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ORIGINAL ARTICLE

Towards resolving the enigma of the dichotomy of resveratrol: *cis*- and *trans*-resveratrol have opposite effects on TyrRS-regulated PARP1 activation

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Abstract Unlike widely perceived, resveratrol (RSV) decreased the average lifespan and extended only the replicative lifespan in yeast. Similarly, although not widely discussed, RSV is also known to evoke neurite degeneration, kidney toxicity, atherosclerosis, premature senescence, and genotoxicity through yet unknown mechanisms. Nevertheless, in vivo animal models of diseases and human clinical trials demonstrate inconsistent protective and beneficial effects. Therefore, the mechanism of action of RSV that elicits beneficial effects remains an enigma. In a previously published work, we demonstrated structural similarities between RSV and tyrosine amino acid. RSV acts as a tyrosine antagonist and competes with it to bind to human tyrosyl-tRNA synthetase (TyrRS). Interestingly, although both isomers of RSV bind to TyrRS, only the *cis*-isomer evokes a unique structural change at the active site to promote its interaction with poly-ADP-ribose polymerase 1 (PARP1), a major determinant of cellular NAD^+-dependent stress response. However, retention of *trans*-RSV in the active site of TyrRS mimics its tyrosine-bound conformation that inhibits the auto-poly-ADP-ribos(PAR)ylation of PARP1. Therefore, we proposed that *cis*-RSV-induced TyrRS-regulated auto-PARylation of PARP1 would contribute, at least in part, to the reported health benefits of RSV through the induction of protective stress response. This observation suggested that *trans*-RSV would inhibit TyrRS/PARP1-mediated protective stress response and would instead elicit an opposite effect compared to *cis*-RSV. Interestingly, most recent studies also confirmed the conversion of *trans*-RSV and its metabolites to *cis*-RSV in the physiological context. Therefore, the finding that *cis*-RSV and *trans*-RSV induce two distinct conformations of TyrRS with opposite effects on the auto-PARylation of PARP1 provides a potential molecular basis for the observed dichotomic effects of RSV under different experimental paradigms. However, the fact that natural RSV exists as a diastereomeric mixture of its *cis* and *trans* isomers and *cis*-RSV is also a physiologically relevant isoform has not yet gained much scientific attention.

Keywords Resveratrol (RSV) · Aminoacyl-tRNA synthetases (aaRSs) · Tyrosyl-tRNA synthetase (YARS · TyrRS) · Nicotinamide adenine nucleotide (NAD^+) · Poly-ADP-ribose polymerase (PARP) · Sirtuins (SIRT) · AMP-activated protein kinase (AMPK) · Nicotinamide (NAM)

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Introduction

Natural resveratrol (RSV or 3,5,4′-trihydroxystilbene) is an important constituent of the ayurvedic medicine "*Drakshasava*," a well-known Indian herbal preparation from grapes prescribed as a cardiotonic [1]. (*Draksha* is the Sanskrit word for grape. "*Asava*" means "distillate,"

"juice," or "extract." Thus, "*Drakshasava*" means "extract from grapes.") Similarly, RSV is also considered responsible for the fundamental principle behind the "*French Paradox*" [2, 3]. It is produced by many different plant species, especially grapevines, pines, and legumes and therefore is abundant in peanuts, soybeans, blueberries, and pomegranates [4]. RSV is produced in plants as a protective agent in response to stressful conditions such as injury or attack by bacterial/fungal pathogens or UV exposure and believed to activate the innate defense mechanism of plants against fungal/microbial pathogens [5]. Interestingly, *Botrytis cinerea* infection in grapes leads to the exclusive synthesis of RSV in the leaf epidermis and grape skins [5–7]. Since grape skins are fermented during red wine production, they contain higher amounts of RSV than white wines. RSV was first isolated in 1939 by Takaoka from *Veratrum grandiflorum* Loes (the root of the white hellebore) [8]. Hence, it is speculated that the name "resveratrol": was created based on its chemical structure and the source of the plant used for its isolation (a resorcinol derivative or polyphenol in resin from a Veratrum species). Despite being a protective molecule in plants, the ingestion of RSV could also evoke similar protective stress responses in animals and was widely expected to overcome stressful/harmful conditions [9], including auto-immune disorders [10]. Unfortunately, despite being one of the widely studied small molecules, the in vivo animal models of diseases and human clinical studies using RSV brought out inconclusive results [11, 12], indicating our understanding of the mechanism of action of natural RSV is not yet complete.

The enigma of the dichotomic and pro-aging effects of RSV

Natural RSV captured widespread scientific and public interest due to its reported anti-cancer [13] and anti-aging effects [14], supported by further longevity demonstrations in other organisms [15–18]. However, unlike widely perceived, RSV decreased the normal (chronological) lifespan in yeast [19–21], and it extended only the replicative lifespan which is calculated based on the number of daughter cells an individual yeast mother cell produces before dying [14]. Moreover, the replicative lifespan effect of RSV in yeast was immediately questioned as it was not reproducible [22] indicating that the mechanism of action of the anti- and pro-aging effects of RSV is not yet understood. Similarly, higher doses of RSV decreased the normal lifespan in mice as well (mice died within 3–4 months) [23] and resulted in kidney toxicity in rats [24]. Consistent with the pro-aging effects of RSV [19–21, 23], it is known to evoke toxic effects such as induction of neurite degeneration [25], atherosclerosis [26], premature senescence [27–32], genotoxicity [33–38], and inhibition of hippocampal neurogenesis [39]. These observations suggest that the mechanism of action of RSV that promoted longevity in other organisms [15–18] is not yet completely understood. Consistently, research works using RSV showed dichotomic effects resulting in inconsistent therapeutic outcomes. For example, while RSV shows protective effects against experimental models of multiple sclerosis (MS) and autoimmune encephalomyelitis (EAE) in some studies [40–42], it exacerbated the progression of MS and EAE in another study [43]. Similarly, RSV protects against peripheral neuropathy in some studies [44, 45] while it exacerbates the disease condition in another study [46]. Likewise, while RSV is known to protect against anxiety and depression [47], it is also shown to exacerbate anxiety and depression [48]. Interestingly, acute RSV treatment enhanced cocaine-induced dopamine neurotransmission and behavioral responses suggesting that RSV promotes drug addiction [49, 50]. However, RSV is also shown to protect against drug addiction through an unknown mechanism [51, 52]. Consistent with the dichotomic effects discussed above, RSV protects against Wallerian degeneration [53], but it also abolishes neuroprotection mediated through Wallerian-slow degeneration mutants [25]. Similarly, RSV acts as an antagonist on aryl hydrocarbon receptor (AhR) [54] and estrogen receptor alpha (ERα) [55], but it also acts as an agonist of AhR [40] and ERα [56, 57]. The dichotomic effect of RSV is also observed in the induction of autophagy. While RSV stimulates autophagy [17, 27, 58], it is also known to inhibit autophagy [59, 60]. Interestingly, although RSV inhibits nuclear factor kappa B (NF-κB) in some studies [61, 62], RSV instead activates NF-κB in other studies [63–66]. Moreover, although RSV exacerbates atherosclerosis [26], it is also shown to prevent atherosclerosis [67, 68]. Consistently, RSV also exacerbated inflammation state and superoxide production and diminishing aortic distensibility in aged mice [69]. Likewise, RSV protects against oxidative stress in some studies [70–72] while it exacerbates oxidative stress in other studies [73, 74]. Consistently, RSV exhibits both pro-oxidant and antioxidant effects [75, 76].

