FORUM REVIEW ARTICLE

Transcriptional Repression of Mitochondrial Function in Aging: A Novel Role for the Silencing Mediator of Retinoid and Thyroid Hormone Receptors Co-Repressor

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Abstract

Significance: Mitochondrial function plays an important role in metabolic homeostasis and has been implicated in aging. Although there is still ongoing debate regarding whether mitochondrion-derived oxidative stress is causative to the aging process, interventions that increase oxidative metabolism and antioxidant pathways in animal models protect against age-related deterioration, such as metabolic diseases and neurodegenerative disorders. **Recent Advances:** One of the well-characterized transcriptional networks known to improve mitochondrial activity is mediated by transcriptional co-activator peroxisome proliferator-activated receptor gamma co-activator 1 α (PGC-1 α), which is activated by AMP-activated protein kinase (AMPK) and sirtuin 1 (SIRT1), two of the major energy sensing molecules that are responsible for the longevity effect of caloric restriction in certain model systems. PGC-1 α co-activates several nuclear receptors, notably members of the peroxisome proliferator-activated receptor (PPAR) family, which are key regulators of mitochondrial oxidative metabolism. **Critical Issues:** Although the AMPK/SIRT1-PGC-1 α -PPAR axis plays a prominent role in activating mitochondrial functions, their activities are down-regulated in older animals, suggesting the involvement of dominant negative regulatory mechanisms in the process of aging. **Future Directions:** In this review, we will discuss the role of a transcriptional co-repressor, silencing mediator of retinoid and thyroid hormone receptors (SMRT), whose activity and expression are increased with age, as a negative regulator of mitochondrial function that promotes aging and age-related metabolic diseases. *Antioxid. Redox Signal.* 19, 299–309.

Introduction

THE MECHANISM THROUGH WHICH we age and develop age-related pathologies remains largely unclear. Mitochondrion, known as the powerhouse of the cell, is responsible for the majority of energy supply in the form of ATP from oxidative phosphorylation. In the mitochondria, NADH and FADH₂ derived from the tricarboxylic acid (TCA) cycle or fatty acid β oxidation are channeled into the electron transport chain (ETC) to generate a proton gradient for the synthesis of ATP from ATP synthase (10, 54). However, oxidative phosphorylation also generates roughly 90% of the reactive oxygen species (ROS) under basal conditions (8). These highly reactive species are thought to exert deleterious oxidizing effects on lipids, proteins, and DNA and ultimately damage the integrity and function of mitochondria. In addition, due to the lack of histone and the close proximity to the source of ROS production, mitochondrial DNA is more susceptible to ROS-induced damage. The free radical theory (28) suggests that the

decline in mitochondrial function as a result of ROS-mediated damage underlies the pathogenesis of aging and age-related diseases such as neurodegeneration, cancer, and metabolic syndrome (8, 11). However, contradicting data exist. For example, in spite of targeted mitochondrial expression of catalase, which converts hydrogen peroxide to water and oxygen, reduces oxidative damage, increases lifespan, and prevents age-associated reductions in muscle mitochondrial function (40), the over-expression of Mn superoxide dismutase has no effects on life span (33). Therefore, a mechanism that involves coordinated regulation of oxidative metabolism and antioxidant scavenger pathways is likely to set the level of oxidative stress which determines the overall mitochondrial function and the outcome of age related changes. Nevertheless, a comparison of transcriptional profiles from worms, flies, mice, and humans has indicated the down-regulation of mitochondria ETC genes as the only common signature associated with aging (83). Conversely, the beneficial effects of caloric restriction (CR) are associated with enhanced ETC

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gene expression and the maintenance of mitochondrial activities (3). CR extends lifespan from yeast to non-human primates (49) and offers protection against diseases such as cancer and the metabolic syndrome. Oxidative stress has also been directly linked to insulin resistance (11, 29). As such, understanding regulatory programs that control mitochondrial functions is vital for designing therapeutic strategies against these diseases.

