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Sirtuins, aging, and cardiovascular risks

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Abstract The sirtuins comprise a highly conserved family proteins present in virtually all species from bacteria to mammals. Sirtuins are members of the highly conserved class III histone deacetylases, and seven sirtuin genes (sirtuins 1–7) have been identified and characterized in mammals. Sirtuin activity is linked to metabolic control, apoptosis, cell survival, development, inflammation, and healthy aging. In this review, we summarize and discuss the potential mutual relations between each sirtuin and cardiovascular health and the impact of sirtuins on oxidative stress and so age-related cardiovascular disorders, underlining the possibility that sirtuins will be novel targets to contrast cardiovascular risks induced by aging.

Keywords Aging · Cardiovascular risk · Heart · Sirtuins · Oxidative stress · Vessel

Introduction

In the last decades, the worldwide population has exhibited an increasing life expectancy with a consequent rise in the elderly population, resulting in enhanced health and social costs. It has been estimated that, in developed countries, the aged population will increase fivefold in the next decades (Pallàs et al. 2008; Ponnappan and Ponnappan 2011). Aging is accompanied by a decline and a progressive deterioration in the physiological functions and metabolic processes of multiple organs and systems (Corbi et al. 2012; Hanahan and Weinberg 2011; López-Otín et al. 2013). Although many theories have been proposed to explain the aging process, neither of them appears to be fully satisfactory.

Aging makes human more susceptible to the onset of pathologies, including cardiovascular diseases (CVDs), cancer, respiratory disorders, osteoporosis, and neurodegenerative diseases (Rahman et al. 2012; Stein et al. 2010). These chronic conditions exert an enormous toll, both in terms of human suffering and economic loss. Although it is well accepted that oxidative stress is involved in the aging process, further studies are needed to study in-depth these relationships in humans or animals.

Aging and cardiovascular diseases

CVDs are the most common cause of death among the elderly patients in developed countries. Aging results in well-defined phenotypic changes that lead the cardiovascular system to develop diseases even in the absence of traditional risk factors. Age-related changes consist of uniform and generalized structural degeneration and/or functional decline, even if different components of the

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cardiovascular system may be affected quite heterogeneously (Ferrari et al. 2003).

Aging induces several CVDs, such as coronary artery disease and its major complication, acute myocardial infarction, heart failure, diabetes mellitus, stroke, and hypertension (Xu et al. 2012).

The heart suffers complex changes during aging that include hypertrophy, altered left ventricular diastolic function, reduced left ventricular systolic reserve capacity, increased arterial rigidity, and impaired endothelial function (Lakatta and Levy 2003; North and Sinclair 2012). With age, the apoptotic and necrotic processes lead to a decrease of cardiomyocytes, an increase of oxidative stress promoting an inflammatory and fibrotic environment, an impaired neovascularization capacity due to a reduction of pro-angiogenic functions, and a decreased capacity of progenitor cells of the bone marrow-derived cells to contribute to functional repair (Bronze-da-Rocha 2014; Dimmeler and Leri 2008; Strait and Lakatta 2012).

Moreover, cardiomyocyte dimensions are somewhat increased, whereas their numbers are decreased; collagen may become more prominent because of both quantitative and qualitative changes, with focal deposits and diffuse increases in the cross-linking between adjacent fibers.

The senescent changes of vascular structure and function have been suggested to result in the increased risk of atherosclerotic CVDs in the elderly. Aging and atherosclerosis run along very similar pathways and determine many similar cardiovascular alterations; vessel aging may be viewed as representing the prodromal stage of atherosclerotic disease, or, conversely, atherosclerosis may be viewed as a form of accelerated arterial aging, probably favored by coexisting noxious stimuli, such as dyslipidemia, smoking, diabetes, and hypertension (Ferrari et al. 2003; Ota et al. 2010; Rivard et al. 1999). Aging promotes also endothelial senescence and it is associated with pathways inducing atherosclerosis in humans (Rodella et al. 2013). Indeed, atherosclerotic plaques show features of cellular senescence in terms of reduced cell proliferation, irreversible growth arrest, apoptosis, elevated DNA damage, epigenetic modifications, and telomere shortening and dysfunction (Wang and Bennett 2012).

According to the free radical theory of aging, reactive oxygen species (ROS) are potential candidates responsible for vascular dysfunction and, upon the production of high levels of ROS, the redox balance is disturbed and cells shift into a state of oxidative stress, which subsequently leads to endothelial dysfunction and senescence (Harman 1992; Kurz et al. 2004; Shi et al. 2010; Ungvari et al. 2008). Moreover, the endothelium modulates vascular tone releasing a variety of vasodilators, including nitric oxide (NO) and prostacyclin, as well as vasoconstrictor agents, such as endothelin-1 (ET-1) and angiotensin II (Ang II) (Wang et al. 2010). These vasoactive factors do not only regulate regional blood flow but also influence proliferation and/or hypertrophy of vascular smooth muscle cells (VSMCs) (Higashi et al. 2009; Ivey et al. 2008; Köhler and Hoyer 2007). For these reasons, endothelial senescence is considered one of the major risk factors for CVDs (Higashi et al. 2009; Ito et al. 2010; Ungvari et al. 2008).

The major age-related alterations observed at cardiovascular system level are summarized in Table 1.

Discovery of sirtuins

The sirtuins are part of family protein homologous to yeast silent information regulator 2 (Sir2) that was cloned and characterized in 1984 as a gene required for maintaining silent chromatin in yeast (Shore et al. 1984). Interest in sirtuins grew when Sir2 was shown to slow aging in yeast mother cells (Kaeberlein et al. 1999). Many subsequent studies showed similar effects on aging, supporting the ideas of sirtuins like longevity-promoting effectors in Saccharomyces cerevisiae, Caenorhabditis elegans, Drosophila melanogaster, and mice (Bauer et al. 2009; Berdichevsky et al. 2006; Finkel et al. 2009; Rizki et al. 2010; Rogina and Helfand 2004; Viswanathan and Guarente 2011; Viswanathan et al. 2005). Banerjee et al. (2012) demonstrated how in D. *M*elanogaster, overexpression of Sir2 extended the lifespan, whereas deletion of Sir2 reduces significantly the lifespan. Mouchiroud et al. (2013) showed that nicotinamide adenine dinucleotide (NAD^+) levels are reduced during aging, and conversely, genetic or pharmacological restoration of NAD^+ level prevents age-associated metabolic decline and promotes longevity. Importantly, these effects are dependent upon the deacetylase activity of Sir2, involving the induction of mitonuclear protein imbalance as well as activation of stress signalling via the mitochondrial unfolded protein response (UPRmt) and the nuclear translocation and activation of forkhead box O (FOXO) transcription factor. Furthermore, Banerjee et al.

