Sirtuins Function as the Modulators in Aging-related Diseases in Common or Respectively

Qi-Lin Wang[1], Shang-Jing Guo[2]

[1]School of Life Science, Liaocheng University, Liaocheng, Shandong 252059, China
[2]School of Pharmacy, Liaocheng University, Liaocheng, Shandong 252059, China

Key words: Aging-related Disease; Deacetylase; Hypoxia Inducible Factor-1α; NAD^+; Peroxisome Proliferator-activated Receptor-γ Coactivator-1α; Sirtuins

Introduction

According to the demographics, the world population over 60 years will double from 605 million to 2 billion people between 2000 and 2050. Aging is a complex process in which the organism and its ability to respond to external stresses become progressive decline. The degenerative aging process is the major underlying cause for aging-related diseases, including hypertension, diabetes, neurodegenerative diseases, cancer and so on [Table 1]. Many factors contribute to aging, for example, increased oxidative stress, changes in gene expression, accumulation of DNA damage.[1] Disorders of metabolism and dysfunctions of key enzymes/proteins in metabolism are also implicated in aging-related diseases. Accumulating studies have revealed that deacetylase Sirtuins exert profound protective functions against aging-related pathologies for the decline of tissues and organs in the elderly, and experimental and genetic studies have linked Sirtuins activity with delaying aging and extending lifespan.[2-5]

Mammalian Sirtuin family contains 7 members (named SIRT1–SIRT7) and is endowed to diverse biological functions in different cellular compartments. Deacetylase activity is the major characteristic of Sirtuins response to the balance of cellular energy and requires NAD^+ as the acceptor of an acetyl group from a target acetyl-lysine residue. Lysine acetylation modulates a variety of metabolic processes, such as fatty acid β-oxidation, tricarboxylic acid (TCA) cycle and oxidative phosphorylation located in mitochondria and another metabolism in cytoplasm by targeting key enzymes or proteins.[6] Epigenetic changes of these enzymes/proteins deacetylation by Sirtuins are involved in the regulation of dysfunction correlated to aging. Sirtuins are also recruited to chromatin and directly deacetylate histones such as H4K16, H3K9, H3K14, H1K26 and so on. Besides the major deacetylase activity of Sirtuins (SIRT1–SIRT3), SIRT4–SIRT7 has been detected no or very weak deacetylase activity. SIRT4 and SIRT6 function as mono-ADP-ribosyltransferases, which transfer the ADP-ribosyl moiety to the substrate protein including glutamate dehydrogenase 1, poly (ADP-ribose) polymerase 1 respectively.[7,8] SIRT4 also has lipoamidase activity that modulates the biological functions of pyruvate dehydrogenase complex[9] and for its deacetylase inhibiting malonyl CoA decarboxylase in lipogenesis.[10] Recently, it has been found that SIRT5 displays demalonylase and desuccinylase activity by removing malonyl or succinyl moiety from target protein, such as carbamoyl phosphate synthase 1.[11] SIRT6 can regulate protein lysine fatty acetylation in endoplastic reticulum as deacetylase.[12] SIRT7 is the least studied Sirtuin family member, but until now it has been investigated that SIRT7 as deacetylase can target substates p53, H3K18, PAF53 and so on.[13] According to studies on Sirtuins, we find that these different Sirtuin members may modulate the aging-related diseases in common or respectively, although they are in different subcellular localization, have different enzymatic activity and variety of secondary effectors or target proteins.[14] In this review, we summarize the regulatory mechanism of Sirtuins on aging as well as in aging-related diseases such as metabolic complications, neurodegenerative diseases and tumorigenesis etc., along with the role of Sirtuins in extending lifespan or longevity.

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.158375

Role of Sirtuins in Extending Lifespan or Longevity

The relationship between longevity and "calorie restriction (CR)" was demonstrated by experiments in 1989 that life span was extended markedly by limiting calorie intake in rodent growth.[15] Although the role of SIRT1 on

Address for correspondence: Dr. Qi-Lin Wang, Liaocheng University, School of Life Science, No. 1, Hunan Road, Dongchangfu District, Liaocheng, Shandong 252059, China
E-Mail: wql@lcu.edu.cn

Table 1: Age-related diseases in elderly population

Cardiovascular and cerebrovascular diseases
Hypertension
Coronary disease
Elder valvular heart disease
Arrhythmia
Cardiac failure
Cerebral infraction
Metabolic related diseases
Diabetes
Osteoporosis
Hyperlipidemia
Uarthritis
Neurodegenerative diseases
Presbyophrenia
Parkinson's disease
Alzheimer's disease
Amyotrophic lateral sclerosis
Others
Scapulohumeral periarthritis
Chronic bronchitis
Cancer

longevity *per se* is not fully convincing because transgenic mice overexpressing SIRT1 did not show to live longer than controls, the efficacy of SIRT1 in protecting mice against age-associated diseases unveils an important role in improving health span and prevention aging. Simic *et al*. have clarified SIRT1 deacetylates β-catenin and facilitates its accumulation in nucleus leading to transcription of genes for mesenchymal stem cells differentiation,[16] which are declined with aging. Another group has also demonstrated that CR enhances cell survival by inducing SIRT1 protein expression.[17] SIRT3 is involved in dealing with oxidative stress for cells at under CR.[18] Latest SIRT2 has been found a key modulator of aging, and it extends lifespan in BubR1 mice model.[19] These studies indicate that Sirtuins have the healthful characteristic of regulating caloric restriction and they are perhaps the natural means of consistently extending lifespan and delaying the onset of aging-related pathologies such as obesity, diabetes, dyslipidemia in mammalian. Though there has been emerging debate on the role of Sirtuins in aging and lifespan extension, mounting evidences suggest that Sirtuins are indeed the critical modulators of aging and the aging-related diseases via different signaling pathways.[20]

Nuclear factor (NF-kappa B) locates primarily in cytoplasm as a heterodimer and is an important NF. NF-kappa B signaling is a canonical pathway that is stimulated by intracellular and extracellular stress. It has been reported that constitutive stimulation of NF-kappa B signaling may accelerate aging in mice by motif module map analysis.[21] Kawahara *et al*. have found SIRT6 binds to the RELA subunit of NF-kappa B and deacetylates H3K9 at NF-kappa B targeted gene promoters resulting in decreased NF-kappa B signaling, thus slowing the aging process.[22] Recently, another experiment has been demonstrated that SIRT6 is correlated with collagen metabolism and acts as a critical factor in skin anti-aging through NF-kappa B signaling pathway.[23] These studies have established the connection between NF-kappa B signaling and SIRT6 in anti-aging process. Therefore, SIRT6 also has the characteristic of extending lifespan and delaying the onset of aging-related pathologies.

