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► **To cite this version:**

Anke Sommerfeld, Anja Krones-Herzig, Stephan Herzig. Transcriptional co-factors and hepatic energy metabolism. *Molecular and Cellular Endocrinology*, 2010, 332 (1-2), pp.21. 10.1016/j.mce.2010.11.020 . hal-00654957

HAL Id: hal-00654957

<https://hal.science/hal-00654957>

Submitted on 24 Dec 2011

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Accepted Manuscript

Title: Transcriptional co-factors and hepatic energy metabolism

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PII: S0303-7207(10)00548-4
DOI: doi:10.1016/j.mce.2010.11.020
Reference: MCE 7690

To appear in: *Molecular and Cellular Endocrinology*

Received date: 3-8-2010
Revised date: 17-11-2010
Accepted date: 18-11-2010

Please cite this article as: Sommerfeld, A., Krones-Herzig, A., Herzig, S., Transcriptional co-factors and hepatic energy metabolism, *Molecular and Cellular Endocrinology* (2010), doi:10.1016/j.mce.2010.11.020

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Transcriptional co-factors and hepatic energy metabolism

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Abstract

After binding to their cognate DNA-binding partner, transcriptional co-factors exert their function through the recruitment of enzymatic, chromatin-modifying activities. In turn, the assembly of co-factor-associated multi-protein complexes efficiently impacts target gene expression. Recent advances have established transcriptional co-factor complexes as a critical regulatory level in energy homeostasis and aberrant co-factor activity has been linked to the pathogenesis of severe metabolic disorders including obesity, type 2 diabetes and other components of the Metabolic Syndrome. The liver represents the key peripheral organ for the maintenance of systemic energy homeostasis, and aberrations in hepatic glucose and lipid metabolism have been causally linked to the manifestation of disorders associated with the Metabolic Syndrome. Therefore, this review focuses on the role of distinct classes of transcriptional co-factors in hepatic glucose and lipid homeostasis, emphasizing pathway-specific functions of these co-factors under physiological and pathophysiological conditions.

Introduction

Given its central location within the systemic circulation, the liver serves as one of the body's critical organ for maintenance of systemic energy homeostasis [1-3]. Indeed, the liver represents the critical control relay in the reception of small molecules arising from food digestion or degradation of endogenous sources, their metabolic conversion or storage, and the final (re-)distribution to the periphery. In this regard, the liver uses carbohydrates, free fatty acids (FFA), and amino acids as energy-yielding substrates, and, in turn, exports two principal energy equivalents, glucose and ketone bodies, that can be used for oxidation and energy generation by other tissues, such as adipose, muscle, or brain. Consequently, as the predominant inter-conversion point for energy substrates in mammals the liver plays an essential role in the adaptive metabolic response during daily/periodic fasting-feeding cycles [1-3].

In the fed state, e.g. after a carbohydrate-rich meal, the peptide hormone insulin is released from β -cells within the pancreatic islets. Activation of the insulin receptor (IR) by its ligand leads to its autophosphorylation and via PI3-kinase to the activation of Akt/PKB, which then activates the recruiting of the tissue-specific glucose transporter GLUT4 to the plasma membrane [4,5]. Thereby insulin potently stimulates glucose uptake in muscle and adipose tissue, and promotes glycogen formation and lipogenesis, respectively [6-8]. As in muscle, high circulating insulin levels favor the synthesis of glycogen in liver. In addition, stimulation of hepatic lipase by insulin facilitates the uptake of FFA derived from chylomicron remnants, their subsequent esterification to triglycerides and packaging into very low density lipoprotein (VLDL) particles that are exported to other tissues. [9-11] [12]. Importantly, apart from its stimulatory effect on glycogen formation and lipogenesis, insulin effectively blocks hepatic glycogenolysis and gluconeogenesis in the fed state [13,14].

On the other hand, fasting and exercise trigger a series of hormonal cues that promote a switch in whole body energy usage. Along with a drop in insulin levels, counter-regulatory hormones gain metabolic control. In particular, the peptide hormone glucagon from the pancreatic islet α -cell and adrenal glucocorticoids are released into the circulation [15-17]. These hormones activate lipolysis via the induction of hormone-sensitive lipase in white adipose tissue and contribute to glycogen degradation in both muscle and liver, thereby leading to the release of previously stored glucose depots [18]. The high availability of circulating, adipose tissue-derived lipids determines the enhanced mitochondrial oxidation of FFA in the liver. The energy released in the process of β -oxidation is—at least in part- used by the liver to carry out *de novo* glucose production, i.e. gluconeogenesis, from substrates such as glycerol, lactate, and amino acids [19]. In addition, acetyl-CoA derived from FFA β -oxidation serves as substrate for the synthesis of ketone bodies that are exported from the liver and used as primary energy source by skeletal muscle or brain after long time starvation [20-23]. Thus, the partitioning of FFA towards oxidative pathways in the liver represents a master switch for the transition from the fed to the fasted state and the provision of energy supply through gluconeogenesis and ketogenesis during fasting [2,3,24,25].

The so-called Metabolic Syndrome is a clustering of metabolic disorders, including insulin resistance, obesity, hyperglycemia, dyslipidemia, and hypertension, mainly caused by over-nutrition and sedentary lifestyles particularly in developed countries as well as genetic predisposition. Progression of the aforementioned disorders can eventually precipitate into end-stage diseases such as type 2 diabetes and cardio-vascular complications associated with the increased mortality observed in these patients [26].

In this regard, defects in hepatic insulin signaling have been demonstrated to importantly contribute to the development of systemic peripheral insulin resistance [27]. Mice bearing a

targeted disruption of the insulin receptor gene in liver display hyperglycemia, hyperinsulinemia, and impaired glucose tolerance [28]. Also, inhibition of the PI3K/Akt-dependent insulin signaling pathway in liver by the Akt-inhibitor tribbles homolog 3 (TRB3) leads to hyperglycemia and glucose intolerance [29]. As mentioned above, Akt is one of the major enzymes in the insulin signalling cascade and it has been shown in Akt2 knockout mice that Akt 2 was required for hepatic lipid accumulation in obese, insulin resistant states besides its function in glucose metabolism [30,31].

