Aging Cell (2017) **16**, pp4–16 Doi: 10.1111/acel.12538

REVIEW

Function of the SIRT3 mitochondrial deacetylase in cellular physiology, cancer, and neurodegenerative disease

Aneesa Ansari,[1]* Md. Shahedur Rahman,[1]* Subbroto K. Saha,[2]* Forhad K. Saikot,[1]* Akash Deep[3] and Ki-Hyun Kim[4]

[1]Department of Genetic Engineering and Biotechnology, Jessore University of Science and Technology, Jessore 7408, Bangladesh
[2]Department of Stem Cell and Regenerative Biology, Konkuk University, 120 Neungdong-Ro, Seoul 05029, Korea
[3]Central Scientific Instruments Organisation (CSIR-CSIO), Sector 30 C, Chandigarh 160030, India
[4]Department of Civil & Environmental Engineering, Hanyang University, 222 Wangsimni-Ro, Seoul 04763, Korea

Summary

In mammals, seven members of the sirtuin protein family known as class III histone deacetylase have been identified for their characteristic features. These distinguished characteristics include the tissues where they are distributed or located, enzymatic activities, molecular functions, and involvement in diseases. Among the sirtuin members, SIRT3 has received much attention for its role in cancer genetics, aging, neurodegenerative disease, and stress resistance. SIRT3 controls energy demand during stress conditions such as fasting and exercise as well as metabolism through the deacetylation and acetylation of mitochondrial enzymes. SIRT3 is well known for its ability to eliminate reactive oxygen species and to prevent the development of cancerous cells or apoptosis. This review article provides a comprehensive review on numerous (noteworthy) molecular functions of SIRT3 and its effect on cancer cells and various diseases including Huntington's disease, amyotrophic lateral sclerosis, and Alzheimer's disease.

Key words: aging; cancer; Silent Information Regulator 2; SIRT3; sirtuin.

Introduction

SIRT3 is a NAD+-dependent protein deacetylase that is a member of the silent information regulator 2 (SIR2) family (Giralt and Villarroya, 2012). SIRT3 can exert controls on a wide range of important biological activities including regulation of nuclear gene expression, metabolic control (Shi *et al.*, 2005), neuroprotection (Kong *et al.*, 2010), cardiovascular disease, cancer (Alhazzazi *et al.*, 2011b), and aging (Bellizzi *et al.*, 2005). SIRT3 is the only sirtuin protein reported to affect human lifespan (Kong *et al.*, 2010; Brown *et al.*, 2013; Kincaid & Bossy-Wetzel, 2013). As it is localized exclusively in mitochondria, SIRT3 can regulate characteristic mitochondrial processes like protein deacetylation (Lombard *et al.*, 2007). Some other organs and active metabolic tissues, including brown adipose tissue (BAT), heart, and kidney, were also reported to accommodate significant concentrations of SIRT3 (Palacios *et al.*, 2009).

Among the mitochondrial sirtuins, only SIRT3 possesses robust NAD+-dependent deacetylase activity (Lombard *et al.*, 2007). SIRT3 can undergo proteolytic cleavage upon translocation to the mitochondrion. Full-length (FL) SIRT3 is proposed to be inactive until it is translocated to and proteolytically processed within the mitochondrion to an active 28 kDa protein (Iwahara *et al.*, 2012). Cleavage of SIRT3 at the mitochondrial localization sequence is known to activate deacetylase activity (Smith *et al.*, 2008).

SIRT3 influences energy metabolism processes (e.g., tricarboxylic acid cycle, respiratory chain, fatty acid β-oxidation, and ketogenesis) by targeting the responsible enzymes (Giralt and Villarroya, 2012). It also controls the flow of mitochondrial oxidative pathways and, ultimately, the rate of reactive oxygen species (ROS) production. SIRT3-mediated deacetylation activates enzymes responsible for reducing ROS in protective action against oxidative stress-dependent phenomena or diseases such as cardiac hypertrophy, aging, cancer, cardiac dysfunction, and neural degeneration. SIRT3 also plays a role in multiple additional metabolic processes from acetate metabolism to BAT thermogenesis, often by controlling mitochondrial pathways through the deacetylation of target enzymes (Shi *et al.*, 2005).

