4. Small molecule modulators of sirtuins

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The family of NAD+-dependent deacylases known as the sirtuins (SIRT1–7) promote longevity in diverse species and may mediate the beneficial health effects of low calorie diets and exercise [1]. For this reason, molecules that activate sirtuins are highly sought after. Here we discuss the recent advances and challenges of developing small molecules that modulate sirtuins. Molecules that activate sirtuins fall in to two main classes: natural and synthetic SIRT1 activating compounds (STACs) that work via a direct allosteric mechanism and those that raise NAD+ levels to activating multiple sirtuins. Both classes provide therapeutic benefits in animal models of human diseases but only further insights into the physiology, safety, and efficacy of sirtuin activators in humans will determine if they can be used widely in medicine.

Introduction

Recently, it has become feasible that a medicine that prevents and treats multiple age-related diseases could be developed. The relatively recent discovery of genes and small molecules that can extend lifespan in yeast, worms, flies, and mice [2)–6)] showed that there are conserved pathways that regulate aging. There are at least three main pathways that control lifespan in eukaryotes: insulin/IGF-1, TSC/mTOR, and the sirtuins [3) 7) 8)]. Molecules that modulate each of these pathways have been shown in animals to prevent a diverse set of age related diseases, including cancer, cardiovascular disease, osteoporosis, and type 2 diabetes [2) 3) 7)–9)]. In this review, we focus on modulation of the sirtuins, an area of research that has undergone considerable progress in the past decade to the point where clinical trials are in progress and more are set to begin.

[Keywords]
sirtuin, deacetylase, STAC, allosteric activation, aging, chromatin, diabetes, cancer, cardiovascular disease, inflammation

1 The Sirtuin longevity pathway

The silent information regulator (SIR) genes promote longevity in diverse species and mediate many of the beneficial effects of calorie restriction (CR) [1)]. In lower organisms they are known as Sir2 genes whereas in mammals they are SIRT1–7, but all fall into the enzyme family known as “sirtuins”. The link between sirtuins and aging was first made in budding yeast [10)], then in worms and flies [11) 12)] when overexpression of

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the Sir2 gene was found to extend lifespan. These results were challenged [13] but followed up by more rigorous positive data [14,15]. Although the debate continues, there is now good evidence from mammals that they can control aging. SIRT6 overexpression extends the lifespan of male mice when overexpressed in the whole body [16], and SIRT1 extends the lifespan of mice when overexpressed in neurons [17].

Sirtuins or "class III histone deacetylases" are distinguished from class I and II deacetylases by their lack of amino acid homology to these enzyme classes and their absolute requirement for β-nicotinamide adenine dinucleotide (NAD^+), which is used as a co-substrate [18]. In mammals, there are seven sirtuins, SIRT1-7. SIRT1, SIRT6, and SIRT7 localize primarily to the nucleus, SIRT3, SIRT4, and SIRT5, localize to mitochondria, and SIRT2 localizes to the cytosol [8]. Sirtuins were originally described as deacetylases, but it is now evident that they have broader activity [8]. In addition to deacetylation, SIRT5 possesses desuccinylase and demalonylase activities [8], SIRT4 and SIRT6 are mono-ADP-ribosyltransferases [8], and SIRT6 can deacylate long chain fatty acids [19]. For this reason, it is now more common to refer to sirtuins as deacylases rather than deacetylases.

Of all the sirtuins, SIRT1 has received the most attention. It deacetylates histones and multiple non-histone protein targets including p53, FOXO1/3, PGC-1α, and NF-κB [8]. By targeting these proteins, SIRT1 is able to regulate numerous vital signaling pathways, including DNA repair and apoptosis, muscle and fat differentiation, neurogenesis, mitochondrial biogenesis, glucose and insulin homeostasis, hormone secretion, cell stress responses, and circadian rhythms, as described elsewhere in this issue [8]. SIRT2-7 also play important roles in the cell such as regulating glucose and insulin homeostasis, mitochondrial reactions, hepatic lipogenesis, DNA damage, brown fat, telomere maintenance, inflammation, and the response to hypoxia [8].