Under conditions of the Metabolic Syndrome, liver metabolism is characterized by an excessive glucose output due to the disturbed control of gluconeogenesis as well as an excessive ketone body production. Both of these pathways are stimulated by high FFA availability which attenuates the ability of insulin to suppress glucose production and provide acetyl-CoA as a critical regulator for gluconeogenic (i.e. pyruvate carboxylase) and ketogenic key enzymes via enhanced FFA oxidation. At the same time, by interfering with pyruvate dehydrogenase activity, acetyl-CoA inhibits glucose utilization, further promoting hepatic insulin resistance [32]. Gluconeogenesis is further stimulated by increased levels of amino acids, thereby exacerbating diabetic hyperglycemia [33-36]. In response to insulin, diacylglycerol (DAG) levels in the cell rise, leading to the activation of protein kinase C (PKC) which phosphorylates glycogen synthase resulting in its inactivity [37]. Different PKC isoforms also inactivate the insulin receptor (IR) by phosphorylation of specific serine residues or by interfering with the tyrosin autophosphorylation of the IR. Persistent high insulin levels and a subsequent high DAG level can finally add to the onset of insulin resistance [38].

In addition to dysfunctional glucose metabolism, aberrant accumulation of lipids in the liver (“fatty liver”, hepatic steatosis) also represents a hallmark of the Metabolic Syndrome and is tightly associated with insulin resistance, obesity and type 2 diabetes as well as long-term

starvation, glucocorticoid therapy or the development of hepatocellular carcinoma [39-41]. Indeed, ectopic accumulation of triglycerides in the liver is an early pathogenic event in the development of nonalcoholic steatohepatitis (NASH), which is characterized by chronic inflammation and liver damage [18] and can further progress into liver cirrhosis and eventually liver cancer [41].

Importantly, the perturbations of liver lipid and glucose metabolism as seen for example in type 2 diabetes and the Metabolic Syndrome can be ascribed not only to changes in enzyme activities based on covalent protein modifications but largely depend on the aberrant transcriptional activity of genes encoding metabolic key enzymes [18,21,42,43].

For example, elevated expression of phosphoenolpyruvate carboxykinase (PEPCK) has been demonstrated in diabetic patients, and overexpression of the PEPCK gene in mice is sufficient to induce hyperglycemia [44-46]. Also, rats in which diabetes has been induced by streptozotocin show increased mitochondrial 3-hydroxy-3-methylglutaryl-coenzym-A (HMG-CoA) synthase mRNA and protein levels compared with the basal values found in normal rats. Insulin reduced the expression of the mitochondrial HMG-CoA synthase gene when injected into diabetic rats [47,48].

Thus, transcriptional regulators of metabolic pathways represent key molecular checkpoints in hepatic and systemic energy homeostasis, concomitantly serving as attractive candidates for novel strategies in the therapy of the Metabolic Syndrome [49].

DNA-binding transcription factors directly regulate gene expression by binding to DNA response elements in promoter or enhancer regions of metabolic genes. One important group of transcription factors regulating metabolic pathways are the nuclear receptors. These receptors comprise classical hormone-regulated as well as orphan and so-called adopted orphan receptors, the latter of which are activated by endogenous ligands such as lipid-

derivatives. Nuclear receptors directly activate or repress target genes by binding as homo- or heterodimers to hormone- or nutrient response elements in promoter or enhancer regions and by binding to other DNA-sequence specific activators. They also can inhibit the transcriptional activities of other classes of transcription factors by trans-repression.

Overall, efficient, signal-dependent and specific transcriptional regulation of nuclear receptors as well as distinct classes of DNA-binding transcription factors requires the recruitment and activity of transcriptional co-regulators [50,51].

Indeed, by wiring distinct DNA-bound transcription units and controlling the assembly and/or activity of the general transcription machinery, transcriptional co-factor complexes have been identified as critical checkpoints in the coordination of metabolic programs and energy homeostasis [52]. Prototypes for these mechanisms are the nuclear receptor co-factors peroxisome proliferator-activated receptor co-activator (PGC) 1, the receptor interacting protein (RIP) 140, or the steroid hormone receptor co-activators (SRC) and their roles in the development of hyperglycemia, hepatic steatosis, and hypertriglyceridemia. Particularly the differential gene expression of these specific transcriptional regulators between healthy and metabolic disease conditions has been found to often reflect a causal, functional role of these factors in the pathogenesis of type 2 diabetes, cancer cachexia, and obesity, respectively [53-56].

After binding to their cognate DNA-binding partner, transcriptional co-factors exert their function through the recruitment of enzymatic, chromatin-modifying activities, including histone acetylation and de-acetylation as well as methylation. Indeed, increased acetylation of histone tails has been correlated with transcriptional activity, whereas hypoacetylation has been associated with repression [57]. Thus, the assembly of co-factor-associated multi-protein complexes efficiently impacts target gene expression and the physiological consequences thereof [51].

In the following sections, the distinct roles of transcriptional co-factors in liver lipid and glucose metabolism are summarized. As most relevant factors have been described to predominantly act as either co-regulators with enzymatic activity, co-activators or co-repressors in hepatic metabolism, we will discuss their roles according to this classification albeit arbitrary (Figure 1, Table 1).

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Co-regulators with enzymatic activity

Methyltransferases

Arginine methylation is a prevalent post-translational modification found on both nuclear and cytoplasmic proteins and plays besides acetylation of histones and phosphorylation of regulatory proteins an important role in transcriptional regulation [58].

CARM1

The co-activator-associated arginine methyltransferase (CARM1) has originally been identified as a binding partner for p160 nuclear receptor co-factor family members [59]. CARM1 was considered to be a transcriptional activator as associated with specific methylation of histon H3 [60]. In hepatocytes, CARM1 was required for cAMP-mediated activation of rate-limiting gluconeogenic genes such as PEPCK and glucose-6-phosphatase via interacting with cAMP-responsive element binding factor CREB [61].

