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Review Article

The role of sirtuins in aging and age-related diseases

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ABSTRACT

Sirtuins, initially described as histone deacetylases and gene silencers in yeast, are now known to have much more functions and to be much more abundant in living organisms. Sirtuins gained much attention when they were first acknowledged to be responsible for some beneficial and longevity-promoting effects of calorie restriction in many species of animals – from fruit flies to mammals. In this paper, we discuss some detailed molecular mechanisms of inducing these effects, and wonder if they could be possibly mimicked without actually applying calorie restriction, through induction of sirtuin activity. It is known now that sirtuins, when adjusting the pattern of cellular metabolism to nutrient availability, can regulate many metabolic functions significant from the standpoint of aging research – including DNA repair, genome stability, inflammatory response, apoptosis, cell cycle, and mitochondrial functions. While carrying out these regulations, sirtuins cooperate with many transcription factors, including PGC-1a, NFKB, p53 and FoxO. This paper contains some considerations about possible use of facilitating activity of the sirtuins in prevention of aging, metabolic syndrome, chronic inflammation, and other diseases.

Contents

1. Introduction . . . 000
2. Review . . . 000
2.1. Sirtuins are NAD$^+$-dependent lysine deacetylases . . . 000
2.2. SIRT1 . . . 000
2.3. SIRT2 . . . 000
2.4. SIRT3 . . . 000
2.5. SIRT4 . . . 000
2.6. SIRT5 . . . 000
2.7. SIRT6 . . . 000
2.8. SIRT7 . . . 000
3. Conclusion . . . 000
References . . . 000

1. Introduction

Sirtuins are orthologues of yeast Sir2 protein, where SIR stands for "silent information regulator", because in yeast, where Sir2 was first discovered, the protein silences certain genes (i.e. inhibits their expression), which results in the extension of replicative lifespan.

Sirtuins attracted some attention of researchers when it was presumed that inducing their activity may be responsible, or at least co-responsible for lifespan-extending effects of calorie restriction (i.e. anti-inflammatory effects, improved glucose tolerance, inhibition of hepatic steatosis and other degenerative disorders, as well as for improved endothelial function, regression of atherosclerotic plaques, and cancer prevention). It was also

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discovered that pharmacological induction of sirtuin activity can mimic beneficial effects of calorie restriction without actually applying calorie restriction. On the other hand, segmental inhibition of sirtuin activity might find some therapeutic use in future, mainly because of its proapoptotic effects in cancer cells, and inhibitory effects on proliferation of parasitic protozoa and human cells infected with viruses.

Initial hopes associated with the discovery of sirtuins [1]:

The findings concerning effects of calorie restriction, extending lifespan of many animal species, aroused presumptions that some molecular mechanisms underlying this beneficial effect may be shared and evolutionarily conserved. In 1998, research studies on *Sacharomyces cerevisiae* showed that gain of function of Sir2 gene results in changes of cellular metabolic pattern, involving – among others – epigenetic silencing of certain genes, improved genomic stability, and extension of the replicative lifespan [2].

In yeast, unequal division of cell content between the budding cell and the budded cell allows defining maximal lifespan on the basis of maximal number of cells which can be budded from a single cell before its death [3]. One of the factors limiting replicative lifespan in yeast cells is accumulation of rDNA circles (i.e. DNA fragments encoding rRNA) in their genome. Such circles can be removed through recombination, but for some reasons they are preferentially left in the budding parental cell [4], which finally results in its death, though the exact underlying mechanism is still unknown. It is known, however, that gain of function of Sir2 extends yeast replicative lifespan indeed through suppressing formation of the rDNA circles in the genome.

Q2 Since the gain of function of Sir2 orthologues in *C. elegans* and *D. melanogaster* also extends their lifespan [5,6], accumulation of the rDNA circles has been excluded as a mechanism of aging in those organisms. Therefore, it has been presumed that lifespan-extending effect of Sir2 (or its orthologue) amplification need not be determined by any definite molecular mechanism of action. Yet, its general beneficial effect on lifespan has been conserved (i.e. adjusted to organism-specific processes responsible for aging, regardless of their exact molecular pattern). Because calorie restriction (CR) has also shown such species-independent beneficial effect on lifespan, and CR was found to result in Sir2 upregulation in yeast, sirtuin activation is presumed to be a significant mechanism, or at least one of the significant mechanisms underlying longevity-promoting effects of CR [7]. A possible mechanism of CR action can be inhibition of insulin and IGF-dependent signaling (IIS), simply through decreasing tissue demand for insulin and IGFs, and correspondingly – secretion of those hormones [8]. During CR, IIS pathway inhibition coexists with the altered expression of sirtuins in various tissues. In *C. elegans*, CR generally stimulates Sir2 expression, but in mammals CR effects are more complex, in both tissue- and particular sirtuin-dependent manner [9]. According to some authors, gain in sirtuins activity seems to be a result of decreased ubiquitination (and hence – decreased degradation), not of increased synthesis [10]. However, additional cross-talk between inhibition of IIS pathway and enhanced activity of some sirtuins can exist (e.g. SIRT6 downregulates c-Jun, which is one of the crucial downstream effectors of IIS pathway; while miRNA encoded in an introne of sterol-regulatory element binding protein 1 (SREBP-1) gene downregulates SIRT6 translation [11,12]). Hence, existence of more than one mechanism underlying beneficial effects of CR is possible. Moreover – several CR induced mechanisms can complement one another.

