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Review

Transcriptional Coregulators: Fine-Tuning Metabolism

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Metabolic homeostasis requires that cellular energy levels are adapted to environmental cues. This adaptation is largely regulated at the transcriptional level, through the interaction between transcription factors, coregulators, and the basal transcriptional machinery. Coregulators, which function as both metabolic sensors and transcriptional effectors, are ideally positioned to synchronize metabolic pathways to environmental stimuli. The balance between inhibitory actions of corepressors and stimulatory effects of coactivators enables the fine-tuning of metabolic processes. This tight regulation opens therapeutic opportunities to manage metabolic dysfunction by directing the activity of cofactors toward specific transcription factors, pathways, or cells/tissues, thereby restoring whole-body metabolic homeostasis.

Introduction

Metabolic programs that synchronize energy homeostasis with external cues are often regulated at the transcriptional level. Transcription factors, and particularly many nuclear receptors, are key mediators in these control circuits, as they can transduce environmental signals and directly influence gene expression (Chawla et al., 2001; Francis et al., 2003). Transcriptional coregulators have emerged as equally important, as it is the delicate balance between the inhibitory actions of corepressors and the stimulatory effects of coactivators on transcription that fine-tunes many homeostatic processes (Feige and Auwerx, 2007; Rosenfeld et al., 2006).

Among many coregulators with metabolic roles, studies of the peroxisome proliferator-activated receptor (PPAR) coactivator 1α (PGC-1α) (Fernandez-Marcos and Auwerx, 2011; Gupta et al., 2011) and sirtuin 1 (SIRT1) (reviewed by Bordone and Guarente, 2005; Cantó and Auwerx, 2012; Haigis and Sinclair, 2010; Houtkooper et al., 2012) have been formative for the field. PGC-1α is highly expressed in mitochondria-rich tissues such as brown adipose tissue (BAT) and cardiac and skeletal muscles. In conjunction with a small set of transcription factors, it controls mitochondrial functions, such as oxidative phosphorylation and mitochondrial biogenesis, through the regulation of large clusters of genes (Fernandez-Marcos and Auwerx, 2011; Gupta et al., 2011; Scarpulla, 2006). SIRT1 is the best-characterized member of the sirtuin family of NAD^+-dependent deacetylases, named after the *Saccharomyces cerevisiae* gene silent information regulator 2 (Sir2p) (reviewed by Cantó and Auwerx, 2012; Haigis and Guarente, 2006; Houtkooper et al., 2012). Most of the metabolic actions of SIRT1, which involve the deacetylation and activation of transcription regulators (such as PGC-1α), also affect mitochondrial function (Cantó et al., 2009, 2010; Rodgers et al., 2005) and may as such contribute to the beneficial effects of caloric restriction on lifespan (Cantó and Auwerx, 2012).

The extensive body of literature on PGC-1α and SIRT1, which illustrates a pleiotropic impact of these cofactors on almost all aspects of metabolism, has increased awareness of this additional layer of physiological regulation and incited researchers to define the metabolic roles of cofactors. In this review, we will provide examples of the regulatory roles played by other cofactors in homeostasis and physiology (Figure 1). Furthermore, we will illustrate how multiple signaling pathways impact the activity of such cofactors. Together, the evidence discussed in this review supports the concept of coregulators fine-tuning transcriptional control of metabolism.

Selected Coregulators and the Control of Metabolism

NCoA1, NCoA2, and NCoA3

The three members of the nuclear receptor coactivator (NCoA, also known as SRC for steroid receptor coactivator) family were among the first coregulators cloned (Halachmi et al., 1994), based upon their ligand-dependent recruitment to nuclear receptors, which was mediated by the three α-helical LXXLL motifs within their sequence (Chen et al., 1997; Oñate et al., 1995; Voegel et al., 1996). Although the molecular underpinning of the interaction of the NCoA coactivators with nuclear receptors was defined early, the first indication of a metabolic role for the NCoA family came much later with the observation that mice with a germline mutation of NCoA2 (SRC2/TIF2/GRIP1) are protected against obesity when fed a high-fat diet (HFD) (Picard et al., 2002). In wild-type mice, a HFD induces NCoA2 expression in WAT, and NCoA2 expression favors adipocyte differentiation in vitro (Louet et al., 2006; Picard et al., 2002), indicating that NCoA2 may play a role in fat storage, likely by coactivating PPARγ. Consistent with an important role in adipose tissue, the $NCoA2^{-/-}$ mice displayed reduced fatty acid uptake and storage and increased lipolysis in white adipose tissue (WAT) and enhanced adaptive thermogenesis in BAT (Picard et al., 2002). NCoA2 also plays multiple roles in the liver, where expression of genes required for fatty acid synthesis, such as *Fasn*, is reduced in the livers of germline *NCoA2*$^{-/-}$ mice (Jeong et al., 2006). Notably, NCoA2 deficiency mimics von Gierke's disease (Chopra et al., 2008), a rare metabolic disease that typically results from inactivation of the glucose-6-phosphatase (*G6PC*)