Interestingly, the pro-oxidant activity of RSV inhibits hydrogen peroxide (H_2O_2)-induced apoptosis [77] and evokes cardiac protection [78] and anti-tumor effects [38]. Although RSV induces premature senescence [27–32], RSV is also known to inhibit senescence through an unknown mechanism [79]. RSV is widely believed to enhance mitochondrial function [80], despite being a potent inhibitor of mitochondria [81–85]. RSV inhibits oxidative phosphorylation (OXPHOS) activity at two sites: mitochondrial complex I and complex III of the electron transport chain [82, 83]. Consistently, RSV increases the mitochondrial H_2O_2 production [84] and decreases ATP production [83, 85]. Therefore, RSV induces mitochondria-driven apoptosis [86] through the elevation in intracellular Ca^{2+}, resulting in the collapse of the membrane potential with mitochondrial permeability transition pore (mPTP) opening and cytochrome c release into the cytosol [87]. Although RSV is known to evoke anti-tumor effects [13, 88–91], it is also known to exacerbate cancer proliferation [56, 92, 93] and shows dichotomic effects in angiogenic response as well [94, 95]. Similarly, despite being reported to evoke anti-obesity effects [96–98], intriguingly, higher doses of RSV rather had a weight-promoting effect when mice were fed with a high-fat diet [89]. Although RSV is shown to evoke anti-diabetic effects [98] and restore insulin sensitivity [99] through inhibition of gluconeogenesis [100], and by facilitating cellular glucose uptake [101–103] through GLUT4 translocation [102, 104, 105], enigmatically, RSV is also known to inhibit cellular glucose uptake [106–108], potentially through the inhibition of class I phosphoinositide 3-kinase (PI3K) [109] and glucose transporter 1 (GLUT1) [110] or through the downregulation of GLUT4 translocation [108, 111]. Furthermore, RSV inhibits coronaviral replication [112, 113] but facilitates herpes simplex virus (HSV) [114], hepatitis B virus (HBV) [115], and hepatitis C virus [116] replication. Therefore, studies spanning over the last two decades show that treatment with RSV can evoke dichotomic effects resulting in either unfavorable or beneficial outcomes.

RSV elicits favorable and unexpected outcomes in human clinical trials

Consistent with the dichotomic effects of RSV, as discussed above, human clinical trials using RSV also ended up in favorable and unexpected outcomes [11, 12]. For example, despite numerous animal models showing neuroprotective effects [80, 98, 117–120], intriguingly, a previous human Alzheimer's disease (AD) clinical trial using high-dose RSV (2000 mg/day) resulted in the upregulation of amyloid-beta (Aβ) levels with exacerbation of the brain volume loss [121]. However, another recent human AD clinical trial using low-dose RSV (5 mg/day) showed beneficial effects [122] and human clinical trial using low-dose RSV (75 mg twice daily) enhanced cognitive benefits in postmenopausal women [123, 124]. Consistently, RSV improved memory performance and increased the functional connectivity of the hippocampus in older human adults [125], but worsened episodic memory in a human clinical trial for schizophrenia (SZ) [126]. Although extensive data show RSV protects against nephropathy [70, 127, 128], renal oxidative DNA damage [129], and kidney diseases [130], a phase 2 clinical trial of RSV targeting multiple myeloma was terminated due to patients developing kidney failure [131]. Similarly, despite known to improve several cardiovascular health parameters [98] and suggested to evoke an anabolic function in exercise-induced adaptations of older persons to reverse sarcopenia [132], RSV supplementation in humans also resulted in the reduction of high-density lipoprotein (HDL) cholesterol concentrations [133] and blunted exercise-mediated effects [134, 135] and impaired the improvements in markers of oxidative stress and inflammation in skeletal muscle [135]. Therefore, for unknown reasons, studies in humans have shown that RSV may reduce training-induced adaptations [95, 134, 135] and lead to bicytopenia in patients treated for non-alcoholic fatty liver disease (NAFLD) [136] and caused an elevation of biomarkers of cardiovascular disease (CVD) risk in overweight older adults [137]. Although some studies did not show any improvement in the glucose intolerance in older adults [138] and type 2 diabetic patients [139, 140], however, RSV has a positive impact on blood pressure [141, 142], improves insulin sensitivity [143], and reduces blood glucose levels [144] in type 2 diabetic patients and patients with non-alcoholic fatty liver disease [145], in the treatment of pre-eclampsia [146] and obese people [97]. Consistently, most recent meta analysis also indicates that RSV improves cardiometabolic health by decreasing some risk factors (HOMA-IR, LDL-C, and T-Chol) associated with cardiovascular disease (CVD) [147, 148] and significantly reduced total cholesterol and increased gamma-glutamyl transferase (GGT) concentrations in patients with metabolic syndrome (MetS) and related disorders

[149]. In conclusion, along with substantial protective/beneficial effects of low-dose RSV demonstrated in various studies, exacerbation of the disease conditions especially by higher doses of RSV is also an accompanying theme in human clinical trials. However, the molecular basis for these dichotomic effects of RSV largely remains unexplained, and these opposing effects observed upon RSV treatment remain an enigma [150].

