Biochemical and Biophysical Research Communications 391 (2010) 6–10

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Mini Review

Is systemic activation of Sirt1 beneficial for ageing-associated metabolic disorders?

Bor Luen Tang *, Christelle En Lin Chua

Department of Biochemistry, Yong Loo Lin School of Medicine, National University Health System, National University of Singapore, 8 Medical Drive, Singapore 117597, Singapore

ARTICLE INFO

Article history:
Received 29 October 2009
Available online 11 November 2009

Keywords:
AMP-activated *k*inase (AMPK)
Caloric restriction
Metabolic syndrome
Sirt1

ABSTRACT

Sir2/Sirt1, a mediator of longevity in several animal models, is a member of the sirtuin family of type III histone deacetylases. Its non-histone substrates include a group of regulatory molecules that modulate energy metabolism, such as *p*eroxisome *p*roliferator-*a*ctivated *r*eceptor-γ (PPARγ), and its transcriptional coactivator, *P*PARγ *c*oactivator-1α (PGC-1α). Sirt1's activity on these substrates may underlie its connection with the metabolic changes brought about by *c*aloric *r*estriction (CR). Recent studies have elucidated new substrates for Sirt1 that are involved in metabolic regulation, and have further delineated Sirt1's functional associations with other metabolic regulators like *AMP*-activated *k*inase (AMPK). Perplexingly, manipulations that either increase or decrease Sirt1 activity have both been associated with a beneficial effect in animal models of ageing-associated disorders, such as neurodegenerative diseases. Sirt1's activation patterns and roles in energy metabolism appear to have tissue specific differences. A deeper understanding of the mechanistic underpinnings of Sirt1's metabolic functions is necessary to effectively design Sirt1-based therapeutic interventions for metabolic disorders.

© 2009 Elsevier Inc. All rights reserved.

Introduction

*C*aloric *r*estriction (CR), a moderate reduction of caloric intake without malnutrition, has been consistently implicated in extension of lifespan across a wide evolutionary spectrum. In mammals, CR also clearly attenuates symptoms of ageing-associated obesity, insulin resistance, hypertension and atherosclerosis. A connection between CR and *Sir2*/*Sirt1*, an evolutionarily conserved longevity-related gene, is of particular interest. Sirt1 and other members of the sirtuin family are *n*icotinamide *a*denine *d*inucleotide (NAD)-dependent class III histone deacetylases [1,2], but also have many non-histone targets. Their unusual deacetylation reaction is coupled to cleavage of NAD into nicotinamide and 1-*O*-acetyl-ADP ribose [3]. The activity of sirtuins is therefore dependent on the level of NAD, and inhibited by the product nicotinamide. It is thus influenced by the cell's metabolic status.

Over-expression of *Sir2* extended the replicative lifespan of yeast, and over-expression or activation of *Sir2* orthologs with resveratrol was shown to increase lifespan in invertebrates like *Caenorhabditis elegans* and *Drosophila* [4–6]. The mammalian genome harbors seven sirtuin paralogs (Sirt1-7), with Sirt1 bearing the most homology to yeast *Sir2* [7]. With the discoveries of its non-histone substrates, Sirt1 has been linked to multiple physiological functions and pathological roles. For example, Sirt1's deacetylation of members of the *f*orkhead b*ox* class *O* (FOXO) family [8], p53 tumor suppressor [9], and *n*uclear *f*actor κB (NF-κB) [10] regulates key aspects of cellular stress response and survival. Sirt1's activity on PPARγ [11] and its transcriptional coactivator PGC-1α [12,13] also regulates a wide range of metabolic activities in skeletal muscle, adipose tissues and the liver [14,15]. These links between nutrient availability/energy metabolism and adaptive changes in transcriptional profiles have implications on multiple aspects of human ageing and related diseases [16,17].

Evidence for Sirt1 being a longevity factor in mammals has been controversial, as Sirt1 appears to have both pro- and anti-ageing activities [18]. However, Sirt1 is still likely to be a key mediator of some beneficial CR-associated metabolic effects [19]. A perplexing aspect of Sirt1 is that both its activation *and* inhibition have been shown to be beneficial in diseases and disorders. For example, Sirt1 activation has been shown to alleviate symptoms of neurodegenerative diseases in several animal models [20–22]. However, nicotinamide and other Sirt1 inhibitors are also known to be neuroprotective in animal models of brain ischemia, Parkinsonism and Alzheimer's disease [23–26]. Transgenic over-expression of *Sir2* ortholog in *Drosophila* promotes apoptosis [27], while reduction of *Sir2* activity improves neuronal survival in flies expressing the neurodegenerative mutant Huntingtin [28]. Another recent report showed that Sirt1 inhibitors or a knockout of *Sirt1* protected neurons from oxidative damage [29]. Similarly, Sirt1 may either be oncogenic or tumor suppressive depending on the type of malignancy and context of analysis [30,31]. Recent advances have also revealed that pharmacological or genetic activation of Sirt1 results in metabolic benefits that mimic the effects of CR. However, gen-

* Corresponding author. Fax: +65 6779 1453.
E-mail address: bchtbl@nus.edu.sg (B.L. Tang).

