Physiological and Pathophysiological Functions of SIRT1

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Abstract: The human SIRT1 is a nuclear enzyme from the class III histone deacetylases (HDACs) which is widely distributed in mammalian tissues. A variety of SIRT1 substrates hints that this protein is involved in the regulation of diverse biological processes, including cell survival, apoptosis, gluconeogenesis, adipogenesis, lipolysis, stress resistance, muscle differentiation, and insulin secretion. This review emphasizes catalytic properties of SIRT1 and its role in apoptosis, insulin pathway, and neuron survival.

Key Words: FOXO factors, NAD^+-dependent deacetylase, p53, resveratrol, Sir2, SIRT1.

INTRODUCTION

The Sirtuin (Silent information regulator, Sir2) proteins, present in prokaryotes and eukaryotes, have been identified as NAD^+-dependent deacetylases. In addition, a few reports indicates that some Sirtuins possess ADP-ribosyltransferase activity [1,2].

It has been well etablished that yeast Sirtuins play an essential role in transcriptional silencing: Sir2-mediated deacetylation of histones results in silencing of transcription at the silent mating-type loci (*HML* and *HMR*) [3], telomeres [4], and the ribosomal DNA (rDNA) region [5]. Besides silencing function, Sirtuins have been implicated in life span extension of yeast [6] and the nematode worm *Caenorhabditis elegans* [7]. In *Saccharomyces cerevisiae*, Sir2 overexpression suppresses recombination and extends replicative life span, whereas deletion of the Sir2 locus increases extrachromosomal rDNA circle formation and significantly shortens life span [6]. In *C. elegans*, increased dosage of the Sir2 homologue *sir-2.1* also extends life span, however, the presence of the FOXO-related protein DAF-16, a component of the insulin-like signaling pathway in C. *elegans*, is required in this process [7].

Based on differences in amino acid sequences of the conserved core domain of Sir2 proteins from bacteria, lower eukaryotes and mammalian cells, Sirtuins have been divided into five classes, designated I, II, III, IV, and U [8]. Prokaryotic Sirtuins belong to classes II and III, whereas yeast have class I proteins. The U class, being intermediate between classes II and III or classes I and IV, includes gram-positive bacterial and *Thermatoga maritima* Sirtuins. The seven human Sirtuins, called SIRT1-SIRT7, have been classified into classes I-V [8]. It is noteworthy that the presence of SIRT1-SIRT7 proteins was detected in different cellular compartments like nucleus (SIRT1, class I; SIRT6, class IV), cytosol (SIRT2, class I), mitochondria (SIRT3, class I; SIRT4, class II; SIRT5, class III), nucleolus (SIRT7, class IV). Much research effort was aimed at determining their physiological functions, but only SIRT1, the closest human homolog of the yeast Sir2, has been well characterized to date. SIRT1 was shown to deacetylate both histones and a wide range of non-histone proteins, including p53 [9], Ku70 [10], the FOXO transcription factors [11, 12], TAF_I68 [13], MyoD [14], NF-κB [15], PPAR-γ (peroxisome proliferator-activated receptor-γ) [16], PGC1α (peroxisome proliferator-activated receptor-γ (PPAR-γ) coactivator-1) [17], and thereby it widely contributes to apoptosis, cell cycle regulation, transcriptional silencing, fat mobilization and aging (Fig. (**1**)).

The most recent studies have revealed a direct connection between SIRT1 and DBC1 (Deleted in Breast Cancer-1). DBC1 forms a stable complex with SIRT1 and negatively regulates SIRT1 activity *in vitro* and *in vivo*, implying that it can act as a tumor suppressor augmenting cell death under stress stimuli [18, 19]. The review summarizes current knowledge about the physiological functions of SIRT1, with a special emphasis on its role in apoptosis, neuron survival and in regulating insulin pathway.

CATALYTIC MECHANISM FOR THE SIRTUIN FAMILY

Recently, a great deal of insight has been gained into the molecular mechanism of Sir2-catalyzed deacetylation, in which the high energy glycosidic bond linking Nicotinamide (NAM) to the ADP-ribose moiety of NAD^+ is cleaved, and in subsequent step released ADP-ribose is converted into the product, 2'-*O*-acetyl-ADP-ribose (2'-*O*AADPr), by transfer of the acetyl moiety from the acetyl-lysine "protein" substrate to the 2'-hydroxyl of ADP-ribose (Fig. (**2**)). Thus, two products are generated in the Sir2-catalyzed deacetylation: *O*-acetyl-ADP-ribose and NAM. Importantly, the catalysis occurs after forming of the ternary complex Sir2 enzyme/NAD^+/acetyl lysine [20]. Data from studies on the reaction mechanism of yeast homolog Hst2 have provided a novel insight into Sir2-mediated catalysis in which the cleavage of NAM from NAD^+ proceeds *via* S_N2-type mechanism with the direct formation of 1'-*O*-alkylamidate intermediate [21]. It has been established that 2'-O-acetyl-ADP-ribose (2'-*O*AADPr) exists in equilibrium with its regioisomer, namely 3'-*O*AADPr, as a result of intramolecular transesterification [22].