Not all laboratories managed to repeat the initial lifespan-extending effect of sirtuins upregulation (e.g. positive correlation between SIRT3 activity and human healthspan, initially described for Italian population, was not confirmed in later studies on other populations) [13,14]. Despite the existence of straightforward correlation in *C. elegans* or fruit flies, sirtuin upregulation in mammals can work in a context-, tissue-, and particular sirtuin-dependent manner (e.g. 12-fold increase in SIRT1 activity in mice was neuroprotective, though it induced cardiac hypertrophy) [15]. Furthermore, studies on SIRT KO mice show a lifespan shortening only as a result of depletion of some sirtuins (SIRT3, SIRT6, SIRT7) but not others (SIRT5) [16]. Despite those controversies as to whether the calorie restriction indeed extends lifespan in all animal species [17], lack of its beneficial effect in Sir2 knock-out organisms [18] seems to support the hypothesis claiming that the lifespan-extending effect of CR can really consist in activation of some sirtuins.

Regardless of whether sirtuins do extend lifespan or not, recent studies on mice have shown that sirtuin modulation may have a beneficial effect on health, alleviating manifestations of many diseases, including diabetes, metabolic syndrome, cardiomyopathies, non-alcoholic hepatic steatosis, hyperinsulinism-induced dyslipidemia, chronic inflammation, neurodegenerative diseases, and some types of cancer. [19,20]

2. Review

2.1. Sirtuins are NAD^+-dependent lysine deacetylases

During the deacetylation catalyzed by sirtuins, a cleavage of chemical bond between nicotinamide and ribose in NAD^+ molecule is coupled with the transfer of acetyl group from the substrate (i.e. acetylated lysine residue) to ribose within the remaining ADP-ribose molecule. The final products of the reaction are: deacetylated lysine residue, O-acetyl-ADP-ribose, and nicotinamide [21]. Thus, sirtuin activity may be determined by the quantity of sirtuin molecules, availability of NAD^+ (as a co-substrate), and local concentration of nicotinamide which inhibits sirtuin activity (as a product, within the frames of end product inhibition). In addition, sirtuin activity may be influenced by other intracellular proteins [22,23].

The NAD^+ concentration in cells is maintained by keeping balance between its synthesis and its use. In humans, NAD^+ can be obtained from the tryptophane, nicotinic acid, or nicotinamide ribose [24]. Synthesis of the new NAD^+ molecules occurs mainly in the course of tryptophane metabolism through kynurenine pathway, as a result of eight reactions, each of them highly conserved in the course of evolution. In yeast, the activity of this pathway is regulated by other yeast sirtuin, Hst2, which serves as a sensor of NAD^+ concentration in the cell, and in case of too high concentration inhibits activity of kynurenine pathway [25]. It has been shown that in mammals SIRT1 can modulate NAD^+ biosynthesis, especially through salvage pathway, consisting in NAD^+ resynthesis from nicotinamide [26,27]. The biggest consumers of NAD^+ in the cell include mono-ADP-ribosyltransferases and poly-ADP-ribosyltranferases, which break glycozidic bond within NAD^+ molecules, and subsequently transfer ADP to other substrates. The DNA repairs, especially the repair of double strand breaks (DSB), requires intense activity of poly-ADP- ribose polimerase (PARP) and sometimes may adversely result in a critical loss of NAD^+ concentration in a cell [28].

Salvage pathway can prevent cellular NAD^+ depletion through re-synthesizing NAD^+ from nicotinamide [1]. Moreover, this can also induce the sirtuin activity by lowering the level of nicotinamide [29–31]. The key enzyme on this pathway is nicotinamide phosphoribosyltransferase (NAMPT) which has been shown to affect both the NAD^+ concentration in cells and the sirtuin activity [29–31]. It has been shown recently that NAMPT expression is regulated by transcription factors related to diurnal activity, which can affect diurnal oscillation of both the NAD^+ concentration and sirtuin activity in cells [26,27].

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NAD^+ is a cofactor of hydrogen transferases which can convert it into NADH (or vice versa). Therefore, redox status of the cell may influence the sirtuin activity by affecting the NAD^+/NADH ratio, and it is presumed that this kind of regulation can play a significant role in inducing the activity of sirtuins in case of CR [32], as well as in the course of some ontogeny-related processes – e.g. muscle differentiation [33] and neurogenesis [34].

Research studies made so far suggest that the activity of various sirtuins in a cell may be regulated at transcriptional level (by redox status of the cell), as well as at posttranscriptional level (by nutritional status of the cell) [35–37].

Sirtuins are class III deacetylases using NAD^+ as the main co-substrate [38]. Protein acetylation or deacetylation, as posttranslatory regulatory modifications, may serve as mechanisms of short-term regulation of their activity. There are 7 described sirtuins in mammals, although not all of them show deacetylase activity; some of them show deacylase activity (SIRT6) or desuccinylase and demalonylase activity (SIRT5). Yet, all of them contain 275-aminoacid catalytic subunit and all of them display equal demand for NAD^+ as a co-substrate during targeting their substrates – from histones to transcription factors [39].

Modulation of the sirtuin actions has been linked to regulation of such processes as gene expression, determining the pattern of cellular metabolism, apoptosis, as well as DNA repair, individual development, inflammatory response and neuroprotection [40,41].

Sirtuins have various sub-cellular locations in mammalian cells. SIRT1 is active mainly in the nucleus [42] whereas SIRT2 in the cytoplasm [43], but each of them can be moved between cell nucleus and cytoplasm [44,45]. SIRT3, SIRT4 and SIRT5 are active in the mitochondria, although it was shown that SIRT3 may be moved between nucleus and mitochondria under cellular stress [40]. SIRT6 and SIRT7 are nuclear proteins [46,47].

2.2. SIRT1

SIRT1 seems to be the most philogenetically similar to yeast Sir2, in terms of both amino-acid sequence and the profile of enzymatic activity. It is also the most frequently studied and best characterized human sirtuin. SIRT1 regulates mainly cellular metabolic pattern, while its own activity is regulated by availability of nutrients, being induced during moderate undernutrition (e.g. due to CR) [48].

SIRT1 stimulates mitochondrial biogenesis, as well as catabolism of triglycerides and cholesterol in liver, skeletal muscles and adipose tissue. In addition, it inhibits glycolysis while activating gluconeogenesis and fatty acid oxidation in most tissues [49]. SIRT1 regulates gluconeogenesis and glycolysis through PGC-1α transcription factor, which also results in the increased number and function of mitochondria, both in laboratory animals and in vitro [50,37].