0006-291X/$ - see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.bbrc.2009.11.016

eral and conditional knockout of Sirt1 in mice have also resulted in improved glucose and lipid homeostasis. In the ensuing paragraphs, we follow these recent findings and discuss the implications of some apparently paradoxical results.

Sirt1's substrates and collaborators in energy metabolism—old and new connections

Sirt1 has a wide range of substrates, and several of these participate in energy regulation in metabolically active tissues such as liver and muscle [14,32,33]. Among these is the Sirt1-PGC-1α axis in liver glucose metabolism [13]. Gluconeogenesis during starvation can be triggered by the hormone glucagon, which induces dephosphorylation and nuclear translocation of *t*ransducer *o*f *r*egulated *C*REB activity *2* (TORC2). TORC2 binds to and activates the DNA-binding transcription factor *Cre b*inding protein (CREB), which then induces the expression of the transcriptional coactivator PGC-1α. The latter complexes with, and coactivates, transcription factors that include PPARα, FOXO1, *g*lucocorticoid *r*eceptor (GR), and *h*epatocyte *n*uclear *f*actor 4α (HNF4α). These in turn induce the transcription of key gluconeogenic genes encoding the rate-limiting enzymes phosphoenolpyruvate carboxykinase and glucose-6-phosphatase (see Fig. 1). In the fed state, insulin-stimulated Akt kinase activity results in phosphorylation of both TORC2 and PGC-1α, thereby shutting down the transcription of gluconeogenic genes. Under conditions of stress and low levels of cellular ATP (another key sensor of metabolic status), the *AMP*-activated *p*rotein *k*inase (AMPK) is activated. AMPK activates catabolic, ATP-generating pathways and shuts down anabolic, energy-consuming ones by phosphorylation of metabolic enzymes. It also exerts longer-term effects at the transcription level by phosphorylating transcription factors [34]. In the liver, AMPK inhibits gluconeogenesis by phosphorylating TORC2 [35], thereby safeguarding hepatic cellular ATP needs. AMPK activation is a key pharmacological role of drugs for type II diabetes which work to suppress hepatic glucose output, such as Metformin [36,37].

Besides phosphorylation, PGC-1α is also regulated by acetylation and deacetylation. Its transcription-activating ability is repressed by acetylation through the acetyl transferase GCN5 [38] and activated by Sirt1-mediated deacetylation [13,39]. Notably, this parallel regulation of gluconeogenesis via PGC-1α activity is not dependent on glucagon or glucocorticoids, but on the levels of metabolic intermediates like pyruvate and NAD [39]. In this connection, several recent findings are noteworthy. Sirt1 may also affect gluconeogenic activity through PGC-1α in an indirect manner. In the liver, STAT3 is known to suppress the expression of PGC-1α and gluconeogenic gene expression. Regulation of gluconeogenesis by STAT3 could be linked to nutritional status via Sirt1, which can directly deacetylate and attenuate the anti-gluconeogenic transcriptional activity of STAT3 [40]. It also turns out that TORC2 is itself regulated by Sirt1 deacetylation [41]. Lys628 acetylation prevents ubiquitination and degradation of glucagon-activated TORC2 during the early stage of fasting. At a later stage, however, Sirt1 activity reduces TORC2 levels