Table 1 Aging structural and functional alterations at cardiovascular system level

Heart	Vessel
Hypertrophy	Arterial rigidity
Increase in heart weight	Impaired endothelial function
Fibrosis	Reduction of pro-angiogenetic factors
Altered left ventricular diastolic function	Altered imbalance between vasodilators and vasoconstriction
Cardiomyocyte necrosis and apoptosis	Increased risk of atherogenesis
Systolic dysfunction	Enhanced arterial wall thickness
Oxidative stress	Oxidative stress
Inflammation	Inflammation

(2013) emphasized the importance of Sir2-FOXO interactions in mediating the longevity pathway. However, contradictory findings about the role of Sir2 in regulating longevity in metazoans have raised concerns about confounding background genetic mutations (Burnett et al. 2011; Viswanathan and Guarente, 2011).

Subsequently, the yeast Sir2 and mammalian ortholog sirtuin 1 (SIRT1) were shown to be NAD^+-dependent deacetylases (Imai et al. 2000; Tang 2011). Although, the effect of Sir2 and the most studied mammalian Sir2 homolog, SIRT1, on longevity is actually highly investigated. Sirtuin family proteins are members of the highly conserved class III histone deacetylases (HDACs) and appear to play important roles in many physiological and pathological processes, including inflammation, apoptosis/proliferation, differentiation, metabolism, lifespan, stem cell pluripotency, and cell cycle regulation (Chung et al. 2010; Guarente 2011; Villalba and Alcain 2012). The activation or modulation of sirtuins leads to measurable increases in resistance to different stress, making them an appealing target to promote improvements in health and aging. Currently, although sirtuins represent promising therapeutic targets, their role in the regulation of mammalian lifespan remains an open question, and the future perspective could be represented by studies performed to identify the efficacy of sirtuin activators in the prevention and/or treatment of age-related disorders (Corbi et al. 2013).

The sirtuin family

In mammals, there are seven sirtuin genes (SIRT1–7) which are localized in different cellular compartments and are capable of diverse actions (Frye 1999; Frye 2000).

Biochemically, sirtuins are a class of proteins that possesses mainly NAD^+-dependent lysine deacetylase activities (Barber et al. 2012; Haigis et al. 2006; Jiang et al. 2013; Liszt et al. 2005; Michishita et al. 2005).

Sirtuins may execute their function by deacetylating many target proteins in the different cellular compartments; in fact, they are broadly recognized as critical regulators of multiple metabolic pathways, and as sensors of energy and redox status in cells, sirtuins modulate the activity of key metabolic enzymes as well as regulate transcription of metabolic genes. In addition, several sirtuins play additional roles in metabolic homeostasis (Choi and Mostoslavsky 2014). Based on their enzymatic activities, sirtuins can also play a pivotal role in oxidative stress modulation (Conti et al. 2015; Li et al. 2015; Zhang et al. 2015). Sirtuins are intimately linked to the cellular response to oxidative stress (Merksamer et al. 2013); they might be activated during redox stress and may modulate crucial responses, including the adaptation to hypoxia and ameliorating ROS-induced pathologies (Webster et al. 2012). Sirtuins also have been studied intensively as potential anti-aging and age-related diseases targets (Baur et al. 2012; Frye 2000; Haigis and Sinclair 2010; Hall et al. 2013; Morris 2013; Roth and Chen 2014). It will be important to develop experimental models in which the levels of oxidative stress and the activities of sirtuins can be precisely modulated to determine how sirtuins have a causative role in lifespan extension. Also, the role of sirtuins in the cardiovascular system has been investigated (Cencioni et al. 2015; D'Onofrio et al. 2015; Pantazi et al. 2013), and sirtuins appear to have a prominent role in cardiovascular biology and may regulate aspects of cardiovascular health and age-dependent CVDs.

In the following paragraphs, we present an overview of the main features of the sirtuin family members

focusing on the impact of each sirtuins on oxidative stress and so on age-related cardiovascular risks. Furthermore, this review discusses sirtuins' potential as an efficient defender against age-related CVDs.

Overview of physiological function of sirtuins at cardiovascular level

Sirtuin 1

SIRT1 is primarily a nuclear deacetylase (Michishita et al. 2005). It contains at least two nuclear localization signals and two nuclear export signals and can shuttle between the nucleus and cytoplasm under specific conditions (Tanno et al. 2007). SIRT1 removes the acetyl group from the ε-amino group of lysine residues in histones and non-histone proteins and regulates target gene expression and protein activities that, in turn, control various cellular processes, such as cell proliferation, differentiation, apoptosis, metabolism, stress response, genome stability, and cell survival (Cheng et al. 2003; McBurney et al. 2003; Sequeira et al. 2008; Zhang et al. 2009).

Endothelial SIRT1 age-dependent depletion or its inactivation is a frequent companion of many CVDs (Chen et al. 2012). SIRT1 is highly expressed in endothelial cells, where it regulates numerous functions, including nitric oxide synthase (NOS) activity, cell senescence, and autophagy (Borradaile and Pickering 2009; Vasko et al. 2014). This spectrum of functions explains the association of endothelial SIRT1 deletion with impaired vasoreactivity and increased endothelial senescence. SIRT1-dependent deacetylation of endothelial NOS (eNOS) is essential for eNOS activation, and age-related reductions in eNOS and SIRT1 expression increase pro-inflammatory gene expression in the aorta (Csiszar et al. 2002), strongly favor perivascular fibrosis and vascular stiffening (Donato et al. 2011; Roos et al. 2013), and provide evidence for a more direct role of sirtuins in regulation of age-related CVDs (Roos et al. 2013). Moreover, inhibition of endothelial SIRT1 blocks endothelium-dependent vasodilatation and decreases bioavailability of NO (Koka et al. 2014).

All sirtuins are expressed at endothelial cell level, but it is important to underline that SIRT1 is the sirtuin shown to uniquely regulate endothelial cell physiology by promoting vasodilatory and regenerative functions of the vascular wall through the modulation of eNOS activity, forkhead box O1 (FOXO1), p53, and Ang II type 1 receptor (AT1R) (Borradaile and Pickering 2009; D'Onofrio et al. 2015; Sanchez-Fidalgo et al. 2012). In particular, SIRT1 appears to play a regulatory role in endothelial function, such as inhibiting endogenously apoptosis by deacetylation of p53 (Alcendor et al. 2004; Ota et al. 2007; Yu et al. 2009) and regulating angiogenic functions via deacetylation of FOXO1 (Potente et al. 2007) and NOTCH1 (Guarani et al. 2011). Notably, SIRT1 activates several members of the FOXO family of transcription factors which promote the expression of stress response genes including antioxidant enzymes (Merksamer et al. 2013; Motta et al. 2004). Sundaresan et al. (2011) demonstrated that whole-body SIRT1 knockout mice have smaller hearts with respect to their wild-type littermates and resist to the development of cardiac hypertrophy related to aging, suggesting that SIRT1 mediates compensated myocardial hypertrophy during ischemia/reperfusion insult (Sunderasan et al. 2011; Yang et al. 2013). In contrast, cardiomyocyte-specific SIRT1 knockout mice do not show any cardiac abnormalities; however, they are more susceptible to ischemic injury (Pillai et al. 2014).

