Review

The Role of Epigenetic Regulator SIRT1 in Balancing the Homeostasis and Preventing the Formation of Specific “Soil” of Metabolic Disorders and Related Cancers

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Abstract

SIRT1 was discovered in 1979 but growing interest in this protein occurred only 20 years later when its overexpression was reported to prolong the lifespan of yeast. Since then, several studies have shown the benefits of its increased expression in preventing or delaying many diseases. SIRT1, as a histone deacetylase, is an epigenetic regulator but it has wide range of non-histone targets which are involved in metabolism, energy sensing pathways, circadian machinery and in inflammatory regulation. Disturbances in these interconnected processes cause different diseases, however it seems they have common roots in unbalanced inflammatory processes and lower level or inactivation of SIRT1. SIRT1 inactivation was implicated in coronavirus disease (COVID-19) severity as well and its low level counted as a predictor of uncontrolled COVID-19. Several other diseases such as metabolic disease, obesity, diabetes, Alzheimer’s disease, cardiovascular disease or depression are related to chronic inflammation and similarly show decreased SIRT1 level. It has recently been known that SIRT1 is inducible by calorie restriction/proper diet, physical activity and appropriate emotional state. Indeed, a healthier metabolic state belongs to higher level of SIRT1 expression. These suggest that appropriate lifestyle as non-pharmacological treatment may be a beneficial tool in the prevention of inflammation or metabolic disturbance-related diseases as well as could be a part of the complementary therapy in medical practice to reach better therapeutic response and quality of life. We aimed in this review to link the beneficial effect of SIRT1 with those diseases, where its level decreased. Moreover, we aimed to collect evidences of interventions or treatments, which increase SIRT1 expression and thus, open the possibility to use them as preventive or complementary therapies in medical practice.

Keywords: health; lifestyle; SIRT1; methylation; metabolism; cancer prevention

1. Introduction

Discovery of SIRT1 goes back to 1979 when it was reported as mating-type regulator protein in Saccharomyces cerevisiae [1]. Emerging interest in this protein occurred 20 years later when its overexpression was reported to extend yeast lifespan [2]. SIRT1 is a conserved protein but its increased complexity of function was described in mammals where seven enzymes are belonging to the sirtuin family [3]. In 2010 it was demonstrated first time that resveratrol induces the expression of SIRT1 protein in human cancer cells [4]. Resveratrol is a polyphenol found in grapes, wines, peanuts and various herbs and functions as phytoestrogen [5]. Since then, numerous studies have shown its beneficial effects through preventing or slowing down the progression of wide range of diseases like diabetes, ischemic injuries, cardiovascular disease, cancer and other age-related diseases [6–9]. SIRT1 inactivation is implicated in COVID-19 severity and its lower level is a predictor of uncontrolled COVID-19 [10]. Its agonistic effect was described in relation to drugs like fenofibrate or statins [11,12].

Metabolic syndrome is described as a disease where at least three of the next symptoms are represented: abdominal obesity, high triglyceride and low high density lipoprotein (HDL) level, high blood pressure, high fasting glucose level, increased risk of blood clotting and tendency to develop inflammation. Severe obesity is a metabolic disease associated with chronic inflammation. Furthermore, chronic inflammation when expression of pro-inflammatory cytokines IL-1β, IL-6, IL-8 and NFκB activation is presented for months or longer, is considered as the primary cause of inflammatory diseases, which represents appropriate physiological soil to cancer development as well [13]. Metabolic syndrome and subsequent cancer development are important parts in recent cancer research, although this link was described more than a century ago [14–19]. It has long been proven that bacterial or viral infections can cause inflammation, but only has recently been identified that saturated fatty acids also can induce pro-inflammatory TNFα release with subsequent oxidative stress and insulin resistance [20], and lead to JNK/NFκB activation [21–23]. Obesity and depression which are associated with inflammatory dysregulation has recently been
implicated as risk factors in COVID-19 mortality \[24\]. It has been known as well that SIRT1 level is elevated as a result of proper diet, appropriate amount of physical activity, and positive emotions which lead to improved metabolic-, energy- and lipid profile compared to inadequate diet, sedentary lifestyle and imbalanced emotional states. Indeed, a healthier metabolic state is characterized by higher expression of SIRT1 (Table 1, Ref. [25–41]) \[25\]. These data suggest that those evolutionary mechanisms which activate the SIRT1/AMPK pathways may be influenced by appropriate lifestyle in order to restore a healthy balance of homeostasis. Therefore, this may serve as useful tool in disease prevention or as complementary therapy along with conventional treatments to reach better therapeutic response and quality of life. It is known that appropriate lifestyle can reduce the number of cancer cases by 40% \[42, 43\] as well as COVID-19 infection and severity \[10\].

With this review, we aimed to demonstrate that well designed interventions can increase SIRT1 expression and, consequently, improve the metabolic and energy profile in diseases where SIRT1 levels are attenuated including COVID-19. Moreover, we aimed to discuss whether these interventions could be part of preventive and complementary therapies in the medical practice.

2. SIRT1 Protein and Its Regulation

SIRT1 is a class III human histone deacetylase enzyme (HDAC) and as the member of sirtuin family, plays crucial role in orchestrating homeostasis \[44, 45\]. As an epigenetic modifier, this protein regulates chromatin structure and transcription processes as well. The sirtuin group is structurally and functionally different from the other three HDAC groups, so the members of this group cannot be modulated by classic HDAC inhibitors \[45–47\]. SIRT1 is a monomer protein consisting of a highly conserved catalytic domain (blue region in Fig. 1A), two nuclear localization sites (NLS) and two nuclear export sites (NES) (Fig. 1A) \[48, 49\]. The catalytic pocket engages both the NAD+ co-factor and the acetyl-lysine substrates \[46, 48\]. The enzymatic reaction is transacetylation (Fig. 1B) \[46, 50\].

The catalytic pocket engages both the NAD+ co-factor and the acetyl-lysine substrates \[46, 48\]. The enzymatic reaction is transacetylation (Fig. 1B) \[46, 50\]. The activity of SIRT1 protein can be modulated by the availability of NAD+ and also by posttranslational modifications (Fig. 1C). Phosphorylation at the terminal sites orchestrates substrate binding, whereas desumoylation reduces and nytrosilation impairs its catalytic activity \[47\].

