Aging leads to a progressive decline in multiple organ systems, including the heart. Heart failure in response to cellular aging and chronic or acute cellular stresses represents one of the major burdens of the western civilization. Over the last 15 years, the interest in the therapeutic use of caloric restriction to prevent aging has emerged. However, it is difficult to determine whether caloric restriction influences longevity in humans because no validated biomarker exists, which can serve as a surrogate marker of aging and it is impossible to conduct a randomized, diet-controlled long-term survival study in humans. Nevertheless, caloric restriction has been shown in several studies to lower fasting plasma glucose concentration and serum low-density lipoprotein cholesterol, to decrease insulin resistance, visceral fat mass and the levels of inflammatory markers. Most of these markers are known to be risk factors for coronary heart disease. Thus, even it is not known whether caloric restriction does prolong maximum life-span, it could increase life expectancy and the quality of late life by reducing the burden of chronic diseases. However, the precise biological and cellular mechanisms responsible for aging and the antiaging effects of caloric restriction are not known. Moreover, even if caloric restriction would result in an increase in maximum life span in humans, it will be difficult to maintain long-term caloric restriction in modern society. Therefore, one major interest is to develop caloric restriction mimetics to provide all of the “healthy” physiological, metabolic and hormonal effects of caloric restriction without the need to reduce food intake. Based on these ideas, it has been proposed, that resveratrol increases lifespan in several different organisms, mimicking the effects of caloric restriction. Recent reports indicate, that resveratrol can even restore the health and lifespan of mice on a high calorie diet to levels seen in mice on a normal diet, rising the hope of “guilt-free gluttony” when adding resveratrol as a dietary supplement. How does resveratrol induce these caloric restriction-like effects on the molecular level? An in vitro screen for activators of the sirtuin/Sirt2 family of NAD-dependent deacetylases identified resveratrol as the most potent of 18 inducers of Sir2 deacetylase activity. Subsequent work has shown that resveratrol extends the lifespans of S. cerevisiae, Caenorhabditis elegans and Drosophila melanogaster, but only if the gene that encodes Sir2 is present in these organisms, providing further evidence that the observed effects of resveratrol are because of an activation of Sir2.

Sirtuins are a conserved family of NAD$\textsuperscript{+}$-dependent deacetylases (class III histone deacetylases) that were named after the founding member, the Saccharomyces cerevisiae silent information regulator 2 (Sir2) protein. In yeast, worms and flies, overexpression of the genes that encode sirtuins are reported to extend lifespan, suggesting that sirtuins are evolutionarily conserved mediators of longevity. Moreover, sirtuins are suggested to play a role in lifespan extension induced by dietary restriction. Of the seven mammalian sirtuins (Sirt1–7), Sirt1 is the closest homologue to Sir2, based on amino acid identity. Inbred knockout mice that lack Sirt1 show developmental defects, have a low survival rate and have a significantly shorter lifespan compared with wild-type mice. Therefore, the main function of sirtuin proteins might be to promote survival and stress resistance, resulting in longevity. It is supposed that an evolutionary advantage arising from the ability to modify lifespan in response to environmental stress might have allowed these enzymes to be conserved as species evolved, and to take on new functions in response to new environmental demands. This could explain why sirtuins have dramatic effects on lifespan in diverse organisms with apparently dissimilar causes of aging. Given the robust expression of sirtuins in human tissues and the evolutionary conserved function in model organisms and mammals, the hope arises that sirtuins may also function as modulators of stress response and aging in humans and thus may represent an interesting target for future preventive or therapeutic strategies. Thus, the data from lower organisms has provoked intense research into the function of sirtuin proteins in mammalian systems.

