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Chapter

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 (PPARγ) is considered to be the main transcription factor responsible for promoting adipogenesis. sirt1, by interacting with two PPARγ 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 PPARγ 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 PPARγ 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 beiging) of white adipocytes is an adaptive and reversible process that occurs in response to various stimuli.

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

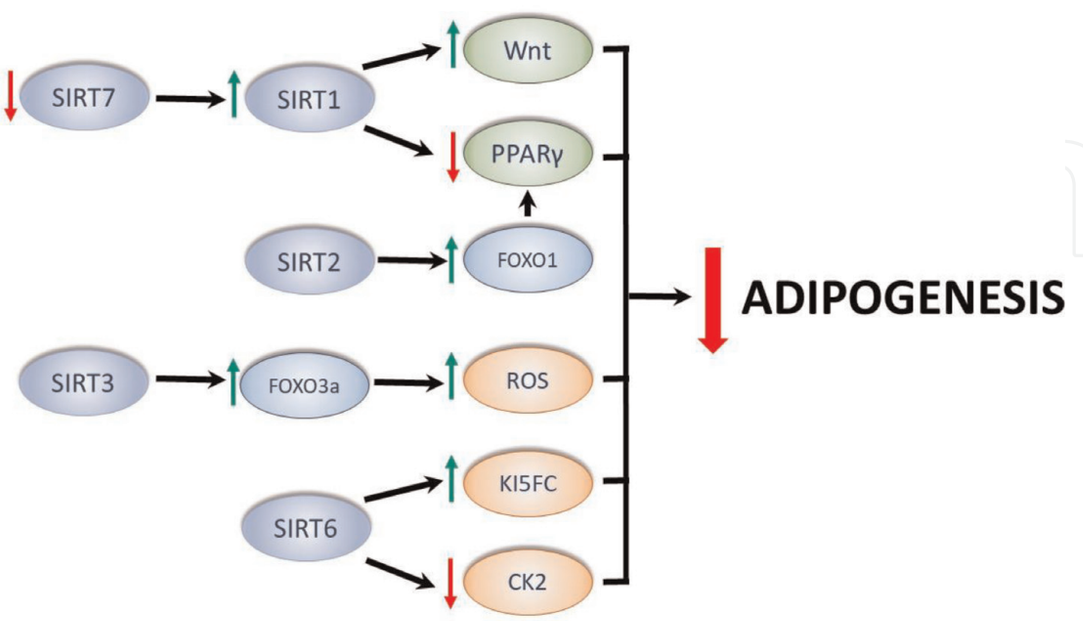


Figure 1.
Role of sirtuins in adipocyte differentiation. CK2, casein kinase 2; FOXO1, forkhead box O1; FOXO3a, forkhead box O3a; KI5FC, kinesin family member 5C; PPARγ, peroxisome proliferator-activated receptor γ; ROS, reactive oxygen species; sirt, sirtuin; Wnt, signaling pathway; ↑, upregulation and stimulation; ↓, downregulation and inhibition.

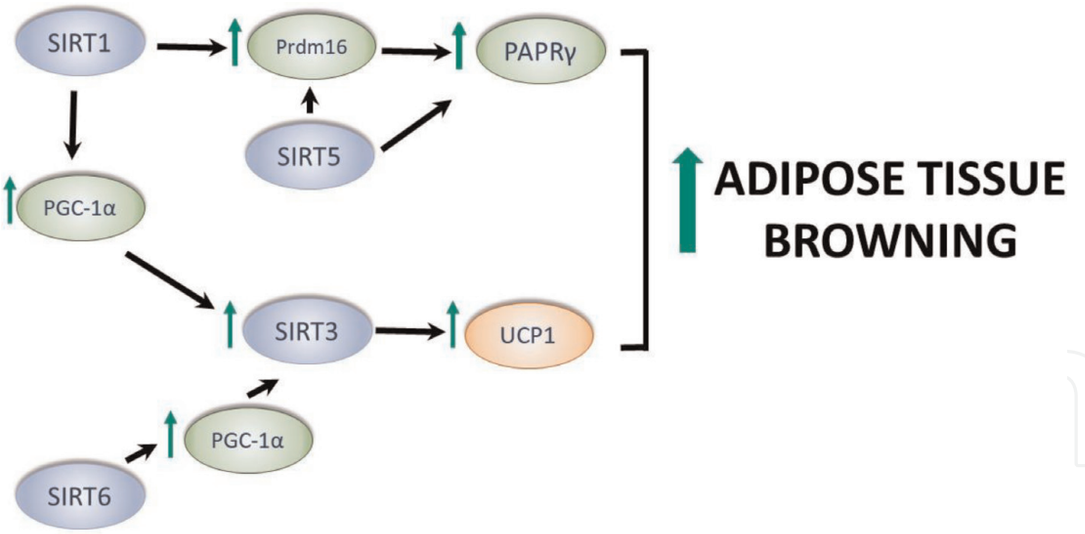


Figure 2.
Role of sirtuins in adipocyte browning. PGC-1α, PPARγ coactivator 1α; PPARγ, peroxisome proliferator-activated receptor γ; Prdm16, PR domain containing 16; sirt, sirtuin; UCP, uncoupling protein 1; ↑, upregulation and stimulation.

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 PPARγ coactivator 1α (PGC-1α) 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-1α 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 *pparγ* 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-1α 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 PPARγ corepressors (FOXO1 and PGC-*1α*), 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 PPARα-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 PPARγ 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 PPARγ 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 κB (NF-κB) 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-κB signaling both directly and indirectly. Acting directly sirt1 deacetylates the RelA/p65 subunit of the NF-κB, leading to its subsequent ubiquitination and degradation. Indirect inhibition of NF-κB by sirt1 takes place by increasing activity of repressive transcriptional complexes, e.g., PPARα, which can bind and inactivate RelA/p65 or increase expression of the gene encoding inhibitor α of κB (IκBα) [50].

Similarly, overexpression of sirt6 suppresses activation of the NF-κB signaling in cell lines, firstly, by the direct interaction with NF-κB 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/EBPα (CCAAT/enhancer binding protein α) increases expression of the *ADIPOQ* gene, while inhibition of endoplasmic reticulum oxidoreductase Ero-Lα 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 derivates 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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