside in adipose tissue.

STAT Target Genes in Mature Adipocytes

The tissue distribution of each STAT is unique, and it is widely accepted that STAT proteins have cell-specific functions. The modulation of tissue-specific genes has been shown to be a physiological role of STAT proteins in a variety of cell types, including adipocytes. Target genes for STATs 1 and 5 in adipocytes have been identified. These adipocyte STAT target genes code for proteins that regulate adipocyte development, insulin action and fat and carbohydrate metabolism. As summarized in this article, numerous investigations have revealed the importance of STAT5 proteins during adipogenesis in vitro and in vivo.[21,23] As shown in **Figure 1**, STAT 5 proteins are activated early during adipocyte differentiation.[21] Studies have also shown that STAT5 proteins are capable of directly binding the PPARγ3 promoter[49] and can transactivate the PPARγ2 and PPARγ3 promoters.[22,49] Although a number of transcription factors have profound effects on adipocyte development, PPARγ is a critical transcriptional regulator that is absolutely required for fat cell differentiation. PPARγ is a STAT5 target during adipocyte development and its modulation by STAT5 likely plays a role in the ability of STAT5 to promote adipocyte differentiation in vitro and in vivo. However, the majority of studies on STAT target genes have focused on fully differentiated adipocytes. The identification of STAT target genes in mature fat cells will be summarized below.

In adipocytes, studies have shown that PPARγ is also a STAT1 target gene. Initially, a probable STAT1 binding site was identified in the PPARγ2 promoter based on the consensus sequence of an interferon-γ-activated site (GAS) element that is known to mediate IFNγ-sensitive regulation in a STAT-dependent manner. In vitro studies revealed that STAT1 homodimers bind to an IFNγ responsive site within the PPARγ2 promoter in 3T3-L1 adipocytes.[50] These data suggest that IFNγ-induced repression of PPARγ2 was mediated by the direct action of STAT1 on the PPARγ2 promoter. Modulation of both PPARγ activation pathways and IFNγ signaling has been associated with the development of insulin resistance.[46,47,51] Accordingly, STAT1 likely mediates the ability of IFNγ to induce insulin resistance[46,47,52,53] and block adipogenesis[44,45] via transcriptional regulation of PPARγ levels. An IFNγ-sensitive binding site for STAT1 was also discovered in the murine lipoprotein lipase (LPL) promoter.[54] 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. In murine adipocytes, IFNγ-activated STAT1 binds to the LPL promoter in a manner that is consistent with IFNγ-induced repression of LPL expression and inhibition of LPL activity.[44,55] While STAT3 also exhibits tyrosine phosphorylation and nuclear translocation in response to IFNγ, STAT1 is a more robust mediator of IFNγ signaling in murine and human adipocytes.[46,56,57] In these studies, STAT3 was unable to bind to the identified STAT1 binding sites within the PPARγ promoter,[50] and LIF, a potent STAT3 activator, did not confer binding of STAT3 to the IFNγ sensitive region of the LPL promoter.[54] In summary, both PPARγ and LPL have been shown to be STAT1 target genes in murine fat cells.

STAT3 is abundantly expressed in adipocytes[7,8] and mediates the action of numerous cytokines in fat cells (**Table 1**). As reviewed in the previous section, STAT3 may play a role in adipogenesis. However, with the exception of C/EBPβ as a potential STAT3 gene target activated early in the adipogenic program,[12] to date no adipocyte-specific direct target genes have been identified for STAT3. Although STAT6 is equivalently expressed in

Table 1. STAT activators in adipocytes

STATs	Activator	Reference(s)
STAT1	Cardiotrophin-1	64
	Growth hormone	56 and 65
	Interferon γ	46, 56 and 57
	Interleukin-11	66
	Leukemia inhibitory factor	56, 57 and 67
	Oncostatin M	56 and 57
STAT3	Cardiotrophin-1	27 and 64
	Ciliary neurotrophic factor	27, 68 and 69
	Growth hormone	65
	Interferon γ	46, 56 and 57
	Interleukin-6	56, 70–72
	Interleukin-11	66
	Leukemia inhibitory factor	56, 57, 67 and 71
	Neuropoietin	73–75
	Oncostatin M	25, 56, 57 and 71
STAT5A and 5B	Growth hormone	22, 26, 56, 65, 76 and 77
	Prolactin	76
STAT6	Unknown	—

