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Sirtuins in Cardiovascular Health and Diseases

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Aging is the common cause for multiple diseases, including cardiovascular disease (CVD), which is the leading cause of death worldwide. The desire of humans to prolong life dates back centuries. In the ancient Qin Dynasty, Emperor Qin (*circa* 219 BC) sent troops to search for the elixir of life to extend his life, but in vain. In medical sciences, researchers have been actively searching for strategies to impede the aging process and extend human lifespan. Sirtuins (SIRT1–SIRT7) are NAD^+-dependent class III histone deacetylases, with distinct tissue distribution and cellular functions [1]. Mounting studies in yeasts, rodents, and primates suggest sirtuins are potential targets in extending human lifespan and improving multiple pathophysiologies [1]. Therapeutically, sirtuin-activating compounds (STAC, such as resveratrol, SRT3025, etc.) are showing promise in preclinical studies and various phases of clinical trials [2,3].

The relationship between sirtuins and the cardiovascular system has been extensively investigated in recent years [2]. Bindu *et al*. [4] comprehensively reviewed our current knowledge on the role of sirtuins in cardiac pathophysiology in a recent issue of *Trends in Endocrinology and Metabolism*. Specifically, this review provides an update on the role of seven individual members of the sirtuin family in heart diseases, focusing on cardiac hypertrophy, heart failure, ischemia/reperfusion injury and cardiomyopathy. This timely review, together with another recent excellent review [2], indicates that sirtuins are potential targets for treating CVD. SIRT1 and SIRT3 are two well-characterized cardioprotective isoforms, with unifying protective functions but varying substrates in the heart [2]. However, a recent study by Luo *et al*. [5] has shown that SIRT4, a mitochondria-localized sirtuin, aggravates pathological cardiac hypertrophy by inhibiting mitochondrial antioxidant manganese superoxide dismutase (MnSOD) binding to SIRT3 and increasing the generation of reactive oxygen species (ROS). This finding, together with a recent study [6] showing that SIRT7 depletion in smooth muscle cells (SMCs) and endothelial cells (ECs) inhibit the proliferation and migration of SMCs and ECs, reinforces the idea that some sirtuin isoforms

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may have unfavorable roles in cardiovascular biology and diseases, in contrast to the well-characterized cardiovasculoprotective action of SIRT1. Both reports also remind us that the cytoprotective and antihypertrophic effects cannot be generalized among all sirtuins. Noticeably, in 2012, Sundaresan *et al.* [7] reported a decrease in SIRT6 expression in human patients with heart failure. By gain- and loss-of-function studies in mice, the authors showed that SIRT6 exerts cardioprotection by targeting c-jun. Another research group [8] reported that cardiomyocytes from SIRT6 transgenic mice are less susceptible to hypoxic stress, compared with those from wild-type (WT) mice. However, the role of endogenous SIRT6 in myocardial ischemia/reperfusion injury *in vivo* remains largely unknown. More recently, Wang *et al.* [9] have reported that SIRT6 haploinsufficency in mice decreased myocardial functional recovery and aggravated ischemia/reperfusion injury, resembling the phenotype of SIRT3 deficiency. Mechanistic studies suggest that SIRT6 increases the AMP/ATP ratio, thereby activating the AMPK/FOXO3a axis to upregulate expression of antioxidant defense genes (including MnSOD and catalase) [9]. This mechanism suggests that SIRT6 restrains myocardial ROS generation under stressed conditions.

Emerging evidence has shown that sirtuins are also implicated in the development of various forms of vascular diseases [2], including atherosclerosis, aortic stenosis, and calcification, which are major causes of heart diseases. However, these aspects were not discussed in this review. In this regard, SIRT1 is well characterized as an atheroprotective gene in general, while the role of other sirtuins, especially SIRT6, is increasingly being recognized only recently [10–12]. In particular, we and others have recently demonstrated that SIRT6 maintains vascular hemostasis and limits atherosclerosis [10–12]. The role of other SIRT isoforms in regulating vascular diseases warrants further studies.

Taken together, the excellent review by Bindu *et al.* [4] highlights the critical role and clinical significance of sirtuins in heart disease, which may translate to cardiac therapeutics. However, we are still facing many questions with uncertain answers. Given the distinct role of individual sirtuins in regulating CVD, isoform-specific sirtuin-activating/inhibiting compounds need to be developed for therapeutic purposes. Transcriptional targets of different sirtuins are often cell-type- and context-specific, so the potential function of individual sirtuin isoforms in cardiac and vascular diseases deserves further investigation using isoform- and tissue-specific knockout animal models. Furthermore, understanding the molecular mechanism of sirtuins in CVD will provide important insight into the intriguing possibility that they can be therapeutically targeted. These considerations are critical for STAC-based therapeutic strategies.

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