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Review Article

Targeting SIRT1 - a multitasker

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CONTENTS

Abstract

The NAD^+-dependent class III histone deacetylase SIRT1 modulates gene expression profiles in target tissues via regulation of transcriptional co-regulators or by directly interacting with transcription factors. Different approaches to targeting SIRT1 can be applied therapeutically. SIRT1 activators show promise as therapies for obesity, diabetes, age-related diseases, Alzheimer's disease and stroke, while SIRT1 inhibition has been postulated for future cancer therapies and anti-HIV treatments. This article reviews the recent advances in SIRT1 research and identifies potential candidates for SIRT1-targeting therapeutics.

Introduction

SIRT1 (sirtuin) is one of seven mammalian orthologues of the yeast protein silent information regulator (SIR2), an NAD^+-dependent class III histone deacetylase (HDAC III) that plays a role in chromatin remodeling associated with gene silencing and the prolongation of lifespan in yeasts. By regulating transcriptional co-regulators or by directly interacting with transcription factors, SIRT1 can modulate gene expression profiles in target tissues. Activation or inhibition of SIRT1 may have very different therapeutic applications.

Activating SIRT1

Activating SIRT1 may lead to new therapeutic approaches for metabolic and age-related syndromes. The life-extending effects of increased cell survival (by suppressing p53) and calorie restriction are mediated by SIRT1, which activates a crucial component of calorie restriction, *i.e.,* fat mobilization in white adipocytes (1). Another physiological adaptation to short-term restriction of food intake is the ability of insulin to promote glucose utilization. SIRT1 can mediate improved glucose tolerance via activation of peroxisome proliferator-activated receptor γ (PPARγ) co-activator 1α (PGC1α) (2). A recent study has shown that SIRT1 functions as a positive regulator of insulin secretion in pancreatic β-cells in response to glucose by directly repressing uncoupling protein 2 (UCP2), a system that could regulate chronic levels of insulin to correspond to levels of food intake (3).

Previous studies have also demonstrated the neuroprotective effects of SIRT1. Activation of SIRT1 has been shown to delay or prevent axonal degeneration following injury (4), and a recent study investigated its cerebroprotective effects following ischemia. Studies in organotypic hippocampal slice cultures revealed that the polyphenol compound found in red wine, resveratrol, mimics ischemic preconditioning via the SIRT1 pathway and may therefore provide a novel therapy for stroke (5).

Furthermore, SIRT1 modulates the acetylation status of the nuclear factor (NF)-κB RelA subunit, which modulates NF-κB signaling, to mediate immune and inflammatory responses. The profound microglia-mediated neurotoxicity evoked by β-amyloid (Aβ) in Alzheimer's disease (AD) is dependent on the activation of NF-κB signaling and enhanced expression of its target genes inducible nitric oxide synthase (iNOS) and the inhibitory protein IκBα. Interestingly, initiation of SIRT1 overexpression markedly prevents Aβ-mediated enhancement of NF-κB signaling. Following from this, application of resveratrol can block NF-κB signaling, markedly attenuate iNOS levels, promote deacetylation of RelA/p65 and provide effective neuroprotection against Aβ toxicity. Thus, SIRT1 activators protect against Aβ neurotoxicity by inhibiting microglial NF-κB signaling (6).

Research undertaken at Elixir Pharmaceuticals has also indicated that SIRT1 may be the gene responsible for the linkage between AD and a region of chromosome 10q, suggesting that SIRT1 may be a useful target in the diagnosis and prevention or treatment of AD (7). Along with resveratrol, several other plant polyphenols have been shown to stimulate SIRT1 catalytic activity (see Fig. 1), including butein, piceatannol, isoliquiritigenin, fisetin and quercetin (8, 9). Recent patents have also claimed novel SIRT1 activators (10) which could be useful as therapies for obesity, diabetes, age-related diseases, AD and stroke (Table I).

