



SIRT6 in Senescence and Aging-Related Cardiovascular Diseases

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SIRT6 belongs to the nicotinamide adenine dinucleotide (NAD⁺)-dependent deacetylases and has established diverse roles in aging, metabolism and disease. Its function is similar to the *Silent Information Regulator 2 (SIR2)*, which prolongs lifespan and regulates genomic stability, telomere integrity, transcription, and DNA repair. It has been demonstrated that increasing the sirtuin level through genetic manipulation extends the lifespan of yeast, nematodes and flies. Deficiency of SIRT6 induces chronic inflammation, autophagy disorder and telomere instability. Also, these cellular processes can lead to the occurrence and progression of cardiovascular diseases (CVDs), such as atherosclerosis, hypertrophic cardiomyopathy and heart failure. Herein, we discuss the implications of SIRT6 regulates multiple cellular processes in cell senescence and aging-related CVDs, and we summarize clinical application of SIRT6 agonists and possible therapeutic interventions in aging-related CVDs.

Keywords: SIRT6, senescence, cardiovascular diseases, autophagy, oxidative stress

INTRODUCTION

Population ageing is a global phenomenon. Virtually every country in the world is experiencing growth in the size and proportion of older persons in their population (United Nations, 2019). With the growing of aged population, the incidence of aging related cardiovascular diseases (CVDs) is increasing. According to a report from the American Heart Association, CVDs (comprising coronary heart disease, heart failure, stroke, and hypertension) currently claims more lives each year than cancer and chronic lung disease combined, and the prevalence of CVD in adults ≥ 20 years of age is 48.0% overall and increases with age in both males and females (Virani et al., 2020). Therefore, aging is an independent risk factor associated with the progressive degeneration of the heart, making them more vulnerable to stressors and contributing to increased morbidity and mortality (Chiao and Rabinovitch, 2015).

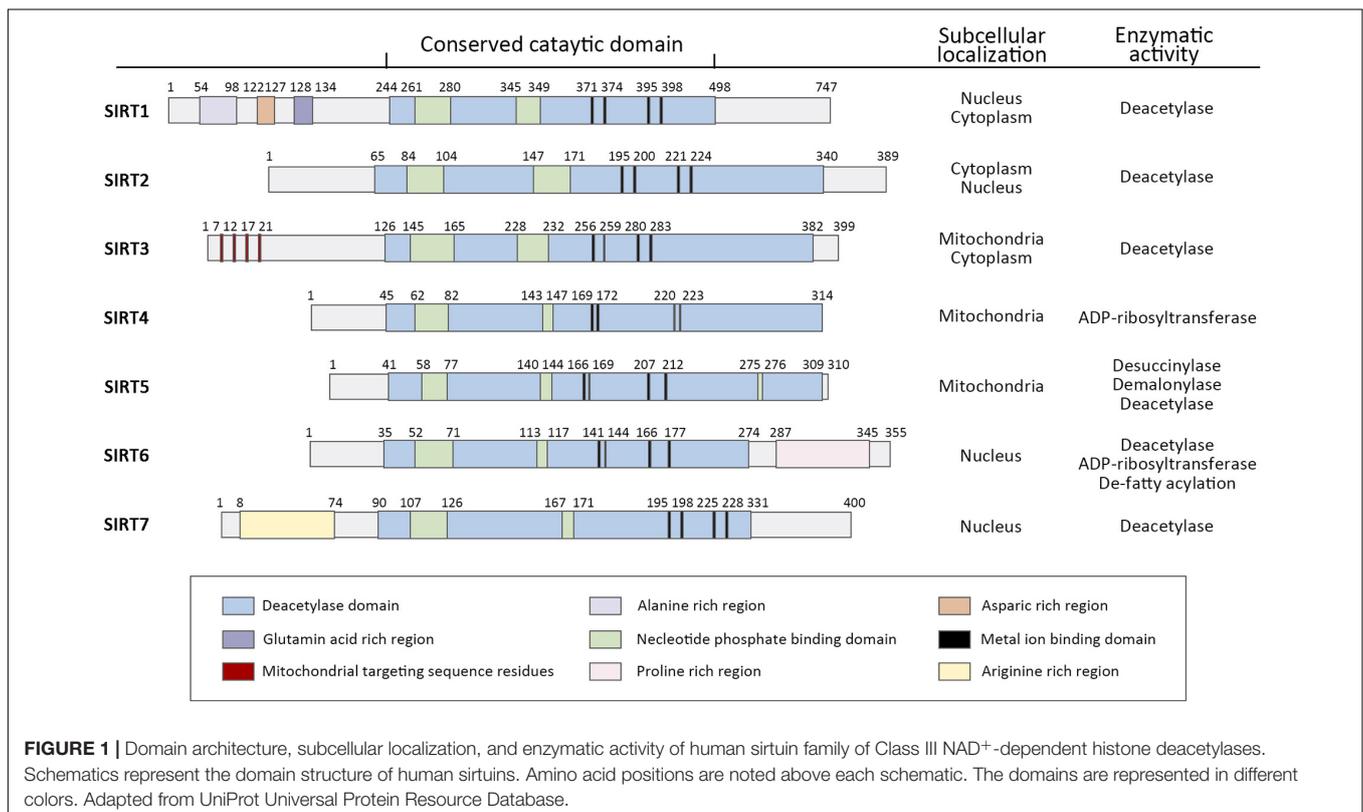
It has been probably 20 years since the Silent Information Regulator 2 (SIR2) gene was found to extend the lifespan of yeast (Kaeblerlein et al., 1999). From that time on, it sparked efforts in many institutions to realize more SIR2-like genes, known as sirtuins, and elucidate their potential to delay the onset of age-related diseases. Sirtuins are a family of histone deacetylases (HDACs) that catalyze deacetylation of both histone and non-histone lysine residues. Their requirement for

nicotinamide adenine dinucleotide distinguishes sirtuins from other HDAC classes and defines them as class III HDACs (Winnik et al., 2015). Mammals contain seven sirtuins (**Figure 1**), SIRT1-7, which are categorized by their different subcellular localization, unique binding substrates and diverse enzymatic activities (Haigis and Sinclair, 2010). These members share a conserved catalytic domain spanning 250 amino acids. The catalytic core comprises an NAD⁺-binding domain and four structural zinc-binding domains. Catalysis occurs in a hydrophobic cleft or pocket situated between these two kinds of domains and the hydrophobic cleft or pocket often provides binding sites for modulators. Additionally, sirtuins contain diverse N and C terminal extensions that can direct cellular localization and protein-protein interactions.

The member SIRT6 is widely expressed in all mammalian organs and regulates multiple senescence associated biological processes, including oxidative stress, glucose and fat homeostasis (Mostoslavsky et al., 2006; Zhong et al., 2010; Tao et al., 2013a), inflammatory responses, autophagy, genome integrity, and telomeres homeostasis (Papamichos-Chronakis and Peterson, 2013; Kugel and Mostoslavsky, 2014; Miller and Sadeh, 2014; Lasry and Ben-Neriah, 2015; Tasselli et al., 2017; Abdellatif et al., 2018; De Meyer et al., 2018). Therefore, SIRT6 is involved in many kinds of aging related disease such as neurodegenerative disease, cancer, CVDs. For instance, recent study demonstrated that SIRT6-deficient cynomolgus monkeys exhibit developmental retardation (Zhang W. et al., 2018). However, in Alzheimer's disease (AD) patients, SIRT6 plays

AD-protective function via maintaining genomic stability and preventing DNA damage in brain (Jung et al., 2016; Kaluski et al., 2017). It not only reveals a pivotal role in brain development, but also shows a close relationship between the aberration of SIRT6 with human neurodegenerative diseases. In the context of cancer, SIRT6 was considered as a double-edged sword due to its dual role of both tumor suppression and promotion, depending on the type of tumors (Desantis et al., 2017). It protects against tumor growth through the functions of controlling DNA damage repair, genomic stability, cellular metabolic homeostasis, and apoptosis, while it also associated with the poor clinical outcomes by its enzyme activity regulating cancer pathways in cancers such as hepatocellular and colon cancers (Sebastian et al., 2012; Vitiello et al., 2017; Khan R. I. et al., 2018). In the cardiovascular system, SIRT6 plays a protective function by improving vascular endothelial dysfunction to some extent, delaying the formation of atherosclerotic plaques and inhibiting cardiac hypertrophy and heart failure (Sundaresan et al., 2012; Liu et al., 2016). In addition, several studies showed that SIRT6 is a principal regulator of glucose metabolism homeostasis (Zhong et al., 2010; Xiong et al., 2016). Targeting it may be a promising strategy for attenuating diabetic cardiomyopathy (DCM) and reducing myocardial vulnerability to ischemia-reperfusion injury in diabetic patients (Yu et al., 2021).