Role of Sirtuins in Obesity and Diabetes

Dietary obesity (DR) is associated with the development of type II diabetes and intra-adipose tissue hypoxia and activation of hypoxia inducible factor-1α (HIF-1α). HIF-1α activation is pivotal to maintain glucose intolerance, insulin resistance and cardiomyopathy, which are all the correlated pathological states in DR. In addition, mitochondrial dysfunction may direct fatty acid to intracellular lipid accumulation, leading to insulin resistance in obesity and type II diabetes. Studies have found that SIRT2 deacetylates HIF-1α and reduces the capability of HIF-1α in response to cellular hypoxia.[24] HIF-1α suppresses β-oxidation partially via transcriptional inhibition of SIRT2 deacetylase activity. Importantly, in visceral adipose tissue from human obese subjects, the expression level of SIRT2 is very low while HIF-1α is high. Depletion of HIF-1α in 3T3-L1 adipocytes causes induction of SIRT2 mRNA and protein, which indicates that SIRT2 dysfunction perhaps is the factor of obesity development. In another study, reduction of cytoplasmic SIRT2 promotes adipogenesis respectively.[25] Thus, by negatively modulating, the SIRT2-HIF-1α regulatory axis may represent an effective prevention method in DR. GLUT4, aP2 and fatty acid synthase, which are involved in adipocyte differentiation, are all regulated by SIRT2 to modulate adipocyte differentiation. This is attributed to a direct interaction between SIRT2 and forkhead box O1 (FoxO1) acetylation patterns in controlling adipogenesis.[26,27]

In Sirtuin family, SIRT1 can fine-tune cellular response to hypoxia by deacetylating HIF-1α. SIRT1 also deacetylates PGC-1α and stimulates its activity, thus inhibits glycolysis and enhances exportation of liver glucose and the gene expression of gluconeogenesis in liver.[28] At the same time, SIRT1 modulates the mitochondrial function and balances the energy and facilitates the oxygen consumption in muscle to induce oxidative phosphorylation and mitochondrial biogenesis. In the process of fatty acid metabolism, SIRT1 deacetylates and activates acetyl-CoA synthetase 1 (AceCS1), and thus promotes acetic salt into fatty acid metabolism and circadian clock.[29] In 3T3-L1 adipocytes, overexpression of SIRT1 by siRNA ablates the lipogenesis.[30] In the differentiation process of adipocytes, the expression levels of SIRT1 protein and mRNA are increased following the increasing of C/EBPα, which binds to the promoter of SIRT1 and regulates the expression of SIRT1 in the lipogenesis.[31] Upregulation of SIRT1 in differentiated adipocytes promotes lipolysis and fat

reduction. As reduction in fat is sufficient to extend murine lifespan, deacetylase SIRT1 displays important regulating functions in the lipid intermediary metabolism and keeps the balance of lipogenesis. Modulation of the enzyme activity in mammalian may intervene with obesity and the related diabetes. These results suggest that SIRT1 and SIRT2 deacetylases not only modulate adipogenic transcription factors, and their expression, and activity may also be crucial for regulating adipocyte differentiation. From this aspect, they perhaps share common regulatory mechanism.

SIRT3 acts as a primary mitochondrial deacetylase and targets multiple of mitochondrial proteins. These proteins are acetylated in TCA cycle and β-oxidation pathways implicated in carbon conversion and energy metabolism within mitochondria. An early study has revealed that ATP content displayed a significant reduction in SIRT3 null mice liver, heart and kidney and the activity of mitochondrial respiratory complex I was reduced.[32] SIRT3 directly regulates the activity of mitochondrial AceCS2 by NAD^+-dependent deacetylation.[33,34] Mass spectrometry of mitochondrial proteins demonstrates that long-chain acyl coenzyme A dehydrogenase (LCAD) is hyperacetylated (K42) in absence of SIRT3, and hyperacetylation of LCAD abolishes its enzymatic activity. While *in vitro* and *in vivo*, LCAD is deacetylated in wild-type mice by SIRT3 under fasting conditions. Mice lacking SIRT3 display fatty-acid oxidation disorders including ATP reduction. This condition will lead to obesity.[35] It has been reported that SIRT3 activates oxidative phosphorylation and inhibits glycolysis and destabilize the association of hexokinase II with the mitochondria via inactivation of cyclophilin D.[36] In addition, SIRT3 deacetylates and activates mitochondrial isocitrate dehydrogenase (IDH2), a key enzyme in TCA cycle and in the supply of NADPH necessary for antioxidant defense.[37] As a regulator of protein translation, SIRT3 deacetylates the mitochondrial ribosome and modulates the activity of respiratory complex II (succinate dehydrogenase).[38,39] From the above results, SIRT3 may serve as a major player in modulation of intermediary metabolism and is associated with many metabolic complication including obesity, diabetes, fatty liver, hypertention, myocardiopathy, etc. In addition, SIRT3 deacetylates FoxO1 and some mitochondrial enzymes such as manganese superoxide dismutase, superoxide dismutase 2 and NADH: Ubiquinone oxidoreductase (mitochondrial respiratory complex I), which are involved in processes of mammalian longevity.[40,41] SIRT3 also reduces reactive oxygen species (ROS) levels *in vivo* by inhibiting the activity and stability of HIF-1α. From this aspect, SIRT3 is a longevity-related deacetylase.

