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Role of Sirtuins in Adipose Tissue Development and Metabolism

Alina Kurylowicz

Abstract

Sirtuins (silent information regulators, sirts) via modification of histones, as well as transcription factors and co-regulators, control expression of other genes, particularly those involved in the organism response to stress. Detection of sirtuin expression in adipocytes initiated interest in their role in adipose tissue development and metabolism. This chapter presents how sirtuins control the critical steps of preadipocytes' differentiation and proliferation, as well as the process of adipose tissue browning. Moreover, it shows in vitro and in vivo data proving that sirtuins are involved in the regulation of lipogenesis, lipolysis, and secretory activity of adipose tissue. Due to all these reasons, sirtuins may constitute potential targets in the treatment of obesity and related complications.

Keywords: sirtuins, adipocytes, adipogenesis, lipid metabolism, adipokines

1. Introduction

Recent research widened our understanding of the role of adipose tissue from the simple energy storage to the metabolically and hormonally active organ that in response to environmental stimuli is able not only to activate lipolysis/lipogenesis but also to secrete several factors to communicate with and regulate the function of other organs. These findings allowed to understand the link between excess adiposity and the development of obesity-related complications and renewed interest in adipose tissue as a possible target for obesity-orientated therapies [1].

However, despite the constant progress in understanding its pathogenesis, the therapeutic potential to prevent and combat obesity is limited. Behavioral interventions, calorie restriction (CR) combined with the increased physical activity, do not assure persistent, long-term effects, while available pharmacological treatments allow for loss of 5–10% of initial weight. Therefore, there is a need for novel methods of treatment of obesity and its complications.

Studies on the influence of CR on the whole body function allow to identify sirtuins (silent information regulators, sirts)—essential players in different cellular metabolic pathways that seem to be crucial for the proper function of adipose tissue and in this way may constitute attractive therapeutic targets in the treatment of obesity and related complications.

2. A short review of the sirt system

The sirts are highly conserved regulatory proteins present almost in all species. Initially, they have been identified as class III histone deacetylases, nicotinamide adenine dinucleotide (NAD)-dependent enzymes responsible for the removal of acetyl groups from lysine residues in proteins, while some members of this family act also as mono-ADP-ribosyltransferases. Since acetylation and deacetylation are essential mechanisms of posttranslational modifications of proteins determining their activity, sirts were found to be involved in the regulation of distinct cellular pathways including, among others, those related to cell survival, apoptosis, inflammatory and stress responses, as well as lipid and glucose homeostases [2].

In human, seven sirt genes (*sirts*) have been identified that encode seven sirt enzymes of different structure, cellular localization, and tissue expression. All of them share a common conserved catalytic core region consisting of approximately 275 amino acids, forming a Rossmann fold domain (characteristic of NAD⁺/NADH-binding proteins) and a zinc-binding domain connected by several loops [2]. Outside the catalytic core, sirt enzymes possess variable N- and C-terminal regions that decide about their enzymatic activities, binding partners and substrates, as well as subcellular localization [3]. sirt1, sirt6, and sirt7 localize predominantly in the nucleus where via modifications of transcription factors, cofactors, and histones they participate in the regulation of energy metabolism, stress and inflammatory responses, DNA repair (sirt1 and sirt6), and rDNA transcription (sirt7) [4]. sirt2 is a cytoplasmic sirtuin and plays a role in cell cycle control [5]. sirt3 can be found in mitochondria where it takes part in the regulation of enzymes involved, e.g., in glycolysis, fatty acid (FA) oxidation, ketone body synthesis, and the catabolism of amino acids as well as of apoptosis and oxidative stress pathways. This sirtuin also has as a nuclear full-length form (FL-sirt3) that is processed to the short mitochondrial form. Therefore, sirt3 may regulate cellular metabolism both at the transcriptional and posttranscriptional levels. sirt4 is also localized in mitochondria and acts as ADP-ribosylase. Another mitochondrial sirtuin—sirt5—has a potent demalonylation and desuccinylation enzymatic activity and is involved in the regulation of amino acid catabolism [6]. Importantly, the subcellular localization of sirts may vary in different cell types and may depend on their molecular interactions as it was shown in the case of sirt1, sirt2, and sirt3 that can be found both in the nucleus and in the cytoplasm [4].

Expression of *sirts* was detected in various human tissues, including those crucial for the regulation of metabolism, e.g., hypothalamus, liver, pancreatic islets, skeletal muscles, and adipocytes [7–10]. In these tissues, sirts control the expression of other genes, particularly those involved in the organism response to stress. It was shown that *sirt* expression and activity of sirt enzymes are highly sensitive to several environmental factors, CR, exercise, and cold exposure that represents an adaptive mechanism in response to environmental stress [3]. Fluctuations in intracellular NAD⁺ levels in response to nutrient availability are believed to mediate in this phenomenon. When nutrients are plentiful, cellular metabolism relies on glycolysis to produce energy, leading to the generation of ATP and conversion of NAD⁺ to NADH. Low levels of NAD⁺ and high levels of NADH result in inactivation of the enzymatic activity of sirts. In turn CR leads to the elevation of NAD⁺ levels in most metabolically active tissues resulting in the increased sirt activity [11]. In humans, obesity leads to downregulation of sirt1 level in adipose tissue that can be restored by the weight loss [12].

3. sirts and adipogenesis

sirts are considered as potential targets for the treatment of obesity that results from their involvement in the regulation of adipogenesis and adipocyte browning.

3.1 Types of adipocytes

In mammals, there are two main types of adipose tissue that differ in their structure, physiology, and function. White adipose tissue (WAT) acts mainly as energy storage that releases FA for the production of adenosine triphosphate (ATP) during the process of β -oxidation.

Small mammals and human newborns, apart from white adipocytes, possess large deposits of brown adipose tissue (BAT) responsible for the non-shivering (adaptive) thermogenesis which is for them the most important regulatory mechanism for maintaining body temperature. The energy produced due to the oxidation of lipolysis-derived FA in the BAT mitochondria is released as heat, mostly thanks to uncoupling proteins (UCP). Age progression in humans was believed to be associated with complete atrophy of BAT; however, novel methods of imaging led to the identification of BAT stores in several areas of the adult human body, as well as of cells reminding brown adipocytes dispersed within WAT also known as beige/brite adipocytes (BeAT). These cells share common morphological features of white and brown adipocytes, and their number may increase upon different stimuli (e.g., cold, exercise, thyroid hormones, resveratrol). There are two theories regarding BeAT origin: they (i) differentiate from the progenitor cells resident in WAT or (ii) arise due to the transdifferentiation of white adipocytes. Given the role of adaptive thermogenesis in the whole body energy expenditure, stimulation of white adipocytes browning seems to be an attractive therapeutic pathway in the treatment of obesity and related metabolic disorders [13].