The level of these metabolites in mammalian cells can be regulated by yet unidentified enzymes, including nuclear

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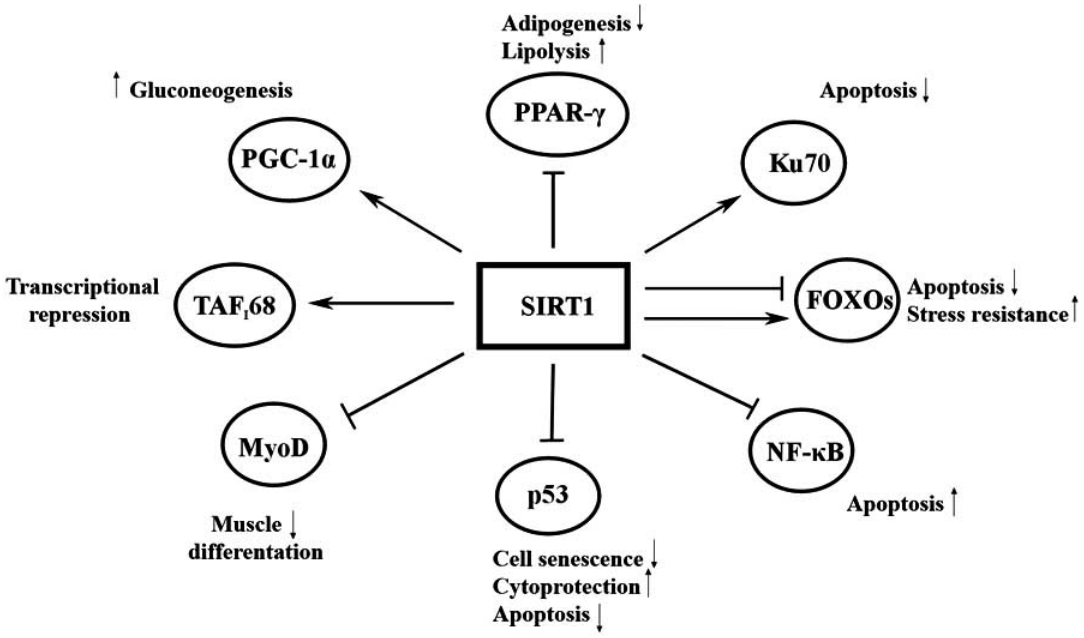

Fig. (1). Target proteins of SIRT1 action.

transacetylases, esterases or Nudix hydrolases [23]. Since AADPr is responsible for blocking of a cell cycle in embryonic development [24] and for the regulation of the transient receptor potential melastatin-related channel 2 (TRPM2) [25], it has been suggested that AADPr could act as an important physiological metabolite or second messenger eliciting a cellular response. Interestingly, Sir2 activity is inhibited by NAM, that attacks the 1'-*O*-alkylamidate intermediate leading to its conversion into NAD^+ and acetylated substrate [26, 27]. It has already been established that NAM essentially decreases the deacetylation reaction at low micromolar concentrations by inducing reverse reaction [28], and that addition of exogenous NAM to yeast cells significantly shortens their life span [29].

Further studies on Sirtuin effectors allowed to identify inhibitors such as sirtinol [30], splitomycin [31], cambinol [32], and resveratrol (3,5,4'-trihydroxy-trans-stilbene) being an activator [33] (Fig. (**3**)). Interestingly, resveratrol possessing antioxidant [34, 35] and cancer preventative properties [36, 37], has been shown to extend life span in *S. cerevisiae*, *C. elegans, D. melanogaster*, and in a vertebrate fish through a Sirtuins-dependent process [38-41]. In mammalian cells, resveratrol enhances SIRT1-dependent processes like axonal protection [42], fat mobilization [16], and inhibition of NF-kB-dependent transcription [15]. Resveratrol was identified as an activator of SIRT1 stimulating its activity by approximately 8-fold and lowering the K_m value for acetylated peptide [41]. The studies *in vitro* on the mechanistic basis for Sir2 activation by resveratrol disclosed that this compound enhances binding and deacetylation of fluorophore-containing substrates, whereas it has no effect on the same acetylated peptides, but lacking the fluorophore [33, 43]. Given the above, Borra *et al.* [33] proposed structural model for the observed resveratrol activation in which the binding of resveratrol to SIRT1 induces a conformational change in the enzyme resulting in tighter fluorophore binding. However, more work is needed to evaluate the precise molecular mechanism of Sir2 activation by resveratrol.

