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Insulin signaling in fatty acid and fat synthesis: a transcriptional perspective

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Abstract

Transcription of enzymes involved in FA and TAG synthesis is coordinately induced in lipogenic tissues by feeding and insulin treatment. The three major transcription factors involved are USF, SREBP-1c, and LXR α . New insights into the insulin-signaling pathway(s) that control(s) lipogenic gene transcription via these factors have recently been revealed. Dephosphorylation/activation of DNA-PK by PP1 causes phosphorylation of USF that in turn recruits P/CAF to be acetylated for transcriptional activation. SREBP-1c can be induced by mTORC1, bifurcating lipogenesis from AKT-activated gluconeogenesis. LXR α may serve as a glucose sensor and, along with ChREBP, may activate lipogenic genes in the fed state. Dysregulation of FA and TAG metabolism often contributes to metabolic diseases such as obesity, diabetes, and cardiovascular diseases. Transcription factors and signaling molecules involved in transcriptional activation of FA and TAG synthesis represent attractive targets for the prevention and treatment of metabolic diseases.

Introduction

Triacylglycerol (TAG) is synthesized by esterification of glycerol-3-phosphate with fatty acids (FA) taken up from the diet as well as with FA synthesized *de novo* (*de novo* lipogenesis) from excess dietary carbohydrates (Figure 1). The two major tissues that synthesize FA and TAG at a high level in adults are the so-called lipogenic tissues, liver and adipose tissue. TAG synthesized in the liver is used for VLDL assembly to be secreted to the circulation so that various tissues take up FA from VLDL-TAG upon hydrolysis. TAG synthesized in adipose tissue, on the other hand, is stored as the main energy storage form in mammals, and is hydrolyzed in adipose tissue to release FA into the circulation to be used by other tissues during periods of energy demand.

Dysregulation of FA and TAG metabolism often contributes to metabolic diseases. Excess synthesis and storage of TAG in adipose tissue due to caloric intake above the expenditure, that is, obesity, is a global health epidemic in modern times and is strongly associated with insulin resistance, liver steatosis, dyslipidemia, and cardiovascular diseases [1,2]. Paradoxically, the metabolic abnormalities usually found in obesity are also associated with lipodystrophy which is characterized by selective loss of adipose tissue mass from particular regions of the body. Although the underlying molecular mechanisms are not clear, in lipodystrophic patients, metabolic complications may result from ectopic storage of TAG in tissues such as liver and muscle. Furthermore, in cancer cells, aerobic glycolysis, instead of oxidative phosphorylation, provides energy (so-called Warburg effect) [3]. Increased glycolysis facilitates an increase in *de novo* lipogenesis, providing FA for membrane

phospholipid biosynthesis in cancer cells. Thus, lipogenic enzymes not only are used as markers for certain types of human cancers, but also are being exploited as potential anti-cancer targets [4]. In light of the implications of this wide range of health problems, it is critical to understand the regulation of fatty acid and TAG synthesis. While this review provides a brief review of the transcriptional regulation of lipogenic genes during fasting/feeding, it focuses mainly on the recent development of the role of USF, SREBP-1c, and LXR α on transcriptional activation of lipogenic genes by insulin.

Regulation of fatty acid and triacylglycerol synthesis

FA and TAG synthesis in lipogenic tissues is under nutritional and hormonal control. Many of the enzymes involved in FA and TAG synthesis are tightly and coordinately regulated during fasting/feeding. The coordinately regulated enzymes include: enzymes in the FA synthetic pathway, such as ATP-citrate lyase (ACL), acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS); enzymes involved in the production of NADPH required for FAS activity, such as malic enzyme and enzymes in hexose monophosphate shunt such as glucose-6-phosphate dehydrogenase; and enzymes for TAG esterification, such as mitochondrial glycerol-3-phosphate acyltransferase (mGPAT) and diacylglycerol acyltransferase (DGAT) (Figure 2). Some glycolytic enzymes such as liver pyruvate kinase (L-PK) and glucokinase (GK) are also regulated in a similar fashion to provide the carbon source for FA and TAG synthesis.