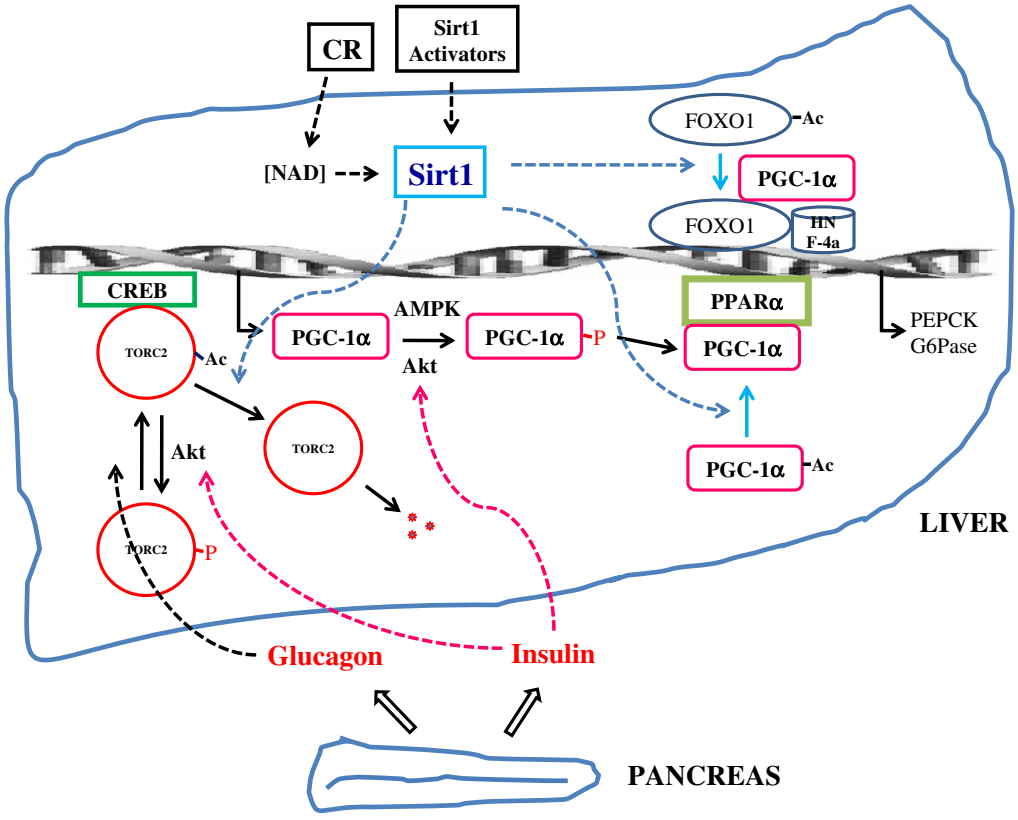

Fig. 1. A simplified schematic diagram of how Sirt1, activated by NAD status, CR or pharmacological means, may regulate PGC-1α activity and the expression of key gluconeogenic enzymes—phosphoenol pyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase). This regulation intersects with hormonal regulation of gluconeogenesis in the liver by pancreatic insulin and glucagon. Sirt1 activation, deacetylation and hormonal influences on phosphorylation are indicated by arrows with dotted lines. For simplicity, several transcriptional components (see text) are not shown. In the fed state, insulin signaling stimulates kinase activities that phosphorylate TORC2 and PGC-1α, while glucagon signaling reverses these phosphorylations during starvation. Deacetylation of PGC-1α by Sirt1 is known to be the parallel pathway for cells to activate gluconeogenesis independently of glucagon. TORC2 has also recently been shown to be deacetylated by Sirt1 (leading to its ubiquitination and degradation), thereby providing, under conditions of prolonged starvation, a switch away from the control of gluconeogenesis by glucagon.

by deacetylation, but sustains gluconeogenesis via deacetylation and activation of FOXO1. Gluconeogenesis during prolonged starvation therefore switches from hormonal regulation by glucagon to one that is regulated by a stress-response network, presumably with better maintenance of energy balance.

Sirt1 activation of PGC-1α in liver cells appears to counteract that of AMPK, which phosphorylates and inactivates the transcription coactivator. Indeed, while AMPK activation inhibits hepatic glucose output, Sirt1 activation leads to increased hepatic gluconeogenesis. The relationship between Sirt1 and AMPK is, however, different in the skeletal muscle, the major energy-consuming organ in a physically active mammal. Activation of AMPK in skeletal muscle increases fatty acid oxidation through enhanced transcription of both PPARα [42,43] and PGC-1α [44], or via direct phosphorylation of PGC-1α [45]. Sirt1 deacetylation also activates PGC-1α in muscles, and this is apparently the way by which Sirt1 activates mitochondrial activity and fatty acid oxidation in muscle cells [46]. AMPK and Sirt1 therefore act in a coordinated manner in this tissue. Recent findings also indicate that (in muscles at least) AMPK may also activate PGC-1α indirectly via Sirt1 activation, through increasing cellular NAD levels [47].

In pancreatic β cells, Sirt1 enhances insulin secretion [48], partly through the suppression of *u*ncoupling *p*rotein *2* (UCP2) [49]. On the other hand, AMPK activation by pharmacological or genetic means blocks glucose-stimulated insulin secretion [50].

