A Review of Sirt1 and Sirt1 Modulators in Cardiovascular and Metabolic Diseases

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Abstract: Sirt1 (member of the sirtuin family) is a nicotinamide adenine dinucleotide (NAD)-dependent deacetylase that removes acetyl groups from various proteins. A wide variety of proteins are Sirt1 substrates; the list includes many transcription factors and cofactors. Deacetylation of these factors may lead to activation or inactivation of the factor, thus impacting downstream gene expression. In addition to direct deacetylation, Sirt1 can modulate protein activity by other mechanisms. Although initial research focused on sirtuin’s role in life span extension especially in lower organisms more recent studies show that Sirt1 activity can impact a wide array of proteins implicated in cardiovascular (CV) and metabolic diseases. Several patents have been published in the last 5 years describing the application of sirtuin compounds in the treatment of metabolic diseases. This review will focus on those Sirt1-modifiable proteins that have an impact on CV and metabolic diseases. Pharmacological agents that activate Sirt1 and thus impact the disease process will also be reviewed.

Keywords: Cardiovascular diseases, Sirt1, Sirt1-Activators, deacetylation. diabetes, obesity, metabolism.

1. INTRODUCTION

Acetylation of the ε-amino group of lysines in proteins is a well-known mechanism for regulating protein activity [1, 2]. This regulation is well studied in the case of histones, where acetylation of a lysine neutralizes the positively charged lysine residues, causing a reduction in the affinity of histone-DNA interactions, leading to increased access of transcription factors to the DNA template. Histone acetyltransferase (HAT) and histone deacetylase (HDAC) are enzymes that selectively deacetylate or acetylate the ε-amino groups of lysine. Altered HDAC (class I and II) and/or HAT activities are present in many types of cancers and selective HDAC inhibitors are in clinical trials for treatment of certain types of cancer [3]. Acetylation-deacetylation is now recognized as a mechanism by which the activity of histones and many other transcription factors can be regulated. In addition, this mechanism may also be relevant for proteins that are not directly involved in gene transcription.

Yeast Sir2 (silent information regulator 2) and its mammalian homologue Sirt1 are members of the sirtuin family [4-6]. In mammals, there are 7 homologues of Sir2 termed sirtuins (SIRT1-SIRT7) among which SIRT1 is the closest human homologue of yeast Sir2. Mammalian sirtuins have diverse cellular localizations and affect numerous cellular functions [4]. Sirt1, Sirt6 and Sirt7 are classified as the nuclear sirtuins; although Sirt1 is also present in nucleus modulate cytosolic targets (see below). Sirt3, Sirt4 and Sirt5 reside in the mitochondria, whereas Sirt2 is localized predominantly in the cytoplasm. Sirt1, Sirt6 and Sirt3 and Sirt5 are NAD-dependent deacetylases, whereas Sirt4 and Sirt6 are primarily mono-ADP-ribosyl transferases with no deacetyl activity on histone substrates in vitro [4,6]. Unlike HDAC I and II, Sirt1 is a nicotinamide adenine dinucleotide (NAD)-dependent deacetylase and removes acetyl groups from many non-histone proteins [5]. Sirt1 bears virtually no sequence homology to class I or II HDACs. The crystal structure of Sirt1 is not known. A three-dimensional comparison model of the Sirt1 protein catalytic core (domain area from residues 244 to 498 of the full length Sirt1) was proposed to assist in the investigation of active site–ligand interactions and in the design of Sirt1 modulators [7]. In the reaction catalyzed by Sirt1, nicotinamide is liberated from NAD+ and the acetyl group of the substrate is transferred to cleaved NAD+, generating the novel metabolite O-acetyl-ADP ribose Fig. (1). Sirt1 can deacetylate a variety of substrates and is, therefore, involved in a broad range of physiological functions, including control of gene expression, metabolism, and aging [4-6]. The list of Sirt1 substrates is continuously growing and includes several transcription factors - tumor suppressor protein p53, members of the FOXO family (Forkhead box factors regulated by insulin/Akt), HES1 (Hairy and enhancer of split 1) and HEY2 (Hairy/ enhancer-of-split related with YRPW motif 2), PPARγ (peroxisome proliferator-activated receptor gamma), CTIP2 [Chicken ovalbumin upstream promoter transcription factor (COUP-TF)-interacting protein 2], p300, PGC-1α (PPARγ coactivator), and NFκB (nuclear factor kappa B) [4-6]. Accumulating evidence implicates Sirt1 in calorie restriction (CR)-mediated health effects, including increased organism longevity. An increase in Sir2 (yeast homologue of Sirt1) protein levels extends lifespan, while a deletion or mutation in Sir2 shortens lifespan. This phenomenon has been demonstrated in yeast, worms and flies [4-6, 8, 9]. While the hypothesis that Sirt1 regulates aging and longevity in higher mammals remains to be validated, Sirt1 has been shown to regulate metabolic responses to changes in nutrient availability and CR in multiple tissues. Nutrient regulation of Sirt1 activity may in part be due to its dependency on NAD.
2. Sirt1 TARGETS WITH RELEVANCE TO METABOLIC AND CARDIOVASCULAR DISEASES

