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Review

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Sirtuins and their role as physiological modulators of metabolism

Sirtuiny i ich rola jako fizjologicznych modulatorów metabolizmu

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Summary

The sirtuins are a family of highly evolutionary conserved NAD^+-dependent deacetylases (SIRT1, 2, 3, 5). Certain human sirtuins (SIRT4, 6) have, in addition, an ADP-ribosyltransferase activity. SIRT1 and SIRT2 are located in the nucleus and cytoplasm; SIRT3 exists predominantly in mitochondria, and SIRT6 is located in the nucleus. The mammalian sirtuins have emerged as key metabolic sensors that directly link environmental nutrient signals to metabolic homeostasis. SIRT1 is involved in the regulation of gluconeogenesis and fatty acid oxidation, as well as inhibiting lipogenesis and inflammation in the liver. In addition, they contribute to the mobilization of fat in white adipose tissue, sense nutrient availability in the hypothalamus; regulate insulin secretion in the pancreas; as well as modulating the expression of genes responsible for the activity of the circadian clock in metabolic tissues. Sirtuins are implicated in a variety of cellular functions ranging from gene silencing, through the control of the cell cycle, to energy homeostasis. Caloric restriction, supported by polyphenols, including resveratrol, which is the SIRT1 activator, plays a special role in maintaining energy homeostasis. On a whole body level, the wide range of cellular activities of the sirtuins suggests that they could constitute a therapeutic target to combat obesity and related metabolic diseases. In addition, this work presents the current state of knowledge in the field of sirtuin activity in relation to nutritional status and lifespan.

Keywords: **sirtuins, metabolism, caloric restriction, resveratrol, life span**

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Abbreviations: **AADPR** – acetyl-ADP ribose nicotinamide, **AMPK** – AMP-activated protein kinase, **AceCS2** – acetyl coenzyme A synthetase 2, **CLOCK** – transcription factor activating the PERIOD gene, **CPS 1** – carbamoyl phosphate synthetase 1, **CR** – caloric restriction, **CRTC2** – coactivator 2 transcription factor **CREB** (CREB – cAMP response element-binding protein), **FOXO** – forheadbox type O transcription factor, **FXR** – farnesoid X receptor, **GDH** – glutamate dehydrogenase, **H4** – histone 4, **LXR** – liver X receptor, **NAD^+** – nicotinamide adeninedinucleotide, **NADH** – reduced nicotinamide

adeninedinucleotide, **NAM** –nicotinamide, **NFκB** – nuclear factor κB, **PDC** – pyruvate dehydrogenase complex, **PDP1** – pyruvate dehydrogenase phosphatase-1, **PDHA1** – pyruvate dehydrogenase E1 component subunit alpha, **PER2** – period circadian protein homolog 2, **PGC-1α** – PPAR γ coactivator 1α (peroxisome proliferator-activated receptor γ coactivator 1α), **PPAR γ** – peroxisome proliferator-activated receptor γ, **SREBP** – steroid regulatory element binding protein, **Sir2p** – silent information regulator 2 protein, **UCP2** – uncoupling protein 2.