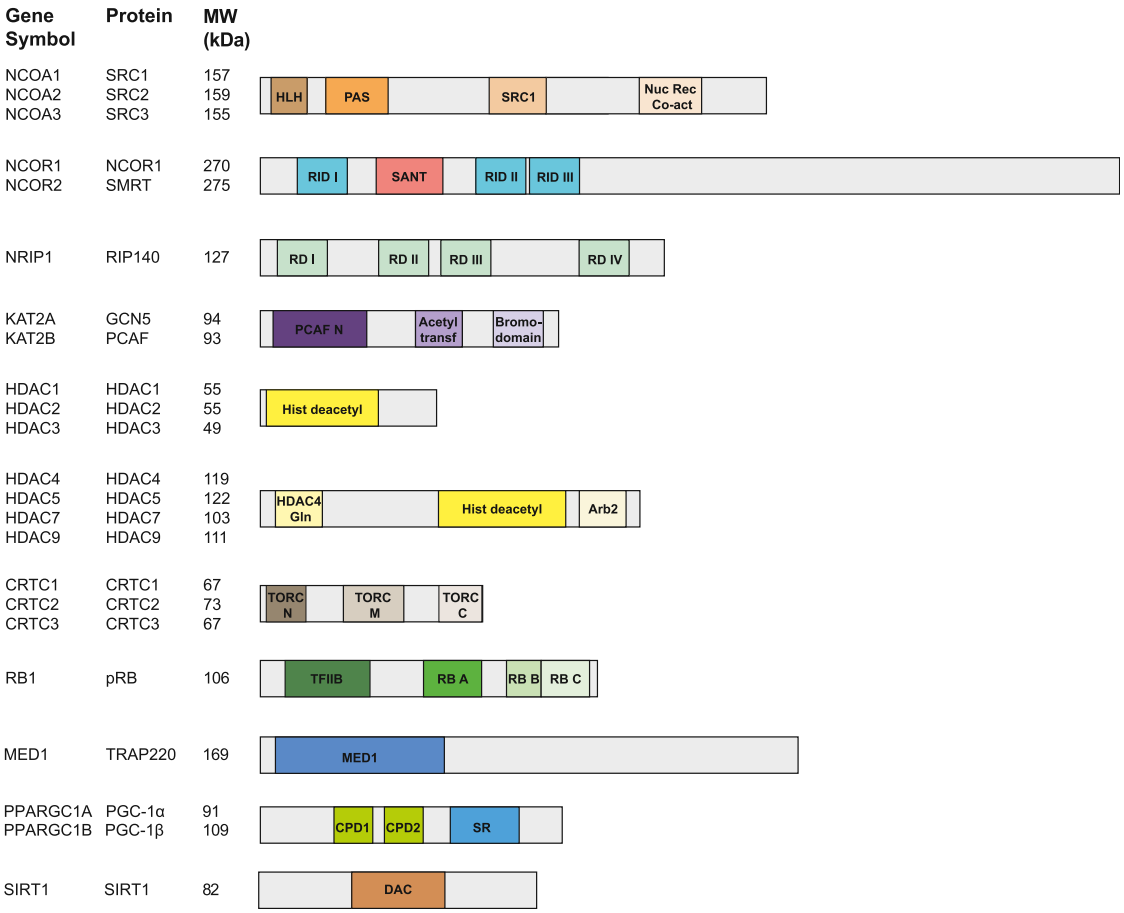

Figure 1. Metabolic Coregulator Protein Families

A representative domain structure of the Pfam-annotated domains is shown for each major protein family discussed in this review. Each color corresponds to one protein family, and differences in shading indicate distinct domains within the same structure. Domain structures are based on the human protein. HLH, basic helix-loop-helix; PAS, Per, Arnt, Sim domain; SRC1, steroid receptor coactivator; Nuc Rec Co-act, nuclear receptor coactivator; SANT, SANT (Swi3, Ada2, N-CoR, and TFIIIB) domain, which contains the DAD or deacetylase activating domain; RID, nuclear receptor interaction domain; RD, repressive domain; PCAF N, PCAF (P300/CBP-associated factor) N-terminal domain; Acetyl transf, acetyltransferase; Hist deacetyl, histone deacetylase; HDAC4 Gln, glutamine-rich N-terminal domain of histone deacetylase 4; Arb2, Arb2 domain; TORC N, transducer of regulated CREB activity, N terminus; TORC M, transducer of regulated CREB activity, middle domain; TORC C, transducer of regulated CREB activity, C terminus; TFIIB, transcription factor TFIIB repeat; RB A, retinoblastoma-associated protein A domain; RB B, retinoblastoma-associated protein B domain; RB C, Rb C-terminal domain; MED1, mediator of RNA polymerase II transcription subunit 1; CPD1, Cdc4 phosphodegron 1; CPD2, Cdc4 phosphodegron 2; DAC, deacetylase catalytic domain.

gene, altering glycogen storage and the production of free glucose by the liver (Lei et al., 1996).

The related coactivator NCoA3 (SRC3/p/CIP/AIB-1/ACTR) is equally important for energy homeostasis. In fact, like *NCoA2*$^{-/-}$ mice, upon high-fat feeding, germline or full-body *NCoA3*$^{-/-}$ mice remain lean and metabolically fit, as defined by insulin sensitization, low lipid levels, cold tolerance, and exercise endurance (Coste et al., 2008). Although reduced adipocyte differentiation via alteration in PPARγ-dependent gene transcription may contribute to this effect (Louet et al., 2006), the robust mitochondrial activation in BAT and skeletal muscle, as a consequence of PGC-1α deacetylation and activation, may explain the lion's share of this phenotype (Coste et al., 2008). NCoA3 stimulates the expression of K (lysine) acetyl transferase 2A (KAT2A, also known as GCN5), the only known PGC-1α acetyl transferase (Lerin et al., 2006), which inhibits PGC-1α function. This oxidative phenotype observed in germline *NCoA3*$^{-/-}$ mice (Coste et al., 2008) was later confirmed in muscle-specific *NCoA3*$^{skm-/-}$ mice (Duteil et al., 2010). As is the case for NCoA2, NCoA3 deficiency also mimics a rare disease, i.e., solute carrier family 25 (carnitine/acylcarnitine translocase), member 20 (SLC25A20) deficiency (York et al., 2012), with its myriad of phenotypes, including hypoglycemia, impaired neurological functions, and myopathy (Rubio-Gozalbo et al., 2004).

Unlike NCoA2 and NCoA3, the third member of the NCoA family, NCoA1, in conjunction with PGC-1α, appears to orient PPARγ activity toward an oxidative program, protecting against obesity and type 2 diabetes mellitus (T2DM) in mice. Indeed, *NCoA1*$^{-/-}$ mice are fatter than littermate controls (Picard et al., 2002), and PGC-1α relies heavily on its interaction with NCoA1 for its activation (Puigserver et al., 1999). The fact that selective recruitment of NCoA1 (and PGC-1α), instead of its family members NCoA2 (Picard et al., 2002; Puigserver et al., 1999) or NCoA3 (Coste et al., 2008; Duteil et al., 2010), has such

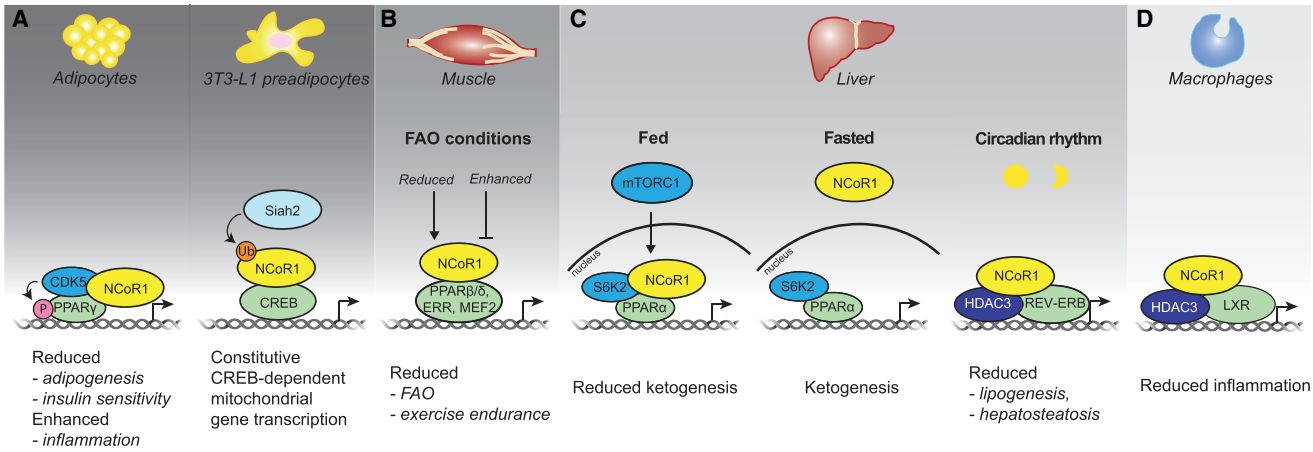

Figure 2. Tissue-Specific Roles of NCoR1

(A) NCoR1 depletion in WAT enhances the activity of the unphosphorylated form of PPARγ, which enhances adipogenesis and insulin sensitivity and reduces inflammation. In 3T3-L1 preadipocytes, the ubiquitin ligase Siah2 targets NCoR1 for proteasomal degradation, promoting the expression of CREB-dependent mitochondrial genes.

(B) In muscle, NCoR1 activity is reduced under conditions in which fatty acid oxidation (FAO) is required. Genetic deletion of NCoR1 in the skeletal muscle enhances exercise endurance through the dereperession of PPARβ/PPARδ, ERRs, and MEF2.

(C) mTORC1 activation in liver during feeding modifies the interaction of S6K2 with NCoR1 and promotes its relocalization in the nucleus, leading to the silencing of the ketogenic target genes of PPARα. Specific genetic disruption of the NCoR1-HDAC3 interaction results in alterations in diurnal gene expression controlled by REV-ERB.

(D) Macrophage-specific NCoR1 mutation reduces inflammation through a selective derepression of the liver X receptor (LXR).

beneficial effects led to a search for selective PPARγ modulators (SPRMs) that favor NCoA1 and PGC-1α recruitment to PPARγ. A first case in point was the compound Fmoc-L-Leu, which changes PPARγ conformation such that it selectively recruits NCoA1, resulting in insulin sensitization without the induction of weight gain commonly associated with PPARγ activation (Rocchi et al., 2001).