Sirt1 has long been considered the anti-aging target. Since aging leads to a progressive decline in multiple organ systems, including the pancreas and heart it is not surprising that Sirt1 benefits are now being realized in diabetes and CVD. Sirt1 targets related to metabolic and cardiovascular diseases are summarized in Fig. (2). Consistent with targets it modulates, Sirt1 transgenic mice show both metabolic as well as cardiovascular benefits [10]. Sirt1 expressing mice are leaner, more metabolically active and have reduced blood cholesterol, insulin and fasted glucose. These animals have reduced adipose-derived inflammatory cytokines and are more glucose tolerant. More recent studies show that even mice with 2-4 fold overexpression of Sirt1 show lower lipid-induced inflammation, better glucose tolerance, and are protected from hepatic steatosis [11]. This is consistent with the data generated with Sirt1 activators such as resveratrol, which is a modest Sirt1 activator yet shows beneficial metabolic and CV effects. (see discussion below for references). Although Sirt1 targets here are grouped based on their potential application in diabetes, inflammation or cardiovascular disease, often these proteins have much broader impact with multiple benefits.

2a. Sirt1 and FOXO1 Function

FOXO1 members of forkhead transcription factor family have important roles in insulin signaling [15, 16]. FOXO1 activity is regulated by acetylation on specific lysine residues or phosphorylation on specific serine residues [15, 17, 18]. cAMP-response element-binding protein (CREB)-binding protein (CBP) acetylates FOXO1, destabilizes FOXO1-DNA interactions and thereby attenuates FOXO1-DNA interactions and thereby attenuates FOXO1-mediated gene expression. Sirt1, in contrast, deacetylates FOXO1 and promotes FOXO1 transcriptional activity [17, 18]. FOXO1, depending on tissue localization, may have protective or negative effects on insulin resistance, diabetes and vascular function [19-21].

- FOXO1 modulates energy homeostasis in adipose through regulation of adipocyte size and adipose tissuespecific gene expression in response to excessive caloric intake [16].
- FOXO1 expression in adipose tissue improved glucose tolerance and insulin sensitivity, accompanied by smaller-sized adipocytes and decreased tumor necrosis factor (TNFα) expression.

**Fig. (1).** Deacetylation reaction catalyzed by Sirt1: Sirtuins act by removing acetyl groups from proteins in the presence of NAD+; they are thus classified as NAD+-dependent deacetylases. They add the acetyl group from the protein to the ADP-ribose part of NAD+ to form O-acetyl-ADP-ribose and nicotinamide.
While FOXO1 may have negative effects in some tissues, Sirt1 can inhibit FOXO1 [22, 23]. It is conceivable that cancer cells and other transformed cell lines showed that FOXO1 will have negative consequences in some tissues (e.g., liver) and positive consequences in others (adipose, pancreas). It is also important to note that early studies in the pancreas). It is also important to note that early studies in

These findings suggest that Sirt1-mediated activation of FOXO1 will have negative consequences in some tissues (e.g., liver) and positive consequences in others (adipose, pancreas). It is also important to note that early studies in cancer cells and other transformed cell lines showed that Sirt1 can inhibit FOXO1 [22, 23]. It is conceivable that while FOXO1 may have negative effects in some tissues, Sirt1 may maintain homeostasis by modifying other proteins in parallel (see below) and thereby nullify FOXO1 effects.