3.2 sirts and preadipocyte differentiation

Peroxisome proliferator-activated receptor γ (PPAR γ) is considered to be the main transcription factor responsible for promoting adipogenesis. *sirt1*, by interacting with two PPAR γ corepressors, nuclear receptor corepressor (N-CoR) and silencing mediator of retinoid and thyroid hormone receptors (SMRT), can attenuate adipogenesis [14]. Consistently, overexpression of ectopic *sirt1* blocks adipogenesis in 3T3-L1 cells, a culture of mouse adipocytes used as a model of adipocyte differentiation [15, 16]. Additionally, via activation of the Wnt signaling pathway, *sirt1* determinates mesenchymal stem cells (MSC) differentiation toward myogenic cells, while its inhibition in MSC promotes adipogenesis [17]. MicroRNA 146b (miR-146b) acts as a negative regulator of *sirt1* during adipocyte differentiation, giving a hope that interference with this miRNA may constitute a therapeutic perspective in the treatment of excess adiposity [18].

Another sirtuin family member—*sirt2*—has also shown an inhibitory effect on adipocyte differentiation [14]. In this process, *sirt2* deacetylates forkhead box O1 (FOXO1) transcription factor and subsequently represses PPAR γ transcriptional activity [19]. Therefore, *sirt2* overexpression inhibits adipogenesis, while its silencing has an opposite effect in 3 T3-L1 preadipocytes. Moreover, this inhibitory influence of *sirt2* on adipocyte differentiation discloses under CR that indicates the role of this sirtuin in the maintenance of energy homeostasis and suggests that *sirt2* activators could provide novel therapeutics of obesity and its complications; however, such compounds have not been developed yet.

sirt3 is essential for the activation of bioenergetic function of mitochondria at the early stage of adipocyte differentiation. Silencing of *sirt3* decreases the protein level of forkhead box O3a (FoxO3a) transcription factor and subsequently downregulates the expression of several antioxidant enzymes and increases oxidative stress in MSCs after adipogenic induction. In this way, *sirt3* depletion diminishes the ability of MSCs to undergo adipogenic differentiation and leads to adipocyte dysfunction [20].

Knockout of *sirt4* (encoding sirt4) leads to the decreased expression of adipogenic differentiation marker genes during differentiation of bovine adipocytes, suggesting that this sirtuin is crucial for the proper adipogenesis too [21].

sirt6 and *sirt7* were also found to be necessary for adipocyte differentiation, and their deficiency inhibits the development of preadipocytes toward white adipocytes. *sirt6* inhibits the expression of kinesin family member 5C (KIF5C) and enhances casein kinase 2 (CK2) and in this way promotes mitotic clonal expansion of adipocytes [22]. Deletion of *sirt7* or inhibition of *sirt7* diminishes the ability of mouse embryo fibroblasts and 3T3L1 cells to undergo adipogenesis. However, its overexpression did not rescue the preadipocyte differentiation, suggesting that *sirt7* is required but not sufficient to perform a full program of adipogenesis. Interestingly, *sirt7* is a metabolic target for miR-93, a negative regulator of adipogenesis, which expression is decreased in genetically obese ob/ob mice [23].

Experimental data suggest a direct interaction between *sirt1* and *sirt7* proteins at the molecular level as it was shown in immunoprecipitation assays and in vivo, where *sirt7* knockout (KO) mice have increased *sirt1* protein levels and enzymatic activity in WAT. Loss of *sirt7* leads to increased *sirt1* activity and recruitment to the PPAR γ promoter, causing downregulation of its expression, that can explain the lipodystrophic phenotype in *sirt7* KO mice [24].

The role of sirts in preadipocyte differentiation is schematically shown in Figure 1.

3.3 sirts and adipocyte browning

One of the approaches to the treatment of obesity is based on the activation in preadipocyte genes specific to BAT, which is characterized by high metabolic activity. Browning (brightening or beigging) of white adipocytes is an adaptive and reversible process that occurs in response to various stimuli.

Since *sirt1*, by direct deacetylation of PPAR γ , recruits the BAT program coactivator Prdm16 (PR domain containing 16) to PPAR γ , it also plays a crucial role

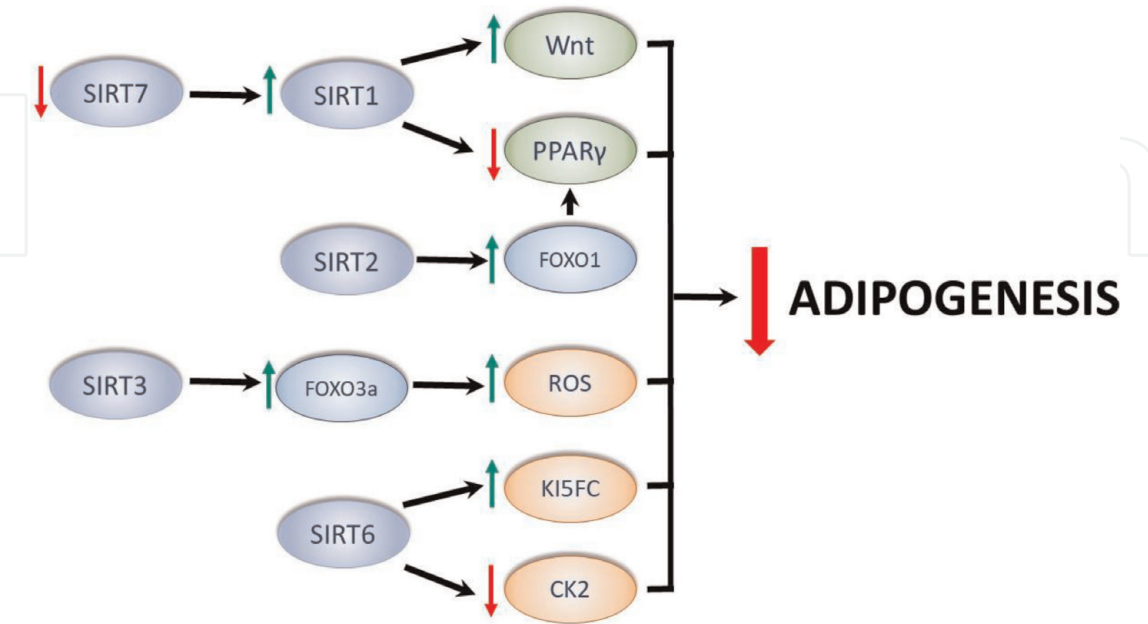


Figure 1.
Role of sirtuins in adipocyte differentiation. CK2, casein kinase 2; FOXO1, forkhead box O1; FOXO3a, forkhead box O3a; KIF5C, kinesin family member 5C; PPAR γ , peroxisome proliferator-activated receptor γ ; ROS, reactive oxygen species; sirt, sirtuin; Wnt, signaling pathway; $\uparrow$, upregulation and stimulation; $\downarrow$, downregulation and inhibition.