Activities of various enzymes mentioned above are very low in the fasted condition, with the increase in circulating glucagon that raises intracellular cAMP levels. Conversely, in the fed condition, especially after a high carbohydrate meal, activities of these enzymes drastically increase with the rise in blood glucose and insulin levels. Some of these enzymes are under allosteric control by metabolites and/or are regulated by phosphorylation/dephosphorylation. For example, ACC, which catalyzes the key regulatory step in FA biosynthesis, is phosphorylated and inactivated by AMP-activated kinase, which senses the low energy state of cells. Malonyl-CoA produced in this way not only is a substrate for FAS, but inhibits CPT-1 activity preventing FA transport into mitochondria, and therefore coordinates synthesis and oxidation of FA. Furthermore, although the mechanism is not well understood, malonyl-CoA can affect transcription of neuropeptide genes in the hypothalamus to control food intake [5]. Nevertheless, the principal mode of long-term coordinate regulation of lipogenic enzymes in liver and adipose tissue is at the transcriptional level; fasting or insulin deficiency suppresses transcription, whereas a high carbohydrate meal or insulin administration activates these lipogenic genes. Studies on transcriptional activation of lipogenic enzymes during fasting/feeding not only provide fundamental information about lipogenic gene regulation, but also provide an excellent model system to study the cellular and metabolic response to insulin.

USF

In the earliest studies of insulin regulation of the FAS promoter, our laboratory showed that binding of the bHLH-LZ transcription factors, upstream-stimulatory factor-1 and upstream-stimulatory factor-2 (USF-1/USF-2) heterodimer, to the -65 E-box is required for transcriptional activation by insulin in 3T3-L1 adipocytes [6–8] (Figure 3a). Overexpression of dominant negative USF impaired FAS promoter activation. Furthermore, functional analysis and chromatin immunoprecipitation (ChIP) in mice transgenic for various 5'-deletions and mutations of the FAS promoter-CAT reporter genes showed that USF binding to the -65 E-box is required for feeding/insulin-mediated FAS promoter activation *in vivo* [9]. The critical role of USF in lipogenic transcription was clearly demonstrated *in vivo* in USF knockout mice that had significantly impaired lipogenic gene induction [10]. In this

regard, quantitative trait mapping studies have identified USF-1 as a candidate gene for familial combined hyperlipidemia [11].

Although USF plays a critical role in lipogenic induction by insulin, USF is bound to the E-box in both fasted and fed states [9]. This observation suggested that USF might recruit coactivators/corepressors in a fasting/feeding-dependent manner. By tandem affinity purification coupled with mass spectrometry, USF interacting proteins have been identified [12^{**}]. In the fasted state, USF recruits HDAC9, which functions as a corepressor in lipogenic gene transcription by deacetylation of USF, as described below. In this regard, USF is the first non-histone substrate for HDAC9 to be identified. Although total HDAC9 levels do not change during fasting/feeding, nuclear abundance of HDAC9 increases upon fasting, suggesting the regulation of HDAC9 by nuclear translocation. In the fed state, USF recruits distinct families of proteins to the lipogenic promoters including coactivator, P/CAF, which functions as a coactivator by acetylation of USF as described below in more detail. In addition, USF recruits DNA break/repair machinery including Ku70, Ku80, PARP-1, TopoII β and DNA-PK, which causes a transient DNA break in the lipogenic gene promoter before the transcriptional initiation, probably for local changes in chromosome architecture [13].

Signaling molecules, including PP1 and DNA-PK, have also been identified as USF interacting proteins and this helped to identify a novel insulin-signaling pathway for lipogenic induction. While many metabolic effects of insulin are mediated through protein phosphorylation via the well-characterized PI3K cascade that activates downstream PKB/AKT, insulin can also exert metabolic effects through dephosphorylation catalyzed mainly by PP1 [14]. Although the underlying molecular mechanism is not well understood, PP1 is known to be compartmentalized in cells by discrete targeting subunits [15]. During fasting and feeding, total DNA-PK levels remain the same. However, upon feeding, DNA-PK is dephosphorylated and activated, increasing its kinase activity by 6-fold. Thus, in the fed state, activated DNA-PK phosphorylates USF-1 at S262, allowing recruitment of and acetylation by P/CAF at K237, leading to promoter activation [12^{**}, 16]. P/CAF-mediated acetylation of USF is reversed by HDAC9 in the fasted state. DNA-PK deficient SCID mice were used to demonstrate its requisite role of DNA-PK in the transcriptional activation of lipogenic genes during feeding/insulin treatment. In contrast, in the fasted state, USF-1 phosphorylation as well as acetylation is attenuated, blunting transcriptional activation of FAS and de novo lipogenesis. Identification of DNA-PK as a signaling molecule in the activation of lipogenic genes by insulin has brought us a step closer to understanding how cells regulate metabolic processes in response to insulin.

