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Mitochondrial Protection by Resveratrol

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Abstract

Mitochondrial dysfunction and oxidative stress are thought to play important roles in mammalian aging. Resveratrol is a plant-derived polyphenol that exerts diverse anti-aging activities, mimicking some of the molecular and functional effects of dietary restriction. This review focuses on the molecular mechanisms underlying the mitochondrial protective effects of resveratrol, which could be exploited for the prevention or amelioration of age-related diseases in the elderly.

Keywords

senescence; bioenergetics; mitochondria; aging; caloric restriction; cardiovascular disease; phytochemicals; 3,5,4′-trihydroxystilbene

Introduction

Age-specific mortality rates from heart disease, stroke, complications of diabetes, Alzheimer disease and cancer increase exponentially with age, which imposes a huge financial burden on the health care systems in the Western world. There is an urgent need for effective therapeutic strategies that have the potential to promote health in the elderly, simultaneously preventing or delaying the development of various diseases of aging. During the past decade dietary supplementation with resveratrol (3,5,4′-trihydroxystilbene) has emerged as a promising approach to counteract age-related diseases. Resveratrol is a naturally occurring polyphenol found in more than 70 species of plants, including grapevines (*Vitis vinifera*), cranberries (*Vaccinium macrocarpon*) and peanuts (*Arachis hypogaea*), which was shown to confer diverse physiological effects in laboratory animals including cancer protection, microvascular protection, neuroprotection, cardioprotection and anti-diabetic effects(4). In this review, we consider the evidence in support of the hypothesis that mitochondrial protective effects of resveratrol underlie its anti-aging action that can prevent/delay the development of age-related diseases in the cardiovascular system and other organs(3, 7, 29). The use of resveratrol as a dietary supplement to promote mitochondrial health in the elderly and diabetic patients is discussed.

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Resveratrol as a dietary restriction mimetic

Dietary restriction (a dietary regimen that restricts calorie intake), when not associated with malnutrition, has been shown to improve health and to slow the aging process in a wide range of animals (for a review see (20)). Sirtuin enzymes are nicotinamide adenine dinucleotide (NAD)-dependent deacetylases that are conserved from yeast to humans, influence lifespan in lower organisms, and appear to mediate at least certain effects of dietary restriction. Resveratrol has been proposed to mimic protective effects of dietary restriction, based on the observation that it can activate the mammalian sirtuin SIRT1 (silent mating type information regulation 2, S. cerevisiae, homolog 1) in an *in vitro* assay (14). However, the precise importance of sirtuins in the effects of dietary restriction and the ability of resveratrol to directly activate these enzymes *in vivo* remain controversial.

Even while the rationale for testing resveratrol as a dietary restriction mimetic has been challenged, evidence for dietary restriction-like effects has continued to emerge. Resveratrol has been shown to extend life in yeast, worms, and flies in a sirtuin-dependent manner(14, 33), although not all groups have reproduced these results(2). Further, resveratrol prevents insulin resistance, enhances mitochondrial biogenesis, improves vascular function, delays functional decline and restores normal longevity in obese mice(3, 15). Perhaps most impressively, resveratrol induces transcriptional profiles in multiple tissues that resemble those of animals consuming fewer calories(1, 22). At the same time, it is clear that resveratrol fails to mimic other aspects of dietary restriction, such as slowing heart rate and decreasing core body temperature (18), or thus far, extending lifespan in non-obese animals (19, 22). Therefore, resveratrol appears to mimic some, but not all, effects of dietary restriction, and much remains to be learned about the mechanisms responsible. A common theme that emerges from studies on mammals is that both dietary restriction and resveratrol treatment can elicit changes in cellular mitochondrial content and alter mitochondrial production of reactive oxygen species (ROS). These effects are likely to have significant, possibly synergistic, impact on cellular aging processes.

Resveratrol promotes mitochondrial biogenesis

Mitochondria are highly dynamic organelles and their biogenesis is likely to be involved in the regulation of cellular metabolism, redox regulation and signal transduction. Impairment of mitochondrial biogenesis has been described during aging and in diabetes and the metabolic syndrome and is thus likely to contribute to cellular energetic imbalance, oxidative stress and organ dysfunction in these pathological conditions. The physiological improvements induced by resveratrol in rodent models of aging and the metabolic syndrome are accompanied by an increase in the mitochondrial content of liver, skeletal muscle(3, 15) and blood vessels(7), which is intriguing since an increase in mitochondrial biogenesis has been observed in liver, adipose tissue and in the central nervous system as well as in the cardiovascular system of mice, and skeletal muscle from humans, during dietary restriction(17). Importantly, resveratrol was shown to increase cellular mitochondrial content even in lean mice, which do not show any benefit in terms of longevity(19, 22).

