Review

Sirtuins and their Biological Relevance in Aging and Age-Related Diseases

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ABSTRACT: Sirtuins, initially described as histone deacetylases and gene silencers in yeast, are now known to have many more functions and to be much more abundant in living organisms. The increasing evidence of sirtuins in the field of ageing and age-related diseases indicates that they may provide novel targets for treating diseases associated with aging and perhaps extend human lifespan. Here, we summarize some of the recent discoveries in sirtuin biology that clearly implicate the functions of sirtuins in the regulation of aging and age-related diseases. Furthermore, human sirtuins are considered promising therapeutic targets for anti-aging and ageing-related diseases and have attracted interest in scientific communities to develop small molecule activators or drugs to ameliorate a wide range of ageing disorders. In this review, we also summarize the discovery and development status of sirtuin-targeted drug and further discuss the potential medical strategies of sirtuins in delaying aging and treating age-related diseases.

Key words: sirtuins, aging, age-related diseases, cancer

In 1979, the discovery of mating-type regulator 1 (MAR1) in Saccharomyces cerevisiae was reported [1]. Lack of this protein resulted in the inhibition of silencing of HM loci, which control mating type and sterility in yeast. Three more proteins with similar functions were discovered later in 1979, and the nomenclature was unified, thus creating a family of silent information regulator proteins, Sirs [2]. Emerging interest in sirtuins occurred in 1999 when it was reported that Sir2 overexpression could extend yeast lifespans by as much as 70% [3]. Further research revealed that sirtuins overexpression also leads to lifespan extension in other model organisms, such as Caenorhabditis elegans and Drosophila melanogaster.

Shortly thereafter, it was shown that sirtuins appear to be conserved from yeast to mammals, however the complexity of their function increases with the complexity of the organism [4]. In yeast, in addition to the chief representative, Sir2, there are four more homologous proteins [2], and the positive effect of sirtuins activity can be attributed to the increase in genomic stability. In mammals there are seven enzymes belonging to the sirtuin family, sirt1–7. Phylogenetic analysis of 60 core domains from different eukaryotes and prokaryotes places the mammalian sirtuins into four different classes (I—IV). Sirt1, sirt2 and sirt3 are known as Class I sirtuins, which groups all yeast sirtuins and also at least one of the sir2-related proteins in most eukaryotes. Class I is divided in
three sub-classes: a, b and c. Sirt1 belongs to Class Ia which also includes Sir2 and Hst1 from S. cerevisiae, C. elegans Sir-2.1 and D. melanogaster D.mel1. Sir2 and sirt3 reside in Class Ib, together with yeast Hst2, fly D.mel2 and other fungi and protozoa sirtuins. Sirt4 is part of Class II, which also includes sirtuins from bacteria, insects, nematodes, mould fungus and protozoans. Sirt5 is the mammalian member of Class III sirtuins, distributed widely in all prokaryotes either bacteria or archaea. Finally, Class IV contains sirt6 and sirt7 in two different sub-classes IVa and IVb respectively; and unlike Class III, sirtuins of this class are not present in prokaryotes, but are broadly distributed in metazoons, plants and vertebrates [5].

In addition, mammalian sirtuins also differ in their sub-cellular localization, and some sirtuins can relocalize depending on the cell or tissue type, the developmental stage, metabolic status, and certain stress conditions. Sirt1 is localized to the nucleus [6], but it shuttles to the cytoplasm when required to act on cytoplasmic targets, such as during inhibition of insulin signaling [7]. In contrast, sirt2 is cytoplasmic. It deacetylates tubulin microtubules [8] and transcription factors those shuttle from the cytoplasm to the nucleus [9]. Sirt3, sirt4 and sirt5 are active in the mitochondria [10] by participating in the regulation of Adenosine Triphosphate (ATP) synthesis, metabolism, apoptosis and intracellular signaling [11]. Among them, sirt3 may be moved between the nucleus and mitochondria under cellular stress [2]. Sirt6 is a nuclear protein, although it is also present in the endoplasmic reticulum, where it deacetylates TNF-α [12]. Sirt7 is a nuclear protein that is mostly expressed in the nucleolar regions [13].

### Table 1. The location and enzymatic catalytic activity of sirtuins.

| Sirtuin | Class | Localization       | Enzymatic Activity                      |
|---------|-------|--------------------|-----------------------------------------|
| Sirt1   | I     | Nuclear/Cytoplasm  | Deacetylase, Deacetylase                 |
| Sirt2   | I     | Nuclear/Cytoplasm  | Deacetylase, Deacetylase                 |
| Sirt3   | I     | Mitochondrial/Nuclear/Cytoplasm | Deacetylase, Decrotonylase |
| Sirt4   | II    | Mitochondrial      | Deacetylase, ADP-ribosyltransferase, Lipoamidase, Deacetylase |
| Sirt5   | III   | Mitochondrial/Nuclear/Cytoplasm | Deacetylase, Desuccinylase, Demalonylase, Deglutarylase |
| Sirt6   | IV    | Nuclear/Cytoplasm  | Deacetylase, Deacetylase, Demyristoylase, ADP-ribosyltransferase, Deacetylase |
| Sirt7   | IV    | Nucleolar/nuclear  | Deacetylase, Desuccinylase              |

### Overview of sirtuins functions

Sirtuins belong to the class III histone deacetylases (HDACs) [14]. The sirtuin family shares a highly conserved catalytic domain, and exerts NAD⁺-dependent protein deacetylase and/or ADP ribosyltransferase activities [15, 16]. However, as shown in Table 1 & Table 2, the sirtuin family members differ from one another with respect to catalytic activities, subcellular localization, protein targets, and biological functions [17].

Studies indicate that, from yeast to humans, sirtuins contain a highly conserved catalytic core domain formed by 275 amino acids, and N,C-terminal extensions which is variable in length and sequence, and can affect the binding with interacting partners, mediate interactions with other sirtuin forms, and direct cellular localization. In addition to their well-studied roles as lysine deacetylases, certain sirtuins can also remove other acyl modifications from lysine residues, including propionyl, butyryl, malonyl, succinyl and the lengthy fatty-acid derived myristoyl and palmitoyl groups [18-22]. In addition, sirtuins possess NAD⁺-dependent deacetylase, deacetylase, desuccinylase, demalonylase, deglutarylase, ADP-ribosyltransferase activities, etc. and regulate many processes in vivo, including metabolism, DNA repair, metastasis, apoptosis, translation, promoting longevity and protecting against cancer via altering substrate activity, localization, stability and protein-protein interactions [23].

