

Biophysical interaction of resveratrol with sirtuin pathway: Significance in Alzheimer's disease

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1. ABSTRACT

Alzheimer disease (AD) is a widespread neurodegenerative condition that leads to progressive cognitive dysfunction in elderly population. Despite several attempts aimed at molecular determinants of AD, effective disease modifying treatment options are highly limited. Recently, use of natural supplements has gained considerable attention in AD research due to their cost effective and long lasting health beneficial properties. Resveratrol (RSV) is a naturally occurring polyphenolic compound found majorly in grapes. RSV has been shown to exert a plethora of medical benefits due to its anti-oxidant, anti-aging, anti-inflammatory, anti-malignant and neuroprotective properties. In particular, RSV has been shown to increase memory performance. The neuroprotective effect of RSV has strongly been linked to the depolymerization of amyloid β fibrils. However, the molecular targets of RSV remain the subject of investigation. This review was aimed to comprehend the existing knowledge on the neuroprotective effects of RSV and recent progress made on understanding the role RSV in the regulation of neural plasticity through a molecular target Sirtuin 1, a potential homeostatic regulator in AD.

2. INTRODUCTION

Alzheimer's disease (AD) is one of the most common neurodegenerative diseases with 80 % of all dementia patients worldwide (1). While, AD is the fifth leading cause of death worldwide, the World Health Organization (WHO) estimated the prevalence of AD in global population that will quadruple in the next decades, reaching 114 million cases by 2050 (2). According to the Alzheimer's Association USA, a significant number of people over the age 65 suffer from AD. The etiology and biology of AD are complex in nature and AD can be classified into two types namely Familial AD (FAD) and late onset sporadic AD (LOAD). FAD is an early onset, which accounts for 2% of AD cases and is caused by hereditary mutation in genes coding for amyloid precursor protein (APP), Presenilins 1 (PS1) and Presenilins 2 (PS2), whereas sporadic AD appears to be adult onset, where aging is considered as the obvious risk factor. However, several other possible biological factors, such as epigenetic alterations, polymorphisms, abnormal immune and inflammatory responses, lifestyle and gene-environment interactions, have also been implicated in the molecular pathway leading to AD (3).

AD has been clinically characterized by progressive deterioration of memory function resulting from the neuropathology changes that include formation of extracellular amyloid- β (A β) aggregates and intracellular neurofibrillary tangles (NFT) of hyper-phosphorylated Tau protein in the brain (4). The amyloid cascade hypothesis remains the most characterized as the fact of the proteolytic cleavage of the amyloid- β precursor protein (A β PP) by β and γ secretases into 38, 40, or 42 amino acid peptides, which are generally viewed as a toxic mediator of AD (5). In addition, changes in the neurotransmitter level, neurodegeneration and synaptic loss have been extensively characterized; however, the mechanism underlying the development of AD is not clearly understood due to the comorbidity (6). Notably, progressive cognitive decline has been well correlated with neurodegenerative process that is characterized by early damage to the synapses (7, 8, 9) with retrograde degeneration of the axons and eventual atrophy of the dendritic tree (10, 11, 12, 13). Thus, the brain imaging studies, postmortem samples and experimental models along with assessment of the cognitive function represent the symptomatic clue for the development and progression of AD. The other common neuropathological features of AD include the reactive astrogliosis and microglia activation in close proximity to neuritic plaques containing A β peptides (14). Though a relationship between the response of glial cells and neurodegeneration with cognitive decline remains unclear, the abnormal generation of pro-inflammatory molecules, including nitric oxide elicited by activated microglia and reactive astrocytes have been implicated in disruption of the homeostasis, abnormal neurotransmission, cellular oxidative damage leading to mitochondrial dysfunction and endoplasmic reticulum (ER) stress, ultimately stimulating progressive neurodegeneration and dementia in AD brains (15,16).

Taken together, the existence of multiple mechanisms in AD raises the possibility of identifying a molecular therapeutic target in activating the body's own defense against age-related deterioration and cell death. One such universal regulator is sirtuin (SIRT1) - the NAD⁺-dependent deacetylase with diverse physiological functions relating to cell survival, inflammation, energy metabolism, and tissue homeostasis (17).