In addition, SIRT1 can be induced in POMC-synthesizing neurons which are important for maintenance of body mass and glycaemic homeostasis through decreasing the intake of energy. Activation of SIRT1 in the hypothalamus is impaired in leptin knock-out mice [51], and lack of SIRT1 activity in hypothalamic neurons contributes to diet-induced obesity – mainly through reducing energy expenditure [52]. Moreover, recent studies have revealed a correlation between individual differences in SIRT1 activity (resulting from single-nucleotide polymorphism) and differences in body mass index, as well as in susceptibility to the diet-induced obesity [53].

Despite the suggested correlations between over-expression of SIRT1 and longevity, no correlations have been found in laboratory animals between individual differences in SIRT1 activity (related to single nucleotide polymorphism) and lifespan [54]. The presumed correlation between SIRT1 over-expression and longevity was attributed to the effect of SIRT1 on p53 (deacetylation, decreasing its proapoptotic activity) [42], and for the same reason, it has been presumed that over-expression of SIRT1 in already transformed tumor cells may promote their viability.

The basic activator of SIRT1 is CR, acting by upregulating AMPK and increasing cellular level of NAD^+ [8,48]. SIRT1 in turn upregulates $FoxO_1$ protein, which downregulates triglyceride lipase – a rate-limiting enzyme in lipogenic pathway [55]. SIRT1 inhibits lipogenesis also by inhibiting SREBP1c actions through deacetylation (DAC), resulting in inhibition of SREBP1c action at its target gene promoters (IATGP) [56,57]. SIRT1 depletion (even haploinsufficiency) promotes obesity in case of applying high fat diet (HFD) [58].

Results of some research studies suggest prevention of detrimental effects of HFD by SIRT1 upregulation [59], although some other studies suggest the reverse [9]. It is possible that these discrepancies result from differences in materials, methods, and contexts.

Selective upregulation of SIRT1 in the forebrain promotes increased expression of lipogenic genes in the white adipose tissue (WAT) [60].

SIRT1 can upregulate SIRT6 after forming a complex with $FoxO_{3a}$ and NRF1 transcription factor [61].

SIRT1 stimulates hepatic gluconeogenesis by acting on PGC-1α [62], and promotes the DNA damage repair during a cellular stress response [63]. Myc protein activity is downregulated by SIRT1 in normal cells through deacetylation of Myc molecule [64].

SIRT1 prevents carcinogenesis [65], because it promotes DNA damage repair, inhibits chronic inflammatory response, downregulates HIF-1α transcription factor (through deacetylation of its molecule), and upregulates another sirtuin – SIRT6. SIRT6 in turn deacylates the H3 histone at Lys 56 (H3 DAC K56), which also promotes DNA repair and conservation through silencing the gene expression [66,67]. However, in the already transformed tumor cells, upregulating SIRT1 may have a cytoprotective effect, which can be associated with upregulation of N-Myc oncoprotein [68] and ER-α estrogen receptor expression, as well as with general inhibition of apoptosis and CSP induction [69,70].

The anti-inflammatory action of SIRT1 occurs through inhibiting two important pro-inflammatory proteins – TNF-α and NF-kB [71–73].

The metabolic actions of SIRT1 include promoting fatty acid oxidation through deacetylating PGC-1α [74], as well as counteracting detrimental effects of hyperglycemia on vascular endothelium – through inhibition of p66Shc molecule [75]. The influence of the SIRT1 upregulation on atherogenesis seems to be context-dependent, because some research studies suggest its anti-atherogenic action [76], while some other studies suggest its pro-atherogenic action [60].

A moderate (7-fold) increase in SIRT1 activity can prevent cardiac hypertrophy, but an excessive increase (12-fold) can promote it [15].

The neuroprotective actions of SIRT1, shown on mouse models of the Alzheimer disease, result from upregulation of the ADAM-10 transcription factor [77] and destabilization of the tau proteins, through promoting their degradation [78]. Neuroprotective actions of SIRT1 have been also shown on mouse models of the Parkinson disease and the Huntigton disease [79–81]. At least some of those actions can result from induction of the chaperon protein synthesis by SIRT1 [79]. SIRT1 also stimulates neurite outgrowth [82], through inhibition of the mTOR signaling pathway [83].

Silencing of the SIRT1 gene accelerates the growth of tumor xenografts (HCT 116 cells), while amplification of SIRT1 has an inhibitory effect. High activity of SIRT1 was found in normal colon mucosa cells, as well as in benign adenomas, whereas over-expression of SIRT1 was found in 25% of colon adenocarcinomas at stages I/II/III and in very few tumors at stage IV [84]. On the other

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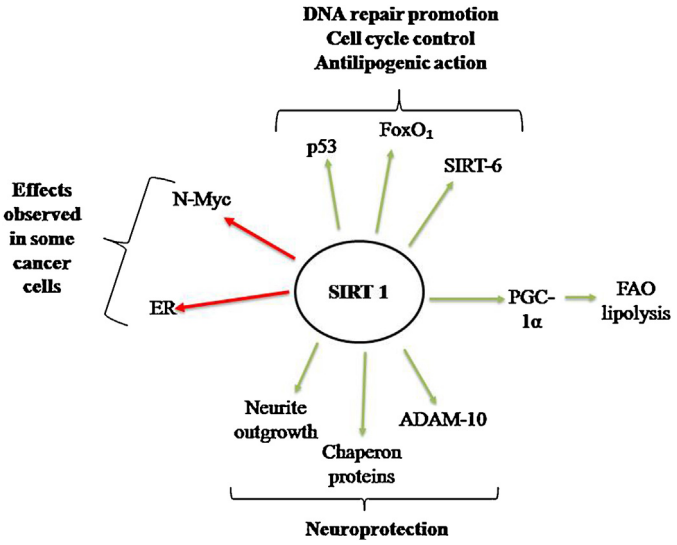

Fig. 1. The best known stimulatory actions of SIRT1.

hand, increased SIRT1 activity has been found in many human cancer cell lines, as well as in healthy tissue cells collected from patients suffering from various types of cancer (lung cancer, prostatic cancer, colon cancer, and CLL) [85,86]. These results may suggest that SIRT1 inhibition in cancer cells could possibly inhibit their growth, yet in some other human cancer cells (e.g. the breast cancer and hepatoma), an abnormally low activity of SIRT1 has been found. Other studies reported only a slightly elevated SIRT1 activity (in some thyroid cancers) or an unchanged activity (in some lung cancers, colon cancers, gastric cancers, urinary bladder cancers, and skin cancers) [87].