Sirt1 is the closest to yeast Sir2 in terms of sequence and enzymatic activity and is also the most extensively studied mammalian sirtuin at present. Sirt1 deacetylates a diverse array of cellular proteins, including histones, transcription factors, DNA repair proteins, autophagy factors, and others, like FOXO3a, PPARα, PGAM-1, SREBP1, FXR, PGC-1α, NF-kB, etc [24] to modulate metabolism, stress responses, and other cellular processes [25]. In vitro, sirt1 possesses deacetylase activity, although the functional significance of this activity in vivo remains unclear [26].

Sirt2 mainly functions in mitosis. Sirt2 regulates mitotic progression by controlling the activity of the anaphase-promoting complex/cyclosome. When DNA damage emerges, sirt2 may halt cell division, effectively guarding the cell against erroneous replication. Sirt2 also plays an important role in controlling the cell cycle. In fact, an increase in sirt2 activity significantly delays cell cycle progression [27]. In addition, the overall effect of sirt2 upregulation on carbohydrate and lipid metabolism is similar to that of sirt1, promoting gluconeogenesis.
through deacetylation of phosphoenolpyruvate carboxykinase (PEPCK) [28] and inhibiting adipocyte differentiation through deacetylation of FoxO1 [9, 29]. Furthermore, sirt2 also has anti-inflammatory effects [30].

Sirt3 is a mitochondrial enzyme, and it deacetylates and activates mitochondrial enzymes to regulate diverse mitochondrial functions, such as ATP production, reactive oxygen species (ROS) management, β-oxidation, ketogenesis, and cell death [31]. The metabolic actions of sirt3 on carbohydrate and lipid metabolism are similar to those of sirt1 (e.g., stimulation of gluconeogenesis, inhibition of lipogenesis, activation of fatty acid oxidation, and some neuroprotective actions) [32]. Furthermore, sirt3 has also been related to adaptive thermogenesis because of its regulation in both white and brown adipose tissue by caloric restriction (CR) and cold exposure [33].

Unlike the other sirtuins, sirt4 is a mitochondrial sirtuin lacking in vitro deacetylase activity [34]. Biologically, sirt4 functions in many important processes, particularly in glutamine and fatty acid metabolism [35]. Sirt4 is also thought to regulate ATP homeostasis. Sirt4 improves the efficacy of ATP synthesis by inhibiting the oxidative phosphorylation uncoupler ANT2 [36].

Table 2. The substrates/targets and functions of sirtuins.

| Substrates/targets | Function |
|--------------------|----------|
| **SIRT1** | Glucose metabolism, fatty-acid and cholesterol metabolism, differentiation, insulin secretion, and neuroprotection, stress responses, DNA repair, vascular protection and other cellular processes |
| H3K9ac, H3K26ac, H3K16ac, H1K26, H1K9, H3K56, H3K14, H4K16, α-tubulin, p53 | NF-KB, p300, p66, mTOR, HIF-1α, TNF-1a, Histone acetylation, SREBP-1c |
| **SIRT2** | Cell-cycle control, carbohydrate and lipid metabolism, tubulin and transcription factors deacetylation and anti-inflammatory |
| α-tubulin, H3K56ac, H4K16ac, | FOXO, c-Myc, G6PD, PEPCK |
| | NF-KB, p53, FoxO1 |
| **SIRT3** | regulation of mitochondrial enzymes deacetylation, ATP production, reactive oxygen species (ROS) management, β-oxidation, ketogenesis, cell death, and carbohydrate and lipid metabolism |
| H3K9, H4K16, H3K56ac, H4K14ac, H2a, H2b, H3 (H3K18) | Ku70, Mn-SOD, FOXO3a, DH2, FAO, GDH, complex I/III, IDH2 |
| | p53, HIF-1α, Ros, lipogenesis |
| **SIRT4** | Insulin secretion, glutamine and fatty acid metabolism and regulate the ATP homeostasis |
| | GDH, AMPK, ROS, PDH |
| **SIRT5** | Urea cycle, regulation of ATP synthesis, metabolism, apoptosis and intracellular signaling, regulation of ammonia detoxification, fatty acid oxidation |
| | CPS1, SOD1 |
| | GLS |
| **SIRT6** | Telomeres and telomeric functions, DNA repair, metabolic homeostasis, inflammation, stress responses, and genomic stability |
| H2BK12, H3K9ac, H3K56ac, WRN | FOXO, PARP1, CIP1, P53, DNA-PKcs, CCNDBP1 |
| | NF-KB, RELA, TNF-α, IGF-1, HIF-1α, Myc, c-Jun, PGC-1α, GCN5 |
| **SIRT7** | regulates the transcription of rDNA and mediate histone desuccinylation |
| H2A, H2B, H3 (H3K18) | FOXO |
| | RNA-POLY-merase, HIF-1α/2a |

Sirt5 is a mitochondrial enzyme [20]. It is now known that newly discovered PTMs removed by sirt5 can regulate the activity of enzymes affecting the redox status of cells and energy utilization, but we have just started to learn about the exact influence of sirt5 on these pathways. In addition to the deacetylase activities of sirt5, recent studies have suggested that sirt5 can mediate protein desuccinylation, demalonylation, and deglutarylation [21, 37, 38].

Sirt6 deacetylates specific cellular targets: H3K9Ac and H3K56Ac, the DNA repair factor CtIP, and the acetyltransferase GCN5 [39]. Recent studies have shown that sirt6 also has a deacetylase activity [19] and interacts physically with some non-histone proteins – not only through deacetylation, but also through direct physical interaction (PIA), inhibition of their binding at the target gene promoters (IATGP) and destabilization of their binding at the target gene promoters (DATGP)[40]. Through these functions, sirt6 plays essential roles in metabolic homeostasis, inflammation, stress responses, and genomic stability [41].
Sirt7 is the only sirtuin localized to the nucleolus and is a component of the RNA polymerase I (Pol I) transcriptional machinery. By interacting with RNA Pol I and histones, sirt7 regulates the transcription of rDNA in mammalian cells [42]. In addition, sirt7 can mediate histone desuccinylation [43].