Mitochondrial biogenesis induced by resveratrol treatment likely has important effects in liver (3) and brain (24), and appears to have significant consequences in skeletal muscle, since resveratrol-treated mice exhibit an approximately two-fold increase in endurance (15). Important for the present review, mitochondria also have crucial role in vascular pathophysiology(28). Previous studies show that dysregulation of mitochondrial biogenesis represents an early manifestation of endothelial dysfunction, shifting cell metabolism toward metabolic hypoxia in animals with impaired NO bioavailability(28). In that regard, it is significant that resveratrol treatment induces mitochondrial biogenesis in the vasculature(7).

Multiple mechanisms may explain resveratrol-induced mitochondrial biogenesis and its contribution to cytoprotection and organismal health (Figure). Activation of SIRT1 by resveratrol can promote deacetyation and activation of peroxisome proliferator activator gamma coactivator 1 alpha (PGC-1α), the "master regulator" of mitochondrial biogenesis. Alternatively, other pathways, such as activation of the energy sensor AMP-activated protein kinase (AMPK) may allow PGC-1α to be activated independently of SIRT1, or many mechanisms may act in concert. Impaired mitochondria (e.g. in diabetes and in aging) may alter ATP production, the synthetic and secretory function of cells, cellular redox homeostasis and nuclear gene expression (by changing retrograde signaling pathways). Resveratrol-induced mitochondrial biogenesis would correct this impairment. Furthermore, because mitochondrial proliferation reduces the flow of electrons per unit mitochondria, resveratrol-induced mitochondrial biogenesis may reduce mitochondrial ROS production in the cells. Indeed, resveratrol, at physiologically relevant concentrations, attenuates mitochondrial oxidative stress in endothelial cells(8).

Resveratrol attenuates mitochondrial oxidative stress

The mitochondrial theory of aging postulates that mitochondrial oxidative stress and the consequential free radical reactions underlie aging(32). According to this theory, increased production of ROS results in a variety of macromolecular oxidative modifications with age and the accumulation of such oxidative damage of proteins, lipids and DNA is the primary causal factor in the aging process. Many previous studies lend support to the mitochondrial theory of aging. First, there is clear evidence that aging in mammals is associated with mitochondrial oxidative stress in virtually every tissue studied(10, 11, 30-32). Mitochondrial oxidative stress is also frequently observed in diabetes and the metabolic syndrome and the theory predicts that mitochondria-derived ROS would accelerate aging in these pathological conditions. Second, although the mitochondrial theory is a subject of ongoing debate due to recent findings in genetically manipulated laboratory mice that are inconsistent with it, comparative studies demonstrate that that in evolutionarily distant species an inverse correlation exists between mitochondrial ROS production and species longevity(32). Third, lifespan extension in dietary restriction has been attributed to a marked reduction of mitochondria-derived ROS production. Fourth, while many genetic manipulations designed to perturb oxidative stress have failed to produce the intended effect, targeting of the peroxide scavenging enzyme catalase to mitochondria significantly extended life in mice(32). Thus, there is a continuing interest in identifying novel therapeutic approaches to attenuate mitochondrial oxidative stress in elderly patients.

Since the original observation that resveratrol mimics some of the anti-aging effects of dietary restriction(33) a large body of evidence has accumulated that resveratrol confers multi-faceted anti-oxidant effects in virtually every organism studied. Important for the current overview, recent studies demonstrate that resveratrol attenuates both steady-state and high glucose-induced mitochondrial $O_2^{\cdot -}$ production in various cell types, including primary human coronary arterial endothelial cells(29). This mitochondrial protective effect of resveratrol is, at least in part, attributed to the induction of mitochondrial antioxidant systems by resveratrol (29). The in vitro effects of resveratrol are consistent with the cytoprotective effects of resveratrol treatment in rodent models of aging and diabetes(22, 35). It should be noted that non-mitochondrial sources of ROS also contribute to age-related cellular oxidative stress. In particular, tumor necrosis factor α (TNFα)-mediated up-regulation of cell membrane-associated NAD(P)H oxidases appears to contribute significantly to aging-induced increases in cellular $O_2^{\cdot -}$ levels in the cardiovascular system(28). Importantly, both TNFα and NAD(P)H oxidase activation can induce mitochondrial oxidative stress in endothelial cells. Because resveratrol treatment of aged mice results in significant down-regulation of TNFα and/or NADP(H) oxidases in the

