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Review

Lifespan and healthspan extension by resveratrol ☆

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ABSTRACT

A number of small molecules with the ability to extend the lifespan of multiple organisms have recently been discovered. Resveratrol, amongst the most prominent of these, has gained widespread attention due to its ability to extend the lifespan of yeast, worms, and flies, and its ability to protect against age-related diseases such as cancer, Alzheimer's, and diabetes in mammals. In this review, we discuss the origins and molecular targets of resveratrol and provide an overview of its effects on the lifespan of simple model organisms and mammals. We also examine the unique ability of resveratrol to extend the healthy years, or healthspan, of mammals and its potential to counteract the symptoms of age-related disease. Finally, we explore the many scientific, medical, and economic challenges faced when translating these findings to the clinic, and examine potential approaches for realizing the possibility of human lifespan extension. This article is part of a Special Issue entitled: Resveratrol: Challenges in translating pre-clinical findings to improved patient outcomes.

1. In pursuit of an elixir of life

The quest to discover of an elixir capable of prolonging lifespan and retarding aging has been on-going since ancient times. However, only recently has modern molecular genetics succeeded in identifying key genes and pathways involved in the aging process, bringing us closer to realizing this goal. Experimental manipulations of insulin signaling [1], AMPK signaling [2], TOR signaling [3], and the Sir2 gene [4] have all been demonstrated to modulate lifespan in diverse organisms. Furthermore, a number of dietary and pharmacological interventions have recently been described that can extend lifespan and prevent age-related diseases, bolstering hope that it may one day be possible to extend human lifespan. For example, caloric restriction (CR), a dietary regimen involving a reduction in caloric intake, extends the lifespan of yeast [5], worms [6], flies [7], and rodents [8]. Moreover, while one study found that CR had no effect on the lifespan of monkeys [9], a series of more recent studies reported that CR can reduce age-related and all-cause mortality in rhesus monkeys [10–12]. As an alternative to CR, dietary supplementation with a small molecule such as rapamycin [13], metformin [14], spermidine [15], or resveratrol [16] has also been shown to extend the lifespan of multiple model organisms. Of these compounds, resveratrol has been the most widely studied molecule in the context of aging-research, not only due its apparent lack of toxicity [17], but also due to its remarkable ability to treat and counteract a number of age-related diseases in mammals, including heart disease, cancer, Alzheimer's disease, and diabetes [17,18]. Here, we provide an overview of lifespan extension by resveratrol in numerous organisms, and discuss its ability to extend the healthspan of mammals. Furthermore, we provide perspective on the many controversies, challenges, and future promises of translating these findings to the clinic.

2. Discovery of resveratrol and its link to the sirtuin longevity pathway

Resveratrol (3,5,4′-trihydroxystilbene) was first described in 1939 in ethanol extracts of the white hellebore *Veratrum grandiflorum*, and initially characterized as a phytoalexin [17,19]. Subsequently, resveratrol was shown to be present in grapevines and in wine [17]. Resveratrol exists in two isomeric configurations, *trans*-(*E*) and *cis*-(*Z*), which may undergo isomerization upon exposure to ultraviolet radiation [20]. The 4-hydroxystilbene skeleton in resveratrol has been shown to act as an antioxidant pharmacophore, displaying a potent ability to scavenge free radicals [21,22].

Following its discovery, multiple studies have demonstrated health-enhancing properties of resveratrol both *in vitro* and *in vivo* in a number of model organisms [18]. Early studies focused on the antioxidant capacity of resveratrol, demonstrating that resveratrol can inhibit formation of copper-catalyzed LDL oxidation [23], and inhibit peroxidation of membrane lipids in liver microsomes [24]. Later, it was discovered that resveratrol could restrict the release of inflammatory mediators contributing to cardiovascular disease [25]. This finding was proposed to resolve the 'French paradox', that certain European populations consuming large amounts of wine have low rates of cardiovascular disease despite their high-fat diets [18]. Furthermore, a landmark study in 1997 demonstrated that topical application of resveratrol is extremely