As reported before, with age, the expression and activity of SIRT1 gradually decrease and in parallel oxidative stress, a major cause of atherosclerosis, increases (Cencioni et al. 2015). Age-related loss of SIRT1 protein expression in human VSMC correlates with a loss of capacity for vascular repair, diminished stress response, and increased senescence (D'Onofrio et al. 2015; Thompson et al. 2014). SIRT1 appears to counteract atherosclerosis (Cardellini et al. 2009) inhibiting VSMC hypertrophy and neointima formation and protecting against DNA damage, medial degeneration, and hypertension (83,84 → D'Onofrio et al. 2015; Gao et al. 2014; Gorenne et al. 2013). In a previous study, our research group indicated that the SIRT1-p53-NO axis may be one of the fundamental determinants of advancing endothelial dysfunction linked to aging and underlined the role of SIRT1 as a driver of cellular stress resistance and longevity. In particular, we observed that melatonin, pineal indoleamine which is known to be decreased during aging as well (Bubenik and Konturek 2011; Reiter et al. 2002), increases SIRT1 expression and improves cellular survival at the aorta level of apolipoprotein E null mice, thereby reducing the progression of atherogenesis (Rodella et al. 2013). SIRT1 may also prevent atherothrombosis by downregulating the endothelial expression of tissue factors; in fact,

treatment of wild-type mice with the SIRT1 inhibitor in vivo enhanced tissue factor activity and markedly reduced the coagulation time in a photochemical vascular injury model (Breitenstein et al. 2011). SIRT1 may be a potential target for the intervention on VSMC hypertrophy age-associated vascular disease, even if the mechanism are actually not well defined (Danz et al. 2009; Guarani and Potente 2010; Li et al. 2011; Rodella et al. 2013).

The activity of SIRT1 has been shown to be rescued by several compounds, such as resveratrol (D'Onofrio et al. 2015; Sanchez-Fidalgo 2012), unacylated ghrelin (D'Onofrio et al. 2015; Togliatto et al. 2014), and ginsenoside Rb1 (D'Onofrio et al. 2015; Song et al. 2014), a steroid glycoside found in ginseng and paeonol (D'Onofrio et al. 2015; Jamal et al. 2014). Resveratrol, a polyphenolic antioxidant found in red wine, activating SIRT1 (Villalba and Alcain 2012; Wallerath et al. 2002) prevents oxidative stress and coronary VSMC proliferation inhibiting extracellular signal regulated kinase (ERK) activation (Chong et al. 2012; El-Mowafy et al. 2008). Recent biophysical data indicate that resveratrol interacts with and modulates SIRT1 activity via an allosteric mechanism (Cencioni et al. 2015; Hubbard et al. 2013; Sinclair and Guarente 2014); these findings interestingly indicate that micromolar levels of resveratrol are sufficient to exert vasculoprotective effects through SIRT1 action (Csiszar et al. 2009; Della-Morte et al. 2009; Pacholec et al. 2010; Ungvari et al. 2007; Yang et al. 2013). However, some data have suggested that resveratrol seems more likely act through a complex indirect mechanism dependent on the inhibition of phosphodiesterases (PDE) paralleled by AMPK activation (Beher et al. 2009; Cencioni et al. 2015; Park et al. 2012; Yang et al. 2013). Furthermore, resveratrol has been further shown to protect coronary endothelial cells against oxidative stress: in fact, it may stimulate in a dose-dependent manner SIRT1 deacetylase activity by increasing its binding affinity to both the acetylated substrate and NAD^+ (Howitz et al. 2003).

Resveratrol-induced SIRT1 activation also appears to mediate protection against ischemia/reperfusion injury by reducing ROS production, switching cardiac myosin heavy chain isoforms to the more stress-resistant forms, inhibiting hypoxia-induced apoptosis, and modulating mitogen-activated protein kinase (MAPK) pathways (Becatti et al. 2012; Tang et al. 2014). Ischemic preconditioning (IPC) is a powerful endogenous mechanism of protection against myocardial ischemia/reperfusion activated by repetitive brief periods of ischemia and reperfusion. The protection afforded by IPC is mediated through activation of multiple signalling pathways, in one of this SIRT1 is activated and, in turn, induces deacetylation of lysine residues in various proteins, including p53 (Bolli, 2007; Yamamoto et al. 2014). Furthermore, Chen et al. (2009) showed that hypoxia-induced apoptosis generated in H9c2 cells in vitro was attenuated by resveratrol acting through SIRT1: the co-incubation of resveratrol with a SIRT1 inhibitor abolished the protective effect. Moreover, resveratrol, via its interaction with SIRT1, suppresses the expression of AT1P-induced vasoconstriction (Higuchi et al. 2007). It is intriguing to consider that the nuclear translocation of SIRT1 could have a role in ischemia/reperfusion-related CVDs (Yang et al. 2013), so SIRT1 could be considered a potential interventional target for ischemia heart disease management in the elderly (Gu et al. 2013).

It is encouraging to know that in addition to resveratrol, another component of wine, tyrosol, also exhibits cardioprotective effects through the activation of SIRT1. In particular, Samuel et al. (2008) evaluated the effect of tyrosol treatment on myocardial ischemic stress, typical of elderly people. Tyrosol-treated rats have shown reduced infarct size, improved myocardial function, and increased phosphorylation of Akt, eNOS, and FOXO3a. Of note, tyrosol induces myocardial protection against ischemia-related stress by inducing survival and longevity proteins, particularly SIRT1, and it may be considered as a new potential target for anti-aging therapy of the heart (Yang et al. 2013) (Fig. 1).

Endogenous mechanisms of lifespan extension are stimulated by low-grade stress, such as calorie restriction. The fact that downregulation of SIRT1 under ischemia/reperfusion is attenuated in the presence of preconditioning suggests that stimulation of SIRT1 by a low grade of repetitive stress may partly mediate the beneficial effect of preconditioning (Hsu et al. 2010).

Yamamoto et al. (2014) observed that since caloric restriction, which protects the heart from ischemia/reperfusion injury, failed to induce cardioprotection in SIRT1 knockout mice, the cardioprotective effect of caloric restriction is in part mediated through activation of the Nampt-SIRT1 pathway, in which Nampt plays a critical role as a regulator for NAD^+ synthesis in cardiomyocyte. SIRT1 confers cardioprotection and cytoprotective effects mainly by preventing apoptotic cell death (Alcendor et al. 2004; Shinmura et al. 2008).