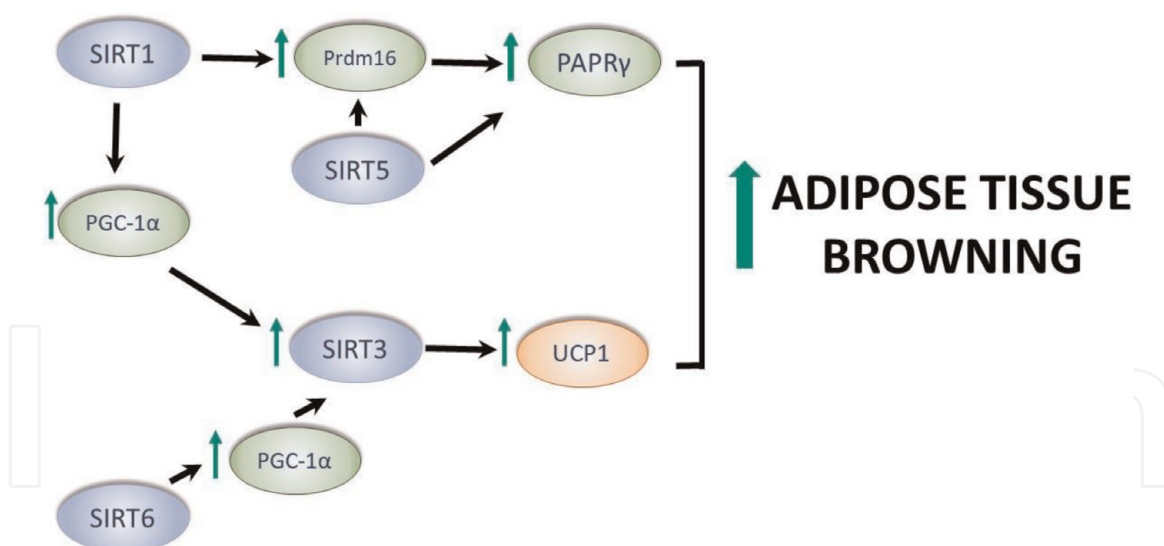


Figure 2.

Role of sirtuins in adipocyte browning. PGC-1 α , PPAR γ coactivator 1 α ; PPAR γ , peroxisome proliferator-activated receptor γ ; Prdm16, PR domain containing 16; sirt, sirtuin; UCP, uncoupling protein 1; $\uparrow$, upregulation and stimulation.

in the induction of genes typical for BAT and repression of WAT genes associated with insulin resistance [25]. Therefore, silencing of *sirt1* in 3T3-L1 preadipocytes leads to their hyperplasia and increased expression of WAT and inflammatory markers with a parallel decrease in BAT markers, whereas its activation results in increased adipocyte browning [26].

Cooperation among different sirtuins is crucial for the proper differentiation of brown adipocytes. For example, nutritional and thermal stress induces *sirt1*, which, by its deacetylation, activates PPAR γ coactivator 1 α (PGC-1 α) which upregulates transcription of *sirt3*. In cultures of brown adipocyte precursors (HIB1B cells), overexpression of *sirt3* resulted in the increased phosphorylation of the *cAMP* response element-binding protein (CREB) which then directly activates PGC-1 α promoter, resulting in the increased expression of UCP1 and in promotion of mitochondrial respiration [27]. However, subsequent experiments showed that the protein produced based on the cDNA used in this experiment lacked proper deacetylase activity, so this finding should be treated with caution [28]. Moreover, *sirt3* KO mice, despite mitochondrial protein hyperacetylation, showed no significant disturbances of the adaptive thermogenesis [29].

sirt5 was found to be essential for activation of brown adipogenic genes, and adipocyte differentiation in vitro and its knockout leads to the decrease in intracellular α -ketoglutarate concentration, which results in elevated histone methylation and transcriptional repression of *ppary* and *Prdm16*. Therefore *sirt5* KO mice present diminished browning capacity of WAT with subsequent cold intolerance [30].

Finally, depletion of *sirt6* in primary brown adipocytes reduces binding of the activating transcription factor 2 (ATF2) to the PGC-1 α promoter and in this way decreases basal mitochondrial respiration and maximal mitochondrial capacity [31].

The role of sirts in adipocyte browning is schematically shown in **Figure 2**.

4. sirts in control of adipose tissue function

Both in vitro and in vivo studies have implicated sirts in the regulation of adipose tissue metabolism. These studies let us understand the complexity of sirt

actions and gave hope that the modulation of their activity may constitute a new therapeutic strategy for the treatment of obesity and its metabolic complications including hyperlipidemia and chronic inflammation.

4.1 sirts in lipid metabolism

sirts are expressed in tissues and organs involved in lipid metabolism including the liver, skeletal muscle, and white and brown adipose tissues, where they control lipid synthesis, storage, and utilization both directly and indirectly (via control of insulin secretion).

During fasting *sirt1*, by deacetylation of PPAR γ corepressors (FOXO1 and PGC-1 α), stimulates in the adipose tissue transcription of the gene encoding adipose triglyceride lipase (ATGL) and subsequent lipolysis. This process is impaired in *sirt1* KO mice [15]. However, the results of animal studies regarding *sirt1* overexpression on body weight and composition are inconsistent [32, 33]. It is suggested that these discrepancies may be attributed to the different levels of *sirt1* expression between the transgenic animals as well as to the differences between strains and species used in the experiments.

Apart from the regulation of PPAR α -related pathways, *sirt1* may influence FA metabolism via downregulation of sterol regulatory element-binding proteins 1 and 2 (SREBP-1 and SREBP-2) transcription factors. *sirt1* overexpression or its activation by, e.g., resveratrol (RSV), prevents cleavage-induced activation of SERBs and their translocation to the nucleus where they promote transcription of genes crucial for sterol biosynthesis [34]. *sirt1* KO mice have lower SREBP-1 mRNA levels in the liver that correlates with decreased serum triglyceride concentrations [35]. Activation of *sirt1* also induces phosphorylation of AMP-activated protein kinase (AMPK) that protects against FA synthase induction and lipid accumulation caused by high glucose [36].

sirt1 also promotes deacetylation of liver X receptor (LXR) proteins and transcription factors that act as cholesterol sensors and regulate whole body cholesterol and lipid homeostasis [37]. LXR deacetylation is necessary both for their activation and induction of LXR target genes and for their subsequent ubiquitination. *sirt1* KO animals have reduced mRNA levels of LXR target genes that result in impaired reverse cholesterol transport—a process by which excess cholesterol is removed from the peripheral cells and transported to the liver where it can be converted to bile and excreted [38].