Sirtuins and aging

Ageing is a conserved phenomenon across all species and imposes an ever-increasing risk of dysfunction and death in older organisms. Growing evidences have shown that sirtuins are essential factors those delay cellular senescence and extend the organisal lifespan through the regulation of diverse cellular processes. Therefore, in the review, we summarize the evidences and controversies regarding the roles of different sirtuins on aging and lifespan extension, and systematically elucidate the functions and pathways of sirtuins on aging and lifespan extension.

The link between sirtuins and longevity was first established 20 years ago in yeast, in which the complex of Sir2/3/4 extended the replicative lifespan of S. cerevisiae [44, 45]. Research interests increased after a report showed that extra copies of Sir2, a member of sirtuins in budding yeast Saccharomyces cerevisiae, extended the lifespan by 30% by preventing the formation of extrachromosomal DNA circles [3]. Subsequently, more and more research shows that sirtuins can regulate longevity in numerous lower organisms, especially yeast Sir2 and its homologues, which extend the lifespan of budding yeast S. cerevisiae, worms C. elegans, fruit flies D. melanogaster, and mice [46-48]. So far, the longevity effect of sir2 has been confirmed in higher organisms, while the mechanisms of exerting longevity effects are different from that in yeast, including changes in mitochondrial function and biogenesis, suppression of inflammation, and regulation of genomic stability [49].

Though several reports have challenged this theory, sirtuins have long been recognized as regulators of aging, and overexpression of some sirtuins has been shown to extend lifespan in several organisms. The suppression of cellular senescence by sirtuin is mainly mediated through delaying the age-related telomere attrition, sustaining genome integrity and promoting DNA damage repair [50]. According to reports, sirt1 deacetylates histones H3, H4 and H1 and more than 50 non-histone proteins, including DNMT1, transcription factors and DNA repair proteins [2]. Sirt1 and sirt6 were shown to be recruited to the damaged sites and promote DNA repair through deacetylating the repair proteins such as poly (ADP-ribose) polymerase (PARP)-1, Ku70, NBS, and Werner (WRN) helicase [12, 51-53]. In mammals, sirtuin upregulation can work in a context-, tissue-, and particular sirtuin-dependent manner [54], and not all laboratories have managed to repeat the initial life span extending effect of sirtuins upregulation [55, 56]. In addition, sirtuins are found to especially interact with all the major conserved longevity pathways, such as AMP-activated protein kinase (AMPK), insulin/IGF-1 signaling (IIS), target of rapamycin (TOR), and forkhead box O (FOXO). Of these, FOXO transcription factor is the most fascinating target of sirtuin. In C. elegans, the extension of lifespan by elevation of sir-2.1 was shown to be dependent on daf-16, the homologue of FOXO in worms [57-59]. Considering that FOXO is a major component in the IIS cascade to promote lifespan extension and stress resistance, several evidences have reported the association of the IIS pathway with the longevity effect of sirtuin. In C. elegans, the deletion of sir-2.1 had no effect on the lifespan of a long-living daf-2 mutants [60]. In mammals, the relationship of IIS and sirtuin has also been well investigated. Sirt1 is reported to play a crucial role in metabolic homeostasis and IIS [61, 62]. AMPK signaling belongs to the protein kinase family and restores cellular energy levels. Increased AMPK activity is known to extend the lifespan of some model organisms. The mutation of AMPK (aak-2) in C. elegans abrogated the lifespan extension by sir-2.1 expression [63], indicating that AMPK also contributes to the sirtuin-induced lifespan extension. Sirt1 activates AMPK through the direct deacetylation of LKB1, a regulator of AMPK [64]. In addition, AMPK contributes to the longevity effect of IIS, suggesting that these longevity pathways intricately cross-talk with each other. Apart from these, several other molecules are also reported to mediate lifespan extension by sirtuin overexpression, including 14-3-3, kat-1, hcf-1, and cts-1 in C. elegans. In addition, a study of mutant screening reported that loss-of-function mutations of ketoacyl thiolase (kat-1) resulted in premature aging and fully suppressed the lifespan extension exerted by overexpression of sir-2.1 [65]. Also, host cell factor-1 (hcf-1), a nuclear co-repressor of FOXO, was shown to act downstream of sir-2.1 to modulate the lifespan in C. elegant [66]. Furthermore, mitochondrial regulators such as cts-1 and fzo-1, and the mitochondrial unfolded protein response (UPRmt) gene hsp-6, were reported to be increased by sir-2.1 overexpression, and the knock-down of UPRmt regulator ubl-5 using RNAi almost completely suppressed the lifespan extension by sir-2.1 overexpression [67]. A more detailed description of the role about different sirtuins on aging and lifespan extension, and the signaling pathways are listed in Table 3.
Among the mammalian sirtuins, *sirt1* has been the most extensively characterized for its role in aging. Although much of the attention has gone to *sirt1* and its protective effects against the onset of chronic diseases, its effect on longevity remains unconvincing. Sirtuins other than *sirt1* are also reported to exert a longevity effect. Recently, *sirt2* has been found to be a key modulator of aging, and it extends lifespan in the *BubR1* mouse model[68]. Additionally, *sirt3* is the only sirtuin that has been shown to be associated with human aging; some (but not all) studies have linked polymorphisms in the *sirt3* genomic locus to survival in elderly individuals [55, 56, 69, 70]. However, no pan- or tissue-specific transgenic animal models overexpressing *sirt3* to determine whether *sirt3* overexpression confers lifespan extension or protects against age-associated pathologies have been described in the literature currently, and some newer studies failed to confirm these correlations in other populations [56, 70]. In contrast, recent work on *sirt6* suggests that this sirtuin might hold the most potential for actual life-span extension [47]. Loss of *sirt6* causes severe metabolic defects and rapid aging [71]. In addition, global *sirt7* depletion contributes to premature aging, especially in the backbone, white adipose tissue and the heart [72, 73].