Low-dose beneficial effects versus high-dose detrimental effects of RSV

Beyond the unexpected outcomes in multiple models of diseases, it is apparent that low doses of RSV evoke health-promoting effects and detrimental effects are generally observed only upon treatment with high doses of RSV as observed in the cases of human AD clinical trails [121, 122]. Therefore, RSV often displays a biphasic dose-response [151] with features consistent with the hormetic dose-response, a phenomenon that is characterized by low-dose stimulation and a high-dose inhibition [152]. RSV inhibits DNA type II topoisomerase [153], and histone deacetylases (HDACs) [154], enzymes that are critical for the maintenance of chromosomal stability [155], and neuronal survival [156, 157], resulting in genotoxic effects. Consistently, treatment with high-dose RSV induces DNA double-strand breaks (DSBs) [153, 158, 159] along with downregulation of DNA repair proteins [160], while low-dose RSV rather upregulates DNA repair proteins [161, 162]. Furthermore, a lower dose of RSV significantly reduced chromosomal instability (CIN) as well as defective spindle assembly checkpoint (SAC), while higher doses of RSV significantly induced them [36]. Therefore, RSV reduces cell growth and induces apoptosis in healthy cells in a dose-dependent manner triggering biphasic effects over low to high concentrations [163, 164]. For example, low-dose RSV enhances self-renewal of stem cells through inhibition of senescence whereas higher dose RSV instead inhibits self-renewal and induces senescence [165–168] through cell cycle arrest at S/G2 phase [36, 169, 170]. Hence, at a lower concentration, RSV can have a positive impact on the proliferation, survival of neuronal progenitor cells (NPCs), and rat hippocampal neurogenesis [167], which is also consistent with its angiogenic effects at a lower dose [94]. Consistently, low-dose RSV protected against amyotrophic lateral sclerosis (ALS) [171] and Huntington's disease (HD) [172], but a higher dose of RSV rather failed to improve motor deficits associated with the HD phenotype in a transgenic mouse model [173]. Intriguingly, pre-treatment with low-dose RSV, however, failed to reduce amyloid beta-mediated elevation of H_2O_2 production [174]. Although RSV was identified as an anti-inflammatory compound [175, 176], RSV modulates the inflammatory response in an ERα-dependent manner [57]. At medium concentrations (10–25 μM), RSV acts as a superagonist of estradiol [177], while at lower concentrations, RSV relatively inhibited the estradiol-driven transcription through a yet unknown mechanism [177]. Similarly, RSV binds directly to mitochondrial complex I and induces oxidative stress in aged mice in a dose-dependent manner [73]. At low doses, RSV stimulated complex I and F0/F1 ATPase activities, whereas, at high doses, it inhibited them [73, 178]. Therefore, low concentrations of RSV trigger and high concentrations inhibit respiratory chain complexes [179]. Similarly, low doses of RSV promoted in vitro muscle regeneration and attenuated the impact of reactive oxygen species (ROS), while high doses exacerbated the reduction in plasticity and metabolism induced by oxidative stress [180]. Intriguingly, lower doses of RSV generate ROS, and higher doses of RSV act as an anti-oxidant in erythrocytes [181] and pro-oxidant properties of low-dose RSV inhibit caspase activation and DNA fragmentation induced by oxidative stress [182]. However, in indomethacin-induced gastric ulcers, high-dose RSV instead exacerbated ulcerative damage in mice [183]. Similarly, a low-dose RSV administration partly improved renal function in mice with kidney damage caused by a unilateral ureteral obstruction (UUO) while high dose of RSV lost its anti-fibrotic effect and exacerbated kidney fibrosis [184]. Likewise, RSV induced a dose-dependent pro-oxidant effect in hepatic stellate cells (HSC) with the highest dose of RSV inducing oxidation-related damage and drastically reducing cell viability [185, 186]. Similarly, high-dose RSV upregulated genes involved in gluconeogenesis [100] and inhibited insulin signaling [108, 187, 188], but low-dose RSV rather downregulated gluconeogenesis [100] and improved insulin sensitivity [99, 103, 143, 145, 189, 190].

RSV attains high micromolar levels in human tissues and plasma after oral ingestion

Although approximately 75% of RSV is absorbed after oral consumption [191], it is rapidly metabolized by the

liver, intestinal tract, and gut microbiota into the sulfated and glucuronidated forms such as RSV-3'-O-β-d-glucuronide (RSV3G), RSV-4′-O-d-glucuronide (RSV4G), and RSV-3-O-sulfate (RSV3S). Interestingly, RSV is more stable in human plasma compared to rat plasma [192], and RSV crosses the blood-brain barrier (BBB) and accumulates in the brain tissue as well [117]. Therefore, the concentrations of these RSV metabolites far exceed the concentrations of their parent compound (free RSV) in human serum [27, 193] and ocular tissues [194]. For example, human oral ingestion of low dose (5 mg) RSV daily can achieve the plasma concentrations of 0.12–0.6 μM RSV [89], and human clinical trials receiving 5–1000 mg daily dose resulted in average peak concentrations of blood levels between 0.6 and 137 μM [89, 194]. Furthermore, sustained intake of 1 g of RSV as a food supplement resulted in a concentration of 50–640 μM RSV in human colonic tissues [27]. Moreover, sulfate metabolites of RSV contribute to the in vivo activity of these metabolites by regenerating free RSV in colorectal cell lines, supporting the hypothesis that RSV metabolites potentially serve as a reservoir for the parent compound [27, 195]. These paradigm shifting studies have not only challenged the classical notion that low bioavailability of RSV is the reason for the lack of therapeutic effects in human clinical trials but have also provided a potential molecular basis for the unexpected effects of high-dose RSV in human clinical trials such as adverse gastrointestinal effects [196, 197]. The recent results from clinical trials and in vivo studies also support the hormetic response of RSV with lower doses retarding age-related cardiac dysfunction [198], preventing cancer [89], slowing down AD symptoms [122], and improving cardiovascular and cerebrovascular functions [23, 196] more potently than higher doses [89].

trans-RSV is a direct activator of SIRT1 at higher micromolar concentrations

Although there are many known targets for *trans*-RSV [199], the most well-studied target is SIRT1 [14]. Later studies also indicated a direct link between *trans*-RSV and 5′ adenosine monophosphate-activated protein kinase (AMPK) and SIRT1 by showing RSV's inhibitory effect on several phosphodiesterases (PDE) that increased cyclic AMP (cAMP) levels to enhance the intracellular Ca^{2+} to activate Ca^{2+}/calmodulin-dependent protein kinase kinase β (CaMKKβ), which phosphorylates AMPK, finally leading to SIRT1 activation [200, 201]. Although, the attempts to modulate the activity and specificity of RSV through different targets or signaling cascades failed to reproduce the complete spectrum of its activity, [202, 203] highlighting some technical problems associated with the "*Fluor-de-Lys*" substrate (FdL) assay used to determine RSV-mediated SIRT1 activation [20, 22, 204, 205], subsequent works finally concluded that *trans*-RSV is indeed a direct activator of SIRT1 [206–208] with a potency of RSV against SIRT1 in the FdL assay (EC_{50} ~ 30–100 μM) [14, 207] whereas the *Km* value of SIRT1 for NAD^+ was found to be 94 ± 5 μM [203]. Finally, patients who received 500 mg/day RSV demonstrated the activation of SIRT1 in peripheral blood mononuclear cell (PBMC), suggesting that oral administration of higher doses of RSV achieve sufficient cellular concentrations to activate SIRT1 (≥ 30 μM) in humans as well [209]. This finding is also consistent with other human clinical trials that used 5–1000 mg/day RSV resulted in average peak concentrations of blood levels between 0.6 and 137 μM [89, 194].