In this review, we chiefly interrogate the role of SIRT6 in cell senescence, the main CVDs involved in cell senescence induced by SIRT6 dysfunction, and possible



clinical application of SIRT6 functional regulatory drugs in CVDs.

SIRT6 AND SENESCENCE

Senescence is a multi-factor process involving the regulation of different age-related molecular and cellular events, including oxidative stress and neurodegeneration, glucose and fat homeostasis (Mostoslavsky et al., 2006; Zhong et al., 2010; Tao et al., 2013a), inflammatory responses, autophagy, genome integrity, and telomeres shorten (Papamichos-Chronakis and Peterson, 2013; Miller and Sadeh, 2014; Lasry and Ben-Neriah, 2015; Abdellatif et al., 2018; De Meyer et al., 2018). The role of sirtuins in senescence was discovered in budding yeast, where overexpression of SIR2 increases replicative lifespan. Subsequently, it was reported that elevated sirtuin levels increase lifespan in the nematode *C. elegans* (Tissenbaum and Guarente, 2001) and the fruitfly *Drosophila* (Rogina and Helfand, 2004), indicating an evolutionarily ancient role of sirtuins in longevity assurance. However, despite recently there have debates about the direct role of SIR2 in aging and lifespan extension, especially in budding yeast and *C. elegans* (Kaeberlein, 2010; Kenyon, 2010), the overwhelming majority of significant results still support a potential role for SIRT6 in regulating mammalian lifespan (Yuan et al., 2009; Burnett et al., 2011; Kanfi et al., 2012). SIRT6 was shown to extend lifespan in mammals, while deficiency of SIRT6 was associated with progeria, an accelerated aging disorder (Liao and Kennedy, 2012, 2014). Studies have confirmed the important roles for SIRT6 in protecting against aging and disease pathologies: SIRT6-deficient mice are small and have severe metabolic defects, and by 2–3 weeks of age, they develop abnormalities that are usually associated with aging (Mostoslavsky et al., 2006). SIRT6-deficient monkeys die hours after birth and exhibit severe prenatal developmental retardation (Zhang W. et al., 2018). However, SIRT6 overexpression led to an increase in lifespan in male mice (Kanfi et al., 2012). Mechanistically, SIRT6, being a deacetylase at the specific site of histone H3K9 H3K56 H3K18 (Michishita et al., 2008, 2009; Tasselli et al., 2016), inhibits the transcription of transcription factors related to senescence, maintains the structure of telomere chromatin, prevents genomic instability after DNA damage, and protects cells from senescence (Tennen and Chua, 2011; Kugel and Mostoslavsky, 2014). Here, we summarized the function of SIRT6 in age-related cellular events (Figure 2).

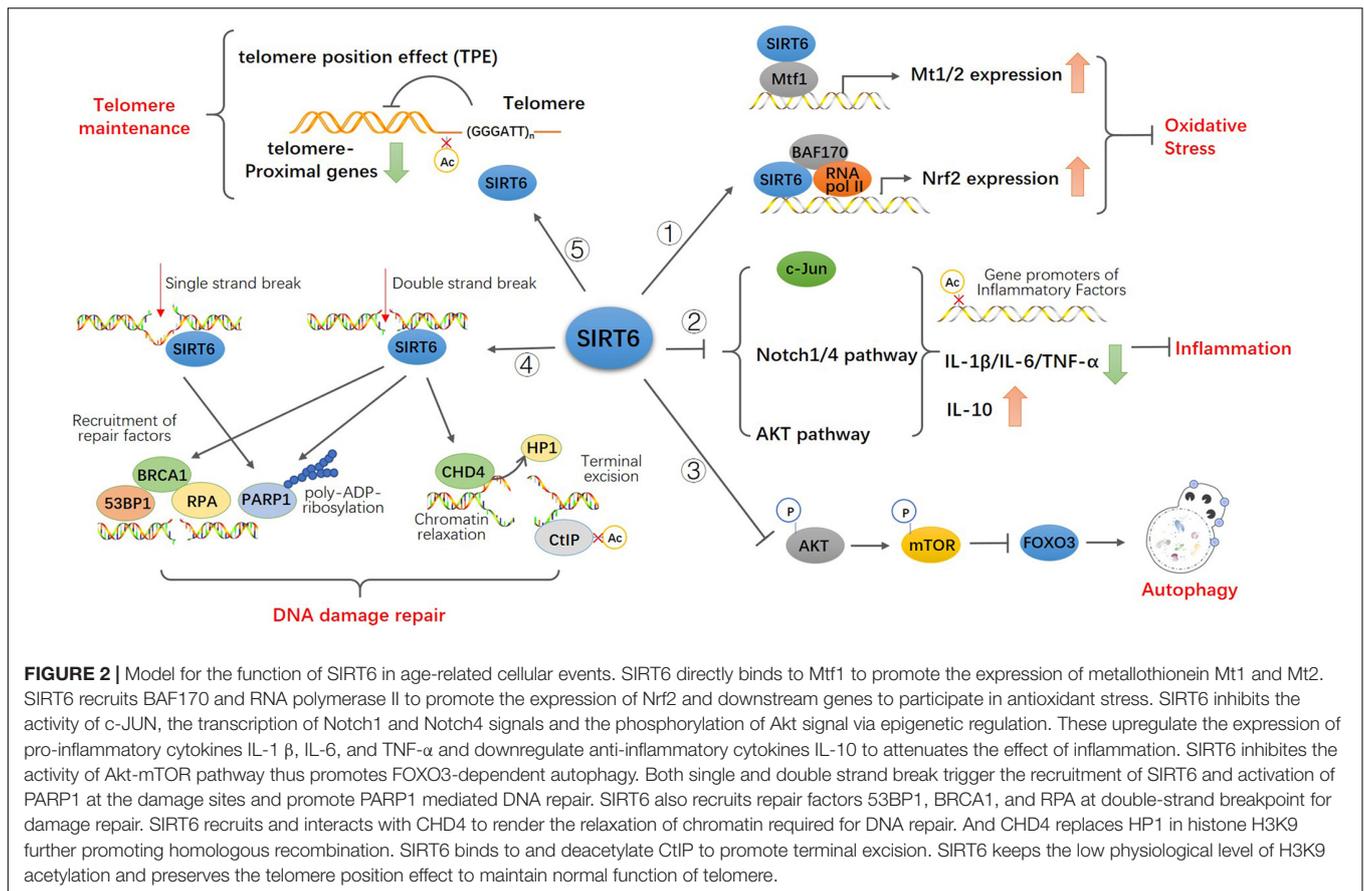
SIRT6 and Oxidative Stress

Based on the free radical theory, aging is triggered by a long-term cumulative damage of toxic free radicals and reactive oxygen species (ROS) to sensitive targets with biological significance. Moreover, early studies revealed that the accumulation of ROS is closely related to the poor prognosis of CVDs (Griendling and FitzGerald, 2003). It is known to all that the maintenance of the heart's pumping action requires functional and morphological integrity of mitochondria to ensure an uninterrupted energy supply. Meanwhile, mitochondria, as heart's energy providers, also

can generate ROS as a by-product. Recent study indicated that an increase in mitochondrial ROS followed by ultrastructural alterations in the mitochondrial cristae lead to cardiomyocyte damage and, ultimately, cell death (Acin-Perez et al., 2018). Treatment of primary fibroblasts with medium, non-lethal doses of exogenous hydrogen peroxide can activate rapid, senescence-like growth arrest (Chen and Ames, 1994). Analogously, cells grown in the company of high oxygen concentrations exhibit a reduced lifespan and show telomeres shorten (von Zglinicki et al., 1995).