However, it is clear that we are just starting to appreciate the importance of identifying specific processes in aging regulated by the different members of the sirtuin family in a tissue-, cell type-, and gene specific context. Thus, identifying these processes might be necessary to gain a better understanding of their role and fill in the current knowledge gaps in the field.

### Sirtuins and ageing-related diseases

Although there has been emerging debate on the role of sirtuins in ageing and lifespan extension, mounting evidence suggests that sirtuins are indeed the critical modulators of ageing and ageing-related diseases via different signalling pathways. The human sirtuin isoforms, *sirt1*–*7*, are considered attractive therapeutic targets for ageing-related diseases listed in table 3, including diabetes, metabolic syndrome, cardiomyopathies, non-alcoholic hepatic steatosis, hyperinsulinism-induced dyslipidaemia, chronic inflammation, neurodegenerative diseases, and some types of cancer [74, 75]. Here, we summarize and discuss some of the recent discoveries in sirtuins biology and their functions in age-related diseases. Table 4 lists some age-related diseases in elderly population.

### Sirtuins and neurodegenerative disease

Although the body’s organ systems experience a general decline in function with age, perhaps the most emotionally and physically devastating decline is associated with the CNS. Impaired CNS function, with its effects on

| Table 3. Functions and signaling pathway of sirtuins in aging. |
|---|---|---|---|
| **Sirtuin** | **Functions in aging** | **Regulatory factor in signal pathway** |
| **Yeast** | Sir2 | Replicative lifespan extension, Cell cycle arrest | NAD+, mTOR, PKA, Sch9 |
| **C. elegans** | sir-2.1, sir-2.2, sir-2.3, sir-2.4 | Lifespan extension, Stress resistance | mTOR, HLF-30, PHA-4, NHR-62, WWP-1, KLF-1, EGL-9, DAF-16, AAK-2, HSF-1, FOXA, DAF-2, IGF-1, SKN-1, SAMS-1, RAB-10, DRR-1, DRR-2 |
| **Drosophila** | dSir2, Sirt4 | Lifespan extension | FOXO,4E-BP |
| **Mammal** | sirt1 | Lifespan extension, DNA repair, Cell cycle arrest, Cellular senescence | eNOS, Erβ, FOXO3 |
| | sirt2 | Cell cycle regulation | BubR1, PPP, NAD+, FOXOs, Mn-SOD |
| | sirt3 | Mitochondrial function, Oxidative stress, Centenarian-linked SNPs | FOXO3A, Mn-SOD |
| | sirt4 | Fatty acid oxidation, Apoptosis | NF-KB, MAPK/ERK, P13K/Akt |
| | sirt5 | Fatty acid oxidation, Oxidative stress | NF-KB, Bax, Caspase, GDH, AMPK |
| | sirt6 | Lifespan extension, DNA repair, Genome stability, Telomere maintenance | P21/1/Waf1, NF-KB, ICM-1, PAI-1 |
| | sirt7 | Epigenetic regulation, Stress resistance, Apoptosis | FOXO3 |

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cognition, memory, hearing, balance, and motor control, can lead to a rapid loss of quality of life. In recent years, the risk of neurodegenerative disease (e.g., Alzheimer’s disease (AD), Parkinson’s disease (PD), Huntington’s disease (HD), and others) has increased sharply with age [76]. Several studies have revealed the important roles of sirtuins in neuronal development and neurodegenerative disease [77, 78]. Though the ability of sirtuins to ameliorate CNS-specific disorders is still a very inchoate area of investigation, the initial findings offer significant promise.

Progress in understanding the neurobiological benefits of sirt1 has been focused on animal models of different human CNS diseases. In mouse models of Alzheimer’s disease, brain-specific knockout of sirt1 caused a significant elevation in β-amyloid plaques and reactive gliosis [79]. Sirt1 also conferred neuroprotection in three different mouse models of Huntington’s disease [80, 81]. Brain-specific deletion of sirt1 exacerbated the neurotoxicity associated with mutant huntingtin protein, whereas overexpression of sirt1 attenuated the toxicity. In addition, in a mouse model of Parkinson’s disease, overexpression of sirt1 reduced α-synuclein aggregates, reduced gliosis, and attenuated lethality [82]. In a mouse model of injury-induced axonal degeneration, NAD+ biosynthesis and its support of sirt1 activity were shown to be essential in preventing axonal loss following axonal transection [83, 84].

Inhibition of sirt2 by pharmacological and genetic means in invertebrate and cell culture models has suggested potential neuroprotective benefits [85]. Unfortunately, sirt2 knockout mice lacked a remarkable phenotype related to neurodegeneration [86], calling into question the effect of sirt2 on neuronal health in mammals.

Less data is available for other sirtuins. It has been found that short-term AD treatment with extracellular Aβ1-42 oligomers enhanced the expression of the sirt4 gene, but prolonged treatment affected all three mitochondrial isoforms (sirt3 to sirt5), suggesting that links between APP/Aβ and sirtuins might be more complex, and possibly reciprocal [87].

**Table 4.** Some age-related diseases in elderly population.

| Aging and age-related disease                                                                 |
|---------------------------------------------------------------------------------------------|
| **Neurodegenerative diseases**                                                               |
| Presbyophrenia, Huntington’s disease, Parkinson’s disease, Alzheimer’s disease, Amyotrophic     |
| lateral sclerosis                                                                           |
| **Cardiovascular and cerebrovascular diseases**                                             |
| Hypertension, Coronary disease, Cardiomyopathies, Elder valvular heart disease, Arrhythmia,   |
| Cardiac failure, Cerebral infraction, Atherosclerosis                                         |
| **Metabolic related diseases**                                                               |
| Diabetes, Metabolic syndrome, Osteoporosis, Hyperinsulinism-induced dyslipidaemia, Uarthritis, |
| Urtthritis, Non-alcoholic hepatic steatosis,                                                  |
| **Others**                                                                                  |
| Scapulohumeral periarthritis, Chronic bronc, Chronic inflammation, Cancer                    |

**Sirtuins and cardiovascular diseases**

In addition, aging results in well-defined phenotypic changes which lead the cardiovascular system to develop diseases even in the absence of traditional risk factors [88]. Sirtuins have been associated with vascular diseases in humans, such as carotid plaques [89], carotid intima media thickness [90], arterial stiffness [91], and plaque area and morphology [92].