Nutrient Sensing Pathways and Metabolic Homeostasis

In mammalian cells, the ATP/AMP, NAD⁺/NADH, and acetyl-CoA pools are three major forms of energy indicators (Fig. 1). Fluctuations in these small molecules are detected by a number of highly conserved energy sensors, which, in turn, dictate a plethora of signaling and transcriptional events that are necessary to maintain the balance between energy supply and demand, partly through the regulation of mitochondrial oxidative phosphorylation. The AMP-activated protein kinase (AMPK) and NAD⁺-dependent deacetylase sirtuins (24), such as sirtuin 1 (SIRT1), have emerged as key energy sensors that elicit adaptive responses to energy deficit in metabolic tissues under conditions such as CR, fasting, and exercise (Fig. 1). A low ATP/AMP ratio triggers the activation of AMPK. A number of cellular targets have been identified that mediate the immediate effects of AMPK activation. In muscles, AMPK regulates trafficking of the glucose transporter GLUT4 (67). In adipocytes, AMPK phosphorylates

hormone-sensitive lipase (77) and adipocyte-triglyceride lipase (1) for the liberation of free fatty acids as energy substrates. In liver, both acetyl-CoA carboxylase 1 and 2 (ACC1 and ACC2), key enzymes involved in fatty acid synthesis, are targets of AMPK (15). The phosphorylation of ACC1/2 inactivates their enzymatic activity shifting the liver from biosynthetic pathways, which consume energy, to fatty acid oxidation. AMPK also regulates the mammalian target of rapamycin complex 1 (mTORC1) *via* direct phosphorylation at the regulatory subunit Raptor (27) or at the upstream regulatory protein tuberous sclerosis complex protein 2 (31). In either case, AMPK activation turns off the mTORC1 signaling pathway that is involved in protein and lipid synthesis. Recently, AMPK has also been shown to directly phosphorylate SREBP-1, a major regulatory node of lipid synthesis (44). Under energy deficiency, the NAD⁺/NADH ratio also increases (14, 16). In the nucleus, SIRT1 is activated by NAD⁺ and deacetylates a number of transcription factors and co-factors. In the liver, SIRT1 increases fatty acid oxidation by enhancing peroxisome proliferator-activated receptor (PPAR) α activity (61), partly through peroxisome proliferator-activated receptor gamma co-activator 1 α (PGC-1 α) (discussed next). SIRT1 also induces gluconeogenesis through the sequential activation of CRTC2 and FOXO1 (48). Both AMPK and SIRT1 promote metabolic fitness and longevity in animal models (14).

Perhaps the best-documented role of AMPK and SIRT1 is the activation of a transcriptional program that coordinately promotes fatty acid oxidation, mitochondrial biogenesis, oxidative phosphorylation, adaptive thermogenesis, and antioxidant defense through the transcriptional co-activator PGC-1 α (Fig. 2). Nevertheless, recent evidence suggests a potential dissociation of SIRT1 and PGC-1 α in the control of mitochondrial biogenesis under certain conditions (26, 35, 79). The action of AMPK on PGC-1 α appears to be both transcriptional and post-transcriptional, although the former mechanism is not clear. AMPK directly phosphorylates PGC-1 α to enhance its stability (32). AMPK activation also increases the NAD⁺/NADH ratio (14), leading to SIRT1 activation and PGC-1 α deacetylation. Deacetylation stabilizes PGC-1 α protein and allows the recruitment of co-activator complex components for PGC-1 α -mediated transcriptional activation (65). Consequentially, activation of the AMPK/SIRT1-PGC-1 α axis shunts acetyl-CoA from glycolysis and β -oxidation into the TCA cycle and, subsequently, oxidative phosphorylation for ATP generation. During energy excess, mitochondrial acetyl-CoA is shuttled out to the cytoplasm as citrate. Citrate can then be converted back to acetyl-CoA as building blocks for fatty acid synthesis by ATP-citrate lyase (ACL). A subset of ACL also resides in the nucleus (78). It is speculated that this enzyme is responsible for the nuclear pool of acetyl-CoA, which can be used to acetylate histones and nuclear proteins. GCN5 and SRC-3 are two acetyltransferases that sense acetyl-CoA levels and acetylates proteins or histones (19, 41). They form a complex with PGC-1 α , and the balance between their acetylation of PGC-1 α and SIRT1-mediated deacetylation determines PGC-1 α activity.

