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Transcriptional targets of sirtuins in the coordination of mammalian physiology

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Abstract

Sirtuins compose a family of NAD⁺-dependent deacetylases and/or ADP-ribosyltransferases, which have been implicated in aging, metabolism and tolerance to oxidative stress. Many of the biological processes regulated by sirtuins result from the adaptation of complex gene-expression programs to the energetic state of the cell, sensed through NAD⁺ levels. To that respect, sirtuins, and particularly the founding member of the family Sirt1, have emerged as important regulators of transcription, which they modulate both positively and negatively by targeting histones and transcriptional complex regulatory proteins. This review will focus on recent advances that have started deciphering how mammalian sirtuins regulate transcriptional networks and thereby control physiology.

In mammals, sirtuins (Sirt) constitute a family of energy sensors which mediate NAD-dependent deacetylation and/or O-ADP-ribosylation in response to a rise in the cellular NAD⁺/NADH ratio (Fig. 1; see [1-3] for review). Sirt1, the founding member of the family, was initially discovered in yeast, where it is named Sir2 and regulates gene silencing and longevity. While these functions extend to higher eukaryotes, sirtuins have emerged as broader integrators of mammalian physiology, which regulate metabolism and homeostasis by coordinating complex gene expression programs through deacetylation of histones, transcription factors and coregulators (Fig. 2). This review will focus on the implication of sirtuins in transcriptional regulation, but it should be noted that sirtuins can also impact on whole-body homeostasis, independently of transcriptional regulation, by directly modulating the activity of enzymes or structural proteins [1-3].

Sub-cellular localization of sirtuins

The duplication of sirtuin genes in higher eukaryotes has been associated with a divergence of the sub-cellular localization of the proteins they encode, to fulfill specialized functions. The localization of sirtuins within the cell determines therefore the action that these proteins can exert on transcription, which occurs predominantly in the nucleus. Consistent with a strong role in the regulation of chromatin structure and gene expression, Sirt1, Sirt6 and Sirt7 are nuclear proteins, which are enriched in the nucleoplasm, in heterochromatin and in nucleoli, respectively [4]. Sirt2 is predominantly cytoplasmic, but it can affect gene expression by deacetylating transcription factors which shuttle from the cytoplasm to the nucleus [5], and it

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can impact on chromatin structure upon disassembly of the cell nucleus during mitosis [6]. In contrast, Sirt3, Sirt4 and Sirt5 are predominantly mitochondrial proteins [4,7,8], and could therefore modulate the transcription of the mitochondrial genome. Since Sirt3 induces global deacetylation of mitochondrial proteins [9], it is possible that also mitochondrial transcription factors are targeted. The static view of sirtuin compartmentalization should, however, be taken with some caution considering that regulatory proteins often dynamically exchange between cellular compartments. This has been recently illustrated by the nucleo-cytoplasmic shuttling of Sirt1 [10], and the observation that Sirt3 can be present in the nucleus and translocate to mitochondria in response to cellular stress [11].

Sirtuins and histone modifications

The complex post-translational modifications (PTM) of histone tails, commonly referred to as the histone code, regulate gene expression by modulating the compaction and the epigenetic state of chromatin [12]. As acetylation of histones strongly correlates with active chromatin, which facilitates transcription, it is logical that the histone deacetylase (HDAC) activity of the sirtuins has been linked to gene silencing. The yeast Sirt1 homologue Sir2 associates with inactive telomeric chromatin and silences the transcription of ribosomal DNA and of mating-type loci [1]. In mammals, only Sirt1-Sirt3 and Sirt5 have a conserved deacetylase domain [1,2], and HDAC activity seems restricted to Sirt1-Sirt3. Sirt1 can affect the acetylation of the four core histones *in vitro*, but seems to preferentially deacetylate histone 3 on lysines 9 and 14 (H3K9 and H3K14) and histone 4 on lysine 16 (H4K16) [13,14]. This direct histone deacetylation activity of Sirt1 synergizes with facilitated tri-methylation of H3K9 [13], a well established mark of facultative heterochromatin and transcriptional repression. The mechanistic basis of the positive action of Sirt1 on H3K9 methylation to further repress transcription involves the activation of the histone methyltransferase Suv39H1 by Sirt1-mediated deacetylation [15].