NCoR1/SMRT and RIP140

Two critical repressors of a number of different nuclear receptors are the nuclear receptor corepressor (NCoR1) and the silencing mediator for retinoid and thyroid hormone receptor (SMRT, also known as NCoR2). Only recently have studies utilizing tissue-specific deletions begun to elucidate the in vivo roles of NCoR1 and SMRT because germline *NCoR1*$^{-/-}$ and *SMRT*$^{-/-}$ mice are embryonic lethal (Jepsen et al., 2000, 2007). These studies have been complemented by analysis of mice with subtle mutations in different domains of SMRT and NCoR1, such as the *SMRT*^{RID}, *SMRT*^{RID1}, liver-specific *NCoRi*, *L-NCoRΔID*, *NCoR-ΔID*, and *NCoR1*^{mDAD} mice (reviewed by Mottis et al., 2013). Analysis of these mice indicated that derepression of the activity of several nuclear receptors was a common feature of NCoR1/SMRT loss of function, as illustrated by the activation of the thyroid receptor (Astapova et al., 2008, 2011; Feng et al., 2011), activation of PPARγ causing enhanced adipogenesis (Fang et al., 2011; Nofsinger et al., 2008; Reilly et al., 2010; You et al., 2013), and alterations in diurnal gene expression patterns controlled by Rev-Erbα (Alenghat et al., 2008) (Figure 2).

In line with this premise, the phenotype of the WAT-specific NCoR1 knockout mouse (*NCoR1*$^{ad-/-}$) reflects PPARγ derepression, which causes weight gain and increased adipogenesis, with an accumulation of active smaller adipocytes, in contrast to the adipocyte hypertrophy typical of obesity (Li et al., 2011). Glucose tolerance and insulin sensitivity are improved, and WAT macrophage infiltration is attenuated in *NCoR1*$^{ad-/-}$ mice. Furthermore, thiazolidinediones, a class of specific PPARγ agonists, failed to improve insulin sensitivity in the *NCoR1*$^{ad-/-}$ mice, reflecting maximal derepression or activation of PPARγ. CDK5 was previously shown to phosphorylate PPARγ and inhibit its activity, promoting insulin resistance (Choi et al., 2010). Notably, NCoR1 depletion in WAT causes enrichment in the unphosphorylated form of PPARγ, which has insulin-sensitizing actions, suggesting that NCoR1 facilitates phosphorylation of PPARγ by CDK5 (Figure 2A).

The increased exercise endurance of mice with a specific NCoR1 deletion in the skeletal muscle (*NCoR1*$^{skm-/-}$) also concurs with the idea of general transcriptional derepression (Yamamoto et al., 2011). The muscle fiber type shift and the induction of oxidative metabolism in *NCoR1*$^{skm-/-}$ mice is the consequence of its repressive interactions with PPARβ/PPARδ and/or ERRs (α and γ) (Pérez -Schindler et al., 2012; Yamamoto et al., 2011), though the interaction of NCoR1 with myocyte enhancer factor 2 (MEF2), a transcriptional regulator of muscle development and remodeling, may also be involved (Figure 2B). Interestingly, NCoR1 activity also appears to be regulated dynamically in the muscle, as its expression and/or nuclear localization was reduced in conditions where fatty acid oxidation was activated, such as in long-term fasting, high-fat feeding, and endurance exercise (Yamamoto et al., 2011). Of relevance to the role of NCoR1 in oxidative muscle metabolism was the recent identification of NCoR1 as a generalized repressor of mitochondrial activity in a genome-wide study mapping nuclear protein degradation (Catic et al., 2013) (Figure 2A).

In the liver of aged mice, NCoR1 is thought to repress PPARα, the main transcriptional activator of ketogenesis. PPARα signaling was attenuated, and fasting-induced ketogenesis was blunted in mice with hyperactive mammalian target of

rapamycin complex 1 (mTORC1) signaling (Sengupta et al., 2010) (Figure 2C). mTORC1 mediated this effect, at least in part, through increasing the nuclear localization of NCoR1. This effect has been attributed to the downstream target of mTORC1, S6 kinase 2 (S6K2), which interacts with and controls the subcellular localization of NCoR1, the predominant corepressor of PPARα (Kim et al., 2012; Sengupta et al., 2010). In line with this, S6K2 was found to associate with NCoR1 in nuclei of *ob/ob* hepatocytes, confirming a direct effect of energy availability and mTORC1 signaling on NCoR1 intracellular localization (Kim et al., 2012). Further work is required to establish the exact impact of NCoR1 in the liver, as both these studies (Kim et al., 2012; Sengupta et al., 2010) appear to contradict a recent report showing that hepatic NCoR1 deletion results in hepatosteatosis (Sun et al., 2013).

It is striking that the phenotypes caused by attenuated NCoR1/SMRT signaling in muscle, liver, and fat, e.g., oxidative muscle metabolism, enhanced ketogenesis, and reduced fat cell size, are all reflective of unopposed PGC-1α activity, highlighting the potential antagonism between corepressors and coactivators on a physiological level. Furthermore, these studies also suggest that inhibiting mTORC1 actions (Kim et al., 2012; Sengupta et al., 2010) and/or insulin signaling (Yamamoto et al., 2011) will attenuate NCoR1 corepressor signaling and alter metabolic homeostasis, providing a molecular mechanism by which insulin and other hormones signaling to mTOR will result in enhanced transcriptional repression of specific nuclear receptor target genes.

One more striking phenotype was observed in mice with a macrophage-specific NCoR1 mutation. Although one could expect that a macrophage NCoR1 deletion would be proinflammatory due to the derepression of the inflammatory response, inflammation was paradoxically attenuated (Li et al., 2013) (Figure 2D). This phenotype was in part explained by the selective derepression of the liver X receptor (LXR), which leads to the induction of several lipogenic genes that drive the production of anti-inflammatory fatty acids (e.g., palmitoleic acid and ω3 fatty acids) within macrophages that inhibit NF-κB-dependent inflammatory pathways (Li et al., 2013).

Another important consideration for all studies of NCoR1 and SMRT function is that they appear to form an obligate complex with the class I histone deacetylase HDAC3. A combination of elegant genetic studies, using a knockin mouse model in which the deacetylase activation domains (DAD, contained within the SANT) of both NCoR1 and SMRT were incapacitated for HDAC3 interaction (You et al., 2013) and liver-specific *NCoR1* and *SMRT* loss-of-function mouse models (Sun et al., 2013), with pharmacological studies with HDAC inhibitors (Sun et al., 2013), confirmed the suggestive biochemistry that these proteins (NCoR1 in particular) are required for a significant part of the activity of HDAC3. Furthermore, these studies also indicated that HDACs have nonenzymatic roles in transcriptional regulation, which are not affected by HDAC inhibitors (Sun et al., 2013).

Finally, another broad-acting repressor of nuclear receptors, which is unrelated in sequence to NCoR1/SMRT, is the nuclear receptor interacting protein 1 (NRIP1 or RIP140), which functions as a corepressor for several nuclear receptors, such as the PPARs and ERRs (Debevec et al., 2007). Genetic ablation of the *Nrip1* gene increases mitochondrial biogenesis and oxidative metabolism in muscle (Seth et al., 2007) and adipose tissue (Debevec et al., 2007) and protects mice against metabolic dysfunction (Leonardsson et al., 2004; Powelka et al., 2006).

KAT2A(GCN5) and KAT2B(pCAF)

KAT2A (GCN5) was discovered and purified based on its histone acetyltransferase activity from the ciliate *Tetrahymena termophila* (Brownell and Allis, 1995; Brownell et al., 1996). The homology of this protein to the putative yeast transcriptional coactivator Gcn5 provided the first basis of an intimate link between histone acetylation and transcriptional activation. Histone acetylation allows the relaxation of chromatin, facilitating access of transcription factors to DNA to initiate transcription (Kouzarides, 2000; Shogren-Knaak and Peterson, 2006). Since this discovery, several other histone acetyltransferases (HATs) were identified and divided into five subclasses (Roth et al., 2001): the GCN5-related N-acetyltransferases (GNATs), the MYST-related HATs (*M*OZ, *Y*bf2/Sas3, *S*as2 and *T*ip60), the p300/CREB binding protein (CBP) HATs, the general transcription factor HATs (which include the TFIID subunit TBP-associated factor-1 [TAF1]), and the nuclear hormone-related HATs, NCoA1–NCoA3 (discussed above).