3. SIRT1 – A HOMEOSTATIC REGULATOR IN HEALTH AND DISEASE

Sirtuins (SIRT) are conserved NAD⁺-dependent protein deacetylases found in a variety of organisms and play primary roles in many physiological processes through some epigenetic modifications (18, 19, 20). Sirtuin was first identified

in yeast, named Sir2 assigned as class III histone deacetylases (HDACs) based on the biochemical property. They function by removing acetyl groups from lysine on both histones and non-histone proteins at the expense of NAD⁺ thereby it is more generally referred as lysine deacetylases (21). Among seven mammalian sirtuins (SIRT 1-7), the biological relevance of SIRT1 has been the best-characterized and the closest homologue Sir2 in yeast. Sirtuins are required for the increased longevity during caloric restriction in yeast, drosophila and mice (22, 23). SIRT1 regulates the role of many genes such as Forkhead box O3 (FOXO3), retinoic acid receptor beta (RAR β), p53, nuclear factor kappa-light-chain-enhancer of activated B cells (NF κ B) (24). It suggests that SIRT1s play a major role in the various cellular processes involved in the development and growth of the organisms. Moreover, it has been established that NAD⁺-dependent post-translational modification of some enzymes and proteins by SIRT1s leads to the regulation of important biological processes at different subcellular compartments and also protective effects on age-related disorders. Besides, metabolic and neurodegenerative disorders have been characterized by dysregulation of biochemical pathways, which can be restored by SIRT1 (25). Thus, defects or dysregulation in SIRT1 genes have been identified as disease modifiers in many age-related disorders. The activities of sirtuin have been shown to be involved in the stimulation of anti-apoptotic, anti-inflammatory, and anti-stress responses as well as the modulation of aggregation of proteins such as A β involved in neurodegenerative disorders (26, 27, 28, 29, 30). Therefore, SIRT1 pathway represents a potential therapeutic target for many disorders including Alzheimer's disease.

4. POSSIBLE LINK BETWEEN THE FUNCTIONAL ROLES OF SIRT1 AND AD

The mechanisms underlying the cytoprotective roles of SIRT1 are complex and multifaceted. Reduction of A β generation by SIRT1 has been a key focus of several studies using experimental models of AD (31, 32, 33). Overexpression of SIRT1 has been shown to improve behavioral phenotypes by decreased formation of toxic A β 42 species acting through α -secretase in APP/PS1 transgenic model of AD (34). In another study, SIRT1 has been shown to ameliorate AD against microglia mediated A β toxicity through the inhibition of inflammatory NF- κ B signaling in primary neuronal culture (35). Reduced expression of SIRT1 has been found to be accompanied with accumulation of Tau in both *in-vitro* and *in-vivo* experimental models of AD (36). SIRT1 protects against neuronal loss in the inducible p25 transgenic mouse, a model of AD mediated by Tauopathy (37).

Table 1. Dietary sources of resveratrol (RSV)

Sources	Trans-resveratrol concentration	References
Red wines	0.1.–14 mg l ⁻²	46–48
White wines	<0.1.–2.1. mg l ⁻²	49
Grapes	0.1.6–3.5.4 µg/ g ⁻¹	48
Dry grape skins	24.0.6 µg /g ⁻¹	50
Red grape juice	0.5.0 mg/ l ⁻²	50
Blueberries	Up to 32 ng ⁻¹	50
Bilberries	Up to 16 ng ⁻¹	50
Peanuts	0.0.2–1.9.2 µg/g ⁻¹	40
Boiled Peanuts	5.1. µg/g ⁻¹	51

We and other have recently reported that SIRT1 expression induces the α -secretase activity and attenuates beta amyloid peptides in primary Tg2576 neuron cultures and CHO-APP_{swe} cells (38, 39). In line with these currently available data, it has been proposed that over-expression of *SIRT1* gene or its hyper-activation could play a therapeutic role in delaying the progression of AD and dementia (40, 41, 42). Accordingly, the development and characterization of agonistic drugs to activate SIRT1 pathway have gained a significant research interest towards the treatment of many adult onset disorders including AD. A recent data provides valuable insights into the effect of RSV on longevity and its potential protective role in age-related human diseases, including AD (43). Therefore RVS has been shown to offer protection against dysregulation of energy homeostasis observed in experimental models for metabolic syndromes by the activation of SIRT1 and the energy sensor protein kinase AMPK (AMP-activated protein kinase) (44, 45).