vasculature(22) and the skeletal muscle(25), it is possible that attenuation of non-mitochondria-derived ROS production also contribute to resveratrol-mediated mitochondrial protection. This view is also supported by the findings that activation of NAD(P)H oxidases decreases the bioavailability of NO in aging animals (reviewed recently in(28)), which has been linked to the age-related impairment of mitochondrial biogenesis.

There are multiple mechanisms by which resveratrol-induced reduction of mitochondrial oxidative stress may promote organismal health (Figure). Increased ROS levels in the mitochondria are known to inactivate critical enzymes involved in mitochondrial metabolism (e.g. α-ketoglutarate dehydrogenase and aconitase), which may diminish ATP production. It is also likely that mitochondrial oxidative stress results in direct damage to mitochondrial DNA, which may play a further role in the development of age-related diseases. Resveratrol-induced attenuation of mitochondrial oxidative stress would correct these impairments. Resveratrol was shown to protect cultured cells against senescence-associated changes(13), however, the role of reduced mitochondrial production of ROS in these effects is presently unclear. Mitochondria-derived $O_2^{\cdot -}$ is membrane-impermeable (except in the protonated perhydroxyl radical form, which represents only a small fraction of total $O_2^{\cdot -}$ produced), whereas H_2O_2 easily penetrates the mitochondrial membranes. Mitochondrion-derived H_2O_2 has important signaling functions, such as activation of Nuclear Factor-kappa-B (NF-κB)-dependent inflammatory pathways in aging(31) and metabolic diseases. Thus, resveratrol-induced attenuation of mitochondrial oxidative stress is likely to confer anti-inflammatory effects. Indeed, resveratrol treatment significantly decreases NF-κB -dependent gene expression in aortas of aged mice and mice with type 2 diabetes(22).

Taken together, these observations suggest that protection of mitochondria by resveratrol is likely to contribute to its anti-aging action(3, 26). Similarly, mitochondrial protection can be achieved through feeding a calorie restricted diet, which also induces pathways activated by resveratrol(6) and attenuates mitochondrial ROS production(16).

Role of SIRT1 activation in mitochondrial protection

Previous studies demonstrated that SIRT1-dependent pathways and NO-dependent mechanisms contribute to the beneficial mitochondrial and cellular effects of dietary restriction(6, 21). Many of the effects that have been observed in resveratrol-treated animals are consistent with the modulation of SIRT1 targets, particularly the transcriptional coactivator peroxisome proliferator activator gamma coactivator 1 alpha (PGC-1α, Figure) (3, 15). SIRT1 likely regulates multiple pathways involved in mitochondrial biogenesis, among which pathways regulated by endothelium-derived NO appear to play a key role(7). Resveratrol is thought to increase NO production by up-regulating eNOS at the level of transcription(22). In addition, previous studies suggest that SIRT1 may directly deacetylate and activate eNOS in endothelial cells.

These findings may be seen as support for the originally proposed mechanism that resveratrol functions as a direct activator of SIRT1. However, resveratrol is known to produce a wide array of effects in mammalian cells, including activation of AMP-activated protein kinase (AMPK), an energy sensor that is involved in some of the same pathways as SIRT1 and phosphorylates PGC-1α directly (3, 34). Although SIRT1 can activate the kinase upstream of AMPK, this pathway does not appear to be necessary for AMPK stimulation by resveratrol (9), and in fact, there is some evidence to suggest that SIRT1 might be downstream of AMPK under some cirumstances (5, 12). In a similar situation, although SIRT1 can activate eNOS, there is evidence that SIRT1 induction is also a downstream

effect of NO production(21). Therefore, it will be important to carefully test the role of SIRT1 in the physiological changes induced by resveratrol.