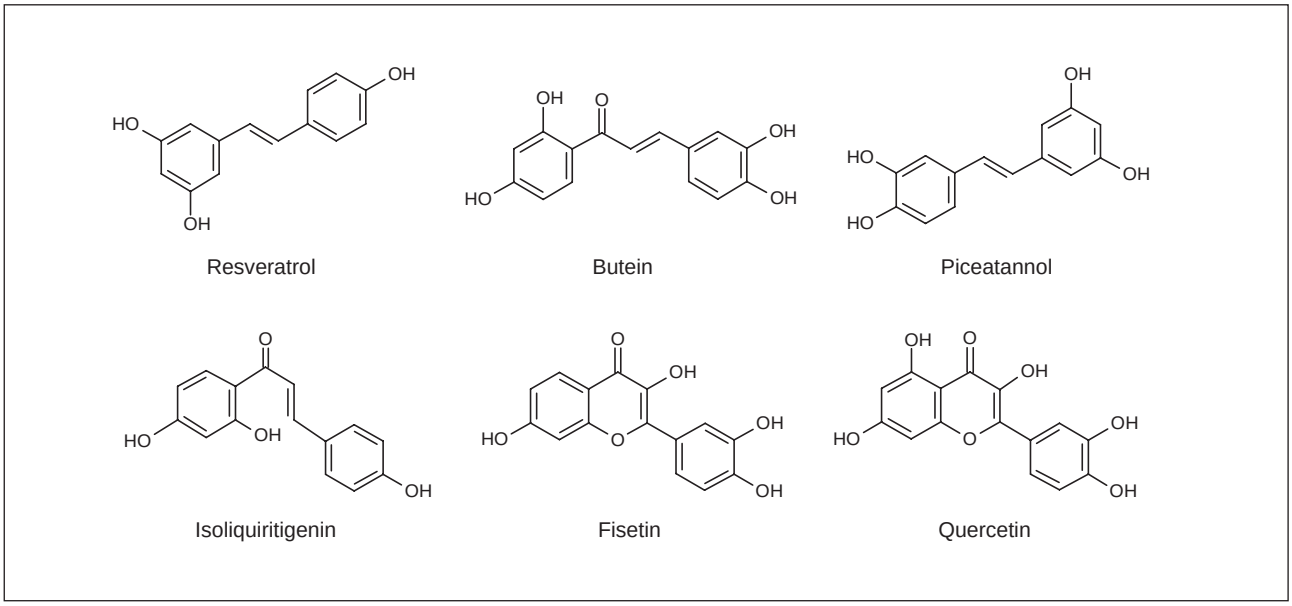
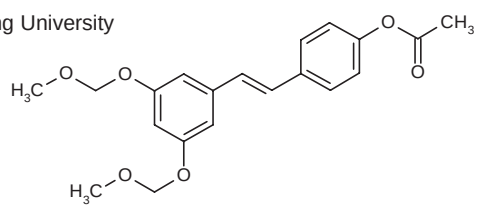
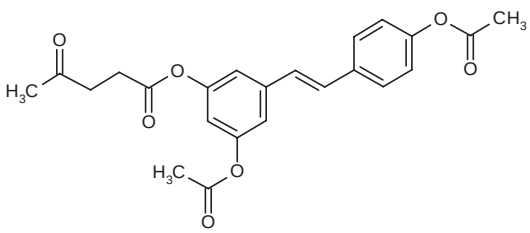
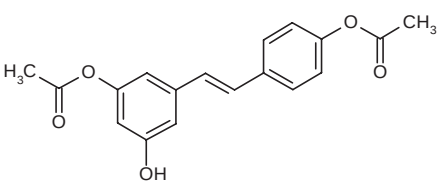
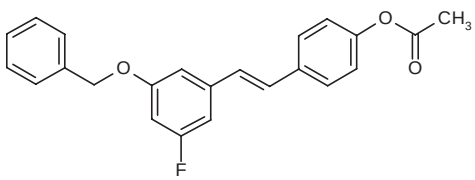


Fig. 1. Plant polyphenols that stimulate SIRT1 catalytic activity (from Ref. 8).