Despite its cytoplasmic localization, Sirt2 can deacetylate H4K16, and to a lesser extent H3K9, during mitosis when the nuclear envelope disassembles [6]. These results suggest, therefore, that Sirt2 could promote cell cycle progression by favoring the condensation of chromatin prior to chromosome segregation during mitosis. Finally, Sirt3 also exhibits HDAC activity directed towards H3K9 and H4K16 *in vitro* [11]. The normal pattern of histone acetylation of Sirt3-deficient cells suggests, however, that the deacetylase activity of Sirt3, if relevant *in vivo*, is most probably restricted to a small proportion of chromatin which remains undetectable at the genome wide level [11]. Altogether, these studies have demonstrated that histones are targets of sirtuin-mediated deacetylation facilitating heterochromatin formation. Further work will, however, be required to understand how the promoter-specific deacetylation of histones by sirtuins can selectively favor the transcriptional silencing of given loci in mammals.

Sirtuins and the basal transcriptional machinery

Sirtuins are major regulators of RNA polymerase (Pol) II transcribed genes encoding messenger RNAs, which they regulate either negatively or positively by deacetylating histones (see above) and transcription factors and coregulators (see below). To our knowledge, sirtuins have until now, however, not been implicated in the regulation of transcriptional initiation by the Pol II basal transcriptional machinery. Transcriptional regulation by sirtuins, however, affects Pol I-mediated transcription of ribosomal RNAs (rRNAs). Sirt1 inhibits Pol I transcription by deacetylating the TATA box-binding protein-associated factor TAF₆₈ [16]. In contrast, the nucleolar Sirt7 stimulates rRNA transcription by directly interacting with Pol I and stimulating its activity [17]. Finally, sirtuins also regulate viral transcription. Sirt1-Sirt3 can deacetylate the human immunodeficiency virus (HIV) 1 transactivator Tat, thereby

promoting viral transcription [18]. Interestingly, the observation that Sirt1 inhibitors can reduce HIV transcription suggests that Sirt1 antagonists could prove useful to combat viral infection.

Transcription factors and coregulators as targets of sirtuins

Nuclear receptors (NRs)

Several NRs are regulated by acetylation and Sirt1-mediated deacetylation plays an important role in adapting the activity of NRs implicated in the maintenance of whole body homeostasis, to the cellular energetic status that is sensed through NAD⁺ levels. By promoting transcriptional repression by the NR corepressor NCoR, Sirt1 inhibits adipocyte differentiation and adiponectin secretion, two processes controlled by the Peroxisome Proliferator-Activated Receptor γ (PPAR γ) [19,20]. Interestingly, the action of Sirt1 in adipocytes seems restricted to a subset of PPAR γ targets [21], which could potentially result from the selective regulation of PPAR γ by corepressors. The glucocorticoid-mediated activation of the uncoupling protein 3 (UCP3) promoter is also inhibited by Sirt1, which prevents acetylation of histones 3 and 4 [22]. The observation that the Sirt1-mediated repression of glucocorticoid action is restricted to certain promoters suggests that the action of Sirt1 results from promoter-specific epigenetic events rather than from a deacetylation of the glucocorticoid receptor itself. The androgen receptor is another NR whose activity is directly inhibited by Sirt1-mediated deacetylation [23,24]. Sirt1 also impedes the transcriptional activity of the estrogen receptor α (Er α), by inhibiting its binding to target DNA after deacetylation of lysines 266 and 268 [25]. Interestingly, many NRs have conserved lysine residues in the proximity of their DNA-binding domain [25], suggesting that regulation by acetylation could be a hallmark of the family.

Sirt1-mediated deacetylation can also stimulate the activity of NRs. Sirt1 regulates cholesterol homeostasis by deacetylating the lysine 432 of the liver X receptor (LXR), which subsequently induces the ubiquitination, destabilization and hence activation of LXR [26]. This direct regulation of LXR most likely synergizes with increased coactivation of LXRs by the PPAR γ Coactivator 1 α (PGC-1 α) [27], which is also activated by Sirt1-mediated deacetylation (see below).