The role of SIRT3 in physiology is crucial and an interesting subject for research. Protein acetylation regulates global mitochondrial function (Kim *et al.*, 2006). Research implementing SIRT3-knockout (KO) mice revealed many significant aspects of SIRT3 in physiology (Ahn *et al.*, 2008). SIRT3 interacts with FOXO3a to activate antioxidant genes like manganese superoxide dismutase (MnSOD) and catalase, whose gene products reduce ROS while positively affecting disorders like cardiac hypertrophy and interstitial fibrosis (Sundaresan *et al.*, 2009). SIRT3-knockout mice are prone to age-related disorders like cancer, cardiac hypertrophy, and metabolic syndrome (Choudhury *et al.*, 2011; Hirschey *et al.*, 2011). Frequent opening of mitochondrial permeability transition pore (mPTP) can lead to mitochondrial dysfunction. Note that mPTP is regulated by cyclophilin D (CypD) which is deacetylated by SIRT3. The absence of SIRT3 in cardiac muscle becomes a stimulus to increase the opening of mPTP. Thus, SIRT3 KO mice was found to suffer from hampering of mitochondrial function in heart with the sign of aging (Hafner *et al.*, 2010). SIRT3-knockout rodents also develop pulmonary arterial hypertension (Paulin *et al.*, 2014). SIRT3 regulates stress response in hematopoietic stem cells (HSC) and improves regenerative capacity in aged HSCs, while it controls tissue homeostasis as well (Brown *et al.*, 2013). SIRT3 can also manage NAD+ levels to regulate mitochondrial function, offering protection against liver injury associated with fatty liver (Kendrick *et al.*, 2011) and/or acute kidney injury (Morigi *et al.*, 2015). Because SIRT3 KO mice cannot maintain SOD2 homoeostasis and ROS level,

Correspondence
Professor Ki-Hyun Kim, Department of Civil & Environmental Engineering, Hanyang University, 222 Wangsimni-Ro, Seoul 04763, Korea. Tel.: 82-2-2220-2325; fax: 82-2-2220-1945; e-mail: kkim61@hanyang.ac.kr
*Equal contributors to this work

Accepted for publication *22 August 2016*

they suffer from mild endothelial dysfunction when fed with high cholesterol diet (Winnik *et al.*, 2016).

This study aims to provide a comprehensive review of the most relevant biological and pathophysiological functions of SIRT3 such as cancer control, neuroprotection, DNA repair, enhanced longevity, energy homoeostasis, oxidative stress tolerance, and many other mechanisms. To this end, most important studies conducted in this field were compiled and reviewed with respect to essential functions of SIRT3.

Molecular functions of SIRT3

SIRT3 plays an important role in numerous molecular functions by controlling many crucial biological activities. As illustrated in Fig. 1, SIRT3 helps maintain the physiology of the body through various routes. (Refer to Table 1 for details.)

Significance of SIRT3 in metabolism

SIRT3 is characterized as a mitochondrial sirtuin protein that is localized in the mitochondrial matrix. It regulates the activity of several metabolic enzymes and Complex I subunit NDUFA9 by deacetylation (Ahn *et al.*, 2008). Protein synthesis by oxidative phosphorylation (OXPHOS) is encoded by the mitochondrial genome, which is carried out by mitochondrial ribosomal protein L10 (MRP L10). However, MRP L10 generally remains in the acetylated form in the mitochondrial ribosome and becomes deacetylated by SIRT3 (Yang *et al.*, 2010). SIRT3 deacetylates and activates acetyl-CoA synthetase 2 and glutamate dehydrogenase (GDH), leading to enhancement of the Krebs cycle (Hallows *et al.*, 2006; Schlicker *et al.*, 2008). SIRT3 also regulates OXPHOS by activating acetyl-CoA synthetase 2 and GDH (Ahn *et al.*, 2008).

Keratinocyte differentiation is known to influence the formation/maintenance of the protective skin barrier (Bause *et al.*, 2013; Chen *et al.*, 2014). However, dysregulation in the balance of ROS homeostasis is known to impact keratinocyte differentiation. Loss of SIRT3 expression in keratinocytes increases superoxide levels and promotes the expression of differentiation markers, while overexpression decreases superoxide levels and reduces the expression of differentiation markers. However, it remains unclear how mitochondrial oxidative stress signaling induces and controls keratinocyte differentiation (Bause *et al.*, 2013). Previous studies have shown that ROS signaling induces keratinocyte differentiation through the protein kinase C/activator protein-1 (PKC/AP-1) pathway (Rutberg *et al.*, 1996; Bose *et al.*, 2012). SIRT3 gene expression may in turn also be regulated through AP-1 transcription factors as a possible regulatory pathway (Bellizzi *et al.*, 2009). Cumulatively, SIRT3 is one of the most remarkable regulators in metabolism. It should be noted that the molecular control of SIRT3 itself is quite abstruse. The maintenance of mitochondrial DNA (mtDNA) is regulated by several components such as TFB1M and TFB2M which are known as very crucial factors determining the mitochondrial transcription specificity in human (Falkenberg *et al.*, 2002). They are also regulated by nuclear respiratory factors (NRF1 and NRF2) (Gleyzer *et al.*, 2005). For instance, as the role of NRF2 in the expression of SIRT3 promoter is significant, such mechanism can make substantial contribution to the mitochondrial biogenesis (Satterstrom *et al.*, 2015).