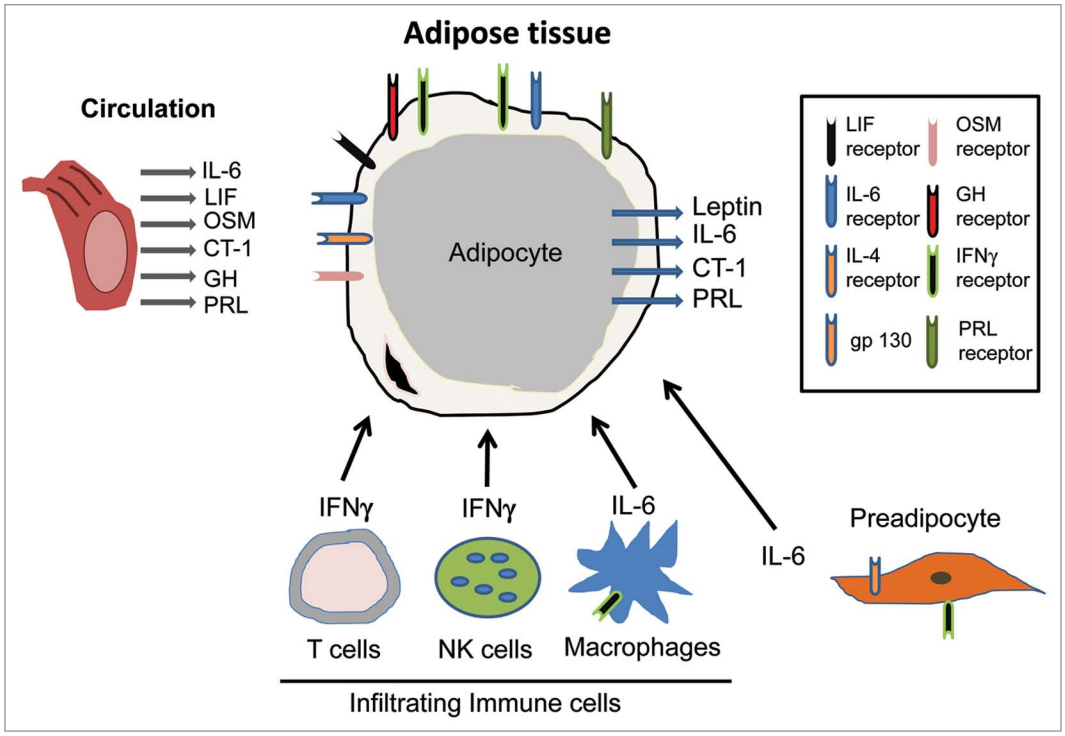

Figure 2. Adipocytes are central players in responding to and producing STAT activating hormones. Adipose tissue is largely comprised of adipocytes but also contains preadipocytes and infiltrating immune cells, including NK cells, T cells and macrophages. Adipocytes are highly responsive to many hormones and growth factors that utilize the JAK-STAT pathway. The receptors for these ligands are indicated in the diagram. Infiltrating immune cells also produce cytokines that act in a paracrine fashion to activated STAT signaling in adipocytes. Adipocytes also have important endocrine properties and four JAK-STAT activating hormones have been shown to be produced from adipocytes.

preadipocytes and throughout fat cell differentiation,[7] only IL-4 has been shown to activate this transcription factor in 3T3-L1 preadipocytes but not in adipocytes.[58] Thus, activators, functions and gene targets of STAT6 in both preadipocytes and adipocytes remain to be elucidated. Overall, there is almost nothing known about the identity of STAT3 and STAT6 target genes in adipocytes.