2b. Sirt1 and PGC1α Function

 Peroxisome proliferator-activated receptor-coactivator (PGC1α) is a transcription coactivator (modulates transcription factor activity without itself directly binding to DNA). The molecule plays a central role in the regulation of cellular energy metabolism [24]. Sirt1 physically interacts with and deacetylates PGC1α at multiple lysine sites, consequently increasing PGC-1α activity [25-27]. PGC1α is involved in a wide variety of biological responses, including adaptive thermogenesis, mitochondrial biogenesis, glucose/fatty acid metabolism, fiber type-switching in skeletal muscle, and heart development [24]. Increased PGC1α induces the transcription of nuclear respiratory factors NRF1 and NRF2, leading to the increased expression of mitochondrial transcription factor A and enhanced mitochondrial biogenesis. PGC1α also interacts with other nuclear hormone receptors such as PPARα, the retinoic acid receptor, and the thyroid receptor to enhance oxidative phosphorylation and energy metabolism [24]. Pharmacological activation of Sirt1 by resveratrol decreases PGC-1α acetylation, as well as increasing both PGC1α activity and the induction of genes for oxidative phosphorylation and mitochondrial biogenesis [27]. These events are associated with increased aerobic capacity (increased running time) and consumption of oxygen in muscle fibers. Resveratrol treatment also protected mice against diet-induced-obesity and insulin resistance. In a study conducted in Finnish subjects, Sirt1 genetic polymorphisms correlated with the degree of energy expenditure, further implicating Sirt1 as a key regulator of energy and metabolic homeostasis [27].

PGC1α is also implicated in heart function and in the pathogenesis of heart failure [28]. In models of chronic pressure overload such as occurs in chronic hypertension, PGC1α levels are downregulated along with the target genes involved in mitochondrial fatty acid oxidation. This is consistent with the fact that mitochondrial respiratory function is known to be reduced in end-stage heart failure. Thus, Sirt1-mediated activation of PGC1α may have beneficial effects in heart disease conditions [29, 30]. Consistent with Sirt1-mediated PGC1α mechanism cardiac overexpression of Sirt1 prevents age-dependent increases in cardiac hypertrophy, apoptosis, cardiac dysfunction, and expression of senescence markers [13,14].

2c. Sirt1 and LXR Function

 Sirt1 has been identified as a positive regulator of liver X receptors (LXR) [31]. LXR is a nuclear receptor which forms heterodimers with the retinoic X receptor and, upon ligand (oxysterols) binding, stimulates the expression of target genes. LXR is acetylated at a single conserved lysine (K432 in LXRα and K433 in LXRβ) adjacent to the ligand-regulated activation domain. Sirt1 interacts with LXR and promotes deacetylation and subsequent activation [32]; mutations of K432 eliminate activation of LXRα by Sirt1. Loss of Sirt1 in vivo reduces expression of a variety of LXR targets involved in lipid metabolism and HDL biogenesis [32].
Since LXR operates as cholesterol sensor to protect the organism from cholesterol overload, Sirt1-mediated activation of LXR may have several positive consequences in metabolic and cardiovascular diseases [31]. The process may function to:

- stimulate cholesterol efflux from cells to high-density lipoproteins through the ATP-binding cassette transporters ABCA1 and ABCG1.
- activate the conversion of cholesterol to bile acids in the liver and facilitate excretion.
- prevent cholesterol-mediated toxicity in tissues such as pancreas and improve pancreatic function in diabetic conditions [33].
- reduce cholesterol loading in macrophages, resulting in reduced atherosclerosis [31].

Thus, deacetylation of LXR by Sirt1 may be a mechanism that affects atherosclerosis and other age-related diseases, including diabetes.