2 Role of sirtuins in calorie restriction (CR)

There is overwhelming evidence that sirtuins underlie many of the health benefits of the dietary regimes known collectively as calorie restriction (CR) [8]. CR is typically instituted in lower organisms by restricting the food supply by 30-75% and in mammals 20-40% or by feeding animals every other day. Early studies showed that lifespan extension by CR in yeast [20], worms [21] and flies [11] is dependent on Sir2. In mammals, SIRT1 is induced by CR in numerous tissues [22], and deletion of SIRT1 prevents many of the health benefits of CR [8]. Furthermore, SIRT1 transgenic mice display phenotypes resembling CR [8] and overexpression of SIRT1 in neurons is sufficient to extend lifespan.

Consistent with its central role in the CR response, SIRT1 can prevent numerous age-related diseases in animal models, including cancer, Alzheimer's disease, and type 2 diabetes [8]. Recently, a mutation in the SIRT1 gene was identified in humans that predisposes affected individuals to hyper-inflammation and type 1 diabetes [23]. Other sirtuins may also play a role in CR [8]. For example, SIRT3 is required for the effects of CR on urea metabolism and the ability of CR to protect mice against age-related hearing loss [8].

3 The sirtuin enzymatic reaction

Sirtuins catalyze an elegant, two-step reaction that involves the consumption of NAD^+ and acylated protein substrate to produce nicotinamide (NAM), 2'O-acetyl-adenosine diphosphate-ribose (O-AcADPR), and deacetylated substrate [8,18]. In the first step of the reaction, ADP-ribose is covalently attached to the acetyl moiety of the substrate, accompanied by release of free NAM [8,18]. Hydrolysis of the acetyl-lysine bond then occurs, liberating O-AcADPR [8,18]. NAM acts as a non-competitive inhibitor of the reaction, and thus provides negative feedback inhibition of the sirtuins *in vivo* [8,18].

4 Small molecule modulators of sirtuin activity

Given their apparent role in mediating the health benefits of CR, and the demonstration of therapeutic value in pre-clinical animal models, sirtuins have attracted considerable interest as drug targets [24]. Over the past decade, both activators and inhibitors of the sirtuins have been discovered. Some act specifically, others across the entire family [8]. Inhibitors of sirtuins include the synthetic inhibitors splitomycin, tenovin-6, salermide, sirtinol, sirtinol derivatives, and the SIRT1-specific inhibitor, EX-527 [25]. SIRT1 activating compounds (STACs) include the natural molecules resveratrol, fisetin, quercetin, and the non-natural SRT1720, SRT2104, and SRT2183, and analogs of NAM. NAM analogs bind in the regulatory C-pocket

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of sirtuins, and increase the V_{max} of the enzyme. Allosteric activators such as resveratrol and SRT1720 work by lowering the K_m for the substrate and for NAD^+ [4) 9) 26)].

5 Pan-sirtuin activators

There are numerous ways to activate sirtuins, most of which are based on raising NAD levels. The first strategy to activate sirtuins was to inhibit sirtuin inhibition [27)]. Nicotinamide (NAM), a product of the sirtuin reaction, is a non-competitive inhibitor that regulates sirtuins *in vivo* by binding to a regulatory site called the C-pocket [18) 28)]. By competing with NAM for binding to sirtuins, the synthetic molecule iso-nicotinamide (iNAM) acts as a pan-sirtuin activator [27)]. Further chemical refinements are likely necessary for this mode of sirtuin activation if it is to be used as a medicine given that iNAM must reach millimolar concentrations within the cell to be effective [27)].

The main approach to developing a pan-sirtuin activator has been to elevate intracellular NAD^+ levels. The first evidence sirtuins could be activated by raising NAD^+ *in vivo* came from genetic experiments in yeast showing that overexpression of NAD salvage pathway genes increased Sir2-dependent silencing and extended lifespan [18) 20) 29)]. Indeed, CR and other stresses extend yeast lifespan by inducing expression of the nicotinamidase gene *PNC1* [29)].

In mammals, NAD^+ levels are maintained by balancing biosynthesis and salvage on one side, and breakdown on the other [30)]. NAD^+ can be synthesized from the amino acid tryptophan, but its main precursors include nicotinic acid (NA) and nicotinamide (NAM), nicotinamide mononucleotide (NMN) and the more recently identified nicotinamide riboside (NR). The main NAD^+ breakdown pathways involve three enzyme classes, i.e. sirtuins, poly(ADP-ribose) polymerases (PARPs) and cyclic ADP-ribose synthases (CD38) [30)]. As in yeast, NAD^+ levels are modulated in response to physiological processes and the cellular environment, such as energy stress via AMPK activation and DNA damage via PARP activation. During aging, NAD^+ levels naturally decline for reasons that are not yet clear.