INTRODUCTION

The „founder" of the sirtuin family is the silent information regulator 2 protein (Sir2p) detected in the cells of *Saccharomyces cerevisiae* yeast. The protein is a nicotinamide adenine dinucleotide (NAD^+) – dependent histone deacetylase which regulates chromatin silencing [5]. Yeast strains with altered Sir2p level show many metabolic disorders including transcriptional and recombination silencing, ageing and repair of DNA. Besides Sir2p, *S. cerevisiae* cells produce four other NAD^+-dependent histone deacetylases – Hist1 – Hist 4. In mammals, seven sirtuin homologues have been identified: SIRT1 – SIRT7 [16, 17]. The unusual homology of sirtuin genes from yeast to human ones indicates that these proteins play a significant vital role [17]. SIRT1 and SIRT2 are found both in the nucleus and cytoplasm, while SIRT6 and SIRT7 are only present in the nucleus. SIRT3, SIRT4 and SIRT5 are called mitochondrial sirtuins [54]. Based on the phylogenetically preserved basic domain, the sirtuins have been divided into five subclasses (I-IV and U). The subclass I includes SIRT1, SIRT2 and SIRT3, which show a deacetylase activity. SIRT4 with ADP-ribosyltransferase activity belongs to the subclass II [2, 21]. The subclass III includes SIRT5, which has a deacylase activity [95] and a weak deacetylase activity [56]. Sirtuins from subclass IV, i.e. SIRT6 and SIRT7, show both deacetylase and ADP-ribosyltransferase activities [34]. The subclass U includes sirtuins present in *archaea* and bacteria; they constitute a bridge between classes I and IV [17]. Mammalian sirtuins belonging to classes I, II and IV contain in their structure zinc as a cofactor. Zinc, as a nucleophilic element, participates in the activation of water molecules and enables hydrolysis of the acetamide bond between acetate and ε-amine residue of lysine [29]. Mammalian deacetylases from class III also contain zinc, but it is not directly involved in the reaction.

Initially, the function of sirtuins was associated with repression of transcription. The acetylated H1, H3 and H4 histones are physiological substrates of sirtuins. Lysine in position 16 of the H4 histone is the critical residue in sirtuin-mediated transcription silencing [38, 88]. It has been disclosed, however, that sirtuin substrates include many important non-histone proteins, such as transcription factors, enzymes, and structural proteins (Table 1).

SIRTUIN STRUCTURE AND MECHANISM OF ACTION

The sequence of seven genes of sirtuins present in humans is known. They encode proteins of molecular masses from 33.8 (SIRT5) to 81.7 kDa (SIRT1). Human sirtuins show a significant homology of sequences and contain conservative catalytic domains and NAD^+-binding domains (Fig. 1).

SIRT1 is the best-known mammalian sirtuin, which is similar to Sir2p in Saccharomyces *cerevisiae* yeast. It is present in the cell nucleus and catalyses the NAD^+-dependent deacetylation of many transcription-regulating factors. SIRT2 is also a deacetylase, but it is found both in the cell cytoplasm and nucleus and it is responsible for polymerisation of α-tubulin and stabilisation of microtubules. SIRT3 is present in the cell nucleus, where it participates in deacetylation of histones, which form nucleosomes, but also in mitochondria, to which it is transported under cellular stress conditions [93].

Sirtuins (SIRT1-SIRT3 and SIRT5) [75] catalyse the particular deacetylation reaction, in which first a hydrolysis occurs of the glycoside bond between nicotinamide and ADP-ribose residue in NAD^+ molecule. Then, the acetyl group is transferred from the bound protein substrate to ADP-ribose residue. That reaction yields 2'-O-acetyl-ADP ribose (AADPR) and nicotinamide (NAM) (Fig. 2). The reaction of deacetylation is inhibited by nicotinamide (final product of the reaction), but can be also regulated by $[NAD^+]/[NADH]$ ratio, which depends on the energy status of the cell. The absolute requirement of the sirtuin-catalysed reaction is the availability of NAD^+ co-substrate, what places sirtuins in the centre of cell energy metabolism regulation and can be a link between the energy status in the cytoplasm and nuclear signalling. Catabolic reactions, such as β-oxidation of fatty acids, glycolysis, degradation of proteins or citrate cycle, reduce NAD^+ to NADH. Under conditions of high energy potential – the intracellular NADH concentration increases significantly, while $[NAD^+]/[NADH]$ ratio usually changes in favour of NAD^+.

It seems that SIRT1 can play the role of a sensor affecting the gene expression process in order to ensure normal cell metabolism. AADPR (acetyl-ADP-ribose nicotinamide), the product yielded in deacetylation reaction catalysed by sirtuins plays also the role of a second messenger. It is involved in the process of transcription silencing and achieving a functional status of heterochromatin [38, 45]. AADPR achieves that in two independent mechanisms. The first one of them is induction of conformational changes in SIRT1, which enhance the silencing [45]. The second mechanism consists in binding AADPR to a macro histone variant (H2A1), which is present in inactive heterochromatin region [38].