CORRELATION BETWEEN STRUCTURE AND FUNCTION

The crystal structures, including yeast Hst2 [44], human SIRT2 [45], and a Sir2 homologs from *Archaeoglobus fulgidus*, Sir2-Af1 [46, 47] and Sir2-Af2 [48, 49], disclosed that the conserved core of protein consists of the large domain with Rossmann fold, and the small domain containing either the zinc-binding or a flexible helical modules [45, 47]. It has been proposed that the acetyl-lysine substrate, placed in a conserved hydrophobic tunnel, can induce NAD^+ binding in the *C*-pocket, in which NAM ring and the *N*-ribose are contacted with highly conserved residues, and the *N*-ribose at the α face is exposed to the carbonyl oxygen of the acetyl-lysine substrate [48]. The sequence specific motif, including the cysteine-rich repeats (Cys-X-X-Cys-$(X)_{15\text{-}20}$-Cys-X-X-Cys), located in the middle of the conserved domain, seemed to be directly involved in the zinc ion binding. However, since Zn^{2+} in the Sir2-Af1 structure is located in the small domain far away from the NAD^+ binding pocket, its participation in catalysis may be excluded [47]. To determine whether four cysteines in the mentioned above motif are individually essential for Sir2 silencing at the *HM* loci, telomeres, and within the rDNA, cysteine to alanine point mutants were analyzed [50]. It has been found that the substitution of cysteines by alanines causes a loss of Sir2 silencing functions [50]. It has been proposed that the cysteines may mediate specific intermolecular interactions, probably protein-protein interactions rather than protein-DNA interactions, that contribute to silencing function [50]. Cocrystallization of Sir2-Af1 with NAD^+ provided important insight into protein-NAD^+ interactions: among amino acids, Ala-21, Glu-26, Phe-32, Arg-33, Gln-98, His-116, Thr-186, Ser-187, Asn-211, Asp-213, and Ala-229 form hydrogen bonds with