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chemopreventive in a model of skin cancer [26], a finding that was extended by reports showing that resveratrol can prevent both the formation and growth of multiple types of cancers [17]. Shortly thereafter, a neuroprotective role for resveratrol was identified [27]. Many of these beneficial effects were shown to be mediated by cyclooxygenases, NF-κB, and AP-1, key mediators of inflammation and carcinogenesis [28,29]. While few studies have reported negative health effects of resveratrol, two early studies implicated dietary administration of resveratrol in increased atherosclerosis [30] and DNA damage [31].

A small molecule screen for activators of the mammalian sirtuin SIRT1 led to the discovery that resveratrol can extend the lifespan of budding yeast [32]. Sirtuins comprise an evolutionary conserved family of NAD^+-dependent (class III) histone and protein deacetylases with a wide variety of biological functions [33,34]. The founding member of this protein class, Sir2, was initially characterized in yeast as a factor involved in transcriptional silencing at mating loci and telomeres [35]. Later, it was discovered that overexpression of Sir2 in yeast results in an ~30% lifespan extension [4,36], and that overexpression of Sir2 homologs in *Caenorhabditis elegans* [37] and *Drosophila melanogaster* [38] also increases lifespan. In mice, whole-body over-expression of SIRT6 extends the lifespan of males [39], and brain-specific over-expression of SIRT1 extends lifespan as well [40], while whole body overexpression of SIRT1 does not appear to affect longevity [41].

Because Sir2 consumes NAD^+, a metabolic intermediate linked to nutrient levels [33,34], it was proposed that the Sir2 enzyme could underlie lifespan extension by caloric restriction [42]. While initial reports [5,42] showing Sir2-dependent lifespan extension by CR in yeast were challenged [43], a critical role for sirtuins in yeast CR was later re-affirmed [44]. In addition, studies in mammals have shown that the Sir2 homologs SIRT1 and SIRT3 are implicated in several of the health benefits attributed to CR [45–48].

SIRT1, which has been proposed to be a central target of resveratrol in mammals [32,49], has been the most well-characterized of the seven mammalian sirtuins (SIRT1–7) [50]. SIRT1 regulates numerous cellular processes such as DNA repair, fat differentiation, glucose output, insulin sensitivity, fatty acid oxidation, and neurogenesis, through deacetylation of a number of key histone and protein targets including H3-K9, H4-K16, H1-K26, nuclear factor NF-κB, PPAR-gamma co-activator 1α (PGC1α), forkhead box transcription factors (FOXOs), and numerous others (Fig. 1) [18,34,50,51]. Importantly, overexpression of SIRT1 has been demonstrated to guard against Alzheimer's disease [52,53], cancer [41,54], type II diabetes [55], and cardiovascular disease [18,56]. Resveratrol and similar polyphenols (*e.g.* flavones, stilbenes, and chalcones) were initially reported to activate SIRT1 *in vitro* through a direct allosteric mechanism involving a lowering of the peptide substrate K_M [32]. Consistent with this hypothesis, lifespan extension in yeast by resveratrol was shown to be Sir2-dependent [32]. Whether or not SIRT1 is directly activated by resveratrol has been the subject of a contentious debate [18]. A series of studies challenged the early *in vitro* data, suggesting that resveratrol could be binding to an artificial fluorophore on the peptide used in the initial high-throughput screening assay, rather than allosterically modulating SIRT1 [57,58]. Furthermore, it was suggested that the *in vivo* effects of resveratrol on SIRT1 could simply be due to off-target effects on other enzymes such as phosphodiesterase (PDE) [59]. However, several recent reports have validated the initial model by identifying an allosteric site on SIRT1 to