Role of Nrf2 activation in mitochondrial protection

There is increasing evidence that activation of NF-E2-related factor 2 (Nrf2) is an important mechanism by which resveratrol confers cytoprotective effects(27). Nrf2 is a basic leucine zipper transcription factor that regulates the coordinated expression of key antioxidant mechanisms in the cell by binding to the antioxidant response (ARE) elements in the promoter regions of target genes (e.g. NAD(P)H:quinone oxidoreductase 1, heme oxygenase-1, enzymes involved in regulation of glutathione synthesis), which regulate mitochondrial and cellular levels of ROS (Figure). Activation of Nrf2-dependent pathways have been shown to promote cardiovascular health and neurocognitive function in rodent models of aging and diabetes. Furthermore, Nrf2 was shown to mediate cancer protection but not increased longevity induced by caloric restriction in mice(23). Because Nrf2-driven pathways can be activated by concentrations of resveratrol readily achievable *in vivo*, future studies should elucidate whether Nrf2 activation contributes to the mitochondrial protective effects of resveratrol in aging and in pathophysiological conditions associated with mitochondrial dysfunction. Recent evidence obtained using Nrf2-/- mice lend support to the hypothesis that Nrf2 activation plays an important role in the vasoprotective action of resveratrol under diabetic conditions(27), but the role of mitochondria in the observed effects remain to be elucidated. Further, induction of the Nrf2 target heme oxygenase-1 (HO-1_ has also been implicated in the cardioprotective effects of resveratrol under conditions of experimentally-induced ischemia, which is known to be associated with mitochondrial oxidative stress and cellular energetic imbalance. Future studies should test the possibility that SIRT1 may modulate Nrf2-driven cellular responses and studies are also warranted to determine whether Nrf2-dependent pathways regulate SIRT1 at the level of transcription.

Conclusions

Although significant progress has been achieved in elucidating the cellular mechanisms activated by resveratrol, the specific roles for pathways regulating mitochondrial function, mitochondrial antioxidant defenses and mechanisms involved in mitochondrial biogenesis require further study. There is a reasonable consensus that in rodents mitochondrial oxidative stress and activation of redox-sensitive pro-inflammatory pathways (e.g. NF-κB) play a central role in the development of many age-related diseases, which may be prevented or reversed by resveratrol treatment. Research efforts should be focused on fully elucidating the links between mitochondrial effects of resveratrol and its cardiac-, cerebrovascular- and neuroprotective action in aging. Furthermore, it is unknown whether administration of resveratrol would affect mitochondrial function in primates. Thus, future studies should determine whether mitochondrial protective effects of resveratrol are manifested in primate models of aging and metabolic diseases. Moreover, clinical studies with resveratrol in the elderly should be encouraged. Because resveratrol is relatively enriched in red wine, it is often speculated that resveratrol explains some of the protective effects of wine consumption in humans, however the doses used to study resveratrol in rodents are typically orders of magnitude higher than what could be obtained from reasonable consumption of wine. Thus, clear guidelines for the effective dose and formulation of resveratrol for human studies should be established. Given the dramatic protection against age-related diseases that is afforded by dietary restriction, every effort should be made to identify and understand compounds like resveratrol that appear to be able to mimic some of its effects on mitochondria and antioxidant defense mechanisms.