It should be noted that despite the observed upregulation of SIRT1, SIRT2 or SIRT7 in the already established cancer cell lines, it is usually accompanied by a loss of function of SIRT6. When considering CR as a possible method of cancer prevention, there are many premises that it is highly effective. Firstly, because upregulation of sirtuins in normal cells prevents their transformation, and secondly, because CR upregulates many other tumor suppressor proteins (TSPs) – like $FoxO_{3a}$, p53, SIRT3 and SIRT6 Q3 (Figs. 1 and 2).

2.3. SIRT2

In humans, SIRT2 is active mainly in the cytoplasm, where one of its substrates is the α-tubulin in microtubules [42,88]. SIRT2 also deacetylates Lys 16 within the H4 histone, which results in (and is probably required for) chromatin condensation at the G2/M checkpoint [89]. A lower expression of SIRT2 has been found in neoplastic cells, which may suggest that the SIRT2 activity restitution could be useful in antineoplastic therapy [90]. Moreover, elevated susceptibility to cancers, in a gender-dependent manner, has been reported in SIRT2 knock-out mice (increased prevalence of breast cancer in females and hepatic cell cancer in males). The research studies discussed above unequivocally suggest that sirtuins are, in practice, tumor suppressors, in spite of their theoretically anti-apoptotic activity. It may be accounted for by the fact that the anti-apoptotic action of sirtuins (through p53 deacetylation) is not their only action, and thus cannot be considered out of the context, because it is accompanied by many other actions, inducible also by calorie restriction – such as increased activity of FoxO proteins, Gadd-45 protein, as well as increased cellular resistance to oxidative stress (which can result from the increased concentrations of O-acetyl-ADP-ribose) [91,92]. Furthermore, increased activity of some sirtuins in the cells of the existing neoplasm gives no information about cause or context of its formation. In other words – it does not mean that an increased sirtuin activity was the primary cause of the disease. Nevertheless, these findings may contribute to development of some novel therapies (temporary inhibition of sirtuins as a pro-apoptotic treatment).

CR seems to be the main SIRT2 activator, probably due to elevating the cellular level of NAD^+. SIRT2 activity can be inhibited by HIF-1α transcription factor [93]. The overall effect of the SIRT2 upregulation on carbohydrate and lipid metabolism is similar to that of SIRT1, promoting gluconeogenesis through deacetylation of phosphoenolopyruvate carboxykinase (PEPCK) [94], as well as inhibition of the adipocyte differentiation [95] through deacetylation of $FoxO_1$ [96]. SIRT2 regulates mitotic progression by controlling the activity of the anaphase-promoting complex/cyclosome [89]. SIRT2 prevents carcinogenesis in normal cells, which has been shown on the basis of the fact that SIRT2 KO mice have increased cancer incidence and prevalence [97]. SIRT2 has also anti-inflammatory effects, because it inactivates NF-kB through deacetylation of its p65 subunit at Lys 310 [98]. In the central nervous system, SIRT2 regulates the oligodendrocyte differentiation, although the direction of this action has not been clearly settled (results of research studies performed so far contain some discrepancies, which may suggest SIRT2 action in a context-dependent manner) [88,99]. SIRT2 stimulates myelin production in Schwann cells by deacetylating Par-3 protein [100]. In spite of this, unlike SIRT1, SIRT2 shows no neuroprotective action.

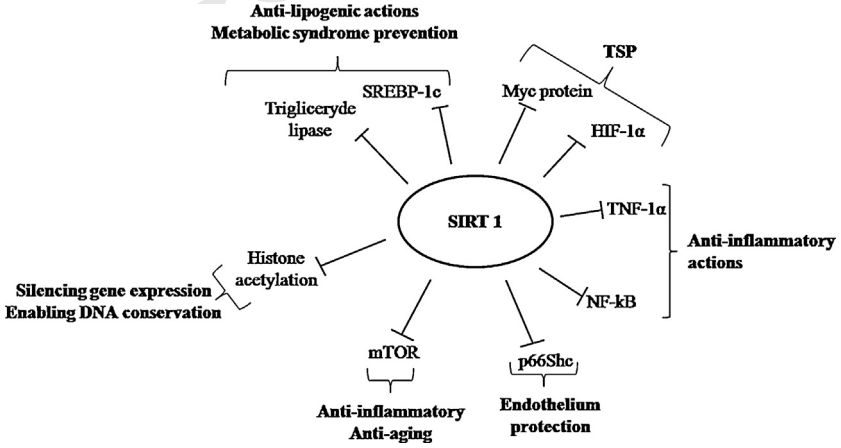

Fig. 2. The best known inhibitory actions of SIRT1.