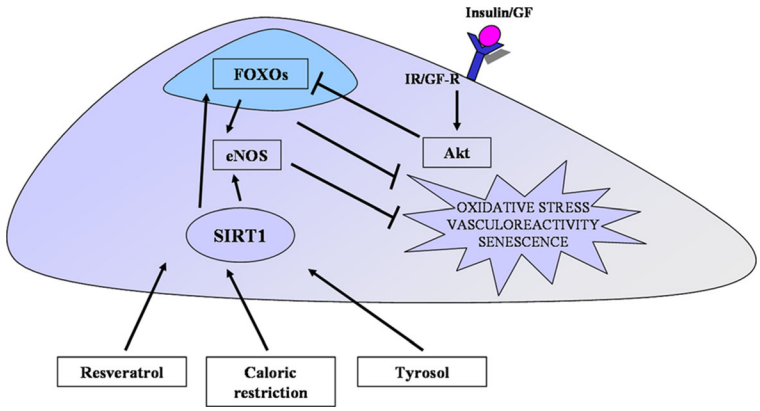

Fig. 1 Sirtuin 1 mechanism of action against cardiovascular aging. In particular, resveratrol, caloric restriction, or tyrosol upregulate sirtuin 1 expression and activity; in turn, sirtuin 1 can activate FOXOs and eNOS to reduce/block oxidative stress and vasculoreactivity alteration, playing a final important role in counteract cardiovascular aging. (Modified from Luo et al. 2014). *eNOS* endothelial nitric oxide, *FOXO* forkhead box O, *SIRT1* sirtuin 1

Unexpectedly, Shinmura et al. (2008) found that myocardial levels of total SIRT1 protein did not change with caloric restriction.

It has been suggested that exercise training and caloric restriction have similar effects. Ferrara et al. (2008) observed an increase in thiobarbituric reactive substances (TBARS), endogenous product of lipid peroxidation, and 4-hydroxynonenal (4-HNE), a key mediator of oxidative stress-induced apoptosis and also a carcinogen and mutagen agent, and a decrease of endogenous antioxidant enzymes activity with the final protective effects of exercise training in aged rats.

Cardiac SIRT1 activity is declined in senescence (Du et al. 2006); in fact, aged heart exhibited lower nuclear SIRT1 level compared with those in young hearts, which was further downregulated under ischemia/reperfusion insult (Tong et al. 2013). On the contrary, Lai et al. (2014) observed no age-related significant different expression of SIRT1 expression, whereas after exercise training, SIRT1 expression level was highly increased, as young rats. These data explain that during aging, the induction of SIRT1 longevity pathway, instead of insulin-like growth factor 1 (IGF1) survival signalling, increases the chance for cardiomyocyte survival.

During the lifespan, the heart may be exposed to a large number of different stresses, like hypertrophic stress or apoptosis (Cencioni et al. 2015). SIRT1 has been confirmed also as a key factor in myocardial hypertrophy; low to moderate SIRT1 heart expression (2.5- to 7.5-fold over endogenous levels) was found to be protective against age-dependent cardiac hypertrophy, apoptosis, and consequent left ventricular dysfunction, whereas SIRT1 overexpression (12.5-fold) induced dilatation, hypertrophy, and cardiac failure (Alcendor et al. 2007; Ma et al. 2010; Yang et al. 2013). SIRT1 also provides protection against apoptosis playing an essential role in mediating the survival of cardiac myocytes under stress in vitro (Alcendor et al. 2004; Alcendor et al. 2007; Wang et al. 2007). Activation of SIRT1 not only suppresses apoptosis but also balances oxidative stress in the heart, while absence of SIRT1 triggers chronic inflammation, oxidative stress, and cell cycle arrest (Gu et al. 2013). Further, Ruan et al. (2015) demonstrated that SIRT1 expression was downregulated in doxorubicin-induced cardiomocyte injury, accompanied by elevated oxidative stress and cell apoptosis, and interestingly, SIRT1 is involved in the protection of the heart from doxorubicin-induced pathway, partly through the inhibition of the p38 MAPK pathway.

As the SIRT1 activity decreases during aging, the ischemic myocardium cannot respond anymore to ischemia with consequent development of cardiac failure (Cencioni et al. 2015; Harihran et al. 2010; Sciaretta et al. 2011). A SIRT1 overexpression was shown to reduce infarct size and improve cardiac function in a mouse model of myocardial infarction (Yang et al. 2013). Tanno et al. (2007) found that normal human cardiomyocytes predominantly expressed SIRT1 in their cytoplasm and chronic heart failure induced a nuclear translocation of SIRT1. The nuclear accumulation of SIRT1, as reported previously, is likely to be an adaptive mechanism of cardiomyocytes against heart failure, as indicated by the potent cell protective effect of nuclear SIRT1 against oxidative stress.

In summary, SIRT1 acts as a cardioprotective molecule that protects from aging and induces resistance against hypertrophic and oxidative stresses, inhibits cardiomyocyte apoptosis, and regulates cardiac energy metabolism (Alcendor et al. 2007; Chen et al. 2009; Hsu et al. 2010; Luo et al. 2014). Moreover, the observations reported in this section strengthen the perception that SIRT1 exerts protective effects against cardiovascular aging and age-related CVDs by mediating multiple signalling pathways. Appropriate upregulation or activation of SIRT1 has emerged as a promising avenue to retard aging and treat age-related CVDs. Nevertheless, as we learn more about the sirtuins, it has become apparent that activation of the paralogs of SIRT1 may be more beneficial under certain circumstances. However, the role of SIRT1 on longevity per se is not fully convincing because transgenic mice overexpressing SIRT1 did not show to live longer than controls, so further studies are needed.

Sirtuin 2

SIRT2 is mainly localized to the cytoplasm, but can shuttle to the nucleus during mitosis (Michishita et al. 2005; North and Verdin 2007; Vaquero et al. 2006). At cytoplasm level, SIRT2 colocalizes with microtubules and deacetylates their major component (α-tubulin) (North et al. 2003).

It might deacetylate many substrates such as histone H4K16, H3K56, α-tubulin, PR-Set7, phosphoenolpyruvate carboxykinase 1, nuclear factor kB (NF-κB) subunit p65, FOXO, and receptor-interacting protein 1 (RIP1), regulating several cell functions like cell cycle progression, cell death, and stress response. It plays a regulatory role in modulating redox stress tolerance, and on the other hand, redox stress has been shown to result in the upregulation of both SIRT2 transcript and protein (Lynn et al. 2008; Wang et al. 2007). Functional characterization of this process suggests that redox stress upregulation of SIRT2 is associated with the induction of the pro-apoptotic protein Bim. In contrast, the basal level of SIRT2, under low-stress conditions, upregulates mitochondrial antioxidant manganese superoxide dismutase (Mn-SOD2) via FOXO3a deacetylation, with the consequent attenuation of oxidative stress (Wang et al. 2007). Moreover, SIRT2 deacetylates FOXO3a and promotes cellular resistance to hydrogen peroxide (Merksamer et al. 2013; Wang et al. 2007), similar to SIRT1 regulation of oxidative stress via FOXO family members (Merksamer et al. 2013).