These highly-simplified descriptions of Sirt1's regulatory activity in metabolically active tissues show that systemic Sirt1-based therapeutic manipulations would result in different responses in different tissues. This will then go onto exert different degrees of impact on the body's metabolic balance. Whether metabolic dysfunction could be corrected or improved would then depend on the sum of these responses. A closer look at Sirt1's metabolic functions, investigated via pharmacological and genetic manipulations in mouse models, is made in the following paragraphs.

Investigation of Sirt1's metabolic functions by pharmacological activators and inhibitors

A potent and classical inhibitor of Sirt1 is the plant polyphenol resveratrol (3,5,4′-trihydroxystilbene) [51], which was already known to be an antioxidant. Its purported anti-ageing efficacy received a greater boost with the demonstration that it could extend the replicative lifespan of yeast, worms, and flies in a manner concomitant with, and dependent on, *Sir2* activation [6,52]. Several recent studies have now expanded this observation to mammalian models. Resveratrol administration was shown to elevate AMPK and PGC-1α activity as well as mitochondrion number, and generally improved the health, motor function and survival of middle-age (1 year old) mice on a high calorie diet [53]. Young (4–8 weeks old) mice on a high-fat diet were protected from the development of insulin resistance and obesity, with increased mitochondrial biogenesis and capacity for aerobic metabolism [54]. Several reports have also shown that resveratrol alleviates both alcoholic and non-alcoholic liver steatosis (fatty liver) [55,56]. Despite the obvious beneficial effects of resveratrol in animal models, whether effective *in vivo* concentrations could be achieved for significant Sirt1 activation remains unclear. An explanation of the beneficial effects of resveratrol is also complicated by the fact that it could activate AMPK independently of Sirt1 [57], which has overlapping effects with Sirt1 activation.

More specific and potent Sirt1 small-molecule activators have now been identified and shown to be therapeutically effective in an animal model of type II diabetes. The animals showed improved glucose homeostasis and insulin sensitivity in liver, adipose tissue and skeletal muscle, as well as enhanced mitochondrial capacity and oxidative metabolism [58]. A follow-up analysis of gene expression elicited by Sirt1 activators indicated that these produce a signaling profile that mimics CR. This is likely a result of a concerted deacetylation of Sirt1 substrates like PGC-1α and FOXO1, as well as elevated AMPK activity [59]. In general, the case for the metabolic benefits of a systemic Sirt1 activation by pharmacological means appears achievable and appealing [33].

Investigation of Sirt1's metabolic function by genetic manipulations of Sirt1 levels

The first *Sir2*/*Sirt1* gene knockout studies indicated that CR response is blunted in the absence of *Sir2*/*Sirt1*. Sirt1 deficiency on its own results in developmental defects and metabolic dysfunctions [60–63]. Phenotypes associated with the effect of CR in mice, such as the increase in physical activity and motor capacity, requires functional Sirt1 [64]. Interestingly, Sirt1 deficiency appears to result in increased insulin sensitivity and lower blood glucose levels. One possible reason for this is the alleviation of UCP2 repression by Sirt1 in pancreatic β cells. In support of this, Sirt1 knockout mice display constitutively high UCP2 expression [49].

Consistent with Sirt1's activation of PGC-1α and gluconeogenesis, knockdown of Sirt1 in liver by small hairpin RNA (shRNA) lowers blood glucose in normal and fasted diabetic *db*/*db* mice that lack the leptin receptor [65]. Likewise, hepatic Sirt1 knockdown with antisense oligonucleotides in a rat model of type II diabetes lowers fasting hyperglycemia [66]. This beneficial effect on glucose homeostasis resulting from Sirt1 deficiency appears to contradict the general beneficial effect of Sirt1 activation. Interestingly, it was recently shown that, unlike other tissues, Sirt1 activity in liver is in fact reduced by CR (and activated by a high calorie diet) [67]. The reason for this anomalous regulation of Sirt1 activity by CR in liver is unclear. On the other hand, liver-specific conditional Sirt1 knockout mice have impaired lipid metabolism [68]. They exhibit defective PPARα signaling, hepatic steatosis and liver inflammation that was easily precipitated by a high-fat diet.