Reports indicate that SIRT6 is highly sensitive to cellular redox state and counteracts the effect of ROS (D'Onofrio et al., 2018). As recently revealed, in response to oxidative stress, SIRT6 is phosphorylated by c-Jun N-terminal kinase (JNK) at residue serine10 and that this modification is necessary for efficient recruitment of poly (ADP-ribose) polymerase 1 (PARP1) to DNA break sites and for efficient repair of DSBs (Van Meter et al., 2016). Moreover, it provides the relationship between oxidative stress and DNA repair that is critical for hormetic response and age-related diseases. Furthermore, SIRT6-deficient human mesenchymal stem cells (hMSCs) exhibited accelerated functional decay, a feature predominately characterized by dysregulated redox metabolism and increased sensitivity to the oxidative stress. In addition, SIRT6 could help assemble nuclear factor erythroid 2-related factor 2 (Nrf2)-RNA polymerase II transcription complex, which was required for the transactivation of Nrf2-regulated antioxidant genes (Pan et al., 2016). SIRT6 has been shown to suppress oxidative stress in the ischemic brain and non-alcoholic fatty liver via regulation of Nrf2 (Ka et al., 2017; Zhang W. et al., 2017).

Nrf2 is an evolutionarily conserved redox-sensitive transcription factor that coordinates antioxidant responses, including enzymes that up-regulate detoxification and repair macromolecular damage induced by ROS (Suh et al., 2004; Ungvari et al., 2011a,b,c). It binds to the antioxidant response elements (AREs) and activates the transcription of many antioxidant genes, including glutathione S-transferases (GSTs), heme oxygenase 1 (HO-1), NAD(P)H: quinone oxidoreductase 1 (NQO1), thioredoxin, thioredoxin reductase, as well as proteins involved in scavenging reactive oxygen species (ROS) (Kovac et al., 2015) and glutathione (GSH) biosynthesis and regeneration (Gorrini et al., 2013; Rezazadeh et al., 2019). More importantly, recent advances have identified that the decline in Nrf2-ARE activity is observed in aged cells, which account for that SIRT6 mediated deacetylation of H3K56 is a crucial event safeguarding age-related cells from oxidative stress-associated functional decay (Bailey-Downs et al., 2012; Valcarcel-Ares et al., 2012; Pan et al., 2016). Interestingly, another result indicated that SIRT6 mono-ADP-ribosylation of BAF170, a subunit of BRG/BRM associated factor (BAF) chromatin remodeling complex, is required for activation of a subset Nrf2 responsive genes upon oxidative stress (Rezazadeh et al., 2019). Anyway, these findings showed that SIRT6 serves as an activator of Nrf2-dependent gene transcription. In cardiovascular studies, especially in ischemia/reperfusion injury and vascular endothelial dysfunction, Nrf2 pathway is the major target of SIRT6 to exert antioxidant effects.



In addition, as an adaptive response to the oxidative stress environment, metal transcription factor (MTF) has been previously shown to be the key transcription factor for the induction of metallothionein (Mt) to participate in antioxidant stress (Ghoshal and Jacob, 2001; Laity and Andrews, 2007). The antioxidant stress function of MT in heart prevents cardiomyocytes from diabetic cardiomyopathy and myocardial infarction (Gu et al., 2017; Xue et al., 2019). Recently study revealed that SIRT6 can promote the expression of Mt1 and Mt2. Indeed, both Mt1 and Mt2 promoters were activated by SIRT6. Moreover, SIRT6 can physically interact with MTF1 to have a synergistic effect on those Mt gene promoters (Kim et al., 2019).

Overall, SIRT6 is involved in the regulation of oxidative stress in a variety of tissue cells. And a series of studies have provided compelling evidence demonstrating the pathogenic effect of oxidative stress in CVDs (Zhao et al., 2015; Förstermann et al., 2017; van der Pol et al., 2019). Therefore, targeting SIRT6 to inhibit the generation of ROS and promote the activation of antioxidants represent reasonable therapeutic strategies for CVDs in the future.

SIRT6 and Inflammation

Inflammation is a complex biophysical response of the body to pathogen infection and tissue damage. Although acute inflammation was considered protective, chronic inflammation was linked to numerous diseases (Xiao et al., 2012). For instance,

the occurrence of human aging-related diseases is related to chronic low-grade inflammation, which is characterized by increased levels of circulating IL-6 and C-reactive protein (CRP) (Ferrucci et al., 2005; Wikby et al., 2006). A considerable number of elderly people showed the activation of inflammatory bodies and elevated levels of IL-1 β , which are associated with the risk of chronic aging diseases (Franceschi and Campisi, 2014; Furman et al., 2017). This phenomenon has also been confirmed in elderly rodents and primates, where pro-inflammatory changes have occurred in gene expression profiles of vascular endothelial cells and smooth muscle cells, including upregulated expression of inflammatory cytokines [such as IL-6, IL-1 β , tumor necrosis factor- α (TNF- α)], chemokines, adhesion molecules, inducible nitric oxide synthase and other pro-inflammatory mediators. Moreover, it increases the risk of CVDs, including atherosclerotic visceral diseases (Csiszar et al., 2002, 2003, 2004; Ungvari et al., 2007; Song et al., 2012). In addition, according to the data and the hypotheses presented in the study (Ferrucci and Fabbri, 2018), modulating inflammation is a promising approach not only to prevent CVD but also to slow the decline of health that occurs with aging.

Within the past few years, sirtuins have been identified as novel regulators of the immune system (Yang et al., 2007; Csiszar et al., 2008; Yoshizaki et al., 2009), and several studies show that SIRT6 can suppress inflammation in different tissues (Kawahara et al., 2009, 2011; Zhang N. et al., 2016). One of

the master regulators of both adaptive and innate immunity is the NF- κ B, which forms complexes with many other proteins, including Rel family members (RelA/p65, c-Rel, and RelB). The NF- κ B complexes can translocate from the cytoplasm into the nucleus to trigger expression of target genes that are largely pro-inflammatory. It has been demonstrated that SIRT6, as a potent inhibitor of the NF- κ B system, providing a mechanistic link between inflammation and aging (Kawahara et al., 2009; Zhang N. et al., 2016). A study revealed that SIRT6 promoted microRNA-21 expression, this reduced the expression of TGF- β 2 and IL-1 α and decreased the production of type I collagen and fibroblast proliferation (Fan et al., 2016). Besides, it has been found that SIRT6 restrained TGF- β signaling by deacetylation of H3K9 and H3K56. SIRT6 haploinsufficiency was sufficient for enhancing myofibroblast generation, leading to multiorgan fibrosis and cardiac dysfunction in mice during aging (Maity et al., 2020). Furthermore, recent report unveiled that overexpression of SIRT6 blocked the expression of NF- κ B downstream regulators, such as interleukin (IL)-1 β , IL-6, and matrix metalloproteinase 9 (MMP-9), all of which promoted fibroblast differentiation in TAC-induced cardiac fibrosis (Zhang et al., 2019).