![Fig. 1. Structure and function of sirtuins.](image-url)
<table>
<thead>
<tr>
<th>Numbered</th>
<th>Life style or treatment</th>
<th>Disease</th>
<th>Tissue type</th>
<th>SIRT1 level mRNA</th>
<th>SIRT1 level protein</th>
<th>Metabolic changes, clinical parameters after intervention OR disease &amp; states</th>
<th>Signaling/ cellular mechanism</th>
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<td>NA</td>
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<td>increased*</td>
<td>increased NOx, decreased PAH &amp; ODI, improved* sleeping architecture &amp; efficiency</td>
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<td>Controlled clinical trial</td>
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<td>blood, skeletal muscle</td>
<td>NA</td>
<td>decreased</td>
<td>NA</td>
<td>decreased weight, BMI, insulin, leptin and increased* FFA</td>
<td>Akt, AS160, S6 kinase, 4E-BP1, FOXO1, insulin/mTOR, ERK, CRE/energy-nutrient sensing pathways</td>
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<td>[26]</td>
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<td>increased*</td>
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<td>p-SIRT1, p-AMPK</td>
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<td>plasma, PBMC</td>
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<td>decreased* AGt, 8-iso-prostanes, VCAM-1, TNFa, RAGE and increased* SIRT1, PPARγ</td>
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<td>15</td>
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<td>15</td>
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<td>skeletal muscle</td>
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<td>NA</td>
<td>decreased* total body and intrabdominal fat-mass, glycated haemoglobin and increased* oxygen consumption, insulin sensitivity, total body fat-free mass</td>
<td>no activation of mitochondrial biogenesis</td>
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<td>11+11+11</td>
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<td>28/59+44</td>
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<td>adipose tissue, liver</td>
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<td>NA</td>
<td>decreased* BMI, fasting glucose, insulin, HOMA, ALT, GMT, CRP, leukocyte count and increased* SIRT1,3,6</td>
<td>liver inflammation, fibrosis, steatosis, adipocytokine expression</td>
<td>Original article</td>
<td>29</td>
<td>[28]</td>
<td></td>
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A0ds, advanced glycation end-products; AHI, apnea-hypopnea index; AI, arousal index; ALP, alkaline phosphatase; BMI, body mass index; CBT, cognitive behaviour therapy; CPAP, continuous positive airway pressure; CR, calorie restriction; E, exercise; F3, triiodothyronine; FFA, free fatty acid; FT4, free thyroxine; LAGB, laparoscopic adjustable gastric banding; NOs, nitric oxide derivatives; ODI, oxygen desaturation index; OSAS, obstructive sleep apnea syndrome; PBMC, peripheral blood mononuclear cells; SNP, single nucleotide polymorphism; WL, weight loss; *, significant change.
The modulation of SIRT1 activity can occur through protein-protein interactions as well [50]. The active regulator of SIRT1 (AROS) enhances SIRT1 activity by binding to its NH2-terminal [47]. The protein called deleted in breast cancer 1 (DBC1) abrogates SIRT1 activity through binding to the catalytic domain. Additionally, SUMO1/Sentrin specific peptidase 1 (SENP1) has also been identified in the reduction of SIRT1 activity [47,51].

The gene expression of SIRT1 is regulated by cellular redox-changes and environmental factors (e.g., nutrients).

The protein expression level of SIRT1 can be modulated by both transcriptional and translational pathways by E2F1 and p53 (Fig. 1D) [52]. The RNA-binding protein HuR increases the stability of SIRT1 mRNA [52,53]. Additionally, the tumor suppressor miR-34a downregulates the expression of SIRT1 and attenuates the resistance to chemotherapy agent 5-fluoro-uracil [54]. The miR499a inhibits SIRT1 expression and miR199a attenuates SIRT1 activity [52].

3. Metabolic Effects of SIRT1

Non-histone proteins deacetylated by SIRT1 are closely related to pathways involved in metabolic adaptation to fasting [55]. During this adaptation process specific gene transcriptions are induced through activation of transcription factor FOXO3 by SIRT1 [56]. SIRT1 has tissue-specific functions in metabolic and energy homeostasis, and plays a significant role in maintaining serum glucose levels during starvation [56]. To achieve the latter, SIRT1 deacetylates and activates PPARα to stimulate fatty acid oxidation and activates the necessary coactivator mammalian target-of-rapamycin complex-1 (mTORC2) in the liver [55]. Furthermore, it represses the differentiation program of adipocytes as well as triggers lipolysis and fat loss in differentiated fat cells by suppressing peroxisome proliferator-activated receptor-γ (PPARγ), which is responsible for fat storage in white adipocytes [57]. Like in white adipose tissues and liver, SIRT1 induces fatty acid oxidation in skeletal muscle as well, mediating essential anti-diabetic function [55]. It also induces secretion of insulin from pancreatic islet cells to promote optimal glucose uptake into the cells of the human body [56]. SIRT1 upregulates the protein levels of oxysterol receptor (LXRα) and the ATP-binding cassette transporter A1 (ABCA1) to reverse cholesterol transport from peripheral tissues. Similarly, it increases the level of bile acid receptor farnesoid X receptor (FXR) which is required for bile acid biosynthesis and cholesterol catabolism [55]. Additionally, SIRT1 deacetylates two central components of the circadian clock (BMAL1 and PER2) in the liver and thus controls liver specific circadian regulation of metabolic processes [55]. As an important part of its effect, SIRT1 also activates PPARγ coactivator-1α (PGC-1α) which connects metabolic and energy dysfunction to the transcriptional output [58]. PGC-1α is expressed mainly in those tissues which have high oxidative capacity included heart, skeletal muscle, liver, brown adipose tissue and brain [59]. PGC-1α is a key factor in glucose production in the liver where it activates the entire gluconeogenic pathway while interacts with FOXO1 in insulin-regulated gluconeogenesis [60]. Additionally, PGC-1α facilitates mitochondrial biogenesis for adaptation to reduced energy status and it is a key player in energy expenditure (EE) as well [55,61]. Therefore, increased expression of PGC-1α resulted in increased number and function of mitochondria and a relatively higher number of type I oxidative fibers in skeletal muscle [62]. Defects in mitochondrial oxidative function with decreased EE may contribute to the metabolic conditions observed in insulin resistance (IR), type 2 diabetes mellitus (T2DM) and aging, and appear to be parallel to intramuscular triglyceride accumulation, which is the most recognized and consistent marker of whole-body IR [58,63]. Insulin resistance is associated with a decrease in the use of fatty acids as an energy source in the skeletal muscle, resulting in storage and increased ectopic lipid deposition [58]. Additionally, obese and diabetic patients have a lower proportion of type I muscle fibers. These fibers have high mitochondrial content and high oxidative capacity compared to type IIb fibers which are glycolytic in nature. This observation is important since insulin sensitivity is positively correlated with the oxidative capacity of the muscle [64]. Indeed, decreased PGC-1α levels have been reported in skeletal muscle of insulin resistant and T2DM patients [65,66], whereas expression has been restored by treatments known to normalize body weight and/or glucose homeostasis [67]. Similarly, high fat diet inhibits PGC-1α by hyperacetylation, and not surprisingly, SIRT1 expression diminished in such circumstances [58].