Whereas KAT2A was initially studied for its role in histone acetylation and locus-specific coactivator functions, it also functions as a simple acetyltransferase for a wide range of transcriptions factors (Bannister and Miska, 2000), including PGC-1α (Lerin et al., 2006) and PGC-1β (Kelly et al., 2009). Although other acetyltransferases, such as p300, NCoA1, and NCoA3, were shown to interact with PGC-1α, only KAT2A was able to acetylate and inhibit PGC-1α in vivo and in vitro, leading (among other effects) to the attenuation of PGC-1α-induced gluconeogenesis (Lerin et al., 2006). Moreover, NCoA3 facilitated the acetylation and inactivation of PGC-1α through its effect on the expression of KAT2A (Coste et al., 2008). Notably, the expression of both NCoA3 and KAT2A is reduced upon fasting, whereas it is induced by HFD, which is exactly the mirror image of the expression of the deacetylase SIRT1, which is induced and reduced by the same conditions (Coste et al., 2008). This coordinated change in expression of NCoA3, KAT2A, and SIRT1 will subsequently, through its consorted effect on PGC-1α (becoming deacetylated and active when energy is limiting and acetylated and inactive when energy is abundant) affect PGC-1α-mediated energy expenditure and synchronize energy expenditure with energy needs (Coste et al., 2008) (Figure 3). In a further twist to this story, SIRT6 has recently been shown to associate with and deacetylate KAT2A (Dominy et al., 2012). The SIRT6-mediated KAT2A deacetylation in turn changes the phosphorylation state of KAT2A, ultimately enhancing its KAT activity toward PGC-1α. In the liver, this SIRT6 → KAT2A → PGC-1α signaling pathway reduces PGC-1α activity, attenuates the expression of gluconeogenic genes, and dampens hepatic glucose output, an observation that can have important therapeutic implications for the management of diabetes (Dominy et al., 2012).

While the role of KAT2A has been best established in the context of the coregulator PGC-1α, there is much to be learned concerning which promoters are most regulated through KAT2A/KAT2B-dependent mechanisms, as opposed to p300/CBP- or other HAT-dependent mechanisms. A recent study found that while KAT2A/KAT2B correlated with H3K9 acetylation on an endogenous PPARβ/PPARδ target in response to ligand

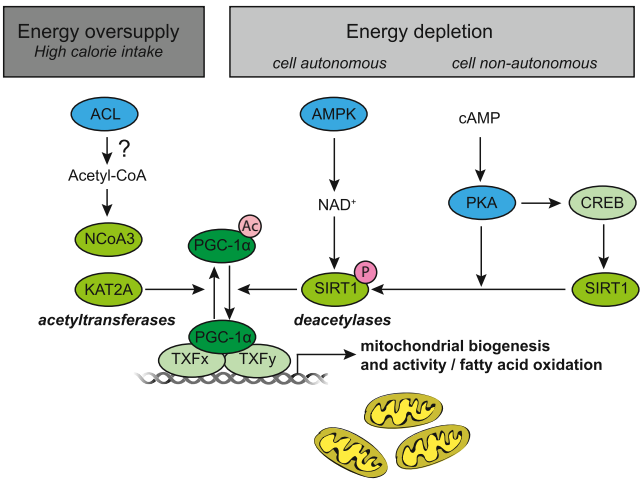

Figure 3. Energy Levels Control AMPK, PKA, SIRT1, and PGC-1α to Govern Mitochondrial Metabolism

In times of energy depletion, such as during caloric restriction or exercise, energy stress is sensed and transduced by the AMP-activated kinase (AMPK). AMPK activation promotes an increase in NAD^+ levels, leading to the activation of the SIRT1 deacetylase, which in turn deacetylates and activates PGC-1α. PGC-1α enhances the expression of genes involved in mitochondrial metabolism, thus improving mitochondrial function. On the other hand, calorie-rich diets or situations in which energy is oversupplied promote the expression of NCoA3, which positively regulates the protein levels of the acetyltransferase KATA2A, which acetylates and decreases the transcriptional activity of PGC-1α. In this metabolic network, the enzyme ATP citrate lyase (ACLY) provides the acetyl-CoA required for the enzymatic reaction of acetylation. Finally, stimulation of cAMP/PKA signaling, as seen after epinephrine and glucagon release, enhances the expression of *Sirt1* and the phosphorylation of SIRT1, reinforcing its deacetylase activity to ultimately promote PGC-1α deacetylation.

stimulation, they were dispensable for ligand-induced gene activation, unlike p300/CBP (Jin et al., 2011). In contrast, however, another study found that p300/CBP recruitment to CREB-dependent targets was dispensable for cyclic AMP (cAMP)-induced gene expression, which relied more heavily on non-HAT coactivators from the CRTC family (Kasper et al., 2010).

The contribution of HATs in cAMP-dependent transcription in liver was, however, underscored in a recent study finding that KAT2B (PCAF) mediates the increase in H3K9 acetylation seen at promoters of gluconeogenic genes under conditions where their expression is elevated, including fasting and in diabetic models (Ravnskjaer et al., 2013).

Collectively, much work is still needed to determine which sets of promoters are predominantly controlled via inducible changes in the acetylation and deacetylation of histones, as opposed to changes in the acetylation and deacetylation of transcription factors and their coregulators.

HDACs

Opposing the action of HATs, histone deacetylases, which are divided into five classes—class I (HDAC1, HDAC2, HDAC3, and HDAC8), class IIa (HDAC4, HDAC5, HDAC7, and HDAC9), class IIb (HDAC6 and HDAC10), class III (sirtuins, discussed above), and class IV (HDAC11)—are responsible for the removal of acetyl moieties from histones and, as such, are considered transcriptional corepressors. However, new findings suggest that class I and II HDACs also deacetylate nonhistone targets and that this can have either an activating or repressive effect on transcription depending on the transcription factor and/or coregulator targeted. Furthermore, studies in several different tissues have identified that these HDACs function as key metabolic coregulators (reviewed by Mihaylova and Shaw, 2013).

Investigation of HDAC function in the heart has implicated these proteins in the regulation of cardiac energy homeostasis. HDAC1 and HDAC2 were shown to play important, but redundant, roles in cardiac development and growth. Conditional deletion of *Hdac1* and *Hdac2* in cardiomyocytes resulted in severe cardiac defects and lethality shortly after birth, and a single copy of either *Hdac1* or *Hdac2* was sufficient to sustain mice through normal development (Montgomery et al., 2007). Similar conditional deletion of *Hdac3* induced cardiac hypertrophy and reprogramming of cardiomyocytes (Montgomery et al., 2008). Increased fatty acid uptake and oxidation were observed, as well as myocardial lipid accumulation, which were attributed to elevated PPARα activity. In a different study, postnatal deletion of *Hdac3* in both cardiac and skeletal muscle, via muscle creatine kinase (MCK) promoter-driven Cre expression, revealed hypertrophic cardiomyopathy and heart failure in mice on a HFD (Sun et al., 2011). Decreased expression of genes involved in fatty acid metabolism, the electron transport chain, and the tricarboxylic acid (TCA) cycle was observed. Furthermore, pharmacological inhibition of class I HDACs, using an apicidin derivative (API-D), protected against cardiac hypertrophy in response to pressure overload, generated by thoracic aortic constriction (Gallo et al., 2008). In contrast, cardiac stress caused severe cardiac hypertrophy in mice deficient in class IIa *Hdac5* and *Hdac9* (Chang et al., 2004; Zhang et al., 2002). While these studies highlight the metabolic roles of HDACs, they also unveil the complexity underlying HDAC function in the heart.