In mouse liver, SIRT6 deacetylates H3K9 on the promoters of pro-inflammatory gene IL-6 and monocyte chemoattractant protein MCP-1 by inhibiting the transcriptional activity of c-JUN. After SIRT6 gene knockout, the expression of pro-inflammatory cytokines IL-1 β , IL-6, and TNF- α was upregulated significantly, while anti-inflammatory cytokines IL-10 was significantly down-regulated, causing chronic inflammation and fibrosis of the liver (Xiao et al., 2012; Kim et al., 2019). In addition, studies have found that SIRT6 also promotes the production and secretion of inflammatory cytokines (Van Gool et al., 2009; Bauer et al., 2012; Jiang et al., 2013, 2016), leading to chronic inflammation, which is the basis of neuronal death in Parkinson's disease and other neurodegenerative diseases (Nicholatos et al., 2018). Therefore, it is worthy of detailed investigation of the relationship between SIRT6 and other aging-related diseases. In mouse glomerular podocytes, SIRT6 inhibits the transcription of Notch1 and Notch4 signals via epigenetic regulation, lowers the expression of inflammatory cytokines IL-1 β , IL-6, and TNF- α , protects podocytes from inflammatory damage, and effectively reduces the occurrence of chronic proteinuria nephropathy (Liu et al., 2017). In the adventitia inflammation induced by TNF- α , SIRT6 attenuates vascular inflammation by inhibiting the phosphorylation of Akt signal and the expression of monocyte chemoattractant proteins MCP-1 and IL-6 (He Y. et al., 2017).

SIRT6 and Autophagy

Autophagy refers to the cellular process of degradation and recycling of long-lived or damaged organelles and proteins. This includes microautophagy (invagination of lysosomal membrane), molecular chaperone-mediated autophagy (transport of soluble proteins to lysosomes through molecular chaperones and lysosomal membrane receptors) and macroautophagy (where impurities are swallowed by double-membrane autophagosomes before lysosome fusion)

(Shirakabe et al., 2016; Delbridge et al., 2017; Nakamura and Yoshimori, 2018; Zhang Y. et al., 2018). Autophagy is initiated by class III phosphatidylinositol-3 kinase (PI-3K) and Beclin-1. Autophagosomes undergo prolongation, microtubule light chain-3 (LC3) recruitment, LC3 proteolysis (lipolysis) to form autophagy lysosomes (fusion of autophagosomes and lysosomes), which regulate cell survival and senescence. Accumulating evidence suggested that autophagy is an essential mechanism for maintenance of tissue homeostasis in the heart during the aging process (Levine and Kroemer, 2008; Rubinsztein et al., 2011; Gatica et al., 2015). Mitophagy is an autophagic response that definitely targets damaged mitochondria. It was critical for the bioenergetics of the cardiovascular system, and mitophagy disorder could develop cardiac dysfunction (Bravo-San Pedro et al., 2017; Nicolas-Avila et al., 2020). Numerous studies have indicated that activate autophagy increase the healthy lifespan of animals, a positive effect that is generally associated with decelerated cardiovascular senescence (Zaglia et al., 2014; Gong et al., 2015; Eisenberg et al., 2016).

The two primary regulatory signal mechanisms implicated in autophagy disorders include inhibition of AMP-dependent protein kinase (AMPK) activation and up-regulation of class I PI-3K/Akt signal, resulting in excessive activation of rapamycin target (mTOR) signal and autophagy disorder (Kennedy and Lamming, 2016). Evidence has emerged that SIRT6 plays critical roles in the process of controlling autophagic degradation (Ng and Tang, 2013). Autophagy could be a harmful process to accelerate aging in some conditions. In a study of human bronchial epithelial cells, it was found that SIRT6 protects human bronchial epithelial cells from senescence by inhibiting insulin-like growth factor signaling-induced autophagy and regulating mTOR signaling (Shao et al., 2016).

However, in cardiovascular cells, autophagy mainly acts as beneficial process to maintain cellular homeostasis and delay aging. In macrophage foam cell from atherosclerosis model, SIRT6 and key autophagy effectors (ATG5, LC3B, and LAMP1) had been observed significantly and the overexpression of SIRT6 markedly reduced foam cell formation by inducing autophagy. The silencing of the key autophagy initiation gene ATG5 reversed the autophagy-promoting effect of SIRT6 with an increase in foam cells, which implied an autophagy-dependent pathway of SIRT6 in protecting against atherosclerosis by reducing foam cell formation (He J. et al., 2017).

Moreover, it has been found that Isoproterenol (ISO)-caused cardiac hypertrophy accompanying with a significant decrease in autophagy activity in primary neonatal rat cardiomyocytes (NRCMs). SIRT6 overexpression enhanced autophagy in NRCMs, whereas knockdown of SIRT6 by RNA interference led to suppression of cardiomyocyte autophagy (Lu et al., 2016). In terms of mechanism, SIRT6 activates FOXO3-dependent autophagy by reducing the level of Akt protein and phosphorylation, thereby enhancing the formation of LC3-II and down-regulating the expression of p62 (Lu et al., 2016). These results are consistent with the previous study that SIRT6 inhibit the transcription of IGF/Akt pathway genes via H3K9 deacetylation, which contributes to suppression of cardiac hypertrophy (Sundaresan et al., 2012).

SIRT6, Genome Stability, and DNA Damage Repair

During the progression of aging, DNA, RNA, and proteins are constantly subjected to chemical alterations that impair their function (Ou and Schumacher, 2018). However, the consequences of DNA damage are much more widespread as DNA contains the information for all RNA and proteins a cell produces. It was considered that thousands of damaging events occur each day in every single one of our cells (De Bont, 2004). Persistent DNA damage can block transcription and replication thus hampering cellular functionality and promoting cellular senescence (Ou and Schumacher, 2018). To counteract the destructive effect of these actions and to maintain genomic integrity, it triggers a DNA damage response (DDR), which ensures efficient repair of all types of damage, including individual DNA base lesions and breaks (Ciccio and Elledge, 2010). The defects in DNA damage response further increases the burden of DNA damage, blocks cell cycle progression and causes the senescence of organs (Niedernhofer et al., 2018). Both endogenous and exogenous factors trigger DNA damage. The endogenous factors are the products of normal cell metabolism, resulting in oxidation, nitrication, and alkylation of DNA (Niedernhofer et al., 2018). On the other hand, exogenous factors, including ionizing radiation, ultraviolet radiation, and alkylating agents trigger DNA single-strand or double-strand breaks, which further causes an increase of inflammatory cytokines and accelerates the aging of the body (Rodier et al., 2009). Many repair mechanisms exist to ensure that nearly all the daily DNA damage is repaired, including base excision repair (BER), nucleotide excision repair (NER), non-homologous end connection (NHEJ), and homologous recombination (HR). Besides, each pathway identifies and repairs specific types of DNA damage to address most DNA damage, but not all DNA damage. It has been discovered that SIRT6 binds closely to chromatin and is an NAD^+ -dependent deacetylase of H3K9 and H3K56. Histone deacetylation is related to chromatin conformational closure and decreased chromatin accessibility. Therefore, the discovery of this enzyme activity confirmed the role of SIRT6 in regulating the dynamic binding of DNA damage repair and chromatin and gene expression (Michishita et al., 2008, 2009; Yang et al., 2014).