RSV is also an indirect inhibitor of SIRT1

Intriguingly, in mammalian cells, RSV is also known to *inhibit* SIRT1 [14], and this inhibitory effect of RSV on SIRT1 is required for its longevity effects in *Caenorhabditis elegans* [15]. Moreover, RSV decreases yeat chronological lifespan in a Sir2-dependent manner [19]. This apparent contradictory observation was termed as the "dichotomy" of RSV's action, and the mechanism remained unknown. Furthermore, later studies also demonstrated that RSV inhibits SIRT1 to mediate part of its biochemical and functional outcomes. For example, while SIRT1 activates vascular endothelial growth factor (VEGF) expression [210, 211], treatment with RSV rather downregulates it [212, 213]. Likewise, activation of SIRT1 inhibits muscle differentiation and mitochondrial biogenesis [214–217], whereas RSV rather potentiates muscle differentiation [218, 219] and acts as an exercise mimetic [220]. Activation of SIRT1 sensitizes neurons to oxidative stress [221, 222] and inhibits neurogenesis [223] while RSV protects neurons against oxidative stress [224, 225] and enhances neurogenesis [226, 227]. Similarly, activation of SIRT1 promotes mitochondrial fission [228], and treatment with RSV rather enhances mitochondrial fusion [229]. Similarly, although brain-specific activation of

SIRT1 drives anxiety and exploratory drive [48, 230], RSV rather protects against autistic features [231–234]. Interestingly, SIRT1 activates monoamine oxidase A (MAO-A) in the brain [230], but RSV inhibits it [235, 236]. Furthermore, RSV is known to exert metabolic benefits by increasing metabolic rate, insulin sensitivity, mitochondrial biogenesis, and physical endurance, and reduce fat accumulation in mice [80, 98, 201]. Although lower doses of RSV (≥ 25 μM) fail to inhibit PDEs [207], RSV is also shown to upregulate the cellular levels of cyclic AMP (cAMP) though phosphodiesterases (PDEs) [201]. However, increasing cAMP levels via the Epac pathway retards the clearance of autophagy substrates and inhibits α-synuclein clearance, and enhances polyglutamine aggregation in the Parkinson's disease (PD) mouse model [237]. Intriguingly, RSV rescues mutant polyglutamine cytotoxicity [118] and alleviates motor and cognitive deficits in the A53T α-synuclein mouse model of PD [238], whereas SIRTuin inhibition also rescues polyglutamine cytotoxicity [239], and PD [240] and motor deficits after peripheral nerve injury [241]. Similarly, SIRT1 inhibits p53 [242], a known anti-tumor protein, and RSV is known to exert anti-cancer effects through p53 activation [13, 243]. Although SIRT1 is essential for coronavirus replication and survival [113], RSV instead inhibits coronavirus replication [112, 113], and the acetylation of p53 is a critical mediator of antiviral response [244]. Interestingly, RSV treatment is known to activate p300 acetyltransferase to protect against rat spinal cord affected by sciatic nerve injury [245] and is also known to activate AMPK independent of SIRT1 in neurons [246] through yet unknown mechanisms. However, RSV activates AMPK in a poly-ADP-ribose polymerase 1 (PARP1)-dependent manner [71], which is also a potent inhibitor of SIRT1 [247]. Although the mechanism of RSV-mediated inhibition of SIRT1 [14, 15] and activations of p53 in human PBMC [209] and AMPK in neurons [246] remain an enigma, the observations mentioned above suggest that the inhibitory effects of RSV on SIRT1 [14, 15] through PARP1 activation [71] may also contribute to the observed physiological functions of RSV.

cis-RSV is present in the commercial wines

RSV exists as a mixture of its diastereomeric *cis* (Z) and *trans* (E) isomers in wines [248–250] (Fig. 1a), and both isomers are stable when protected from light for at least 6 weeks at 4 °C and are not prone to oxidation within at least 48 h of exposure to air [248]. Although *cis*-RSV has not been detected in fresh grapes [5–7], it is nevertheless a significant component of commercial wines from every wine-producing region of the world as well [248, 250]. This observation suggests that *cis*-RSV is produced during fermentation through an unknown mechanism. Wines that are high in *trans*-RSV tend to be also high in *cis*-RSV, and their concentrations may be subject to the same variables such as cultivar, climate, soil composition, and drainage characteristics, fungal pressure, and wine-making techniques [248]. In general, the absorbance of *cis*-RSV is lower than that of *trans*-RSV [250], and the accurate quantitation of *cis* forms showed that the concentration of *cis*-RSV could sometimes be the predominant form in specific grape varietals such as Pinot noir [248, 250].

cis-RSV exerts anti-inflammatory and anti-oxidant effects

Although *cis*-RSV is not well-explored, the limited amount of scientific literature shed light on its biological effects. *cis*-RSV inhibits both canonical and non-canonical inflammasome activation in macrophages resulting in the downregulation of caspases 1 and 4 and reduction in the secretion of the pro-inflammatory cytokine, interleukin-1β (IL-1β) [251]. Interestingly, the reduction of IL-1β secretion was more pronounced with *cis*-RSV pre-treatment than *trans*-RSV [251]. *cis*-RSV also scavenges intracellular reactive oxygen species (ROS) and downregulates mRNA and protein levels of NOS-2 and COX-2, resulting in the attenuation of the pro-inflammatory responses [252]. *cis*-RSV modulates the pro-inflammatory transcription factor, NF-κB, reducing the expression of chemokines such as monocyte chemoattractant protein-1 (MCP-1) and regulated on activation normal T cell expressed and secreted (RANTES), pro-inflammatory cytokines that attract monocyte–granulocyte cells such as M-CSF (colony-stimulating factor 1), GM-CSF (colony-stimulating factor 2) and G-CSF (colony-stimulating factor 3), the cytokine tumor growth factor-beta (TGF-β), and the extracellular ligand IL-1α [253]. The methylated forms of both isomers have anti-tumorogenic properties, but the *cis*-RSV-derived methylated forms have a higher anti-tumor effect than the *trans* derivatives [254]. In contrast, for the unmodified isomers, *trans*-RSV has greater anti-cancer activity [255]. RSV has vasorelaxant

properties, and in this aspect, both isomers showed similar effects on the reduction of intracellular calcium levels when pre-treated in vascular myocytes, although co-treatment with angiotensin II, *cis*-RSV showed more potent effects [256, 257]. However, when tested in mice model against angiotensin II (AngII)-mediated vascular inflammation, only the *trans*-isomer was found to be effective, although it is not clear whether such a result is caused by a difference in potency or is due to different mechanisms [258]. Interestingly, both *cis*-RSV and *trans*-RSV suppress the platelet aggregation induced by pro-aggregatory stimuli such as collagen, ADP, and thrombin [259, 260]. Although one study showed the potency of the *cis*-RSV was lower than that of the *trans*-RSV [260], an earlier study showed that *cis*-RSV is more potent than *trans*-RSV to inhibity the platelet aggregation [259]. Despite early indications of the physiological effects, *cis*-RSV did not gain much scientific attention in terms of the number of publications (Fig. 1b) majorly due to the lack of commercial availability of *cis*-RSV in early days [261].