PRMT1

The protein arginine methyltransferase 1 (PRMT1) is a member of the PRMT family of arginine methyltransferases and was identified as a binding partner for mitogen immediate-early response protein TIS21 (BTG2) and for leukemia-associated protein B-cell translocation gene 1 (BTG1) in a yeast two-hybrid screen [62]. PRMT1 specifically methylates arginine 3 (Arg 3) of H4 *in vitro* and *in vivo* [63] and is also able to methylate diverse non-histone protein substrates such as transcription factors and transcriptional co-regulators [64].

In non-obese, diabetic Goto-Kakizaki (GK) rats it was found that hepatic and pancreatic PRMT1 activity was decreased, which was associated with an impaired arginine methylation of several proteins in the tissues. This impaired PRMT1 activity may be implicated in glucose

intolerance through disturbed hepatic glucose metabolism by suppression of gluconeogenic genes expression in hepatocytes and aberrant pancreatic insulin secretion [65].

Acetyltransferases

The process of acetylation to overcome repressive effects of chromatin structure on transcription is mediated by histone acetyltransferases first identified by Brownell (1996) [66]. Furthermore, they are also known to participate in transcriptional regulation by acetylating proteins other than histones [67].

CBP/p300

The histone acetyltransferase activity of CREB-binding protein (CBP) and adenovirus E1A-binding protein (p300) was discovered in 1996 [68,69]. p300 catalyzed the acetylation of lysine residues not only in nucleosomal histones, but also in non-histone proteins, such as nuclear receptors, co-factors, and basal transcription factors, resulting in enhanced gene transcription [70,71]. It was shown that inhibition of hepatic p300 activity may be beneficial for treating fatty liver disease and related metabolic disorders [72]. In mouse liver and HepG2 cells, p300 acted as a critical co-activator for the farnesoid X receptor (FXR)-mediated induction of the small heterodimer partner (SHP) by acetylating histones at the SHP promoter and FXR itself. Down-regulation of p300 substantially reduced SHP expression and further, altered expression of other hepatic FXR target genes involved in lipoprotein and glucose metabolism. Similar results were observed with the related acetyltransferase, CBP [72]. The activation of the cAMP signaling pathway leads to the stimulation of gluconeogenesis by phosphorylation of CREB and the recruitment of CBP/p300 [53,73-75]. Phosphorylation of CBP at Ser436 by insulin signaling has been proposed by Zhou et al. (2004) as a potential mechanism regulating gluconeogenesis during feeding. They observed hyperglycemia in

knock in animals carrying a mutant form of CBP (S436A), which could bind to CREB and activate gluconeogenesis even in the fed state [76].

Another study showed that in HepG2 cells the recruitment of the CBP co-activator protein which is important for the expression of FoxA2, a transcription factor critical for regulating expression of hepatic gluconeogenic genes during fasting [77], was stimulated by the formation of a C/EBP-alpha (CCAAT enhancer binding protein) and HNF6 complex [78]. It has also been shown by Kohler et al. (2009) that the acetylation of FoxA transcription factors, especially FoxA1, by p300 attenuated the FoxA binding to DNA and that this reduced its ability for chromatin remodelling [79]

TRRAP

Together with the general control non-repressed protein 5 (GCN5), the histone acetyltransferase transformation/transcription domain-associated protein (TRRAP, (PCAF-associated factor 350/400 (PAF400)) belongs to one of the three classes of co-activator complexes for nuclear receptors, two of which contain histone acetyltransferase activity [80]. In HepG2 cells transfected with antisense TRRAP RNA, a significant reduction in the ligand-dependent transactivation function of LXR-alpha and FXR, but not PPAR-gamma, was observed. Furthermore, antisense TRRAP RNA expression abolished the ligand-induced expression of LXR target genes such as ATP-binding cassette transporter A1 and G1 (ABCA1 and ABCG1), stearoyl-CoA desaturase (SCD), and high density lipoprotein binding protein (HBP), showing that TRRAP regulates cholesterol metabolism and/or efflux and bile acid metabolism in hepatic cells through LXR-alpha/FXR function [81].

GCN5 and PCAF

In mice and humans, the GCN5 subclass of acetyltransferases is represented by two closely related proteins, GCN5 and p300/CREB-binding protein-associated factor (PCAF). In mouse liver and cultured hepatocytes it was found that adenoviral-mediated expression of GCN5

largely repressed PGC1-alpha-induced activation of gluconeogenic gene expression and decreased hepatic glucose secretion. GCN5 acetylated PGC1-alpha resulting in a transcriptionally inactive protein that re-localized from promoter regions to nuclear foci [82]. Further, it was found that in db/db mice, metformin, which inhibits gluconeogenesis, increased hepatic levels of GCN5 and sirtuin 1 (SIRT1) protein relative to controls and untreated db/db mice. GCN5 and SIRT1 modulated levels and activity of the co-activators cAMP-response element binding protein-regulated transcription co-activator 2 (CRTC2 or TORC2) and PGC1-alpha. TORC2 protein levels were reduced, gene expression and activation of the PGC1-alpha target gene PECK was decreased, and plasma glucose and insulin levels were lower. The data suggested the induction of hepatic GCN5 as a potential therapeutic strategy for treatment of type 2 diabetes [83].

Histon deacetylases (HDACs)

The reversible acetylation of several lysine residues of histones leads to an increase in gene transcription due to a better accessibility of the promoter region for the transcriptional machinery. The deacetylation of histones by histone deacetylases (HDACs) leads to a repression of gene transcription. These enzymes are classified according to their sequence and domain structure. The class I of histone deacetylases comprises amongst others HDAC1, HDAC2, and HDAC3 [84].