Forkhead Box class O (FOXO) transcription factors

Sirtuins can modulate the activity of at least three of the four mammalian FOXOs to regulate cell survival and metabolism. Sirt1 deacetylates FOXO 1, 3 and 4, resulting in most cases in the repression of FOXO-mediated transcription [28-32]. Deacetylation by Sirt1 requires the LXXLL motif of FOXO1 [33], and transcriptional repression of FOXO by Sirt1 synergizes with the LIM domain FOXO1 corepressor FHL2 [34]. Altered FOXO signaling by Sirt1-dependent deacetylation inhibits forkhead-dependent apoptosis [28,29] and promotes vascular growth by reducing the anti-angiogenic actions of FOXO1 [35]. In some cases, however, Sirt1 can stimulate FOXO activity. This is for example the case for FOXO1, following deacetylation of lysines 242, 245 and 262 [30], or for a subset of FOXO3 and FOXO4 genes controlling resistance to oxidative stress [29,31]. Sirt1-dependent activation of FOXO1 has important metabolic consequences such as the stimulation of adiponectin production in adipocytes [36] and the induction of gluconeogenic genes in hepatocytes [32].

FOXO signaling relies on a nucleo-cytoplasmic shuttling mechanism where phosphorylation reduces FOXO transcriptional activity by inducing its cytoplasmic retention. Post-translational modifications often occur in an inter-dependent manner and emerging evidence suggests that acetylation can impact on protein phosphorylation. While Sirt1 most likely cross-talks with FOXO signaling when this last transcription factor is localized in the nucleus, the predominantly cytoplasmic Sirt2 can regulate FOXO signaling from the cytoplasm by affecting its state of phosphorylation. By interacting with and deacetylating FOXO1 in adipocytes, Sirt2

inhibits the insulin/akt-dependent phosphorylation of FOXO1 [5]. This leads subsequently to the activation of FOXO1 signaling by inducing its nuclear accumulation, thereby inhibiting adipogenesis.

p53

Sirt1 is a well recognized regulator of p53 activity, which it represses by the direct deacetylation of lysines 317, 370 and 379 [37]. Sirt1-mediated deacetylation inhibits p53-dependent apoptosis in response to DNA damage and oxidative stress [37-39]. At the molecular level, this regulation relies, at least in part, on the recruitment of Sirt1 to promyelocytic leukemia (PML) bodies, a sub-compartment of the nucleus where p53 is enriched [40]. p53 has also recently emerged as a metabolic regulator, which among other functions, inhibits glycolysis and promotes oxidative metabolism through the induction of the TP53-induced glycolysis and apoptosis regulator (TIGAR) and of the synthesis of cytochrome c oxidase 2 (SCO2) protein [41]. It is therefore worth exploring whether Sirt1 can affect metabolic homeostasis by inhibiting the metabolic actions of p53.

Other transcription factors

Sirt1 also exerts anti-apoptotic functions by deacetylating and inhibiting the pro-apoptotic factors p73 and E2F1 and by preventing Bax-dependent apoptosis through Ku70 deacetylation (see [1] for review). In addition, the deacetylation of SMAD7 by Sirt1 promotes its ubiquitination and degradation and thereby inhibits TGF β -dependent apoptosis [42].

Sirt1 also antagonizes inflammatory mechanisms by inhibiting NF- κ B activity through the deacetylation of p65/RelA on lysine 310 [43]. Interestingly, this action of Sirt1 on NF- κ B signaling promotes apoptosis induced by TNF α [43], and inhibits the neurotoxicity of amyloid β peptides [44].

Coregulators

As outlined above, Sirt1 interacts with NCoR and SMRT to repress PPAR γ activity [19]. It is, however, currently unclear whether corepressors are directly deacetylated by Sirt1 or whether they merely cooperate with Sirt1 to repress PPAR γ -dependent gene expression through histone deacetylation. In addition, it remains to be determined whether the interplay of Sirt1 with these pleiotropic corepressors extends to pathways regulated by other transcription factors. Similarly, transcriptional repression by the COUP-TF corepressor, CTIP2, is also enhanced by Sirt1-mediated deacetylation of histones 3 and 4 [45].

Sirt1 also represses gene expression by inhibiting the activity of a number of coactivators. Sirt1 interacts with the acetyltransferases pCAF and GCN5 to prevent their auto-acetylation as well as that of the muscle-specific transcription factor MyoD [29,46], which was shown to inhibit skeletal muscle differentiation [46]. Another example is the coactivator p300, which is inhibited by Sirt1-dependent deacetylation of lysine residues 1020 and 1024 [28,29,47], most probably because these residues become available for SUMOylation following deacetylation [47].