In mammals, NAD^+ levels have been modulated pharmacologically using a variety of approaches including inhibition of the NAD^+-consuming PARP enzymes [31)], inhibition of the NAD glycohydrolase CD38 [32)], and supplementation with NAD^+ precursors such as NMN and NR [33) 34)] (**Figure 1**). Administration of PARP inhibitors, CD38 inhibitors, or NAD^+ intermediates, typically raise NAD^+ levels by 20–50% [33) 34)]. These levels of NAD^+ increase have clearly been shown to activate the sirtuins *in vivo* and boost oxidative mitochondrial metabolism, ultimately improving metabolic homeostasis on a whole body level, as reflected by the improved exercise endurance, glucose tolerance and protection against weight gain/obesity [33) 34)]. Whether pan-sirtuin activators can treat specific diseases in humans or reverse aspects of aging is an ongoing effort in the field.

6 Allosteric sirtuin activators

The first potent sirtuin activating compounds (STACs) were identified in a high-throughput screen [4)] using an assay based on a peptide substrate with a fluorescent group, AMC (7-amino-4-methylcoumarin). Several classes of plant derived metabolites such as flavones, stilbenes, chalcones and anthocyanidins directly activate SIRT1 *in vitro* via an apparent allosteric mechanism involving the lowering of peptide substrate K_m [4)]. Most of these STACs have a structure-activity relationship characterized by planar multi-phenyl rings bearing hydroxyl groups (**Figure 2**) [4)].

Of all the natural SIRT1 activators, resveratrol (3,5,4'-trihydroxystilbene) is the most potent, enhancing SIRT1-mediated deacetylation by eight-fold in the AMC-based assay. Resveratrol activates Sir2 from yeast, fly and worm and multiple studies show that resveratrol extends lifespan in these species in a Sir2-dependent manner [4) 6) 15)]. Prior to its discovery as a SIRT1 activator, resveratrol and related polyphenolic compounds had been documented to possess many health-enhancing effects [35)], ostensibly due to their antioxidant properties. In the 1990's, resveratrol and related molecules in red wine were proposed as an explanation for the 'French paradox', the fact that certain European populations with high wine consumption have low rates of cardiovascular disease despite a fat-rich diet [35)].

The discovery of natural STACs prompted screens for more potent SIRT1 synthetic activators. The first synthetic STACs were derivatives of an imidazothiazole scaffold (e.g. SRT1460, SRT1720, and SRT2183) and chemically distinct from any of the polyphenols [9)]. Molecules such as SRT1720 (see **Figure 2**) activated SIRT1 via the same K_m-lowering mechanism as that of resveratrol but with a lower EC_{50} (the concentration

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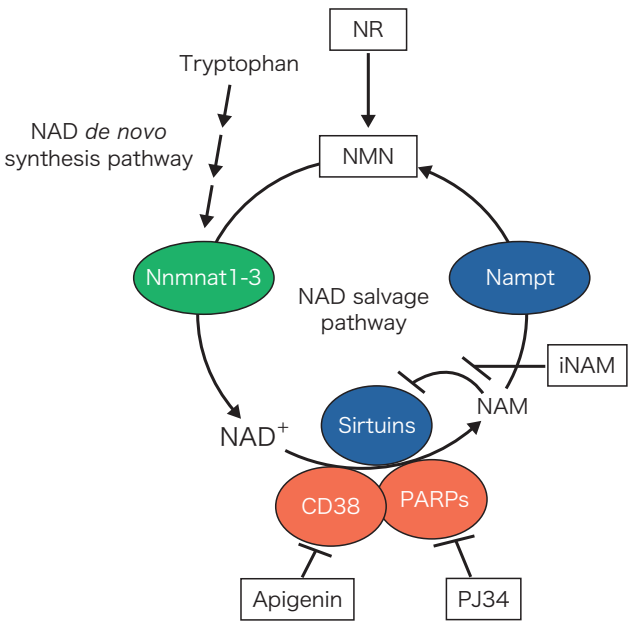