Transcriptional Regulation of Mitochondrial Function

PGC-1 α co-activates a number of transcription factors that modulate mitochondrial functions (Fig. 2). Its targets include

FIG. 1. The adaptive responses to energy deficit. AMP/ATP, NAD⁺/NADH, and acetyl-CoA are the three main forms of energy indicators in mammalian cells. On fasting, caloric restriction or exercise, the AMP/ATP, and NAD⁺/NADH ratio increase, while acetyl-CoA level decreases. These changes activate energy sensing pathways that engage several adaptive responses in major metabolic tissues. The arrow sign, ↑ or ↓, indicates an increase or decrease, respectively, in a certain metabolic process. BAT, brown adipose tissue; WAT, white adipose tissue.

FIG. 2. The energy sensing pathways and mitochondrial functions. Energy deprivation elevates the AMP/ATP and NAD^+/NADH ratios and down-regulates the nuclear acetyl-CoA level. These changes activate AMPK and NAD^+ -dependent deacetylase SIRT1 and prevents GCN5/SRC-3 mediated acetylation. The combined effect of AMPK and SIRT1 pathways leads to the phosphorylation and deacetylation of PGC-1 α , which increase its activity. PGC-1 α co-activates a number of transcription factors to turn on mitochondria biogenesis, ETC, antioxidant defense, uncoupling, fatty acid oxidation, and heme synthesis. Ac, acetylation; AMPK, AMP-activated kinase; ETC, electron transport chain; P, phosphorylation; PGC-1 α , peroxisome proliferator-activated receptor gamma co-activator 1 α ; SIRT1, sirtuin 1; TRs, thyroid hormone receptors.

nuclear respiratory factor 1 and 2 (NRF1/2) (80) and many nuclear receptors, such as thyroid hormone receptors (TRs) (60), the estrogen-related receptor family (ERRs) (51), and PPARs (60, 75). Activation of NRF1/2 induces the heme synthesis pathway that is required for the normal function of mitochondrial ETC complexes and enhances the expression of Tfam, which leads to mitochondrial DNA synthesis (18). PGC-1 α interacts with nuclear receptors through its three LXXLL receptor interaction motifs. The ability to integrate different ligand signals of nuclear receptors allows PGC-1 α to induce mitochondrial function under a variety of physiological conditions. For example, cold exposure induces the release of thyroid hormone, which along with the β -adrenergic signaling pathway, turns on the adaptive thermogenesis program *via* PGC-1 α [reviewed in (45)]. On fasting or cold challenge, lipolysis from adipose tissue supplies fatty acids as energy substrates. The PPAR family of nuclear receptors senses the increased flux of fatty acids and activates a transcriptional program that regulates lipid metabolism in partnership with PGC-1 α (Fig. 3). Therefore, the integration of

PGC-1 α and PPARs allows mitochondria to adapt to increased lipid metabolism. In the liver, the activation of PPAR α promotes fatty acid oxidation. Mice with PPAR α deletion have little metabolic phenotype. However, fasting causes severe fatty liver and hypoglycemia due to the inability to use fatty acids as an energy source (36). PPAR α also regulates hepatic ketogenesis and white adipose tissue (WAT) lipolysis *via* the fibroblast growth factor 21 (7, 30). In WAT, PPAR γ is the master regulator of adipogenesis (66) and governs the production of adipokines that have diverse roles in modulating whole body metabolic homeostasis. Activation of PPAR γ allows the partitioning of lipids into WAT to reduce lipotoxicity. The third member of the PPAR family, PPAR β/δ exhibits a ubiquitous expression pattern and is abundantly expressed in tissues specialized in oxidative phosphorylation such as the brown adipose tissue (BAT) and type I fiber muscles (22). Using an active form of PPAR δ where the N-terminus is fused with the VP16 activation domain, PPAR δ was shown to activate fatty acid oxidation genes such as carnitine palmitoyltransferase 1, acyl-CoA oxidase, and

FIG. 3. Diverse functions of the PPAR nuclear receptor family. PPAR α , PPAR β/δ , and PPAR γ are nuclear receptors that control metabolic gene expression in response to dietary fats. PPARs form heterodimers with the obligate partner RXR and recognize the DR-1 type (direct repeats of AGGTCA with one intervening nucleotide) response element in target gene promoters. On binding to ligands, such as FAs and PLs, a conformational change in the ligand binding domain of the receptor allows the recruitment of co-activator complexes to turn on the transcriptional regulation of various aspects of lipid metabolism. FA, fatty acid; PL, phospholipids; PPAR, peroxisome proliferator-activated receptor; RXR, retinoid X receptor.

long-chain acyl-CoA dehydrogenase in BAT. It also induces thermogenesis and uncoupling gene expression (UCP1 and UCP3). In WAT, constitutive PPAR δ activation leads to a BAT-like phenotype (75); whereas in the muscle, PPAR δ enhances muscle fiber-type switch to type I fibers, promotes fatty acid catabolism, and induces the genes involved in oxidative phosphorylation (76). Consistently, PPAR $\delta^{-/-}$ mice demonstrated several reciprocal phenotypes (39).