Two sirtuins: SIRT4 and SIRT6 have no deacetylase activity (Table 1) but show the activity of NAD^+-dependent ADP--ribosyltransferase. The ability of human sirtuins to catalyse ADP-ribosylation of target proteins was suggested already in the first reports on those enzymes [83]. The detailed mechanism of that reaction has not been fully elu-

Table 1. Characteristics of human sirtuins.

Sirtuin	Intracellular localization	Enzymatic activity	Destinations	Biological effects	References
SIRT 1	*Cell nucleus*	Deacetylation	PGC-1α, FOXO, NFκB	Metabolism, inflammation, neurodegeneration	[23]
SIRT 2	*Cytoplasm, cell nucleus*	Deacetylation	H4, α-tubulin FOXO 3a	Cell cycle, carcenogenesis	[61, 89, 91]
SIRT 3	*Cell nucleus, mitochondrion*	Deacetylation	AceCS2,	Metabolism, ATP synthesis, thermogenesis	[1, 24, 28, 70, 77, 79, 82, 84]
SIRT 4	*Mitochondrion (matrix)*	ADP-ribozylation Lipoamidation	GDH PDC	ROS generation, Insulin secretion β-oxidation	[22, 42, 49, 57]
SIRT 5	*Mitochondrion, cytoplasm*	Deacetylation Demalonylation Desuccinylation	CPS1	Urea cycle	[11, 56, 67]
SIRT 6	*Cell nucleus*	ADP-ribozylation	DNA polimerase β	DNA repair, metabolism, inflammation	[32, 52, 53, 94]
SIRT 7	*Cell nucleus*	Deacetylation	RNA polimerase 1	DNA repair, transcription	[15, 86]

PGC-1α – PPAR γ coactivator 1α (peroxisome proliferator-activated receptor γ coactivator 1α), **PPAR** γ – peroxisome proliferator-activated receptor γ, **FOXO** – forheadbox type O transcription factor, **NFκB** – nuclear factor κB, **H4** – histone 4, **AceCS2** – acetyl coenzyme A synthetase 2, **GDH** – glutamate dehydrogenase, **PDC** – pyruvate dehydrogenase complex, **CPS 1** – carbamoyl phosphate synthetase 1.

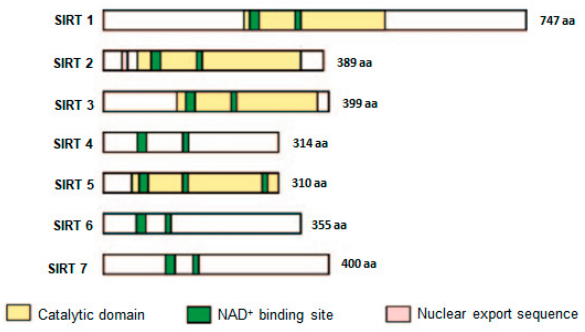

Fig. 1. Schematic structure of human sirtuins.
Presented acc. to [22], aa – amino acids.

cidated and remains the subject of studies [13, 25, 26]. The hypothesis by Hawse and Wolberger [26] seems most likely, suggesting that acetylated lysine is the target point for sirtuins. At the first stage of the reaction, acetyllysine reacts with NAD^+ to yield intermediate O-alkylamide. O-alkylamide can react with nicotinamide to regenerate the initial reagents (NAD^+ and acetyllysine) or with arginine, leading to ADP-ribosylation of the protein substrate and repeated acetylation of lysine.