Figure 1 Pan sirtuin activators
Various strategies have been devised to activate the sirtuin family of enzymes. The first was to interfere with inhibition by the product of the sirtuin reaction, nicotinamide (NAM). Analogs of NAM such as iso-NAM (iNAM) were found to prevent NAM from binding to a conserved C-pocket in sirtuins. More recent approaches have focused on increasing the available NAD^+, either by decreasing degradation or increasing the synthesis of NAD via the salvage pathway. Molecules that raise NAD^+ by inhibiting NAD^+ degradation include PJ34 (a PARP inhibitor) and apigenin (a CD38 inhibitor). Molecules that stimulate NAD biosynthesis include nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN), two precursors of NAD. All four of the pan-sirtuin activators improve metabolism in obese or elderly mice.

required to increase activity by 50%) [9]. Extremely potent third generation STACs based on benzimidazole and urea-based scaffolds were subsequently developed [26) 38)], as were STACs based on quinoxaline dihydropyridine [36], and acylhydrazone backbones [37].

7 Mechanisms of STAC-mediated activation

It is generally accepted that STACs increase SIRT1 activity *in vivo*, although mechanism by which they activate SIRT1 has been the subject of debate [39) 40)]. Direct allosteric activation of SIRT1 through a lowering of peptide substrate K_m was first proposed in 2003 [4) 26)]. As mentioned above, the initial screen used a fluorometric assay called "Fluor de Lys" [4] in which an acetylated peptide substrate was conjugated to aminomethylcoumarin (AMC) [4]. Questions soon arose about the validity of the assay used because a fluorophore was apparently necessary to observe activation on peptide substrates [41) 42)], leading some to conclude that SIRT1 activation was an *in vitro* artifact [41]. Synthetic SIRT1 activators (e.g. SRT1460, SRT1720, and SRT2183) were discovered in a fluorescence polarization assay using a carboxytetramethyl-rhodamine (TAMRA)-tagged substrate and verified using mass spectrometry but again, the fluorescent moiety was essential to observe activation *in vitro* [9) 24) 26) 38)–41)].

During this debate, numerous studies showed that the effects of resveratrol and synthetic STACs were SIRT1-dependent [4) 8) 9) 43)]. Both resveratrol and the synthetic STACs were shown to mimic the effect of SIRT1 activation *in vivo* [4) 44)], and these effects were lost or abrogated in SIRT1 knockout mice [45]. SRT1720 was also shown to induce gene expression profiles that are highly similar to those of mice on CR [25].

Recent studies have greatly clarified why a fluorophore stimulates activation *in vitro*. There is now good evidence that the fluorescent moiety on the substrates

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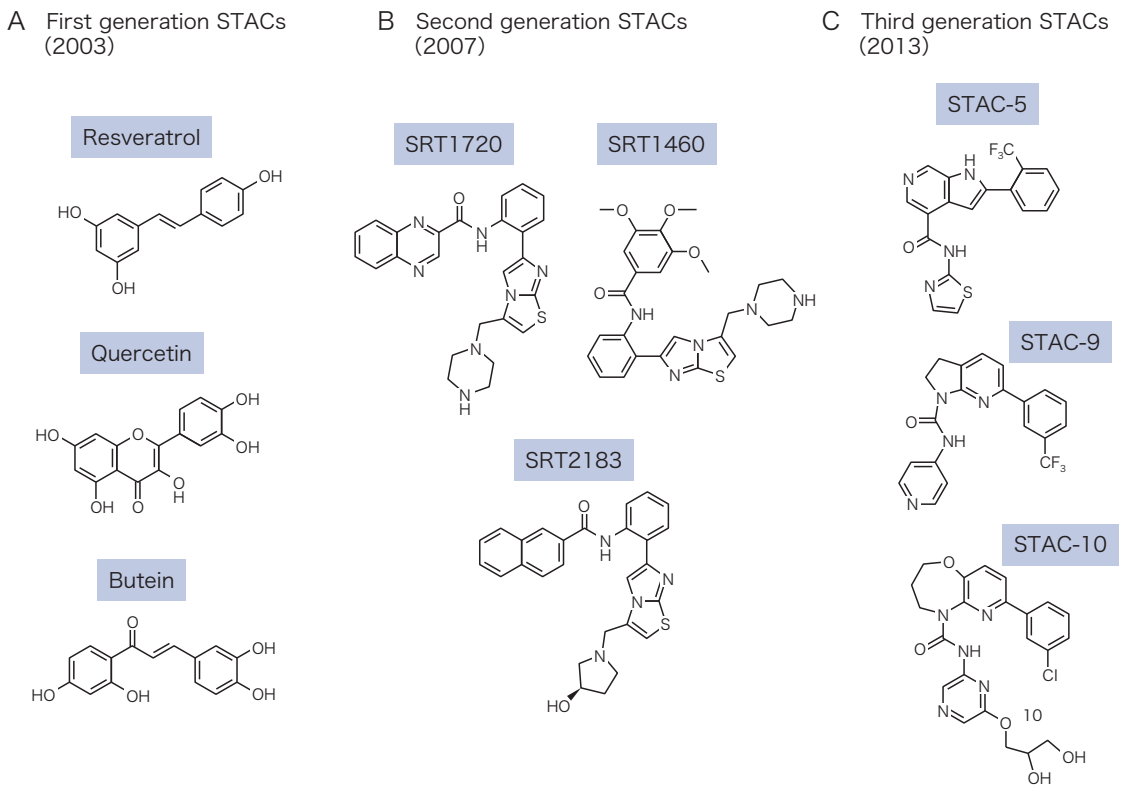