DNA damage is linked to several human diseases, including cancer, neurodegeneration, aging and CVDs (Madabhushi et al., 2014; Ou and Schumacher, 2018; Nakada et al., 2019; Reisländer et al., 2020). In the early stage of DNA damage, SIRT6 recruited SNF2H (an ATP-dependent chromatin remodeling) to DNA double-stranded breakpoint (DSB), to prevent genomic instability via local deacetylation of H3K56, and effectively recruited repair factors 53BP1, BRCA1, and RPA for damage repair (Toiber et al., 2013). In mammalian cells subjected to oxidative stress, SIRT6 was recruited to the DSB to bind to poly (ADP ribose) polymerase 1 (PARP1) and stimulated its activation by catalyzing the ADP ribose glycosylation of the K521 residue of PARP1, thus promoting the repair of DNA damage by connecting with non-homologous ends and HR (Mao et al., 2011). However, overactivation

of PARP depletes the level of NAD content (Bürkle, 2001; Jagtap and Szabo, 2005), which is essential for the activity of sirtuins. It is critical to limit the overactivation of PARP1 in the heart to optimize its cardioprotective effect (Liu et al., 2014).

Further, reports indicate that stress-activated protein kinase JNK phosphorylates SIRT6 on serine 10 to promote DNA double-strand break (DSB) repair in response to oxidative stress. This post-translational modification helps to mobilize SIRT6 to the DNA damage site, effectively recruit PARP1 to the DNA cleavage site and promote repair factors 53BP1 and NBS1 to repair effectively (Van Meter et al., 2016). Chromatin relaxation is a prerequisite for the repair of DNA damage. Recent studies suggest that during DNA damage, SIRT6 rapidly shifts to the site of DNA damage, interacts with chromatin remover CHD4, and recruits CHD4, to promote the repair of DNA damage caused by chromatin relaxation. Once the damage site is reached, CHD4 replaces heterochromatin protein 1 (HP1) in histone H3K9 trimethylation (H3K9me3), whereas CHD4-dependent chromatin relaxation and H3K9me3 competition for the release of HP1, in damaged chromatin, are both necessary for precise HR (Hou et al., 2020). When repairing DNA damage via homologous recombination pathway, SIRT6 binds to DSB excision protein CtIP (carboxyl-terminal binding protein acting protein) and deacetylate CtIP to promote terminal excision (Kaidi et al., 2010). Highly unstable genomes were found in patients with multiple myeloma. A high level of SIRT6 promotes the repair of Chk1 DNA damage by triggering ERK2/p90RSK signal inactivation and offering resistance to DNA damage. The deletion of the SIRT6 gene enhances the sensitivity to DNA damage (Cea et al., 2016). It has been found that SIRT6 will be located at the damage site of single-strand breaks in a PARP1-dependent manner, and downstream repair factors will be recruited to promote base excision and repair of BER. In addition, the efficiency of BER decreased significantly with the increase of age, and overexpression of SIRT6 in senescent cells could significantly improve the efficiency of BER (Xu et al., 2015).

SIRT6 and Telomere Homeostasis

Mammalian telomeres are the terminal structures of chromosomes, which comprise TTAGGG tandem repeats and associated protein complexes (protegerins). This complex protects chromosomes from end-to-end fusion and degradation by forming a special tring-like structure to avoid the ends of chromosomes being identified as double-stranded DNA breaks (Griffith et al., 1999; de Lange, 2005; Palm and de Lange, 2008). With each round of cell division, telomeres become shorter and when the shortened telomeres reach the critical length, it would trigger a sustained DDR and cell senescence (Shay, 2016). To escape senescence, cells might active or up-regulate telomerase, a cellular reverse transcriptase that adds new DNA to telomeres at the end of chromosomes. However, most normal human cells lack the telomerase that maintains telomeres (Baur, 2001). Therefore, telomere length is widely considered as a marker of biological aging, although this parameter does not strictly satisfy the criteria of cell senescence by the American

Federation for Aging Research (Mather et al., 2011; De Meyer et al., 2018). The most factors that can modulate telomere length are also cardiovascular risk factors. In clinical studies, an association between short leukocyte telomere length (LTL) and cardiovascular disorders, including atherosclerosis, myocardial infarction, heart failure, and hypertension, has been repeatedly shown (Nowak et al., 2002; Samani and van der Harst, 2008).

In human fibroblasts with specific knockout of the SIRT6 gene, an apparent end-to-end fusion of chromosomes and premature senescence were observed, which could be effectively reversed by ectopic expression of telomerase, suggesting that SIRT6 is implicated in maintaining telomere stability. The lack of SIRT6 caused the excessive acetylation of H3K9, thus leading to telomere dysfunction (Michishita et al., 2008). Furthermore, the function of SIRT6 in maintaining telomere to protect from senescence is also proved in other tissues including vascular smooth muscle cells (VSMCs) (Cardus et al., 2013; Grootaert et al., 2021).

The deficiency of SIRT6 not only causes telomere damage, but also destroys the closed chromatin environment near the telomere and triggers telomere position effect (TPE) dysfunction (Tennen et al., 2011). TPE refers to the epigenetic silencing of proximal telomere genes (Aparicio et al., 1991; Buck and Shore, 1995; Ng et al., 2002; Altaf et al., 2007) and the intensity of telomere silencing enhances with the increase of telomere length (Kyrion et al., 1993; Buck and Shore, 1995). It has been found that the depletion of SIRT6 in human cells elicits TPE dysfunction, while the restoration of SIRT6 expression is sufficient to reconstruct the silencing of the telomere gene (Tennen et al., 2011). Together, these findings establish new roles for SIRT6 in regulating an aging-associated epigenetic silencing process and provide new mechanistic insights into chromatin silencing at telomeres (Baur, 2001; Tennen et al., 2011; Robin et al., 2014).

In addition, telomere repeat binding factor 2 (TRF2), as a significant regulator of telomere integrity, it exerts telomere protection by blocking ATM signal and non-homologous terminal connection to (NHEJ) and promoting telomere replication (van Steensel et al., 1998; Denchi and de Lange, 2007; Ye et al., 2010). Early research confirmed that plaque VSMCs senescence associated with the loss of TRF2 that plays a critical role in process of atherosclerosis (Wang et al., 2015). Interestingly, recent study reveals a novel molecular mechanism that SIRT6 specifically interacts with TRF2 and promotes TRF2 degradation in response to DNA damage (Rizzo et al., 2017).

Taken together, we reviewed the implication of SIRT6 in maintaining the telomere stability. However, recent studies uncover a telomere-dependent control of sirtuins expression and raise the possibility of a feed forward loop whereby damaged telomeres decrease sirtuins expression, which could further impair telomere integrity, leading to a progressive deterioration (Amano et al., 2019). Telomere dysfunction and sirtuins repression, independently, are highly associated with susceptibility to CVDs, accelerated aging, and lifespan reduction, and these two pathways are closely intertwined and cooperate to drive disease.

SIRT6 AND AGING RELATED CARDIOVASCULAR DISEASES

Mounting evidence indicates that activation of SIRT6 can have beneficial effects in CVDs, including atherosclerosis (Zhang Z. et al., 2016; Wang et al., 2020; Grootaert et al., 2021), cardiac hypertrophy (Sundaresan et al., 2012; Lu et al., 2016; Zhang X. et al., 2016), hypertension (Guo et al., 2019), and heart failure (Li et al., 2017; **Table 1**).

It has been established as a significant factor and regulates essential molecular pathways in multiple pathological conditions. In addition, cardiocytes with SIRT6 specific knockout show accumulation of lactate, indicating compromised mitochondrial oxidation. The mechanism involves the activation of FOXO1-mediated transcription of PDK4 to modulate cardiac glucose metabolism (Khan D. et al., 2018). Furthermore, it is important for pancreatic beta cells to improve insulin secretion through the activation of SIRT6. Therefore, pharmacological activation of SIRT6 may be useful to enhance insulin secretion and it has potential for the development of effective drugs to treat diabetic cardiomyopathy (Xiong et al., 2016). When subjected to prolonged hypoxia, cardiomyocytes from transgenic mice with overexpression of SIRT6 showed the improved survival owing to the block of necrosis/apoptosis pathways (Maksin-Matveev et al., 2015).