2d. Sirt1 and NFκB Function

Nuclear factor-kappa B (NFκB) controls the expression of genes involved in inflammation and cell survival [34, 35]. NFκB is typically composed of a heterodimeric protein complex that contains a DNA-binding component and a transactivation domain (e.g. heterodimer consisting of p65/Rel and p50/p52). In unstimulated cells, NFκB resides in the cytoplasm bound by its inhibitory protein IκB. Following cellular stimulation by cytokines and other inflammatory agents, IκB is phosphorylated and targeted for degradation. Degradation of IκB liberates NFκB, allowing the transcription factor to translocate to the nucleus, where it interacts with promoter gene targets to enhance transcription of genes involved in inflammation and cell survival. Sirt1 physically interacts with the RelA/p65 subunit of NFκB and inhibits transcription by deacetylating RelA/p65 at lysine 310 [36]. Because of the pivotal role of NFκB in the cytokine signaling pathway, multiple downstream effects result from Sirt1-mediated inhibition of NFκB [35-37]. Of primary importance are overall inhibition of inflammatory cytokines (TNFα, MCP-1) and adhesion molecules (VCAM-1) that are known to contribute to atherosclerosis and cardiovascular disease [38]. Cytokines and inflammation also play a critical role in the pathogenesis of insulin resistance and diabetes [38, 39]; thus, Sirt1-mediated inhibition of NFκB may have beneficial effects in both cardiovascular and metabolic diseases.

2e. Sirt1 and eNOS

Nitric oxide (NO) is generated from the conversion of L-arginine to L-citrulline by the enzymatic action of NO synthase (NOS) [40]. In the vessels, NO is produced from the endothelium by the constitutively expressed endothelial isoform of NOS (eNOS). NO has a variety of functions, but its action as the endothelium-derived relaxing factor is the most important for the maintenance of vascular homeostasis. Endothelial dysfunction is characterized by an impairment of endothelium-dependent relaxation, and reduced eNOS-derived NO bioactivity. Sirt1 promotes endothelium-dependent vasodilation by targeting endothelial nitric oxide synthase (eNOS) for deacetylation [41]. Sirt1 and eNOS colocalize in endothelial cells, and Sirt1 deacetylates eNOS, stimulating eNOS activity and increasing endothelial nitric oxide (NO). The Sirt1-induced increase in endothelial NOS activity is mediated through lysines 496 and 506 of eNOS. Inhibition of Sirt1 in the endothelium of arteries inhibits endothelium-dependent vasodilation and decreases bioavailable NO. Thus, Sirt1 plays a fundamental role in regulating endothelial NO and endothelium-dependent vascular tone by deacetylating eNOS. Surprisingly, nitric oxide appears to reciprocate the favor by activating Sirt1 expression [42]. This interesting circle of events (Sirt1 → eNOS → NO → Sirt1) may further enhance the beneficial effects on vasculature.

2f. Sirt1 and IRS

Insulin signaling in cells is initiated by autophosphorylation at a tyrosine site on the insulin receptor upon insulin binding, and subsequent tyrosine phosphorylation of key adaptor proteins including insulin receptor substrates 1 and 2 (IRS-1 and -2) [43]. The phosphorylated IRS proteins transmit the insulin signal further downstream, resulting in increased glucose uptake and reduced gluconeogenesis. Although Sirt1 can interact with both IRS-1 and -2, in response to insulin, Sirt1 deacetylates IRS-2 and promotes insulin-induced IRS-2 phosphorylation [44]. Suppression of Sirt1 activity also selectively inhibits insulin-induced tyrosine phosphorylation of IRS-1 and insulin responses, suggesting a major role for Sirt1 in insulin signaling.

2g. Sirt1 and p53

p53 originally identified as a tumor suppressor gene is an important transcriptional regulator of cell proliferation and apoptosis [45]. Although much of the initial work focused on its role in tumor cell growth, more recent studies show that its activity has a wide array of implications in vasculature controlling smooth muscle cell and macrophage activity [46]. p53 regulates the transcription of target genes by binding to a specific sequence. This usually results in cell cycle arrest in G1 phase and subsequent apoptosis. p53 activity can be regulated by phosphorylation, acetylation, poly-ADP-ribosylation, or sumoylation. Acetylation of p53 occurs at the C-terminal lys-382, and the binding capacity of p53 to specific DNA is enhanced by acetylation [45]. Sirt1 and deacetylases C-terminal lys-382 residue thereby reducing the transcriptional activity of p53 [47]. The implications of this down regulation are not completely clear in part due to the controversial data connecting p53 to atherosclerosis [46]. Overexpression of p53 reduces smooth muscle cell proliferation in the rat carotid artery or migration in the human saphenous vein and conversely, inhibition of p53 increase proliferation. p53 overexpression induces VSMC apoptosis and plaque rupture in a collar model of atherosclerosis in ApoE knockout mice that develop accelerated atherosclerosis. However, direct in vivo evidence from separate studies is contradictory; mice deficient for p53 crossed onto a variety of atherosclerosis-prone mice develop accelerated atherosclerosis compared with p53+/+ mice.