5. BIOAVAILABILITY OF RSV AND ITS EFFECTS ON METABOLISM AND CELLULAR FUNCTIONS THROUGH SIRT1

RSV, 3, 5,4' -Trihydroxystilbene, has been reported to be first isolated in 1940 as a constituent of the roots of white hellebore (*Veratrum grandiflorum* O. Loes). Since then, RSV has been identified in various plants, including grapes, berries, peanuts, red grapes and red wine (Table 1). Reports from *ex-vivo* and animal studies have provided a sufficient detail on the absorption, metabolism, and consequent bioavailability of RSV (45). RSV exhibits lipophilic characteristics, which lead to high absorption and is dependent upon the way and type of food that is ingested (52). The oral bioavailability of RSV is low due to rapid excretion and extensive metabolism into various glucuronide and sulfate conjugates of unknown potential biological

activities (53). Despite its low bioavailability, RSV still proved to exhibit efficacy *in vivo* due to the conversion of both sulfates and glucuronides (RSV conjugates) again to RSV in target organs such as the liver (54). Another important possible mechanism could be the enterohepatic recirculation of RSV metabolites, followed by its deconjugation in the small intestine and reabsorption (55).

Several classes of plant derived metabolites such as flavones, stilbenes, chalcones and anthocyanidins were shown to directly activate the SIRT1 pathway *in vitro* through an apparent allosteric mechanism (20, 24). Resveratrol (RSV), the most viable natural product that has been shown to activate SIRT1 and promote the lifespan in yeast models in a Sir2-dependent manner (24, 56, 57). The functional role of RSV has been widely studied for its efficacy in raising SIRT activity and reported to influence a variety of SIRT-mediated response in many types of cells such as adipocytes (58), Skeletal muscle cells (43), hepatocytes, pancreatic beta cells (59), renal cells (60) cardiomyocytes (62, 62), the brain and neuronal cells (63). Thereby a number of data support the evidence for a direct link between RSV and SIRT1 (64, 65).

Vingtdeux *et al.*, (66) demonstrated that SIRT1 activation is one of the main targets defined for the pharmacological effects of RSV. It was initially demonstrated that RSV could significantly increase binding affinity of substrate by lowering its Michaelis constant (K_m) value without affecting the overall turnover rate (V_{max}) of SIRT1, and thereby promoting deacetylase activity of SIRT1 (67, 68). It has been reported that SIRT1 activation by RSV increases the lifespan of *Saccharomyces cerevisiae* (24), *Caenorhabditis elegans* (57) *Drosophila melanogaster* (56), and the short-lived seasonal fish *Nothobranchius furzeri* (69). SIRT1 activation was found to prevent neurodegeneration (70) and axonal degeneration (71). However, the

legitimacy of RSV as direct SIRT1 activators has been widely debated. Recent biological studies have revealed that RSV does activate SIRT1 toward certain substrates containing a bulky hydrophobic group, such as a 7-amino-4-methylcoumarin (AMC) moiety or a tryptophan residue, directly adjacent to the acetylated Lys at the +1 position. Moreover, a recent crystallographical structure of SIRT1 in complex with p53AMC revealed the co-binding of three RSV molecules in the N-terminal domain (NTD) of SIRT1, mediating enzyme-substrate interaction (68). The other mechanistic explanation of RSV in the activation of SIRT1 showed that lamin A directly interacts with SIRT1 thereby aiding in the nuclear matrix (NM) localization of the latter that further enhances the deacetylase activity of SIRT1 (72). These reports strongly suggest that besides its beneficial role in anti-oxidant, anti-inflammatory, anti-cancer properties and reduced oxidative stress (73, 74, 75, 76), RSV proved to be the powerful activator of SIRT1. Interestingly reports from our laboratory showed RSV as a potent SIRT1 enhancer in an animal model for AD (75), CHO-APP^{swe} cell lines (39), aged rats (77) where RSV exhibited key beneficial regulatory activity in various aspect of neurodegeneration.