cis-RSV is metabolized faster than its *trans* counterparts in humans

Although glucuronidation of RSV is done preferentially by different UDP-glucuronosyltransferase (UGT) isoforms resulting in the formation of two glucuronides (RSV 3-O- and 4*-O-glucuronides (RSV3G and RSV4G)), interestingly, this enzymatic action can be selective with different reaction rates and occurs at a faster rate with the *cis*-RSV [262, 263]. For example, *trans*-RSV is glucoronidated by bilirubin conjugating UGT1A1 and *cis*-RSV is glucoronidated by the phenol conjugating UGT1A6 [262, 264]. However, both *cis*- and *trans*-RSV isomers are actively glucuronidated by enzymes like UGT1A9 and 1A10 [262, 264] and the biological significance of faster glucuronidation of *cis*-

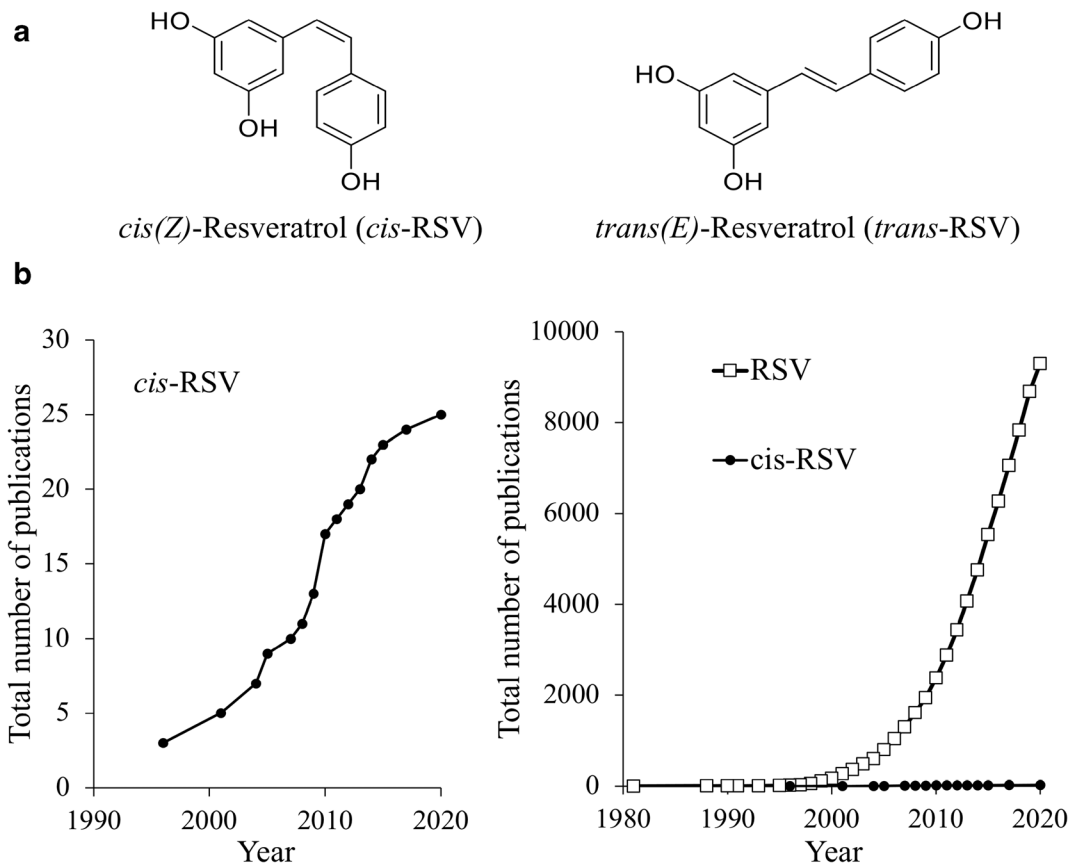

Fig. 1 **a** Natural resveratrol (RSV or 3,5,4′-trihydroxystilbene) exists as two diastereomeric forms (*cis* (Z)- and *trans*(E)-RSV). **b** Number of Pubmed publications on RSV. Graphical representation of the total number of publications obtained by searching in Pubmed using the term "resveratrol" and "*cis*-resveratrol" in the titles of the publications as of 15th September, 2020

RSV remains to be evaluated. Moreover, the gastrointestinal (GI) tract contributes significantly to the first pass metabolism of these naturally occurring polyphenols [263] and *cis*-RSV sulfates and glucuronides (*cis*-RSV3G, *cis*-RSV4G, and *cis*-RSV3S) are found in higher concentrations than their *trans* counterparts in urine of subjects given a 250-ml single dose of red wine [265].

trans-RSV and its metabolites convert to *cis*-RSV in the physiological context

Interestingly, *trans*-RSV is known to be converted to *cis*-RSV in the physiological context [78, 195], and both *trans*- and *cis*-RSV metabolites with a preference for *cis*-isomer are detected in the profiles of culture media and lysates of cells exposed to *trans*-RSV [195]. Importantly, in endothelial cells, when the RSV metabolites (RSV3G, RSV4G, and RSV3S) were converted back to their parent form, i.e., free RSV, they were preferentially converted to *cis*-RSV through a yet unknown mechanism [195]. Similarly, another recent study also showed that *trans*-RSV is converted to *cis*-RSV in the physiological context to evoke cardioprotective functions [78]. This *trans* to *cis*-RSV conversion exploits a novel thiol-dependent mechanism to activate protein kinase 1α (PKG1α) that mediates the beneficial actions of RSV. However, the thiol oxidation-mediated activity of RSV is restricted to the pro-oxidative environment of tissues [78]. In light of the new findings that *trans*-RSV converts to *cis*-RSV and RSV reaches high micromolar concentrations in target tissues [27, 89, 194], and RSV metabolites potentially serve as a reservoir for the parent compound [27, 195] and *cis*-RSV is glucuronidated faster than *trans*-RSV [262–264, 266] and *cis*-RSV sulfates and glucuronides are found in higher concentrations than their *trans* counterparts in humans [265], it is critical to explore whether a combination of *cis*- and *trans*-RSV would elicit synergistic or antagonistic effects in future studies.

"Moonlighting" functions of aminoacyl-tRNA synthetases (aaRSs)

Aminoacyl-tRNA synthetases (aaRSs) are ancient proteins that activate L-amino acids for protein synthesis (translational function) [267]. However, during evolution, aaRSs also progressively accrued "moonlighting" functions activated under conditions of diminished protein synthesis, such as cellular stress, which is well reviewed in many recent publications [268]. These functions beyond protein synthesis (non-translational "moonlighting" functions) enable aaRSs to play critical roles in various cellular functions, including metabolic homeostasis and modulation of signal transduction pathways [268]. However, the molecular mechanisms by which aaRSs "switch ON" their "moonlighting" functions and "switch OFF" their role in protein synthesis are not very well understood. Intriguingly, knocking down aaRSs enhances longevity in *C. elegans* [269] but decreases it in *Drosophila* [270], indicating that the non-canonical functions of aaRSs are probably significant only in higher eukaryotic organisms [271]. Each aaRS has a unique active site that precisely differentiates closely related amino acids. Interestingly, the depletion of tryptophan from the active site of tryptophanyl-tRNA synthetase (TrpRS) activates its "moonlighting" nuclear function poly-ADP-ribose-polymerase 1 (PARP1)-dependent activation of p53 [272]. Therefore, potential binding of natural amino acid analogs (metabolites, neurotransmitters, and bioactive compounds) to the active sites of aaRSs could "switch ON" their "moonlighting" functions by temporarily transforming them to catalytic nulls [273].