SIRT2 knockout mice have no cardiac abnormalities and they are protected from ischemic injury, because of attenuated programmed heart necrosis (Pillai et al. 2014; Lynn et al. 2008). The modulation in the expression of SIRT2 does not alter basal H9C2 myoblast cell viability. However, the SIRT2 transcript is induced by anoxia oxygenation stress and its genetic knockdown is cytoprotective against anoxia-reoxygenation injury.

Moreover, SIRT2 inhibitor in non-diabetic cardiomyocytes may have significant impact on cardiomyocyte contractile function. Further studies are warranted to precisely define the role of the SIRT2 in cardiac contractile function under physiological and pathological conditions.

Hashimoto-Komatsu et al. (2011) showed that SIRT2 mediates microtubule reorganization induced by Ang II and cyclic stretch in endothelial cells, suggesting that SIRT2 is a key regulator of endothelial remodelling. Further studies are needed to elucidate the role of Ang II-induced deacetylation of α-tubulin and the involvement of SIRT2 in vascular remodelling.

Sirtuin 3

SIRT3 is present in the mitochondrial matrix (Michishita et al. 2005; Onyango et al. 2002; Schwer et al. 2002), but it is also detected in the nucleus (Nakamura et al. 2008; Scher et al. 2007). An interesting correlation exists between a VNTR polymorphism in intron 5 of the SIRT3 gene and extended human lifespan. Of note, the allele completely lacking enhancer activity is virtually absent in males older than 90 years (Bellizzi et al. 2005). Another study indicates that SIRT3 is a marker associated with longevity in Italian females and German males (Bellizzi et al. 2007; Wang et al. 2014). It will be important to carry out comprehensive analyses of SIRT3 polymorphisms to confirm the link between SIRT3 and human longevity.

SIRT3 is a protein deacetylase (Lombard et al. 2007) and plays a crucial role in cellular energy metabolism or redox regulation by deacetylating key mitochondrial proteins, including acetyl-coenzyme A synthetase 2, glutamate dehydrogenase (GDH), and Mn-SOD2 (Kim et al. 2010; Someya et al. 2010).

SIRT3-deficient mice looked normal, with no apparent signs of any disorder. However, they exhibit cardiac hypertrophy at 8 weeks of age, expressed cardiac stress markers, had significantly higher heart/body weights ratio and interstitial fibrosis, and the ability to withstand oxidative stress is significantly reduced compared with

wild-type mice (Hafner et al. 2010; Sundaresan et al. 2009; Wang et al. 2014, Loffredo et al. 2014). Moreover, cardiomyocytes cultured from SIRT3-deficient hearts produced higher levels of oxidative stress than did myocytes cultured from wild-type hearts (Ishikawa et al. 2013; Sundaresan et al. 2009). Overexpression of SIRT3 blunts cardiac hypertrophy by decreasing oxidative stress via upregulation of endogenous antioxidants (like Mn-SOD2 and catalase). Importantly, increased expression of SIRT3 protects myocytes from genotoxic and oxidative stress-mediated cell death (Chen et al. 2013; Sundaresan et al. 2009).

In myocardial tissues, SIRT3 reduces levels of ROS by deacetylating the transcription factor FOXO3a, which can then enter the nucleus and bind to the promoter of the genes encoding Mn-SOD and catalase, increasing their expression (Qiu et al. 2010; Sundaresan et al. 2009; Tan et al. 2008; Wang et al. 2014). Other reports also demonstrate that SIRT3 increases the activity of these antioxidant enzymes by the NF-kB pathway (Chen et al. 2013; Wang et al. 2014).

Sundaresan et al. (2009) observed that SIRT3 is a negative regulator of cardiac hypertrophy and demonstrated that SIRT3 is a stress-responsive deacetylase that blocks the cardiac hypertrophic response through activation of FOXO3 that in turn activated Mn-SOD2 and catalase, as well as by suppressing ROS-mediated Ras activation and the downstream MAPK/ERK and PI3K/Akt signalling pathways. Moreover, Tseng et al. (2014) observed that hypoxia induces SIRT3 to deacetylate FOXO3 and so preserves mitochondrial function and ensures cell survival at endothelial cell level. Wang et al. (2014) propose that overexpression of SIRT3 enhances cells' ability to deal with oxidative stress and reduces stress-mediated cell injury by activating Mn-SOD and catalase; although, they did not detect any differences in gene and total protein expression of SIRT3 between young and old cardiac tissues.

Klishadi et al. (2015) showed that during acute myocardial ischemia reperfusion, when myocardium is exposed to an influx of ROS, SIRT3 protein levels in left ventricular ischemic tissue reduced significantly, indicating that the effect of ischemia on SIRT3 protein level is a local effect limited to the area of ischemia. Furthermore, the administration of losartan, an AT1R blocker, normalized and also magnified SIRT3 protein actions in heart ischemic tissue and consequently makes the heart more resistant against damage.

Hafner et al. (2010) have identified a role for SIRT3 in cell protection and mitochondrial function in heart tissue during aged and induced stress: SIRT3 deacetylates cyclophilin D, inhibiting apoptosis by the opening of the mitochondrial permeability transition pore, while the loss of SIRT3 activity leads to increased cardiac stress and so to a decline in cardiac function. SIRT3 has been shown to block cardiac hypertrophy by reducing ROS synthesis from the mitochondria (Kim et al. 2010). A recent study of Porter et al. (2014) showed that under ischemic/reperfusion insult, at heart level, $SIRT3^{+/-}$ adult and wild-type aged mice showed a similar phenotype of injury, resulting in a significant myocardial infarction area with respect to wild-type adult hearts. Moreover, the mitochondria isolated from wild-type aged heart possess a higher level of protein acetylation as observed in $SIRT3^{+/-}$ hearts. These observations underlined that SIRT3 deficiency exacerbates cardiac ischemia/reperfusion injury and may contribute to age-related loss of resistance to ischemia/reperfusion insult. Furthermore, Cheung et al. (2015) reported that the accumulation of mitochondrial bioenergetic damage and increased oxidative damage are critical steps for doxorubicin-induced cardiotoxicity. The protective role of SIRT3 in the H9c2 cells treated with doxorubicin is associated with increased mitochondrial function, increased cardiolipin, and reduced oxidative damage.

Furthermore, unlike endothelial cells, cardiomyocytes are not predominantly regulated by SIRT1, but other sirtuins, such as SIRT3, SIRT6, and SIRT7, play a very important and non-redundant role (Cencioni et al. 2015).

All of these data indicate that SIRT3 plays significant roles in the cardioprotective stress responses, which are beneficial for lowering the risk of age-related CVDs. The correlation between SIRT3 expression, oxidative stress, and senescence implies that manipulation of SIRT3 levels lead to more effective therapeutics in aged populations.