Genetic gain-of-function manipulations of Sirt1 levels have generally produced beneficial outcomes, although the phenotypes observed in different settings were not exactly identical. Sirt1 transgenic mice bearing a hemizygous knockin at the β-actin locus are leaner, metabolically more active, and have a CR-like blood glucose and lipid profile [69]. Mice carrying a bacterial artificial chromosome with Sirt1 under its own promoter have moderate overexpression of Sirt1, with no alterations in body weight/fat mass, and are protected from metabolic disorders induced by a chronic high-fat diet [70]. In another report using a similar transgenic approach, however, mice exhibited decrease in food intake and locomotor activity. In any case though, they also exhibited improved glucose tolerance as a result of decreased glucose production by the liver and increased adiponectin levels [71]. As alluded to above, specific expression of Sirt1 in pancreatic β cells enhanced insulin secretion and improved glucose tolerance [48]. Transgenic expression of Sirt1 in endothelial cells reduced atherosclerotic lesions in apolipoprotein E null mice, although blood glucose and lipid levels in these were not significantly different from control [72].

On the whole, therefore, moderate transgenic over-expression of Sirt1 phenocopies systemic Sirt1 activation by pharmacological activators, in terms of metabolic benefits. Although Sirt1 overexpression in liver could potentially elevate hepatic glucose output by activating PGC-1α, this has not been observed. One possible reason is that Sirt1's deacetylation and downregulation of TORC2 effectively attenuated glucagon-induced gluconeogenesis [41]. It also appears that a generalized elevation of Sirt1 activity in multiple tissues attains a net result of improved glucose homeostasis.

Concluding remarks

The discussions above highlight some differences in the activities of Sirt1 in metabolically active tissues. Indeed, Sirt1 has a wide range of substrates and subcellular expressions. It affects the expression of gene networks through deacetylation of transcription factors, and epigenetic histone modifications. A general and systemic elevation of Sirt1 activity, by both pharmacological and genetic interventions in experimental animals, appears consensually supportive of a beneficial effect on age-related metabolic disorders. However, several potential caveats need to be kept in mind. Firstly, widespread Sirt1 activation in all human tissues may not completely mimic CR—at the very least, the effect of Sirt1 elevation in liver gluconeogenesis warrants further investigation. Specifically, in the case of type II diabetes, potential elevation rather than suppression of hepatic glucose output could nullify all other benefits on metabolic balance. Secondly, it has been cautioned that the CR state may compromise immune responses to infection and increase frailty to infectious pathogens [73]. Especially for those with natural or acquired immune deficiencies, one would think that Sirt1's attenuation of NF-κB activity would further increase risks of infection. Thirdly, Sirt1 activation may not be beneficial, and could in fact exacerbate or worsen certain neurodegenerative disorders, and in some organs may promote oncogenesis.

It is clear that we are only beginning to understand the elaborate role that Sirt1 plays in metabolic regulation. New activities and substrates of Sirt1 continue to be revealed at an amazing rate. A particularly exciting series of new findings have revealed that the core circadian rhythm regulator protein *c*ircadian *l*ocomotor *o*utput *c*ycles *k*aput (CLOCK) is a histone acetyltransferase, and its activity is counterbalanced by NAD and Sirt1. As the circadian rhythm modulates metabolic activities on a long-term basis, the cumulative effects of systemic Sirt1 activation over time should therefore be investigated.

Acknowledgments

The authors are funded by a grant from the National University Health System (NUHS), and declare no financial conflict of interest.