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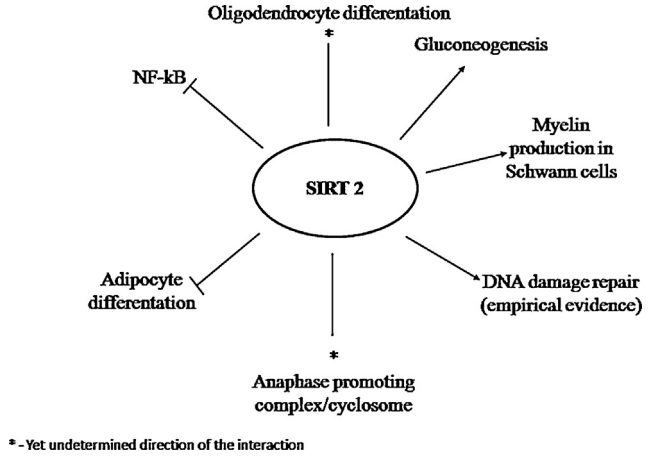

Fig. 3. The best known actions of SIRT2.

Moreover – neuroprotective effect has been correlated with the inhibition of SIRT2 [101] (Fig. 3).

2.4. SIRT3

It has been mentioned above that SIRT1 promotes mitochondrial biogenesis. SIRT3, SIRT4, and SIRT5 are active in the mitochondria by taking part in regulation of ATP synthesis, metabolism, apoptosis and intracellular signaling [102]. Among human sirtuins, correlation between a single nucleotide polymorphism and lifespan was found only for SIRT3. The VNTR polymorphism in the intron 5 of its encoding gene determines its enhancer activity, and interestingly enough – allele that lacks the enhancer activity is practically not found in living humans older than 90 years of age [13].

SIRT3 is a mitochondrial enzyme, and its mitochondrial substrates include: complex I, complex III, manganese superoxide dismutase (MnSOD) and isocitrate dehydrogenase 2 (IDH2) [103]. By deacetylating complex I and complex III, SIRT3 improves overall efficacy of the electron transport chain (ETC), thus preventing production of reactive oxygen species (ROS) as oxidative phosphorylation byproducts [104,105]. Besides, SIRT3 activates MnSOD (through deacetylation of its molecule at Lys 122) [106,107] and thus improves the efficacy of ROS removal from cells.

SIRT3$^{-/-}$ cells show a long-lasting, elevated concentration of ROS, which promotes the DNA damage and activates the HIF-1α transcription factor [108,109]. Excessive activity of HIF-1α is responsible for the metabolic reprogramming of tumor cells, widely known as the Warburg effect [108,110]. SIRT3 downregulates HIF-1α by decreasing the cellular concentration of ROS [109]. When considered together with the DNA damage-preventing action of SIRT3 (also dependent on the ROS depletion), it is clear that SIRT3 is a mitochondrial TSP [104,105].

SIRT3 actions as TSP include:

- decreased ROS production, combined with increased ROS inactivation by MnSOD (thus preventing the ROS-induced DNA damage and mutations)
- suppressing ATP production in cancer cells (through inhibition of HIF-1α and preventing expression of its target genes) [109,111]. In this field, SIRT3 cooperates with SIRT6, especially that both of them have the same activators
- activation of p53 through deacetylation [112]

Although some findings show upregulation of SIRT3 in already established tumor cells [113,114], this is nothing more than a confirmation of possibly cytoprotective role of sirtuins, found for most sirtuins, excluding SIRT6. However, SIRT3 KO mice have increased cancer incidence [103,108], which obviously suggests cancer-preventive actions of SIRT3 in normal cells.

A cohort study on Italian population revealed a correlation between the high activity of SIRT3 and longevity [13]. However, some newer studies failed to confirm the correlation for other populations [14,115].

The main activators of SIRT3 include CR and increased level of cellular NAD$^+$ [10,116]. Metabolic actions of SIRT3 (on carbohydrate and lipid metabolism) are similar to those of SIRT1 (stimulation of gluconeogenesis, inhibition of lipogenesis, activation of fatty acid oxidation, and some neuroprotective actions) [10] (Fig. 4).

2.5. SIRT4

SIRT4 was initially identified as an ADP-ribosylase affecting insulin secretion [117,118]. Unlike the other sirtuins, SIRT4 inhibits both lipolytic enzymes and AMPK [119]. What is interesting enough, the SIRT4 activity is inhibited by CR [119], which is also a unique effect, opposite to the effects observed for all the other sirtuins. Therefore, SIRT4 is thought to regulate the ATP homeostasis and to provide the retrograde signaling from the mitochondria to the nucleus, mediated by AMPK [119].

Mitochondrial action of SIRT4 includes improving the efficacy of ATP synthesis, through inhibition of the oxidative phosphorylation uncoupler – ANT2 [118,119].

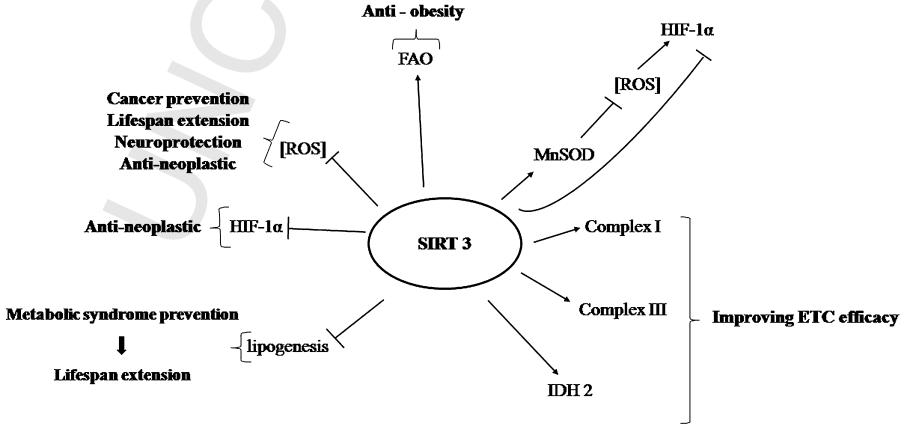

Fig. 4. The best known actions of SIRT3.