The majority of studies on STATs in adipocytes have focused on the identification of STAT5 target genes in mature fully differentiated adipocytes. Since STAT5 proteins are activated early during adipocyte differentiation and have been shown to play such a key role in adipocyte development, it is not surprising that most studies have focused on the functions of STAT5 proteins in mature adipocytes. The promoter for acyl CoA oxidase (AOX), the rate limiting enzyme in peroxisomal fatty acid β-oxidation, contains a STAT5 binding site that modulates its gene expression in fat cells.[59] Transfection studies have shown that the promoter activity of aP2, an abundantly expressed lipid binding protein in fat cells, can be activated by STAT5.[60] Conversely, STAT5 mediates the inhibition of aP2 expression in rat primary preadipocytes,[61] which was the first study to suggest that STAT5 proteins could act as transcriptional repressors. Since that time, our own research has revealed that STAT5A can act as a transcriptional repressor in adipocytes. A STAT5A binding site in the murine fatty acid synthase (FAS) promoter mediates the repression of FAS transcription that occurs with growth hormone (GH) or prolactin (PRL) treatment.[62] FAS catalyzes the production of long chain fatty acids and is a crucial enzyme involved in de novo lipogenesis. In addition to modulation of genes associated with lipid metabolism such as AOX and FAS, STAT5 can also increase the transcription of pyruvate dehydrogenase kinase (PDK)-4, a known regulator of glycolysis, that is highly induced in adipocytes by PRL or GH in a STAT5 dependent manner.[63] Under these conditions, insulin resistance accompanies the induction of PDK4. It is well known that PRL and GH are important modulators of lipid metabolism and are also potent inducers of STAT5 in adipocytes.[56,60] Hence, many of the metabolic actions of these anterior pituitary hormones could be mediated by STAT5's direct modulation of target genes. Although relatively few STAT5 target genes have been identified in adipocytes, we hypothesize that several other STAT5A target genes that play a role in lipid or glucose metabolism will be identified. **Figure 3** illustrates that STAT5 can modulate genes that are associated with all of the critical functions of adipocytes. Our unpublished data indicate that STAT5 proteins also substantially regulate the expression of adiponectin, an important adipocyte hormone that modulates insulin sensitivity. Another fat secreted hormone, lipocalin-2, appears to be regulated by STAT1. As indicated in **Table 2**, a collection of studies reveal that STATs 1 and 5 are important transcriptional regulators in adipocytes that contribute to hormone

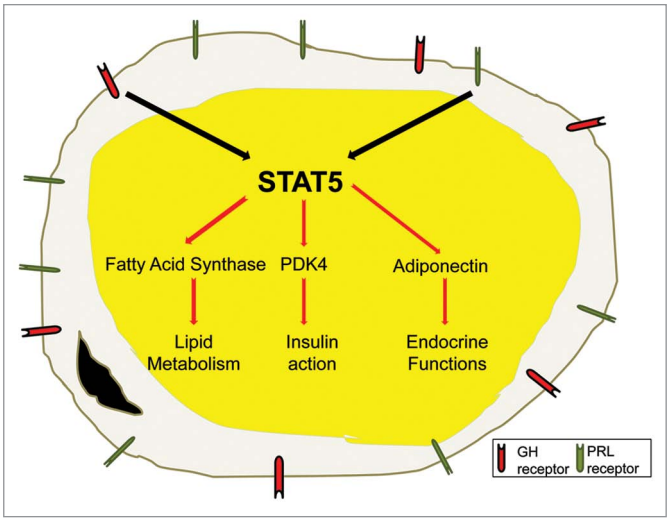

Figure 3. Growth hormone and prolactin induce STAT5 to modulate key genes associated with adipocyte function. To date, only growth hormone (GH) and prolactin (PRL) have been shown to be physiological activators of STATs 5A and B in adipocytes. Adipocytes have several key functions that include lipid accumulation, carbohydrate and lipid metabolism, insulin sensitivity and endocrine functions. Recent studies have shown that STAT5 proteins can directly modulate the transcription of genes that contribute to all of these critical fat cell functions.

induced modulation of genes that contribute to lipid and glucose metabolism, insulin sensitivity and the endocrine properties of adipocytes.

Summary and Future Outlook

Overall, relatively few STAT-regulated genes have been identified in adipocytes. Nonetheless, the STAT 1, 3 and 5 target genes identified thus far encode proteins that are important for fat cell development and for adipocyte-specific functions, such as insulin sensitivity and lipid and carbohydrate metabolism. Although STATs were originally identified as positive regulators of transcription, they act as both transcriptional activators[12,49,59,60,63,64] and repressors[50,54,61,62] in fat cells. Additional studies in both cultured adipocytes and in adipose tissue are needed to reveal the complete regulatory potential of the STAT family members in adipocytes. Future studies are also necessary to determine how tyrosine phosphorylation of STATs that is typically associated with STATs ability to modulate transcription is affected by other covalent modifications such as serine phosphorylation, acetylation, methylation and sumoylation. In addition, the non-canonical mechanisms and functions of STATs in adipocytes have not been investigated. Other studies that indicate that STATs can participate in chromatin organization and mitochondrial respiration in ways that are independent of transcriptional regulation[65] will likely be an intense area of investigation in adipocyte biology in the near future.

Table 2. STAT target genes in mature adipocytes

Cytokine or hormone	STAT transcription factor	Target gene
GH, PRL	STAT5	FAS
GH	STAT5A	aP2
GH	STAT5A	AOX
GH, PRL	STAT5	PDK4
GH	STAT5	Adiponectin
IFNγ	STAT1	LPL
IFNγ	STAT1	Lipocalin-2

Disclosure of Potential Conflict of Interest

No potential conflicts of interest were disclosed.

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