References

[1] G. Blander, L. Guarente, The Sir2 family of protein deacetylases, Annu. Rev. Biochem. 73 (2004) 417–435.
[2] J.M. Denu, The Sir 2 family of protein deacetylases, Curr. Opin. Chem. Biol. 9 (2005) 431–440.
[3] K.G. Tanner, J. Landry, R. Sternglanz, et al., Silent information regulator 2 family of NAD-dependent histone/protein deacetylases generates a unique product, 1-*O*-acetyl-ADP-ribose, Proc. Natl. Acad. Sci. USA 97 (2000) 14178–14182.
[4] H.A. Tissenbaum, L. Guarente, Increased dosage of a sir-2 gene extends lifespan in *Caenorhabditis elegans*, Nature 410 (2001) 227–230.
[5] B. Rogina, S.L. Helfand, Sir2 mediates longevity in the fly through a pathway related to calorie restriction, Proc. Natl. Acad. Sci. USA 101 (2004) 15998–16003.
[6] J.G. Wood, B. Rogina, S. Lavu, et al., Sirtuin activators mimic caloric restriction and delay ageing in metazoans, Nature 430 (2004) 686–689.
[7] M.C. Haigis, L.P. Guarente, Mammalian sirtuins—emerging roles in physiology, aging, and calorie restriction, Genes Dev. 20 (2006) 2913–2921.
[8] H. Huang, D.J. Tindall, Dynamic FoxO transcription factors, J. Cell Sci. 120 (2007) 2479–2487.
[9] I. van Leeuwen, S. Lain, Sirtuins and p53, Adv. Cancer Res. 102 (2009) 171–195.
[10] A. Salminen, A. Kauppinen, T. Suuronen, et al., SIRT1 longevity factor suppresses NF-kappaB-driven immune responses: regulation of aging via NF-kappaB acetylation?, Bioessays 30 (2008) 939–942
[11] F. Picard, M. Kurtev, N. Chung, et al., Sirt1 promotes fat mobilization in white adipocytes by repressing PPAR-gamma, Nature 429 (2004) 771–776.
[12] S. Nemoto, M.M. Fergusson, T. Finkel, et al., SIRT1 functionally interacts with the metabolic regulator and transcriptional coactivator PGC-1α, J. Biol. Chem. 280 (2005) 16456–16460.
[13] J.T. Rodgers, C. Lerin, W. Haas, et al., Nutrient control of glucose homeostasis through a complex of PGC-1alpha and SIRT1, Nature 434 (2005) 113–118.
[14] C. Cantó, J. Auwerx, PGC-1alpha, SIRT1 and AMPK, an energy sensing network that controls energy expenditure, Curr. Opin. Lipidol. 20 (2009) 98–105.
[15] M. Sugden, P. Caton, M. Holness, et al., PPAR control: it's SIRTainly as easy as PGC, J. Endocrinol. (2009), in press.
[16] V.D. Longo, B.K. Kennedy, Sirtuins in aging and age-related disease, Cell 126 (2006) 257–268.
[17] L. Guarente, Sirtuins in aging and disease, Cold Spring Harb. Symp. Quant. Biol. 72 (2007) 483–488.
[18] V.D. Longo, Linking sirtuins, IGF-I signaling, and starvation, Exp. Gerontol. 44 (2009) 70–74.
[19] C. Cantó, J. Auwerx, Caloric restriction, SIRT1 and longevity, Trends Endocrinol. Metab. 20 (2009) 325–331.
[20] D. Kim, M.D. Nguyen, M.M. Dobbin, et al., SIRT1 deacetylase protects against neurodegeneration in models for Alzheimer's disease and amyotrophic lateral sclerosis, EMBO J. 26 (2007) 3169–3179.
[21] B.L. Tang, Sirt1's complex roles in neuroprotection, Cell. Mol. Neurobiol. (2009), in press.
[22] B.L. Tang, C.E.L. Chua, SIRT1 and neuronal diseases, Mol. Aspects Med. 29 (2008) 187–200.
[23] Z.Z. Chong, S.H. Lin, F. Li, et al., The sirtuin inhibitor nicotinamide enhances neuronal cell survival during acute anoxic injury through AKT, BAD, PARP, and mitochondrial associated "anti-apoptotic" pathways, Curr. Neurovasc. Res. 2 (2005) 271–285.
[24] D. Liu, R. Gharavi, M. Pitta, et al., Nicotinamide prevents NAD+ depletion and protects neurons against excitotoxicity and cerebral ischemia: NAD+ consumption by SIRT1 may endanger energetically compromised neurons, Neuromol. Med. 11 (2009) 28–42.
[25] T.F. Outeiro, E. Kontopoulos, S.M. Altmann, et al., Sirtuin 2 inhibitors rescue alpha-synuclein-mediated toxicity in models of Parkinson's disease, Science 317 (2007) 516–519.