Sirtuin 4

SIRT4 is localized in the mitochondria (Michishita et al. 2005). It is the only member of the sirtuin family with no detectable deacetylase activity; in fact, it is a NAD^+-dependent protein ADP-ribosyl transferase, which catalyzes the transfer of ADP-ribosyl groups onto target proteins. Under genotoxic stresses, SIRT4 has also exhibited an anti-apoptotic function by maintaining

mitochondrial NAD^+ levels together with SIRT3 (Haigis et al. 2006). SIRT4 is found to be specifically enriched in the heart, kidney, brain, and liver. Some evidence suggests that SIRT4 level is tightly associated with metabolism status and significant change in SIRT4 expression could affect cell viability, even result in cellular apoptosis (Liu et al. 2013a). In their study, Liu et al. (2013a) investigated the role of SIRT4 in the survival of H9c2 cardiomyoblast cells against hypoxic stimulus: they found that SIRT4 exerts cardioprotective effects against hypoxia-induced apoptosis, whereas the inhibition of caspases activation and Bax translocation, another key player in the process of cellular apoptosis (Brunelle and Letai 2009), plays an important role in mediating the SIRT4 anti-apoptotic effect. In particular, SIRT4 could significantly regulate H9c2 cell viability and affect caspase s activity. Furthermore, SIRT4 expression could affect the ratio of pro-caspase 9/caspase 9 or pro-caspase 3/caspase 3 and change Bax translocation, which in turn alter the development of H9c2 cell apoptosis (Liu et al. 2013a).

Furthermore, SIRT4 can also modulate negatively insulin secretion, fatty acid oxidation, and mitochondrial gene expression in cardiomyocytes and the liver, although the mechanism remains elusive and in vivo data are actually absent (Ahuja et al. 2007; Jeong et al. 2013; Nasrin et al. 2010).

Sirtuin 5

SIRT5 is localized mainly in the mitochondria (Michishita et al. 2005; Schlicker et al. 2008). In their studies, Matsushita et al. (2011) and Park et al. (2013) showed that there are two isoforms of human SIRT5 differing in the C-terminal sequence, with the shorter isoform ($SIRT5^{iso2}$) mainly localized in the mitochondria and the longer form ($SIRT5^{iso1}$) localized in both the cytoplasm and mitochondria. Variants in SIRT5 gene have been found to be associated with the risk of carotid plaque development (D'Onofrio et al. 2015; Dong et al. 2011).

SIRT5 has NAD^+-dependent deacetylase, deacylase, demalonylase, and desuccylase activities the in mitochondria (Du et al. 2011). Loss of SIRT5 in mice causes enhanced blood ammonia levels under fasting, calorie restriction, or high protein diet compared to that in the wild-type mice (Nakagawa et al. 2009) and has not shown other metabolic phenotypes (Cha and Kim 2013).

In their study, Liu et al. (2013b) have demonstrated in vivo that SIRT5 plays a critical role in regulating cell viability in cardiomyocytes due to its high abundance in the mitochondria in response to oxidative stress: SIRT5 protects cardiomyocyte from hydrogen peroxide-induced apoptosis through the upregulation of Bcl expression, suggesting that the physiological and pharmacological regulation of SIRT5 can directly regulate the apoptosis development in cardiomyocytes during ischemia/reperfusion injury.

Any change in SIRT5 activity may affect the maintenance of energy homeostasis such as energy intake, storage, and expenditure, which in turn results in the occurrence of cardiac diseases (Nakagawa et al. 2009; Ogura et al. 2010).Interestingly, SIRT5 expression is significantly reduced both during isoproterenol-induced cardiomyopathy and exercise-induced cardiac hypertrophy, providing significant evidence that SIRT5 is involved in the pathogenesis of cardiac alterations (Galindo et al. 2009). Future studies are required to investigate the correlations between SIRT5 level and the occurrence on the effect of SIRT5 on various pathologic pathways of CVDs (Liu et al. 2013b).

Sirtuin 6

SIRT6 can be found in different cellular compartments: it is mainly localized to the nucleus, having both deacetylase and mono-ADP-ribosyltransferase activity (Liszt et al. 2005; Jiang et al. 2013; Michishita et al. 2008). In addition, it was recently shown that SIRT6 is also present in the endoplasmic reticulum where it can upregulate the secretion of TNF-α via the removal of long-chain fatty acyl groups from lysines K19 and lysines K20 (Jiang et al. 2013). SIRT6 has been implicated in the regulation of transcription, genome stability, metabolism, cellular proliferation and differentiation, inflammation, oxidative stress, cancer, and lifespan (Jia et al. 2012; McCord et al. 2009).

Based on the striking phenotype of SIRT6 knockout mice, which are predisposed to accelerated senescence, significant researches have shown in vivo that SIRT6 can also regulate cardiac hypertrophy and age-related cardiovascular alterations (Kim et al. 2010; Jia et al. 2012). In particular, SIRT6-deficient mice are smaller compared to the wild-type mice and, remarkably, show a premature aging-like phenotype that includes cardiac hypertrophy and heart failure, lymphopenia, reduced

subcutaneous fat, lordokyphosis, genomic instability, hypoglycemia, low blood insulin-like growth factor (IGF) level, increased glucose uptake, and fatty liver (Kim et al. 2010; Schwer et al. 2010; Xiao et al. 2010). As result, SIRT6-deficient mice die around 4 weeks after birth (Mostoslavsky et al. 2006; Pillai et al. 2014). However, SIRT6 overexpression in mice protects them from various metabolic pathologies caused by high-fat diet-induced obesity (Kanfi et al. 2010).

Among nuclear sirtuins, SIRT1 and SIRT6 play an important role in prevention and delay of CVDs (Cencioni et al. 2015). In fact, SIRT6 expression blocks the development of cardiac hypertrophy and heart failure (Sundaresan et al. 2011; Sundaresan et al. 2012), whereas some data suggested that SIRT1 promoted cardiomyocyte hypertrophy (Yang et al. 2013) and others indicated that SIRT1 attenuated cardiomyocyte hypertrophy (Alcendor et al. 2007). Consistent with this observation, SIRT6 levels were reduced in different mouse models of cardiac failure as well as in human failing hearts, showing the robust activation of many transcription/translational factors and growth factors and their receptors related to IGF/Akt signalling (Pillai et al. 2014).

Of note, Cardus et al. (2013) demonstrated that the presence of SIRT6 in endothelial cells protects from telomere and genomic DNA damage, thus preventing a decrease in replicative capacity and the onset of premature senescence. These observations suggest that SIRT1 and SIRT6 collaborate at different levels to maintain endothelial homeostasis: SIRT6 regulates chromatin functions and DNA repair and SIRT1 modulates intracellular signalling networks (Cardus et al. 2013). Furthermore, the depletion of SIRT6 reduced the proliferation and increased the senescence of endothelial cells and it may interestingly regulate the expression of eNOS and, in turn, endothelial functions (Pillai et al. 2014).

To date, the molecular events through which SIRT6 exerts a protective role at cardiovascular level, regulating the endothelial cell and cardiomyocyte response to stress, reducing oxidative stress and hyperglycemia, are still unclear.