According to the above analysis, SIRT1, SIRT2, and SIRT3 are also associated with HIF-1α in regulation obesity and diabetes. Zhong *et al*. discovered that SIRT6 inhibited the transcriptional factor HIF-1α.[42] SIRT6 deficient cells displayed an increased HIF-1α activity, and a decreased mitochondrial respiration. In addition, SIRT6 knockout mice showed an aging symptom such as glycopenia, loss of subcutaneous fat and lordokyphosis.[43] These above studies indicate that SIRT6 keeps the balance of blood sugar and lipid synthesis, and may be as an important molecular target of glucose homeostasis. In conclusion, by targeting these Sirtuin members, it will provide some novel therapeutic methods for metabolic disorders including obesity and diabetes.

Role of Sirtuins in Myocardiopathy

Vascular differentiation and blood vessel growth are associated with SIRT1 expression. In human umbilical vein endothelial cells (HUVECs), the levels of genes involved in vascular differentiation are reduced, and the initiation of vascular generation is inhibited when SIRT1 is knocked down.[44] SIRT1 induces the expression of vascular endothelial growth factor (VEGF), VEGF receptor and nitric oxide (NO) synthase via inhibition of FoxO1, the necessary negative regulator of NO synthase. In HUVECs, SIRT1 interacts with and deacetylates FoxO1, which leads to FoxO1 activity diminished and facilitates the vascular formation.[45] In 2007, Sano *et al*. found that constitutive stress load in the left ventricle induced upregulation of p53. p53 is the anti-vessel formation factor and inhibits the activity of SIRT1 while HIF-1α promotes SIRT1 expression.[46,47] HIF-1α inactivity is correlated with down-regulation of VEGF, and also with the reduction of density of myocardium blood capillary and muscular hypertrophy transition into heart disease.[48] So fine modulation between SIRT1 and p53 determines the degree of vessel formation in the loaded heart, and whether the compensatory myocardial hypertrophy turns into noncompensatory heart diseases.

In the death-receptor-mediated apoptosis pathways, tumor necrosis factor-α (TNF-α) activates cell apoptosis by stimulating the formation of receptor-interacting protein 1 (RIP1)-RIP3 complex. Narayan *et al*. have found that deacetylase SIRT2 binds to RIP3 and deletion of SIRT2 blocks the formation of RIP1-RIP3 complex in mice.[49] Further studies demonstrate that RIP1 is a critical target of SIRT2 deacetylation, and acetylation of RIP1 (K530) modulates the formation of RIP1-RIP3 complex and TNF-α-mediated necrosis. Inhibition of SIRT2 blocks cellular necrosis induced by TNF-α. RIP1 is also deacetylated by SIRT2 in the condition of ischaemia-reperfusion injury. In addition, the hearts of wild-type mice treated with SIRT2 specific inhibitor display distinct protection from ischemic injury. These results indicate SIRT2 acts as an important modulator of programmed cell necrosis, and inhibition of SIRT2 may provide a novel approach to prevent from necrotic injuries, such as myocardial infarction and ischaemic stroke. SIRT7 is primarily located in nucleus (especially in nucleolar regions). In cardiomyocytes, SIRT7 directly deacetylates p53, and depletion of SIRT7 leads to hyperacetylation of p53 and increases basal cell apoptosis *in vivo*.[50] In addition, SIRT7 may be involved in protection during ischemic episodes because SIRT7-deficient cardiomyocytes are more sensitive to oxidative and genotoxic stress.[51] In our study,

we found that Salermide (inhibitor of SIRT1 and SIRT2) induced cell apoptosis in human lung cancer cells.[52] We all know that vessel formation is the key factor in the tumor development and metastasis. If SIRT1/2 acts as the target protein, it would be beneficial to the tumor invalid in clinical for therapy.

Heart failure occurs when the long-term cardiac workload exceeds the ability of the heart and this pathological progression of heart will reach cardiac hypertrophy. The leading risk factor to heart failure is increasing age coupling with dysfunction of tissues and organs, such as hypertension, cardiac arrhythmias and renal insufficiency. The correlation between mitochondrial dysfunction in heart failure and the advancing age has been clarified. Heart and skeletal muscle are highly energetic organs, and they are heavily dependent on mitochondria-derived energy.[53] It has been known that heart failure is often regarded as a pathological state with impaired energy homeostasis, that is to say, the cardiomyocyte ATP and creatine pools in mitochondrial has been depleted. This phenomenon is consistent with the study that SIRT3$^{-/-}$ mice are depleted cardiac ATP levels in liver and brown adipose tissues and the global mitochondrial proteins display hyperacetylation. These data indirectly implicate the role of mitochondrial SIRT3 dysfunction in heart failure. Sundaresan *et al*. have found that SIRT3 facilitates cardiomyocyte cell survival during genotoxic and oxidative stress, and SIRT3 transgenic mice are resistant to cardiac hypertrophy induced by agonist via upregulation of antioxidant genes.[54] In cardiomyocytes, SIRT3 is a functional prosurvival deacetylase via deacetylating NF Ku70 and promotes proapoptotic protein Bax sequestration resulting in apoptosis inhibition. Under stress conditions, the expression level of SIRT3 is increased, which can protect cardiomyocytes by partly hindering translocation of Bax into mitochondria. This study indicates an essential role of SIRT3 in cardiomyocytes survival in stress situation.[55] In another study, the agonist-induced cardiac hypertrophy is abrogated in a SIRT3-dependent manner in which mice are administrated with exogenous NAD^+.[56] In addition, NAD^+-salvaging enzyme nicotinamide phosphoribosyltransferase (Nampt) is overexpressed in transgenic mice, and the infarct size of ischemia-reperfusion injury is reduced because of the increased NAD^+ cardioprotective effect mediated by SIRT1.[57] Therefore, we see that Sirtuin family members, such as SIRT1, SIRT2, SIRT3 and SIRT7 both have cardioprotective effects. If we find the common regulatory mechanism among them, prevention and therapy for myocardiopathy may be operated effectively through multiple ways by targeting the same regulatory factor.