Table I: Novel SIRT1 activators claimed in recent patent literature (Ref. 10).

Patent	Chemical name	Source	Structure
WO 2005069998	*trans*-4'-Acetoxy-3,5-bis(methoxy-methoxy)stilbene; Acetic acid 4-[2(*E*)-[3,5-bis(methoxymethoxy)phenyl]vinyl] phenyl ester	Brigham Young University	
	trans-3,4'-Diacetoxy-5-(4-oxopentan-oyloxy)stilbene; 4-Oxopentanoic acid 3-acetoxy-5-[2(*E*)-(4-acetoxyphenyl)vinyl] phenyl ester		
	trans-3,4'-Diacetoxy-5-hydroxystilbene; Acetic acid 4-[2(*E*)-(3-acetoxy-5-hydroxy-phenyl)vinyl]phenyl ester		
	trans-4'-Acetoxy-5-benzyloxy-3-fluo-rostilbene; Acetic acid 4-[2(*E*)-[3-(benzyloxy)-5-fluorophenyl]vinyl]phenyl ester		

Inhibiting SIRT1

Neoplastic cellular transformation requires evasion of senescence, a state of permanent loss of replication. The induction of senescence-like growth arrest can therefore determine the antitumor activity of chemotherapeutic agents. Previous studies have shown the antiproliferative effects of class I and II HDAC inhibitors (for review see 11, 12). A recent study examined the potential antitumor effects of targeting SIRT1, a class III HDAC that plays an important role in DNA repair, recombination, aging and cellular survival.

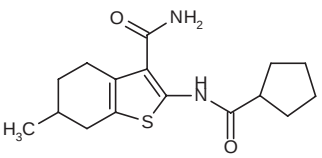
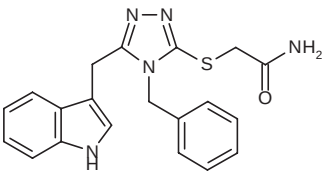
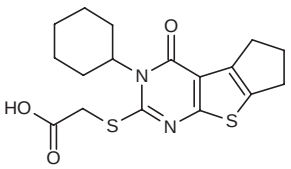
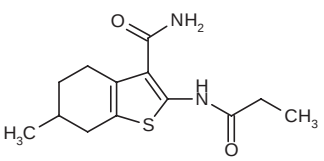
In vitro studies have demonstrated that the SIRT1-specific inhibitors sirtinol (13) and splitomicin induce senescence-like growth arrest in human breast (MCF7) and lung (H1299) cancer cell lines. These effects were associated with impaired activation of Ras mitogen-activated protein kinase (MAPK) pathways (ERK, the *c*-Jun *N*-terminal kinase JNK/SAPK and p38 MAPK) in response to growth factors. Importantly, sirtinol can evoke senescence-like growth arrest in tumor cells independent of the oncogenes *p53, p21* or *p16*, which may be significant for the treatment of malignancies not expressing or mutating *p53* and *p16* (14).

Another study applied synthetic small interfering RNA to silence SIRT1. These investigations indicated that SIRT1 silencing evokes growth arrest and apoptosis in human epithelial cancer cells, while normal human fibroblasts and epithelial cells are refractory. This work therefore suggests that SIRT1 could be a tumor-specific target (15). These SIRT1 RNA interference methods are claimed in patent literature (16). Furthermore, Isis Innovation has claimed SIRT1 as a tumor antigen in patent literature (17).

SIRT1 also represents a novel therapeutic target for HIV infection. Its acts as a specific HDAC for the Tat protein of HIV-1, which, upon acetylation, is responsible for transcriptional activation of the virus. A novel potent SIRT1 inhibitor structurally related to splitomicin, HR-73, markedly inhibits HIV gene expression in Jurkat T-cells (18). Two recent patents describe methods of inhibiting SIRT1 Tat deacetylase activity for novel anti-HIV treatments (19, 20; see Table II).