The liver specific knockout of HDAC3 resulted in hepatomegaly (i.e. hepatocyte hypertrophy) and genes which are involved in lipid and cholesterol biosyntheses became de-repressed (e.g. acetyl CoA carboxylase or squalene epoxidase). This resulted in a marked increase in liver and serum triglycerides and cholesterol [85]. Further analysis revealed that HDAC1 and HDAC3 but not HDAC2 interacted with sumoylated C/EBP-delta and thereby repressed the transcription of PPAR-gamma 2 which is involved in hepatic lipogenesis [86,87]. These results point to a critical role for HDAC3 in liver lipid metabolism.

HDAC3 also interacted with the nuclear receptor co-repressor N-CoR1, which activates HDAC3 [88]. Interestingly, the disruption of this complex resulted in an aberrant regulation of clock genes and thereby altered the oscillatory pattern of several metabolic genes such as carnitine palmitoyltransferase 1a, medium chain acyl-CoA dehydrogenase or PPAR-alpha and this aberrant regulation resulted in increased energy expenditure [89]. The HDAC3-N-CoR complex has also been described to repress the basal transcription of some of the thyroid hormone (TH) induced genes [90].

A different role for HDACs in the control of liver metabolism has been described for HDAC2. In livers of ob/ob mice, an interaction between HDAC2 (transcriptional regulator homolog RPD3 (RPD3L1)) and insulin receptor substrate 1 (IRS1) was observed. This interaction led to a reduced acetylation and a reduced phosphorylation of IRS1 in response to insulin, which could be reversed by treatment with an HDAC inhibitor or HDAC2 specific siRNA knockdown. The authors suggest that the treatment with HDAC inhibitors might be a different approach to rescue insulin sensitivity in insulin resistant tissues [91].

Finally, HDAC1 has been shown to be intimately linked to liver lipid handling. GR-dependent inhibition of the transcriptional repressor hairy enhancer of split 1 (Hes1) led to aberrant accumulation of lipids in the liver. This repression occurred through direct interference of GR with Hes1 promoter activity by triggering the recruitment of cellular HDAC1 activity to the Hes1 gene and simultaneous disassembly of transcriptional co-activator complexes [92].

SIRT1

Sirtuin 1 (SIRT1 (silent mating type information regulation 2, homolog) 1 (*S. cerevisiae*)) belongs to the group of NAD⁺ dependent deacetylases and is involved in energy metabolism during caloric restriction [93,94]. SIRT1 influenced metabolic pathways by up-regulation of PGC1-alpha and down-regulation of PPAR-gamma [95]. In the liver, SIRT1 affected lipid

and mitochondrial metabolism through the regulation of PPAR-gamma, ERR (estrogen related receptor) -alpha and HNF4-alpha [96]. During fasting, SIRT1 induced hepatic gluconeogenesis by inducing PEPCK, fructose-1,6-bisphosphatase (FBPase), and glucose-6-phosphatase (G6Pase) gene expression and liver specific knockdown of SIRT1 in a type 2 diabetic rat model reduced fasting hyperglycemia and increased hepatic insulin sensitivity [97]. It could be shown by Nie et al. (2009) that SIRT1 deacetyled STAT3 (signal transducer and activator of transcription 3) in a nutritional status dependent manner and thereby regulated gluconeogenesis. The deacetylation of STAT3 by SIRT1 resulted in a suppression of the inhibitory effect of STAT3 on gluconeogenic gene expression and an increase in PGC1-alpha and FOXO1 transcription [98]. Consequently, the SIRT1 activator resveratrol has been suggested to treat metabolic disorders, as mice fed with resveratrol were protected against diet induced obesity and insulin resistance [99].

Co-Activators

PGC1

The peroxisome proliferator activator receptor-gamma co-activator alpha (PGC1-alpha) is a key co-activator in the regulation of metabolic function [100]. It was originally cloned as a co-activator for nuclear receptor PPAR-gamma in brown adipocytes, responsible for the tissue-specific induction of thermogenesis in response to cold-exposure and β -adrenergic signaling. Subsequent studies identified PGC1 as a co-activator for multiple nuclear receptors including the glucocorticoid receptor [101,102] in various cell types [103-106].

In liver, cAMP responsive element binding protein (CREB) was found to induce expression of the gluconeogenic program through PGC1. Glucose homeostasis and expression of gluconeogenic genes were restored by overexpression of PGC1 in CREB-deficient mice. Furthermore, PGC1 promoted co-operativity between cyclic AMP and glucocorticoid signalling pathways during the induction of hepatic gluconeogenesis [53]. Therefore, overexpression PGC1 in livers of diabetic mice importantly contributed to the pathogenesis of type 2 diabetes. Indeed, the aberrant activation of hepatic PGC1 by fasting signals and the subsequent activation of the TRB3 pseudokinase seem to importantly contribute to fasting hyperglycemia and insulin resistance as associated with type 2 diabetes and may also provide a potential molecular explanation for the insulin resistance which has been observed under chronic fasting conditions and in response to glucocorticoid therapy [29,53,107].

The co-factor BRG1-associated factor 60a (BAF60a) was found in a genome-wide high-throughput co-activation screen to examine the biological role of PGC1-alpha binding partners in metabolic regulation assays [108]. BAF60a is a key regulator of hepatic lipid homeostasis [108] and acts as a factor that links the SWI/SNF complexes which is important in the process of chromatin remodelling to regulate gene transcription [109], to the transcriptional co-activator PGC1-alpha. Adenoviral-mediated expression of BAF60a

stimulated the entire program of peroxisomal and mitochondrial fat oxidation via recruitment of BAF60a to PPAR-alpha binding sites through PGC1-alpha and lowered liver triglyceride content in mouse models of hepatic steatosis. Furthermore, BAF60a was required for the activation of hepatic fat oxidation during fasting [108].

Apart from PGC1-alpha, the related protein PGC1-beta also functions as a metabolic co-activator. PGC1-beta knockout mice had defects in fat metabolism and mitochondrial function [110,111]. Lack of PGC1-beta impaired hepatic lipid metabolism in response to acute high fat dietary loads, resulting in hepatic steatosis and reduced lipoprotein-associated triglyceride and cholesterol content [110].