Regulatory Role of Sirtuins in Neurodegenerative Diseases

In several neurodegenerative diseases models, such as Alzheimer's disease (AD), amyotrophic lateral sclerosis and Parkinson's disease (PD), SIRT1 activation can protect neuron cells exposed to neurotoxic insult. But in this condition, it is dependent on cellular NAD^+ status.[58] If the NAD^+ level reduces, SIRT1 inhibition rather than SIRTI activation actually protect neuron cells from apoptosis. Because during cerebral hypoxia, the levels of ATP and oxygen in neuron cells are lowered, which stimulate both bioenergenic and oxidative stress leading to SIRT1 activation. SIRT1 activation will further reduce the NAD^+ and trigger the neuron cells apoptosis. In mice AD model, studies have found that SIRT1 inhibition can restore cognition by stabilizing tau protein.[59] Deacetylase SIRT2 involves in neuron cells apoptosis by mediation of different proteins. In the model of PD, SIRT2 deacetylates FoxO3a and increases the expression levels of Bim RNA and protein to induce cell apoptosis treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).[60] While neurodegeneration induced by chronic MPTP administration is averted by genetic deletion of SIRT2 in mouse model. SIRT2 knockdown increases the acetylation level of FoxO3a and diminishes Bim levels leading to the reduction of apoptosis. Therefore, designing inhibitors in pharmacology may be beneficial to develop valid treatments for neurodegeneration. But it should be elaborately considered these modulators are adapt to the specific case and cell-dependent because deacetylase inhibitors not only affect neural cells but also glia and astrocytes cells.[61]

Regulatory Role of Sirtuins in Tumorigenesis

Cancer is also age-related disease and occurs in an exponential increase pattern in the elderly. In general, it is difficult to ascribe Sirtuins as oncogenic proteins or tumor suppressor. SIRT1, 2, 3, 4, 6 and 7 have all been shown to modulate tumorigenesis in mouse models. At present, the collected evidence *in vivo* supports mostly SIRT1 as an anti-tumor factor.[62] Wang *et al*. have showed that SIRT1 is downregulated in human tumor samples.[63] While other studies have shown that pancreatic cancer cells displayed senescence and apoptosis via SIRT1 RNAi knockdown experiment. Several SIRT1 activators are used in clinical trials for cancer therapy.[64,65] SIRT2 deacetylates p53 and regulates its effect on cellular apoptosis. Therefore, inhibition of SIRT2-dependent p53 deacetylation is of great interest for cancer therapy.[66]

In cancer cells, oxidative phosphorylation impaired and glycolytic metabolism preference are the primary hallmarks of the Warburg Effect, which meet to tumor cells rapid growth demand. As previously mentioned, SIRT3 modulates multitude of mitochondrial proteins potentially, and dysfunction of SIRT3 contributes to reprogram metabolism in tumor cells.[67] Deacetylase SIRT3 is involved in cancer cell apoptosis and mostly serves as a tumor suppressor. But it also promotes cell survival. SIRT3 induces HCT116 epithelial cancer cell apoptosis in JNK-dependent manner via silencing Bcl-2.[68,69] SIRT3 mitochondrial deacetylase is regulated by Nampt, the rate-limiting enzyme in NAD^+-salvage pathway.[70] In prostate cancer cells, Nampt is necessary for cell survival and de novo lipogenesis,

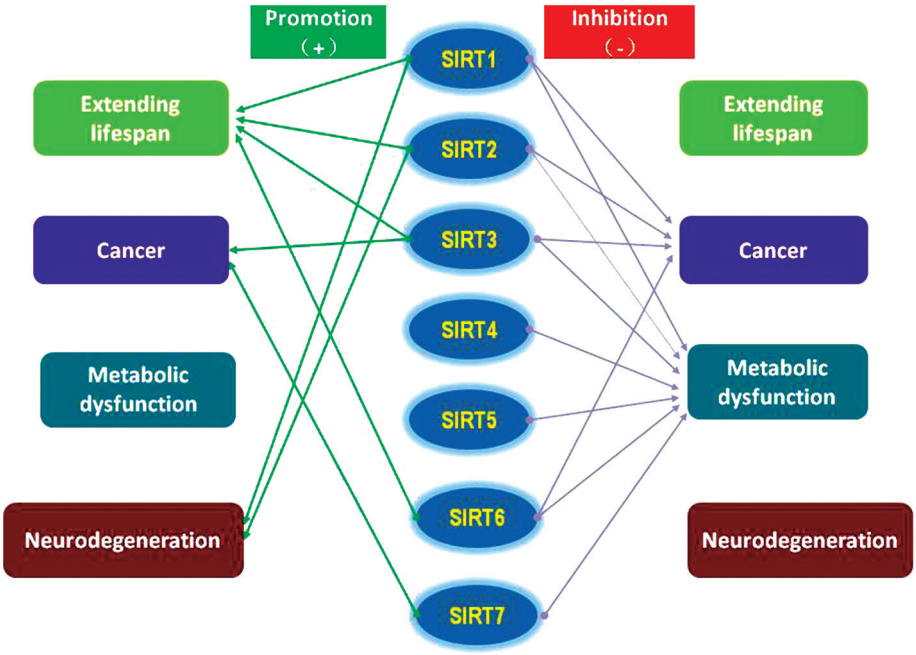

Figure 1: Regulatory correlation between Sirtuins and the age-related diseases.

Table 2: Characteristics and target substrates of different Sirtuin members

Sirtuins	Localization	Molecular weight (KDa)	Catalytic activity	Target substrates
SIRT1	Nucleus cytoplasm	120	Deacetylase	HIF-1α
				PGC-1α
				FoxO1
				p53
				AceCS1
				Nitric oxide synthase
				VEGF
				VEGFR
				H3K9, H4K16, H3K14, H1K26
SIRT2	Cytoplasm nucleus	43	Deacetylase	HIF-1α
				PGC-1α
				FoxO1
				p53
				FoxO3a
				RIP1/RIP3 complex
SIRT3	Mitochondria cytoplasm nucleus	28, 44	Deacetylase	HIF-1α
				PGC-1α
				FoxO1
				p53
				AceCS2
				LCAD
				IDH2
				PDH
				SDH

Contd...

Table 2: Contd...