Whole body augmentation of sirt1 activity confers resistance to many cardiovascular sequelae associated with metabolic syndrome. Study indicated that endothelial sirt1 age-dependent depletion or its inactivation is a frequent companion of many cardiovascular diseases (CVDs) [93]. Sirt1 is highly expressed in endothelial cells, and activation of sirt1 in endothelial tissues may be beneficial in the protection of endothelial cell function with age [94]. Conversely, sirt1 insufficiency results in greater foam cell formation and atherosclerotic lesioning [95]. 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 [96, 97]. Sirt1 appears to counteract atherosclerosis by inhibiting VSMC hypertrophy [98] and neointima formation and protecting against DNA damage, medial degeneration, and hypertension [99, 100]. In summary, sirt1 acts as a cardioprotective molecule that protects from aging, induces resistance against hypertrophic and oxidative stresses, inhibits cardiomyocyte apoptosis, and regulates cardiac energy metabolism [101, 102]. However, the role of sirt1 on longevity and human cardiovascular diseases is not fully convincing, so further studies are needed.

Hashimoto-Komatsu et al. 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 remodeling [103]. However, sirt2 knockout mice have no cardiac abnormalities. Thus, further studies are warranted to precisely define the role of sirt2 in cardiac contractile function under physiological and pathological conditions. Sirt3 is necessary to prevent mitochondrial dysfunction and cardiac hypertrophy during ageing [104, 105]. Overexpression of sirt3 blunts cardiac hypertrophy by decreasing oxidative stress via
upregulation of endogenous antioxidants (like Mn-SOD2 and catalase). Sirt4 is found to be specifically enriched in the heart, kidney, brain, and liver. Furthermore, sirt4 can also negatively modulate 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 [106]. Variants in sirt5 gene have been found to be associated with the risk of carotid plaque development [96]. In addition, Liu et al. have demonstrated in vivo that sirt5 plays a critical role in regulating cell viability in cardiomyocytes [107]. Future studies are required to investigate the correlations between sirt5 level and on the effect of sirt5 on various pathologic pathways of CVDs.

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 [108, 109]. Among nuclear sirtuins, sirt1 and sirt6 play an important role in prevention and delay of CVDs [110]. In fact, sirt6 expression blocks the development of cardiac hypertrophy and heart failure [111, 112], whereas some data suggested that sirt1 promotes cardiomyocyte hypertrophy [113]. 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. Vakhrusheva et al. have demonstrated that sirt7 plays an important role in preventing progressive functional deterioration of the heart [73]. Sirt7 deletion leads to various pathological changes in the heart, which further aggravates with age, including heart hypertrophy, fibrosis, lipofuscin accumulation and inflammatory cardiomyopathy.

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.

**Sirtuins and metabolic diseases**

Furthermore, declines in basal metabolic rate and physical activity contribute to an elevated incidence of insulin resistance, obesity, and metabolic syndrome with age [114]. Sensing of the metabolic state and regulation of the sirtuin function and expression are critical components of the metabolic machinery. Thus, activation of pathways that restores insulin sensitivity and improves the utilization of glucose and fatty acids would be of benefit in stemming the pathologies associated with age-related metabolic dysfunction [115]. In the next review, we summarize an overview and update on the function of different sirtuin in metabolism, and further touch the correlation between each sirtuin and disorders of metabolism.

Many studies have indicated that sirt1 is an important target for mitigating metabolic dysfunction. Sirt1 is directly involved on metabolic pathways such as lipogenesis, stimulation of fatty acid β-oxidation, and gluconeogenesis. Its overexpression is thought to be beneficial and generates phenotypes in mice similar to calorie restriction conditions. All the major mitochondrial processes including the Krebs cycle, the fatty acid metabolism, the antioxidant response, the amino acid catabolism, and so on, are regulated by the balance of N”-lysine acetylation/deacetylation. Several transgenic models have shown that heightened sirt1 activity protects against the metabolic derangement associated with obesity [116]. Sirt1 and sirt1 activators can prevent and reverse insulin resistance and diabetic complications, and have been proven to be promising therapeutic targets for type 2 diabetes (T2D) [117-119]. In addition, the protective effects of sirt1 may occur through attenuation of inflammatory responses, as sirt1 overexpression mitigates HFD-induced hepatic steatosis and adipose tissue specific inflammation [120, 121].

Compared to sirt1, sirt2 is abundant in adipocytes. Current evidence suggests a role for sirt2 in regulating adipose tissue development and function. Sirt2 activates the PEPCK via deacetylation and enhances gluconeogenesis during times of glucose deprivation [122]. Meanwhile, recent studies have proposed that, with regard to insulin sensitivity, sirt2 may act in opposing roles in different tissues [123]. Thus, sirt2 activation may prove to be protective against obesity, and its role in metabolic homeostasis deserves further exploration.

Sirt3 may regulate cellular energy status both at transcriptional level in the nucleus and by posttranscriptional mechanisms in mitochondria, and its expression is higher in metabolically active tissues including brain, liver, heart, brown adipose tissue and skeletal muscle [124]. Sirt3 functions by activating important enzymes during CR, such as 3-hydroxy-3-methylglutaryl-CoA synthase 2 for generation of ketones [125] and long chain acyl-CoA dehydrogenase for the oxidation of long-chain fatty acids [126]. Sirt3 also activates glutamate dehydrogenase (GDH), facilitating gluconeogenesis from amino acids[127]. In addition, sirt3 indirectly destabilizes the transcription factor HIF1α and subsequently inhibits glycolysis and glucose oxidation [128]. Intriguingly, recent studies have shown that sirt3 levels in pancreatic islets are reduced in patients afflicted with type 2 diabetes [129], and sirt3 overexpression in pancreatic β-cells promotes insulin secretion and
abrogates endoplasmic reticulum (ER) stress that is connected to β-cell dysfunction and apoptosis [130].