The role of the class IIa HDACs in muscle physiology has been well studied and provides a key example of these HDACs functioning as coregulators that direct precise metabolic outcomes. The class IIa HDACs are thought to play a suppressive role in myogenesis and muscle fiber switching via specific repression of MEF2 family members (Kim et al., 2008; Lu et al., 2000; McKinsey et al., 2000a). MEF2s are believed to be key transcriptional regulators for the oxidative, slow twitch (type I) myofibers. Genetic deletion of multiple class IIa HDACs in skeletal muscle promoted derepression of MEF2 target genes and the corresponding metabolic reprogramming of glycolytic to oxidative fibers (Potthoff et al., 2007). Furthermore, it has been suggested that direct HDAC3-dependent deacetylation of MEF2 may be another mode of MEF2 regulation in myogenesis (Grégoire et al., 2007). Considering that the class IIa HDACs themselves bear minimal intrinsic deacetylase activity (Lahm et al., 2007; Schuetz et al., 2008), and the deacetylase activity found associated with them in vivo has been attributed to their association with HDAC3 (Fischle et al., 2001, 2002; Greco et al., 2011), it is conceivable that recruitment of HDAC3 to MEF2 may contribute to class IIa HDAC function in muscle (Nebbioso et al., 2009). Importantly, the class IIa HDACs are often found in complex with the HDAC3-NCoR1/SMRT complex (discussed above) (Downes et al., 2000; Fischle et al., 2002; Guenther et al., 2000; Huang et al., 2000; Kao et al., 2000; Li et al., 2000; Yang and Seto, 2008; Yoon et al., 2003), and the interplay between the HDACs and this corepressor complex determines

the transcriptional output. Consistent with this mechanism, *NCoR1*$^{skm-/-}$ mice display an increase in exercise endurance, oxidative muscle metabolism, and mitochondrial quantity, which can be attributed to the derepression of PPARβ/PPARδ, ERRs, and MEF2 and linked to MEF2 hyperacetylation (Yamamoto et al., 2011). An elegant dissection of a role for class IIa HDACs in denervation-induced expression of the muscle-wasting-inducing E3 ligases atrogin-1 and MuRF1 reveals that these HDACs may also be controlling neurogenic muscle atrophy (Moresi et al., 2010).

Important roles of HDAC3 and class IIa HDACs in liver metabolism have also recently emerged. Conditional *Hdac3* deletion resulted in severe hepatic steatosis and elevated expression of lipogenic enzymes (Feng et al., 2011; Knutson et al., 2008). Furthermore, HDAC3 binding exhibited a circadian pattern, which correlated inversely with histone acetylation (Feng et al., 2011). Recruitment of HDAC3 to lipogenic gene loci required the nuclear receptor Rev-Erbα, a component of the circadian clock machinery, to repress lipogenic gene expression during the day (Figure 2C). Further metabolic phenotypes of *Hdac3* deletion were also observed, including lower fasting blood glucose and insulin levels (Knutson et al., 2008; Sun et al., 2012). Although these studies underscore the importance of HDAC3 in glucose and lipid metabolism, it is important to note that many of the effects of HDAC3 on metabolism are independent of its deacetylase activity (Sun et al., 2013).

Class IIa HDACs are also important in the control of hepatic glucose metabolism. Class IIa *Hdac* knockdown resulted in glycogen accumulation and decreased blood glucose in murine models of the metabolic syndrome (Mihaylova et al., 2011). Mechanistically, under fasted conditions or treatment with the fasting hormone glucagon, class IIa HDACs induce the expression of gluconeogenic genes, including *G6pc* and *Pck1*, by recruiting HDAC3 to deacetylate and activate the transcription factor, FOXO1. Altogether, this study reveals that class IIa HDAC-mediated deacetylation of a nuclear, nonhistone target, FOXO1, mediates the translation of a hormonal signal into the regulation of metabolic homeostasis.

Finally, pharmacological and genetic experiments suggest that class I HDACs (HDAC1, HDAC2, and HDAC3) play roles in adipocyte differentiation and may be therapeutic targets in diabetes and other metabolic diseases (Fajas et al., 2002b; Galmozzi et al., 2013; Haberland et al., 2010). In the case of HDAC3, the mechanism has been attributed to the inhibition of PPARγ by a complex of HDAC3 and the retinoblastoma protein pRb (Fajas et al., 2002a). The role of class I and class IIa HDACs in different metabolic tissues and the impact of HDAC inhibitors of the metabolic function of different tissues in vivo are very active areas of research.

CRTCs

Members of the cAMP-regulated transcriptional coactivator (CRTC) protein family act as transcriptional coactivators of the cyclic AMP-responsive element (CRE)-binding protein (CREB). The family consists of CRTC1, CRTC2, and CRTC3. CRTC2, the CRTC family member most enriched in the liver, has been shown to regulate the CREB-dependent hepatic gluconeogenic program (Koo et al., 2005; Saberi et al., 2009). Fasting and glucagon treatment activate CRTC2, and fasting signals were required for CRTC2-induced glucose production in hepatocytes and the induction of gluconeogenesis in vivo. Conversely, RNAi-mediated reduction of *Crtc2* in vivo resulted in fasting hypoglycemia (Koo et al., 2005), similar to that observed upon CREB depletion by both targeted disruption and in vivo expression of a dominant-negative CREB inhibitor (Herzig et al., 2001). These observations were attributed in large part to CRTC2/CREB control of gluconeogenic gene expression, including that of *Pepck1*, *G6pc*, and *Ppargc1a* (Herzig et al., 2001; Koo et al., 2005; Saberi et al., 2009; Wang et al., 2010). As aberrant regulation of glucose homeostasis is central to type 2 diabetes, the effects of *Crtc2* knockdown in models of metabolic syndrome were assessed. Depletion or knockout of *Crtc2* in mice fed a HFD reduced fasting hepatic glucose production and hyperglycemia and improved insulin sensitivity in both liver and skeletal muscle (Saberi et al., 2009; Wang et al., 2010). Hyperglycemia was also improved in Zucker diabetic fatty rats upon reduction of CRTC2. These results delineate the potential impact of CRTC coregulators in diabetes.

Mouse models have revealed that metabolic regulation by the CRTCs extends to tissue contexts beyond the liver, including the hypothalamus and adipose tissue. CRTC1 and CREB appear to have a role in the hypothalamus, from which they coordinate metabolic regulation in response to nutrient signals. CRTC1 is predominantly expressed in the brain, yet *Crtc1*$^{-/-}$ mice are obese (Altarejos et al., 2008). These mice are hyperphagic, display hypertriglyceridemia and hyperglycemia, and have elevated circulating insulin and leptin levels. These metabolic phenotypes were attributed to the misregulation of leptin signaling in the hypothalamus of *Crtc1*$^{-/-}$ mice due to direct control of *Cartpt* and *Kiss1*, components of leptin signaling, by CRTC1 and CREB.

Furthermore, *Crtc3*$^{-/-}$ mice revealed that CRTC3 contributes to catecholamine signaling in adipose tissue (Song et al., 2010). Catecholamines are hormones produced by the sympathetic nervous system and are recognized by adrenergic receptors. Activation of adrenergic receptors stimulates the production of cAMP, ultimately promoting lipolysis in WAT and fat burning in BAT. Catecholamine signaling was found to activate CRTC3, inducing the expression of the metabolic syndrome susceptibility gene, *Rgs2*, a direct CREB target. *Crtc3*$^{-/-}$ adipocytes displayed increases in insulin and catecholamine signaling and, correspondingly, enhanced glucose and fatty acid oxidation. Systemically, *Crtc3*$^{-/-}$ mice exhibited increased energy expenditure and resistance to diet-induced obesity. Notably, a human *CRTC3* variant associated with increased transcriptional activity correlates with adiposity, linking CRTC3 function to obesity (Song et al., 2010).

In keeping with the emerging role of the CRTCs as integrators of systemic glucose handling, CRTC2 may also have important metabolic functions in pancreatic β cells. CREB activity is required for normal function of insulin-producing β cells of pancreatic islets, as transgenic expression of dominant-negative *A-Creb* in β cells induced apoptosis and caused mice to develop diabetes (Jhala et al., 2003). It has also been established that cAMP and calcium signal through CRTC2 in pancreatic islet cells to affect the CREB-mediated response to nutrient cues (Screaton et al., 2004). As such, in vivo studies are likely to reveal important contributions of CRTC2 to CREB function in this context.