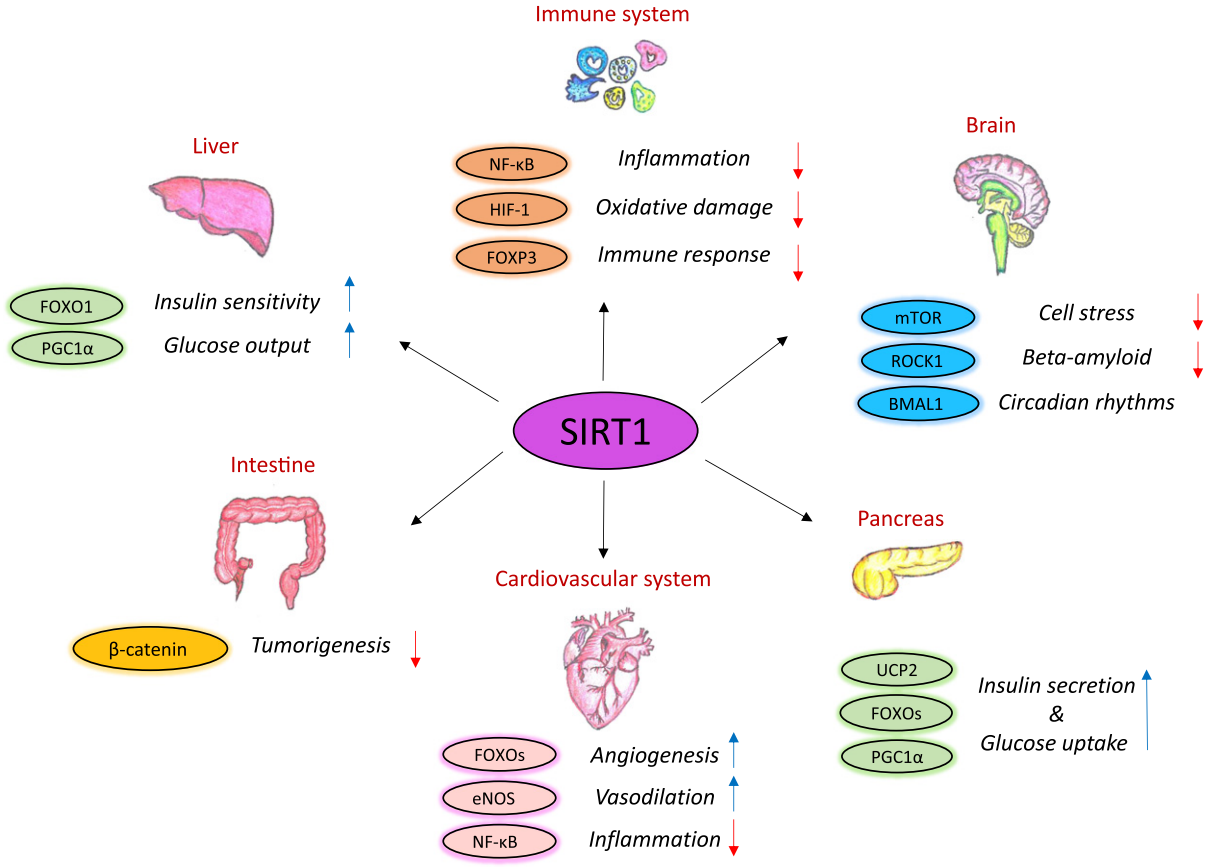

Fig. 1. Physiological functions and molecular targets of SIRT1. SIRT1 deacetylates a wide array of important non-histone targets, resulting in effects on many cellular processes. BMAL: Brain and muscle Arnt-like protein-1, eNOS: Endothelial NOS synthase, FOXO1: Forkhead box O1, FOXOs: Forkhead box proteins, FOXP3: Forkhead box P3, HIF-1: Hypoxia-inducible factor 1, mTOR: Mammalian target of rapamycin, ROCK1: Rho-associated protein kinase 1, NF-κB: Nuclear factor kappa-B, PGC1α: Peroxisome proliferator-activated receptor gamma co-activator 1-alpha, UCP2: Uncoupling protein 2.