SIRT1 can activate AMPK through deacetylating and activating its upstream activator, liver-kinase-B1 (LKB1). Similarly, AMPK can induce SIRT1 expression by increasing NAD+ level [68]. Moreover, AMPK can activate PGC-1α by both direct phosphorylation and NAD+-dependent activation via SIRT1 [69]. This means that there is a positive regulatory cycle between SIRT1 and AMPK, and both can activate PGC-1α [68]. AMPK maintains the energy homeostasis, senses the energy stress at cellular level through the increased AMP/ADP to ATP ratio, resulting in its activation [70]. AMPK is a kinase which can activate or inactivate the targeted metabolic enzymes by phosphorylation, and interestingly, many of these targets are regulated by SIRT1 as well [71]. Generally, AMPK activates catabolic processes to produce ATP, while inhibits almost all anabolic processes consuming ATP. In this regard, it inhibits protein synthesis by inhibiting mammalian target-of-rapamycin complex-1 (mTORC1) which promotes cell growth and proliferation in the presence of growth factors, nutrient availability and energy status [69]. AMPK also promotes the mRNA expression of bile salt export pump protein in hepatocytes which allows the efficient absorp-
tion of lipids from food [70]. During evolution, this system adopted to the multicellular organism and interacted with hormones to balance energy intake and expenditure at the whole-body level [70]. Indeed, ghrelin released from gut activates AMPK in hypothalamus, increasing food intake. Adiponectin and thyroid hormones induce fatty acid oxidation in liver, skeletal muscle and in brown adipose tissue. In contrast, leptin released from adipocytes inhibits AMPK, reduces appetite, and increases biosynthesis and energy storage. Leptin/adiponectin ratio is also a known marker of insulin resistance [69,70]. Leptin activates the PI3-kinase-Akt-mTORC1-S6K1 pathway which is implicated in obesity-related pathophysiological conditions such as diabetes, cardiovascular disease and cancer [72]. Additionally, AMPK is the site of action of metformin [61]. These data show that SIRT1 and AMPK can acutely restore energy balance but also reprogram the cell metabolism through transcription [69].

3.1 Effect of Calorie Restriction on SIRT1 Levels and Associated Metabolic Changes

Clinical trials and human studies investigating calorie restriction (CR) (Table 1) described that adipose tissues in lean people showed 120% higher SIRT1 level compared to obese patients at the baseline [26]. Long-term CR significantly increased the SIRT1 mRNA expression levels (130% higher) compared to baseline levels in obese women [26], and significantly increased the activation levels of SIRT1 and AMPK proteins in peripheral blood monocytes (PBMCs) as well [25]. However, in short-term CR, neither SIRT1 level nor activation of AMPK pathway was changed, although activation of insulin/mTOR pathway was significantly reduced [27]. On the contrary, both short and long-term CR significantly decreased body weight, BMI, insulin level (with unchanged level of insulin receptor β/IRβ), leptin, triglycerides, T3 levels, while significantly increased growth hormones, free fatty acids, ketone bodies, FT4, SHBG, cortisol, alkaline phosphatase and creatinine levels [26,27]. One of the studies investigating long-term CR showed a significant decrease in basal metabolic rate, mean blood pressure, homeostasis model assessment for insulin resistance (HOMA-R) and insulin resistance index (IRI). Moreover, there was a significant increase in VO2 max and a significant decrease in inflammation-related IL-6 and visfatin, but not the CRP and ICAM-1 [25].

CR also has a beneficial effect on the circulatory system based on studies showing that SIRT1 and endothelial nitric oxide synthase (eNOS) positively regulate each other upon CR when eNOS induces SIRT1 expression, while SIRT1 deacetylates eNOS and promotes its activity. Vascular endothelium produces nitric oxide (NO) through eNOS and supports general endothelial health; as NO is important in relaxing muscle and lowering blood pressure. Additionally, CR improves myocardial ischaemic tolerance by facilitating SIRT1 entry into the nucleus by eNOS, and up-regulation of SIRT1 protects against cardiac hypertrophy resulting from PPARα activation and increased fat oxidation [55,56]. Additional cardiovascular benefit of SIRT1 in addition to promote lipolysis and improve insulin sensitivity, is the ability to limit proinflammatory macrophage activity [73]. The effect of COVID-19 in patients with low SIRT1 levels may lead to mitophagy and programmed cell death with relevance to myocardial infarction and ischemic heart disease [10]. SIRT1 upregulation through low calorie diets, lifestyle changes and physical activity may also protect COVID-19 patients against chronic and cardiovascular disease and complications [74,75].

Hypothalamus is the main systemic coordinator of mammalian physiology including regulation of diurnal activities like feeding, body temperature, energy expenditure and other metabolic functions. CR increases SIRT1 levels in the dorsomedial and lateral hypothalamus triggering behavioral changes to higher physical activity and increased body temperature [55]. SIRT1 upregulates the core transcription factors, BMAL1 and CLOCK, and directly regulates their cyclic repressors as well by leading to degradation. Because AMPK is also able to induce degradation in cyclic repressors which suppress many nuclear receptors thus it is also able to modify nuclear receptor-dependent gene expression programs [69].

Metabolic parameters negatively correlated by SIRT in a clinical trial using laparoscopic adjustable gastric banding (LAGB) to ensure CR. Significantly decreased BMI, fasting glucose, insulin, HOMA, liver enzymes such as ALT, GGT, inflammatory CRP and leukocyte counts after 6 months of weight loss compared to the baseline. The mRNA levels of SIRT1, 3 and 6 significantly increased in the adipose tissue. In the liver, SIRT1 and 3 protein levels increased as well. Expression of all three mRNA significantly and negatively correlated with BMI and serum glucose, and SIRT1 mRNA expression showed significantly negative correlation with liver portal fibrosis, steatosis, GGT levels, adipo-cytokines and receptor expressions in both tissue types (Table 1) [28].

SIRT1 regulates lipid and glucose metabolism, thus consequently lipid profile, where dyslipidaemia is a cardiovascular risk with high LDL-C (low-density lipoprotein-C) and low HDL-C (high-density lipoprotein-C) levels. The genetic variant haplotype 2 of SIRT1 significantly decreased LDL-C and increased HDL-C levels in both sexes but only with low n-6/n-3 polyunsaturated fatty acid (PUFA) intake [29].

3.2 Effect of Physical Activity on SIRT1 Levels and Associated Metabolic Changes

Clinical trials investigating the effect of exercise alone or with CR have found similar result to CR interventions (Table 1). In more details, acute and chronic stimuli due to one- and three-days cycling, respectively, increased mitochondrial biogenesis through significantly in-
Increased PGC-1α, SIRT1, citrate synthase and cytochrome-c levels in skeletal muscle compared to pre-exercise samples [30]. Furthermore, a high positive correlation between PGC-1α and SIRT1 mRNA levels and significantly increased mitochondrial function were detected based on PGC-1α, eNOS, SIRT1, TFAM, PARL levels, and mitochondrial DNA content. Moreover, significantly decreased DNA-damage were found. Additionally, whole-body EE, triiodothyronine and insulin levels decreased significantly with improved insulin-sensitivity, although TCA cycle and β-oxidation did not change significantly [31]. Another study found a significant correlation between higher baseline level of SIRT1 mRNA and weight lost. In the SIRT1 high group weight loss improved continuously over the entire 12 months intervention, while the SIRT1 low group for only 5-month period. Weight loss highly correlated with significantly increased SIRT1 mRNA expression, NAD+ synthesis, and significant decrease in PPARγ levels in white adipose tissue [32]. Interesting results were seen after a 30 second sprint anaerobic exercise, where glucose ingested and fasting control groups were compared. In fasting control group SIRT1 protein expression levels significantly increased after a single, 30 seconds sprint exercise with elevated Thr172-AMPKα phosphorylation. Both effects were blunted in the glucose group. PGC-1α level, however, remained unchanged in both groups. It suggests that AMPK phosphorylation induced by sprint exercise, as a short-term and anaerobe exercise, is not sufficient alone to induce PGC-1α level, regardless of glucose intake [33]. In a clinical trial comparing small-side rugby as an alternative to stationary cycling, glycated haemoglobin, total body fat-mass and intra-abdominal fat-mass were significantly reduced in both groups, but oxygen consumption, insulin sensitivity and total body fat-free mass were significantly increased only in the rugby group. However, they found no significant differences in the protein levels related to glucose regulation and mitochondrial biogenesis (PGC-1α, SIRT1, p53, GLUT4, AKT, complex I-IV subunits, ATP synthase subunits) between the two groups after the interventions [34].