SIRT6 and Atherosclerosis

Atherosclerosis is the primary trigger of vascular diseases across the globe with ischemic heart disease being one of its major complications (Herrington et al., 2016). Several studies have shown that endothelial cell dysfunction, abnormal lipid metabolism, and other factors are implicated in the occurrence of atherosclerosis (Gimbrone and García-Cardena, 2016; Musunuru and Kathiresan, 2016). Vascular smooth muscle cells (VSMCs) comprise a major cellular component of the atherosclerotic plaque. VSMCs in human atherosclerotic plaques are characterized by apoptosis, DNA damage, inflammation and an altered energy metabolism (Grootaert et al., 2018). Furthermore, VSMCs from human atherosclerotic plaques undergo senescence and it promotes atherosclerosis and plaque instability (Wang et al., 2015), while removal of senescent cells can reduce atherosclerosis (Childs et al., 2016). Recent study has demonstrated that SIRT6 protein (but not mRNA) expression is declined in VSMCs in human and mouse atherosclerotic plaques (Grootaert et al., 2021). Besides, VSMC-specific overexpression of SIRT6 restrains atherogenesis and decreases tissue markers of cell senescence and inflammation, dependent upon its deacetylase activity. This indicates that endogenous levels of SIRT6 is a critical regulator of VSMC senescence and reveals a therapeutic potential of SIRT6 in atherosclerosis.

SIRT6 and Endothelial Dysfunction

Early study has revealed that vascular endothelial maintains vascular tension, inhibits atherosclerosis, and forms a barrier to control the migration of various substances between blood vessels and tissues (Galley and Webster, 2004). It is an important locus of critical regulatory nodes to retain the homeostasis of the

TABLE 1 | SIRT6 is directly involved in the regulation of cardiovascular diseases.

SIRT6-linked CVD	Targets		SIRT6-linked cellular function	Species	References
Atherosclerosis	H3K9		Telomere homeostasis	Human/mouse	Grootaert et al., 2021
	H3K9/H3K56	NKG2D ligands			Zhang Z. et al., 2016
	Msr1		Autophagy	Mouse	Wang et al., 2020
Cardiac fibrosis	H3K9/H3K56	TGF- β		Mouse	Arsiwala et al., 2020
	AMPK-ACE2		Inflammation	Diabetic patients	Balestrieri et al., 2015
	NF- κ B			Mouse	Maity et al., 2020
Cardiac hypertrophy	H3K9	c-JUNIGF-AKT		Human/mouse	Sundaresan et al., 2012
	NF- κ B	PI3K/Akt	Autophagy	Rats	Lu et al., 2016
	STAT3			Rats	Shen et al., 2016
	NF- κ B			Rats	Zhang X. et al., 2016
	NFATc4			Rats	Yu et al., 2013
Cardiac glucose metabolism	FOXO1/PDK4			Mouse	Khan D. et al., 2018
Cardioprotection against apoptosis	TIP60-GATA4			Mouse	Peng et al., 2020
Cardioprotection against hypoxia	pAMPK α /NF- κ B			Mouse	Maksin-Matveev et al., 2015
Heart failure			Telomere homeostasis	Mouse	Li et al., 2017
Hypertension	H3K9	Nkx3.2-GATA5		Mouse	Guo et al., 2019
Coronary artery disease	Two tagSNPs rs352493 and rs3760908 within SIRT6 Gene			Chinese Han population	Tang et al., 2016
Myocardial infarction	Two tagSNPs rs3760905 and rs4359565 within SIRT6 Gene		–	MI patients	Wang et al., 2016

cardiovascular system. Endothelial cell dysfunction encompasses a constellation of various non-adaptive alterations in functional phenotype, which have important implications for the regulation of hemostasis and thrombosis, local vascular tone and redox balance, and the orchestration of acute and chronic inflammatory reactions within the arterial wall (Gimbrone and García-Cardeña, 2016). Therefore, it is significant to point out that endothelial cell dysfunction is involved in many disease processes, including atherosclerosis, pulmonary arterial hypertension and sepsis (Gimbrone and García-Cardeña, 2016; Joffre et al., 2020; Evans et al., 2021). Here we focus on the involvement of SIRT6 in atherosclerosis and endothelial cell dysfunction.

In the process of atherosclerosis, there exist several factors of endothelial cell dysfunction, including endothelial vasodilation damage, endothelial cell injury and repair disorder, abnormal expression of endothelial adhesion molecules as well as cytokines. Endothelial cell dysfunction manifested in lesion-prone areas of the arterial vasculature results in the earliest detectable changes in the life history of an atherosclerotic lesion (Stary, 2000; Virmani et al., 2000).

SIRT6 is expressed in endothelial-rich tissues including the aorta, lung, and brain. In SIRT6 gene knockout mice and endothelium-specific knockout mice, endothelium-dependent vasodilation of aorta to acetylcholine (ACh) was significantly impaired (Xu et al., 2017). To prevent atherosclerosis, maintain

the health of endothelial cells, and slow down the aging process of endothelial cells, it is significantly vital to repair damaged endothelial cells (Lappas, 2012). SIRT6 protects endothelial cells from telomere and DNA damage, prevents premature senility, and maintains the ability of cell replication and angiogenesis *in vitro*, all of which are known to inhibit the development of endothelial dysfunction (Cardus et al., 2013). Endothelial cell adhesion molecules, including vascular cell adhesion molecule (VCAM-1), play an important role in atherosclerosis by promoting the adhesion of monocytes to inflammatory endothelium (Libby et al., 2009, 2011). The role of SIRT6 in monocyte adhesion to endothelial cells was evaluated by transfecting SIRT6 into human umbilical vein endothelial cells or interfering with its expression. It has been shown that SIRT6 inhibited monocyte adhesion by lowering the expression of VCAM-1 in endothelial cells induced by TNF- α (Xu et al., 2017).

Also, the abnormal expression of endothelial inflammatory factors regulated by SIRT6 is implicated in the formation of atherosclerosis. Damaged vascular cells (endothelium and smooth muscle) are active in secreting cytokines including IL-1, monocyte chemoattractant protein-1 (MCP-1) and granulocyte-monocyte stimulating factor (GM-CSF). These cytokines produce local intercellular autocrine and paracrine signal rings in the vascular wall to promote the progression of atherosclerosis (Pober and Sessa, 2007; Gimbrone and García-Cardeña, 2016).

In the progression of atherogenesis, NF- κ B signal tends to play a central role in the pro-inflammatory activation of endothelial cells by regulating the expression of many downstream molecules such as VCAM-1 and MCP-1 (Collins and Cybulsky, 2001). Noteworthy, SIRT6 interacts with NF- κ B RELA subunits and deacetylates H3K9 on the promoter of NF- κ B target gene to attenuate NF- κ B signal (Kawahara et al., 2009). Furthermore, recent studies found that the activation of NF- κ B might trigger fundamental changes in the chromatin structure of endothelial cells via the formation of super-enhancer complexes, hence, regulating the epigenetic level of the phenotype of pro-inflammatory endothelial cells in the process of atherosclerosis (Brown et al., 2014).