SIRT3, SIRT4 and SIRT5 sirtuins are present in the mitochondrial matrix. They contain at the N-terminus of the peptide chain the targeting sequences enabling their transportation from the cytoplasm to the mitochondria. Among the three sirtuins present in the mitochondria, SIRT3 is the main mitochondrial deacetylase playing an important role in controlling the energy metabolism [47]. For that reason, SIRT3 expression is very high in many metabolically active tissues, such as the heart, brain, kidneys, liver, brown adipose tissue and muscles [62]. SIRT3 is synthesized in the form of inactive protein and in that form is transported to the mitochondrial matrix. After translocation, in a reaction catalysed by peptidase, 142 amino acids are detached from the N-terminal domain, what causes an activation of SIRT3 [64, 74, 78].

SIRT4 plays a significant role in the regulation of energy substrate consumption in the mitochondria [22, 58] and is strongly expressed in tissues, such as pancreatic β cells, liver, heart, brain and kidneys [2, 22, 54]. SIRT4 shows mono-ADP-ribosyltransferase and lipoamidase activities [22]. The basic substrate of SIRT4 is glutamate dehydrogenase (GDH). ADP-ribosylation of GDH leads to an inhibition of its enzymatic activity [44].

SIRT5 is a sirtuin, which is a demalonylase and desuccinylase [67]. SIRT5 shows a weak deacetylase activity and no ADP-ribosyltransferase activity [90]. SIRT5 removes acylic residues from lysine and therefore it seems to be more a deacylase than deacetylase [95].

Mitochondrial sirtuins also control the activity of pyruvate dehydrogenase complex (PDC) through allosteric regulation. Pyruvate dehydrogenase is a multienzymatic complex transforming pyruvate into acetyl-CoA, CO2 and NADH. Succinylation of PDC increases the activity of that complex [65]. PDC activity reduction occurs in the effect of SIRT5-catalysed desuccinylation of Lys residue [11]. SIRT3 increases PDC activity through deacetylation of pyruvate dehydrogenase (PDHA1) and pyruvate dehydrogenase phosphatase (PDP1). SIRT4 inhibits PDC activity through lipoamidase activity [49].

THE ROLE OF SIRT1 IN THE REGULATION OF METABOLISM

The proteins from the sirtuin family are a link between the nutrition status of the body and life span [20, 92]. The activity of sirtuins, as protein deacetylases and ADP-ribosyltransferases, is directed towards histones, transcription

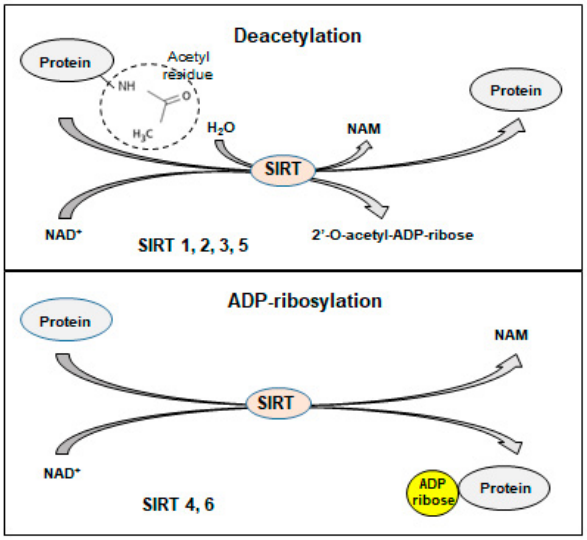

Fig. 2. Mechanism of reactions catalysed by sirtuins: deacetylation and ADP--ribosylation SIRT 1, 2, 3 and 5 sirtuins catalyse the reaction of acetyl residue transfer from ε-N-acylated lysine of the protein substrate to ADP-ribose in NAD^+ molecule. SIRT 4 and 6 sirtuins catalyse the reaction of protein ADP-ribosylation. **NAM** – nicotinamide.

factors, co-regulators and also enzymes involved in the regulation of gene expression and metabolism adjusted to the energy status of the cells [30, 41, 81]. Many of those enzymes, including also Sir2p, are related to the ageing process of many organisms – from yeasts to mammals. The protective effect of those proteins includes a positive regulation of response to stress and maintaining energy homeostasis [5, 72, 76, 92]. SIRT1, similarly as its yeast homologue Sir2p, is often called the master metabolic regulator due to the ability to modify and control many transcription factors involved in the homeostasis of the whole body (Fig. 3) [76].