In contrast to sirt3, hepatic sirt4 expression declines slightly during caloric restriction (CR) and increases in genetic models of diabetes [34, 131, 132]. Little is known about the physiological relevance of sirt4 and its role in metabolism. Sirt4, initially reported as a unique ADP ribosyltransferase, appears to blunt insulin secretion by reducing GDH activity [133]. In addition to GDH, a diverse range of sirt4 targets are identified in the regulation of insulin secretion, including ADP/ATP carrier proteins, insulin-degrading enzymes, ANT2 and ANT3 [133]. Recently, Haigis and coworkers showed that sirt4 promoted lipid synthesis and inhibition of fatty acid oxidation by deacetylation of malonyl CoA decarboxylase [134].

In contrast to other sirtuins, sirt5 displays deacetylase and NAD+ dependent demalonylase and desuccinylase activities. Sirt5 facilitates glycolysis by demalonylating the glycolytic enzyme glyceraldehyde phosphate dehydrogenase (GAPDH) [38]. A recent study proposed that sirt5 might be positively correlated with insulin sensitivity, the biological significance of which still remains to be confirmed [135].

The indication of the connection between sirt6 and metabolism was first provided by Mostoslavsky et al. who showed that sirt6-deficient mice had a loss of subcutaneous fat, lymphopenia and acute hypoglycemia [136]. Conversely, one recent study revealed that sirt6 overexpression protects mice from diet-induced obesity, showing increased glucose tolerance and reduced fat accumulation [137]. In addition, sirt6 may positively mediate glucose stimulated insulin secretion and overexpression of sirt6 enhances insulin sensitivity in skeletal muscle and liver, which implicates that sirt6 may act as an attractive therapeutic target for T2D [138].

In addition, sirt7 knockout mice were resistant to glucose intolerance, and insulin sensitivity was improved in sirt7 knockout mice receiving a high-fat diet [46], revealing a novel role for sirt7 in glucose metabolism.

**Sirtuins and Cancer**

Based upon statistics from the National Cancer Institute, 54% of all cancer cases occur in people over the age of 65. Cancer is recognized as an age-related disease and occurs in an exponentially increasing pattern in elderly individuals. In recent years, cancer has become a grim hurdle in our way to longer and healthier ageing lives.

Currently, accumulating evidence has shown that the aberrant epigenetic activation of sirtuin signaling pathways contributes to tumor carcinogenesis and may be potential therapeutic targets for future treatments and biomarkers in predicting prognosis in cancers [23, 139]. Interestingly, sirtuins seem to have a dual role in cancer [140]. On the one hand, some sirtuins help protect DNA from damage and oxidative stress, maintain genomic stability, limit replicative life-span, and protect organisms against cancer. On the other hand, some data suggest that the promotion of cell survival under stress conditions by sirtuins could be directly involved in tumorigenesis, as it would inhibit senescence and allow unchecked cell division [141].

The role of sirtuins, especially sirt1 in carcinogenesis, appears to be opposing and complicated. Under normal conditions, in response to stress or to DNA damage, sirt1 might promote cell survival via cell cycle arrest, DNA repair, or inhibition of apoptosis. If the stress signal becomes chronic or the levels of damage cross a certain threshold, sirt1 could induce cell senescence and prevent carcinogenesis [116]. However, following chronic stress or DNA damage, the loss of a tumor suppressor or of any other checkpoint-related factor could cause an imbalance in these regulatory processes and induce sirt1 overexpression beyond a critical limit. The aberrant overexpression of sirt1 would in turn contribute to transformation and tumor formation by promoting cell growth and inhibiting apoptosis [142].

In fact, sirt1 acts as a tumor keystone, and its level and action maintain a fine and delicate balance between suppression and promotion of oncogenesis. It is plausible that sirt1 acts as a suppressor and then a promoter (or vice versa) depending on the stage and situation of tumourigenesis. The dual role of sirtuins in different cancers has been summarized and shown in Table 5. Studies have shown that sirt1 is upregulated in many human cancer cell lines, as well as in tissues collected from patients suffering from various types of cancer (e.g., lung cancer, prostatic cancer, colon cancer, breast cancer, ovarian cancer, leukaemia, neuroblastomas, osteosarcomas, etc.), suggesting that sirtuins might be cancer therapeutic targets and the sirt1 inhibition in cancer cells could possibly inhibit cancer cell growth [143-145]. Other research, however, points to a tumor suppressive role for sirt1. Certain cancer types, such as oral squamous cell carcinoma (OSCC), restoration of sirt1 levels in these cells results in inhibition of tumor growth [146]. In other cancer mouse models, sirt1 can protect against the development of intestinal tumors in a β-catenin-driven colon cancer model [147], sarcomas, lymphomas, teratomas, and carcinomas arising from deletion of p53 [148], HFD-induced hepatocarcinomas [116], and age-associated spontaneous tumor development [116]. In addition, other studies reported only slightly elevated sirt1 activity (in some thyroid cancers) or unchanged activity in some lung cancers, colon cancers, gastric cancers, urinary bladder cancers, and skin cancers [148].
Similar to sirt1, sirt2 is either a positive or a negative regulator of the tumorigenic process. The expression of sirt2 has been found downregulated in several cancers, such as gliomas, breast cancer, head and neck squamous cell carcinoma, non-small cell lung cancer, and esophageal adenocarcinoma, and elevated in others, such as neuroblastoma, pancreatic cancer, and acute myeloid leukemia [149, 150].

The case of sirt3 is more complex. Several studies indicate that sirt3 is a tumor suppressor, mainly through mechanisms linked to oxidative response, energetic balance, and metabolic regulation [11, 151]. Sirt3 expression is decreased in many human cancers, especially in 40% of human breast and ovarian cancers [108, 128]. However, in specific cancer types, sirt3 turns out to be an oncogene and promote tumorigenesis [152, 153].