4. Effect of SIRT1 on Inflammatory Processes

The sequential course of inflammation is directed by transcription factors, which controls various inflammatory and metabolic processes that alter the immune system, was implicated to diabetes and multiple organ dysfunction syndrome [77]. During acute systemic inflammation response, which could be induced by COVID-19 as well, cardiovascular and microvascular functions are impaired leading to multiple organ failure [73]. On the contrary, at the molecular level, the shift in NAD+ availability increases nuclear NAD+ level and activates SIRT1, which then induces facultative heterochromatin formation for gene silencing in promoter regions of proinflammatory genes such as TNF-α and IL-1/β [78]. In this process activated SIRT1 binds, deactivates and leads NFκB RelA/p65 to proteasome degradation. Additionally, in association with RelB which is also induced, SIRT1 deacetylates histone H1 and recruits a multunit repressor complex to form heterochromatin at proinflammatory genes [79,80].

Obstructive sleep apnoea syndrome (OSAS) is described as poor sleeping quality with decreased blood oxygen levels due to repeated airway obstruction. This increases blood pressure, hypoxia/re-oxygenation events, activates the pro-inflammatory NFκB and AP-1, and results in oxidative stress, systemic inflammation, nervous system dysfunction, reduced NO levels, atherosclerosis and increased aging. SIRT1 protein levels and its activity are significantly reduced in blood of OSAS patients, but may be reverted in parallel with nitrogen oxide derivatives by continuous positive airway pressure treatment (Table 1). This change can be explained as a consequence of decreased oxidative stress [35]. In addition, consumption of white wine as a source of resveratrol significantly increased lung function based on forced expiratory volume in 1 second (FEV1) and also reduced the risk of airway obstruction [36].

It has been known for a long time that PPARγ regulates adipocyte differentiation, fat storage, glucose metabolism, and it is a target of antidiabetics. But it has recently become known that it can also direct inflammatory processes toward the anti-inflammatory phenotype [81]. The dietary composition called advanced glycation end products (AGEs) caused high oxidative stress and inflammation, and suppressed SIRT1 and PPARγ, the two host defense molecules which regulate inflammation and metabolic functions [81]. Similarly, the AGE restriction diet restored mRNA levels of SIRT1 and PPARγ and significantly decreased inflammatory and stress markers (i.e., AGEs, 8-isoprostanes, VCAM-1, mononuclear TNFα and RAGE) in healthy people (Table 1) [37]. Furthermore, it was effective in normalization of expression levels of SIRT1 mRNA, AGE receptor 1 (AGER1), and marked increases in adiponectin levels, as well as decreases in insulin, HOMA, leptin, TNFα, NFκB, serum AGEs, 8-isoprostane levels in T2DM patients (Table 1) [82].

The association between low back pain and oxidative stress has already been reported [83,84]. However, a recent clinical study also found that exercise intervention was effective in reducing nonspecific low back pain due to signif-
icanently decreased TLR-4 related pro-inflammatory signals (TLR-4 mRNA, IFN-γ and IP-10, IL-1β, IL-6, IL-8, TNFα). SIRT1 and PGC-1α mRNA levels were significantly increased, while p53 mRNA levels significantly decreased. FOXO1/3 mRNA levels as well as activity of targeted antioxidant enzymes, catalase and SOD were significantly up-regulated in parallel with decreased oxidative stress as measured by blood H$_2$O$_2$ levels [38].

Age-related diseases, such as cardiovascular disease, Alzheimer’s and Parkinson’s diseases or cancers, are supposed to be developed by a low degree of systemic inflammation with advanced age [73,85,86]. Oxidative stress is significantly increased by aging and is closely related to mitochondrial dysfunction, which promotes the production of reactive oxygen species [87]. SIRT1 and AMPK, however, regulate mitochondrial biogenesis and clearance of defected mitochondria (mitochondria fission) through PGC-1α [69]. This might be the reason why aging significantly increases SIRT1 protein levels. SIRT1 shows significant positive correlation with HDL in older people. Moreover, a significant negative correlation was detected between SIRT1 level and LDL in adults [39]. SIRT1 has anti-aging activity by activating AMPK, PGC-1α, FOXO and inactivating p53 and NFκB [88]. SIRT1 and AMPK promote each other and their cyclic regulation mechanism highlights their common roles both in energy balance metabolism and aging processes [68,89]. SIRT1 prevents endothelial senescence by activating PGC-1α and PPARα through deacetylation. Consequently, this results in the downregulation of production of NADPH oxidase-mediated reactive oxygen species and reactivation of endothelial smooth muscle relaxation due to reverted nitrogen-monoxide level [90]. Swimming inhibits apoptosis in aging hippocampal cells, improves muscle functions and reduces inflammation in aging rats through AMPK/SIRT1/PGC-1α pathway [89,91,92].

5. SIRT1 Level in Emotional and Cognitive States

Stress level and emotional state are also important risk factors in development of metabolic disorders and cancer [93,94]. Patients with mood disorders such as major depressive disorder and bipolar disorder have been studied in both depressed and remission states. The mRNA levels of SIRT1, 2 and 6 were significantly decreased in peripheral blood monocytes in mood disorders and depressed states compared to healthy controls. In contrast, in remission state these were comparable to those seen in healthy subjects. This result suggests that SIRT1, 2 and 6 are state-dependent and might be associated with pathogenesis and pathophysiology of mood-disorders. However, serum cortisol level did not change dramatically during remission and there was no significant correlation with SIRT levels. It suggests that chronic stress factor was still present (Table 1) [40].

Cognitive behavioral therapy has been applied to support weight loss in another study. Carriers of double minor allele of SIRT1 (rs1467568; AG or AA) and CLOCK (rs1801260, TC or CC) showed significantly higher resistance to weight loss, lower weekly weight loss at higher plasma ghrelin concentration, evening preference and lower adherence to Mediterranean diet compared to homozygotes for both major alleles (GG and TT, respectively) (Table 1) [41].

Calorie restriction, adequate physical activity and emotional state increase the level of SIRT1 in the body, resulting in beneficial changes in levels of inflammatory and stress markers, thus promoting balanced epigenetic regulation and increasing healthy life expectancy (Table 1) [88,95].

6. SIRT1 in Cellular Processes of Autophagy and Apoptosis

SIRT1 regulates the availability of several target genes and transcription factor genes involved in epigenetic regulation [96], and many of which are also involved in aging and age-related diseases [52].