PGC1-beta mRNA levels were increased significantly in the liver during fasting, suggesting a possible role for this factor in the regulation of hepatic gluconeogenesis and/or fatty acid oxidation [112]. High-fat feeding, which induces hyperlipidemia and atherogenesis, stimulated the expression of both PGC1-beta and sterol regulatory element-binding protein 1c (SREBP1c) and SREBP1a in liver. PGC1-beta co-activated the SREBP transcription factor family and stimulated lipogenic gene expression. PGC1-beta reduced fat accumulation in the liver while greatly increasing circulating triglycerides and cholesterol in VLDL particles. The stimulation of lipoprotein transport upon PGC1-beta expression was likely due to the simultaneous co-activation of the liver X receptor, LXR-alpha, a nuclear hormone receptor with known roles in hepatic lipid transport [113]. Furthermore, PGC1-beta co-activated the forkhead box transcription factor FoxA2 thereby activating genes involved in hepatic lipid metabolism leading to increased oxidation and secretion of fatty acids in the form of triglycerides, a process impaired in type 2 diabetes. FoxA2-PGC1-beta induced the expression of microsomal transfer protein, thereby increasing apolipoprotein B (ApoB)-containing VLDL secretion and contributing to hypertriglyceridemia [114].

SRC/p160 family

The SRC/p160 family of steroid receptor co-factors comprises three members SRC-1, SRC-2 and SRC-3, which are functionally and structurally related [115]. They show a sequence identity of about 43-48% between the members, encode for proteins of about 160 kDa and are widely expressed throughout different tissues [116]. These co-factors interact with ligand-bound nuclear receptors and recruit acetyltransferases (CREB-binding protein (CBP), p300, p/CAF) and methyltransferases (CARM1, PRMT1) to promoter and enhancer regions, thereby facilitating histone modification and gene transcription [117,118].

SRC-1 (also referred to as nuclear receptor co-activator 1 (NCoA1)) was originally identified in a yeast 2 hybrid screen as a co-activator for all steroid receptors [119,120]. The SRC-1 knockout mouse showed a higher sensitivity to diet induced obesity and a lower energy expenditure due to reduced activation of PPAR-gamma in brown adipocytes [121,122]. In the liver, microarray analysis of SRC-1 knockout mice showed that the expression of SRC-1 target genes involved in glycolysis and glycogen synthesis (e.g. pyruvate kinase, aldolase 1 or glycogenin 1) were up-regulated [115].

SRC-2 (NCoA2, transcriptional intermediary factor 2 (TIF2), glucocorticoid receptor interacting protein 1 (GRIP-1)) functions as a transcriptional activator in the liver as SRC-2 target genes involved in fatty acid synthesis, cholesterol biosynthesis and steroid synthesis (e.g. 3-hydroxy-3-methylglutaryl-CoA reductase, low-density lipoprotein receptor, aldo-keto reductase family 1 c6) were found to be down-regulated in the livers of SRC-2 knockout animals [115]. Interestingly and in contrast to the SRC-1 knockout mice, the SRC-2 knockout mice were protected against high fat diet induced obesity due to higher energy expenditure [121].

According to microarray analysis of gene expression in the liver by Jeong et al. (2006), the ablation of SRC-3 (NCoA3, p300/CBP-interacting protein (p/CIP), thyroid hormone receptor activator molecule 1 (TRAM1)) did not affect liver specific gene regulation but showed a more preferable metabolic profile due to an increase in mitochondria function and energy expenditure via activation of PGC1-alpha [115,123]. It has been shown by Nikolaidou-Neokosmidou et al. (2006) that SRC-3 activated the hepatocyte nuclear factor 4 (HNF4) and thereby the transcription of the HNF4 target gene apolipoprotein C3 (APOC3), which was involved in the binding of apolipoprotein E-containing lipoproteins to cell receptors and their subsequent catabolism [120].

TORC

The transducers of regulated CREB activity (TORC) family were characterized in 2003 [124,125]. It consists of three family members TORC 1, 2 and 3. They enhance CRE-dependent transcription via a phosphorylation-independent interaction with the b-Zip DNA binding/dimerization domain of CREB. In pancreatic β -cells, TORC2 was shown to mediate the synergistic effects of cAMP agonists (including glucagon-like peptide-1) and glucose on gene expression [126]. TORC2 also plays an important role in promoting hepatic gluconeogenesis during fasting. TORC phosphorylation and nuclear/cytoplasmic shuttling may be a focal integration point for multiple factors regulating gene expression in the liver, including glucagon, insulin, and AMP-kinase [127].

Apart from phosphorylation, it has been shown that also O-glycosylation of TORC2 has an impact on gluconeogenesis [128]. O-glycosylated TORC2 due to higher levels of glucose led to an increase in nuclear TORC2 and increased expression of gluconeogenic enzymes in hepatocytes as well as in the liver *in vivo* [128]. TORC2 is also involved in glucose induced ER stress in the liver [129]. The authors described a dual role for TORC2 as a sensor for ER-stress and fasting in the liver as acute ER-stress triggered de-phosphorylation of TORC2 and

its subsequent translocation into the nucleus and its recruitment to ER-stress inducible promoters by interaction with activating transcription factor 6 alpha (ATF6-alpha) [129].

TRAP220

The nuclear receptor co-activator thyroid receptor-associated protein complex 220 kDa component (TRAP220, mediator complex subunit 1 (Med1), PPAR binding protein (PBP)) is a component of the TRAP/DRIP/ARC complex, which is recruited to nuclear receptors in a ligand-dependent manner [51,130].

TRAP220 functions as a co-activator for PPARs or other nuclear receptors like LXR/RXR (retinoic X receptor) with which it can interact either with LXR alone [131,132] or with both LXR and RXR [133]. In liver parenchymal cells, TRAP220 served as a co-activator for PPAR-alpha dependent gene transcription and is thereby involved in peroxisome and liver cell proliferation [134].