The main activator of SIRT4 seems to be the DNA damage, possibly through such proteins as ataxia-teleangiectasia mutated protein (ATM), as well as ATM and RAD3-related protein (ATR) [120]. During cell response to the DNA damage, SIRT4 inhibits the glutamine metabolite entrance to the tricarboxylic acid cycle (TCA) [120], which allows the use of the glutamine-derived nitrogen atoms in the purine nucleotide synthesis (necessary during the DNA repair). The SIRT4 depletion impairs the DNA damage repair and promotes the DNA damage accumulation. Although resistant to the diet-induced obesity, the SIRT4 KO mice have increased their cancer incidence, especially of the lung tumors [120,121].

CR is unlikely to promote DNA damage accumulation, despite having an inhibitory effect on the SIRT4 activity. Firstly, because CR stimulates SIRT1, SIRT6 and SIRT3 at the same time. Secondly, because moderate cellular undernutrition abrogates the ROS production per se [91], and in most cases, ROS are the main factor directly contributing to the DNA damage (Fig. 5).

Apparently, the mitochondrial sirtuins closely cooperate with SIRT1, not only through PGC-1α transcription factor, but also through enhancing the activity of SIRT6 by SIRT1. Thus, SIRT1 may regulate mitochondrial activity through affecting the rate of synthesis of the intermediate metabolites [122] and upregulating SIRT6 – by creating an activating complex of three proteins: $FoxO_{3a}$, p53, and the NRF transcription factor. SIRT5 can deacetylate cytochrome C, regulating not only the apoptosis but the cellular respiration as well [123].

2.6. SIRT5

SIRT5 is a mitochondrial enzyme showing the desuccinylase and demalonylase activity [124]. The significance of succinylation and malonylation as post-translatory modifications (PTMs) is still not fully understood. SIRT5 enhances the urea cycle by activating carbamoylophosphate synthetase (CPS) [125,126]. Indeed, the SIRT5 KO mice show a slightly elevated level of ammonia in their blood [16]. No other obvious metabolic abnormalities have been observed in the SIRT5 KO mice, although it might have been due to a relatively short time of observation (26 weeks) [16]. Another study found that SIRT5 can activate Cu/Zn SOD (SOD1), thus decreasing the cellular ROS concentration [127]. The same study found a cancer-preventive function of SOD1 upregulation in the cell culture in vitro [127]. It is now known that newly discovered PTMs removed by SIRT5 can regulate the activity of enzymes affecting the redox status of cells and energy utilization, but we have just started to learn about the exact influence of SIRT5 on these pathways.

2.7. SIRT6

SIRT6 plays the key role in the DNA repair and in the maintenance of genomic stability – mainly by integrating the actions of the DNA-damage signaling factors with the recruitment and activation of the DNA-repairing enzymes, especially during the oxidative stress [128]. SIRT6 knock-out mice develop significant metabolic disorders which cause their death within four weeks from their birth [129]. SIRT6 overexpression induces intense apoptosis in the cancer cells but not in normal cells, which makes it an attractive "target" for the future antineoplastic medications [130].

SIRT6 is thought to be a significant tumor suppressor protein (TSP) and an important regulator of mammalian lifespan. In mice, SIRT6 is most abundantly expressed in liver, heart, and skeletal muscles [129]. As to the subcellular location, SIRT6 is a nuclear protein, although it is also present in the endoplasmic reticulum, where it deacetylates TNF-α [131]. Nuclear substrates of SIRT6 include the H3 histone (deacylated by SIRT6 at Lys 9 or 56)[131,132] and the H2B histone (deacylated at Lys 12) [133]. SIRT6 was initially found to have a relatively small deacetylase activity in reference to the soluble histones [134], however, it has a much stronger activity toward nucleosome-bound histones [134]. Recent studies have shown that SIRT6 has also a deacylase activity [133] and interacts physically with some non-histone proteins – not only through deacylation, but also through direct physical interaction (PIA), inhibition of their binding to the target gene promoters (IATGP) and destabilization of their binding at the target gene promoters (DATGP) [135].

SIRT6 inhibits TNF-α by deacylating its molecule at Lys 19 and 20 [133,135], which is thought to be responsible for the anti-inflammatory actions of SIRT6. Another protein inhibited by SIRT6 is the RELA subunit of NF-kB. Interaction of SIRT6 with the RELA subunit of NF-kB leads to inactivation of the NF-kB action through IATGP and DATGP [135].

The main activators of SIRT6 include: calorie restriction (CR) [61], p53 (independently of the nutritional status of the cell) [10], c-Fos protein [136], and an increased concentration of NAD^+ within the cell [20]. CR activates SIRT6 indirectly, by upregulating SIRT1,

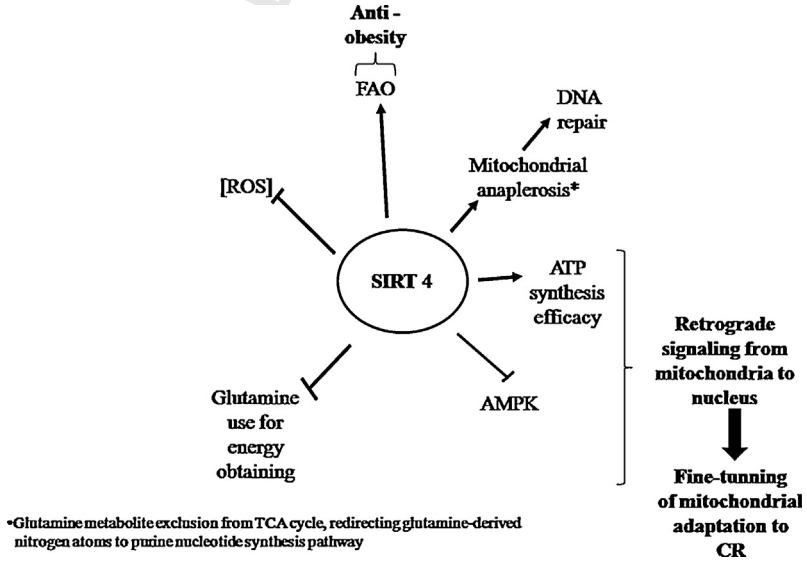

Fig. 5. The best known actions of SIRT4.