Sirt1-specific activators have not been tested in models of atherosclerosis although resveratrol (whose activity includes but not limited to Sirt1) has been shown to reduce
atherosclerosis [48]. Moreover, endothelial expression of Sirt1 decreases atherosclerosis in apoE null mice [49].

2h. Indirect Effects of Sirt1

In addition to its deacetylase activity on transcription factors and other proteins as mentioned above, Sirt1 can also indirectly modulate critical players involved in insulin signaling and lipid metabolism including AMP-activated protein kinase (AMPK), PPARγ, PTP-1B and UCP2 Fig. (2) [50-54]. AMPK serves as a sensor of cellular energy status, activated by an increased AMP/ATP ratio or by the upstream kinase LKB1 [55]. LKB1 phosphorylates and activates AMPK. Dysfunction of AMPK can contribute to hepatic lipid accumulation and hyperlipidemia or muscle insulin resistance. In addition, metformin, an anti-diabetic drug, acts in part via activating LKB1/AMPK signaling [56]. LKB1 activity can be regulated by acetylation and Sirt1 appears to interact with LKB1 and reduces lysine-48 acetylation of LKB1 and concurrently increased its activity [57]. Pharmacological activation of Sirt1 with resveratrol also increases LKB1/AMPK phosphorylation and increases their activity [50]. Consequently, Sirt1 activation is associated with reduced lipid accumulation in liver cells exposed to high glucose [50]. Thus Sirt1 functions as a novel regulator for LKB1/AMPK signaling and plays an essential role in the regulation of hepatocyte lipid metabolism.

In adipocytes, Sirt1 represses PPARγ actions by docking with its cofactors NCoR (Nuclear Receptor co-Repressor) and SMRT (Silencing Mediator of Retinoid and Thyroid hormone receptors) [52]. PPARγ is an essential player in adipogenesis [58], thus overexpression of Sirt1 in adipocytes attenuates PPARγ-dependent adipogenesis, and RNA interference of Sirt1 enhances the process [52]. In differentiated fat cells, upregulation of Sirt1 triggers lipolysis and loss of fat. Reduction in fat may be one possible molecular pathway connecting caloric restriction to life extension in mammals.

Protein tyrosine phosphatase (PTP) 1B negatively regulates insulin and leptin signaling. Inhibition of PTP1B has emerged as a highly validated, attractive target for treatment of both diabetes and obesity [59]. Sirt1 reduces PTP1B levels via transcriptional repression [53]. The mechanism of this repression is unknown; it is conceivable that Sirt1 controls the transcription of PTP1B via modulation of specific histones.

3. PHARMACOLOGY OF Sirt1

Based on the foregoing observations, Sirt1 activation is expected to have a wide spectrum of beneficial effects in metabolic diseases including diabetes and obesity, as well as cardiovascular diseases. Although Sirt1 tissue-specific effects may result in unwanted consequences, overall the positive effects of Sirt1 outweigh the negative Fig. (3). Pharmacological activation of Sirt1 yields beneficial effects in animal models of disease; Resveratrol is the first and well known activator of Sirt1. Resveratrol acts as an allosteric activator and induces conformational changes in Sirt1 that better accommodate substrate groups [60]. While the off-target effects of resveratrol demand further investigation, more specific Sirt1 activators have emerged in the recent past and the beneficial effects of resveratrol align with those of the selective Sirt1 activators.

![Fig. (3). Biological and pharmacological validation studies show that Sirt1 activation leads to overall beneficial effects - see text for details](image)

Beneficial effects of Sirt1 activators in animal models of disease:

3a. Diabetes and Obesity
- Resveratrol enhances insulin sensitivity *in vitro* in a Sirt1-dependent manner and attenuates high-fat diet-induced obesity and insulin resistance *in vivo* [27].
- Resveratrol significantly increased aerobic capacity, as evidenced by increased running time and consumption of oxygen in muscle fibers [27].
- In diet-induced obese and genetically obese mice, highly selective Sirt1-activating compounds improved insulin sensitivity, lowered plasma glucose, and increased mitochondrial capacity [61]. In the Zucker fa/fa rat model of insulin resistance, these Sirt1 activators improved whole-body glucose homeostasis and insulin sensitivity in adipose tissue, skeletal muscle and liver.
- In a model for type I/type II diabetes (streptozotocin induced diabetes) resveratrol reduced diabetes symptoms, significantly decreased insulin secretion and delayed the onset of insulin resistance [62].