Recent reports argued that the epigenetic regulation of NKG2D ligands is also involved in atherosclerosis of SIRT6 heterozygous mice. The down-regulation of SIRT6 up-regulates the expression of NKG2D ligand and causes an increased expression of inflammatory cytokines, which could be nearly completely blocked by NKG2D ligand inhibition (Zhang Z. et al., 2016). Notably, Tumor necrosis factor superfamily member 4 (TNFSF4) is a gene affecting atherosclerosis susceptibility and encodes OX40 ligand. SIRT6 inhibits atherosclerosis by deacetylating H3K9 on the promoter of the TNFSF4 gene (Wang et al., 2005). Studies have found trace cholesterol crystals (CCs) in atherosclerotic plaques, which represent one of the mechanisms causing endothelial dysfunction. In HUVECs, SIRT6 significantly promotes eNOS activity and down-regulates the expression of intercellular adhesion molecules (ICAM-1) and VCAM1 by activating Nrf2, thereby alleviating endothelial dysfunction induced by CCs (Jin et al., 2020). In SIRT6 knockout mice, atherosclerotic plaque was enlarged, plaque vulnerability was enhanced, and the expression of ICAM-1 in aortic endothelial cells was significantly up-regulated, implying that SIRT6 is the primary negative regulator of endothelial dysfunction and atherosclerotic development (Liu et al., 2016).

SIRT6 and Lipid Metabolism

Sources of evidence from clinical studies suggest that low-density lipoprotein-cholesterol causes atherosclerosis-related CVDs (Ference et al., 2017). As such, regulating homeostasis of LDL-cholesterol is significantly critical to body health. Further, additional evidence asserts that proprotein converting enzyme subtilin/Kexin 9 (PCSK9) binds to liver low-density lipoprotein receptor (LDLR) and promotes its degradation in lysosomes, causing a decrease in LDL uptake and an increase in LDL cholesterol concentration (Bergeron et al., 2015). Besides, overexpression of the SIRT6 gene could reduce the level of LDL-cholesterol in hepatocytes of mice fed with a high-fat diet. It has been confirmed that SIRT6 could be recruited by FOXO3 to the promoter region of the PCSK9 gene and inhibit its expression through deacetylation of H3K9 and H3K56, thereby reducing the level of LDL-cholesterol. SIRT6 deficiency can lead to an upregulated expression of the PCSK9 gene and an increase of LDL-cholesterol (Tao et al., 2013a). Also, sterol regulatory element-binding protein (SREBP)-2, which controls the expression of cholesterol biosynthesis rate-limiting enzyme HMG-CoA, is a

vital regulator of cholesterol biosynthesis. At the mechanism level, SIRT6 was also recruited to the (SREBP)-2 gene promoter by FOXO3 to inhibit its expression and reduce cholesterol biosynthesis via deacetylation of H3K9 and H3K56 (Tao et al., 2013b).

Additionally, the formation of macrophage foam cells is a typical pathological change of early atherosclerotic (AS), which is primarily due to the imbalance between cholesterol inflow and efflux in mononuclear macrophages and the accumulation of cholesterol ester (CE) in cytoplasmic lipid droplets (LDs) (Moore and Tabas, 2011). Moreover, oxidized low-density lipoprotein cholesterol (ox-LDL), which binds to scavenger receptor (Sr) and accumulates in the cytoplasm has been reported to play a pathogenic role in the occurrence and development of AS (Mitra et al., 2011). Under the condition of ox-LDL, SIRT6 inhibits the expression of miR-33 (an mRNA that negatively regulates ABCA1 and ABCG1), promotes autophagy and cholesterol efflux, and reduces the formation of macrophage foam cells, thereby delaying the progress of AS. SIRT6 gene knockout promotes the formation of macrophage foam cells, hence promoting the formation of atherosclerosis (He J. et al., 2017). Generally, these findings suggest that SIRT6 plays a vital role in low-density lipoprotein cholesterol metabolism, potentially counteracting the formation of atherosclerosis.

SIRT6, Myocardial Hypertrophy, and Heart Failure

After birth, cardiomyocytes withdraw from the cell cycle and become terminally differentiated cells. In adult hearts, compensatory cardiac hypertrophy develops into cardiac hypertrophy by increasing the size of individual cardiomyocytes rather than the number of cardiomyocytes to cope with increased workload. This compensatory mechanism is accompanied by an increase in the size of cardiomyocytes, and the imbalance of fetal genetic programming as well as an increase of protein synthesis (Rohini et al., 2010). Hypertrophy is initially an adaptive response to physiological and pathological stimuli, however, pathological hypertrophy usually progresses to heart failure under the regulation of different cellular signaling pathways (Nakamura and Sadoshima, 2018). The incidence of cardiac hypertrophy sharply increases with age, implying that aging-related mechanisms might play a key role in the molecular regulation of myocardial hypertrophy (Lakatta and Levy, 2003). Reports have confirmed that SIRT6 plays a negative regulatory role in cardiac hypertrophy. SIRT6 knockout mice have cardiac hypertrophy and heart failure, while SIRT6 transgenic mice are not influenced by hypertrophy (Sundaresan et al., 2012). In addition to myocardial hypertrophy, studies have shown that the progression of heart failure is also related to extensive fibrosis, abnormal activation of insulin-like growth factor (IGF)-Akt signal, cardiac hyperstress mediated by β -adrenoceptor, and damage of autophagy (Tian et al., 2015; Lu et al., 2016; Zhang W. et al., 2016).

In the model of hypertrophic cardiomyocytes induced by angiotensin II and coarctation of the abdominal aorta, SIRT6 inhibits the transcriptional activity of NF- κ B by deacetylating

H3K9, thereby inhibiting cardiac hypertrophy (Yu et al., 2013). In addition, in cardiac fibroblasts stimulated by angiotensin II and rat myocardium treated with coarctation of the abdominal aorta, it was further confirmed that SIRT6 inhibited the transcriptional activity of NF- κ B via deacetylation of H3K9, and inhibited cardiac fibroblasts differentiation into myofibroblasts, thus inhibiting cardiac fibrosis. In SIRT6 knockout cardiac fibroblasts, extracellular matrix deposition and α -SMA increase promote the transformation into myofibroblasts and trigger extensive cardiac fibrosis (Tian et al., 2015).

Additionally, the level of intracellular NAD plays a crucial role in cardiomyocyte hypertrophy. The expression of Nmnat2 (central enzyme of NAD biosynthesis) is down-regulated in hypertrophic cardiomyocytes induced by angiotensin II and constriction of abdominal aorta. Overexpression of Nmnat2 promotes the activation of SIRT6 and blocks angiotensin II-induced cardiac hypertrophy (Cai et al., 2012). Increasing evidence reveals that overactivation of PARP-1 plays a key role in the pathogenesis of cardiac hypertrophy and heart failure. Nonetheless, excessive activation of PARP-1 depletes its substrate NAD and causes cell death. Being a new PARP-1 inhibitor, AG-690/11026014 protects cardiomyocytes from angiotensin II-induced hypertrophy by restoring the NAD level and SIRT6 activity (Liu et al., 2014). The abnormal activation of insulin-like growth factor (IGF)-Akt signal is closely linked to the occurrence and development of numerous diseases including heart failure. Studies on the hearts of mice confirmed that SIRT6 inhibits the activation of the IGF-Akt signal by inhibiting c-Jun transcriptional activity and deacetylation in H3K9, thereby blocking cardiac hypertrophy. Nonetheless, SIRT6 knockout mice promotes the over-activation of multiple IGF signal-related genes, leading to cardiac hypertrophy and heart failure (Sundaresan et al., 2012).