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References

1. Barger JL, Kayo T, Vann JM, et al. A low dose of dietary resveratrol partially mimics caloric restriction and retards aging parameters in mice. PLoS ONE. 2008; 3:e2264. [PubMed: 18523577]
2. Bass TM, Weinkove D, Houthoofd K, Gems D, Partridge L. Effects of resveratrol on lifespan in Drosophila melanogaster and Caenorhabditis elegans. Mech Ageing Dev. 2007; 128:546–552. [PubMed: 17875315]
3. Baur JA, Pearson KJ, Price NL, et al. Resveratrol improves health and survival of mice on a high-calorie diet. Nature. 2006; 444:337–342. [PubMed: 17086191]
4. Baur JA, Sinclair DA. Therapeutic potential of resveratrol: the in vivo evidence. Nat Rev Drug Discov. 2006; 5:493–506. [PubMed: 16732220]
5. Canto C, Jiang LQ, Deshmukh AS, et al. Interdependence of AMPK and SIRT1 for metabolic adaptation to fasting and exercise in skeletal muscle. Cell Metab. 2010; 11:213–219. [PubMed: 20197054]
6. Cohen HY, Miller C, Bitterman KJ, et al. Calorie restriction promotes mammalian cell survival by inducing the SIRT1 deacetylase. Science. 2004; 305:390–392. [PubMed: 15205477]
7. Csiszar A, Labinskyy N, Pinto JT, et al. Resveratrol induces mitochondrial biogenesis in endothelial cells. Am J Physiol Heart Circ Physiol. 2009; 297:H13–20. [PubMed: 19429820]
8. Csiszar A, Labinskyy N, Podlutsky A, et al. Vasoprotective effects of resveratrol and SIRT1: attenuation of cigarette smoke-induced oxidative stress and proinflammatory phenotypic alterations. Am J Physiol Heart Circ Physiol. 2008; 294:H2721–2735. [PubMed: 18424637]
9. Dasgupta B, Milbrandt J. Resveratrol stimulates AMP kinase activity in neurons. Proc Natl Acad Sci U S A. 2007; 104:7217–7222. [PubMed: 17438283]
10. Figueiredo PA, Ferreira RM, Appell HJ, Duarte JA. Age-induced morphological, biochemical, and functional alterations in isolated mitochondria from murine skeletal muscle. J Gerontol A Biol Sci Med Sci. 2008; 63:350–359. [PubMed: 18426958]
11. Figueiredo PA, Powers SK, Ferreira RM, Appell HJ, Duarte JA. Aging impairs skeletal muscle mitochondrial bioenergetic function. J Gerontol A Biol Sci Med Sci. 2009; 64:21–33. [PubMed: 19196905]
12. Fulco M, Cen Y, Zhao P, et al. Glucose restriction inhibits skeletal myoblast differentiation by activating SIRT1 through AMPK-mediated regulation of Nampt. Dev Cell. 2008; 14:661–673. [PubMed: 18477450]
13. Giovannelli L, Pitozzi V, Jacomelli M, et al. Protective Effects of Resveratrol Against Senescence-Associated Changes in Cultured Human Fibroblasts. J Gerontol A Biol Sci Med Sci. 2011; 66:9–18. [PubMed: 20884849]
14. Howitz KT, Bitterman KJ, Cohen HY, et al. Small molecule activators of sirtuins extend Saccharomyces cerevisiae lifespan. Nature. 2003; 425:191–196. [PubMed: 12939617]
15. Lagouge M, Argmann C, Gerhart-Hines Z, et al. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. Cell. 2006; 127:1109–1122. [PubMed: 17112576]
16. Lopez-Lluch G, Hunt N, Jones B, et al. Calorie restriction induces mitochondrial biogenesis and bioenergetic efficiency. Proceedings of the National Academy of Sciences of the United States of America. 2006; 103:1768–1773. [PubMed: 16446459]
17. Lopez-Lluch G, Irusta PM, Navas P, de Cabo R. Mitochondrial biogenesis and healthy aging. Exp Gerontol. 2008; 43:813–819. [PubMed: 18662766]