The pivotal role of mitochondria in aging and age-related pathologies makes the pathways just described desirable targets for intervention. The functions of AMPK, SIRT1, and PGC-1 α in modulating these disease conditions have been extensively discussed, and we, therefore, refer to several excellent reviews (13, 45, 50, 68). Phenotypes of PPAR δ activation overlap with PGC-1 α transgenic models (46), suggesting that it may be a major downstream effector of PGC-1 α in metabolic tissues. Interestingly, the expression (69) or activity (57) of PGC-1 α was shown to be regulated by PPAR δ . However, PPAR δ has not been directly linked to lifespan regulation. Due to its role in regulating fatty acid oxidation and oxidative metabolism in BAT and muscle, targeting PPAR δ represents a potential therapeutic strategy to intervene age-related metabolic disorder. In muscle and fat-specific PPAR δ transgenic models, mice were protected from diet-induced

insulin resistance (75, 76). Similarly, administration of the synthetic ligand GW501516 improved metabolic function in high-fat-diet-induced or genetic obese mice (ob/ob or db/db) (39, 73). GW501516 treatment can also act as an exercise mimetic in the muscle (53). In addition to the pathways just described, other transcription factors and co-factors, such as FOXO1 (17) and PGC-1 β (71), have also been implicated in the integration of hormonal and nutrient signals with mitochondrial functions.

Role of Co-Repressor Silencing Mediator of Retinoid and Thyroid Hormone Receptors in Mitochondrial Function and Aging

The AMPK/SIRT1-PGC-1 α -PPAR axis plays a prominent role in promoting mitochondrial functions; however, this axis is down-regulated in older animals (20, 64), suggesting the involvement of dominant negative regulatory mechanisms in the process of aging. Of note, the transcriptional activities of nuclear receptors are negatively regulated by two major co-repressors: silencing mediator of retinoid and thyroid hormone receptors (SMRT) and nuclear receptor co-repressor (NCoR). They interact with nuclear receptors through their receptor interaction domains (RIDs) that contain a crucial

IXXI/VI motif termed CoRNR box (59). In the absence of agonistic ligands (for non-steroidal receptors) or in the presence of antagonists (for steroidal receptors), they dock onto nuclear receptors *via* their RIDs and recruit a co-repressor complex consisting of histone deacetylases (HDACs) to turn off target gene expression through chromatin remodeling (34). Deletion of either NCoR or SMRT is incompatible with life due to their involvement in a wide range of transcriptional programs, including development and differentiation. However, the embryonic lethality appears to be mediated by transcription factors other than nuclear receptors, as both the knockin mutations of the deacetylase activation domain of NCoR (NCoR^{DADm}), which is specifically required for nuclear receptor-mediated repression, and RID mutations of SMRT are normal during development and live to adulthood (2, 55).

Interestingly, NCoR^{DADm} mice have increased hepatic fatty acid oxidation and metabolic capacity, conferring protection against high-fat-diet-induced insulin resistance. These phenotypes are thought to be mediated *via* the enhanced activities of selected nuclear receptors, such as PPAR α in the liver and PPAR δ and ERRs in the muscle (81). Mice with adipose tissue-specific deletion of NCoR have elevated PPAR γ activity and are protected against diet-induced metabolic disorders (42). The mTOR signaling pathway has been shown to promote nuclear translocation of NCoR in the liver to repress PPAR α -mediated ketone body production during feeding (70). This finding indicates that the activities of co-repressors are also subjective to regulation by nutrient sensing mechanisms.