Fasting and cold exposure were found to increase the expression of *sirt2* in WAT. That results in the deacetylation of FOXO1 and subsequent repression of PPAR γ activity, lipolysis, and release of FA. Similar effect can be obtained by administration of isoproterenol that confirms the role of adrenergic signaling in the regulation of *sirt2* expression in WAT [19]. *sirt2* may also inhibit lipogenesis by deacetylation of ATP-citrate lyase (ACLY), an enzyme crucial for FA synthesis. A deacetylated form of ACLY is then ubiquitinated and degraded, while lipogenesis is reduced [39].

Livers from *sirt3* KO mice showed higher levels of FA oxidation intermediate products and triglycerides during fasting that was associated with decreased levels of FA oxidation when compared to wild-type animals. These findings are consistent with the fact that deacetylation of the long-chain acyl-coenzyme A dehydrogenase by *sirt3* was found to determine proper mitochondrial FA oxidation [40].

There are experimental data that other sirts are also involved in lipid metabolism: in adipose tissue, e.g., deacetylation of malonyl-CoA-decarboxylase by *sirt4* and desuccinylation of the hydroxyl-coenzyme A dehydrogenase by *sirt5* determine

proper mitochondrial FA oxidation [41, 42], while downregulation of sirt4 level results in the increased expression of genes involved in FA oxidation [43]. In experimental animals, sirt6 deficiency leads to impaired lipolytic activity and subsequent adipocyte hypertrophy [44]. On the molecular level, sirt6 deficiency increases the acetylation and phosphorylation of FOXO1, leading to its nuclear exclusion and decrease in its transcriptional activity that downregulates the expression of the gene encoding ATGL [44]. In turn, sirt6 overexpression in adipose tissue counteracts lipotoxicity caused by the high-fat diet by decreasing PPAR γ signaling and diacylglycerol acyltransferase 1 (DGAT1) activity [45]. The role of sirt7 in lipid metabolism is yet to be determined. In some studies sirt7 KO mice, due to the impaired management of the endoplasmic reticulum stress, have increased lipogenesis in the liver that results in liver steatosis and dyslipidemia [23], while sirt7 upregulation restores hepatic homeostasis in diet-induced obesity [46]. On the contrary, other researchers showed that sirt7 via inhibition of testicular receptor 4 (TR4) degradation promotes FA uptake, triglyceride biosynthesis, and storage [47].

These results constituted the basis for studies on the use of sirtuin-activating compounds in order to increase lipolysis and to prevent excess adiposity.

4.2 sirts in control of adipose tissue inflammation and secretory activity

Recent years widened our understanding of the role of WAT which is now considered not only an energy storage but also an important endocrine organ that via secreted mediators (e.g., cytokines and adipokines) may influence the function of the whole organism and be responsible for the development of obesity-related complications.

sirt1, by interference with the nuclear factor κ B (NF- κ B) signaling pathway, represses inflammatory gene expression in adipocytes and in macrophages infiltrating adipose tissue, which results in the improvement of insulin signaling and in the reduction of hyperinsulinemia accompanied by an increase in insulin sensitivity *in vivo* [48, 49]. sirt1 can inhibit NF- κ B signaling both directly and indirectly. Acting directly sirt1 deacetylates the RelA/p65 subunit of the NF- κ B, leading to its subsequent ubiquitination and degradation. Indirect inhibition of NF- κ B by sirt1 takes place by increasing activity of repressive transcriptional complexes, e.g., PPAR α , which can bind and inactivate RelA/p65 or increase expression of the gene encoding inhibitor α of κ B (I κ B α) [50].

Similarly, overexpression of sirt6 suppresses activation of the NF- κ B signaling in cell lines, firstly, by the direct interaction with NF- κ B subunit and, secondly, by deacetylation of histone H3 lysine 9 at target gene promoters leading to inhibition of the transcription of the proinflammatory genes [51]. Moreover, sirt6 by binding to the c-Jun downregulates expression of its target genes including interleukin 6 (IL-6), tumor necrosis factor α (TNF- α), and monocyte chemoattractant protein 1 (MCP-1) [52]. Subsequently, in model animals, sirt1 and sirt6 deficiency increases macrophage infiltration in adipose tissue and subsequent inflammation [44]. Moreover, sirt1 deficiency in adipocytes (probably due to the decreased expression of IL-4) led to the shift between the profiles of macrophages from the anti-inflammatory (M2) to the proinflammatory (M1) [53]. Therefore, sirt1- and sirt6-deficient adipocytes are more potent in promoting macrophages migration than wild-type cells that can be reversed by addition of MCP1 or adiponectin.

This last adipokine is a protein hormone with many desirable metabolic properties (including anti-inflammatory and anti-oxidative effects) almost exclusively produced in adipocytes. sirt1 tightly regulates the expression and secretion of adiponectin by adipocytes: enhancing formation of the complex between FOXO1

and C/EBP α (CCAAT/enhancer binding protein α) increases expression of the *ADIPOQ* gene, while inhibition of endoplasmic reticulum oxidoreductase Ero-L α decreases secretion of the high-molecular-weight (HMW) adiponectin [54]. Omentin-1 (intelectin-1) is another adipokine secreted, but not only by adipose tissue with anti-inflammatory properties that via activation of sirt1 exert its molecular effects on target genes [55].

In contrary, resistin is a hormone with biological characteristics opposite to adiponectin and omentin. It is secreted, apart from other sites, by adipose tissue; however, resistin expression in isolated human adipocytes is low, and its content in adipose tissue is proportional to the intensity of macrophages infiltration, which are the primary source of this adipokine [56]. Stimulation of sirt1 by RSV reduces resistin mRNA level and protein expression in macrophages, whereas sirt1 KO results in the opposite effect. On the molecular level, sirt1 interacts directly with the resistin promoter region at an activator protein 1 (AP-1) transcription factor response element as well as inhibits transactivation of the resistin gene by c-Jun pathway [57]. In animal model RSV, via activation of sirt1 was also found to decrease expression of visfatin—another adipokine secreted by macrophages infiltrating adipose tissue [58].