[26] K.N. Green, J.S. Steffan, H. Martinez-Coria, et al., Nicotinamide restores cognition in Alzheimer's disease transgenic mice via a mechanism involving sirtuin inhibition and selective reduction of Thr231-phosphotau, J. Neurosci. 28 (2008) 11500–11510.
[27] A.J. Griswold, K.T. Chang, A.P. Runko, et al., Sir2 mediates apoptosis through JNK-dependent pathways in *Drosophila*, Proc. Natl. Acad. Sci. USA 105 (2008) 8673–8678.
[28] J. Pallos, L. Bodai, T. Lukacsovich, et al., Inhibition of specific HDACs and sirtuins suppresses pathogenesis in a *Drosophila* model of Huntington's disease, Hum. Mol. Genet. 17 (2008) 3767–3775.
[29] Y. Li, W. Xu, M.W. McBurney, et al., SirT1 inhibition reduces IGF-I/IRS-2/Ras/ERK1/2 signaling and protects neurons, Cell Metab. 8 (2008) 38–48.
[30] C.X. Deng, SIRT1, is it a tumor promoter or tumor suppressor?, Int J. Biol. Sci. 5 (2009) 147–152.
[31] T. Liu, P.Y. Liu, G.M. Marshall, et al., The critical role of the class III histone deacetylase SIRT1 in cancer, Cancer Res. 69 (2009) 1702–1705.
[32] M. Fulco, V. Sartorelli, Comparing and contrasting the roles of AMPK and SIRT1 in metabolic tissues, Cell Cycle 7 (2008) 3669–3679.
[33] N. Chaudhary, P.T. Pfluger, Metabolic benefits from Sirt1 and Sirt1 activators, Curr. Opin. Clin. Nutr. Metab. Care 12 (2009) 431–437.
[34] L.G. Karagounis, J.A. Hawley, The 5′ adenosine monophosphate-activated protein kinase: regulating the ebb and flow of cellular energetics, Int. J. Biochem. Cell Biol. 41 (2009) 2360–2363.
[35] S.H. Koo, L. Flechner, L. Qi, et al., The CREB coactivator TORC2 is a key regulator of fasting glucose metabolism, Nature 437 (2005) 1109–1111.
[36] G. Zhou, R. Myers, Y. Li, et al., Role of AMP-activated protein kinase in mechanism of metformin action, J. Clin. Invest. 108 (2001) 1167–1174.
[37] N. Musi, M.F. Hirshman, J. Nygren, et al., Metformin increases AMP-activated protein kinase activity in skeletal muscle of subjects with type 2 diabetes, Diabetes 51 (2002) 2074–2081.
[38] C. Lerin, J.T. Rodgers, D.E. Kalume, et al., GCN5 acetyltransferase complex controls glucose metabolism through transcriptional repression of PGC-1alpha, Cell Metab. 3 (2006) 429–438.
[39] J.T. Rodgers, C. Lerin, Z. Gerhart-Hines, et al., Metabolic adaptations through the PGC-1alpha and SIRT1 pathways, FEBS Lett. 582 (2008) 46–53.
[40] Y. Nie, D.M. Erion, Z. Yuan, et al., STAT3 inhibition of gluconeogenesis is downregulated by SirT1, Nat. Cell Biol. 11 (2009) 492–500.
[41] Y. Liu, R. Dentin, D. Chen, et al., A fasting inducible switch modulates gluconeogenesis via activator/coactivator exchange, Nature 456 (2008) 269–273.
[42] M. Bronner, R. Hertz, J. Bar-Tana, et al., Kinase-independent transcriptional co-activation of peroxisome proliferator-activated receptor alpha by AMP-activated protein kinase, Biochem. J. 384 (2004) 295–305.
[43] W.J. Lee, M. Kim, H.S. Park, et al., AMPK activation increases fatty acid oxidation in skeletal muscle by activating PPARalpha and PGC-1, Biochem. Biophys. Res. Commun. 340 (2006) 291–295.
[44] M. Suwa, H. Nakano, S. Kumagai, et al., Effects of chronic AICAR treatment on fiber composition, enzyme activity, UCP3, and PGC-1 in rat muscles, J. Appl. Physiol. 95 (2003) 960–968.
[45] S. Jäger, C. Handschin, J. St-Pierre, et al., AMP-activated protein kinase (AMPK) action in skeletal muscle via direct phosphorylation of PGC-1alpha, Proc. Natl. Acad. Sci. USA 104 (2007) 12017–12022.
[46] Z. Gerhart-Hines, J.T. Rodgers, O. Bare, et al., Metabolic control of muscle mitochondrial function and fatty acid oxidation through SIRT1/PGC-1alpha, EMBO J. 26 (2007) 1913–1923.