6. ROLE OF RSV IN ATTENUATING A β MEDIATED TOXICITY

It has been shown that RSV attenuates A β levels by promoting proteasome-dependent intracellular degradation (73). A β peptides, the major component of senile plaques, interact with various Toll like receptors (TLRs) such as TLR4 and can trigger microglial activation. Anti-inflammatory action of RSV has shown to prevent lipopolysaccharide (LPS, a TLR4 ligand)-induced activation of murine RAW 264.7 macrophages and microglial BV-2 cells. RSV treatment has been reported to prevent pro-inflammatory effect of A β on macrophages by inhibiting activation of STAT1, STAT3 and NF κ B activation by interfering with IKK and I κ B phosphorylation (78). In addition, oral administration of RSV in a mouse model of cerebral amyloid deposition significantly reduced microglial activation related to amyloid deposition. Moreover, studies showed that RSV can improve cognition, mood changes, enhance hippocampal plasticity and adult hippocampal neurogenesis (79, 80). RSV treatment also shown to protect the integrity of blood brain barrier (BBB) in autoimmune encephalomyelitis mice, an experimental model for multiple sclerosis (81). These results raised the hope of using RSV as a potential therapeutic agent, that adds on to the current evidences on its protective role against metabolic events and further RSV maintaining BBB integrity might exhibit significant effect during AD like conditions that are widely damaged

by inflammation (82). However, further *in-vivo* experiments are required to confirm these effects that may shed light on new therapeutic avenues for targeting many neurological diseases. However, a limited knowledge on the direct interaction and spatio temporal relation of RSV with SIRT pathway has been a major drawback in understating the direct role of RSV on SIRT1 mediated process. The neuroprotective effect of resveratrol against A β mediated toxicity in AD is depicted in Figure 1.

7. BIOINFORMATICS APPROACH TOWARDS RSV'S MODE OF ACTION

Investigations into system biology approach on interaction between SIRT1 and other pathway using STRING database provided a more detailed evidence for the functional regulation of SIRT1 pathway (Figure 2). Hou *et al.*, (83) proposed a novel mechanism of action of RSV. With experimental reports suggesting that RSV may act as allosteric regulator of SIRT1, their team used molecular dynamic simulation studies to explore additional possibilities of RSV to be an independent regulator of other factors. They used 3 model substrates to study the effect of RSV on SIRT1 namely p53AMC, p53W and native p53 (Figure 3). They found that binding of native substrate p53 on N-terminal domain (NTD) facilitates the opening of large binding pockets in the NTD, thereby facilitating the binding of other two substrates. In the same approach, it has been proved that RSV also binds to p53 binding region and increases the binding affinity for the other two substrates. Moreover, they used three RSV molecules, which bind in the same fashion to that of p53 and restored the tight interaction of the p53AMC/p53W and SIRT1. Through this study, it is possible to understand that RSV can act as a direct regulator of SIRT1. In near future, it is possible to develop new therapeutic targets towards the activation of SIRT1 through RSV administration due its ability to modulate the SIRT1 binding pockets.

Marchal *et al.*, (84) reported that RSV can exhibit the calorie restriction (CR) like effect in the mouse in which the effect of insulin has improved and it was measured by homeostasis model assessment of insulin resistance (HOMA-IR index). It has experimentally been demonstrated that the co-occurrence of PPAR-gamma coactivator 1-alpha (PPAR-GC1A) along with SIRT1 plays a vital role in the metabolic reprogramming in response to dietary availability through coordination of the expression of a wide array of genes involved in glucose and fatty acid metabolism. RSV by improving SIRT1 may regulate PPAR-GC1A thereby projecting the possible role of RSV in regulating the metabolic events and reverting energy imbalance *in-vivo* (<http://string-db.org/cgi/network.pl?taskId=W6yV7eNOBs99>).