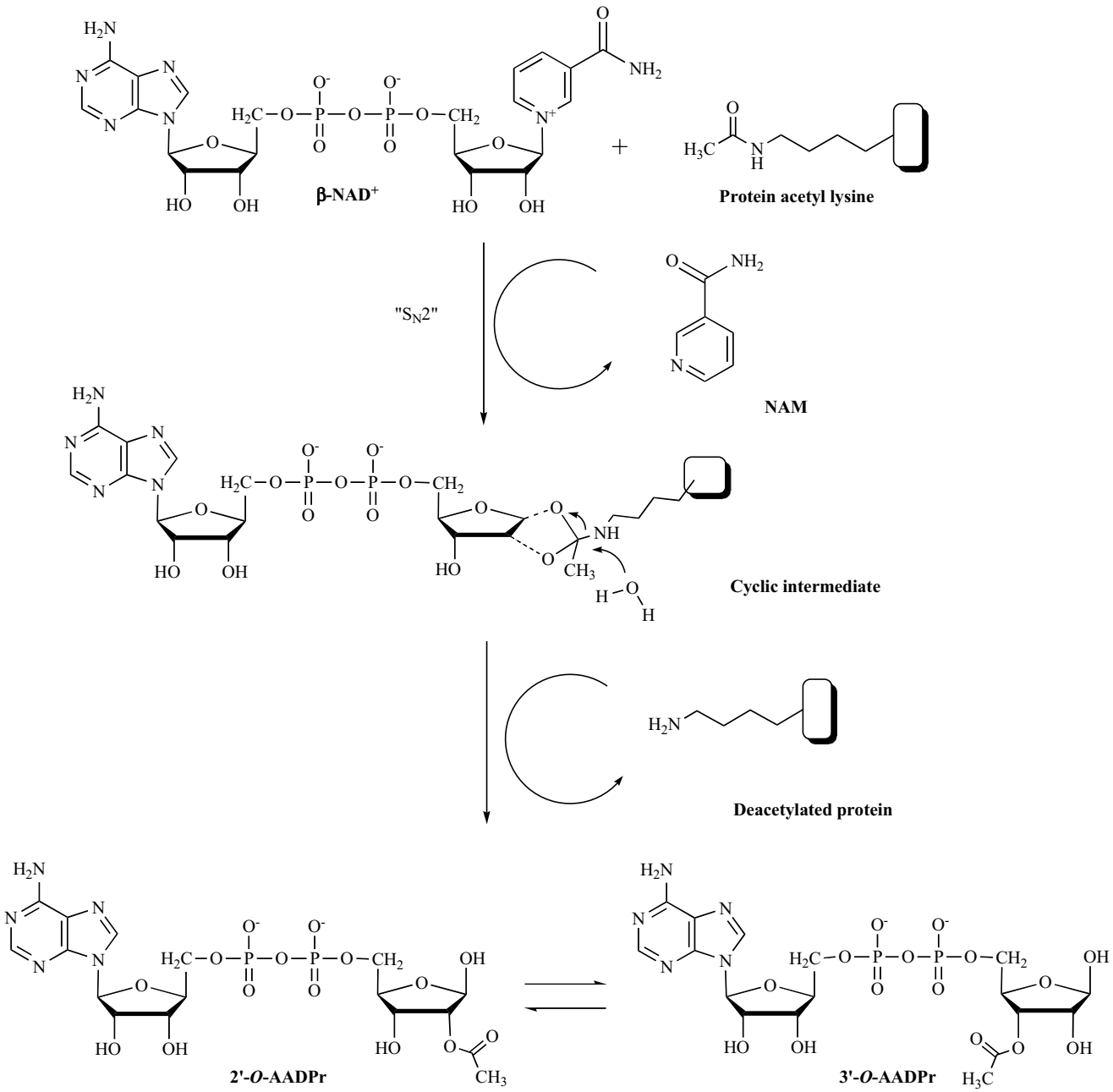

Fig. (2). Histone or non-histone protein containing acetylated lysine binds to Sirtuin enzyme as well as the second substrate β-NAD^+. After hydrolysis of the glycosidic linkage in NAD^+, NAM is released, whereas ADP-ribose binds to the acetylated lysine giving an *O*-alkylamidate intermediate. The enzyme-intermediate complex releases the deacetylated protein and 2'-*O*AADPr that spontaneously equilibrates with the regioisomer 3'-*O*AADPr through intramolecular transesterification reaction.

particular components of NAD^+ [47] (Fig. (**4**)). In the case of the yeast Hst2 protein deacetylase, a site directed mutagenesis studies disclosed that Gly-32, Ser-36, Asn-116, His-115, Asn-248 are essential for NAD binding and, moreover, Asn-116 and His-135 may also play a role in catalysis [21]. Kinetic analyses of two Hst2 mutants with strictly conserved residues Val-228 and Pro-230, making Van der Waals contacts with the acetyl lysine in the ternary Hst2 structure, confirmed their importance in acetyl-lysine binding. Moreover, Arg-45 was predicted to be involved in stabilizing the 1'-*O*-alkylamidate intermediate [21].

SIRT1 IN APOPTOSIS

Apoptosis, or programmed cell death is an essential part of animal tissue development and crucial for tumor suppression mechanism. The functional linkage between apoptosis and acetylation/deacetylation of lysines in Ku70, FOXO forkhead subfamily of transcription factors (FOXOs), p53, NF-κB was investigated [15, 51]. The factor Ku70, known as DNA repair protein, has been proposed to suppress Bax-mediated apoptosis [51]. Deacetylases target Ku70 protein and maintain this protein in unacetylated state enabling interaction between Ku70 and the exposed Bax-binding do-

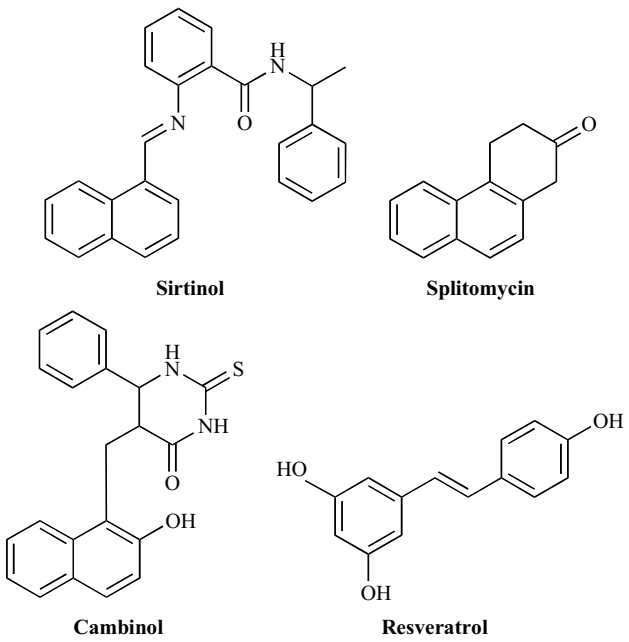

Fig. (3). Chemical structures of chosen modulators of SIRT1 deacetylase activity.