SIRT1 deacetylates not only histone proteins but also many transcription factors and cofactors. SIRT1 contains no DNA-binding domain, what causes that the transportation to the target promoters is realised through a specific sequence of transcription factors and leads to chromatin remodelling and then to regulation of gene expression [69]. SIRT1 can also bind to the heterochromatin region and promote H1 histone deacetylation [88]. That epigenetic modification causes silencing of gene transcription and plays an important integral role, both in respect of health and life span of the organism [80]. The multitude of SIRT1 functions: deacetylation, epigenetic modifications and modulation of transcription factors indicate that SIRT1 is regarded as a molecular bridge between metabolic status and adaptive cell response at gene expression level.

CALORIC RESTRICTION AND SIRTUIN ACTIVITY

The activity of sirtuins is strictly controlled by various environmental factors. One of the regulators is the food consumption regimen [20]. Caloric restriction (CR) of 20–40% below calorie consumption ad libitum, but without signs of undernutrition, is a strong inductor of sirtuin activity [92]. An effect of CR has also been observed on the mean and maximum life span of many organisms, from yeasts, through: worms, fish, birds, to mammals. In mammals, CR application alleviates many pathologies associated with obesity and metabolic syndrome through reduction of fat content in the adipose tissue, reduction of triglyceride and LDL cholesterol concentrations in serum and increase of insulin sensitivity [14, 35]. SIRT1 is also an important factor regulating autophagia [43], which is the basic mechanism ensuring cell survival under hunger conditions [33, 73].

SIRT1 protein concentration under CR conditions increases in the brain, white adipose tissue, muscles, liver and kidneys [60, 68]. CR activates not only SIRT1 but also SIRT6. It has been found that fat-rich as well as carbohydrate-rich diet can inhibit both SIRT1 and SIRT6, what is consistent with its observed unfavourable effect on the hepatocytes (non-alcoholic fatty liver disease) [59].

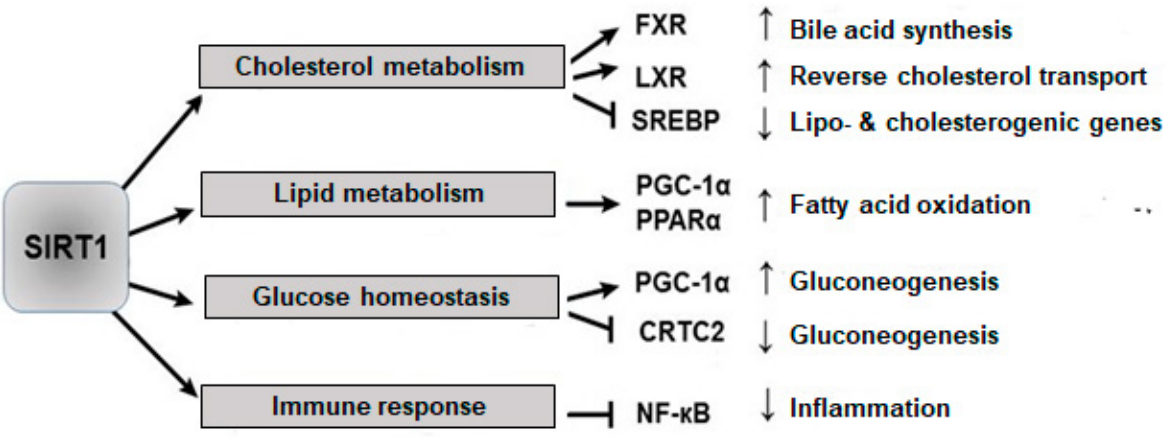

Fig. 3. SIRT1 activity in the regulation of metabolism
FXR – farnesoid X receptor, **LXR** – liver X receptor, **SREBP** – steroid regulatory element binding protein, **PGC-1α** – PPAR γ coactivator 1α (peroxisome proliferator-activated receptor γ coactivator 1α), **PPARα** – peroxisome proliferator-activated receptor α, **CRTC2** – coactivator 2 transcription factor CREB (CREB - cAMP response element-binding protein), **NF-κB** – nuclear factor κB.