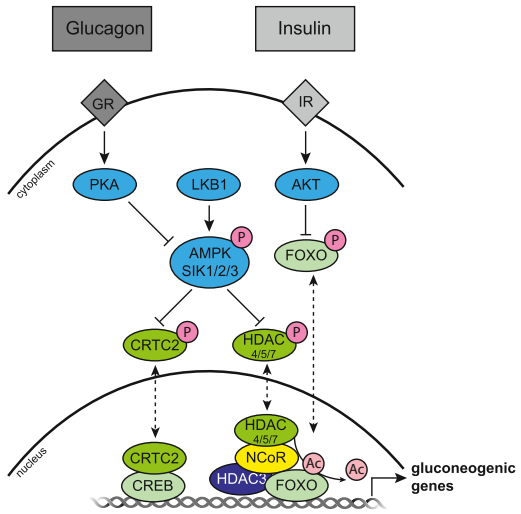

Figure 4. Molecular Model of Kinase-Mediated Control of CRTC2 and HDAC4/HDAC5/HDAC7 Subcellular Localization and Activity

The metabolic hormones glucagon and insulin signal through the glucagon receptor (GR) and insulin receptor (IR), respectively, to initiate signaling cascades downstream of changes in metabolic status. PKA and LKB1 phosphorylate (dark pink circles with a P) the AMPKRs (AMPK-related kinases), including AMPK and SIK1/SIK2/SIK3, which, when active, phosphorylate CRTC2 and HDAC4/HDAC5/HDAC7, resulting in their cytoplasmic sequestration. When unphosphorylated, CRTC2 and HDAC4/HDAC5/HDAC7 translocate to the nucleus (dashed lines), where they are free to promote the activation of gluconeogenic gene expression programs through CREB and the NCoR, HDAC3, FOXO complex, respectively. CRTC2 coactivates CREB, and nuclear FOXO is activated upon HDAC4/HDAC5/HDAC7-mediated deacetylation (light pink circles). In parallel, AKT phosphorylation regulates the activity of FOXO.

Retinoblastoma Protein

The retinoblastoma protein (pRb) was identified as a tumor suppressor that inhibits cell-cycle progression through inhibition of the transcription factor E2F1. Upon phosphorylation by the CDK/cyclin complex, pRb becomes unable to bind and inhibit E2F1, thereby allowing cells to enter S phase. The functions of pRb have since expanded to include roles ranging from cellular differentiation to the control of whole-body metabolism. In fact, pRb has a major impact on oxidative metabolism, through its repressive actions on E2F1, which is a key regulator not only of cell proliferation, but also of metabolism (Blanchet et al., 2011; Fajas et al., 2002b, 2004). The absence of pRb hence favors the development of more oxidative metabolic programs in BAT (Calo et al., 2010; Dali-Youcef et al., 2007; Fajas et al., 2002a; Scimè et al., 2005) and skeletal muscle (Blanchet et al., 2011), as evidenced by studies in both cells and mouse models. This makes pRb a very unique nodal point that directly connects metabolism with cell proliferation and differentiation.

TRAP220/Mediator1

The mediator complex is a large multiprotein complex of coactivators that forms a bridge between transcription factors and the basal transcriptional machinery (Malik and Roeder, 2010). Subunit 1 of this complex, Med1 (also known as TRAP220/DRIP205/PBP), is important for adipocyte differentiation as it coactivates PPARγ and is required for enforced adipocyte differentiation of MEFs (Ge et al., 2002). However, since Med1 links many nuclear receptors (also including the thyroid hormone and vitamin D receptors) with the mediator complex, it remains possible that the absence of Med1 has more promiscuous effects, depending on the interacting partner and the cellular context. Indeed, specific aspects of constitutive androstane receptor (CAR) and PPARα signaling, mainly related to genes involved in peroxisome proliferation and hepatocellular regeneration, were attenuated in a mouse model with a liver-specific *Med1* inactivation (Jia et al., 2004; Matsumoto et al., 2007). Paradoxically, and despite impaired hepatic PPARα signaling, these mice are protected against HFD-induced hepatic steatosis, due to impaired expression of PPARγ-stimulated lipogenic genes (Bai et al., 2011). A specific knockout of *Med1* in skeletal muscle improves insulin sensitivity and glucose tolerance and results in resistance to diet-induced obesity (Chen et al., 2010). These beneficial effects are accompanied by an increase in mitochondrial density and expression of genes specific to type I and type IIA fibers in white muscle, suggesting a switch between fast-to-slow fibers (Chen et al., 2010). In contrast, transcription factors outside the nuclear receptor family do not seem to be critically dependent on Med1 for contacting the mediator complex, since MyoD-stimulated myogenesis is normal in *Med1*$^{-/-}$ fibroblasts; however, additional transcription factors need to examined (Ge et al., 2002).

Modulation of Coregulator Activity by Upstream Signaling Pathways

Signaling Pathways

There are a number of metabolic signaling pathways that converge on the coregulators under discussion to coordinate their activity in response to nutritional and hormonal cues. In particular, there are a limited number of serine/threonine kinases that directly phosphorylate different subsets of these transcriptional regulators, thus coordinating their activity to achieve specific metabolic adaptations following activation of signaling pathway. Three kinases are particular notable: AKT, the central kinase activated by insulin, plays key roles in glucose and lipid homeostasis (Manning and Cantley, 2007); AMPK, activated under conditions of low intracellular ATP following metabolic stress or nutrient deprivation, as well as in reaction to adiponectin and other metabolic cytokines (Cantó and Auwerx, 2010; Hardie et al., 2012; Mihaylova and Shaw, 2011); and the p38 family of MAPKs, which are activated by oxidative stress and inflammatory cytokines (Evans et al., 2002). As one could devote an extensive review to any one of these regulatory modules, we will only touch upon the mechanisms employed in the control of transcriptional regulators.

Subcellular Compartmentalization and Nuclear Translocation

Control of coregulator subcellular localization has been revealed as a major regulatory mechanism utilized to mediate metabolic outcomes. Here, we discuss two examples sharing a common regulatory mechanism: the class IIa HDACs and the CRTCs (Figure 4). Several studies have shown that class IIa HDACs are regulated downstream of the CaMK, PKD, and AMPK kinase families (Berdeaux et al., 2007; Kim et al., 2008; McGee et al., 2008; McKinsey et al., 2000b; Mihaylova et al., 2011; Passier et al., 2000; Vega et al., 2004; Walkinshaw et al., 2013). Upon phosphorylation, the class IIa HDACs bind to 14-3-3 scaffold proteins and are sequestered into the cytoplasm, where they

are largely inactive. However, when dephosphorylated, they shuttle to the nucleus, where they can play their regulatory role in transcription (Grozinger and Schreiber, 2000; Kao et al., 2001; McKinsey et al., 2000a; Wang et al., 2000). Indeed, several studies have highlighted how the regulation of class IIa HDACs through this mechanism contributes to control of physiology. Phosphorylation of the class IIa HDACs by AMPK in myotubes may be an upstream mechanism regulating HDAC-mediated MEF2 control of GLUT4 expression and glucose uptake in muscle (McGee et al., 2008). Furthermore, fasting or treatment with the fasting hormone glucagon leads to rapid dephosphorylation of hepatic class IIa HDACs, resulting in their nuclear accumulation (Mihaylova et al., 2011). Conversely, activation of AMPK induced direct phosphorylation of class IIa HDACs and their exclusion from the nucleus, ultimately suppressing FOXO-dependent gluconeogenesis and glycogen storage. A study in *Drosophila* found that insulin was able to induce the phosphorylation and corresponding nuclear exclusion of class IIa HDACs by activating the AMPK-related family member, salt-inducible kinase 3 (SIK3) (Wang et al., 2011a). Depletion of dHDAC4, a class IIa HDAC, reduced dFOXO-dependent control of fat-body lipase expression initiating from dSIK3 deletion, suggesting an evolutionarily conserved role for the class IIa HDACs as mediators of metabolic hormonal signals downstream of AMPK-related kinases.