Compared with NCoR, relatively less is known about the role of SMRT in metabolic regulation by nuclear receptor signaling. Whole body glucose and insulin tolerance of heterozygous SMRT knockout (SMRT^{+/-}) mice are virtually identical to their wild-type counterparts when placed on a high fat diet (72). The lack of apparent whole body metabolic phenotype suggests complex downstream programs mediated by both nuclear receptors and other transcription factors. Indeed, mice with knockin mutations of the two RIDs that abolish all nuclear receptor interactions demonstrated strong endocrine phenotypes: They have reduced survival rate due to altered TR actions that are required to generate type I pneumocytes and maintain normal lung functions (58). Those that survive through adulthood have greatly enhanced adiposity, similar to that in adipocyte-specific NCoR knockout mice (42).

The two major RIDs (RID1 and RID2) of SMRT show distinct receptor interaction profiles. Retinoic acid receptors (RARs) interact preferentially with RID1; whereas most lipid-sensing nuclear receptors, including PPARs and retinoid X receptors, interact with RID2 (47, 59) (Fig. 4). RARs are involved in vertebrate development and differentiation early in life (25). Consistent with this role, their expression declines on aging (56). On the contrary, the relative expression and protein levels of SMRT increase in older mice (63). These changes may lead to altered repression dynamics of SMRT, in which more SMRT proteins are available for RID2-mediated interaction. In support of this notion, the SMRT RID construct containing the mutated RID1 with intact RID2 (SMRT^{mRID1})

FIG. 4. Domain structure of SMRT and the mode of action by SMRT RID1 mutant. The nuclear receptor co-repressor SMRT has three RDs that recruit HDACs, notably HDAC3, to repress transcription through chromatin remodeling. The two nuclear RIDs near the c-terminus contain a crucial IXXII motif, termed CoRNR box, that mediates nuclear receptor binding. Each RID has its interaction preference, with the RID1 mainly interacting with RARs and RID2 binding to PPAR, RXR, and TRs. A SMRT knockin mouse model with mutations of the RID1 CoRNR box from ISEII to ASEAA has been generated, termed SMRT^{mRID1} mice, to examine RID-specific function. This mutant is expected to release the interaction between SMRT and RAR, which makes SMRT readily available to suppress the activity of RID2 interacting receptors, such as PPARs (63). HDAC, histone deacetylases; RAR, retinoic acid receptors; RD, repression domains; RID, receptor interaction domain; SMRT, silencing mediator of retinoid and thyroid hormone receptors.

exhibits a stronger interaction with PPARs compared with unmodified RID1/2 in mammalian two-hybrid assay (63). In addition, chromatin-Immuno-Precipitation demonstrated increased SMRT occupancy of PPAR δ binding sites on the MCAD gene promoter in BAT and liver from 6-month old mice, compared with 2-month-old animals (63). To explore the physiological outcome of this age-dependent shift of SMRT utilization by RID2 nuclear receptors, an SMRT RID1 mutant knockin animal model (SMRT^{mRID1} mice) was used by Reilly *et al.* (Fig. 4) (63). These animals have enhanced SMRT interaction with PPARs, mimicking the molecular events on aging. The metabolic fitness of these mice declined progressively with age. At 6 months, SMRT^{mRID1} mice were obese, had increased circulating lipid and glucose levels, and displayed systemic insulin resistance. Gene expression profiling revealed the down-regulation of several factors involved in fatty acid oxidation and oxidative phosphorylation in BAT, WAT, and muscle. PPAR δ has been shown to mediate such processes in these tissues. Indeed, there was an increased repression of PPAR δ signaling in SMRT^{mRID1} mice, suggesting the enhanced association between SMRT and PPAR δ as a plausible mechanism for age-dependent metabolic deterioration.

Interestingly, SMRT^{mRID1} mice died prematurely with signature aging phenotypes such as the development of cataracts, alopecia and gray hair, and diminished sensorimotor neuron function. As mentioned earlier, transcriptional coupling of oxidative phosphorylation with ROS scavenging pathways is key to maintaining mitochondrial function in normal physiology (8). Disruption of these pathways leads to not only metabolic syndrome but also aging phenotypes through excessive oxidative damage. A number of genes involved in oxidative phosphorylation (COX3, Nudfab, and SDHA) and antioxidant response (Catalase, Gstp1, GPx1, and