Sirtuin 7

SIRT7 is localized into the nucleus and nucleolus and it has a NAD^+-dependent HDAC activity (Ford et al. 2006; Michishita et al. 2005). The deletion of SIRT7 in mice leads to a reduction of life span; they die around 1 year of age, interestingly, due to the development of heart hypertrophy; inflammatory cardiomyopathy; as well as enhanced cardiomyocyte apoptosis, kyphosis, and loss of subcutaneous fat. These observations underline that SIRT7 impact importantly on heart functions.

Both SIRT3 and SIRT7 knockout mice exhibited cardiac hypertrophy; however, SIRT3 null mice predominantly displayed interstitial fibrosis, while SIRT7 null mice showed inflammatory cardiomyopathy (Cencioni et al. 2015; Sundaresan et al. 2009; Vakhrusheva et al. 2008a). Furthermore, Vakhrusheva et al. (2008a) have

Table 2 Sirtuins localization at cellular and tissue levels and enzymatic activity

	Cellular compartment	Tissues expression	Enzymatic activity
SIRT1	Nucleus and cytoplasm	Adipose tissue, heart, kidney, liver, retina, skeletal muscle, vessels	Deacetylase
SIRT2	Cytoplasm (nucleus)	Adipose tissue, brain, heart, liver, skeletal muscle, vessels	Deacetylase
SIRT3	Nucleus and mitochondrial matrix	Adipose tissue, brain, heart, kidney, liver, oocytes, skeletal muscle, vessels	Deacetylase
SIRT4	Mitochondria	Brain, heart, kidney, liver, vessels	ADP-ribosyl transferase
SIRT5	Mitochondria and cytoplasm	Heart, liver, vessels, thymus, brain, kidney	Deacetylase, demalonylase, desuccinylase, deacylase
SIRT6	Nucleus and endoplasmic reticulum	Brain, heart, liver, retina, skeletal muscles, thymus, vessels, kidney, liver, testis, skeletal muscle	Deacetylase, ADP-ribosyl transferase
SIRT7	Nucleus and nucleolus	Heart, vessels, liver, brain, skeletal muscle	Deacetylase

Table 3 Sirtuins knockout mice features (modified from Pillai et al. 2014)

SIRT1-KO	Smaller heart and resistance to the development of age-related cardiac hypertophy
Cardiomyocyte-specific SIRT1-KO	Susceptible to ischemic injury and no cardiac abnormalities
Endothelial cell-specific SIRT1-KO	Impaired angiogenic process
SIRT2-KO	Protection from ischemic injury, no cardiac abnormalities, and attenuate programmed heart necrosis
SIRT3-KO	Cardiac hypertrophy, interstitial fibrosis, contractile dysfunction, high heart/body weight ratio and reduce ability to counteract oxidative stress
SIRT6-KO	Premature aged phenotype (lymphopenia, cardiac hypertrophy, heart failure, reduced subcutaneous fat, lordokyphosis, genomic instability, hypoglicemia, fatty liver, etc.). Mice die around 4 weeks of age
SIRT7-KO	Cardiac hypertrophy and apoptosis, inflammatory cardiomyopathy and fibrosis. Mice die around 1 year of age

demonstrated that SIRT7 plays an important role in preventing progressive functional deterioration of the heart. SIRT7 deletion leads to various pathological changes in the heart, which further aggravates with age. These changes include heart hypertrophy, fibrosis, lipofuscin accumulation, inflammatory cardiomyopathy, and increased apoptosis under basal conditions and in response to oxidative and genotoxic stress. They have also reported how SIRT7 is an essential regulator of heart homeostasis and that this function becomes

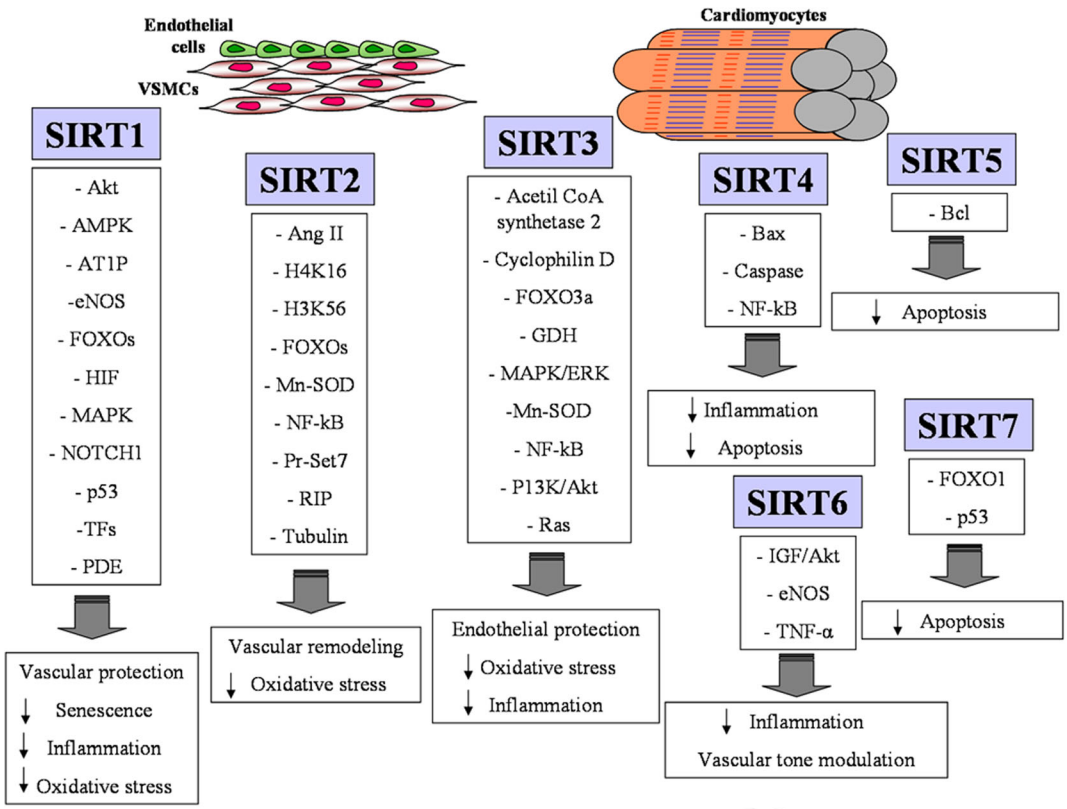

Fig. 2 Cardiovascular targets modulated by each sirtuins; endothelial cells, vascular smooth muscle cells, and cardiomyocytes might regulate, through different targets, various physiopathological processes. *Ang II* angiotensin II, *AT1P* angiotensin II type 1 receptor, *eNOS* endothelial nitric oxide, *FOXO* forkhead box O, *GDH* glutamate dehydrogenase, *HIF* hypoxia inducible factor, *NF-kB* nuclear factor kB, *Mn-SOD* manganese superoxide dismutase, *PDE* phosphodiesterases, *RIP* receptor-interacting protein, *SIRT* sirtuin, *TF* transcription factors, *TNF-α* tumor necrosis factor

increasingly important during aging, when general maintenance mechanisms gradually fail and regulatory networks undergo deterioration (Vakhrusheva et al. 2008a, 2008b).