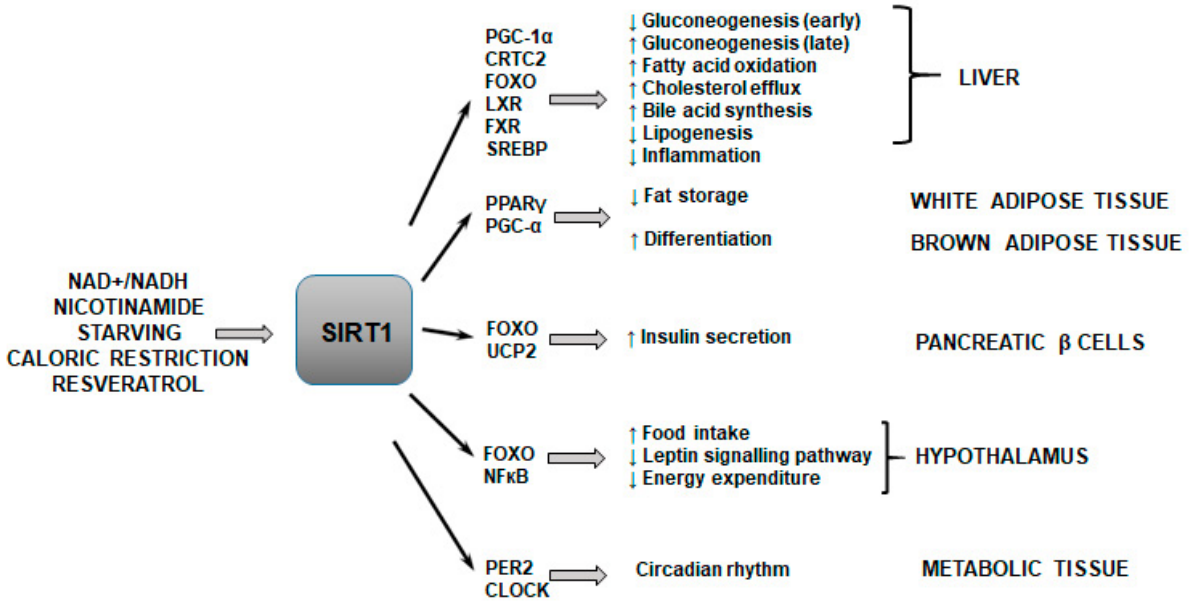

Fig. 4. Effect of SIRT1 on the energy metabolism of various tissues and organs
PPAR γ – peroxisome proliferator-activated receptor γ, **FOXO** – forhead box type O transcription factor, **UCP2** – uncoupling protein 2, **PER2** – period circadian protein homolog 2), **CLOCK** – transcription factor activating the PERIOD gene. The remaining abbreviations as under Fig. 3.

The fact that cellular NAD^+ concentration and NAD^+/NADH ratio, as important factors in the mechanism of SIRT1 activity regulation, are different in individual tissues, suggests that under CR conditions the changes of SIRT1 activity in various tissues occur in various directions [9]. SIRT1 activity is also independently modulated by various stimulators. For example, in murine myogenic cells (myoblasts) of C2C12 line, SIRT1 activity is stimulated by AMP-dependent protein kinase (AMPK) and by increased cellular NAD^+ concentration [7, 8]. In such cells SIRT1 activity is also controlled by adiponectin as a result of Ca^{2+}-mediated signalling and changes in the NAD^+/NADH ratio [31]. It should be mentioned, however, that the mechanisms regulating cellular NAD^+ concentration and SIRT1 activity in various physiological conditions have not been learned in detail and still remain not elucidated. Some study results suggest straight out that not the NAD^+/NADH ratio but rather posttranslational modifications and interactions between proteins significantly regulate SIRT1 activity [12].