cis-RSV evokes a tyrosine-free (*apo*) conformation in human tyrosyl-tRNA synthetase (TyrRS)

We astutely observed structural similarities between RSV and tyrosine (RSV harbors a tyrosine-like phenolic ring), and interestingly, human serum levels of L-tyrosine remain elevated under conditions that drive various metabolic dysfunctions [274–282], including cancer [283, 284]. Therefore, we tested if RSV would behave as an "active site-directed inhibitor" of TyrRS and consistently found that RSV is a direct inhibitor of TyrRS catalytic activity with an inhibition constant (Ki) value of 22 μM [285]. Unlike other known biological targets of RSV (F0/F1 ATPase, ERα, SIRT3, COX-1/2) that bind to its *trans*-isomer [57, 286–288], intriguingly, we found that despite using *trans*-RSV, we obtained the crystal structure of TyrRS bound with only the *cis*-isomer of RSV. Therefore, TyrRS is the first and so far, the only biological target that binds to the *cis*-RSV. While the phenolic ring of RSV and tyrosine have the same disposition in the respective co-crystals, accommodation of the *cis* conformation of the dihydroxy ring of RSV forces a local structural change near the linker to

the C-terminal domain of TyrRS. Based on the structural information, we proposed that RSV-triggered conformational switch in the active site of TyrRS might drive the predominant *trans*-RSV into a *cis* conformation in the physiological context. Consistently, downregulation of the cellular protein levels using siRNA against the mRNA of TyrRS mitigated the signaling effects of low-dose *trans*-RSV and overexpression of TyrRS was sufficient to mimic at least in part, the signaling events evoked by low dose (≥ 10 μM) *trans*-RSV. Therefore, we concluded that while high-dose RSV (≥ 25 μM) inhibits tyrosine-AMP formation [285] and activates SIRT1 [14, 207], at lower concentrations of RSV (≤ 15 μM), TyrRS protein would instead facilitate the conversion of *trans*-RSV to *cis*-RSV in the physiological context, providing an underappreciated contribution of TyrRS in the biological effects of natural RSV. Moreover, a structural comparison between *cis*-RSV bound TyrRS, and its the tyrosine-free (*apo*) form demonstrated that *cis*-RSV mimics a tyrosine-free "*apo*" state of TyrRS (Fig. 2a) and the physiological significance of this observation remains to be explored in the future. Because mutations in human TyrRS are known to cause neuropathy [289] and multi-system diseases [290–292] in a protein synthesis function-independent manner [293], our findings suggested that RSV would be a potent modulator of the emerging "moonlighting functions" of TyrRS [46, 294–296]. In this context, it is interesting to note that inflammation drives the matrix metalloproteinase (MMP)-mediated cleavage of TyrRS [297] and RSV is a known inhibitor of MMP-2 and MMP-9 [298, 299]. Therefore, it is apparent that RSV would contribute to the systemic protein levels of TyrRS and vice versa, TyrRS would contribute to the distinct physiological outcomes of RSV, if any that are mediated through the *cis* and *trans* isomers of RSV.

cis- and *trans*-RSV have opposite effects on TyrRS-regulated PARP1 activation

Although RNA does not activate PARP1 [300], broken DNA ends are the best-known activators of PARP1 [301]. Intriguingly, the presence of PARP1 on the broken DNA impairs efficient DNA repair [302, 303], suggesting that eviction of PARP1 from the DNA through auto-poly-ADP-ribos(PAR)ylation is required for efficient DNA repair [304, 305]. Consistently, NAD^+ supplementation that enhances auto-PARylation of PARP1 facilitates PARP1-dependent DNA repair [306]. Interestingly, our work demonstrated that nuclear localization of TyrRS after either serum starvation, heat shock, or endoplasmic reticulum (ER) stress stimulates the auto-PARylation of PARP1 suggesting that eukaryotic TyrRS activates PARP1 in a DNA-independent manner [285] to facilitate TyrRS-mediated DNA repair [295, 296]. Because our previous work [272] provided the structural basis of amino acids mediated inhibition of the "moonlighting" functions of aaRSs, we hypothesized that RSV that binds to TyrRS would modulate its PARP1-activating "moonlighting" function as well. Importantly, RSV was previously shown to activate PARP1-dependent protection against oxidative stress and mitochondrial dysfunctions [71]. As expected, we found that binding of *cis*-RSV induced conformational switch promoted the interaction of TyrRS with PARP1 and stimulated the generation of nicotinamide (NAM) and ADP-ribose (ADPR)- two potent inhibitors of SIRT1 [285]. Most significantly, RSV potentiated TyrRS-mediated auto-PARylation of PARP1 in vitro at nanomolar (nM) levels with a half-maximal effect (EC_{50}) at roughly 10 nM, indicating that TyrRS/PARP1 complex is the biological target of RSV rather than TyrRS by itself. TyrRS-*cis*-RSV-PARP1-driven NAD^+ signaling thus upregulated the expression and activation of a battery of genes, proteins, and signaling cascades that elicit a protective stress response. Most importantly, we observed significant upregulation of the acetylome of proteins, including p53, upon treatment with RSV in vitro and in vivo [285]. This observation was also consistent with RSV-mediated stimulation of the acetylation of nuclear proteins that drives autophagy [58] and CR stimulated upregulation of acetylome, including p53 [307]. However, TyrRS-regulated auto-PARylation of PARP1 was lost in the presence of broken DNA [285], suggesting that factors that induce DNA damage would abolish TyrRS/PARP1-mediated protective stress response.

Because *cis*-RSV and tyrosine evoke two distinct conformations in TyrRS, treatment with a higher affinity tyrosine-adenylate analog (Tyr-SA, (5'-O-[N-(9 L-tyrosyl) sulfamoyl] adenosine)) resulted in the inhibition of *cis*-RSV/TyrRS-regulated auto-PARylation of PARP1 both in vitro and in vivo in mice; however, we were intrigued by the observation that despite using the commonly available *trans*-RSV, we obtained only the *cis*-isomer of RSV bound to TyrRS. To better understand it, we performed in silico modeling using the *trans*-RSV in the active of TyrRS. This modeling