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$FoxO_{3a}$ and nuclear respiratory factor 1 (NRF-1). These three proteins form a complex which is subsequently phosphorylated at the SIRT6 gene promoter binding sites [137]. Some studies suggest that CR upregulates SIRT6 through stabilizing the already existing SIRT6 molecules, because actinomycin D (a widely known inhibitor of the mRNA transcription) does not abrogate the SIRT6 upregulation by CR [10]. c-Fos activates SIRT6 through binding to the activating protein 1 (AP-1) binding site at a SIRT6 gene promoter [136]. SIRT6 can be downregulated by miR-33b (encoded in an introne of the SREBP gene) [12].

The histone deacylation results in a decreased distance between the histones and the DNA (because a hydrogen atom is much smaller than the acyl group). The reduced distance between the histones and the DNA makes it more difficult for the transcription factors to access DNA, and this is thought to be a mechanistic rationale for both the gene silencing and for promoting DNA conservation/repair. Indeed, in $SIRT6^{-/-}$ cells, a global hyperacylation of histones has been found, especially during the cell response to a DNA damage [133]. These cells also showed loss of genomic stability and impairment of the DNA damage repair [133].

SIRT6 promotes stabilization of Werner syndrome ATP-dependent helicase (WRN) molecule – both when repairing double strand breaks (DSBs) and during DNA replication [138]. Increased WRN stabilization prevents appearance of the telomere abnormalities during DNA replication [138]. Another group of proteins upregulated by SIRT6 includes the DNA damage dependent protein kinases (DNA-PKcs) – also significant for effective DNA repair [138].

The H3 histone deacylation at Lys 56 (DAC H3K56) also contributes to the improved efficacy of the DNA damage repair. Increased acylation of H3K56 promotes genomic instability, and SIRT6 upregulation prevents this effect [132]. The H3K56 deacylation by SIRT6 is most marked during the S phase of the cell cycle [132,139].

SIRT6 also upregulates CtIP (the CtBP-interacting protein). Upregulation of CtIP by SIRT6 is important for the DSB repair through homologous recombination (HR) [140–142], because CtIP protein is needed for excision of the damaged DNA fragments from both strands [141]. SIRT6 upregulates CtIP through deacylation of its molecule at Lys 432, 526 and 604 [143].

Artificial mutation of the CtIP (substitution of lysines with arginines, which makes acylation impossible) partially rescues the DSB repair through HR, even in the $SIRT6^{-/-}$ cells [143].

SIRT6 activates PARP-1 through mono-ADP-ribosylation at Lys 521 [128]. PARP-1 binds to the DNA damage sites and subsequently activates itself by auto-ADP-ribosylation [144]. In this context, PARP-1 activation by SIRT6 promotes the DSB repair during an oxidative stress – both through HR and through the non-homologous end joining (NHEJ) [144]. All these three proteins (i.e. PARP-1, WRN, and DNA-PKcs) seem to be necessary for an effective DSB repair [144].

$SIRT6^{-/-}$ cells show hyperacylation of H3K9 in telomeres, which leads to increased expression of the subtelomeric genes (e.g. ISG-16). [145]. This suggests that SIRT6 also protects the telomeres – thus protecting the cells not only from genotoxic, but also from replicative stress [146,147].

SIRT6 KO mice do not show abnormalities at birth, but after 3 weeks of life they develop metabolic disorders, such as: loss of subcutaneous fat, lordokyphosis, colitis, severe lymphopenia, osteopenia, decreased serum level of IGFs, and progressive hypoglycaemia which finally leads to their death about 4 weeks after birth [148]. The lifespan of the SIRT6 KO mice can be slightly extended through inactivation of the NF-kB RELA subunit. In normal mice, physical interaction between SIRT6 and RELA inhibits the NF-kB action at its target gene promoters [149], which prevents such NF-kB dependent processes as induction of the cellular senescence phenotype (CSP) and apoptosis. Another method used for lifespan extension of the SIRT6 KO mice is counteracting hypoglycaemia by replacing water with 10% glucose solution. The hypoglycaemia in SIRT6 KO mice is due to massive uptake of glucose by too many cells at the same time [148], and this effect results from hyperactivity of the HIF-1α transcription factor. In healthy mice, HIF-1α is inhibited by SIRT6 [150]. Hyperactivity of HIF-1α is responsible both for the lethal hypoglycaemia occurring in SIRT6 KO mice [148] and for the metabolic reprogramming occurring in tumor cells, known as the Warburg effect (increased activity of the GLUT1 and GLUT4 glucose transporters, increased glycolysis even during oxygen deprivation, increased lactic acid production) [151,152]. The Warburg effect is crucial for energy obtaining by cancer cells, and inhibition of the Warburg effect accounts for tumor suppressive function of SIRT6 and SIRT3 [108,153]. SIRT6 inhibits the action of c-Jun (through DAC H3K9 at its target promoters) [11], so it inhibits activity of the whole IIS pathway, because the c-Jun protein is an important element of the IIS pathway [11]. The beneficial, longevity promoting effects of the IIS inhibition are widely known, and the inhibitory effect of SIRT6 on c-Jun can be partly responsible for extending the lifespan by CR.

SIRT6 deacylates the GCN-5 protein, and thus it affects the activity of PGC-1α, modulating the hepatic gluconeogenesis [154]. The SIRT6 overexpression protects mice from the detrimental effects of HFD, such as: accumulation of the epididymal fat, hypertriglyceridemia and insulin resistance [155]. Selective depletion of the neuronal SIRT6 in mice results in growth attenuation, increased appetite and obesity [156].

SIRT6 extends the maximum lifespan in male, but not in female mice – probably through inhibition of IIS pathway in the white adipose tissue [157]. The underlying reasons of this gender-related specificity remain unknown. Perhaps the IIS pathway is constitutively less active in female mice (hence the less obvious effects of its inhibition by SIRT6).