Autophagy is a process in which organelles and macromolecules are directed into lysosomes for degradation. This process is used by cells for normal turnover or production of nutrients in response to energy shortage [69]. AMPK is also involved in this process by activating pro-autophagic complexes, directly triggering the autophagy cascade, initiating autophagosome formation or inhibiting mTOR, an autophagy suppressor molecule [97,98]. P53 can also inhibit mTOR and activate AMPK thus inducing autophagy. Although in most cases p53 is positively regulated by AMPK [68], it can also inhibit autophagy [99].

P53 is a tumor suppressor gene and is also able to arrest the cell cycle by DNA repair and apoptosis [68]. It controls the metabolic switch between glycolysis and oxidative phosphorylation (Wartburg effect) and favors TCA cycle while limiting glycolytic flux [100]. P53 can regulate SIRT1 expression depending on the nutrient status of the cells [52,56]. In starving cells, p53 complexed with FOXO3 induces SIRT1 expression, while under normal conditions HIC1, an epigenetically regulated repressor, mediates the suppression of SIRT1 gene expression [52].

However, SIRT1 can also regulate p53 through deacetylation thus inhibiting DNA damage and stress induced cellular senescence [88]. SIRT1 prevents nuclear translocation of p53 and blocks transcription-dependent induction of apoptosis, while promotes its cytosolic accumulation and transport to mitochondria, suggesting transcription-independent induction of apoptosis. Although firstly SIRT1 was considered as a tumor promoter, recent studies have suggested it to be a tumor suppressor by facilitating mitochondria-dependent apoptosis [101]. Moreover, in chronic stress condition SIRT1 can inhibit corticosterone-induced autophagy and enhances apoptosis [102].
Fig. 2. SIRT1 has central role in several biological processes and is an important regulator of normal healthy homeostasis.

The main role of SIRT1 in biological processes and its regulatory targets for normal healthy homeostasis are summarized in Fig. 2 [27,31,48,52,56,101,103–105].

7. SIRT1 in the Four Main Cancer Types

Research on metabolic disorders and cancers has increased interest in lifestyle factors such as diet, physical activity, stress level, habits and behaviors as these significantly influence human physiology during the actual duration of their effects. These factors, whether they exist continuously or for a short time but regularly, take their effects into account over a long period of time. Thus, because they act through specific epigenetic modifications [44,103], they can modify homeostasis, resulting in further genetic alterations [106,107]. It has been established that lifestyle factors may have a greater impact on colorectal cancer risk than genetics, based on a Spanish cohort study [108].

Although the clear positive effect of SIRT1 and AMPK is still controversial in the development of cancer, several studies have found a positive correlation between SIRT1 expression and longer overall survival (OS) in cancer patients [109,110].

Colorectal cancer. Several studies have found significant correlation between higher expression or overexpression of SIRT1 and TNM stages (classification of malignancies, T - tumor, N - Node, M - metastases), depth of invasion, lymph node metastasis, increased stem cell markers and decreased suppressors of metastasis [111–115]. Similarly, in serrated lesions, which are alternative routes for colorectal cancer formation, high expression of SIRT1 and c-Myc was strongly associated with higher grades of malignancy along with the presence of KRAS or BRAF mutations [116]. In two prospective studies, overexpression of SIRT1 was more common in microsatellite unstable-high (MSI-high), CpG island methylator phenotype (CIMP-high) and CIMP-high/MSI-high tumors, but only in BRAF-mutated tumors that were positively and significantly associated with CIMP-high/MSI-high tumors. SIRT1 was also associated with overexpression of FASN and hypermethylation of several promoters and CpG islands [117]. In contrast, another study reported that lymph node metastasis was negatively correlated with SIRT1 [118]. Beneficial effect of resveratrol through apoptosis induced in colon cancer cells and sensitization of chemoresistant colon cancer cells to various drugs has been demonstrated in another study as well [119]. Moreover, it has been suggested that exercise-induced alterations in the systemic milieu can influence important regulatory mechanisms in the tumor microenvironment such as angiogenesis, immune regulation and metabolism, and lead to cumulative antitumorigenic effect (Table 2, Ref. [17,111–118,120–135]) [136].
<table>
<thead>
<tr>
<th>Numbered</th>
<th>Cancer type/ SIRT1 inducer</th>
<th>Disease</th>
<th>Tissue type</th>
<th>SIRT1 level</th>
<th>Metabolic changes, clinical parameters after intervention OR disease &amp; states</th>
<th>Signaling/ cellular mechanism</th>
<th>Study type</th>
<th>Cases no.</th>
<th>Reference</th>
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<tr>
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<td>CRC cancer</td>
<td>colorectal cancer tissue (FFPE-IHC)</td>
<td>NA</td>
<td>increased*</td>
<td>NA depth of invasion, lymph node metastasis, TNM stage, poor prognosis</td>
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<td>Systematic review and meta analysis</td>
<td>50-497/7</td>
<td>[111]</td>
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<td>increased*</td>
<td>NA metastasis (0.02), poor prognosis (p &lt; 0.01), poor OS (0.003) colocalization with CD133+</td>
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<td>102</td>
<td>[112]</td>
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<tr>
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<td>increased*</td>
<td>NA Fra-1, OS</td>
<td>NA</td>
<td>Original article</td>
<td>90</td>
<td>[113]</td>
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<tr>
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<td>increased*</td>
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<td>miR199b-CREB-KISS1/progression</td>
<td>Original article</td>
<td>60 (16 meta)</td>
<td>[114]</td>
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<td>normal colon, colon adenoma, colon carcinoma</td>
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<td>increased*</td>
<td>NA diagnosis, prognosis</td>
<td>NANOG, NCF2, ELF, TGFβ</td>
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<td>167</td>
<td>[115]</td>
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<td>NA differentiation, stage/lymph node metastasis</td>
<td>differentiation, progression</td>
<td>Original article</td>
<td>40</td>
<td>[118]</td>
</tr>
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<td>NA</td>
<td>c-Myc/KRAS, BRAF mutation</td>
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<td>121</td>
<td>[116]</td>
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<td>colorectal cancer tissue (FFPE-IHC)</td>
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<td>increased*</td>
<td>NA tumour grade (0.003), mucinous component (0.04), CIMP-high (0.002), MSI-high (p &lt; 0.0001), CIMP-high/MSI-high (p &lt; 0.0001), FASN (p = 0.008)</td>
<td>BRAF, MSI, CIMP, FASN/methylation of CACNA1G, IGF2, MLH1, NEUROG1, RUNX3, SOCS1, MINT31 and p14</td>
<td>Original article</td>
<td>485</td>
<td>[117]</td>
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<td>NA TNM, DFS, OS</td>
<td>NA</td>
<td>Meta-analysis</td>
<td>28-200/6 studies</td>
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<td>NA</td>
<td>decreased*</td>
<td>NA DFS, OS, \ Notch1/Snail</td>
<td>NA</td>
<td>Original article</td>
<td>150</td>
<td>[127]</td>
</tr>
<tr>
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<td>breast cancer (microarray)</td>
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<td>NA</td>
<td>NA metastasis</td>
<td>EMT</td>
<td>Meta-analysis</td>
<td>1181/12 studies</td>
<td>[128]</td>
</tr>
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<td>breast cancer tissue (FFPE-IHC)</td>
<td>NA</td>
<td>decreased* <em>(HRBC, H2BC) increased</em> (TNBC)</td>
<td>NA LNM, LVM, DFS, OS, HRBC/H2BC/TNBC</td>
<td>NA</td>
<td>Original article</td>
<td>427</td>
<td>[129]</td>
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<td>NA</td>
<td>NA grade3, IDC</td>
<td>NA</td>
<td>Original article</td>
<td>64</td>
<td>[130]</td>
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<td>31</td>
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<td>increased*</td>
<td>NA LNM, DFS, TNBC</td>
<td>NA</td>
<td>Original article</td>
<td>344</td>
<td>[131]</td>
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<tr>
<td>32</td>
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<td>breast cancer tissue (FFPE-IHC)</td>
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<td>increased*</td>
<td>NA LNM, DFS</td>
<td>E-cadherin, Vimentin, Snail/ EMT</td>
<td>Original article</td>
<td>319</td>
<td>[132]</td>
</tr>
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<td>NA</td>
<td>increased*</td>
<td>NA LNM, OS</td>
<td>NA</td>
<td>Original article</td>
<td>105</td>
<td>[133]</td>
</tr>
<tr>
<td>34</td>
<td>L cancer</td>
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<td>HIF1, hypoxia, oxidative stress</td>
<td>Original article</td>
<td>125</td>
<td>[120]</td>
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<td>NA DFS, OS</td>
<td>NA</td>
<td>Original article</td>
<td>163</td>
<td>[122]</td>
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<tr>
<td>36</td>
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<td>increased*</td>
<td>NA TNM, LNM, DFS, OS</td>
<td>contactin</td>
<td>Original article</td>
<td>295</td>
<td>[123]</td>
</tr>
<tr>
<td>37</td>
<td>L cancer</td>
<td>NSCLC tissue (FFPE-IHC)</td>
<td>NA</td>
<td>increased*</td>
<td>NA TNM, DFS, OS, chemotherapy resistance</td>
<td>chemotherapy resistance</td>
<td>Original article</td>
<td>295</td>
<td>[125]</td>
</tr>
<tr>
<td>38</td>
<td>L cancer</td>
<td>NSCLC tissue (FFPE-IHC, PCR)</td>
<td>increased*</td>
<td>increased*</td>
<td>NA OS, prognosis</td>
<td>HIC-SIRT1-p53 loop, acetyl-p53</td>
<td>Original article</td>
<td>97</td>
<td>[124]</td>
</tr>
<tr>
<td>39</td>
<td>L cancer</td>
<td>sputum</td>
<td>NA</td>
<td>NA</td>
<td>NA OS, risk of SCC</td>
<td>SNP, haplotype</td>
<td>Nested case-control study</td>
<td>17 000 (267-383 selected)</td>
<td>[125]</td>
</tr>
<tr>
<td>40</td>
<td>P cancer</td>
<td>PIN, PCA tissues</td>
<td>decreased*</td>
<td>NA</td>
<td>NA H2A.Z</td>
<td>H2A.Z, mTOR, c-Myc</td>
<td>Original article</td>
<td>57</td>
<td>[133]</td>
</tr>
<tr>
<td>41</td>
<td>P cancer</td>
<td>prostate cancer tissue</td>
<td>increased*</td>
<td>NA</td>
<td>NA Ki67</td>
<td>Ki67, methylation</td>
<td>Original article</td>
<td>47</td>
<td>[134]</td>
</tr>
<tr>
<td>42</td>
<td>P cancer</td>
<td>prostate cancer tissue</td>
<td>increased*</td>
<td>NA</td>
<td>NA Gleason grade</td>
<td>Gleason grade</td>
<td>Original article</td>
<td>41</td>
<td>[135]</td>
</tr>
</tbody>
</table>