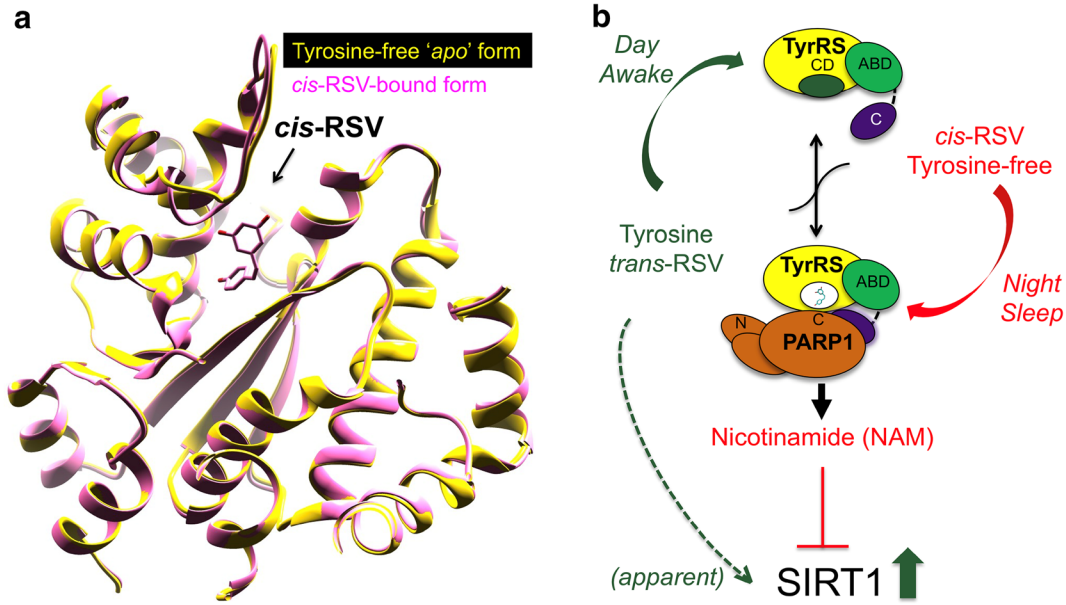

Fig. 2 a RSV mimics/induces a tyrosine-free (*apo*) conformation in TyrRS. Ribbon illustration of structural comparison between the superimposed stuctures of TyrRS. Structures of TyrRS with *cis*-RSV bound at the active site and a tyrosine-free (*apo*) form does not show any significant conformational differences. **b** *cis*- and *trans*-RSV have opposite effects on TyrRS-regulated PARP1 activation. Cartoon illustration of the mechanism of isomer-specific opposite effects of *cis*- and *trans*-RSV on TyrRS-regulated PARP1 activation. *cis*-RSV facilitates TyrRS-regulated PARP1 activation, which results in the production of nicotinamide (NAM). Similarly, circadian downregulation of tyrosine in the night would also facilitate TyrRS-regulated PARP1 activation. In contrast, *trans*-RSV and tyrosine inhibit TyrRS-regulated PARP1 activation and the production of NAM, which is a well-known inhibitor of SIRT1. Therefore, treatment with *trans*-RSV or the circadian upregulation of tyrosine in the day time would also result in an *apparent* activation of SIRT1 due to the absence of NAM production by TyrRS-regulated PARP1 activation

showed that the binding of *trans*-RSV to TyrRS did not induce any conformational change and is identical to its tyrosine-bound form [285]. This data indicated that unlike *cis*-RSV, retension of *trans*-RSV in the active site of TyrRS by higher concentrations of RSV (≥ 25 μM) would prevent the interaction of TyrRS with PARP1, leading to inhibition of PARP1 and an apparent activation of SIRT1 (due to the absence of PARP1 activation) (Fig. 2b). Thus, our previous work for the first time suggested that the "*cis*" and the "*trans*" isomers of RSV and lower (≤ 15 μM) and higher (≥ 25 μM) doses of RSV would have opposite effects on TyrRS-regulated PARP1 activation and associated NAD^+ signaling [285] and indicated a potential molecular basis to resolve the "*dichotomy*" of RSV.

PARP1 maintains genomic stability and inflammation inhibits PARP1-mediated DNA repair

PARP1 senses and responds to DNA damage [305, 308–310], oxidative, and environmental stresses by transcriptionally activating cytoprotective and DNA repair pathways [303, 311]. To protect cells from damage, PARP1 metabolizes NAD^+ to nicotinamide and ADP-ribose resulting in the activation of cellular cytoprotective pathways [312–319] along with rapid nuclear ATP synthesis that sustains the transcriptional upregulation of stress response genes [318, 320]. PARP1 modulates the function of the CCCTC-binding factor (CTCF) [321, 322] and feeding behavior [323] in a circadian transcription-dependent manner [311, 324]. Consistently, dopamine activates the PARP1/CTCF-regulated transcriptional network to trigger morphological remodeling in astrocytes [325]. PARP1 is not only a potent modulator of SIRTuin activity [326] but also protects against genotoxic stress [315, 327, 328], optimizes efficient DNA repair [303], and facilitates long-term memory formation [329–332] and neuronal survival under stress [333–335]. PARP1 plays a critical role in induced pluripotent stem cells (iPSCs) generation [336] and neuronal differentiation [337]. Interestingly, PARP1 knockout mice exhibited decreased neurogenesis with a concomitant increase in gliosis [338], exacerbates diet-induced obesity [339], induces

schizophrenia-like symptoms such as anxiety, depression, social interaction deficits, and cognitive impairments in mice [340]. Interestingly, treatment with nerve growth factor (NGF) [341, 342] and NAD^+ supplementation [343] activate PARP1 and protect neuron-like PC-12 cells from H_2O_2-mediated cell death [344, 345], despite the accumulation of poly-ADP-ribose (PAR) [343]. Furthermore, activation of PARP1 is required for nuclear proteasome function [346, 347] that prevents the accumulation of misfolded protein aggregates, a hallmark of neurodegenerative diseases. Basal PARP1 activation is higher in the CNS of young mice [348], and it is downregulated in AD [349]. PARylation protects against coronavirus [350] and modulates glucose metabolism [351], and consistently, PARylation is downregulated in an age-dependent manner [352, 353]. Interestingly, naked mole-rat (NMR) has higher basal PARylation levels than the mouse [354] and is resistant to Alzheimer's disease (AD) [355]. Most significantly, inhibition of PARP1 leads to the induction of DNA damage and cytotoxicity [356, 357] and mitochondrial dysfunction [358] through the upregulation of aerobic glycolysis [359–361], which are implicated in the etiology of various metabolic disorders and cancer. Moreover, inflammation inhibits PARP1-dependent DNA repair [359, 362, 363] and depletion of PARP1 not only triggers sustained induction of interferon-stimulated genes (ISGs) [364] and senescence [365] but also exacerbates autoimmune diseases [366–368] and spontaneous cancer formation through accelerated aging [369]. In this context, it is interesting to note that inflammation also drives the cleavage of TyrRS [297], indicating a potential role of full-length TyrRS in PARP1-mediated DNA repair [359, 362, 363]. Consistently, emerging works suggest that inhibition of PARP1 induces DNA damage-dependent pro-inflammatory response [362, 363, 370–372] and results in cancer metastasis [373] and dampens the anti-cancer immune response through the induction of programmed death-ligand 1 (PD-L1) [374]. These observations suggested that activation of PARP1 not only enhances DNA repair but also triggers an anti-inflammatory signaling cascade [362–365] to maintain genomic stability. Consistent with the inhibitory role of PARP1 on DNA repair [302, 303], recently, PARP "trapping" has gained much attention in the anti-cancer treatment regimen [375]. Intriguingly, PARP1 inhibition protects neurons from toxic effects [376–382], suggesting that PARP-dependent DNA repair and survival are context dependent.