3b. CVD
- S17834, a synthetic polyphenol Sirt1 activator, prevents lipid accumulation in hepatocytes exposed to high glucose [63]. In diabetic atherosclerosis mouse models, S17834 prevented any decrease in AMPK lipid accumulation in the liver, and inhibited hyperlipidemia as well as the acceleration of aortic lesion development.
In the streptozotocin-induced rat diabetes model, resveratrol demonstrated significant reduction in glucose levels and improved left ventricular function during ischemia-reperfusion [64]. Resveratrol-treated diabetic rats showed decreased infarct size and cardiomyocyte apoptosis as compared with diabetic animals. Resveratrol also effectively suppresses infarct size from the damaging effects of focal cerebral ischemia in Long Evans rats [65].

- Resveratrol prevented renal dysfunction, oxidative stress and nephropathy in diabetic rats [65].
- Polyphenols and resveratrol inhibit atherosclerosis development in mouse models [48, 66].

4. Patent Activity and Emerging SIRT1 Activators

Patent applications covering Sirt1 utility in life extension, diabetes, adipogenesis, and heart disease have appeared numerous times in the last 3-4 years. At present, none of these patents have been issued. The majority of these patents disclose structures that are analogues of resveratrol Fig. (4), Table 1 [67-75]. The activities of these analogues are also very similar to that of resveratrol. Some patents disclosed Sirt1 activity of other commercially available compounds (e.g. camptothecin); however, these are less potent compared to resveratrol. Resveratrol and other polyphenols have poor pharmaceutical properties; contain other promiscuous activities including antioxidant functionality; hence their potential as drug candidates is limited. SRT501 is an oral formulation of resveratrol being developed by Sirtris Pharmaceuticals (now owned by GSK) for the potential treatment of diabetes and obesity (currently in Phase 2). Sirtris is also the most active player among non-resveratrol Sirt1 activators, with many chemical compositions and target applications [61]. Sirtris is investigating a series of Sirt1 activators for the potential treatment of diabetes, aging and cancer. Potential lead compound structures (SRT-1460, SRT-1720 and SRT-2183) are given in Fig. (5). The company planned to advance the lead compound to clinical studies in the first half of 2008.

5. Sirt1 Safety

Although the fact that Sirt1 modulates a number of proteins with a wide spectrum of activities is a cause for concern from a therapeutic target standpoint; all the current data suggests that Sirt1 is a safe target. As discussed above mice overexpressing Sirt1 are leaner and metabolically active; display reductions in blood cholesterol and fasted glucose [10]. As shown in Fig. (3), a close review of Sirt1 targets show that its positive effects outweigh the negative effects. For example, although one could argue that LXR/FOXO modulation in liver might lead to fatty liver and insulin resistance, animal data show that overexpression of Sirt1 results in superior metabolic profile and resistance to hepatic steatosis [11]. This may in part be due to its balancing act on other targets such as AMPK and PGC1α [25, 57]. Moreover, cardiac-specific overexpression of Sirt1 shows delayed aging and protection against oxidative stress in the heart [13]; and endothelium-specific SIRT1 overexpression suppresses atherogenesis via improving endothelial cell survival and function [49]. Thus, Sirt1 overexpression in liver, heart, brain and vasculature appear to have beneficial effects. Although not covered in this review, Sirt1 targets also include proteins involved in cell proliferation and cancer. Since histone deacetylase inhibitors have been used in the treatment of cancer and the fact that Sirt1 can down regulate tumor suppressor p53 raised

![Examples of Resveratrol and related Sirt1 activators.](Fig. (4))
Table 1. Selected Patents Covering Sirt1 Biology and Pharmacology