Whole body knock out of the TRAP220 gene resulted in embryonic lethality. Liver specific knock out showed that this gene was involved in liver regeneration and hepatocarcinogenesis, as TRAP220 knock out hepatocytes did not respond to the hepatocyte growth factor (HGF) anymore [135]. Additionally, the liver specific ablation of TRAP220 attenuated hepatic steatosis induced by the glucocorticoid receptor (GR) agonist dexamethasone [136].

Co-Repressors

N-CoR/SMRT

Key regulators of nuclear receptor signaling are nuclear receptor co-repressor 1 (N-CoR) and silencing mediator of retinoid and thyroid receptors (SMRT). Both proteins are highly homologous in the N-terminal region and in the C-terminal receptor interaction domain. Both N-CoR and SMRT recruit histone deacetylases like HDAC3, thereby repressing gene transcription [137-139]. In the absence of ligands it has been shown that N-CoR and SMRT interact with LXR and repress LXR-dependent transcription [140]. Furthermore, the expression of gluconeogenic PEPCK gene expression under pro-inflammatory conditions was down-regulated due to TNF-alpha (tumor necrosis factor alpha) treatment. The down-regulation was due to the inhibition of the activity of CREB on the PEPCK promoter by recruiting HDAC3 and SMRT through the nuclear factor kappa B (NF-kappa B) subunit p65 [141,142]. The involvement of SMRT in metabolic processes was also shown by Nofsinger et al. (2008), who demonstrated that mice expressing a version of SMRT with a disrupted nuclear receptor domain had a changed glucose metabolism. These mice had higher fasting glucose levels, were glucose intolerant and showed a higher hepatic glucose production. Their adipose tissue displayed normal insulin sensitivity, whereas the muscle showed a decreased insulin stimulated glucose uptake rate. These results demonstrated a role for SMRT in hepatic and extra-hepatic metabolic homeostasis [143].

TGIF1

TG-interacting factor 1 (TGIF1) is a co-repressor described to be involved in regulating apolipoprotein gene expression in liver [144]. The TGIF gene encodes a homeodomain protein that interacts with TGF-beta-activated Smad proteins [145] and acts as a context-independent transcriptional repressor [146]. Furthermore, TGIF1 interacts with RXR and

recruits transcriptional co-repressors [147]. The closely related TGIF2 functions similarly to TGIF1 [148,149]. Melhuish et al. (2010) were able to demonstrate that TGIF1 effectively regulated a specific subset of LXR-responsive genes in mice. Two conserved apolipoprotein gene clusters were de-regulated in the absence of TGIF1: *Apoa4*, regulating cholesterol metabolism and promoting transport of cholesterol from extra-hepatic tissue to the liver [150], and *Apoc2* appeared to be the most affected genes within these clusters [144].

TRIM24

The tripartite motif-containing 24 (TRIM24, TIF-1alpha (transcriptional intermediary factor 1)) interacts with the retinoic acid receptor (RAR) in a ligand-dependent fashion and functions as a co-repressor. In liver it has been described by Khetchoumian et al. (2007, 2008) that TRIM24 functioned as a tumor suppressor gene by attenuating RAR-alpha (retinoic acid receptor isotype alpha) dependent gene transcription as TRIM24 knockout mice showed a high incidence for the development of hepatocellular carcinoma [151,152].

DAX1

DAX1 (dosage-sensitive sex reversal adrenal hypoplasia congenital critical region on X chromosome, gene 1, nuclear receptor subfamily 0, group B, member 1 (NR0B1)) belongs to the group of orphan nuclear receptors [153] and it has been shown that DAX1 is involved in the development of the hypothalamic–pituitary–adrenal–gonadal (HPAG) axis [154]. Despite that DAX1 has been identified as a nuclear receptor, its annotated function is that of a transcriptional repressor [155]. In liver metabolism, it has been shown that DAX1 inhibited HNF4-alpha trans-activation capacities and negatively regulated gluconeogenic gene expression [156]. Additionally, it has been shown by the same authors that DAX1 interacted with LXR-alpha and competed with the co-activator SRC-1 for repressing LXR-alpha transcriptional activity [157]. DAX1 was also involved in the regulation of steroidogenesis by

repression of the SREBP-1a and steroidogenic factor-1 (SF-1) dependent activation of the high-density lipoprotein receptor (HDL-R) promoter, thereby interfering with the cellular uptake of cholesterol [158].

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Dual-function co-factors

RIP140

Receptor-interacting protein 140 is a nuclear receptor co-repressor that was originally identified by its ability to interact with estrogen receptors and found to repress their transcriptional activity [159]. Recent evidence indicates that RIP140 is a multi-functional co-regulator important in regulating gene expression in metabolic tissues, specifically adipose tissue, muscle and liver [160-162]. Loss of RIP140 resulted in a lean phenotype, resistance to obesity and increased insulin sensitivity [160]. It has been shown that RIP140 acts as a co-factor for LXR in liver activating genes required for lipogenesis and repressing genes required for gluconeogenesis [163]. However, in a different study loss of hepatic RIP140 determined hepatic and serum TG levels by a combinatorial mechanism comprising increased FFA oxidation, enhanced VLDL secretion and reduced peripheral LPL activity, which was dependent on its repressor function for LXR-dependent expression of fatty acid synthase (FAS) and SREBP1-c in liver cells [56], suggesting that this co-factor can act as either co-activator or co-repressor, depending on the cellular/gene context. Indeed, in gene-specific contexts, RIP140 serves as a co-activator for NFkappaB, a master transcriptional regulator of inflammation. Intriguingly, RIP140's co-activator function in this setting relied on direct protein-protein interactions with the NFkappaB subunit RelA and histone acetylase CBP [164]. Intriguingly, RIP140 gene expression was found to be induced in livers of septic and tumor-bearing mice. Liver-specific knockdown of RIP140 led to alleviated hepatic steatosis in tumor-bearing, cachectic animals. Under these conditions, hepatic RIP140 was found to control lipogenic, apolipoprotein and lipid transporter gene expression in liver. By preventing the relocation of TG from hepatic stores to the systemic circulation, the induction of RIP140 in liver seems to contribute to hepatic steatosis in inflammatory cancer cachexia [56].