SIRTUINS AND LIFE SPAN

It has been stressed in many reports that SIRT1 is the basic mediator of longevity. That view is, however, highly controversial. It has been demonstrated that SIRT1 overexpression in mice causes the so-called healthy ageing but the changes observed have not contributed to prolongation of life [27]. Furthermore, the conditions of maintaining full health harmony seem most important and such chance may be offered by adequate control of the calorie supply/consumption, in which sirtuins can be absolutely helpful. In caloric restriction, a significant effect on sirtuin (particularly SIRT1) activity was exerted by resveratrol, a natural vegetal polyphenol contained in grapes and berries [19, 50]. The mechanisms of the protective effect of resveratrol have not been fully elucidated as yet. Resveratrol shows many activities, important for the development of obesity, which include in the first place: anti-inflammatory effect, regulation of glucose metabolism or insulin sensitivity [46, 66, 85]. Not without significance are also its cardioprotective, neuroprotective or antitumour effects [3, 37, 40, 50, 71]. Among many activities of resveratrol, particular attention has been attracted by the reports on its participation in the secretion of many myokines and adipokines [36]. Moreover, resveratrol not only promotes SIRT1 activity but also enhances SIRT5 activity, which is confirmed by the engagement of another sirtuin in the energy homeostasis and the effect on the life span of cells [39]. The question of resveratrol effect remains, however, open: does resveratrol activate SIRT1 directly, or is its effect mediated by many signalling pathways? [4, 63].

SUMMARY AND PERSPECTIVES

In summary, sirtuins, being potential modulators under caloric restriction conditions, participate in important biological processes in mammals, including cell survival and ageing, DNA repair, DNA transcription, and in many metabolic pathways. The activity of sirtuins, particularly mitochondrial ones (SIRT3, SIRT4, SIRT5) is closely related to the development of diseases exacerbating with age, including cardiomyopathies, insulin resistance, immunity reduction, neurodegenerative diseases or other disorders [51, 87]. Among many functions of sirtuins, the important functions of SIRT1 come to the fore, indicating its ability to regulate and maintain homeostasis of the whole body, including the metabolism of cholesterol, fatty acid, glucose homeostasis and immune response (Fig. 3).

SIRT1 activity is regulated by cell energy status, micromolecular activators, interactions between proteins and posttranslational modifications. After activation, SIRT1 modulates various metabolic processes, both systemic and local (Fig. 4), which concern, among other processes: hepatic metabolism of lipids, adipose tissue activity, control of food intake, and expression of genes responsible for the circadian rhythm.

The findings suggesting life span prolongation in simple organisms (e.g. Saccharomyces cerevisiae yeast), in which an overexpression of sirtuins was observed, caused a significant development of studies on their role in the metabolism and ageing processes in humans. Energy metabolism disorders, genome instability and also response to stress in mice with sirtuin deficit, seem to suggest that human sirtuins are a significant element, of decisive importance for the balance between metabolism and ageing process. The multitude of activities of SIRT1 suggest that a pharmacological modulation of its effect can be an important therapeutic goal, particularly in obesity-related metabolic diseases of civilisation [55]. Much attention has been recently paid to caloric restriction mimetics [10, 18, 48]. Micromolecular SIRT1 activators, such as polyphenols (resveratrol) could be potentially used in the future in the treatment of metabolic diseases [6, 50, 55], although their future still remains the subject of an interesting debate: are they direct SIRT1 activators or whether their function is prevention of development of obesity and/or diabetes? [4, 63]. Therefore, further studies are indispensable, concerning systemic and tissue-specific effects of sirtuins also in other aspects of the ageing process, such as stem cell regeneration or control of protein quality in the mechanism of autophagia.

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