SIRT6 as a TSP:

SIRT6 can suppress carcinogenesis through inhibition of the Warburg effect [150,158], through inhibition of survivin actions (deacylating H3K9 at its target gene promoters) [136], and through inhibition of c-Jun (deacylating H3K9 at its target gene promoters). Because c-Jun inhibits p53, inhibition of c-Jun by SIRT6 can rescue the p53 function [11,131,159,160]. Besides, SIRT6 inhibits actions of the Myc protein (deacylating H3K56 at its target gene promoters) [161] and attenuates some NF-kB dependent actions that can be cancer-promoting in a context dependent manner [91,149]. SIRT6 also activates other TSPs, including CCNDBP1 [135,162] and CtIP [140–142] (Fig. 6).

2.8. SIRT7

SIRT7 is a nuclear protein, mostly expressed in the nucleolar regions [163]. SIRT7 promotes the rDNA transcription [164–166], especially in young, proliferating cells. The replicative senescence correlates with the SIRT7 dislocation from the nucleolar regions to chromatin and to cytosol [166]. The main substrate of SIRT7 is the H3 histone, deacetylated by SIRT7 at Lys 18 (H3K18 DAC) [167]. Deacetylation of the H3 histone at Lys 18 represses gene expression. It is interesting to note that many TSPs are encoded in target regions for H3K18 DAC [167]. The ELK-4 transcription factor takes part in recognition of the SIRT7 target regions in chromatin [167–169]. Thus, on one hand SIRT7 can contribute to maintenance of a transformed cell phenotype in tumor cells by suppressing the expression of some TSPs [167], while on the other hand, the SIRT7 KO mice develop a progeroid phenotype and an inflammatory cardiomyopathy [170,171]. Despite the fact that the SIRT7 overexpression seems to be crucial for maintenance of tumor phenotype in the already established cancer cells [167], SIRT7 does

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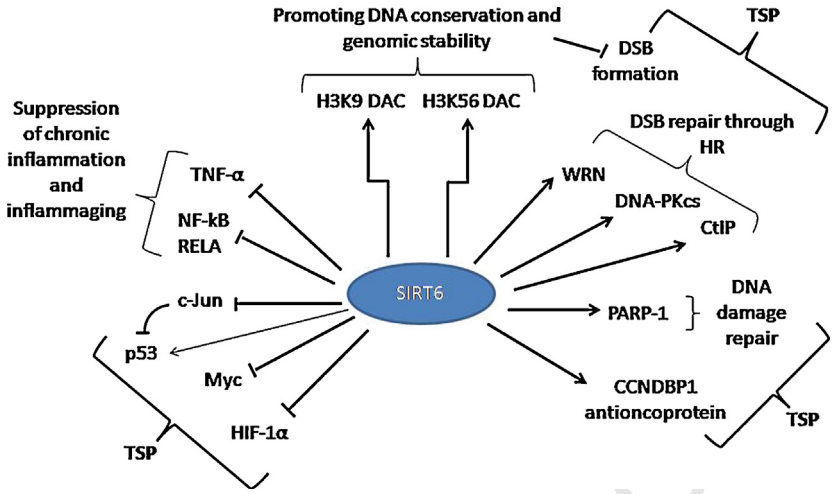

Fig. 6. The best known actions of SIRT6 as a tumor suppressor protein (TSP).

not contribute to the initiation of carcinogenesis, which has been experimentally proved, as no correlation between SIRT7 upregulation in normal cells and their susceptibility to transformation has been found [167,172]. Summing up, SIRT7 is a protein which may exhibit a window of optimal activity. Global SIRT7 depletion contributes to premature aging, referring especially to the backbone, white adipose tissue and the heart [170,171], whereas SIRT7 overexpression is observed mainly in cancer cells [164,167].

3. Conclusion

The broad spectrum of processes in which sirtuins are involved suggests their possible role in the pathogenesis of many diseases, including the metabolic syndrome, neurodegenerative diseases, the inflammatory response, circulatory system diseases, neoplasms, and other age-related diseases. Hence, the sirtuin activation can be a useful method of healthspan extension, or even of lifespan extension. There are two basic approaches to sirtuin activation. One of them is the use of exogenous activators (sirtuin-activating compounds; STACs), the other one is replenishment of the cellular NAD^+ [20,173]. The first discovered exogenous SIRT1 activator was resveratrol [85,173]. A treatment with resveratrol and its derivatives allowed to achieve some beneficial effects of the SIRT1 induction without applying CR [174–176]. Following the discovery of resveratrol, a few researchers tried to find some selective activators – not only of SIRT1, but also of other sirtuins [176]. However, a more recent, and generally more useful approach involves using direct NAD^+ precursors, such as the nicotinamide mononucleotide (NMN) or the nicotinamide ribose (NR) to replenish the cellular NAD^+ [20].

It should be noted that the DNA damage can result in NAD^+ depletion, because PARP requires NAD^+ as a cofactor. Since the DNA-repairing enzymes and sirtuins share NAD^+ as a cofactor, a recurrent DNA damage can create a vicious circle by causing the NAD^+ depletion and a secondary loss of sirtuin function, thus promoting not only a further DNA damage, but also a mitochondrial derangement. Some research studies do confirm that this kind of vicious circle may contribute to organismal aging [20]. Moreover, the vicious circle can be experimentally broken by the replenishment of cellular NAD^+ using its direct precursors.

The competitive interplay between PARP and sirtuins can provide putting multiple theories of aging together, and thus, better understanding of dependences between the DNA damage, loss of the mitochondrial function, and the oxidative stress. This in turn can allow final and complete explanation of mechanisms of organismal aging, providing the development of safe and effective methods of lifespan extension in the future.

Note

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Conflict of interests

The authors declare no conflict of interests.

Financial disclosure

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