Outlook

As outlined above, a metabolic checkpoint function for hepatic energy homeostasis can in many cases be attributed to the activity of transcriptional co-factors, integrating and translating dietary, hormonal, and inflammatory signals into alterations of genetic and metabolic programs in glucose- and lipid-metabolizing biochemical pathways. Indeed, aberrations in normal transcriptional co-factor functions are causally linked not only to the pathogenesis of obesity-related type 2 diabetes but also to metabolic aberrations in the tumor-bearing state. Due to non-complete (i.e. pathway/gene-specific) data on the global mode of action of most of the described co-factors, a common action pattern is still difficult to define.

However, as demonstrated by a few single examples thus far (PGC1, RIP140) it is tempting to speculate that most –if not all- co-factors will play a dominant role in the coordination of metabolically interconnected pathways (i.e. cholesterol and bile acid homeostasis, gluconeogenesis and fatty acid oxidation) to ensure an integrated hepatic response and adaptation to changing metabolic situations. It is envisaged that novel technologies including high throughput chromatin immunoprecipitation sequencing strategies will substantially contribute to the future elucidation of the composition and signal-dependent regulation of distinct transcriptional co-factor complexes at a systemic level. These systems-oriented approaches will then allow a more integrated and global view on the role of co-factors in specific lipid-metabolizing pathways in the liver and help to establish a systemic pattern of co-factor function in this context. Along this line, future systems-oriented approaches can also be anticipated to stimulate the development of alternative molecular therapies for metabolic disorders. Emerging strategies in pharmacological co-factor manipulation (e.g. resveratrol) underline the importance of further translational research in this direction.

Acknowledgements

We apologize to our colleagues whose contributions could not be cited due to space limitations. We thank Mauricio Berriel Diaz and Adam J. Rose for critically reading the manuscript and discussions. Our work is supported by grants from the Deutsche Forschungsgemeinschaft, the European Foundation for the Study of Diabetes, the German Cancer Aid, and the Network Aging Research.

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Figure Legends

Fig.1: Transcriptional co-activators and co-repressors in hepatic energy homeostasis.

Shown transcriptional co-regulators are (arbitrarily) sub-classified according to their major mode of action with respect to either DNA-binding partner (e.g. nuclear receptors, transcription factors) or enzymatic activity ((de-)acetylation, methylation of histones or proteins). NR, nuclear receptor; CREB, cAMP-binding protein, PolII, RNA polymerase II, TBP, TATA box binding protein, TAFs, transcription activating factors, X, protein.

A: Major transcriptional co-regulators of histones and proteins by (de-)acetylation and methylation.

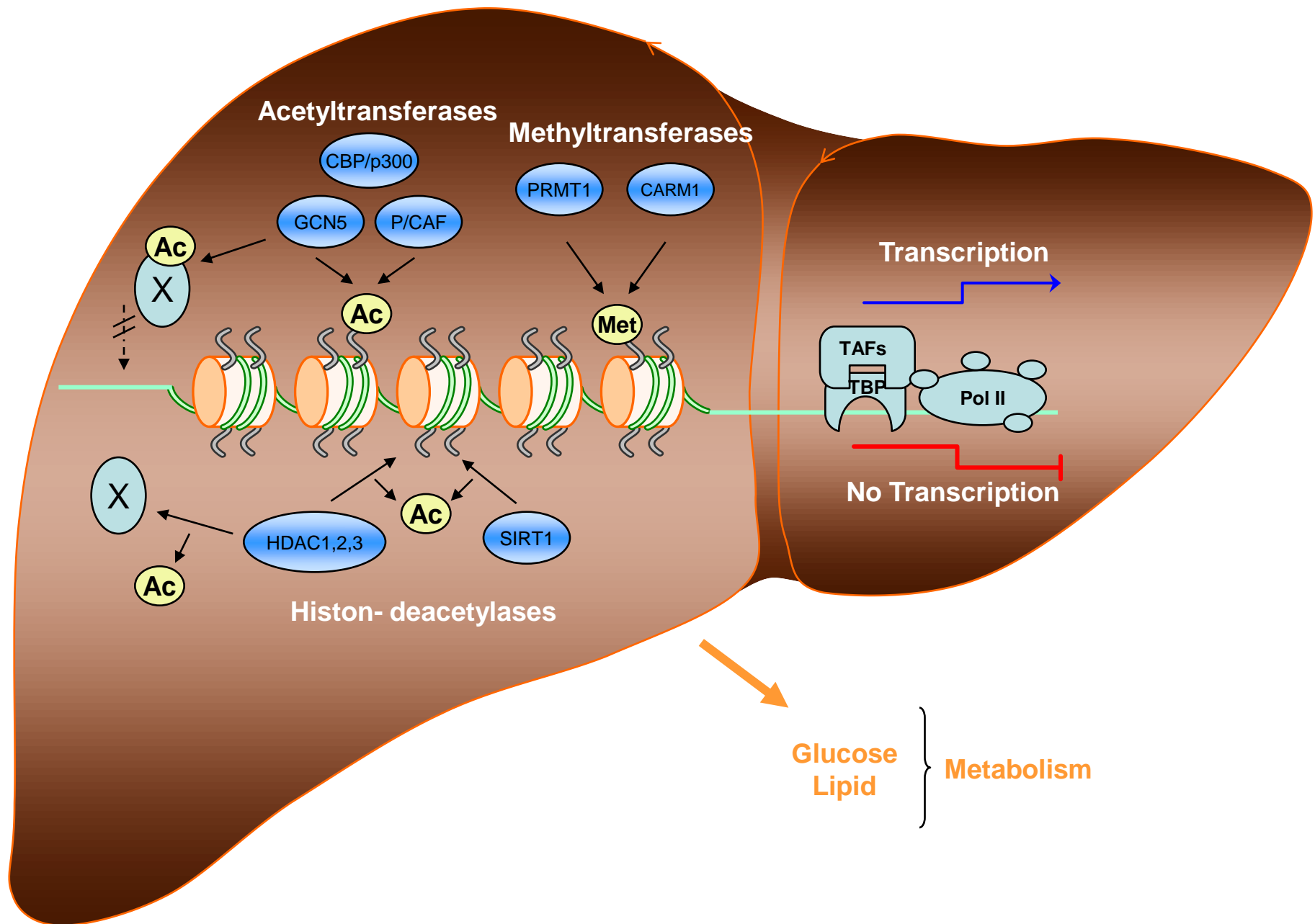
B: Major transcriptional co-activators in hepatic glucose and lipid metabolizing pathways.