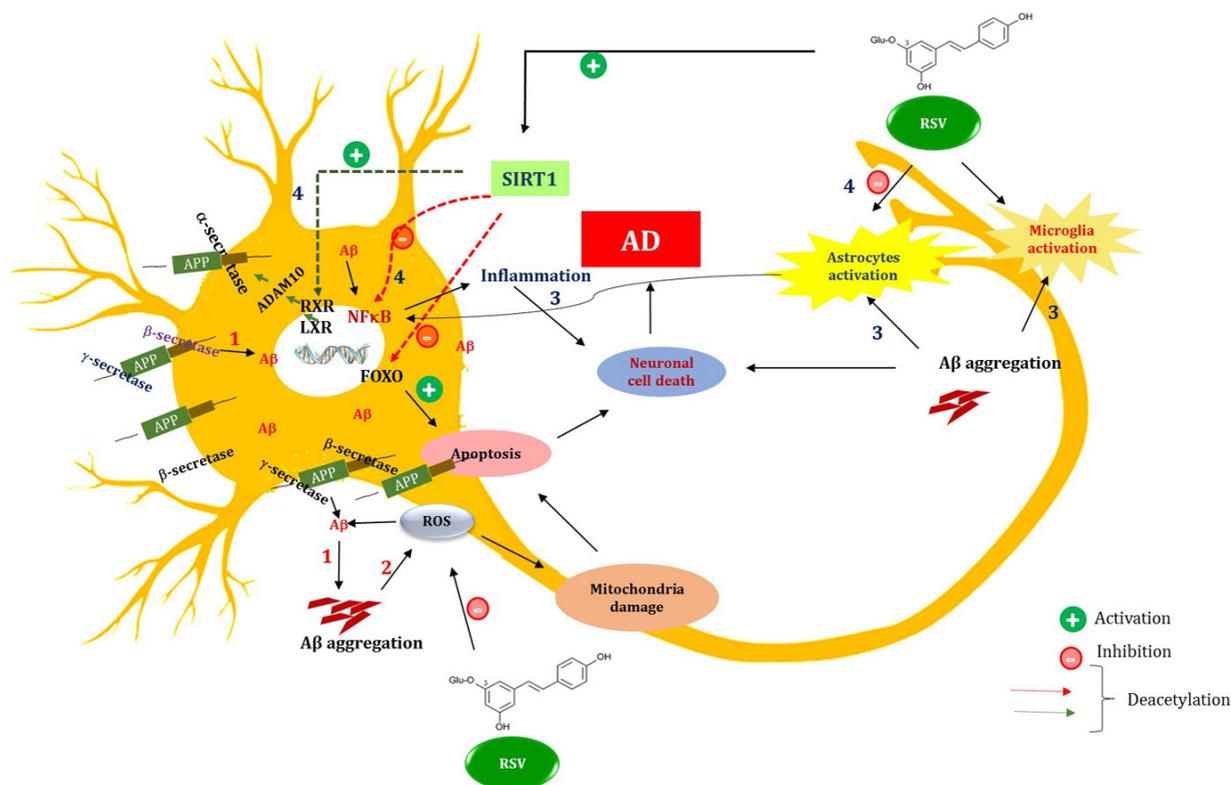


Figure 1. Neuroprotective effect of RSV: (1) APP is cleaved by β and γ secretases and the overproduction of $A\beta$ leads to the extracellular accumulation of $A\beta$ aggregates. (2) $A\beta$ stimulates the ROS production which leads to mitochondrial dysfunction and further leads to apoptosis and neuronal cell death. RSV promotes the $A\beta$ clearance and reduced the ROS production and prevents the neurons from degeneration. (3) $A\beta$ aggregation is responsible for the activation of astrocytes and microglia, and activates the transcription of NF- κ B, foxo which inhibits the inflammation and apoptosis. RAR deacetylation by SIRT1 positively regulates the ADAM10 (α -secretase) expression and prevents the amyloidogenic cleavage of APP and AD pathogenesis.