[47] C. Cantó, Z. Gerhart-Hines, J.N. Feige, et al., AMPK regulates energy expenditure by modulating NAD+ metabolism and SIRT1 activity, Nature 458 (2009) 1056–1060.
[48] K.A. Moynihan, A.A. Grimm, M.M. Plueger, et al., Increased dosage of mammalian Sir2 in pancreatic beta cells enhances glucose-stimulated insulin secretion in mice, Cell Metab. 2 (2005) 105–117.
[49] L. Bordone, M.C. Motta, F. Picard, et al., Sirt1 regulates insulin secretion by repressing UCP2 in pancreatic beta cells, PLoS Biol. 4 (2006) e31.
[50] G. da Silva Xavier, I. Leclerc, A. Varadi, et al., Role for AMP-activated protein kinase in glucose-stimulated insulin secretion and preproinsulin gene expression, Biochem. J. 371 (2003) 761–774.
[51] M.D. Knutson, C. Leeuwenburgh, Resveratrol and novel potent activators of SIRT1: effects on aging and age-related diseases, Nutr. Rev. 66 (2008) 591–596.
[52] K.T. Howitz, K.J. Bitterman, H.Y. Cohen, et al., Small molecule activators of sirtuins extend *Saccharomyces cerevisiae* lifespan, Nature 425 (2003) 191–196.
[53] J.A. Baur, K.J. Pearson, N.L. Price, et al., Resveratrol improves health and survival of mice on a high-calorie diet, Nature 444 (2006) 337–342.
[54] M. Lagouge, C. Argmann, Z. Gerhart-Hines, et al., Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha, Cell 127 (2006) 1109–1122.
[55] J.M. Ajmo, X. Liang, C.Q. Rogers, et al., Resveratrol alleviates alcoholic fatty liver in mice, Am. J. Physiol. Gastrointest. Liver Physiol. 295 (2008) G833–G842.
[56] L. Bujanda, E. Hijona, M. Larzabal, et al., Resveratrol inhibits nonalcoholic fatty liver disease in rats, BMC Gastroenterol. 8 (2008) 40.
[57] B. Dasgupta, J. Milbrandt, Resveratrol stimulates AMP kinase activity in neurons, Proc. Natl. Acad. Sci. USA 104 (2007) 7217–7222.
[58] J.C. Milne, P.D. Lambert, S. Schenk, et al., Small molecule activators of SIRT1 as therapeutics for the treatment of type 2 diabetes, Nature 450 (2007) 712–716.
[59] J.J. Smith, R.D. Kenney, D.J. Gagne, et al., Small molecule activators of SIRT1 replicate signaling pathways triggered by calorie restriction in vivo, BMC Syst. Biol. 3 (2009) 31.
[60] S.J. Lin, P.A. Defossez, L. Guarente, et al., Requirement of NAD and SIR2 for life-span extension by calorie restriction in *Saccharomyces cerevisiae*, Science 289 (2000) 2126–2128.
[61] M.W. McBurney, X. Yang, K. Jardine, et al., The mammalian SIR2alpha protein has a role in embryogenesis and gametogenesis, Mol. Cell. Biol. 23 (2003) 38–54.
[62] H.L. Cheng, R. Mostoslavsky, S. Saito, et al., Developmental defects and p53 hyperacetylation in Sir2 homolog (SIRT1)-deficient mice, Proc. Natl. Acad. Sci. USA 100 (2003) 10794–10799.
[63] G. Boily, E.L. Seifert, L. Bevilacqua, et al., SirT1 regulates energy metabolism and response to caloric restriction in mice, PloS One 3 (2008) e1759.
[64] D. Chen, A.D. Steele, S. Lindquist, et al., Increase in activity during calorie restriction requires Sirt1, Science 310 (2005) 1641.
[65] J.T. Rodgers, P. Puigserver, Fasting-dependent glucose and lipid metabolic response through hepatic sirtuin 1, Proc. Natl. Acad. Sci. USA 104 (2007) 12861–12866.
[66] D.M. Erion, S. Yonemitsu, Y. Nie, et al., SirT1 knockdown in liver decreases basal hepatic glucose production and increases hepatic insulin responsiveness in diabetic rats, Proc. Natl. Acad. Sci. USA 106 (2009) 11288–11293.
[67] D. Chen, J. Bruno, E. Easlon, et al., Tissue-specific regulation of SIRT1 by calorie restriction, Genes Dev. 22 (2008) 1753–1757.
[68] A. Purushotham, T.T. Schug, Q. Xu, et al., Hepatocyte-specific deletion of SIRT1 alters fatty acid metabolism and results in hepatic steatosis and inflammation, Cell Metab. 9 (2009) 327–338.
[69] L. Bordone, D. Cohen, A. Robinson, et al., SIRT1 transgenic mice show phenotypes resembling calorie restriction, Aging Cell. 6 (2007) 759–767.
[70] P.T. Pfluger, D. Herranz, S. Velasco-Miguel, et al., Sirt1 protects against high-fat diet-induced metabolic damage, Proc. Natl. Acad. Sci. USA 105 (2008) 9793–9798.
[71] A.S. Banks, N. Kon, C. Knight, et al., SirT1 gain of function increases energy efficiency and prevents diabetes in mice, Cell Metab. 8 (2008) 333–341.
[72] Q.J. Zhang, Z. Wang, H.Z. Chen, et al., Endothelium-specific overexpression of class III deacetylase SIRT1 decreases atherosclerosis in apolipoprotein E-deficient mice, Cardiovasc. Res. 80 (2008) 191–199.
[73] S.I. Imai, SIRT1 and caloric restriction: an insight into possible trade-offs between robustness and frailty, Curr. Opin. Clin. Nutr. Metab. Care 12 (2009) 350–356.