Besides lipogenesis, it is interesting to note that USF has been shown to activate the transcription of an inhibitor, small heterodimer partner (SHP), to repress PEPCK and glucose-6-phosphatase transcription through the DNA-PK signaling pathway [17]. Last but not least, with DNA-PK's role as an insulin-signaling molecule to activate lipogenesis, DNA-PK could possibly serve as a pharmacological target for obesity and diabetes treatment.

SREBP-1c

Sterol-regulatory element binding protein (SREBP), another bHLH-LZ transcription factor, was originally identified as a transcription factor that binds to SRE for cholesterol regulation [18]. SREBP is present in the endoplasmic reticulum membrane as a transmembrane protein precursor. Nuclear entry of SREBP requires proteolytic cleavage of the cytoplasmic N-terminal domain. Of the three members of the SREBP family, SREBP-1a, SREBP-1c and SREBP-2, SREBP-1c is highly expressed in lipogenic tissue, and is itself induced by

feeding/insulin. A critical role of SREBP-1 in the transcriptional activation of lipogenic genes has been shown by hepatic overexpression of SREBP-1a in transgenic mice as well as in SREBP-1c knockout mice [19]. Interestingly, many of the lipogenic gene promoters have both the E-box and the SRE in proximity (Figure 3b) [20^{**}]. Others reported that SREBP-1c binds to the -65 E-box upon feeding/insulin treatment in activating FAS transcription. Because of an atypical tyrosine residue in place of arginine at its DNA-binding domain [21,22], SREBP-1 can bind E-box *in vitro* and there has been a debate on the 'true' binding site of SREBP-1c. We performed reporter activity and ChIP assays in transgenic mice harboring different deletions and mutations of the FAS promoter as well as double transgenic mice for various FAS promoter-reporters and for hepatic SREBP-1 overexpression. In these experiments, SREBP-1c failed to occupy the transgenic FAS promoter when the SRE was mutated *in vivo* even under high carbohydrate feeding, and the reporter activity was also blunted in these mice [9,22], clearly showing that the SRE (Figure 3a), not the E-box, is the binding site for SREBP-1c on the FAS promoter *in vivo*. The closely spaced arrangement of the E-box and SRE in many lipogenic promoters may allow USF and SREBP-1c to cooperatively activate lipogenic gene transcription [20^{**}]. In this regard, SREBP-1c binding to the SRE is USF dependent, as SREBP-1c could not bind the SRE in the FAS promoter when the nearby E-box was mutated [9]. The bHLH domain of USF directly interacts with the bHLH and an N-terminal region of SREBP-1c for their synergistic activation of the promoter [20^{**}]. Thus, USF bound to the -65 E-box recruits SREBP-1c to bind the nearby SRE during feeding/insulin [12^{**}]. This interaction might also explain how excess SREBP-1 was reported to bind to the E-box. SREBP-1 might associate with the E-box indirectly through its interaction with USF. The p53 promoter contains an E-box but does not normally respond to insulin. However, upon insertion of an SRE nearby, USF could recruit SREBP-1 to the SRE and this artificial p53 promoter responded to insulin [12^{**},16], demonstrating the cooperative action of USF and SREBP-1.

As mentioned above, unlike USF whose levels remain constant, SREBP-1c itself is induced upon feeding or insulin treatment. The exact molecular details linking insulin and SREBP-1c transcription are still missing. The SREBP-1c promoter is regulated by SREBP-1c itself, potentially functioning together with USF, and by LXR α [12^{**}, 23]. However, what coactivators are recruited by SREBP-1c is not clear. Although SREBP-1a and SREBP-2 have been shown to interact with various transcriptional coregulators, such as CBP/p300, PGC1 β , ARC105 mediator, SIRT1, and SRC1, SREBP-1c interacts with these factors weakly, due to a missing activation domain. Therefore, identification of a 'true' coactivator for SREBP-1c may help in understanding the mode of function for SREBP-1c in lipogenesis.