ADC, adenocarcinoma; DFS, disease free survival; FASN, fatty acid synthase; H2BC, Her2 positive breast cancer; HRBC, hormon receptor-positive breast cancer; LNM, lymph node metastasis; TNM, tumor node metastasis; LVI, lymphovascular invasion; NSCLC, non-small cell lung cancer; OS, overall survival; PCA, prostate carcinoma; PIN, prostatic intraepithelial neoplasia; SCC, squamous cell carcinoma; TNBC, triple negative breast cancer; *, significant change.
<table>
<thead>
<tr>
<th>Numbered</th>
<th>Cancer type/ SIRT1 inducer</th>
<th>Disease</th>
<th>Tissue type</th>
<th>SIRT1 level mRNA protein activity</th>
<th>Metabolic changes, clinical parameters after intervention OR disease &amp; states</th>
<th>Signaling/ cellular mechanism</th>
<th>Study type</th>
<th>Cases no.</th>
<th>Reference</th>
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<tbody>
<tr>
<td>43</td>
<td>resveratrol</td>
<td>healthy, obese</td>
<td>skeletal muscle</td>
<td>NA increased*</td>
<td>decreased* ALT, insulin, HOMA, triglycerides, leptin, intrahepatic lipid, leukocyte number, TNFα, sleeping metabolic rate, systolic blood pressure, mean arterial pressure and increased* RQ, complex I-II, MOG, MOGS, intramyocellular lipid</td>
<td>p-AMPK, PGC-1α, citrate synthase/mitochondrial oxidative phosphorylation, flexibility of metabolism</td>
<td>Randomized, double-blind study</td>
<td>11</td>
<td>[137]</td>
</tr>
<tr>
<td>44</td>
<td>SRT21204</td>
<td>healthy</td>
<td>plasma</td>
<td>NA NA NA</td>
<td>decreased* IL-6, IL-8, CRP and increased* F1+2, TATc</td>
<td>LPS /inflammation</td>
<td>Randomized, double-blind placebo controlled trial</td>
<td>24</td>
<td>[138]</td>
</tr>
<tr>
<td>45</td>
<td>SRT21204</td>
<td>healthy old</td>
<td>serum</td>
<td>NA NA NA</td>
<td>decreased* serum cholesterol, triglycerides, half-life of recovery after exercise (ADP,PCr) and increased* HDL:LDL ratio</td>
<td>mitochondrial oxidative phosphorylation</td>
<td>Phase I clinical trial</td>
<td>24</td>
<td>[139]</td>
</tr>
<tr>
<td>46</td>
<td>SRT21204</td>
<td>healthy, cigarette smokers</td>
<td>serum</td>
<td>NA NA NA</td>
<td>decreased* cholesterol, LDL, triglycerides, no effect on blood flow rate, coagulation factors, macrophage activation</td>
<td></td>
<td>Randomized, double-blind placebo controlled, crossover trial</td>
<td>24</td>
<td>[140]</td>
</tr>
<tr>
<td>47</td>
<td>Selisistat</td>
<td>healthy</td>
<td>blood</td>
<td>NA NA NA</td>
<td>NA</td>
<td>gene expression differences</td>
<td>Randomized, double-blind placebo controlled, crossover trial</td>
<td>22+66</td>
<td>[141]</td>
</tr>
</tbody>
</table>

F1+2, prothrombin fragment; MOGs, malate/octanoyl-carnitine/glutamate substrate; MOGS, MOG/succinate substrate; TATc, thrombin-antithrombin complex; *, significant change.
**Lung cancer.** SIRT1 showed significantly higher expression in lung tumors than in normal tissues and was positively associated with Ki67 index, TNM stage and lymph node invasion. It is suggested as an independent prognostic factor for shorter disease free survival (DFS) and OS, and for higher chance to chemotherapy resistance [120–123]. In squamous cell carcinomas (SCCs), high levels of SIRT1 effectively deacetylated and inactivated p53. In SIRT1 positive non-small cell lung cancer (NSCLC) cases, low HIC1, a suppressor of SIRT1, was associated with poor prognosis [124]. However, a case-control study investigating SNPs suggested that SIRT1 is a tumor suppressor in radon-induced cancer in miners (Table 2) [125].