<table>
<thead>
<tr>
<th>Patent Number</th>
<th>Assignee</th>
<th>Subject</th>
<th>Structures</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Pat. App 11/499,901 - Filed Aug 4, 2006</td>
<td>Sirtris Pharmaceuticals, Inc.</td>
<td>Sirt1 modulating compounds</td>
<td>See Fig. (5) [67]</td>
</tr>
<tr>
<td>US Pat. App 11/440,584 - Filed May 24, 2006</td>
<td>NA</td>
<td>Treatment of eye disorders with sirtuin modulators</td>
<td>Formulations for resveratrol related compounds [69]</td>
</tr>
<tr>
<td>US Pat. App 11166892 - Filed Jun 24, 2005</td>
<td>NA</td>
<td>Compositions and methods for selectively activating human sirtuins - Sirt1/Sirt5 activating compounds</td>
<td>Resveratrol related structures - see Fig. (4) [70]</td>
</tr>
<tr>
<td>US Pat. App 11/174,000 - Filed Jul 1, 2005</td>
<td>Harvard</td>
<td>Compositions for treating or preventing obesity and insulin</td>
<td>Resveratrol analogues, stilbenes, chalcones and flavones [71]</td>
</tr>
<tr>
<td>US Pat. App 10/884,022 - Filed Jul 1, 2004</td>
<td>Harvard</td>
<td>Compositions for manipulating the lifespan and stress response</td>
<td>Flavones and other miscellaneous compounds [72]</td>
</tr>
<tr>
<td>US Pat. App 11/374,295 - Filed Mar 16, 2006</td>
<td>Milburn M et al.</td>
<td>Methods and related compositions for treating or preventing obesity, insulin resistance etc.</td>
<td>Resveratrol related structures - see Fig. (4) [73]</td>
</tr>
<tr>
<td>US Pat. App 10/885,977 - Filed Jul 6, 2004</td>
<td>MIT</td>
<td>Sirt1 modulation of adipogenesis and adipose function</td>
<td>Polyphenols [74]</td>
</tr>
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Fig. (5). Novel Sirt1 activators being developed by Sirtris Pharmaceuticals (GSK).

Concerns that long term Sirt1 activation may promote tumorigenesis [76, 77]. At present there is no clear indication that Sirt1 activation promotes carcinogenesis. As in the case of metabolic targets, in cancer as well, Sirt1 can affect proteins that have both positive and negative consequences on cancer progression. For example, Sirt1 deacetylates beta-catenin and suppresses its ability to activate transcription and drive cell proliferation [78] or inhibit NFκB and sensitize cancer cells to chemotherapy [35, 36]. A significant inverse correlation was found between the presence of nuclear Sirt1 and the oncogenic form of beta-catenin in human colon tumor specimens analyzed [78]. Currently, there is no long term safety data available on highly specific Sirt1 activators. Long term treatment with resveratrol in mice showed no negative effects but prolonged life span on high caloric diet [79, 80]. Resveratrol however is a promiscuous compound and its effects may not be solely attributed to Sirt1 [75]. Long term studies with emerging Sirt1 activators to address
adverse effects of chronic Sirt1 activation. It is also important to note that perhaps a modest in vivo activation of Sirt1 is sufficient to realize the beneficial effects of Sirt1 (3-5 fold) and higher activation may result in unwanted side effects like those seen cardiac overexpression of Sirt1 [13].

6. CURRENT & FUTURE DEVELOPMENTS

Although the potential Sirt1 in life extension has been demonstrated in lower animals, it will be difficult to demonstrate such an effect in higher species including humans. Based on the data available, the potential of Sirt1 activators may best be realized in age related disorders such as diabetes and CVD. Sirt1 target and Sirt1 activators have been thoroughly validated in many preclinical models of metabolic and CVD. Sirtris Pharmaceuticals (now GSK) is currently targeting these indications with resveratrol, as well as novel chemicals with relatively more potent Sirt1 activation. It remains to be seen how well the preclinical data will translate in humans. Based on the transgenic animal data overall benefits from Sirt1 overexpression may outweigh negative effects if any. However, modest in vivo Sirt1 activators (2-4 fold activation) rather than potent activators (10 fold or greater) may be ideal to realize all the benefits of Sirt1 without side effects.

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[41] Mattagajasingh I, Kim CS, Naqvi A, et al. Sirt1 promotes endothelium-dependent vascular relaxation by activating...