main under normal growth conditions. Three classes of deacetylases participate in Ku70 deacetylation in cells since NAM (a SIRT1 inhibitor) and trichostatin A (TSA; an inhibitor of class I and II histone deacetylases) abolish the interaction between Ku70 and Bax in human epithelial carcinoma (HeLa). Cell stress induces CBP (CREB-binding protein) and/or PCAF-mediated acetylation of specific lysine residues in the C-terminal linker of Ku70, resulting in a conformational change in this region, releasing Bax protein and promoting apoptosis. Two lysine residues (K539 and K542) within the C-terminal linker are critical for the regulation of Bax-mediated apoptosis [10]. Besides Ku70, SIRT1 can also regulate FOXOs of the forkhead subfamily. All FOXOs possess a highly conserved DNA-binding domain (also known as the Forkhead box) in the central part of the molecule [52]. To date, four members of the FOXO subgroup (FOXO1/FKHR, FOXO3/FKHRL1, FOXO4/AFX, and FOXO6) have been identified in mammals and their participation in regulating of apoptosis [53, 54], cell cycle arrest [55], genes involved in DNA repair [56], oxidative stress resistance [57], differentiation of myoblasts [58] and adipocytes [59], gluconeogenic pathway [60] has been demonstrated. It is known that FOXOs are negatively regulated by growth hormone/insulin induced activation of the phosphatidylinositol-3-kinase (PI-3K)/protein kinase B (PKB/Akt) pathway resulting in inactivation of FOXO proteins by retention in the cytoplasm [61]. Recently, much attention has been focused on acetylation and deacetylation of FOXOs as an alternative pathway of their regulation within cells. It has been established that acetylation of FOXO transcription factors causes inhibition of their transcriptional and biological activities [62]. In response to stress, the enhanced acetylation of FOXO3 and FOXO4, homologues of the nematode DAF-16 protein, mediated by p300- and CBP-acetyltransferases has been reported [11, 12, 62]. The acetylated proteins are deacetylated within cells by either SIRT1 or histone deacetylases from class I and II [11]. Additionally, SIRT1 may deacetylate p300 and repress p300-mediated activation of FOXO3 [12]. It has been reported that SIRT1 represses FOXO3-dependent transcription from various promoters in HeLa cells, however, natural promoters like p27 and bim are preferred [12]. Considerable evidence implicates a role of SIRT1 in inhibiting of FOXO4-induced apoptosis in U2OS cells [12]. In addition, decreased FOXO3-induced apoptosis in pre-sence of the increased SIRT1 in primary cultures of cerebellar neurons has been observed [11]. Since FOXO3 stimulates cell death in response to stress stimuli in non-neuronal cells and an increased level of SIRT1 represses the FOXO3-dependent apoptosis, *sirt1*-knockout mouse embryonic fibroblasts (MEFs) are more sensitive to stress-induced cell death [11]. Thus, SIRT1 can attenuate FOXO-induced apoptosis under stress conditions. Taken together, these data suggest that SIRT1 can tip the balance of FOXO function toward survival and away from apoptosis. Recently, SIRT1-mediated deacetylation has been shown to be involved in the suppression of transcriptional activity of FOXO1 by FHL2 protein, known as a regulator of stress response in cardiomyocytes, in prostate cancer cells [63]. It has been postulated that FHL2 can serve as an adaptor coupling SIRT1 and FOXO1. SIRT1 deacetylates FOXO1 and inhibits its action resulting in the enhancement of prostate tumorigenesis [63]. On the other hand, it has also been shown that nuclear

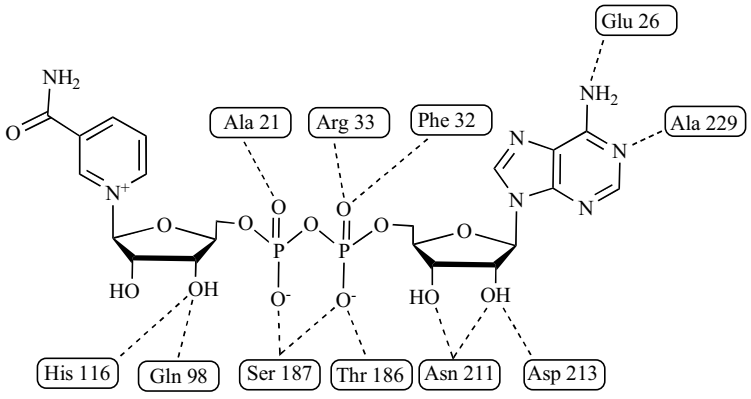

Fig. (4). Hydrogen bonds (broken line) between amino acids of Sir2-Af1 and NAD.