Since SREBP-1c auto-regulates itself by binding to the SRE of its own promoter, USF binding to the E-box in the promoter may also be required to recruit SREBP-1c. In that case, SREBP-1c transcription might be via USF action and would be regulated through the DNA-PK signaling pathway in response to feeding/insulin [12^{**}]. So far, multiple insulin-signaling pathways that can induce SREBP-1c expression have been reported. For example, insulin-mediated activation of atypical PKC λ , PKC ζ and AKT via the PI3K pathway induces SREBP-1c expression and lipogenesis [24–27]. Recently, the Brown and Goldstein laboratory reported that the mammalian target of rapamycin complex 1 (mTORC1) mediates insulin-stimulated induction of SREBP-1c and that the induction was S6K-independent [28^{**}]. In this regard, due to inactive AKT, insulin suppression of glucose production is impaired in the insulin resistant state, but lipogenesis and TAG synthesis are still active for VLDL production, causing hyperlipidemia. It has been proposed that, independent of AKT, mTORC1 is activated due to high circulating amino acid levels in insulin resistance, and SREBP-1c induction through mTORC1 may be responsible for differing effects of impaired suppression of gluconeogenesis yet robust lipogenesis in insulin resistance [29]. Besides

transcriptional regulation, insulin was reported to stimulate processing and nuclear translocation of SREBP-1c, which then initiates a feed-forward auto-regulatory loop [30]. In addition, MAPK was shown to phosphorylate SREBP-1a and 1c, and mutation of these sites abolished the transcriptional activation by SREBP [31]. In addition, GSK-3, which is inhibited by AKT phosphorylation, was reported to phosphorylate SREBP-1a at a site conserved in SREBP-1c, enhancing degradation [32]. Interestingly, a recent report suggests that SREBP-1 is acetylated by SIRT1 orthologs in the fasted state to downregulate SREBP by ubiquitination and degradation, thus affecting lipid homeostasis in response to fasting cues [33**].

LXR

Liver X receptor (LXR) is a ligand-activated transcription factor that belongs to nuclear receptor superfamily. Of the two LXR isoforms, LXR α is abundantly expressed in lipogenic tissues and, by activating the SREBP-1c promoter, it plays an important role in the transcriptional activation of lipogenic genes. Thus, in LXR α knockout as well as LXR α / β double knockout mice, SREBP-1c and FAS levels were lower resulting in a decrease in hepatic and plasma TAG levels. Furthermore, LXR agonists such as T0901317 activated SREBP-1c and FAS transcription but had no effect in the LXR α deficient animals [34]. In contrast, LXR α transgenic mice showed higher expression of these genes [35]. LXR α , but not LXR β , binds to LXRE of the SREBP-1c promoter. LXRE is also found in other lipogenic genes, such as FAS and ACC. Although the canonical LXRE consists of two AGGTCA hexameric half sites, LXREs on LXR target genes vary considerably and LXR α and LXR β may have different affinities for various LXREs [36*]. LXR may increase lipogenesis by activating SREBP-1c transcription, as well as by directly activating lipogenic genes by binding to their LXREs. Interestingly, recent studies showed that LXR α interacts with RIP140 to upregulate SREBP-1c, but the same interaction negatively affected gluconeogenic gene transcription [37].

Furthermore, LXR α itself is regulated by high carbohydrates/insulin at the transcriptional and post-translational levels. Insulin induces LXR α expression in the liver *in vivo* [38], and the LXR α promoter is regulated by an auto-regulatory mechanism since there are three LXREs in its promoter. In addition, as may be the case during fasting, PKA phosphorylates LXR α to inhibit binding to LXRE by impairing dimerization of LXR α with RXR, DNA binding and transactivation [39]. LXR α has also been shown to be phosphorylated by MAPK, and this phosphorylation may have functional implications in insulin regulation of LXR α [40]. It has been reported that LXR α can activate the transcription of ChREBP, an E-box binding bHLH/LZ transcription factor that hetero-dimerizes with Mlx to bind carbohydrate-response element (ChoRE) present in lipogenic genes to confer glucose-mediated activation in liver [41].

Although oxysterols are known to be ligands for LXR, a report suggests a role for LXR α as a glucose sensor since glucose or glucose-6-phosphate directly binds and activates LXR α [42**,43]. A recent study showed that SREBP-1c induction upon high carbohydrate feeding in the liver was completely blunted in LXR α / β double knockout mice. However, FAS induction was still present although blunted in some degree, whereas expression of ChREBP, L-PK, GK, or ACC was not affected in these mice [44]. This indicates complex and potentially varying mechanisms as well as synergistic action of multiple transcription factors for transcriptional activation of lipogenic genes by feeding/insulin.