Sirt4 mRNA levels were reduced in several human cancers, such as small cell lung carcinoma [154], gastric cancer [155], breast cancer and leukemia [156]. Lower sirt4 expression is associated with shorter survival time in lung tumor patients [157]. A recent study has also shown that sirt4 is a crucial regulator of stress resistance in cancer cells and sirt4 loss sensitizes cells to DNA damage or ER stress [158].

Similar to other sirtuins, sirt5 has been considered as a potential oncogene or tumor suppressor. Sirt5 acts as a potential oncogene, and is overexpressed in non-small cell lung cancer [159] and ovarian carcinoma [160]. However, sirt5 also emerged as a tumor suppressor in squamous cell carcinoma [161] and endometrial carcinoma [162].

Sirt6 is thought to be a significant tumor suppressor protein (TSP), given its major role as a guardian of genome stability [163, 164]. Sirt6 overexpression induces intense apoptosis in cancer cells but not in normal cells, which makes it an attractive “target” for future antineoplastic medications [165]. In addition, as with sirt1, sirt6 plays both tumor suppressing and promoting roles. sirt6 expression is downregulated in head and neck squamous cell carcinoma, and colon, pancreatic, liver and non-small cell lung cancers [161, 166, 167]. Conversely, increased sirt6 expression has been reported in human skin squamous cell carcinoma and pancreatic, prostate, liver and non-small cell lung cancers whose high expression suggests a poor prognosis and chemotherapy resistance [168-171].

Although sirt7 has received comparatively less attention than other sirtuins, sirt7 appears to have been regarded as a potential oncogene for its upregulation in all the cancer types studied so far, such as thyroid cancer, hepatocellular carcinoma, bladder cancer and colorectal cancer [172-174]. Sirt7 can contribute to the maintenance of a transformed cell phenotype in tumor cells by suppressing the expression of some TSPs [15]. However, sirt7 does not contribute to the initiation of carcinogenesis, which has been experimentally proven, as no correlation between sirt7 upregulation in normal cells and their susceptibility to transformation has been found [6, 15].

**Activators and inhibitors of sirtuins**

As the area of molecular science consolidates and advances, the sirtuin family members are gaining...

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**Table 5. The dual role of sirtuins in different cancer.**

| Oncogene/Tumor suppressor | Expression in tumor tissue |
|---------------------------|---------------------------|
| **SIRT1** Both | lung cancer, prostatic cancer, colon cancer, breast cancer, ovarian cancer, leukemia, neuroblastomas, osteosarcomas, and non-melanoma skin carcinomas | early onset–mutant (BRCA1) breast cancer, beta-catenin–driven colon cancer model, sarcomas, lymphomas, teratomas, and carcinomas arising from deletion of p53, HFD-induced hepatocarcinomas, and age-associated spontaneous tumor development |
| **SIRT2** Both | acute myeloid leukemia, pancreatic cancer, neuroblastoma, high-grade human HCC and prostate cancer | glioma, liver cancer, and esophageal and gastric adenocarcinomas |
| **SIRT3** Both | oral cancer | 40% of human breast and ovarian cancers |
| **SIRT4** Tumor suppressor | | small cell lung carcinoma, gastric cancer, breast cancer and leukemia |
| **SIRT5** Both | non-small cell lung cancer, ovarian carcinoma | squamous cell carcinoma, endometrial carcinoma |
| **SIRT6** Both | human skin squamous cell carcinoma and pancreatic, prostate and breast cancers | head and neck squamous cell carcinoma, colon, pancreatic, liver and non-small cell lung cancers |
| **SIRT7** Oncogene | thyroid cancer, hepatocellular carcinoma, bladder cancer and colorectal cancer | |
significance in human biology and disease. All of the above findings suggest that sirtuins show strong potential to become valuable predictive and prognostic markers for disease and therapeutic targets for the management of a variety of cancer types and other age-related diseases. Therefore, in the following review, we summarize the common activators and small molecule inhibitors of sirtuins in relieving aging symptoms and age-related diseases, which is shown in table 6.

Table 6. Activators and inhibitors of sirtuins.

| SIRT | Activators | Inhibitors |
|------|------------|------------|
| SIRT1 | Piceatannol, Resveratrol, SRT1720, SRT2104, 1,4-DHP derivative, SRT1460, SRT2183 | Ex-527, ELT-11c |
| SIRT2 | 1,4-DHP derivative | AGK2, 3’-(fluoro-phenethyloxy)-2-anilino-benzamide, SirReal2, Compound 15e, UBCS0137, ELT-11c, Compound 28e, AEM2, TM, Chroman-4-one analogue, RK-9123016, NPD11033 |
| SIRT3 | Piceatannol, Resveratrol, 1,4-DHP derivative | Compound 8, ELT-11c, SDX-437 |
| SIRT4 | | |
| SIRT5 | Piceatannol, Resveratrol, UBCS039 | |
| SIRT6 | UBCS039 | Compound 1 |
| SIRT7 | | |

Small molecule activators of sirtuins

Dietary restriction (DR)/CR (the reduction of calorie intake without causing malnutrition) is the only known intervention able to increase the lifespan in many species, including yeast, fruit flies, nematodes, fish, rats, mice, hamsters and dogs [175, 176] and possibly even primates [177].

Since sirtuin is commonly believed to mediate the beneficial effects of CR, the activators of sirtuins are considered to mimic these beneficial effects and are hence attractive therapeutics for age-related diseases [178]. The search for molecules those activates sirtuins began more than a decade ago. These sirtuin-activating compounds (STACs) are mainly divided into two categories. One is the use of exogenous activators, the other is replenishment of the cellular NAD⁺ [75, 179]. The first STACs were discovered for sirt1 in 2003, and the most potent of which was resveratrol. This initial discovery was important because it proved that allosteric activation of sirtuins was possible [179]. Treatment with resveratrol and its derivatives brought some beneficial effects of sirt1 induction without applying CR [180, 181]. Moreover, studies have shown that the sirtuin activator resveratrol has chemo preventive activity against various cancers, including leukemia, DMBA-induced mammary tumors in rats, skin cancer, and prostate cancer [182-184]. Following the discovery of resveratrol, a few researchers tried to find other selective activators [181]. High-throughput screening and medicinal chemical efforts have since identified more than 14,000 STACs from a dozen chemical classes, including several classes of plant derived metabolites such as flavones, stilbenes, chalcones, and anthocyanidins, which directly activate sirt1 in vitro [179]. Synthetic STACs include a number of agents such as imidazothiazoles (e.g., SRT1720) [185], thiazolopyridines (e.g., STAC-2), benzimidazoles (e.g., STAC-5), bridged ureas (e.g., STAC-9), cilostazol [186], paeonol [187], statins [188], hydrogen sulfide [189, 190] and persimmon [191]. All of these chemical classes activate sirt1 by lowering the Km value of the substrate through a K-type allosteric activation mechanism [192, 193]. In addition, there are some natural anti-ageing compounds, such as quercetin, butein, fisetin, kaempferol, catechins and proanthocyanidins [194].