FOXO1 and SIRT1 are capable of forming a complex in PML (promyelocytic leukemia) bodies during oxidative stress, suggesting that SIRT1 deacetylates FOXO1 resulting in its activation, thereby providing stress resistance [64]. Similar to FOXOs factors, the tumor suppressor protein p53 is target for the inhibitory effect of SIRT1 on apoptosis. The p53 protein, present at low level in unstressed cells, is responsible for invoking antiproliferation effects (cell growth arrest, apoptosis) in response to various types of stress, by regulating genes, such as mdm2 [65], WAF/p21/CIP1 [66], cyclin G [67], IGF-BP3 [68], and Bax [69]. Posttranslational modifications of p53 in response to DNA damage include phosphorylation and acetylation, which regulate p53-mediated gene transcription [70-73]. Acetylation of K373/K382 and K320 within p53 by transcriptional coactivators p300/CBP and p300/CBP-associated factor (PCAF), respectively, was found to enhance p53 DNA binding activity [73-76] and to increase transcription of p53-responsive genes [73, 75, 77]. SIRT1 tightly binds to p53 both *in vitro* and *in vivo* and it specifically deacetylates p53, thereby impairing its DNA binding activity [9, 78]. It has been clearly shown that the negative regulation of DNA binding causes reduction of p53-mediated apoptosis in cultured cells in response to DNA damage as well as oxidative stress. Moreover, SIRT1 specifically attenuates p53-dependent apoptosis, since it has no effect on p53-independent, Fas-mediated apoptosis [78, 79]. It was postulated that the combining of DNA damage-inducing antitumor drugs and both types of deacetylase inhibitors should be particularly valuable for testing in cancer therapy [78]. In line with SIRT1 function in p53 regulation, SIRT1 deficient thymocytes exhibit p53 hyperacetylation after DNA damage and a significant increase in p53-dependent apoptosis [80]. The above data have been extended by recent studies with using RNAi to test effects of silencing SIRT1 expression in cancer and non-cancer cells on their viability under normal, non-stressed cell growth conditions [81]. Remarkably, SIRT1 enables cancer cell viability, whereas it is nonessential for the viability of non-cancer cells. Interestingly, apoptosis induced by SIRT1 silencing is independent of p53. In light of these results, it should be pointed out that SIRT1 can be a novel target for selective killing of human cancer versus non-cancer cells.

The next important substrate for SIRT1 is a nuclear transcription factor NF-κB, responsible for regulation of expression of various genes involved in inflammation, cytoprotection and carcinogenesis, thereby it participates in tumor formation and progression [82]. The most prevalent form of NF-κB is a heterodimer consisting of p50 and RelA/65 subunits. Since its transcriptionally active form resides in the nucleus, it interacts with p300- and CBP- histone acetyltransferases [83, 84], which acetylate RelA/p65 affecting its ability to the DNA-binding and transcriptional activity [85, 86]. SIRT1 directly associates with RelA/p65 *in vivo* and it deacetylates lysine 310 [15], a residue critical for NF-κB transcriptional activity [86]. In consequence, NF-κB-mediated transcription is inhibited and cells are sensitized to TNFα-induced apoptosis.

Resveratrol has been found to modulate the activity of relevant mediators of cell cycle and survival. With regard to NF-κB, resveratrol stimulates SIRT1 activity, inhibits acetylation of RelA/p65, blocks TNFα-induced NF-κB transcription, and sensitizes NSCLC (non-small-cell lung cancer) to TNFα-induced apoptosis [15]. In addition, resveratrol augments the expression p300 [87], an acetyltransferase stimulating either NF-κB [88, 89] or p53 [88].

SIRT1 IN REGULATING INSULIN PATHWAY

SIRT1 has also been established to play the role in a broad array of processes involved in glucose homeostasis in liver, insulin secretion in pancreas and regulating of PPAR-γ level in white adipose tissue (WAT). It is known that during fasting, gluconeogenesis is stimulated in liver to generate glucose for release into the circulation [90]. Rodgers *et al*. [17] determined a role of SIRT1 in the regulation of either gluconeogenesis or glycolysis. They established that in response to fasting signals, endogenous SIRT1 interacts with, and deacetylates PGC-1α at specific lysine residue, resulting in the induction of gluconeogenic gene expression (phosphoenolpyruvate carboxykinase (PEPCK), glucose-6 phosphatase (G6Pase) and hepatic glucose output. Moreover, the protein complex consisting of SIRT1, PGC-1α and hepatocyte nuclear factor 4α (HNF 4α) is required for the regulation of gluconeogenic genes. Most likely, in this protein complex SIRT1 is a sensor for nutrient fluctuations through NAD+ control. Additionally, SIRT1 controls the glycolytic pathway in liver in response to fasting and pyruvate through PGC-1α [17]. Thus, deacetylation of PGC-1α by SIRT1 in liver causes enhanced gluconeogenesis and impaired glycolysis (Fig. (**5**)).