Sirtuins	Localization	Molecular weight (KDa)	Catalytic activity	Target substrates
				MnSOD, SOD2, Ku70, Cyclophilin D
				Catalase
				Respiratory complex I
				Respiratory complex II
SIRT4	Mitochondria	35	Deacetylase	MCD
			ADP-ribosyl transferase	GDH1
			Lipoamidase	PDH
SIRT5	Mitochondria	34	Deacetylase	CytC
			Demalonylase	Malonyl protein
			Desuccinylase	Succinyl protein
				CPS1
SIRT6	Nucleus	37	Deacetylase	HIF-1α, H3K9
			ADP-ribosyl transferas	Long-chain fatty acyl groups
				PARP1
SIRT7	Nucleus	45	Deacetylase	p53, H3K18, PAF53

HIF-1α: Hypoxia inducible factor-1α; PGC-1α: Peroxisome proliferator-activated receptor-γ coactivator-1α; FoxO1: Forkhead box O1; AceCS1: Acetyl- coenzyme A synthetase 1; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor 1; LCAD: Long-chain acyl coenzyme A dehydrogenase; IDH2: Isocitrate dehydrogenase; PDH: Pyruvate dehydrogenase; SDH: Succinate dehydrogenase; MnSOD: Manganese superoxide dismutase; SOD2: Superoxide dismutase 2; MCD: Malonyl coenzyme A decarboxylase; GDH1: Glutamate dehydrogenase 1; CPS1: Carbamoyl phosphate synthase 1; PARP1: Poly (ADP-ribose) polymerase 1; PAF53: platelet activating factor.

especially in the condition of fasting and induced genotoxic stress.[71] Recently, two different experiments have been demonstrated that SIRT3 is associated with the regulation of p53 in cell growth arrest.[72,73] In EJ bladder carcinoma cell, SIRT3 partially abrogates p53 activity to exert growth arrest and senescence. While inactivation of SIRT3 increases mitochondrial ROS production and leads to p53 upregulation and alterations of gene expression in downstream pathways. All these mean that SIRT3 can antagonize the action of p53 in cell growth arrest and promote cell survival.

As discussed above, other Sirtuins, especially, SIRT4 is also a mitochondrial deacetylase as SIRT3 and functions as tumor suppressor via modulating glutamine metabolism.[74] Latest SIRT2 has been identified as an anti-oncogenic protein in nonsmall cell lung cancer by targeting JMJD2A.[75] SIRT6 plays an important role in preventing tumorigenesis. Overexpression of SIRT6 induces apoptosis in some cancer cells.[76] SIRT6 acts as a tumor suppressor by inhibition of Warburg Effect in a mouse model of colon cancer and higher expression levels of SIRT6 in colorectal cancer patients have a positive correlation with a better prognosis clinically.[77] In contrast, SIRT7 has 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.[78]

According to the above analysis on Sirtuins at present, we find that Sirtuin members display different regulatory role in aging-related diseases [Figure 1]. These Srituins modulate or interact with the same transcriptional factors, such as HIF-1α, PGC-1α, FoxO1 and p53. Especially SIRT1, SIRT2 and SIRT3 as the major deacetylases of Sirtuin family, all of them interact with HIF-1α, PGC-1α, FoxO1 and p53. Beyond that, each of Sirtuins has its own catalytic activity and specific substrates [Table 2]. Therefore, these Sirtuin family members regulate the aging-related diseases in common or respectively.

With advancing age, diabetes, myocardiopathy, neurodegenerative diseases, and cancer are emerging pathophysiological states. Accumulating studies have been reported that epigenetic alteration of acetylation mode in mitochondrial proteins is highly correlated with aging-related diseases.[41] Most of the Sirtuin members participate in the epigenetic changes in human. At gene level, a guanine to thymine (G477T) single nucleotide polymorphism of SIRT3 gene is identified to be located in exon three with survivorship in elderly male.[79,80] A variable number of tandem repeat (VNTR) polymorphisms discovered by Bellizzi *et al*. suggest that active VNTR enhancer is related with longevity.[81,82] GATA-2 and AP-1 sites in SIRT3-VNTR are found conserved in SIRT1 and SIRT2 genes, which indicate that the three Sirtuin members have high-level similarity in biological functions, or in other words they may share commonly modulated mechanism.[83]

Perspectives

Mammalian Sirtuins as the critical modulators in age-related diseases, take part in diverse metabolic processes by targeting different substrates or via different signaling pathways. In addition, Sirtuins are mostly NAD^+-dependent deacetylases and response to cellular nutrient and energy, and thus regulate the expression of downstream genes in metabolism to enhance nutrient resistance and improve the ability to counteract oxidative stress. Transcriptional factors such as HIF-1α, PGC-1α, p53 and FoxO1, are sensitive to changes of nutrient and energy *in vitro* and *in vivo*, and are all involved in these regulatory metabolism processes. So according to the above evidence and analysis, there must exist correlations between Sirtuin family members and these transcriptional factors though the interaction may have not the same biological effects in metabolism regulation. We suspect additional signaling pathways or modulating factors may exist among these Sirtuins with further studies, especially for the lesser studied SIRT4, SIRT5 and SIRT7. Therefore, Sirtuins as the targets for therapy of aging-related pathologies indeed merit consideration in the more and more graying society. At present, some inhibitors and activators have been in clinical trials. However, it is worth considering that these Sirtuins inhibitors or activators for therapy must be in specific case and cell-dependent. In addition, different Sirtuin member locates in diverse cellular compartments and has specific catalytic activity and biological function. So analysis of mammalian Sirtuins genomic variation at the locus respectively, functional study, identification of their substrate targets and constructions of transgenic animals, especially analysis of the common or respective regulatory mechanism may be beneficial to longevity and retarding onset of the aging, and it is also contributed to provide efficient prevention and remedy methods for aging-related diseases.