SOD1) had reduced expression in BAT, WAT, and muscle of SMRT^{mRID1} animals. As a consequence, the fatty acid oxidation rate was down-regulated, and mitochondria numbers were reduced in SMRT^{mRID1} tissues. Consistent with this, there was increased lipid content in BAT and liver, and whole body metabolic rate and core body temperature dropped significantly. The deterioration of mitochondrial functions could also explain the increased susceptibility to oxidative insults from H₂O₂ or paraquat and premature senescence in SMRT^{mRID1} mouse embryonic fibroblasts (MEFs). Treatment with the antioxidant N-acetylcysteine (NAC) improved the survival rate of SMRT^{mRID1} MEFs on oxidative damage. Although the long-term effects of antioxidant treatment in alleviating the premature aging phenotype of SMRT^{mRID1} mice have yet to be determined, the short-term treatment of NAC significantly improved the metabolic fitness of these animals. These data reflect a central role of ROS in mediating both the metabolic and aging phenotypes of SMRT^{mRID1} animals. The seemingly specific enhancement of SMRT-mediated repression on PPAR δ targets on aging represents a potential therapeutic value of PPAR δ agonists in reverting age-dependent pathologies. In fact, the treatment of SMRT^{mRID1} MEFs with a PPAR δ synthetic ligand GW501516 up-regulated antioxidant gene expression and rescued impaired cell survival on oxidative insults. Using SMRT^{mRID1} mice, the previously under-appreciated role of co-repressors in modulating nutrient sensing and the age-associated pathologies was unveiled (Fig. 5).

Conclusion and Future Studies

The identification of SMRT as a negative regulator of oxidative metabolism implicates an antagonistic action between SMRT and PGC-1 α , at least in PPAR-dependent

FIG. 5. Age-dependent repression of PPAR signaling via SMRT interaction. In young mice, the activation of PPARs in tissues high in oxidative phosphorylation such as BAT and muscle up-regulates fatty acid oxidation and antioxidant gene expression, leading to an enhanced mitochondrial activity. These coordinated effects prevent lipid and ROS accumulation. In older mice, an age-dependent increase in SMRT expression and repression of PPAR signaling reduces mitochondrial function. As a result, lipids and ROS accumulate, causing metabolic dysfunction and accelerated aging phenotypes. ROS, reactive oxygen species.

transcriptional controls. As such, the relative activity of SMRT versus PGC-1 α sets the level of cellular oxidative stress and damage. It should be noted that the relationship between lipid metabolism, ROS production, and mitochondrial dysfunction is complex. It has been shown that mitochondrial ROS production is dependent on membrane potential (8). In events of decreased mitochondria ETC activity, the ROS level should be reduced. Furthermore, the acute up-regulation of lipid synthesis genes has been shown to be protective against metabolic disorders (47). The contrasting evidence reiterates the importance of maintaining a balanced control of mitochondrial functions that meet metabolic demands. Along this line, a coordinated regulation of mitochondrial oxidative metabolism and antioxidant pathway is likely critical in promoting metabolic capacity without overt oxidative damage. In fact, in the SMRT^{mRID1} model, the metabolic defects appear to be mediated partly by the suppressive effect of SMRT on antioxidant gene expression. It is possible that the reduced mitochondrial activity observed in SMRT^{mRID1} mice is a sec-

ondary event and is independent of PGC-1 α signaling. This raises the possibility that pharmacological and nutritional interventions, which directly lift the repression by SMRT (or NCoR), may be sufficient to elevate mitochondrial functions. The mechanism underlying increased SMRT expression in aged animals is unclear. Since CR is known to activate the AMPK/SIRT1-PGC-1 α axis, it would be interesting to determine the impact of SMRT^{mRID1} mutation on CR-mediated metabolic improvement and lifespan extension. Therapeutically, it has yet to be determined whether the long-term treatment of PPAR δ ligands is able to alleviate the premature aging phenotypes in SMRT^{mRID1} mice and whether the PPAR δ ligand is able to extend the lifespan. In the liver, SMRT expression does not increase on aging, and SMRT^{mRID1} mutation has limited impact on the expression of hepatic genes involved in fatty acid oxidation and oxidative phosphorylation. Instead, NCoR expression is increased in the liver of older animals. This is in contrast with the tissues specialized in oxidative metabolism (BAT and muscle), where