An alternative approach to activating sirtuins is to regulate NAD⁺ level by activating enzymes involved in biosynthesis of NAD or by inhibiting the CD38 NAD hydrolase [195-197]. It has been known since 2003 that upregulation of the NAD salvage pathway, which recycles NAD⁺ from NAM, can extend lifespan and mimic calorie restriction in yeast [198, 199]. NAD-boosting molecules constitute a newer class of STACs those are gaining attention as a way to restore NAD⁺ levels in elderly individuals and potentially activate all seven sirtuins with a single compound. Examples of NAD-boosting molecules include NMN, nicotinamide riboside67 [200-203], and inhibitors of CD38 such as apigenin [196], quercetin [196] and GSK 897-78c [204]. In addition, targeting the enzymes that regulate NAD⁺ levels, such as CD38, CD157 and NAMPT, may also be worth exploring for their therapeutic potential. Moreover, malate dehydrogenase, MDH1, which is involved in energy metabolism and reduces NAD+ to NADH during its catalytic reaction, also plays a critical role in cellular senescence.
Small molecule inhibitors of sirtuins

The inhibition of sirtuins has attracted more interest as a potential therapeutic anticancer strategy. Here, the fundamental principle of developing inhibitors is that they should have two characteristics: they should be potent and selective. The mechanism of a potent inhibitor is as follows: combining of the inhibitor and the sirtuin may be easier than that of Nε-acyl-lysine and the sirtuin, and the inhibitors may be processed by the sirtuin into a non-catalytic intermediate which can bind tightly to the active site of the sirtuin to prevent the normal binding and processing of the substrate [205]. A selective inhibitor should perfectly inhibit one certain sirtuin, for example sirt2, while not reacting with other sirtuins. Based on these 2 principles, there are some inhibitors already designed, such as NAM and thioacyllysine-containing compounds. However, there are still limits for such inhibitors.

Except for the mechanism-based inhibitor discussed above, there is another common way to develop an inhibitor for sirtuin, which is by chemical library screening. In this way, thousands of molecules can be screened. Of these screened molecules, there are 5 compounds potent and selective enough, including sirtinol and its analogues, splitomycin and its derivatives, indole derivatives, and tenovin and its analogues, to presumably work by noncovalently binding to the sirtuin active site and blocking substrate binding.

Compound 6 was found to be a highly potent inhibitor of the deacetylation reaction catalysed by sirt1. Compound 6 may have much less inhibitory effect on reactions catalysed by sirt2 and sirt3 compared with sirt1. SirReal 2 and Compound 7 were screened from an internal compound library, and were demonstrated to be potent sirt2 inhibitors [206, 207]. Compound 8 is another potent and selective sirt2 inhibitor. X-ray analysis showed that when this compound binds to the active domain of sirt2, it may form a rigid cyclic structure by intramolecular hydrogen bonding. Therefore, it may tightly bind with sirt2, highly potently and selectively inhibiting the activity of sirt2 [205]. In addition, AK-7 is a brain-permeable selective sirt2 inhibitor. It is neuroprotective in vitro, by reducing polyglutamine inclusions and cholesterol levels in neurons [208]. Tenovin-6, salermide and benzodeazaoxaflavin are small-molecule inhibitors of sirt1 and sirt2 [209, 210]. Suramin inhibits sirt5 by binding into the B- and C-pockets of the NAD⁺ binding site as well as to the substrate-binding site [211]. In total, segmented inhibition or activation of sirtuin activity might confer therapeutic potentials in the future, mainly because of its double-edged sword effects in cancer cells.

In addition, Natural compounds present in the diet, classed as functional food/nutrients, are a great promise for health and longevity promotion and prevention of age-related chronic diseases [212]. Such compounds are nontoxic, easy to use and commonly available and could be included into a normal diet for long lasting supplementation. Several reports emphasized that dietary supplementation of polyphenols may protect against neurodegenerative, cardiovascular, inflammatory, metabolic diseases and cancer by enhancing sirt1 deacetylase activity. However, in humans, the therapeutic and pharmacological potential of these natural compounds remains to be validated in clinical conditions.

Implications and future perspectives

Since the discovery of the yeast Sir2, sirtuins have been focused on their functions in ageing and age-related disease. Accumulating studies have revealed that sirtuins exert profound protective functions against ageing-related pathologies and the degeneration of tissues and organs in elderly individuals. Their multivalent roles in blocking the development of ageing and ageing-related diseases further mark them as promising targets for developing interventions for several age-associated pathologies.

The intense efforts in the past ~15 years to develop isomeric specific small molecule modulators of the sirtuins have yielded key insights into the pathophysiological roles of sirtuins and have seen great strides in understanding the enzymatic reaction mechanisms. Initial drug development efforts focused on sirt1 and sirt2 have yielded a number of potent sirt2 inhibitors and sirt1 activators, which have now been passed the first clinical trials, with evidence of safety and efficacy.

However, there is little standardization of the disease models currently used to study sirtuin therapeutic biology, leading to contradictory reports with limited cross-validation of the findings. There is still a long way to go for a molecule to be applied in treatment, with hurdles of regarding side effects, stability, and selectivity. The field of sirtuin modulators has clearly matured into an exciting path of drug development that holds the promise for treating common and rare diseases, with considerable unmet demand.

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Competing interests

The authors declare that they have no competing interests.

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