Interestingly, sirtuins have recently also emerged as positive regulators of gene expression. Perhaps one of the best known examples of this is provided by the activation of the PPAR γ coactivator 1 α (PGC-1 α), the master regulator of mitochondrial function which strongly impacts metabolic homeostasis [48]. During fasting, the hepatic stimulation of Sirt1 activity by elevated NAD $^{+}$ levels promotes the transcriptional activity of PGC-1 α through the direct deacetylation of 13 lysine residues. This Sirt1-dependent deacetylation and activation of PGC-1 α contributes to the stimulation of gluconeogenesis and subsequent restoration of glucose levels after fasting [27,49]. The activation of PGC-1 α by Sirt1-mediated deacetylation

also extends to gene expression programs controlling mitochondrial oxidative functions, which are particularly prominent in skeletal muscle, but occur also in liver and brown adipose tissue [50-52]. The pharmacological activation of Sirt1 with natural or synthetic Sirt1 agonists hence could provide an effective mean to combat diet-induced metabolic disorders by indirectly activating PGC-1 α -regulated energy expenditure [51-53]. Finally, Sirt3 can stimulate PGC-1 α expression to promote mitochondrial function and adaptive thermogenesis in brown adipose tissue [54].

Concluding remarks

Over the past four years, sirtuins, and especially Sirt1, have emerged as important regulators of mammalian transcription and physiology by targeting and modulating the activity of both histones and additional components of transcriptional complexes. Although the deacetylase activity of sirtuins underlies many of these regulatory actions, future research efforts will undoubtedly reveal novel mechanisms through which the sirtuins integrate complex physiological pathways. To that respect, particular attention should be given to regulations controlled by the often under-looked sirtuins Sirt2 to Sirt7. Given the possibility to pharmacologically target the enzymatic activities of sirtuins and the promise this holds in the treatment of metabolic and age-related diseases [51-53], it will also be of great importance to understand the subtle mechanisms which dictate the selectivity of sirtuin action. Towards that goal, the characterization of the tissue-specific activities of sirtuins as well as of the modulation of their enzymatic activities through their own post-translational modification, such as phosphorylation or SUMOylation [55-57], will provide a way to integrate the action of these transcriptional regulators in broader signaling networks. In addition, the recent identification of a Sirt1 coactivator which enhances its deacetylase activity also opens these networks to additional regulation [58].

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Figure 1. Sirtuins catalyze deacetylation and/or O-ADP-ribosylation reactions

The two enzymatic reactions catalyzed by sirtuins use nicotinamide-adenine-dinucleotide (NAD⁺) as a cofactor and produce nicotinamide (NAM). In the deacetylation reaction, the acetyl group of a target lysine residue is transferred to the ADP-ribose moiety of NAD⁺ to generate 2'-O-acetyl-ADP-ribose. Sirtuins can also catalyze the mono ADP-ribosylation of a non-acetylated protein substrate by transferring the ADP-ribose moiety of NAD⁺ to the target protein. The principal reaction of each sirtuin is depicted but it should be noted that most sirtuins harbor both activities to different degrees. For example, Sirt6 also has a weak deacetylase activity while Sirt1, Sirt2 and Sirt3 can catalyze O-ADP-ribosylation. The reactions catalyzed by Sirt7 remain to be determined.

Figure 2. Transcriptional targets of sirtuins

The main molecular mechanisms through which sirtuins regulate gene expression are depicted according to the nature of the transcriptional regulator interacting with sirtuins, and to the action that sirtuins exert on the activity of this factor. Transcriptional activation mediated by sirtuins (indicated by green boxes) can result both from the enhanced activity of a transcriptional activator and from the inhibition of a repressor, although examples of this latter case have not been documented to date. In contrast, Sirt-mediated transcriptional repression (indicated by red boxes) is caused both by enhanced repressor activity and from the inhibition of an activator. Abbreviations are PPAR: peroxisome proliferator-activated receptor; NCoR: nuclear corepressor; COUP-TF: chicken ovalbumin upstream promoter transcription factor; CTIP2: COUP-TF-interacting protein 2; Suv39H1: suppressor of variegation 3–9 homologue 1; PGC-1 α : PPAR γ coactivator 1 α ; LXR: liver X receptor; FOXO: Forkhead Box class O; Tat: transactivator; Pol I: RNA polymerase I; NF κ B: nuclear factor κ B; AR: androgen receptor; ER: estrogen receptor; MyoD: myoblast determination protein 1; p/CAF: p300/CBP-associated factor; TAF₆₈: TATA box binding protein-associated factor I 68.