FIG. 6. Reciprocal regulation of circadian rhythm and nutrient sensing pathways as novel regulatory mechanisms of mitochondrial function. The core circadian clock system consists of several feedback loops to ensure their self-sustained periodic gene expression and the diurnal expression of metabolic pathways in ordinance with the feeding and fasting states. These metabolic pathways modulate circulating concentrations of energy substrates (*e.g.*, glucose and fatty acids) as well as cellular levels of AMP/ATP and NAD⁺/NADH. The change in metabolic flux is then detected by several nutrient-sensing pathways, such as AMPK and SIRT1, and downstream transcription factors/co-factors, including PPARs, PGC-1 α , and SMRT/NCoR. In turn, the activation of these signaling pathways regulate circadian clock functions *via* transcriptional and post-transcriptional mechanisms. Using mouse genetic models, the coordinated regulation between the core circadian clock regulatory circuit and nutrient sensing pathways has been shown to play an important in maintaining mitochondrial function and metabolic homeostasis. In addition, this regulatory loop is disrupted in the process of aging. NCoR, nuclear receptor corepressor.

NCoR expression is minimally affected by age. Recently, the HDAC3-NCoR-Rev-erb α complex was shown to regulate circadian expression of lipogenic genes in the liver (2, 23), suggesting that NCoR may play a predominant role in liver pathologies associated with aging. The circadian rhythm machinery exists in virtually all cell types and integrates environmental cues to modulate processes such as behavior and metabolism (9) (Fig. 6). Interestingly, circadian rhythm is often disrupted in the elderly. The AMPK/SIRT1-PGC-1 α -PPARs nutrient sensing pathway has been shown to impose extensive controls over circadian clock machinery. SIRT1 (4) and PARP1 (5) deacetylates and acetylates the core clock transcription factor Bmal1, leading to the degradation or stabilization of Bmal1 protein, respectively. AMPK phosphorylates Cry1 that promotes its degradation in response to low glucose or a synthetic activator AICAR (38). PGC-1 α co-activates the RAR-related orphan receptor (ROR) family of orphan nuclear receptors to stimulate the expression of Bmal1 and Rev-erb α [reviewed in (6)]. In addition, PPAR α (12) and PPAR γ (74) regulate the expression of Bmal1 in the liver and vasculature, respectively. The direct evidence for the circadian clock to modulate lifespan came from the discovery that the deletion of Bmal1 led to a premature aging phenotype in mice. These mice had elevated ROS levels in multiple tissues, suggesting the disruption of mitochondrial functions as the underlying cause of premature aging (37). Dominant negative mutation of the clock also displayed accelerated aging (21). Intriguingly, the premature aging phenotype in genetic mouse models may result from the reciprocal regulation of the aforementioned nutrient sensing pathways (38, 43, 52, 62, 82). While the role of SMRT in nutrient sensing was revealed, its mechanism of actions is likely multi-tiered. Whether SMRT exerts its physiological or pathophysiological activity, in part, through the circadian regulatory circuit warrants further studies.

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Abbreviations Used

ACC1/2 = acetyl-CoA carboxylase 1 and 2
 ACL = ATP-citrate lyase
 AICAR = 5-aminoimidazole-4-carboxamide
 1- β -D-ribofuranoside
 AMPK = AMP-activated protein kinase
 BAT = brown adipose tissue
 Bmal1 = brain and muscle ARNT-like 1
 CR = caloric restriction
 Cry1 = cryptochrome 1
 ERR = estrogen related receptor
 ETC = electron transport chain
 FA = fatty acids
 HDAC = histone deacetylase
 MEF = mouse embryonic fibroblast
 mTORC1 = mammalian target of rapamycin complex 1
 NCoR = nuclear receptor corepressor
 NRF1/2 = nuclear respiratory factor 1 and 2
 PARP1 = poly(ADP-ribose) polymerase 1
 PGC-1 α = peroxisome proliferator-activated receptor
 gamma co-activator 1 α
 PL = phospholipids
 PPAR = peroxisome proliferator-activated receptor
 RAR = retinoic acid receptor
 RID = receptor interaction domain
 ROR = RAR-related orphan receptor
 ROS = reactive oxygen species
 RXR = retinoid X receptor
 SIRT1 = sirtuin 1
 SMRT = silencing mediator of retinoid and thyroid
 hormone receptors
 TCA = tricarboxylic acid
 TR = thyroid hormone receptor
 WAT = white adipose tissue