18. Mayers JR, Iliff BW, Swoap SJ. Resveratrol treatment in mice does not elicit the bradycardia and hypothermia associated with calorie restriction. FASEB J. 2009; 23:1032–1040. [PubMed: 19056839]
19. Miller RA, Harrison DE, Astle CM, et al. Rapamycin, But Not Resveratrol or Simvastatin, Extends Life Span of Genetically Heterogeneous Mice. J Gerontol A Biol Sci Med Sci. 2011; 66:191–201. [PubMed: 20974732]
20. Minor RK, Allard JS, Younts CM, Ward TM, de Cabo R. Dietary interventions to extend life span and health span based on calorie restriction. J Gerontol A Biol Sci Med Sci. 2010; 65:695–703. [PubMed: 20371545]
21. Nisoli E, Tonello C, Cardile A, et al. Calorie restriction promotes mitochondrial biogenesis by inducing the expression of eNOS. Science. 2005; 310:314–317. [PubMed: 16224023]
22. Pearson KJ, Baur JA, Lewis KN, et al. Resveratrol Delays Age-Related Deterioration and Mimics Transcriptional Aspects of Dietary Restriction without Extending Life Span. Cell Metab. 2008; 8:157–168. [PubMed: 18599363]
23. Pearson KJ, Lewis KN, Price NL, et al. Nrf2 mediates cancer protection but not prolongevity induced by caloric restriction. Proc Natl Acad Sci U S A. 2008; 105:2325–2330. [PubMed: 18287083]
24. Robb EL, Winkelmolen L, Visanji N, Brotchie J, Stuart JA. Dietary resveratrol administration increases MnSOD expression and activity in mouse brain. Biochem Biophys Res Commun. 2008; 372:254–259. [PubMed: 18486604]
25. Ryan MJ, Jackson JR, Hao Y, et al. Suppression of oxidative stress by resveratrol after isometric contractions in gastrocnemius muscles of aged mice. J Gerontol A Biol Sci Med Sci. 2010; 65:815–831. [PubMed: 20507922]
26. Smith JJ, Kenney RD, Gagne DJ, et al. Small molecule activators of SIRT1 replicate signaling pathways triggered by calorie restriction in vivo. BMC Syst Biol. 2009; 3:31. [PubMed: 19284563]
27. Ungvari Z, Bagi Z, Feher A, et al. Resveratrol confers endothelial protection via activation of the antioxidant transcription factor Nrf2. Am J Physiol Heart Circ Physiol. 2010; 299:H18–24. [PubMed: 20418481]
28. Ungvari Z, Kaley G, de Cabo R, Sonntag WE, Csiszar A. Mechanisms of vascular aging: new perspectives. J Gerontol A Biol Sci Med Sci. 2010; 65:1028–1041. [PubMed: 20576649]
29. Ungvari Z, Labinskyy N, Mukhopadhyay P, et al. Resveratrol attenuates mitochondrial oxidative stress in coronary arterial endothelial cells. Am J Physiol Heart Circ Physiol. 2009; 297:H1876–1881. [PubMed: 19749157]
30. Ungvari ZI, Labinskyy N, Gupte SA, Chander PN, Edwards JG, Csiszar A. Dysregulation of mitochondrial biogenesis in vascular endothelial and smooth muscle cells of aged rats. Am J Physiol Heart Circ Physiol. 2008; 294:H2121–2128. [PubMed: 18326800]
31. Ungvari ZI, Orosz Z, Labinskyy N, et al. Increased mitochondrial H2O2 production promotes endothelial NF-kB activation in aged rat arteries. Am J Physiol Heart Circ Physiol. 2007; 293:H37–47. [PubMed: 17416599]
32. Van Remmen H, Jones DP. Current thoughts on the role of mitochondria and free radicals in the biology of aging. J Gerontol A Biol Sci Med Sci. 2009; 64:171–174. [PubMed: 19181714]
33. Wood JG, Rogina B, Lavu S, et al. Sirtuin activators mimic caloric restriction and delay ageing in metazoans. Nature. 2004; 430:686–689. [PubMed: 15254550]
34. Zang M, Xu S, Maitland-Toolan KA, et al. Polyphenols stimulate AMP-activated protein kinase, lower lipids, and inhibit accelerated atherosclerosis in diabetic LDL receptor-deficient mice. Diabetes. 2006; 55:2180–2191. [PubMed: 16873680]
35. Zhang H, Morgan B, Potter BJ, et al. Resveratrol Improves Left Ventricular Diastolic Relaxation in Type 2 Diabetes by Inhibiting Oxidative/Nitrative Stress. Am J Physiol Heart Circ Physiol. 2010; 299:H985–94. [PubMed: 20675566]

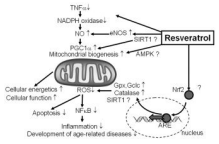

Figure.

Proposed mechanism by which resveratrol confers mitochondrial protection in aging. During aging a decline in mitochondrial mass and mitochondrial dysfunction impairs cellular energetics and increases mitochondria-derived reactive oxygen species (ROS) production promoting inflammatory processes (including NF-κB activation) and cell death. These changes lead to an age-related functional decline of multiple organ systems and the development of various age-related diseases (including cardiovascular disease, neurocognitive decline and sarcopenia). The model predicts that resveratrol, by activating SIRT1 and/or AMPK, up-regulates Nrf2-driven antioxidant enzymes and eNOS, and down-regulates TNFα-activated NADPH oxidases (which are a major extramitochondrial source of ROS). By reducing oxidative stress resveratrol increases the bioavailability of nitric oxide (NO), promoting activation of PGC1α, which confers mitochondrial protection and increase mitochondrial biogenesis. The formation of youthful mitochondria and the decline in mitochondrial ROS production significantly attenuate cellular oxidative stress and inflammation, restore cellular energetics and limit cell death, all of which act to prevent the development of age-related disease. We posit that resveratrol exerts similar mitochondrial protective effects in aging and in metabolic diseases. ARE: antioxidant response element