Elsewhere, studies found that the activation of signal transducer and activator of transcription 3 (STAT3) is critical in β -adrenergic receptor-mediated pathological remodeling and heart failure. In phenylephrine (PE)-induced hypertrophic cardiomyocyte model and isoproterenol (ISO) induced hypertrophic rat model, the mRNA and protein expression of STAT3 and phosphorylation level (P-STAT3) was significantly upregulated, while the hypertrophic biomarkers including ANF and BNP increased. In contrast, the deacetylase activity of SIRT6 decreased, while the effect of PE-induced hypertrophy could be eliminated by overexpression of the SIRT6 gene. Similarly, the up-regulation of ANP and BNP caused by SIRT6 gene knockout can be reversed by silencing of STAT3. Besides, SIRT6 has been suggested to protect cardiomyocytes from hypertrophy by preventing PE-induced STAT3 activation (Zhang X. et al., 2016).

In the heart, autophagy promotes survival primarily by clearing misfolded protein aggregates and damaged organelles accumulated in cardiomyocytes during cellular stress and nutritional deprivation. While long-term up-regulation of autophagy triggers self-destruction and leads to heart failure (De Meyer and Martinet, 2009). After treatment of primary neonatal rat cardiomyocytes with ISO, apparent hypertrophy and autophagy damage were observed. Also, it was confirmed that SIRT6 could protect cardiomyocytes from hypertrophy

by inhibiting the Akt signal, thus, promoting the activation of FOXO3 transcription factor, and enhancing autophagy (Lu et al., 2016).

In addition, compensatory hypertrophy of cardiomyocytes is related to the increase of protein synthesis. One of the master regulators of protein synthesis inside the cell is the nutrient and energy sensor kinase mechanistic target of rapamycin (mTOR) (Laplante and Sabatini, 2009; Saxton and Sabatini, 2017). It has been found that SIRT6 acts as a key regulator of cellular protein synthesis by transcriptionally regulating the mTOR signaling in partnership with the transcription factor Sp1, and the whole process independent of its deacetylase activity (Ravi et al., 2019). Besides, in the hypertrophic heart induced by ISO, the expression of SIRT6 was down-regulated, while the inhibition of mTOR restored cardiac function in muscle-specific SIRT6 knockout mice, which spontaneously developed into cardiac hypertrophy (Saxton and Sabatini, 2017; Ravi et al., 2019). Taken together these data establish a critical connection between SIRT6, mTOR signaling, protein synthesis and cardiac hypertrophy. It will contribute toward understanding and treating diverse pathologies associated with aging.

CLINICAL APPLICATION PROSPECT IN AGING AND CVDs

Given the advantaged effects of SIRT6 in regulating cell senescence and CVDs, targeted activation of SIRT6 and its downstream mechanism signals will be a potential way of delaying aging and treating CVDs. Here, we mainly discuss the activators of SIRT6 in the existing or potential clinical application in aging and CVDs.

Caloric restriction (CR), the significant decrease in calorie intake, is a strategy for improving health and increasing lifespan (Madeo et al., 2019). It has been shown to improve heart function, suppress markers of inflammation and reduce the risk of CVDs and diabetes in humans (Caristia et al., 2020; Kirkham et al., 2020). The beneficial effects of CR occur through an extreme wide range of molecular mechanisms, largely overlapping with epigenetic factors like sirtuins (Gensous et al., 2019) and the promotion of autophagy process (Abdellatif et al., 2018). However, CR has been shown to increase risk of diminishing muscle strength, aerobic capacity, and bone mineral density (Mattison et al., 2012). Therefore, proper exercise in addition to a CR diet is crucial. Recent study found that calorie restriction and physical exercise effectively regulate the activity of sirtuins. For instance, exercise training can effectively regulate the activity of SIRT6 in the skeletal muscle of aged rats and delay the aging process (Koltai et al., 2010). Moreover, caloric restriction significantly improved the renal insufficiency of aged rats, enhanced the expression of SIRT6 and inhibited the transduction of NF- κ B signal (Koltai et al., 2010; Zhang N. et al., 2016). These findings suggested that CR was a beneficial life habit that can delay the aging process by regulating SIRT6, which is worthy of the attention of patients with aging-related diseases.

So far, the compounds that can specifically regulate the activity of SIRT6 in CVDs are still limited. The Chinese herbal

medicine, icariin, widely used in eastern countries to treat specific age-related diseases, including CVDs and the improvement of neurological function, has been proved to be an activator of SIRT6. In an *in vitro* cell model, it was discovered that 10^{-16} – 10^{-8} mol/L icariin could effectively activate the expression of SIRT6 protein and delay cell senescence by inhibiting NF- κ B signal transduction (inhibiting the expression of TNF- α , ICAM-1, IL-2, and IL-6). In the future, we need to supplement the clinical research of icariin in the treatment of CVDs (Chen et al., 2015).

As a water-soluble natural amino acid, ergothioneine (Egt) exists widely in animals and plants. It accumulates a high concentration in some tissues via food chain intake (Halliwell et al., 2018). Several lines of evidence show that it has the effect of anti-oxidation and anti-cell aging, including the protective effect on CVDs and chronic inflammatory injury (D'Onofrio et al., 2016; Servillo et al., 2017). Moreover, it has been found that Egt inhibits the aging process by activating the expression of SIRT1 and SIRT6 protein in endothelial cells, thus reducing the production of ROS and suppressing the downstream NF- κ B pathway (Tang et al., 2015). Nonetheless, so far, while acknowledging the absence of toxicity in the range of millimoles of intracellular concentration, the number of clinical studies to evaluate the efficacy and safety of dietary supplementation of Egt is still limited. As such, enriching additional studies on the treatment of CVDs with large samples of Egt is critical.

Other activators of SIRT6 have the biological function of anti-cancer, while the potential effect of these activators in CVDs needs further studies. UBCS039 directly binds to SIRT6 at the hydrophobic pocket and induces H3K9 and H3K56 deacetylation in breast cancer and colorectal cancer cells (Iachettini et al., 2018). Quinoline-4-carboxamides is an excellent selective SIRT6 activator with the function of antiviability and antiproliferation activities in pancreatic ductal adenocarcinoma (PDAC) cells through decreased acetylation level of H3K9, H3K18, and H3K56 (Chen et al., 2020). Moreover, recent studies have identified allosteric SIRT6 activators, MDL-800, MDL-801, and MDL-811, which bound to the surface allosteric site of SIRT6 and activate SIRT6 deacetylation by promoting the binding affinity of acetylated substrates to cofactor. They also exert a tumor suppressor effect by reducing the acetylation level of H3K9 and H3K56, thus leading to cell cycle arrest in hepatocellular carcinoma, colorectal cancer and non-small cell lung cancer (Huang et al., 2018). We predict that MDL-800 could reduce the Ischemia reperfusion injury in cardiomyocytes, direct evidence

of the function of MDL-800 in heart has yet to be reported. Given the importance of deacetylation of histones in CVDs more in-depth studies on these SIRT6 activators in CVDs are essential in the future.

In conclusion, existing studies have shown that SIRT6 is an endogenous regulatory molecule for the inhibition of cell senescence and the prevention and treatment of CVDs. Specifically, SIRT6 performs its different cellular functions via acetyl and long-chain fatty acyl deacetylation as well as ADP-ribosylation, maintains genomic stability by regulating DNA repair and telomere homeostasis. Moreover, it inhibits cell aging by regulating oxidative stress and inflammatory autophagy, plays a profound role in CVDs by regulating triglyceride synthesis and (LDL) cholesterol homeostasis. Therefore, the regulation of SIRT6 activity might influence various human diseases and prolong life. Nonetheless, the molecular mechanism of regulating the activity and function of SIRT6 in the process of anti-aging as well as prevention and treatment of CVDs warrants deeper understanding. With a better understanding of biology, novel clinical treatments can also be designed to activate SIRT6. Additional biological targets are likely to be discovered in the future, laying a basis for understanding the importance of SIRT6 in human aging and CVDs.

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All authors conceptualized and wrote the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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