**Breast cancer.** In a meta-analysis of non-stratified studies, SIRT1 expression was significantly and positively correlated with high TNM stages, decreased DFS and a higher rate of lymph node metastases (LNMs) [126]. However, other studies found opposite correlations where increased SIRT1 level reduced EMT markers [127,128]. In stratified evaluations, lower expression of SIRT1 correlated with the presence of LNMs in hormone receptor-positive breast cancer (HRBC), HER2 overexpressed/amplified and ER/PR negative breast cancer (H2BC), and in invasive ductal carcinoma (IDC). Similarly, in another study, lower SIRT1 expression correlated with poorer DFS only in HRBC group [129,130]. Increased level of SIRT1 was associated with increased LNMs only in TNBC groups [129,131,132]. Additionally, SIRT1 expression was significantly lower in TNBC than in hormone positive HER2 negative breast cancers. Moreover, low SIRT1 expression was associated with worse OS in the latter group, while in TNBC, high SIRT1 level was associated with a poor prognosis [110]. However, metabolic syndrome is associated with an increased risk of breast cancer, poor prognosis and mortality, and is also associated with a decreased SIRT1 level (Table 2) [17].

**Prostate cancer.** mRNA expression of SIRT1 was significantly downregulated in prostatic intraepithelial neoplasia (PIN) and prostate carcinoma (PCa) [133]. In contrast, other studies have reported that SIRT1 mRNA levels were significantly increased in prostate cancer tissues, positively correlated with Ki67 mRNA expression [134], and were associated with the Gleason grade 3 (Table 2) [135].

8. **SIRT1 as a Therapeutic Target — Activators and Inhibitors**

Resveratrol, a natural compound, has been used to mimic calorie restriction [137] because it is known to significantly increase forced vital capacity (FVC) function of the lung [36] and respiratory quotient (RQ) as well, while significantly decreasing sleeping metabolic rate, systolic blood pressure, mean arterial pressure and many other clinical and systemic parameters [137]. Resveratrol treatment significantly decreased intrahepatic lipid content but increased that in muscle cells. Resveratrol significantly increased AMPK phosphorylation, PGC-1α, citrate synthase and SIRT1 level in muscle biopsies as well. Similarly, genes involved in mitochondrial oxidative phosphorylation were up-regulated as well. No adverse effects were observed during the 30-day treatment period (Table 3, Ref. [137–141]) [137].

In parallel with exercise, the small molecule SIRT1 activator, SIRT2104, significantly attenuated plasma cytokines IL-6, IL-8 and CRP in lipopolysaccharide-injected human patients but increased the levels of prothrombin fragment and thrombin-antithrombin complex. There was no effect on the level of von Willebrand Factor, fibrinolytic response, number of leukocytes and gene expression profile [138]. Other studies have recorded significantly decreased recovery period after exercise as well as significantly decreased serum lipid levels after SIRT2104 treatment (Table 3) [139,140].

The SIRT1 inhibitor Selisistat (SEN0014196) has a specific transcriptional signature in blood cells, involving transmembrane transport, cholesterol/lipid/steroid homeostasis and redox processes genes (Table 3) [141].

9. **Summary**

Experimental knowledge of the beneficial effects of proper diet and exercise has been known since ancient times and can be used effectively, however, the molecular mechanism behind these has only recently been revealed. Our primary aim was to explore lifestyle specific changes of SIRT1, a key epigenetic regulator, which influences the development of metabolic syndrome and related cancer, and describe the molecular aspects of these mechanisms.

In general, we found that optimal levels of lifestyle factors correlated to increased levels of SIRT1 improving metabolic and inflammatory parameters; some of them increased mitochondrial function and increased the flexibility of alternation between different energy sources. Briefly, SIRT1 are activated and/or induced by AMPK in energy/nutrient-sensing pathways by glucose deprivation or exercises in many tissues. This is the result of increased AMP level which is the sign of low cellular energy [142]. Moderate and high-intensity exercise increases the AMP/ATP ratio [143,144], while low-intensity exercise only if it prolongs to exhaustion [145]. SIRT1 activation then leads to increased fat mobilization and lipid oxidation in both skeletal muscle and differentiated adipocytes [57, 146,147]. During exercise, increased mitochondrial respiration results in elevated NAD+/NADH.H+ ratio which also induces SIRT1 levels, so this feedback loop maintains the activity of the proper metabolic pathways to meet energy demand. However, beside the activation loops, there are inhibition circles as well in this regulation which impede biosynthetic pathways including fatty acids, and thus diminish fat-induced inflammation levels [148]. Improved exercise tolerance has other benefits such as decreased ROS production, oxidative stress and subsequent DNA–damage
Despite the beneficial effects of a long-term CR with elevated SIRT1 levels, initially low baseline levels of SIRT1 in adipose tissue can significantly reduce the effectiveness of CR [32]. Similarly, the minor alleles of SIRT1 and CLOCK in the carriers also increased resistance to weight loss, increased ghrelin levels and lower adherence to the Mediterranean diet [41]. These results suggest that SIRT1 level may serve as a predictive marker of metabolic imbalances or effectiveness of a complementary therapy for weight loss, high blood pressure, cardiovascular disease, T2DM or cancers. However, a well-defined range of healthy and unhealthy levels of SIRT1 in different tissues, like adipocytes, skeletal muscle cells or PBMCs, should be determined which requires further studies for its appropriate use in health services.

Based on the results of the cited human clinical trials and human studies, we described that SIRT1 interplays with major components of health-regulatory processes, such as metabolic/energy sensing system, pro-inflammatory cytokine release, oxidative stress control, however, the circadian rhythms itself cannot discussed as a separate entity from all others (Fig. 3). Circadian rhythm is the basis of all diurnal behaviors, like eating or activity level in general, and all energy and metabolic processes required for these functions. Therefore, it is necessary to outline this essential component and its connections to all the above mentioned mechanism related to SIRT1 expression. The proper alignment of the circadian clock with the environmental “time generators” is necessary for normal, healthy metabolic regulation [149]. Therefore, desynchrony resulting from a generally imbalanced lifestyle can cause similarly elevated leptin, glucose and insulin levels, as well as increased blood pressure leading to increased risk of obesity, T2DM, hyperlipidaemia, high blood pressure and cardiovascular disease.