Human serum L-tyrosine level is circadian regulated and RSV has circadian effects

Physiologically, human serum L-tyrosine level is modulated in a circadian manner with a peak of serum tyrosine in the morning to noon (at light) and a drop in the night (at dark) [383, 384]. Therefore, during deep sleep, humans have low serum tyrosine levels [385]. Likewise, there is a daily rhythm in the content and utilization of tyrosine in the whole mouse [386]. Interestingly, tyrosine transaminase that modulates the serum tyrosine levels [387] is regulated by vagal cholinergic nerves, which in turn, is regulated by the central nervous system (CNS) [388, 389]. Consistent with RSV being a modulator of L-tyrosine-mediated signaling [285] and tyrosine kinases [390], RSV also restores circadian rhythm in mice [391] and upregulates circadian gene expression in fibroblasts [392, 393]. Because rhythmic histone acetylation regulates circadian gene transcription [394], these studies are also consistent with RSV's role as a modulator of histone acetyltransferases (HDACs) [154, 207]. Intriguingly, when administered during the activity phase (at dark) in rat, RSV behaved as a potent antioxidant in the heart, the liver, and the kidney [395], but, when administered during the rest phase (at light), RSV instead exerted pro-oxidant effects in the organs for unknown reasons [395]. Furthermore, RSV supplementation significantly increased the proportion of active-wake time, occurring mainly during the resting phase of the sleep-wake cycle (+ 163%) of adult mouse lemurs. The increase in active-wake time with RSV supplementation was accompanied by a significant reduction of both paradoxical sleep (− 95%) and slow-wave sleep (− 38%). Therefore, RSV can act as a potent modulator of sleep-wake rhythms [396, 397]. Furthermore, the nocturnal administration of RSV sharply decreased tumor frequency up to 40% and lowered tumor incidence [398]. However, daytime administration of RSV in the same N-methyl-N-nitrosourea (NMU) rat model was significantly less effective with no change in tumor incidence [398]. These observations are consistent with the recent finding that different circadian cycles in nocturnal rodents versus diurnal humans may contribute to the failure in human translational studies [399]. Therefore, an important consideration should be given to the timing of RSV administration (day vs. night) in the future clinical trials to make the best out of the circadian effects of L-tyrosine and RSV.

Calorie restriction (CR) lowers serum L-tyrosine, a biomarker for metabolic dysfunctions and aging

The most recent human metabolomic analysis demonstrated that serum L-tyrosine level is upregulated during aging [400, 401], and its downregulation is an indicator of CR in humans [402, 403]. However, the potential mechanisms for an association between reduced serum levels of L-tyrosine and improvement in metabolic dysfunctions during CR remain unclear. Nevertheless, recent studies have confirmed the long-standing observation that elevated L-tyrosine level is a biomarker for various metabolic dysfunctions including the development of type 2 diabetes, obesity [274–282], cancer [283, 284], and memory dysfunction in human Alzheimer's disease (AD) [404, 405]. Moreover, serum L-tyrosine level has also emerged as a novel marker that links diabetes and cardiovascular disease (CVD) susceptibility [406]. Interestingly, L-tyrosine influences developmental decisions and longevity in *Caenorhabditis elegans* [407, 408] and potentiates the detrimental effects of oxidative stress either by decreasing glutathione and stimulating lipid and protein oxidation in rat cerebral cortex [409] or by increasing the thiobarbituric acid reactive species levels in the hippocampus and the carbonyl levels in the cerebellum, hippocampus, and striatum [410]. Moreover, chronic administration of L-tyrosine increased DNA damage frequency and damage index in the hippocampus, striatum, cerebral cortex, and blood [411, 412]. Recent studies demonstrated that chronic administration of L-tyrosine inhibited the activity of complex I, II–III, and IV in the striatum, which can be prevented by antioxidant treatment [413, 414]. Consistently, oral supplementation of L-tyrosine impairs glucose uptake and insulin secretion in rats [415], and the capacity to detoxify excess L-tyrosine is an essential life trait for the blood-sucking arthropods [416, 417]. Quite interestingly, L-tyrosine was negatively correlated with hypothalamic transcriptional levels of *Drd5*, a dopamine receptor expressed in the limbic regions of the brain [418] that not only activates memory formation [419] but also evokes anti-tumor effects through autophagy induction [420]. Moreover, unlike branched-chain amino acids (BCAA) that upregulate BDNF levels [421], the acute administration of L-tyrosine instead decreased BDNF levels in the hippocampus and striatum of rats [422]. Consistently, the administration of L-tyrosine exacerbates the cognitive decline in aged people [423]. Most significantly, a tyrosine-restricted diet stimulates human immunocompetence [424], and CR significantly downregulates tyrosine biosynthesis and serum tyrosine levels in mice [418] as well as in humans [402, 403]. Intriguingly, similar to RSV-mediated antiatherogenic effects modulated through the focal adhesion kinase (FAK) [425] and anti-tumor effects [426, 427], a tyrosine-free diet is also known to evoke anti-tumor effects against melanoma [428–430] in a FAK-dependent manner [431].

cis- and *trans*-RSV would exert opposite effects in the physiological contexts

Although a significant bottleneck in tapping the therapeutic potential of RSV is the lack of a proven physiologically relevant mechanism of action, our previous work addressed some fundamental aspects of this issue and laid a foundation to bridge the gap between the observed in vitro and in vivo effects of RSV. Moreover, our discovery of TyrRS being a biologically significant and physiologically relevant target of RSV that facilitates the conversion of *trans*-RSV to *cis*-RSV suggests that the *cis*-isomer of RSV is also a major isomer that evokes protective stress response. Other recent studies have also confirmed the TyrRS-PARP1 signaling in mediating the protective effects of RSV [120, 229, 296, 432–434]. However, there are still critical gaps in our knowledge. The biological significance of the two distinct conformations induced by *cis*-and *trans*-RSV in TyrRS (Fig. 2) [285] has not been explored extensively. Moreover, the biological significance of *cis*-RSV has not gained scientific attention in terms of the number of publications (Fig. 1b) despite showing significant physiological effects, as mentioned above. In light of the new findings that RSV attains high micromolar levels in human tissues and plasma after oral ingestion [27, 89, 193, 194] and *trans*-RSV converts to *cis*-RSV in the physiological context [78, 195], and *cis*-RSV has anti-inflammatory [251–253] and anti-platelet [259] and anti-cancer activities [88] and *cis*-RSV sulfates and glucuronides are found in higher concentrations in humans [265], future studies should determine if *cis*- and *trans*-RSV would evoke distinct physiological outcomes in various experimental paradigms.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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