8. CONCLUSION

The clearance of neurotoxic amyloid beta ($A\beta$) remains one of the leading challenges to Alzheimer's research. Mitochondrial damage mediated oxidative stress has been implicated in the progression of many neurodegenerative diseases including AD. Studies have shown that RSV can quench the free radicals-mediated elevated oxidative stress through SIRT1 to maintain via cellular homeostasis in various experimental models. There are persuasive evidences suggesting that RSV can relieve the pathological grip of amyloid plaques and facilitate attenuation of the expression of BACE1 which is the rate limiting enzyme involved in the production of amyloid plaques. As a result, the neuroprotective potential of RSV in association with SIRT1 pathway is widely being considered in the treatment protocol for AD. However, the more specific effect of RSV on degradation of $A\beta$, combinatorial effect of RSV with other compound, therapeutic doses, and interaction of RSV with other molecular pathway need to be established. Thereby, it is possible to estimate the preventive effect of RSV by clinical trials in an effective manner.

Among the natural compounds, RSV has its own place in attracting many researchers to work on its therapeutic applications in AD like condition. Studies have shown that RSV can repress the levels of oxidative stress and free radicals that could mimic the action of caloric restriction (CR) and it increases the expression of genes like AMPK and SIRT1 to maintain homeostasis in animals. Although unmodified RSV appears to have a weak bioavailability, several studies have clearly demonstrated the *in vivo* neuroprotective properties of the red wine derived polyphenols, strongly supporting the notion that natural metabolites of RSV may have biological activities. Furthermore, recent findings have shed light on the potential role of RSV in transcription- and degradation-dependent anti-amyloidogenic mechanisms, suggesting that natural metabolites or potent synthetic analogues of RSV may have a therapeutic potential in preventing and/or treating AD.