SIRT7 has been implicated in oxidative stress resistance through an investigation of primary cardiomyocytes from SIRT7 knockout mice (Merksamer et al. 2013; Vakhrusheva et al. 2008a). As SIRT1 and SIRT7 can resist stress- and aging-associated myocardial dysfunction through the deacetylation of p53 and FOXO1 (Borradaile and Pickering 2009; D'Onofrio et al. 2015), to date, at endothelial level, only a reduced SIRT7 mRNA expression during high glucose exposure has been reported (D'Onofrio et al. 2015; Mortuza et al. 2013).

Further studies are required to examine whether SIRT7 targets are related to cardiovascular functions (Hall et al. 2013).

To summarize, each sirtuin cellular and tissue localization and the main phenotypic features of sirtuin knockout mice and the main cardiovascular targets are provided respectively in Tables 2 and 3 and Fig. 2.

Conclusion

Throughout the entire life of an organism, the efficiency of endogenous natural defenses declines, leading to disorders typical of elderly people such as systolic hypertension, atrial fibrillation, orthostatic hypotension, and heart failure. Sirtuin-targeted small molecules might represent a promising tool to develop new therapeutic protocols to contrast age-associated impairment of cardiovascular functions (Cencioni et al. 2015). In fact, myocardial and vascular protection is achieved by the activity of both nuclear (SIRT1, SIRT6 and SIRT7) and mitochondrial (SIRT3) sirtuins. Their activity ameliorates the negative consequences of a prolonged exposure to oxidative or genotoxic stresses, protecting cardiovascular structure and physiology (Fig. 3). In vitro and

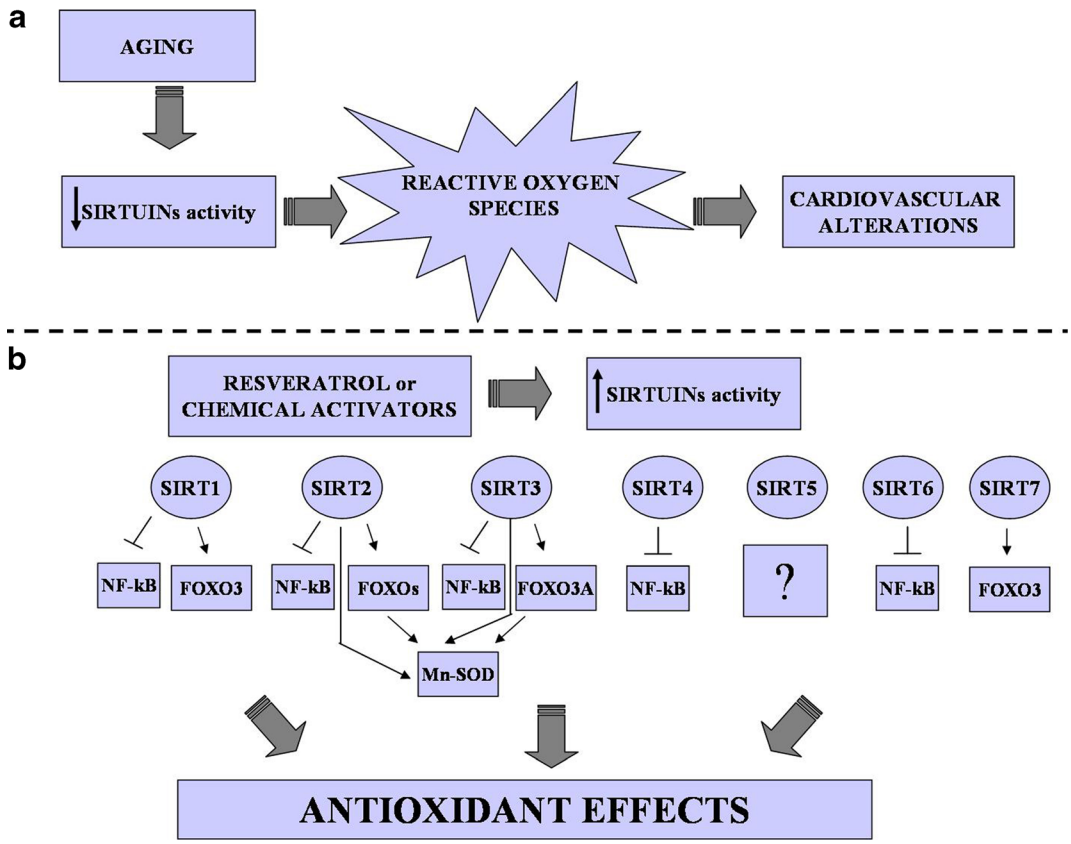

Fig. 3 Aging depresses sirtuin activity and increases oxidative stress leading to cardiovascular alterations (**a**). Upon activation by resveratrol or other chemical activators, each sirtuin might deacetilate several proteins that promote resistance to oxidative stress (**b**). *FOXO* forkhead box O, *NF-kB* nuclear factor kB, *Mn-SOD* manganese superoxide dismutase, *SIRT* sirtuin

in vivo experimental models, along with a consistent number of clinical trials, have focused on the pharmacokinetics of sirtuin modulators, including resveratrol, SRT1720, and SRT3025 (D'Onofrio et al. 2015; Gano et al. 2014; Milne et al. 2007; Sanchez et al. 2012). In a mice model, the compound SRT1720, a potent SIRT1 activator (Milne et al. 2007), reduces glucose levels and liver triglyceride content and recover mitochondrial functions after acute oxidant injury (Funk et al. 2010). Furthermore, an extension in lifespan and an improved general health has been observed in mice fed on standard diet with SRT1720 supplementation (D'Onofrio et al. 2015; Mitchell et al. 2014). Further, activation of SIRT1 by SRT3025 has been demonstrated enhance LDL receptor expression in atherosclerosis-prone apolipoprotein E null mice, leading to a decreased plaque formation (D'Onofrio et al. 2015; Miranda et al. 2015).

To date, the most effective class of sirtuin activators has been reported for SIRT1, whose activation has emerged as a promising therapeutic approach to treat cardiovascular disorders and to retard aging-related CVDs (Cencioni et al. 2015; D'Onofrio et al. 2015). In the light of the consistent number of the ongoing clinical trials with either SIRT1 inhibitors or activators, it is conceivable that in the next future one or more of them will enter in the clinical practice.

However, there are many unsolved issues regarding the function of sirtuins at cardiovascular level, and undoubtedly, more work is needed to understand the role of the different sirtuins in cardiac and vascular cell biology before they can be considered as a valuable therapeutic target against age-related cardiovascular diseases.

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Conflict of interest The authors declare that they have no competing interests.

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