As with the class IIa HDACs, phosphorylation of hepatic CRTC2 by SIKs and AMPK results in cytoplasmic sequestration and association with 14-3-3 scaffold proteins (Koo et al., 2005; Uebi et al., 2010) (Figure 4). In fasted conditions, attenuation of AMPK and SIK1 activity results in dephosphorylation of CRTC2 at S171 and S307 (Koo et al., 2005; Uebi et al., 2010). Unphosphorylated hepatic CRTC2 is then free to translocate to the nucleus, where it coactivates CREB to promote gluconeogenesis by inducing gluconeogenic genes, including *Pepck1*, *G6pc*, and *Ppargc1* (Herzig et al., 2001; Koo et al., 2005; Saberi et al., 2009). The CRTCs hence participate in a finely tuned system in which phosphorylation states determine cellular shuttling and protein activity in order to translate nutrient availability signals into appropriately timed CREB-mediated glucose handling. Interestingly, a mechanism to coordinate this phosphorylation to the entrainment by the circadian clock was recently uncovered when SIK1 was identified as a CREB-induced mRNA in the light-entraining center of the brain, the suprachiasmatic nuclei (Jagannath et al., 2013). The highly CREB-dependent nature of the SIK1 promoter also provides a negative feedback mechanism to enforce the inhibition of CRTC-dependent gene expression (via SIK1 phosphorylation of CRTCs) as well as a mechanism for CREB to crosstalk with other transcriptional programs via SIK1 phosphorylation and inhibition of class IIa HDACs (Berdeaux et al., 2007).

Metabolites

An emerging theme is that metabolite availability can function as an upstream signal to determine coregulator activity. For example, the availability of acetyl coenzyme A (acetyl-CoA), which acts as an acetyl donor for the acetyltransferases CBP/p300, KAT2A, or NCoAs, may regulate the ability of these coregulators to acetylate their targets. There is, in fact, evidence of biological fluctuations in intracellular levels of acetyl-CoA, supporting the notion that this metabolite may function as a signal of metabolic status whose levels could contain important biological information useful for directing coregulator activity into relevant metabolic responses (Kaelin and McKnight, 2013). However, most of the causal data are derived from budding yeast, so an open question in the field is whether acetyl-CoA levels are sufficiently dynamic in mammalian cells to allow acetyl-CoA to act as a rate-limiting factor in some acetylation reactions. In budding yeast, it is clear that acetyl-CoA levels are dynamically regulated and, in turn, dictate histone acetylation and gene expression (Cai et al., 2011). In yeast, acetyl-CoA is produced by two acetyl-CoA synthetases (Acs1p and Acs2p). While Acs1p is localized within the mitochondria, Acs2p is a cytoplasmic and nuclear protein. Acs2p is essential for histone acetylation by HATs (Friis et al., 2009; Takahashi et al., 2006). Indeed, high levels of nutrients drive the production of acetyl-CoA through the activation of Acs2p, leading to histone acetylation via the stimulation of Gcn5p (Friis et al., 2009; van den Berg et al., 1996). Whereas two acetyl-CoA synthases exist in mammals, AceCS1 and AceCS2, their impact on nuclear acetyl-CoA production is negligible. Mammals possess another enzyme, ATP citrate lyase (ACLY), which is critical for cytoplasmic and nuclear production of acetyl-CoA (Wellen et al., 2009). Acetyl-CoA produced by ACLY synchronizes information about the cellular energy balance with histone acetylation through KAT2A (Wellen et al., 2009). The regulation of KAT2A-mediated histone acetylation by acetyl-CoA/ACLY suggests that a similar mechanism may acetylate nonhistone proteins, such as PGC-1α, in an energy-dependent manner. Further studies are therefore warranted to explore the coupling between metabolism and protein acetylation.

Not only acetyl-CoA levels, but also other metabolites, control coregulator activity. We briefly discuss the role of NAD^+ and hexosamine intermediates in the section below on integrated signaling. For more in-depth coverage of the role of these metabolites, we refer the readers to other recent reviews (Houtkooper et al., 2010; Oosterveer and Schoonjans, 2014; Ruan et al., 2013).

When solving the structure of HDAC3 in complex with the SMRT deacetylase activating domain (DAD), the metabolite inositol-(1,4,5,6)-tetraphosphate (Ins[1,4,5,6]P_4) was discovered as a key and essential component of this complex (Watson et al., 2012). Together with inositol polyphosphate multikinase (IPMK), the phosphatase and tensin homolog (PTEN) leads to the formation of Ins(1,4,5,6)P_4, which acts as an adhesive molecule for the SMRT/HDAC3 complex, enhancing the repressive activity of these corepressors (Watson et al., 2012). This observation has been expanded by demonstrating that Ins(1,4,5,6)P_4 enhances the activity of the HDAC3/SMRT complex as well as the HDAC1/MTA1 complex (Millard et al., 2013). Furthermore, the concentrations of Ins(1,4,5,6)P_4 necessary to promote HDAC complex formation are within the range found in cells (Millard et al., 2013). Whether the levels of Ins(1,4,5,6)P_4 fluctuate under physiological circumstances remains to be established; however, there is evidence that such modulations can occur during the cell cycle (Mattingly et al., 1991). Together, these studies illustrate that a metabolite can function as a necessary structural component of coregulator complexes, thus providing a different mechanism through which metabolites can translate metabolic regulatory signals into functional cellular responses via coregulator proteins.

The fact that cofactor activity can be controlled by signaling pathways and metabolites also raises the possibility that these features can be exploited within a therapeutic context. Certainly, novel chemical entities or natural compounds can be identified to mimic the impact of metabolites and signaling factors on cofactor function. The fact that cofactors have pleiotropic effects and can target multiple pathways poses a challenge for the development of coregulator drugs, however. Furthermore, not all coregulators may be equal when it comes to drug development. Coregulators with an enzymatic activity, or an activity subject to control by signaling pathways or small molecules, may be easier to target. On the other hand, the complexity of the regulatory circuit controlled by these coregulators also provides an opportunity, as drugs can be developed that specifically target some, but not all, pathways that are controlled by cofactors. As a case in point, recent studies show that HDACs can have an effect on transcriptional regulation that is independent of their enzymatic activity as deacetylases (Sun et al., 2013). HDAC inhibitors, which are already undergoing advanced clinical testing within the cancer field, may therefore have a different phenotypic footprint than molecules that disrupt the interaction between HDACs and NCoR1/SMRT by altering the quantity (or quality) of Ins(1,4,5,6)P_4 (Sun et al., 2013; Watson et al., 2012).

Coregulators as Energy Sensor Effectors: Integrated Signaling

From the information above, it becomes clear that a yin-yang between corepressors and coactivators fine-tunes transcriptional networks that control many aspects of metabolism. We will illustrate this through two exemplars. On the one hand, we will discuss the interaction of corepressors (such as NCoR1 and SIRT1) and coactivators (like PGC-1α, the NCoAs, and KAT2A/KAT2B) to control muscle energy homeostasis; on the other hand, we will discuss the interconnectivity of the CRTCs and class IIa HDACs to control hepatic gluconeogenesis.

How the activity of various signaling pathways and coregulators equilibrate energy harvesting pathways in the mitochondria with cellular energy requirements illustrates this principle well. During situations when energy supplies are limiting, such as during caloric restriction (Cantó et al., 2010; Chen et al., 2008) or upon fasting and exercise (Cantó et al., 2009, 2010), the cellular ATP/AMP ratio will decrease and activate AMPK. This AMPK activation is concomitant with a rise in cellular NAD^+ levels, which will activate SIRT1. The increase in the activity of AMPK and SIRT1 will then activate PGC-1α (Cantó et al., 2009; Jäger et al., 2007; Rodgers et al., 2005). Reduced energy levels will also attenuate mTORC1 and insulin signaling, which will lead to the inhibition of the repressive activity of NCoR1, which will no longer oppose the transcriptional coactivation by PGC-1α (Sengupta et al., 2010; Yamamoto et al., 2011). Whereas the changes discussed above are occurring in a cell-autonomous context, reduction of energy will, on an organismal level, translate into increased glucagon signaling. Glucagon will activate cAMP/PKA signaling and increase SIRT1 phosphorylation (Gerhart-Hines et al., 2011) and SIRT1 gene expression (Noriega et al., 2011), two effects that will reinforce the activity of these cofactor pathways. Together, this shift in cofactor balance favors transcriptional programs that will promote oxidative mitochondrial metabolism, thereby enhancing the use of stored energy during caloric restriction, fasting, or exercise (Figure 3). Beyond the strict physiological context, NAD^+ levels can be increased pharmacologically by administration of either NAD^+ precursors, such as nicotinamide riboside, or inhibitors of NAD^+-consuming enzymes, such as the PARP inhibitors (for review see Houtkooper and Auwerx, 2012; Houtkooper et al., 2010).