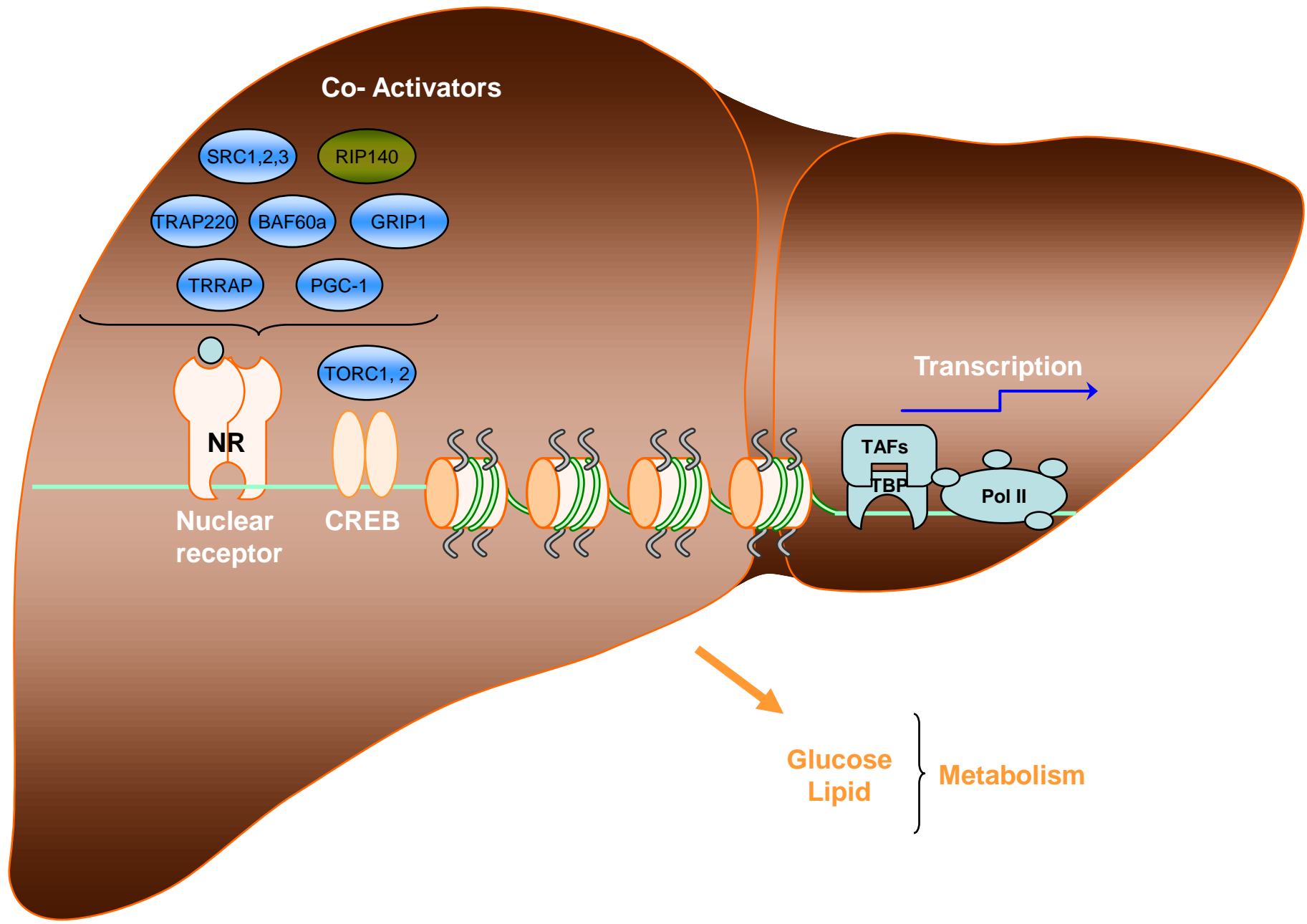
C: Major transcriptional co-repressors in hepatic glucose and lipid metabolizing pathways.

Table 1: Co-regulators and their interaction partners described in liver metabolism.

	Co-factors	Binding partner described in liver
Co-regulators with enzymatic activity		
Methyltransferases	CARM1 PRMT1	Histone 3, CREB Histone 4
Acetyltransferase	CBP/p300 TRRAP	FXR, CREB, FoxA1, FoxA2 LXR-alpha, FXR
Histone deacetylases	GCN5/PCAF HDAC1 HDAC2 HDAC3 SIRT1	PGC1-alpha, CRTC2 C/EBP-delta, Hes1 IRS1 N/CoR-1, C/EBP-delta PPAR-gamma, ERR-alpha, HNF4-alpha, STAT3
Co-Activators		
SRC/p160 family	PGC1-alpha PGC1-beta TRAP220 SRC-1	PPARalpha, BAF60a SREBP, LXR-alpha, FoxA2 PPARs, LXR/RXR nuclear receptors, CBP, p300, p/CAF, CARM1, PRMT1
	SRC-2 SRC-3 TORC2 (CRTC2)	nuclear receptors nuclear receptors, HNF4 CREB, ATF6-alpha
TORC family		
Co-Repressors		
	N-CoR/SMRT TGIF1 TRIM24 Dax-1	LXR, HDAC3 SMAD, RXR, LXR RAR-alpha HNF4-alpha, LXR-alpha, SREBP1-alpha, SF-1
Dual function		
	RIP140	LXR, NFkappaB

Figure 1



B

C