9. ACKNOWLEDGMENTS

The authors have declared that no competing interests exist. The authors also

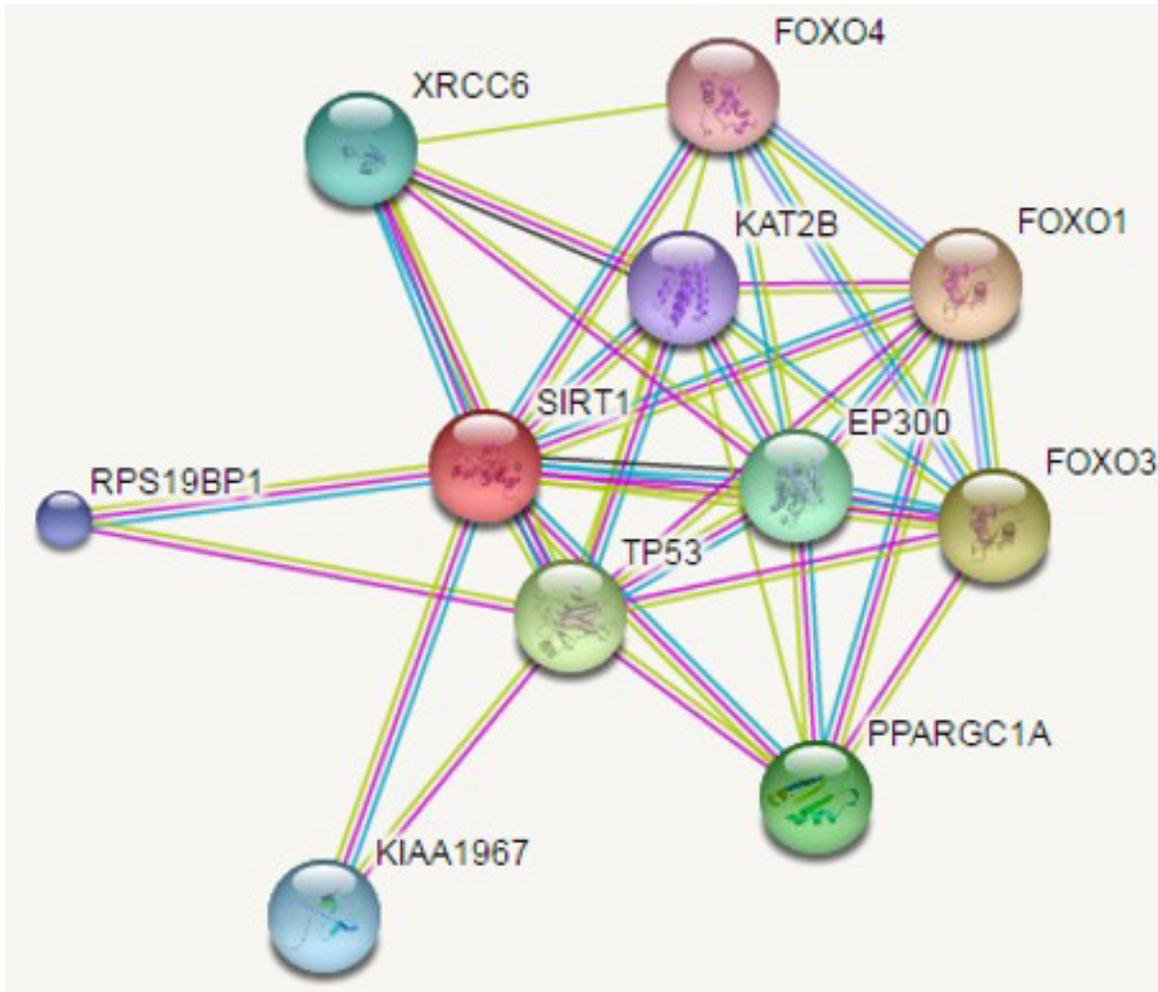


Figure 2. Protein-Protein interaction results obtained from STRING database with SIRT1 as query protein shows the association of SIRT 1 with other major signal pathways.

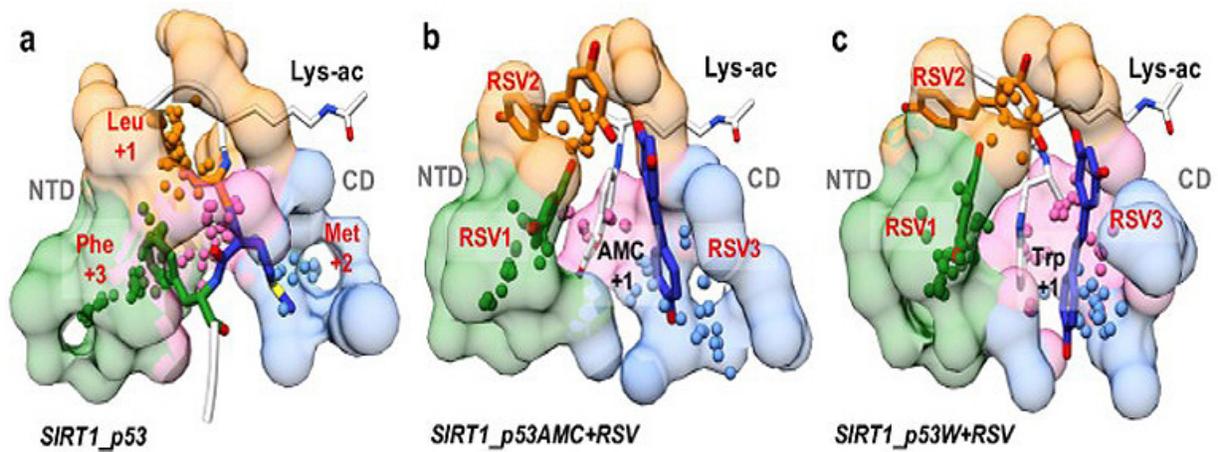


Figure 3. Comparison of binding pockets of (a) p53, (b) SIRT1_p53AMC+RSV, (c) SIRT1_p53W+RSV complex. The Leu, Met and Phe residues in p53 substrates and three RSV molecules in SIRT1_p53AMC+RSV complex and SIRT1_p53W+RSV complex are colored in orange, blue and green respectively. Residues lys -ac, AMC and Trp are shown as white ribbon, side chain pockets for three residues (Leu, Met and Phe) in p53 system and pockets for three RSV molecules (RSV1, RSV2 and RSV3) in p53AMC/RSV complex and p53W/RSV complex are presented as alpha -atom spheres and transparent surfaces, using the same colour as each residue (or as the molecule). Backbone pocket for three p53 residue and pockets for +1 residues (AMC and TRP) in p53W are presented as pink alpha spheres with transparent surfaces (82, 83).

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