These processes are reversed by situations of excessive energy intake, when the activity of AMPK and SIRT1 is attenuated due to high intracellular ATP and low NAD^+ levels. Calorie-dense diets, furthermore, induce the expression of the acetyltransferases, NCoA3 and KAT2A, while concomitantly reducing SIRT1 levels (Coste et al., 2008; Noriega et al., 2011). One result is the acetylation and inhibition of PGC-1α, which in turn attenuates mitochondrial activity. Furthermore, NCoR1 is activated by insulin and mTORC1 signaling, accentuating the decreased transcription of genes governing mitochondrial activity, ultimately enabling the storage of excess calories in times of excessive caloric intake.

The transcriptional control of gluconeogenesis in the liver by coregulators is another case in point to illustrate the complexity of coregulator signaling. Ten years ago, it was appreciated that CREB and FOXO transcription factors are critical mediators of the promoters of the core gluconeogenic enzymes *Pepck* and *G6pc*, with CREB mediating positive effects from glucagon and FOXO being suppressed by insulin-dependent signaling. Onto that simple framework has now emerged the realization that the CRTC family of CREB coactivators is shuttled into the nucleus in response to glucagon and shuttled out in response to insulin. Perfectly parallel to that are recent findings that the class IIa family of HDACs promotes FOXO activation at these gluconeogenic targets and is also shuttled into the nucleus following glucagon and shuttled out following insulin (Figure 4). It is striking that the functional activity of both the class IIa HDACs and the CRTCs is regulated downstream of glucagon signaling in an identical manner through a phosphorylation-dependent mechanism involving 14-3-3 binding and cytoplasmic sequestration. In fact, of all of the transcription factors and coregulators known as AMPK substrates, the class IIa HDACs and the CRTCs are the only targets identified to date that function in this manner.

In addition to the hormonal control by phosphorylation of CRTCs, acetylation and ubiquitylation were shown to regulate the temporal component of hepatic CRTC2 coregulatory function (Liu et al., 2008). CRTC2 protein stability is enhanced by CBP/p300-mediated acetylation at K628 in response to glucagon, promoting the induction of gluconeogenesis (Liu et al., 2008; Ravnskjaer et al., 2007). Prolonged fasting, however, induces SIRT1 via a PKA-dependent mechanism (Gerhart-Hines et al., 2011; Noriega et al., 2011) and ultimately results in the deacetylation of CRTC2. Ubiquitylation and proteasome-dependent degradation then follow, decreasing CRTC2 activity in order to dampen the gluconeogenic program. Finally, CRTC2 can also be O-glycosylated at S171 (Dentin et al., 2008), one of the sites whose phosphorylation status determines CRTC2 cellular localization. Indeed, CRTC2 O-glycosylation blocked phosphorylation at S171, resulting in its nuclear localization and enhanced CREB activity. CRTC2 O-glycosylation was also linked to elevated circulating glucose. Considering that elevated glucose levels result in increased flux through the hexosamine

biosynthetic pathway and, thereby, induce protein O-glycosylation, the O-glycosylation of CRTC2 provides an elegant example of metabolic cues utilizing posttranslational modifications (PTMs) to direct the activity of coregulatory proteins (Oosterveer and Schoonjans, 2014).

The emergent complexity of these regulatory circuits hence illustrates how multifaceted transcriptional coregulator networks convert signals not only associated with cellular energy status, but also with organismal endocrine balance, into coherent and coordinated changes of transcriptional activity, thereby modulating whole-body metabolic homeostasis.

Future Perspectives

Coregulators are now recognized as central, evolutionarily conserved players in metabolism. On top of regulation by transcription factors, coregulators provide a second, more subtle, global level of transcriptional metabolic adaptation. Although an impressive body of work already implicates the PGC-1α and sirtuin coregulators as central to many metabolic regulatory networks, the work reviewed herein highlights the involvement of other coregulators in metabolic homeostasis. Whereas most of these studies addressed the role of coregulators in energy storage and expenditure in muscle and fat and in hepatic glucose and lipid metabolism, our knowledge on how they contribute to the control of metabolic homeostasis in the CNS, pancreas, and intestine is still incomplete. One emerging theme in many tissues is that the final transcriptional output is determined by a context-specific and dynamic balance between the opposing actions of coactivators and corepressors.

It has also become clear that several coregulators are not only transcriptional effectors, but also exquisitely sensitive metabolic sensors that capture discrete changes in nutrient and metabolite availability and transform them into transcriptional responses, much like ligand-activated transcription factors. A few examples are as follows: (1) coregulator regulation through acetylation is linked to the availability of metabolic intermediates such as acetyl-CoA, which acts as an acetyl donor for acetyltransferases such as CBP/p300, KAT2A, and NCoAs (Jeninga et al., 2010; Wellen et al., 2009); (2) cellular NAD^+ levels, which are tightly regulated by the cellular energy balance, are likewise indispensable for the deacetylase activity of the sirtuins (Houtkooper et al., 2010); (3) the activity of class I HDACs is inhibited by high concentrations of hydroxyl butyrate, one of the ketone bodies (Shimazu et al., 2013); and (4) the control of hexosamine/O-glycosylation by elevated glucose levels (Dentin et al., 2008) (reviewed by Oosterveer and Schoonjans, 2014).

Research that combines molecular, cellular, and pharmacological studies with gain- and loss-of-function genetic approaches in different model organisms should improve our knowledge of how coregulators orchestrate metabolic networks. Human genetic studies to link coregulators with metabolic phenotypes and diseases are also urgently required if we want to validate coregulators as therapeutic targets, as has already been done in the cancer field (Gryder et al., 2012). Another research goal should be to elucidate the contribution of the different transcription factors to the physiological actions of coregulators. Defining the signaling pathways—second messengers, hormones, metabolites—that modulate the interaction between transcription factors and coregulators is in that context highly relevant. This last line of investigation is of particular importance with respect to the identification and development of novel compounds that alter (increase or decrease) the affinity between coregulators and transcription factors and direct the activity of cofactors toward specific pathways or cells/tissues (Feige and Auwerx, 2007; Rosenfeld et al., 2006).

If all of these goals are met, therapeutic targeting of transcriptional nodes under coregulator control may become a reality in the not too distant future. SIRT1 and PGC-1α are already prime candidate targets. Several pathways interfering with SIRT1 activity, ranging from synthetic small molecule agonists to pharmacological strategies that increase the levels of its natural cosubstrate, NAD^+, are already in late-stage clinical testing and are reviewed elsewhere (Cantó and Auwerx, 2012; Houtkooper and Auwerx, 2012). Also for PGC-1α, pharmacological interventions that target its expression or activity or favor its selective recruitment to specific transcription factors have been described (see Andreux et al., 2013 for review). Dissections of the action of HDAC inhibitors in metabolic tissues suggest that potential therapeutic avenues may also exist for these coregulator targets (Fajas et al., 2002a; Galmozzi et al., 2013), and the recent development of new class II-specific HDAC inhibitors provides an opportunity to examine their potential use in specific metabolic disorders (Lobera et al., 2013). Recent high-throughput screening efforts have also identified small molecule inhibitors that directly bind NCoA1 and NCoA3 (Wang et al., 2011b). We are furthermore hopeful that other coregulators will join the list of potential metabolic targets in the near future.

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