Figure 2 Allosteric sirtuin activating compounds (STACs)
Small molecule allosteric SIRT1 activators include (A) first generation molecules such as resveratrol and structurally-related polyphenols [4], (B) second generation STACs such as the imidazothiazoles [9], and (C) third generation STACs such as benzimidazoles and urea-based scaffolds [26) 38]. STACs from the first two generations improve metabolism, reduce inflammation and protect against neurodegeneration in mice.

in the initial assays mimics a hydrophobic amino acid [26]. Native peptide substrates such as PGC-1 α and FOXO3a contain hydrophobic residues at the +1 and +6 positions relative to the acetylated lysine [38], the same positions as the fluorophores in the original assays [4) 9].

Additional clues to SIRT1 activation by STACs have come from analysis of SIRT1 by genetic and biophysical approaches. A screen of random SIRT1 mutants identified a single-base mutation in SIRT1 (SIRT1-E230K) that is required for both activation and STAC binding [38] (**Figure 3**). Consistent with a common mechanism of activation for all K_m-lowering STACs, the E230K substitution abrogated activation by all STACs tested, including 117 synthetic STACs from several distinct chemical classes. Furthermore, primary fibroblasts and myocytes reconstituted with SIRT1-E230K were unable to respond to the compounds, providing evidence that STACs can act directly on SIRT1 *in vivo* [38]. The current model is that SIRT1 activation occurs through an assisted-allosteric activation (AAA) mechanism [38] in which STACs bind to a substrate-induced exosite on SIRT1 that facilitates substrate binding and subsequent deacetylation [38].

8 Effects of STACs *in vivo*

Considerable work over the past decade has been focused on understanding the role of sirtuin in aging. Similar to SIRT1 overexpression, resveratrol and other related STACs extend the lifespan of numerous organisms including *S. cerevisiae* [4], *C. elegans*, *D. melanogaster* [6], *N. furzeri*, a short-lived fish [46], and *A. mellifera*, the common honeybee [47]. In the first three instances, the longevity effects are known to require

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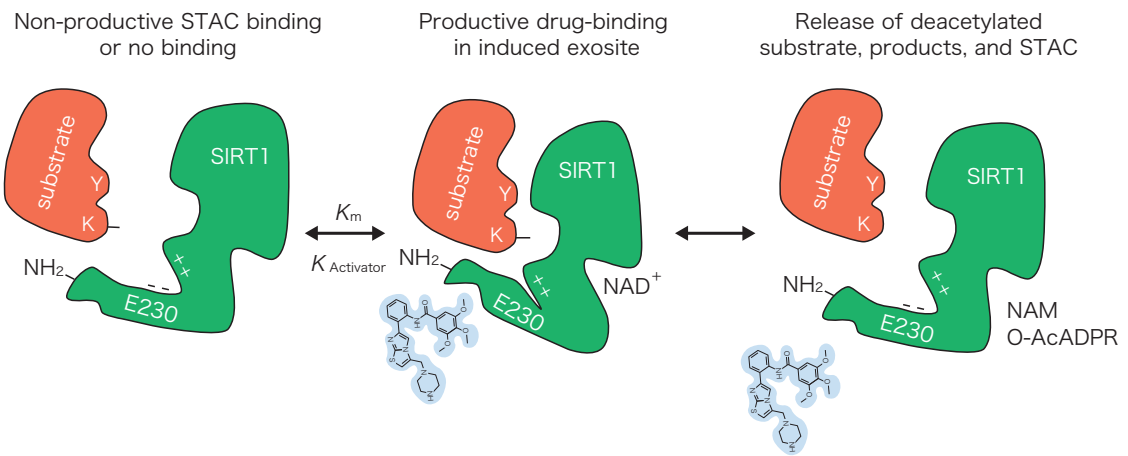

