Endothelial Nrf2 activation: a new target for resveratrol?

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ACCUMULATING EVIDENCE SUGGESTS that Mediterranean diets rich in plant-derived polyphenols may be one of the factors responsible for the lower incidence of coronary heart disease among Mediterranean populations (16, 21). Resveratrol (3,4',5-trihydroxystilbene), a plant-derived polyphenolic compound belonging to a class of stilbenes (abundantly found in some roots, grapes, berries, peanuts, etc.) received rekindled scientific attention following its identification in red wine almost two decades ago (29). It has been speculated that resveratrol might be the red wine constituent to provide an explanation for the phenomenon known as the “French paradox” (French people suffer a relatively low incidence of coronary heart disease presumably because of the consumption of red wine) (14). Reports on the potential for resveratrol to extend life span in cell culture and in lower model organisms (18, 39, 41) and to inhibit the development of cancer (19) have continued to generate tremendous interest to further investigate the mechanisms and/or the potential therapeutic benefits of this natural compound both in vitro as well as in different preclinical disease models (4, 15). Resveratrol attenuated myocardial ischemic-reperfusion injury and atherosclerosis (14) as well as was shown to confer vasoprotection in rodent models of metabolic diseases (26, 28, 32, 34, 43) and in aged mice without extending life span (26, 37). The available evidence has suggested that it can mimic, at least in part, the antiaging effects of caloric restriction in rodents (2, 3, 30).

Despite the growing evidence that resveratrol confers cardiac and vascular protective effects in preclinical disease models, the precise molecular and cellular mechanisms of its action remain elusive. From the recent literature the view emerges that resveratrol elicits complex cellular responses by promoting cell survival, maintaining cellular energetics, and attenuating proinflammatory phenotypic changes induced by oxidative stressors.

In this issue of the American Journal of Physiology-Heart and Circulatory Physiology, Ungvari et al. (35) provide evidence that the activation of NF-κB-related factor-2 (Nrf2) is an important mechanism by which resveratrol exerts its beneficial effects in the vascular endothelium. Nrf2 is a transcription factor that regulates coordinated antioxidant responses in cells, and its activation is therefore capable of protecting in a wide variety of animal models of oxidative stress-related injury and inflammatory disease (22). Ungvari et al. (35) demonstrate that in cultured human coronary arterial endothelial cells, resveratrol increases the transcriptional activity of Nrf2, which is associated with the upregulation of several Nrf2 target genes such as NAD(P)H:quinone oxidoreductase 1, γ-glutamylcysteine synthetase, and heme oxygenase-1. Many of these Nrf2 targets [e.g., NAD(P)H:quinone oxidoreductase 1 and heme oxygenase-1] have been implicated in promoting endothelial health under conditions of metabolic stress (37). Indeed, resveratrol treatment was shown to attenuate mitochondrial and cellular oxidative stress induced by hyperglycemia in endothelial cells in vitro, and these effects were significantly reversed by the small interfering RNA-mediated knockdown of Nrf2 or by the overexpression of the protein that inactivates Nrf2 (Kelch-like erythroid cell-derived protein 1) (35). Importantly, the in vivo relevance of resveratrol-induced Nrf2 activation was supported by using Nrf2 knockout mice fed on a high-fat diet, in which the endothelial protective effects of resveratrol were largely diminished compared with those of their wild-type littermates fed on the same diet.

Recent studies provide compelling evidence that resveratrol treatment can improve endothelial function in rodents models of type 2 diabetes (26, 36, 44), as well as in aged mice and rats (26, 37), by attenuating reactive oxygen/nitrogen species generation and vascular inflammation and by decreasing endothelial apoptosis. Since resveratrol can activate Nrf2-driven pathways at concentrations that were likely achieved in these rodent models, one can envision that Nrf2 activation may also contribute to the vasoprotective effects of resveratrol observed in diabetic and aging animals. As mentioned above, resveratrol can mimic some of the molecular events characteristic of caloric restriction (30, 38), which can also induce Nrf2 activation in rodents (27).

There are most likely multiple synergistic effects of resveratrol that are responsible for its vasoprotective potential (Fig. 1). These may include an upregulation of endothelial nitric oxide synthase causing an increased nitric oxide bioavailability (5, 33, 44), a promotion of mitochondrial biogenesis (8), an inhibition of NF-κB (9, 10, 42), a downregulation of TNF-α, an inhibition of NADPH oxidases (44), and a proliferation of vascular smooth muscle cells (7, 40), an attenuation of mitochondrial reactive oxygen species generation (36), and an inhibition of platelet aggregation (31).

Because vascular oxidative-nitrosative stress, endothelial activation, and an increased rate of endothelial cell death are hallmarks of cardiovascular aging and are known to be involved in the pathophysiology of multiple diabetic complications (1, 11–13, 20, 23, 24), it is desirable to develop pharmacological treatment approaches that can simultaneously target several of these pathophysiological processes. Another potential interesting, but much more risky, avenue (in terms of unexpected side effects) is the targeting of master regulators of cellular programs such as Nrf2. Nevertheless, based on the results of the preclinical studies discussed above, together with the absence of the significant adverse effects of resveratrol in humans (4), resveratrol may offer a safe way to pharmacologically target several simultaneous pathways involved in the
development of cardiovascular diseases in high-risk patients. However, to achieve this goal, the poor oral absorption and bioavailability of resveratrol in humans should be resolved by the optimization of formulation and delivery, and the promising animal data should be confirmed in controlled human trials.

Until very recently, it was widely held that resveratrol is a direct activator of the silent information regulator 2/sirtuin 1 (SIRT1) pathway that was proposed to be the major effector for many of the biological actions of resveratrol (4). SIRT1 and other sirtuins catalyze NAD+-dependent protein deacetylation and are critical regulators of transcription, apoptosis, and metabolism (17). Even though recent studies using cell-free assays question that resveratrol activates SIRT1 directly (25), it is very likely that resveratrol (or its metabolites) in vivo or ex vivo can promote SIRT1 activation. Importantly, the overexpression of SIRT1 can mimic many of the effects of resveratrol in endothelial cells (36), whereas the depletion of SIRT1 tends to attenuate resveratrol-induced cellular effects (6–9). On the basis of the available evidence, it is possible that SIRT1 acts as a permissive factor, modulating Nrf2-driven responses in the vasculature. Further studies are also warranted to test the possibility that the expression of SIRT1 is regulated by Nrf2 and that downstream pathways regulated by SIRT1 and Nrf2 might act synergistically.

Collectively, the present study of Ungvari et al. (35) describes some exciting novel findings that contribute to our understanding of the multifaceted cardiovascular protective effects of resveratrol treatment in mammals, and it also raises new questions on the possibility of the interaction between Nrf2 and SIRT1, which remains to be seen in upcoming studies.

**REFERENCES**

Editorial Focus

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