5. Sirtuins as targets for obesity treatment

Given their role in the regulation of lipid metabolism, adipogenesis and secretory activity of adipose tissue sirts constitute promising targets for novel therapies, targeting excess adiposity and associated metabolic disorders. However, the discovery of a compound that would be able to activate some sirt isoforms and to inhibit others is still a challenge. Another obstacle is to obtain tissue specificity of action for these compounds, since sirt activity may depend on the cell type and environmental factors.

Several sirt isoforms bear the potential for being used as therapeutic targets, but to date, only modulators of sirt1 have entered into the clinic. The most effective sirtuin-activating compound able to increase sirt1 activity in vitro by >10 fold is RSV [59]. RSV, naturally present in grapes and red wine, successfully inhibited maturation of preadipocytes and induced adipocyte apoptosis in cell cultures [60]. When administered to mice on the high-calorie diet, RSV was able to improve their metabolic and inflammatory profiles [61]. A reformulated version of RSV (resVida) with improved bioavailability was effective in decreasing glucose and triglyceride levels, reducing the intensity of inflammation and liver steatosis in obese men [62]. Another micronized formulation of RSV, SRT501, via activation of the similar set of genes as in the case of CR, was able to counteract negative consequences of a high-calorie diet in mice [63]. A composition containing RSV, leucine, β -hydroxymethyl butyrate (HMB), and ketoisocaproic acid synergistically activating sirt1 and sirt3 can induce FA oxidation and mitochondrial biogenesis. This combination, when tested on 3LT3-L1 preadipocytes, was more effective in activation of sirt1 than RSV alone but also able to activate sirt3. In c57/BL6 mice, treatment with a combination of low doses of RSV with either HMB or leucine resulted in a reduction of body weight and improvement of body composition accompanied by increased insulin sensitivity [64].

A variety of synthetic RSV derivatives with lower toxicity and higher potency to activate sirt1 have been invented. The example of them is SRT1720, able to increase deacetylation of sirt1 substrates in vitro and successfully applied in vivo to treat

insulin resistance in animal models of type 2 diabetes [63, 65, 66]. Apart from the favorable influence on glucose metabolism, SRT1720, by decreasing expression of lipogenic genes, occurred to be effective in the treatment of animal models of liver steatosis [67]. However, some studies question the beneficial effect of SRT1720 on metabolic parameters in animals fed a high-fat diet [68]. Moreover, RSV and other sirt1 activators (SRT1720, SRT2183, SRT1460) were found not to activate sirt1 directly but by the activation of AMPK that increases intracellular NAD⁺ levels and in this way induces deacetylation of sirt1 targets [69]. However, studies on sirt1 mutations that influence the protein structure suggest that there is also a direct interaction of RSV derivatives with the sirt1 enzyme molecule [64]. In humans, administration of SRT2104 (another RSV analogue) caused a decrease in serum total cholesterol and triglycerides levels as well as a significant reduction of the inflammatory response to *lipopolysaccharide* stimulation [70].

Despite their beneficial effects on adipose tissue metabolism, the critical issue that may arise during the use of sirt1 activators in everyday practice is their limited target specificity that might result in unexpected adverse effects [71]. That is why sirt modulators are still under consideration before they can be approved for the routine treatment of obesity and metabolic disorders.

Till now, the only aspects in which sirt inhibitors can be used to treat obesity-associated metabolic disorders are to induce favorable changes in body composition. sirt1-inhibiting compounds such as splitomycin, suramin, salermide, EX-527, or sirtinol can be used to increase the amount of skeletal muscle. This concept is based on animal studies where sirt1 KO mice display higher muscle growth than wild-type animals and mice with muscle-specific *sirt1* overexpression [64]. However, sirt1 inhibitors were not tested for that purpose in humans.

Recently there has been a rapidly growing interest in the role of miRNAs in fat cell development and obesity, and there is also evidence that miRNA plays a role in the regulation of sirt activity [18, 23, 46, 72]. Therefore, one can assume that strategies based on modifying the action of sirts by specific miRNAs may also be useful in treating obesity. However, these studies are still at a preliminary stage.

6. Final remarks and conclusions

If the remarkable effects of sirts on adipose tissue development and metabolism coming from animal studies hold up in humans, their activators and inhibitors may revolutionize the treatment of obesity and associated complications. However, one should remember that sirt activities are not limited to the regulation of metabolism and include, also, e.g., control of longevity, oncogenesis as well as the function of neural and cardiovascular systems. Therefore, compounds targeting sirts' system in order to combat excess adiposity have to be adipose tissue-specific to avoid potentially harmful and counterproductive side effects of global sirt activation/inactivation. Till now such compounds have not been accepted for the clinical practice; however, many of them are under evaluation, and it is very likely that shortly new therapeutic strategies aimed at selective and tissue-specific modulation of sirt activity will be registered for the treatment of obesity and its complications.