Figure 3 Proposed mechanism for allosteric SIRT1 activation by STACs
SIRT1 deacetylates target proteins (red) using NAD^+ as a cosubstrate to generate a O-acetyl-ADP ribose (O-AcADPR) and nicotinamide (NAM). Biochemical and structural data favor a mechanism of direct "assisted-allosteric activation" by STACs that is mediated by an N-terminal activation domain. Mutation of a conserved glutamate (E230) to lysine or alanine in a structured N-terminal domain blocks activation by resveratrol and 117 synthetic STACs, arguing for a common mechanism of activation. Fluorophores that were initially thought to be required for activation *in vitro* are now believed to mimic natural hydrophobic amino acids adjacent to the acetylated lysine at positions +1 and +6 (denoted by a Y in substrate, but can also be F or W). Binding of substrates with hydrophobic motifs near the acetyl site induce a conformational change upon binding, forming a specific exosite that allows activators to bind in a productive manner and in turn stabilize the docked substrate. Positive charges of C-terminal to E230K interact with the negative charge of E230 to assist with the enzyme-STAC-substrate complex.

Sir2 [4) 6)]. The STACs also induce physiological and gene expression changes consistent with CR [2) 48)]. Resveratrol did not extend the lifespan of mice when provided in a standard chow *ad libitum* [49)] but it did when provided in a high calorie diet or in standard chow fed to mice every other day [2)]. Similarly the synthetic SIRT1 activator SRT1720 extended the lifespan of mice fed a high-calorie diet and protected against age-related changes in multiple tissues [43)]. Whether or not synthetic STACs extend mouse lifespan on standard chow is not yet known.

Resveratrol and STACs show promising effects in numerous age-related disease models. Considerable data exists on the role of SIRT1 and the effects of resveratrol in cancer [35)]. In 1997, a landmark study showed that topical application of resveratrol is chemopreventative in a model of skin cancer [35)], mediated, in part, by SIRT1 [45)]. Resveratrol slows the growth of numerous other cancers including colon [50)], prostate, and lymphoma [51)] but resveratrol has proven ineffective in breast cancer [35)], spontaneous tumor formation and cancer-related deaths in old mice [49)].

Another one of the main roles of SIRT1 is dampening inflammation [8)]. This has led to considerable excitement about the use of STACs for the treatment of inflammatory and autoimmune disorders [35)]. Resveratrol reduces levels of inflammatory cytokines in LPS-stimulated macrophages [52)] and peripheral blood mononuclear cells [53)], protects cartilage against experimentally-induced inflammatory arthritis in rabbits [54)], and inhibits inflammation caused by *Listeria monocytogenes*, a pathogen that typically affects immunocompromised individuals [55)]. Other mouse models of tissue inflammation have also responded well to resveratrol, including chronic obstructive pulmonary disease (COPD) [56)], and Crohn's disease [57)]. The synthetic activator SRT1720 has beneficial effects in mouse models of COPD [58)] and asthma [59)].

STACs also show promise in the treatment of neurodegeneration and cognitive decline. Resveratrol can cross the blood-brain barrier and protect against stroke and brain damage, prevent cognitive decline, and attenuate symptoms of age-related neurological diseases such as Alzheimer's [60)], Parkinson's disease [61)],

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and multiple sclerosis [62]. Resveratrol slows the accumulation of amyloid-beta peptide, a causative agent in Alzheimer's disease [63] and dramatically reduces plaque formation in several regions of the brain [64]. Both learning and memory are improved in normal aged mice treated with resveratrol [65]. Numerous studies are consistent with SIRT1 activation underlying these effects. For example, neuroprotection by resveratrol requires SIRT1 [60], SRT1720 is protective in a model of multiple sclerosis [62] and SRT3025 mimics the effects of CR on the brain and protects against neurodegeneration [66].