Conclusion

FA and TAG synthesis is a highly regulated cellular process crucial to the metabolic homeostasis of organisms. Dysregulation of lipid metabolism can often lead to adverse consequences such as obesity, hepatic steatosis, diabetes and cardiovascular diseases. Therefore, it is crucial to dissect the process of FA and TAG synthesis. Transcription of lipogenic enzymes is highly regulated by insulin and glucose. For insulin-mediated regulation, the major transcription factors involved are USF, SREBP-1c, and LXR α (Figure 4). The inter-relationship among these transcriptional factors is complex as they regulate each other in a distinct manner. For example, SREBP-1c is crucial to lipogenic gene transcription, but its binding to SRE is USF dependent. LXR α regulates the expression of SREBP-1c, FAS and, although still in debatable, ChREBP. FAS induction is still detected in LXR-deficient mice that have impaired SREBP-1c induction showing the involvement of other transcription factors such as USF. Furthermore, FAS promoter-reporter transgenic mice studies showed that the FAS promoter that contains both an E-box and SRE, but lacks a LXRE, is sufficient for high level activation of the FAS promoter during fasting/feeding, suggesting that binding of USF and SREBP-1c is sufficient for the insulin response of FAS *in vivo* [9]. Furthermore, ChREBP, together with LXR α that may function as a glucose sensor, may mediate glucose responsiveness to lipogenic induction upon feeding, in parallel with USF and SREBP-1c that mediate insulin signaling.

Many questions remain in our understanding of lipogenic promoter activation by these transcription factors. How are these transcription factors activated in response to glucose/insulin? Apart from HAT/HDAC, what other coactivators/corepressors, chromatin remodeling machinery, and mediators are required for lipogenic gene activation? Are there common mechanisms to explain the transcriptional regulation of coordinately regulated lipogenic genes? Is chromatin folding involved in sharing transcription machineries among lipogenic gene promoters? Further studies are necessary to understand the details of the transcriptional activation of lipogenic genes and will be critical for developing new drug targets for the prevention and treatment of obesity, diabetes, and other associated diseases.

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Figure 1.

Upon eating a high carbohydrate diet, de novo lipogenesis takes place in lipogenic tissues, liver and adipose tissue. In liver, de novo synthesized FA are incorporated into TAG to be packaged into VLDL and secreted into the circulation. Peripheral tissues take up FA from VLDL-TAG to use for oxidation. In adipose tissue, de novo synthesized FA, along with FA taken up from circulation, are esterified into TAG for storage. FA, fatty acids; TAG, triacylglycerol; VLDL, very low-density lipoprotein.

Figure 2. Pathway of de novo lipogenesis and TAG synthesis. ACL, ATP-citrate lyase; ME, malic enzyme; ACC, acetyl-CoA carboxylase; FAS, fatty acid synthase; mGPAT, mitochondrial glycerol-3-phosphate acyltransferase; DGAT, diacylglycerol acyltransferase; GPAT, glycerol-3-phosphate acyltransferase; AGPAT, 1-acylglycerol-3-phosphate acyltransferase; PAP, phosphatidate phosphatase.

Figure 3.

(a) The *cis*-acting elements and *trans*-acting factors involved in the regulation of transcription of the FAS gene by insulin. Numbers indicate the positions of each element relative to the transcription start site. SRE, sterol-regulatory element; SREBP, SRE-binding protein; TATA, TATA-box; USF, upstream-stimulatory factor. LXR, liver X receptor; ChoRE, carbohydrate-response element; ChREBP, ChoRE-binding protein. Upon feeding, DNA-PK, which is dephosphorylated/activated by PP1, phosphorylates USF-1, which then recruits SREBP-1 and other USF-1-interacting proteins. Thus, DNA-PK-catalyzed phosphorylation of USF-1 allows P/CAF recruitment and subsequent acetylation of USF-1.

(b) Schematic of E-box and SRE present in the proximal promoter regions of various genes encoding enzymes in FA and TAG synthesis.

Figure 4. Activation of the lipogenic transcription factors, SREBP-1c, USF and LXR α , as well as ChREBP during feeding.