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References

- [1] Galic S, Oakhill JS, Steinberg GR. Adipose tissue as an endocrine organ. *Molecular and Cellular Endocrinology*. 2010;**316**:129-139. DOI: 10.1016/j.mce.2009.08.018
- [2] Sanders BD, Jackson B, Marmorstein R. Structural basis for sirtuin function: What we know and what we don't. *Biochimica et Biophysica Acta*. 2010;**1804**:1604-1616. DOI: 10.1016/j.bbapap.2009.09.009
- [3] Haigis MC, Guarente LP. Mammalian sirtuins—Emerging roles in physiology, aging, and calorie restriction. *Genes & Development*. 2006;**20**:2913-2921. DOI: 10.1101/gad.1467506
- [4] Haigis MC, Sinclair DA. Mammalian sirtuins: Biological insights and disease relevance. *Annual Review of Pathology*. 2010;**5**:253-295. DOI: 10.1146/annurev.pathol.4.110807.092250
- [5] Wang F, Nguyen M, Qin FX, Tong Q. sirt2 deacetylates FOXO3a in response to oxidative stress and caloric restriction. *Aging Cell*. 2007;**6**:505-514. DOI: 10.1111/j.1474-9726.2007.00304.x
- [6] Parihar P, Solanki I, Mansuri ML, Parihar MS. Mitochondrial sirtuins: Emerging roles in metabolic regulations, energy homeostasis and diseases. *Experimental Gerontology*. 2015;**61**:130-141. DOI: 10.1016/j.exger.2014.12.004
- [7] Zakhary SM, Ayubcha D, Dileo JN, Jose R, Leheste JR, Horowitz JM, et al. Distribution analysis of deacetylase sirt1 in rodent and human nervous systems. *The Anatomical Record*. 2010;**293**:1024-1032. DOI: 10.1002/ar.21116
- [8] Moschen AR, Wieser V, Gerner RR, Bichler A, Enrich B, Moser P, et al. Adipose tissue and liver expression of sirt1, 3, and 6 increase after extensive weight loss in morbid obesity. *Journal of Hepatology*. 2013;**59**:1315-1322. DOI: 10.1016/j.jhep.2013.07.027
- [9] Caton PW, Richardson SJ, Kieswich J, Bugliani M, Holland ML, Marchetti P, et al. Sirtuin 3 regulates mouse pancreatic beta cell function and is suppressed in pancreatic islets isolated from human type 2 diabetic patients. *Diabetologia*. 2013;**56**:1068-1077. DOI: 10.1007/s00125-013-2851-y
- [10] Acs Z, Bori Z, Takeda M, Osvath P, Berkes I, Taylor AW, et al. High altitude exposure alters gene expression levels of DNA repair enzymes, and modulates fatty acid metabolism by sirt4 induction in human skeletal muscle. *Respiratory Physiology & Neurobiology*. 2014;**196**:33-37. DOI: 10.1016/j.resp.2014.02.006
- [11] Chalkiadaki A, Guarente L. Sirtuins mediate mammalian metabolic responses to nutrient availability. *Nature Reviews Endocrinology*. 2012;**8**:287-296. DOI: 10.1038/nrendo.2011.225
- [12] Kurylowicz A, Owczarz M, Polosak J, Jonas MI, Lisik W, Jonas M, et al. sirt1 and sirt7 expression in adipose tissues of obese and normal-weight individuals is regulated by microRNAs but not by methylation status. *International Journal of Obesity*. 2016;**40**:1635-1642. DOI: 10.1038/ijo.2016.131
- [13] Zwick RK, Guerrero-Juarez CF, Horsley V, Plikus MV. Anatomical, physiological, and functional diversity of adipose tissue. *Cell Metabolism*. 2018;**27**:68-83. DOI: 10.1016/j.cmet.2017.12.002
- [14] Jing E, Gesta S, Kahn CR. sirt2 regulates adipocyte differentiation through FoxO1 acetylation/deacetylation. *Cell Metabolism*. 2007;**6**:105-114. DOI: 10.1016/j.cmet.2007.07.003

- [15] Picard F, Kurtev M, Chung N, Topark-Ngarm A, Senawong T, Machado De Oliveira R, et al. Sirt1 promotes fat mobilization in white adipocytes by repressing PPAR-gamma. *Nature*. 2004;**429**:771-776. DOI: 10.1038/nature02583
- [16] Puri N, Sodhi K, Haarstad M, Kim DH, Bohinc S, Foglio E, et al. Heme induced oxidative stress attenuates sirtuin1 and enhances adipogenesis in mesenchymal stem cells and mouse preadipocytes. *Journal of Cellular Biochemistry*. 2012;**113**:1926-1935. DOI: 10.1002/jcb.24061
- [17] Zhou Y, Zhou Z, Zhang W, Hu X, Wei H, Peng J, et al. sirt1 inhibits adipogenesis and promotes myogenic differentiation in C3H10T1/2 pluripotent cells by regulating Wnt signaling. *Cell & Bioscience*. 2015;**5**:61. DOI: 10.1186/s13578-015-0055-5
- [18] Ahn J, Lee H, Jung CH, Jeon TI, Ha TY. MicroRNA-146b promotes adipogenesis by suppressing the sirt1-FOXO1 cascade. *EMBO Molecular Medicine*. 2013;**5**:1602-1612. DOI: 10.1002/emmm.201302647
- [19] Wang F, Tong Q. sirt2 suppresses adipocyte differentiation by deacetylating FOXO1 and enhancing FOXO1's repressive interaction with PPARgamma. *Molecular Biology of the Cell*. 2009;**20**:801-808. DOI: 10.1091/mbc.E08-06-0647
- [20] Wu YT, Chi KT, Lan YW, Chan JC, Ma YS, Wei YH. Depletion of Sirt3 leads to the impairment of adipogenic differentiation and insulin resistance via interfering mitochondrial function of adipose-derived human mesenchymal stem cells. *Free Radical Research*. 2018;**52**:1398-1415. DOI: 10.1080/10715762.2018.1489130
- [21] Hong J, Li S, Wang X, Mei C, Zan L. Study of expression analysis of *sirt4* and the coordinate regulation of bovine adipocyte differentiation by *sirt4* and its transcription factors. *Bioscience Reports*. 2018;**38**(6):pii: BSR20181705. DOI: 10.1042/BSR20181705
- [22] Chen Q, Hao W, Xiao C, Wang R, Xu X, Lu H, et al. sirt6 is essential for adipocyte differentiation by regulating mitotic clonal expansion. *Cell Reports*. 2017;**18**:3155-3166. DOI: 10.1016/j.celrep.2017.03.006
- [23] Shin J, He M, Liu Y, Paredes S, Villanova L, Brown K, et al. sirt7 represses Myc activity to suppress ER stress and prevent fatty liver disease. *Cell Reports*. 2013;**5**:654-665. DOI: 10.1016/j.celrep.2013.10.007
- [24] Fang J, Ianni A, Smolka C, Vakhrusheva O, Nolte H, Krüger M, et al. Sirt7 promotes adipogenesis in the mouse by inhibiting autocatalytic activation of Sirt1. *Proceedings of the National Academy of Sciences of the United States of America*. 2017;**114**:E8352-E8361. DOI: 10.1073/pnas.1706945114
- [25] Qiang L, Wang L, Kon N, Zhao W, Lee S, Zhang Y, et al. Brown remodeling of white adipose tissue by SirT1-dependent deacetylation of Pparg. *Cell*. 2012;**150**:620-632. DOI: 10.1016/j.cell.2012.06.027
- [26] Abdesslem H, Madani A, Hani A, Al-Noubi M, Goswami N, Ben Hamidane H, et al. sirt1 limits adipocyte hyperplasia through c-Myc inhibition. *The Journal of Biological Chemistry*. 2016;**291**:2119-2135. DOI: 10.1074/jbc.M115.675645
- [27] Shi T, Wang F, Stieren E, Tong Q. sirt3, a mitochondrial sirtuin deacetylase, regulates mitochondrial function and thermogenesis in brown adipocytes. *The Journal of Biological Chemistry*. 2005;**280**:13560-13567. DOI: 10.1074/jbc.M414670200
- [28] Jin L, Galonek H, Israelian K, Choy W, Morrison M, Xia Y, et al. Biochemical characterization,

localization, and tissue distribution of the longer form of mouse sirt3. *Protein Science*. 2009;**18**:514-525. DOI: 10.1002/pro.50