Since pancreatic β cells are responsible for maintaining glucose homeostasis and express SIRT1, it was of great interest to determine whether SIRT1 may participate in the regulation of insulin secretion in pancreas [91, 92]. Recently, it has been demonstrated that β cell-specific Sirt1-overexpressing (BESTO) transgenic mice exhibit either the improvement of glucose tolerance or the enhancement of insulin secretion in response to glucose compared to the wild type [92]. This hypersensitivity of the BESTO β cells to glucose is correlated in part with the SIRT1-mediated down-regulation of uncoupling protein 2 (UCP2), belonging to a family of mitochondrial inner membrane proteins, previously identified as a negative modulator of insulin secretion [93, 94]. To the end, isolated BESTO islets have reduced UCP2 and increased ATP levels and exhibit enhanced insulin secretion in response to both glucose and KCl [92]. These findings suggest that the reduced level of UCP2 through SIRT1 could enhance ATP synthesis from glucose, which results in the closing of the ATP-dependent K^+ channels, the activation of the voltage-gated Ca^{2+} channels, and Ca^{2+} influx. The increased Ca^{2+} level within cells leads to the induction of insulin secretion [93]. Bordone *et al.* confirmed that SIRT1 is a positive regulator of insulin secretion in response to glucose [91]. Additionally, they found that SIRT1 represses UCP2 transcription by binding directly at the UCP2 promoter (Fig. (**5**)). It has been implied that changes in the NAD/NADH ratio in pancreas can regulate SIRT1 activity and insulin secretion in response to diet since a significant decrease in the level of NAD measured in pancreas of the starved mice was observed. Together, these results indicate on the role of either SIRT1 or UCP2 as physiologically relevant regulators of insulin production.

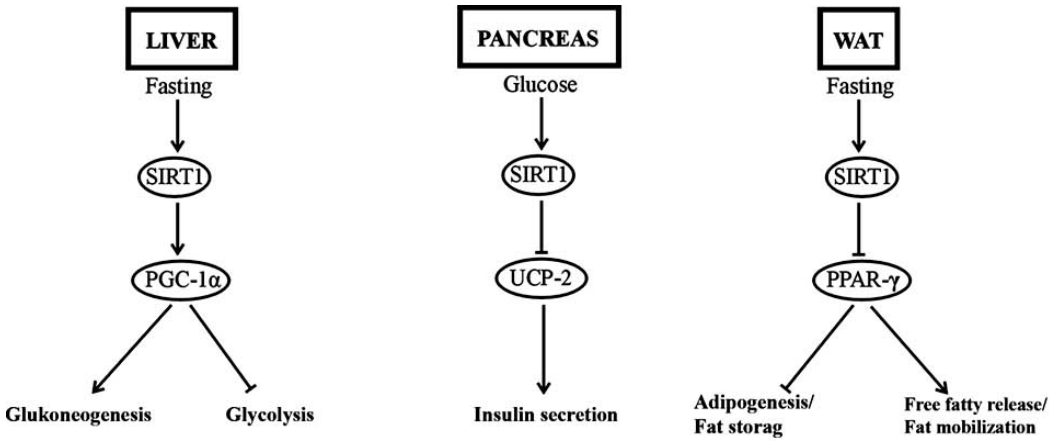

Fig. (5). Effect of SIRT1 upregulated in response to fasting or glucose on metabolic process in liver, pancreas and WAT (white adipose tissue). In response to fasting, SIRT1 interacts with, and deacetylates PGC-1α in the liver, promoting gluconeogenesis, but repressing glycolysis. In response to glucose, SIRT1 induces insulin secretion in pancreating β cells through down-regulation of UCP2. In response to fasting, SIRT1 interacts with PPAR-γ and inhibits its transcriptional activity towards genes mediating fat storage resulting in either impaired fat synthesis or adipogenesis, but enhanced fat mobilization.