As reported, circadian rhythm alterations are frequent in metabolic syndrome, cancers and mood disorders [149, 150]. Food availability is predominant for peripheral clocks in the peripheral tissues, and is able to resynchronize them independently from the central clock. Thus, not surprising that a number of metabolic pathway regulator transcription factors (such as Rev-erb-alpha, ROR-alpha, PPAR) display tissue specific circadian expression in peripheral tissues (liver, white and brown adipose tissue, skeletal muscle). It has been identified that smoking is also able to disrupt circadian rhythm, decrease SIRT1 expression and is strongly associated with metabolic imbalance and inflammation as well [151,152]. The CLOCK/NAD+ -SIRT1 loop couples circadian oscillation to nutrient/energy metabolism at the CLOCK-BMAL1 transcription factor through SIRT1, which drives the cyclic expression of Bmal1, Per2 and Cry1
Although smoking habits of patients are usually found in medical records, sleeping habits and its normalization are not well-followed and do not count into the optimal results of conventional treatment of metabolic and cardiovascular diseases or cancers. However, as our results suggest, it also has a significant impact on the effectiveness of a therapy.

Defense mechanisms related to inflammation are also important regulators of homeostasis (Fig. 3). They include SIRT1, AGER and pattern recognition receptors (PRR), like TLRs, and stop infections and other non-desired mechanisms in the human system [37,82]. TLR is originally activated by bacterial lipids leading to subsequent release of IFN-γ and IP-10 [155]. However, as we have shown, specific nutrient component, AGEs are also able to activate these mechanisms. Chronic exposure to such excessive nutrient oxidants, such as during prolonged hyperglycemia, leads to impairment of these native antioxidant defense mechanisms. Exhaustion of these system can be prevented by restriction of AGEs and/or the presence of polyunsaturated fatty acids in the diet, and similarly, by exercise or even specific treatment of OSAS patients, which are able to decrease inflammation and related oxidative stress as well by increased SIRT1 levels [35,37,38,156,157].

As we described earlier, oxidative stress is involved not only in immune system function but in aging, telomere attrition, DNA-damage, apoptosis and angiogenesis, and increases the level of MMP9, which is also known in cancer development, however, SIRT1 is able to block MMP-9 expression and regulates all these functions as well [158–161]. Interestingly, a recent paper suggests that Treg cells, which are also the focus of recent cancer research, sustain and amplify tumor suppressor capacity in the microenvironment through oxidative stress [162]. However, it is promising that repeated exercise may reprogram these important regulatory mechanisms induced by oxidative stress in distant tissue microenvironments, i.e., in tumors or other tissues that are not directly involved in the training response, resulting in a cumulative antitumorigenic effect [136]. In addition, we found that SIRT1 inducers exert a similar effect as CR and exercises without side effects during the duration of the studies, which may be an alternative if the other two are inappropriate for some reason [137–141]. In tumors, SIRT1 expression varied by tumor types and subgroups. However, as we have found, the main drawback of all cancer papers is that mostly only the tumor samples and the surrounding normal tissues were examined. Unfortunately, these data do not allow us to compare these results with epidemiology papers that measured wider and systemic effect of SIRT1, rather than local tissue changes in cancer studies. Therefore, these data can give information for diagnostic, progression or local treatment purposes but do not explore the background and causal factors of tumor development. Higher levels of SIRT1 could reflect a necessity of higher defense in the body to eliminate a more aggressive tumor. However, data suggest that DNA damaging agents probably would not be sufficient in tumors overexpressing SIRT1 because SIRT1-regulated pathways bypass this by induction of survival [52]. Additionally, non-cancer related data detailed above suggest that higher SIRT1 expression is able to reduce MMP-9 either by downregulation of NFκB or by reducing the response to oxidative stress through several connected tumor-promoting processes. Therefore, SIRT1 may decrease metastatic progression under specific circumstances [68,158] and could be a target for state specific therapies by regulating autophagy and apoptosis [101,102].

In summary, in our review we focused on SIRT1 and related pathways as a molecular aspect of different lifestyles. Our findings support that interventions to prevent metabolic disorders can similarly prevent the development of cancer, as it has known relation to chronic inflammation and metabolic syndromes. With this review, we aimed to promote health science-related research and highlight the importance of beneficial lifestyle factors as effective tools for prevention and complementary treatment to reduce the development of diseases.

**Abbreviations**

ABC1, ATP-binding cassette transporter A1; ADPR, Adenosin-diphosphate-ribose; AGEs, glycation end products; AGER1, AGE receptor 1; AROS, active regulator of SIRT1; CIMP-high, CpG island methylator phenotype; CLOCK, circadian locomotor output cycles kaput; COVID-19, coronavirus disease; CR, caloric restriction; DBC1, deleted in breast cancer 1; DFS, diseases free survival; EE, energy expenditure; EMT, epithelial to mesenchymal transition; eNOS, endothelial nitric oxide synthase; FXR, farnesoid X receptor; FEV1, forced expiratory volume in 1 s; FOXO1, FOXO3, Forkhead box O 1 or 3; FVC, forced vital capacity; H2BC, HER2 overexpressed and/or amplified and ER and/or PR negative breast cancer; HDAC, histone deacetylase enzyme; HDL(-C), high-density lipoprotein(-C); HOMA-R, homeostasis model assessment for insulin resistance; HRBC, hormone receptor-positive breast cancer; IR, insulin resistant; IRI, insulin resistance index; IDC, invasive ductal carcinoma; LAGB, laparoscopic adjustable gastric banding; LDL(-C), low-density lipoprotein(-C); LNM, lymph node metastases; LXRα, oxysterol receptor; mTOR1, mammalian target-of-rapamycin complex-1; mTOR2, mammalian target-of-rapamycin complex-2; MSI-high, microsatellite instable-high; NAD+, Nicotinamid-adenin-dinucleotid; NO, Nitrogen-monoxide; NES, nuclear export sites; NLS, nuclear localization sites; NSCLC, non-small cell lung cancer; OSAS, obstructive sleep apnoea syndrome; OS, overall survival; PBMCs, peripheral blood monocytes; PUFAs, polyunsaturated fatty acid; PCa, prostate carcinoma; PER1/2/3, circadian clock period proteins; PIN, prostatic intraepithelial neoplasia; PPARα, peroxisome proliferator-activated receptor-α; PPARγ, peroxisome
proliferator-activated receptor-γ; RQ, respiratory quotient; PRR, pattern recognition receptors; SCCs, squamous cell carcinomas; SENP1, SUMO1/Sentrin specific peptidase 1; SOD, superoxide dismutase; T2DM, type 2 diabetes mellitus; TNBC, triple negative breast cancer; TNM stages, classification of malignancies (T, tumor, N, Node, M, metastases); WL, weight loss.

**Author Contributions**

ZN—design, data collection, visualization, writing manuscript, paper review, final approval; EK—paper review; IT—paper review.

**Ethics Approval and Consent to Participate**

Not applicable.

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**Conflict of Interest**

The authors declare no conflict of interest.

**References**