[29] Lombard DB, Alt FW, Cheng HL, Bunkenborg J, Streeper RS, Mostoslavsky R, et al. Mammalian Sir2 homolog sirt3 regulates global mitochondrial lysine acetylation. *Molecular and Cellular Biology*. 2007;**27**: 8807-8814. DOI: 10.1128/MCB.01636-07

[30] Shuai L, Zhang LN, Li BH, Tang CL, Wu LY, Li J, et al. sirt5 regulates brown adipocyte differentiation and browning of subcutaneous white adipose tissue. *Diabetes*. 2019;**68**(7):1449-1461. DOI: 10.2337/db18-1103

[31] Yao L, Cui X, Chen Q, Yang X, Fang F, Zhang J, et al. Cold-inducible sirt6 regulates thermogenesis of brown and beige fat. *Cell Reports*. 2017;**20**: 641-654. DOI: 10.1016/j.celrep.2017.06.069

[32] Bordone L, Cohen D, Robinson A, Motta MC, van Veen E, Czopik A, et al. sirt1 transgenic mice show phenotypes resembling calorie restriction. *Aging Cell*. 2007;**6**:759-767. DOI: 10.1111/j.1474-9726.2007.00335.x

[33] Banks AS, Kon N, Knight C, Matsumoto M, Gutiérrez-Juárez R, Rossetti L, et al. SirT1 gain of function increases energy efficiency and prevents diabetes in mice. *Cell Metabolism*. 2008;**8**:333-341. DOI: 10.1016/j.cmet.2008.08.014

[34] Ye X, Li M, Hou T, Gao T, Zhu WG, Yang Y. Sirtuins in glucose and lipid metabolism. *Oncotarget*. 2017;**8**: 1845-1859. DOI: 10.18632/oncotarget.12157

[35] Wang GL, Fu YC, Xu WC, Feng YQ, Fang SR, Zhou XH. Resveratrol inhibits the expression of SREBP1 in cell model of steatosis via Sirt1-FOXO1 signaling pathway. *Biochemical and Biophysical Research*

Communications. 2009;**380**:644-649. DOI: 10.1016/j.bbrc.2009.01.163

[36] Hou X, Xu S, Maitland-Toolan KA, Sato K, Jiang B, Ido Y, et al. sirt1 regulates hepatocyte lipid metabolism through activating AMP-activated protein kinase. *The Journal of Biological Chemistry*. 2008;**283**: 20015-20026. DOI: 10.1074/jbc.M802187200

[37] Li X, Zhang S, Blander G, Tse JG, Krieger M, Guarente L. sirt1 deacetylates and positively regulates the nuclear receptor LXR. *Molecular Cell*. 2007;**28**:91-106. DOI: 10.1016/j.molcel.2007.07.032

[38] Groen AK, Oude Elferink R, Verkade HJ, Kuipers F. The ins and outs of reverse cholesterol transport. *Annals of Medicine*. 2004;**36**:135-145

[39] Lin R, Tao R, Gao X, Li T, Zhou X, Guan KL, et al. Acetylation stabilizes ATP-citrate lyase to promote lipid biosynthesis and tumor growth. *Molecular Cell*. 2013;**51**:506-518. DOI: 10.1016/j.molcel.2013.07.002

[40] Hirschey MD, Shimazu T, Goetzman E, Jing E, Schwer B, Lombard DB, et al. sirt3 regulates mitochondrial fatty-acid oxidation by reversible enzyme deacetylation. *Nature*. 2010;**464**:121-125. DOI: 10.1038/nature08778

[41] Savastano S, Di Somma C, Colao A, Barrea L, Orio F, Finelli C, et al. Preliminary data on the relationship between circulating levels of Sirtuin 4, anthropometric and metabolic parameters in obese subjects according to growth hormone/insulin-like growth factor-1 status. *Growth Hormone & IGF Research*. 2015;**25**:28-33. DOI: 10.1016/j.ghir.2014.10.006

[42] Park J, Chen Y, Tishkoff DX, Peng C, Tan M, Dai L, et al. sirt5-mediated lysine desuccinylation impacts diverse metabolic pathways. *Molecular*

Cell. 2013;**50**:919-930. DOI: 10.1016/j.molcel.2013.06.001

[43] Nasrin N, Wu X, Fortier E, Feng Y, Bare' OC, Chen S, et al. sirt4 regulates fatty acid oxidation and mitochondrial gene expression in liver and muscle cells. *The Journal of Biological Chemistry*. 2010;**285**:31995-32002. DOI: 10.1074/jbc.M110.124164

[44] Kuang J, Zhang Y, Liu Q, Shen J, Pu S, Cheng S, et al. Fat-specific Sirt6 ablation sensitizes mice to high-fat diet-induced obesity and insulin resistance by inhibiting lipolysis. *Diabetes*. 2017;**66**:1159-1171. DOI: 10.2337/db16-1225

[45] Kanfi Y, Peshti V, Gil R, Naiman S, Nahum L, Levin E, et al. sirt6 protects against pathological damage caused by diet-induced obesity. *Aging Cell*. 2010;**9**:162-173. DOI: 10.1111/j.1474-9726.2009.00544.x

[46] Cioffi M, Vallespinos-Serrano M, Trabulo SM, Fernandez-Marcos PJ, Firment AN, Vazquez BN, et al. MiR-93 controls adiposity via inhibition of Sirt7 and Tbx3. *Cell Reports*. 2015;**12**:1594-1605. DOI: 10.1016/j.celrep.2015.08.006

[47] Yoshizawa T, Karim MF, Sato Y, Senokuchi T, Miyata K, Fukuda T, et al. sirt7 controls hepatic lipid metabolism by regulating the ubiquitin-proteasome pathway. *Cell Metabolism*. 2014;**19**:712-721. DOI: 10.1016/j.cmet.2014.03.006

[48] Yoshizaki T, Milne JC, Imamura T, Schenk S, Sonoda N, Babendure JL, et al. sirt1 exerts anti-inflammatory effects and improves insulin sensitivity in adipocytes. *Molecular and Cellular Biology*. 2009;**29**:1363-1374. DOI: 10.1128/MCB.00705-08

[49] Yoshizaki T, Schenk S, Imamura T, Babendure JL, Sonoda N, Bae EJ, et al. sirt1 inhibits inflammatory pathways in macrophages and modulates insulin

sensitivity. *American Journal of Physiology. Endocrinology and Metabolism*. 2010;**298**:E419-E428. DOI: 10.1152/ajpendo.00417.2009

[50] Kauppinen A, Suuronen T, Ojala J, Kaarniranta K, Salminen A. Antagonistic crosstalk between NF- κ B and sirt1 in the regulation of inflammation and metabolic disorders. *Cellular Signalling*. 2013;**25**:1939-1948. DOI: 10.1016/j.cellsig.2013.06.007