References

1. Haigis MC, Yankner BA. The aging stress response. Mol Cell 2010;40:333-44.
2. Haigis MC, Guarente LP. Mammalian sirtuins – Emerging roles in physiology, aging, and calorie restriction. Genes Dev 2006;20:2913-21.
3. Finley LW, Haigis MC. Metabolic regulation by SIRT3: Implications for tumorigenesis. Trends Mol Med 2012;18:516-23.
4. Giralt A, Villarroya F. SIRT3, a pivotal actor in mitochondrial functions: Metabolism, cell death and aging. Biochem J 2012;444:1-10.
5. Fu J, Jin J, Cichewicz RH, Hageman SA, Ellis TK, Xiang L, *et al.* trans-(-)-e-Viniferin increases mitochondrial sirtuin 3 (SIRT3), activates AMP-activated protein kinase (AMPK), and protects cells in models of Huntington Disease. J Biol Chem 2012;287:24460-72.
6. Hirschey MD, Shimazu T, Goetzman E, Jing E, Schwer B, Lombard DB, *et al.* SIRT3 regulates mitochondrial fatty-acid oxidation by reversible enzyme deacetylation. Nature 2010;464:121-5.
7. Komlos D, Mann KD, Zhuo Y, Ricupero CL, Hart RP, Liu AY, *et al.* Glutamate dehydrogenase 1 and SIRT4 regulate glial development. Glia 2013;61:394-408.
8. Mao Z, Hine C, Tian X, Van Meter M, Au M, Vaidya A, *et al.* SIRT6 promotes DNA repair under stress by activating PARP1. Science 2011;332:1443-6.
9. Mathias RA, Greco TM, Oberstein A, Budayeva HG, Chakrabarti R, Rowland EA, *et al.* Sirtuin 4 is a lipoamidase regulating pyruvate dehydrogenase complex activity. Cell 2014;159:1615-25.