In recent years, various transcriptional factors have been identified as regulators of the expression of a set of genes involved in glucose and lipid metabolism. Among them, PPAR-γ, belonging to the superfamily of nuclear receptors, has been shown to play a crucial role in the regulation of WAT differentiation [95, 96] since the several adipogenic genes, including the adipocyte fatty acid-binding protein (aP2) [97], PEPCK [98], lipoprotein lipase (LPL) [99] are targets for PPAR-γ, and ectopic expression of PPAR-γ promotes adipogenesis in non-adipogenic fibroblastic cells such as NIH-323 cells [96]. SIRT1 interacts with PPAR-γ and inhibits its transcriptional activity towards genes mediating fat storage through docking with its cofactors such as the nuclear receptor co-repressor (NCoR) and the silencing mediator of retinoid and thyroid receptors (SMRT) [16]. Thus, SIRT1 is a negative regulator of adipogenesis (Fig. (**5**)). Gene expression analyses on mouse 3T3-L1 fibroblasts overexpressing SIRT1 revealed markedly decreased triglycerides content compared to this occurring normally in cells [16]. Additionally, up-regulation of SIRT1 by resveratrol in fully differentiated adipocytes results in either the decrease of fat content or the stimulation of fat mobilization [16]. Picard's findings from fasting SIRT1$^{+/-}$ mice clearly indicate that their starvation causes the activation of SIRT1 that, in turn, triggers fat mobilization in WAT. Most likely, SIRT1 stimulation in fasting is on the contrary to insulin-induced fat storage and WAT differentiation [16].

It is worth noting that, besides SIRT1, FOXO1 (also known as FKHR) was identified as a PPAR-γ interacting protein that antagonizes the transcriptional activation properties of PPAR- γ, at least in part, by inhibiting PPAR-γ DNA binding activity [100].

SIRT1 IN NEURON SURVIVAL

The axonal degeneration has been observed in either peripheral neuropathies or neurodegenerative diseases like Alzheimer's disease [101] and amyotrophic lateral sclerosis [102]. The axonal protection was found in Wallerian degeneration slow (Wlds) mice with the overexpression of the nicotinamide nucleotide adenylyltransferase 1 (NMNAT1), catalyzing the condensation of NAM or nicotinic acid with AMP to generate NAD+ [42]. This study suggested that the molecular mechanism of axonal protection depends on the increased nuclear NAD biosynthesis that results from increased NMNAT1 activity and consequent activation of a NAD-dependent nuclear deacetylase SIRT1 [42]. In contrast to the above findings, Wang *et al*. [103] provided evidence for the existence of a SIRT1-independent local mechanism that is involved in NAD-mediated protection, implying new strategies for preventing and delaying axonal degeneration in patients with Alzheimer's disease and other neurodegenerative disorders. However, recent studies have revealed a functional link between SIRT1-mediated deacetylase activity and the generation of Aβ peptide in the non-amyloidogenic pathway of Alzheimer's disease. In this pathway, amyloid precursor protein (APP) is cleaved within the Aβ domain by the α-secretase, precluding generation and deposition of intact amyloidogenic Aβ peptides in the brain [104]. Qin *et al.* [105] found that SIRT1-mediated deacetylase activity promotes the α-secretase in non-amyloidogenic pathway of APP processing, attenuating Aβ generation in the brain during calorie restriction (CR). It was suggested that a mechanism by which SIRT1 activation promotes the α-secretase may be through SIRT1-mediated down-regulation of the serine/threonine Rho kinase (ROCK1) expression [105]. Thus, SIRT1 activation in the brain can be potentially pharmacological approach for preventing of Alzheimer's disease.

In conclusion, SIRT1 is broadly distributed in mammalian tissue and it deacetylates many transcriptional factors, regulating their activities. SIRT1 plays an essential role in a wide range of biological processes. Among them, the suppression of apoptosis through deacetylation of p53, FOXO proteins, and Ku70, the increase of cellular stress resistance, the decrease of WAT formation, and the protection against neural degeneration may imply the role of SIRT1 in extending life span in mammals. On the other hand, another studies raise the possibility that SIRT1 can negatively affect life span participating in promoting tumorigenesis. Since the molecular mechanism for aging in mammals has not been established, some studies employ SIRT1 activators for its

explaining. It has been established that from the standpoint of ageing research, resveratrol improves glucose homeostasis, endurance, and survival in obese mice, most likely due to the increased activity of SIRT1 and AMPK (AMP-activated protein kinase) [106, 107]. In addition, resveratrol improves cardiovascular function, bone density, and motor coordination, and delays cataracts even in non-obese rodents [108]. Recently, a new synthetic SIRT1 activators structurally unrelated to resveratrol have been identified and characterized in diet-induced obese and genetically obese mice [109]. It has been demonstrated that these compounds improve insulin sensitivity, decrease glucose level in plasma, and increase mitochondrial capacity. In addition, Feige *et al*. [110] found that SRT1720, a selective synthetic SIRT1 activator, strongly protects from died-induced obesity and insulin resistance by promoting fat consumption in skeletal muscle, liver, and brown adipose tissue (BAT). We can hope that this new generation of drugs will be a promising therapeutic approach for treating diseases of ageing.

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