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A toast to your health, one drink at a time[1–3]

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Red wine gained considerable interest when it was postulated to confer protective effects against cardiovascular diseases—the so-called French paradox. The subsequent discovery that resveratrol was found in red wine led to an exponential growth of publications on the cardioprotective effects of resveratrol. Since then, increasing evidence indicates that resveratrol exerts a plethora of biological activities against chronic illnesses, including cancer, neurodegeneration, type 2 diabetes, and ischemic injuries (1). Resveratrol has a myriad of targets and physiologic effects, in particular in the cardiovascular system. A number of studies have shown that resveratrol was effective in suppressing plaque development in various animal models, lowered LDL oxidation, regulated vascular smooth muscle proliferation, and modulated nitric oxide (NO) production and platelet aggregation. Resveratrol both in vivo and in vitro has antiinflammatory effects that contribute to its cardioprotective effects. Resveratrol can act as an antioxidant and induces various antioxidant enzymes in vascular and cardiac cells (2), which result in a marked attenuation of oxidative stress. Resveratrol was shown to be a potent inhibitor of mitochondrial reactive oxygen species (ROS) in the vasculature (3). It is known that impaired NO bioavailability leads to dysregulation of mitochondrial biogenesis in the vasculature (4, 5), inducing oxidative stress and endothelial dysfunction during aging and metabolic diseases, and resveratrol is able to counteract these effects by up-regulating endothelial NO synthase (eNOS) and increasing NO bioavailability (6–8). It is clear from the literature that resveratrol activates many cytoprotective signaling pathways to combat or prevent cardiovascular disease. These include vasorelaxation, antiinflammatory response, ROS scavenging, and pharmacologic preconditioning effects as well as inhibition of platelet aggregation and favorable actions on lipid profiles. In this issue of the Journal, Fischer-Posovszky et al (9) and Hamed et al (10) have contributed further to our knowledge on the therapeutic effects of resveratrol (and thereby red wine) against both obesity-associated comorbidities and cardiovascular disease using both in vitro and in vivo approaches.

First, Fischer-Posovszky et al (9) examined the effects of resveratrol on fat cell biology and set out to elucidate whether sirtuin 1 [silent mating type information regulation 2 homolog 1 (Sirt1)] is involved in these resveratrol-mediated changes. Adipocytes are important mediators in physiologic and pathologic processes regarding energy metabolism. Adipocyte proliferation and differentiation are highly controlled processes that exert pleiotropic, including endocrine, functions. Dysregulation of adipocyte proliferation and differentiation can cause obesity, cardiovascular disease, and type 2 diabetes. They show that resveratrol influences adipose tissue mass by the inhibition of preadipocyte proliferation and adipogenic differentiation and that knockdown of Sirt1 by small interfering RNA prevented the effects of resveratrol. Another interesting aspect of this study is that in human adipocytes resveratrol stimulated glucose uptake and concurrently inhibited de novo lipogenesis. Furthermore, resveratrol influenced the secretion of adipokines in a partially Sirt1-dependent manner. Overall, these results indicate that resveratrol in a Sirt1-dependent manner influences adipose tissue mass and function in a way that might positively interfere with the development of obesity-related endocrine and metabolic adverse effects.

Second, Hamed et al (10) studied the effect of moderate red wine consumption on endothelial progenitor cell (EPC) migration and the underlying mechanisms of red wine–induced effects on EPC functional activity in healthy young subjects. They report that moderate consumption of red wine (250 mL red wine daily for 21 consecutive days) was associated with an improvement on vascular endothelial function. They show that red wine may confer vascular protection by activating the expression levels of several members of the Pi3K/Akt/eNOS (phosphatidylinositol 3-kinase/protein kinase B/endothelial nitric oxide synthase) signaling pathway in endothelial cells. Taken together, these findings suggest that moderate wine consumption provides cardiovascular protection. However, these findings raise further questions about whether red wine, resveratrol, can reverse or attenuate established cardiovascular disease. A beneficial effect in human clinical trials with cardiovascular disease will be essential to substantiate these findings.

Both studies provide new insights into the mechanisms underlying the potential benefits of resveratrol in metabolic disease. From these studies it is clear that resveratrol acts both indirectly (through adipose tissue) and directly (through endothelial cells) to prevent cardiovascular disease. There are a few questions that remain unsolved, namely, *1*) Does resveratrol act directly or does it resemble an endogenous signaling molecule? and *2*) Are some of resveratrol's metabolites bioactive molecules in their own right?

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Despite these and other lingering questions, the potential effect of resveratrol in preventive medicine and treatment of metabolic diseases cannot be overlooked. There is a need to conduct well-controlled, long-term clinical studies to determine the potential use of this molecule in preventive and therapeutic interventions for metabolic disorders.

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