10. Laurent G, German NJ, Saha AK, de Boer VC, Davies M, Koves TR, *et al.* SIRT4 coordinates the balance between lipid synthesis and catabolism by repressing malonyl CoA decarboxylase. Mol Cell 2013;50:686-98.
11. Du J, Zhou Y, Su X, Yu JJ, Khan S, Jiang H, *et al.* Sirt5 is a NAD-dependent protein lysine demalonylase and desuccinylase. Science 2011;334:806-9.
12. Jiang H, Khan S, Wang Y, Charron G, He B, Sebastian C, *et al.* SIRT6 regulates TNF-a secretion through hydrolysis of long-chain fatty acyl lysine. Nature 2013;496:110-3.
13. Kiran S, Anwar T, Kiran M, Ramakrishna G. Sirtuin 7 in cell proliferation, stress and disease: Rise of the Seventh Sirtuin! Cell Signal 2015;27:673-82.
14. Brenmoehl J, Hoeflich A. Dual control of mitochondrial biogenesis by sirtuin 1 and sirtuin 3. Mitochondrion 2013;13:755-61.
15. Guarente L, Picard F. Calorie restriction – the SIR2 connection. Cell 2005;120:473-82.
16. Simic P, Zainabadi K, Bell E, Sykes DB, Saez B, Lotinun S, *et al.* SIRT1 regulates differentiation of mesenchymal stem cells by deacetylating ß-catenin. EMBO Mol Med 2013;5:430-40.
17. Cohen HY, Miller C, Bitterman KJ, Wall NR, Hekking B, Kessler B, *et al.* Calorie restriction promotes mammalian cell survival by inducing the SIRT1 deacetylase. Science 2004;305:390-2.
18. Zhang D, Liu Y, Chen D. SIRT-ain relief from age-inducing stress. Aging (Albany NY) 2011;3:158-61.
19. Cosentino C, Mostoslavsky R. Sirtuin to the rescue: SIRT2 extends life span of BubR1 mice. EMBO J 2014;33:1417-9.
20. Baur JA, Ungvari Z, Minor RK, Le Couteur DG, de Cabo R. Are sirtuins viable targets for improving healthspan and lifespan? Nat Rev Drug Discov 2012;11:443-61.
21. Adler AS, Sinha S, Kawahara TL, Zhang JY, Segal E, Chang HY. Motif module map reveals enforcement of aging by continual NF-kappaB activity. Genes Dev 2007;21:3244-57.
22. Kawahara TL, Michishita E, Adler AS, Damian M, Berber E, Lin M, *et al.* SIRT6 links histone H3 lysine 9 deacetylation to NF-kappaB-dependent gene expression and organismal life span. Cell 2009;136:62-74.
23. Baohua Y, Li L. Effects of SIRT6 silencing on collagen metabolism in human dermal fibroblasts. Cell Biol Int 2012;36:105-8.
24. Seo KS, Park JH, Heo JY, Jing K, Han J, Min KN, *et al.* SIRT2 regulates tumour hypoxia response by promoting HIF-1a hydroxylation. Oncogene 2015;34:1354-62.
25. Krishnan J, Danzer C, Simka T, Ukropec J, Walter KM, Kumpf S, *et al.* Dietary obesity-associated Hif1a activation in adipocytes restricts fatty acid oxidation and energy expenditure via suppression of the Sirt2-NAD+system. Genes Dev 2012;26:259-70.
26. Wang F, Tong Q. SIRT2 suppresses adipocyte differentiation by deacetylating FOXO1 and enhancing FOXO1's repressive interaction with PPARgamma. Mol Biol Cell 2009;20:801-8.
27. Jing E, Gesta S, Kahn CR. SIRT2 regulates adipocyte differentiation through FoxO1 acetylation/deacetylation. Cell Metab 2007;6:105-14.
28. Lagouge M, Argmann C, Gerhart-Hines Z, Meziane H, Lerin C, Daussin F, *et al.* Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. Cell 2006;127:1109-22.
29. Sahar S, Masubuchi S, Eckel-Mahan K, Vollmer S, Galla L, Ceglia N, *et al.* Circadian control of fatty acid elongation by SIRT1 protein-mediated deacetylation of acetyl-coenzyme A synthetase 1. J Biol Chem 2014;289:6091-7.
30. Picard F, Kurtev M, Chung N, Topark-Ngarm A, Senawong T, Machado De Oliveira R, *et al.* Sirt1 promotes fat mobilization in white adipocytes by repressing PPAR-gamma. Nature 2004;429:771-6.
31. Jin Q, Zhang F, Yan T, Liu Z, Wang C, Ge X, *et al.* C/EBPalpha regulates SIRT1 expression during adipogenesis. Cell Res 2010;20:470-9.
32. Ahn BH, Kim HS, Song S, Lee IH, Liu J, Vassilopoulos A, *et al.* A role for the mitochondrial deacetylase Sirt3 in regulating energy homeostasis. Proc Natl Acad Sci U S A 2008;105:14447-52.
33. Schwer B, Bunkenborg J, Verdin RO, Andersen JS, Verdin E. Reversible lysine acetylation controls the activity of the mitochondrial enzyme acetyl-CoA synthetase 2. Proc Natl Acad Sci U S A 2006;103:10224-9.
34. Kim SC, Sprung R, Chen Y, Xu Y, Ball H, Pei J, *et al.* Substrate and functional diversity of lysine acetylation revealed by a proteomics survey. Mol Cell 2006;23:607-18.
35. Rinaldo P, Matern D. Disorders of fatty acid transport and mitochondrial oxidation: Challenges and dilemmas of metabolic evaluation. Genet Med 2000;2:338-44.
36. Shulga N, Wilson-Smith R, Pastorino JG. Sirtuin-3 deacetylation of cyclophilin D induces dissociation of hexokinase II from the mitochondria. J Cell Sci 2010;123:894-902.
37. Someya S, Yu W, Hallows WC, Xu J, Vann JM, Leeuwenburgh C, *et al.* Sirt3 mediates reduction of oxidative damage and prevention of age-related hearing loss under caloric restriction. Cell 2010;143:802-12.
38. Yang Y, Cimen H, Han MJ, Shi T, Deng JH, Koc H, *et al.* NAD+-dependent deacetylase SIRT3 regulates mitochondrial protein synthesis by deacetylation of the ribosomal protein MRPL10. J Biol Chem 2010;285:7417-29.
39. Cimen H, Han MJ, Yang Y, Tong Q, Koc H, Koc EC. Regulation of succinate dehydrogenase activity by SIRT3 in mammalian mitochondria. Biochemistry 2010;49:304-11.
40. Zhang B, Cui S, Bai X, Zhuo L, Sun X, Hong Q, *et al.* SIRT3 overexpression antagonizes high glucose accelerated cellular senescence in human diploid fibroblasts via the SIRT3-FOXO1 signaling pathway. Age (Dordr) 2013;35:2237-53.
41. Zhao S, Xu W, Jiang W, Yu W, Lin Y, Zhang T, *et al.* Regulation of cellular metabolism by protein lysine acetylation. Science 2010;327:1000-4.
42. Zhong L, D'Urso A, Toiber D, Sebastian C, Henry RE, Vadysirisack DD, *et al.* The histone deacetylase Sirt6 regulates glucose homeostasis via Hif1alpha. Cell 2010;140:280-93.
43. Finkel T, Serrano M, Blasco MA. The common biology of cancer and ageing. Nature 2007;448:767-74.
44. Potente M, Ghaeni L, Baldessari D, Mostoslavsky R, Rossig L, Dequiedt F, *et al.* SIRT1 controls endothelial angiogenic functions during vascular growth. Genes Dev 2007;21:2644-58.
45. Heather LC, Cole MA, Tan JJ, Ambrose LJ, Pope S, Abd-Jamil AH, *et al.* Metabolic adaptation to chronic hypoxia in cardiac mitochondria. Basic Res Cardiol 2012;107:268.
46. Sano M, Minamino T, Toko H, Miyauchi H, Orimo M, Qin Y, *et al.* p53-induced inhibition of Hif-1 causes cardiac dysfunction during pressure overload. Nature 2007;446:444-8.
47. Chen R, Dioum EM, Hogg RT, Gerard RD, Garcia JA. Hypoxia increases sirtuin 1 expression in a hypoxia-inducible factor-dependent manner. J Biol Chem 2011;286:13869-78.
48. Fukuda S, Kaga S, Zhan L, Bagchi D, Das DK, Bertelli A, *et al.* Resveratrol ameliorates myocardial damage by inducing vascular endothelial growth factor-angiogenesis and tyrosine kinase receptor Flk-1. Cell Biochem Biophys 2006;44:43-9.
49. Narayan N, Lee IH, Borenstein R, Sun J, Wong R, Tong G, *et al.* The NAD-dependent deacetylase SIRT2 is required for programmed necrosis. Nature 2012;492:199-204.
50. Ford E, Voit R, Liszt G, Magin C, Grummt I, Guarente L. Mammalian Sir2 homolog SIRT7 is an activator of RNA polymerase I transcription. Genes Dev 2006;20:1075-80.
51. Vakhrusheva O, Smolka C, Gajawada P, Kostin S, Boettger T, Kubin T, *et al.* Sirt7 increases stress resistance of cardiomyocytes and prevents apoptosis and inflammatory cardiomyopathy in mice. Circ Res 2008;102:703-10.
52. Liu G, Su L, Hao X, Zhong N, Zhong D, Singhal S, *et al.* Salermide up-regulates death receptor 5 expression through the ATF4-ATF3-CHOP axis and leads to apoptosis in human cancer cells. J Cell Mol Med 2012;16:1618-28.
53. Di Donato S. Multisystem manifestations of mitochondrial disorders. J Neurol 2009;256:693-710.
54. Neubauer S. The failing heart – An engine out of fuel. N Engl J Med 2007;356:1140-51.
55. Sundaresan NR, Samant SA, Pillai VB, Rajamohan SB, Gupta MP. SIRT3 is a stress-responsive deacetylase in cardiomyocytes that protects cells from stress-mediated cell death by deacetylation of Ku70. Mol Cell Biol 2008;28:6384-401.
56. Pillai VB, Sundaresan NR, Kim G, Gupta M, Rajamohan SB,