Prous Science Integrity® reports five SIRT1 inhibitors that have reached at least preclinical testing, as outlined in Fig. 2. From this group, nicotinamide (21, 22) is under clinical investigation for cancer. Two phase III studies are currently recruiting patients to determine whether nicotinamide enhances responses to radiotherapy in patients with cancer of the larynx or bladder (23, 24).

Table II: Novel SIRT1 inhibitors claimed in recent patent literature (Ref. 20).

Patent	Chemical name	Source	Structure
WO 2005072412	2-(Cyclopentylcarboxamido)-6-methyl-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide	Elixir Pharmaceuticals	
	2-[4-Benzyl-5-(1H-indol-3-ylmethyl)-4H-1,2,4-triazol-3-ylsulfanyl]acetamide		
	2-(3-Cyclohexyl-4-oxo-4,5,6,7-tetrahydro-3H-cyclopenta[4,5]thieno[2,3-d]pyrimidin-2-ylsulfanyl)acetic acid		
	6-Methyl-2-propionamido-4,5,6,7-tetrahydro-1-benzothiophene-3-carboxamide		

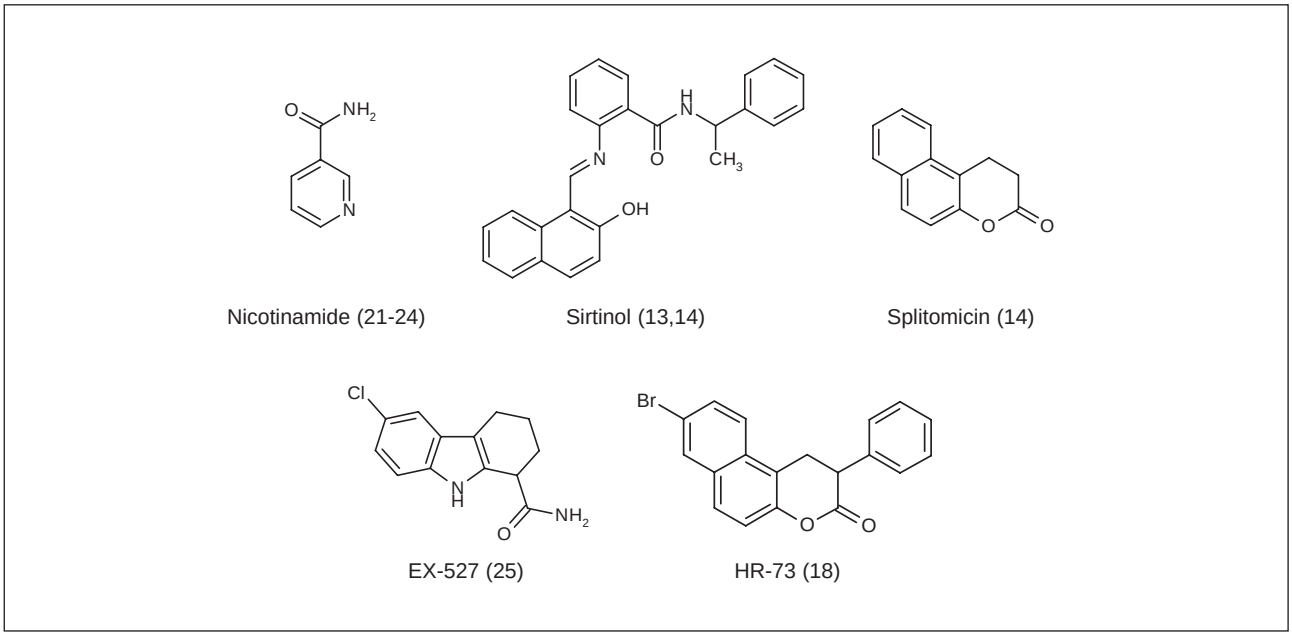


Fig. 2. SIRT1 inhibitors that have reached at least preclinical testing, according to Prous Science Integrity® (references in parentheses).

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Online Links

Subscribers to Drugs of the Future can access an online animation of how SIRT1 modulates gene expression.