One of the best-studied effects of STACs is their ability to prevent and reverse the effects of obesity and age-related metabolic decline [43]. In mice fed a high calorie diet, resveratrol improves metabolism, protects against obesity, insulin resistance, and premature death [2,35]. Additionally, resveratrol prevents the formation of a fatty liver and induces genes for mitochondrial function, such as PGC-1 α [2,35]. Several studies have also noted a remarkable ability for resveratrol to allay secondary phenotypes associated with diabetes such as diabetic nephropathy and tissue inflammation [67]. Resveratrol has also enhances metabolism in non-human primates [68]. Similar to resveratrol, SRT1720 improves whole-body glucose homeostasis and insulin sensitivity, increases mitochondrial capacity [9], and decreases expression of oxidative stress markers and lipogenic enzymes [69]. Furthermore, SRT1720 extends both the mean and maximum lifespan of adult mice fed a high-fat diet, and improves mitochondrial bioenergetics in a SIRT1-dependent manner [43]. SRT2104 was reported to be well tolerated in humans, and to ameliorate the lipid profile of cigarette smokers [70].

In humans, resveratrol has had mixed results. SRT501, a proprietary formulation of resveratrol, improved glucose tolerance in type 2 diabetics in the absence of any adverse side-effects [71]. This study was supported by later work in humans describing an insulin-sensitizing effect of resveratrol [71]. Resveratrol supplementation also decreased the oxidative stress and inflammation caused by consumption of a high calorie meal [72]. A 30-day resveratrol supplementation was shown to induce calorie restriction-like effects on energy metabolism and metabolic profile in obese humans [73]. However, a separate study demonstrated that resveratrol does not improve metabolic function in non-obese women with normal glucose tolerance [74]. The reason for the differences between these studies is not clear but it may be that STACs work to restore homeostasis in metabolically compromised individuals, and less so on healthy individuals, a possibility consistent with known functions of SIRT1 in animal studies. Clearly, additional clinical studies for resveratrol and synthetic STACs are warranted.

Perspectives

The sirtuins are some of the most interesting and important molecules in biology. The breadth of their reach into almost every process in cell biology makes them an exciting drug target. This reach, however, is precisely why we should proceed with caution to ensure that unexpected effects are not encountered. Raising overall NAD^+ levels also comes with some risk as NAD^+ serves as a redox carrier that is essential to glycolysis, which cancer cells heavily rely upon. Clearly, more work is required to determine the long-term effects of increasing NAD^+ throughout the body. Some solace can be found in the fact that sirtuin activity and NAD^+ levels cycle naturally depending on diet and even the time of day. If it is simply a restoration of youthful NAD^+ levels and sirtuin activity that is lost during aging, there may be minimal adverse effects. Over the next few years, many types of sirtuin activator are expected to enter clinical trials, including more potent, soluble STACs, NAD precursors, and CD38 inhibitors. Only then will we know if sirtuin activation has a chance of living up to its promise.

Acknowledgements

D. Sinclair is supported by the NIH, the Paul F. Glenn Foundation, The Ed Schulak Fund, UMDF and JDRF. DAS is a consultant to GSK, a company aiming to develop sirtuin-based medicines. This review is based on select portions of a review we authored in Trends in Pharmacological Sciences. We apologize that some references were not included for lack of space.

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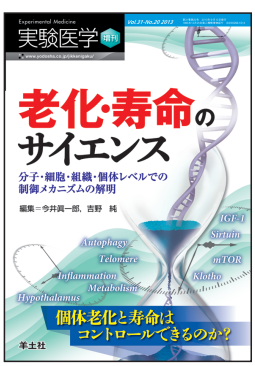

実験医学増刊　Vol.31 No.20

老化・寿命のサイエンス

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個体老化と寿命はコントロールできるのか？

今井眞一郎，吉野　純／編

B5判　230ページ　ISBN978-4-7581-0335-0

http://www.yodosha.co.jp/jikkenigaku/book/9784758103350/

[発行元]
株式会社　羊　土　社
〒101-0052
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