Pillai JB, *et al.* Exogenous NAD blocks cardiac hypertrophic response via activation of the SIRT3-LKB1-AMP-activated kinase pathway. J Biol Chem 2010;285:3133-44.
57. Hsu CP, Oka S, Shao D, Hariharan N, Sadoshima J. Nicotinamide phosphoribosyltransferase regulates cell survival through NAD+synthesis in cardiac myocytes. Circ Res 2009;105:481-91.
58. Kim D, Nguyen MD, Dobbin MM, Fischer A, Sananbenesi F, Rodgers JT, *et al.* SIRT1 deacetylase protects against neurodegeneration in models for Alzheimer's disease and amyotrophic lateral sclerosis. EMBO J 2007;26:3169-79.
59. Green KN, Steffan JS, Martinez-Coria H, Sun X, Schreiber SS, Thompson LM, *et al.* Nicotinamide restores cognition in Alzheimer's disease transgenic mice via a mechanism involving sirtuin inhibition and selective reduction of Thr231-phosphotau. J Neurosci 2008;28:11500-10.
60. Liu L, Arun A, Ellis L, Peritore C, Donmez G. Sirtuin 2 (SIRT2) enhances 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced nigrostriatal damage via deacetylating forkhead box O3a (Foxo3a) and activating Bim protein. J Biol Chem 2013;288:24163.
61. Dietz KC, Casaccia P. HDAC inhibitors and neurodegeneration: At the edge between protection and damage. Pharmacol Res 2010;62:11-7.
62. Herranz D, Serrano M. SIRT1: Recent lessons from mouse models. Nat Rev Cancer 2010;10:819-23.
63. Wang RH, Sengupta K, Li C, Kim HS, Cao L, Xiao C, *et al.* Impaired DNA damage response, genome instability, and tumorigenesis in SIRT1 mutant mice. Cancer Cell 2008;14:312-23.
64. Zhao G, Cui J, Zhang JG, Qin Q, Chen Q, Yin T, *et al.* SIRT1 RNAi knockdown induces apoptosis and senescence, inhibits invasion and enhances chemosensitivity in pancreatic cancer cells. Gene Ther 2011;18:920-8.
65. Chauhan D, Bandi M, Singh AV, Ray A, Raje N, Richardson P, *et al.* Preclinical evaluation of a novel SIRT1 modulator SRT1720 in multiple myeloma cells. Br J Haematol 2011;155:588-98.
66. Hoffmann G, Breitenbücher F, Schuler M, Ehrenhofer-Murray AE. A novel sirtuin 2 (SIRT2) inhibitor with p53-dependent pro-apoptotic activity in non-small cell lung cancer. J Biol Chem 2014;289:5208-16.
67. Lombard DB, Alt FW, Cheng HL, Bunkenborg J, Streeper RS, Mostoslavsky R, *et al.* Mammalian Sir2 homolog SIRT3 regulates global mitochondrial lysine acetylation. Mol Cell Biol 2007;27:8807-14.
68. Kim HS, Patel K, Muldoon-Jacobs K, Bisht KS, Aykin-Burns N, Pennington JD, *et al.* SIRT3 is a mitochondria-localized tumor suppressor required for maintenance of mitochondrial integrity and metabolism during stress. Cancer Cell 2010;17:41-52.
69. Allison SJ, Milner J. SIRT3 is pro-apoptotic and participates in distinct basal apoptotic pathways. Cell Cycle 2007;6:2669-77.
70. Yang H, Yang T, Baur JA, Perez E, Matsui T, Carmona JJ, *et al.* Nutrient-sensitive mitochondrial NAD+levels dictate cell survival. Cell 2007;130:1095-107.
71. Bowlby SC, Thomas MJ, D'Agostino RB Jr, Kridel SJ. Nicotinamide phosphoribosyl transferase (Nampt) is required for de novo lipogenesis in tumor cells. PLoS One 2012;7:e40195.
72. Li S, Banck M, Mujtaba S, Zhou MM, Sugrue MM, Walsh MJ. P53-induced growth arrest is regulated by the mitochondrial SirT3 deacetylase. PLoS One 2010;5:e10486.
73. Kawamura Y, Uchijima Y, Horike N, Tonami K, Nishiyama K, Amano T, *et al.* Sirt3 protects *in vitro*-fertilized mouse preimplantation embryos against oxidative stress-induced p53-mediated developmental arrest. J Clin Invest 2010;120:2817-28.
74. Jeong SM, Lee A, Lee J, Haigis MC. SIRT4 protein suppresses tumor formation in genetic models of Myc-induced B cell lymphoma. J Biol Chem 2014;289:4135-44.
75. Xu W, Jiang K, Shen M, Qian Y, Peng Y. SIRT2 suppresses non-small cell lung cancer growth by targeting JMJD2A. Biol Chem 2015 [Epub ahead of print].
76. Van Meter M, Mao Z, Gorbunova V, Seluanov A. SIRT6 overexpression induces massive apoptosis in cancer cells but not in normal cells. Cell Cycle 2011;10:3153-8.
77. Sebastián C, Zwaans BM, Silberman DM, Gymrek M, Goren A, Zhong L, *et al*. The histone deacetylase SIRT6 is a tumor suppressor that controls cancer metabolism. Cell 2012;151:1185-99.
78. Kim JK, Noh JH, Jung KH, Eun JW, Bae HJ, Kim MG, *et al.* Sirtuin7 oncogenic potential in human hepatocellular carcinoma and its regulation by the tumor suppressors MiR-125a-5p and MiR-125b. Hepatology 2013;57:1055-67.
79. Hoshino I, Matsubara H. Recent advances in histone deacetylase targeted cancer therapy. Surg Today 2010;40:809-15.
80. Rose G, Dato S, Altomare K, Bellizzi D, Garasto S, Greco V, *et al.* Variability of the SIRT3 gene, human silent information regulator Sir2 homologue, and survivorship in the elderly. Exp Gerontol 2003;38:1065-70.
81. Bellizzi D, Rose G, Cavalcante P, Covello G, Dato S, De Rango F, *et al.* A novel VNTR enhancer within the SIRT3 gene, a human homologue of SIR2, is associated with survival at oldest ages. Genomics 2005;85:258-63.
82. Lescai F, Blanché H, Nebel A, Beekman M, Sahbatou M, Flachsbart F, *et al.* Human longevity and 11p15.5: A study in 1321 centenarians. Eur J Hum Genet 2009;17:1515-9.
83. Voe-Mahlknecht S, Letzel S, Mahlknecht U. Fluorescence *in situ* hybridization and chromosomal organization of the human Sirtuin 7 gene. Int J Oncol 2006;28:899-908.

Received: 12-12-2014 **Edited by:** Yi Cui
How to cite this article: Wang QL, Guo SJ. Sirtuins Function as the Modulators in Aging-related Diseases in Common or Respectively. Chin Med J 2015;128:1671-8.

Source of Support: This work was supported by grants from the National Natural Science Foundation of China (No. 20971063) and doctoral scientific research funds (No. 318051315). **Conflict of Interest:** None declared.