In this context, Alcendor et al report in this issue of Circulation Research on the expression of the longevity factor Sirt1 (Sir2α) and its potential role as an endogenous inhibitor of aging and oxidative stress induced by paraquat in vivo. The idea that Sirt1 could play a role in myocardial protection is not entirely new, because in a previous article, Alcendor et al reported that Sirt1 is an essential endogenous apoptosis inhibitor in isolated cardiac myocytes. Moreover, resveratrol has been shown to prevent Ang II-induced cardiomyocyte hypertrophy and myocardial ischemia/reperfusion injury. However, it is not clear whether resveratrol exerted its favorable actions of myocardial protection indeed via the activation of Sirt1 and how Sirt1 is involved in cardiac aging and stress response. Thus, the data now presented by Alcendor et al are groundbreaking because they provide for the first time compelling evidence for Sirt1’s cardioprotective potential in vivo.
The authors describe here that Sirt1 is protective at levels of 2.5 to 7.5-fold overexpression. However, a further increase in protein levels (12.5-fold overexpression) augmented oxidative stress and cardiomyocyte damage. So why exerts Sirt1 deleterious effects at higher expression levels? One explanation for this could be a side effect of NAD⁺ consumption by high levels of Sirt1. Because NAD⁺ is required for mitochondrial respiration, depletion of NAD⁺ could lead to deficiency in ATP, resulting in cellular dysfunction and cell death.

The presented data further indicate that Sirt1 is already upregulated 3 to 9-fold in response to stresses, suggesting that the cell upregulates Sirt1 under situations of cellular stress to almost optimal levels itself. Thus, extreme caution will be necessary when inducing Sirt1 expression in novel therapeutic approaches. Because there exist no data on the overall Sirt1 activity in the stressed or failing heart or following overexpression, further investigations will have to clarify, whether or not the activation of endogenous Sirt1 might be an alternative to inducing Sirt1 protein expression.

Given the available data and the several different pathways known for Sirt1 (see Figure 1) some further key questions remain: Is the observed cardioprotection a rather general effect of an anti-aging mechanism induced by Sirt1 or a specific molecular effect of Sirt1 itself, and, if so, how does Sir2 mediate cardiomyocyte protection? In their previous work, Alcendor et al reported that Sir2 inhibition increases acetylation of p53, stimulates its transcriptional activity and results in cell death. Moreover, overexpression of a dominant negative p53 mutant rescued the cells from death induced by inhibition of Sirt1, indicating that the protective effects of Sirt1 are because of its inhibitory effect on p53. Additionally, Alcendor et al now demonstrate that the favorable effects of Sirt1 overexpression in vivo are in part because of an upregulation of catalase which prevents oxidative stress-induced cardiomyocyte damage. The upregulation of catalase seems to be because of a transcriptional activation of FoxO1a, because overexpression of a dominant negative form of FoxO1a prevents the Sirt1-induced catalase expression. Indeed, Sirt1 was previously reported to stimulate catalase expression and resistance to oxidative stress via FoxO1a in fibroblasts. By because FoxOs are simply inactivated by phosphorylation, deacetylation by Sirt1 seems to differentially modulate the activation/repression of numerous FoxO target genes thereby changing the FoxO-dependent transcriptome to the expression of merely cytoprotective- and stress resistance genes while preventing the transactivation of apoptosis promoting genes (see Figure 2). Besides the assumption that inactivation of p53 might be involved in the cardioprotection seen in Sirt1 transgenic mice too, further studies will be necessary to clearly characterize the effect of Sirt1 on its numerous downstream targets and their contribution to cardiomyocyte protection.

Despite the excitement on the dramatic cardioprotective effects, we have to face that overexpression of Sirt1 in the heart alone seems not to be sufficient to induce lifespan extension in mice. Besides the various other organ systems, the functional integrity of the vasculature largely accounts for aging related disease and death and is essential for cardiac function. Therefore, determining the role of Sirt1 in the development, homeostasis and pathophysiology of the vasculature might be of great interest to understand and eventually modulate Sirt1-dependent longevity.

In summary, the study of Alcendor et al describes some exciting novel findings that, as any good study, answer 1 and raise a bunch of new questions. Most importantly, we will have to wait for upcoming studies in different mouse strains, higher mammals and humans before we can start thinking on how to reengineer our longevity and Surviving programs.

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References


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