[51] Lappas M. Anti-inflammatory properties of sirtuin 6 in human umbilical vein endothelial cells. *Mediators of Inflammation*. 2012;**2012**:597514. DOI: 10.1155/2012/597514

[52] Xiao C, Wang RH, Lahusen TJ, Park O, Bertola A, Maruyama T, et al. Progression of chronic liver inflammation and fibrosis driven by activation of c-JUN signaling in Sirt6 mutant mice. *The Journal of Biological Chemistry*. 2012;**287**:41903-41913. DOI: 10.1074/jbc.M112.415182

[53] Hui X, Zhang M, Gu P, Li K, Gao Y, Wu D, et al. Adipocyte sirt1 controls systemic insulin sensitivity by modulating macrophages in adipose tissue. *EMBO Reports*. 2017;**18**:645-657. DOI: 10.15252/embr.201643184

[54] Qiao L, Shao J. sirt1 regulates adiponectin gene expression through Foxo1-C/enhancer-binding protein alpha transcriptional complex. *The Journal of Biological Chemistry*. 2006;**281**:39915-39924. DOI: 10.1074/jbc.M607215200

[55] Zhang YY, Zhou LM. Omentin-1, a new adipokine, promotes apoptosis through regulating Sirt1-dependent p53 deacetylation in hepatocellular carcinoma cells. *European Journal of Pharmacology*. 2013;**698**:137-144. DOI: 10.1016/j.ejphar.2012

[56] Patel L, Buckels AC, Kinghorn IJ, Murdock PR, Holbrook JD, Plumpton C,

et al. Resistin is expressed in human macrophages and directly regulated by PPAR gamma activators. *Biochemical and Biophysical Research Communications*. 2003;**300**:472-476

[57] Carter S, Miard S, Roy-Bellavance C, Boivin L, Li Z, Pibarot P, et al. Sirt1 inhibits resistin expression in aortic stenosis. *PLoS One*. 2012;**7**:e35110. DOI: 10.1371/journal.pone.0035110

[58] Asadi S, Goodarzi MT, Saidijam M, Karimi J, Azari RY, Farimani AR, et al. Resveratrol attenuates visfatin and vaspin genes expression in adipose tissue of rats with type 2 diabetes. *Iranian Journal of Basic Medical Sciences*. 2015;**18**:537-543

[59] Howitz KT, Bitterman KJ, Cohen HY, Lamming DW, Lavu S, Wood JG, et al. Small molecule activators of sirtuins extend *Saccharomyces cerevisiae* lifespan. *Nature*. 2003;**425**:191-196. DOI: 10.1038/nature01960

[60] Rayalam S, Yang JY, Ambati S, Della-Fera MA, Baile CA. Resveratrol induces apoptosis and inhibits adipogenesis in 3T3-L1 adipocytes. *Phytotherapy Research*. 2008;**22**:1367-1371. DOI: 10.1002/ptr.2503

[61] Pearson KJ, Baur JA, Lewis KN, Peshkin L, Price NL, Labinskyy N, et al. Resveratrol delays age-related deterioration and mimics transcriptional aspects of dietary restriction without extending life span. *Cell Metabolism*. 2008;**8**:157-168. DOI: 10.1016/j.cmet.2008.06.011

[62] Timmers S, Konings E, Bilet L, Houtkooper RH, van de Weijer T, Goossens GH, et al. Calorie restriction-like effects of 30 days of resveratrol supplementation on energy metabolism and metabolic profile in obese humans. *Cell Metabolism*. 2011;**14**:612-622. DOI: 10.1016/j.cmet.2011.10.002

[63] Smith JJ, Kenney RD, Gagne DJ, Frushour BP, Ladd W, Galonek HL, et al. Small molecule activators of sirt1 replicate signaling pathways triggered by calorie restriction in vivo. *BMC Systems Biology*. 2009;**3**:31. DOI: 10.1186/1752-0509-3-31

[64] Mellini P, Valente S, Mai A. Sirtuin modulators: An updated patent review (2012–2014). *Expert Opinion on Therapeutic Patents*. 2015;**25**:5-15. DOI: 10.1517/13543776.2014.982532

[65] Milne JC, Lambert PD, Schenk S, Carney DP, Smith JJ, Gagne DJ, et al. Small molecule activators of sirt1 as therapeutics for the treatment of type 2 diabetes. *Nature*. 2007;**450**:712-716. DOI: 10.1038/nature06261

[66] Feige JN, Lagouge M, Canto C, Strehle A, Houten SM, Milne JC, et al. Specific sirt1 activation mimics low energy levels and protects against diet-induced metabolic disorders by enhancing fat oxidation. *Cell Metabolism*. 2008;**8**:347-538. DOI: 10.1016/j.cmet.2008.08.017

[67] Yamazaki Y, Usui I, Kanatani Y, Matsuya Y, Tsuneyama K, Fujisaka S, et al. Treatment with SRT1720, a sirt1 activator, ameliorates fatty liver with reduced expression of lipogenic enzymes in MSG mice. *American Journal of Physiology. Endocrinology and Metabolism*. 2009;**297**:E1179-E1186. DOI: 10.1152/ajpendo.90997.2008

[68] Pacholec M, Bleasdale JE, Chrnyk B, Cunningham D, Flynn D, Garofalo RS, et al. SRT1720, SRT2183, SRT1460, and resveratrol are not direct activators of sirt1. *The Journal of Biological Chemistry*. 2010;**285**:8340-8351. DOI: 10.1074/jbc.M109.088682

[69] Cantó C, Gerhart-Hines Z, Feige JN, Lagouge M, Noriega L, Milne JC, et al. AMPK regulates energy expenditure by modulating NAD⁺ metabolism and sirt1

activity. *Nature*. 2009;**458**:1056-1060.
DOI: 10.1038/nature07813

[70] Dai H, Sinclair DA, Ellis JL, Steegborn C. Sirtuin activators and inhibitors: Promises, achievements, and challenges. *Pharmacology & Therapeutics*. 2018;**188**:140-154. DOI: 10.1016/j.pharmthera.2018.03.004

[71] Villalba JM, Alcaín FJ. Sirtuin activators and inhibitors. *BioFactors*. 2012;**38**:349-359. DOI: 10.1002/biof.1032

[72] Kuryłowicz A, Wicik Z, Owczarz M, Jonas MI, Kotlarek M, Świerniak M, et al. NGS reveals molecular pathways affected by obesity and weight loss-related changes in miRNA levels in adipose tissue. *International Journal of Molecular Sciences*. 2017;**19**:E66. DOI: 10.3390/ijms19010066