SIRT3 in the protection of neurons

One of the important functions of SIRT3 is the protection of neurons attained by the interaction with NAD+ and poly (ADP-ribose) polymerase-1 (PARP-1). PARP-1 is a DNA repair nuclear enzyme that helps prevent chromatid exchange (Schreiber *et al.*, 2006). However, some stressful conditions like excitotoxicity, ischemia, inflammation, and oxidative stress cause over-activation of PARP-1, which is the key pathway responsible for neuronal cell death in the aforementioned consequences (Virág & Szabó, 2002). Nevertheless, over-activation of PARP-1 selectively decreases cytosolic NAD+ (Alano *et al.*, 2004, 2010); PARP-1-mediated NAD+ depletion then accompanies colossal ROS production in the neuronal cell, which increases the expression of mitochondrial SIRT3. An overexpression of SIRT3 suppresses ROS generation, thereby preventing neuronal death (Kim *et al.*, 2011). SIRT3 can also directly mediate adaptive neuronal responses to bioenergetic, oxidative, and excitatory stress. According to some experiments made with SIRT3 KO mice, cortical neurons lacking SIRT3 exhibited sensitivity to above-mentioned physiological challenges. On the contrary, SIRT3 gene delivery can restore resistance to stress. The absence of SIRT3 was thus accompanied by hyperacetylation of SOD2 and CypD (Cheng *et al.*, 2016).

Amyotrophic lateral sclerosis (ALS), an invariably fatal neurodegenerative disease, is characterized by the degeneration of both upper and lower motor neurons (Boillée *et al.*, 2006; Zhao *et al.*, 2013). Mutations in the related gene encoding Cu/Zn superoxide dismutase (SOD1) can affect an inherited form of ALS. Note that more than 150 types of *SOD1* gene mutations have been described, while most of them are transmitted in an autosomal dominant pattern (Battistini *et al.*, 2005). The exact mechanism underlying SIRT3-mediated protection against mutant SOD1-induced toxicity remains elusive; however, the co-presence of SIRT3 and peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) protects against mitochondrial fragmentation and neuronal cell death (Kong *et al.*, 2010; Kincaid & Bossy-Wetzel, 2013). The mitochondrial SIRT3 promoter region carries an estrogen-related receptor (ERR)-binding element (ERRE) located 399- to 407-bp downstream (Kong *et al.*, 2010). As oxidative stress increases, PGC-1α recruits ERRα, a well-known mitochondrial regulator, to the ERRE. The overexpression of SIRT3 is thus executed based on this mechanism (Kong *et al.*, 2010). SIRT3 lowers ROS levels by deacetylating SOD2, while increasing its enzymatic activity (Bruijn *et al.*, 2004; Qiu *et al.*, 2010; Someya *et al.*, 2010). Furthermore, SIRT1 is known to upregulate SIRT3 transcription through PGC-1α (Tao *et al.*, 2010; Giralt *et al.*, 2011) (Fig. 2). PGC-1α also co-activates NRF2, another novel regulator of SIRT3 (Satterstrom *et al.*, 2015). As neuroprotection by SIRT3 in above disease is mediated through PGC1α, it may help find future remedies of such disorders.

Function of SIRT3 in different muscle types

The expression of SIRT3 also plays a role in heart and skeletal muscles (Shi *et al.*, 2005; Lombard *et al.*, 2007). SIRT3 is a stress-responsive deacetylase in cardiomyocytes and protects cells from genotoxic and oxidative stress-mediated damage. As SIRT3 is a stress-responsive deacetylase, its increased expression protects genotoxic and oxidative stress-mediated cell death in murine cardiomyocytes. Under stressful conditions, SIRT3 levels increase in mitochondria as well as in cardiomyocyte nuclei. SIRT3 can then be physically bound to Ku70 for its deacetylation to promote interaction between Ku70 and the pro-apoptotic protein Bax (Sundaresan *et al.*, 2008). In addition, the antihypertrophic effects of exogenous NAD+ are also mediated through the activation of SIRT3 instead of SIRT1. As SIRT3 is able to deacetylate and activate liver kinase B1 (LKB1), it can augment LKB1–AMPK pathway activity. NAD+, while acting as an inhibitor of cardiac hypertrophic signaling, is regulated to protect against cardiac hypertrophy and heart failure (Miao & St Clair, 2009; Pillai *et al.*, 2010). In mice, SIRT3 is activated by the natural biphenolic compound honokiol and protects

Table 1 Molecular functions of SIRT3

Molecular Function	Associated Enzyme/Protein	Activity of SIRT3	Location	Reference
Energy homeostasis	Absence of deacetylase	Reduction of ATP	Heart, kidney, liver	(Ahn *et al.*, 2008)
	Protein acetylation	Increase in ATP	Mitochondria	
Suppression of ROS	Increase of superoxide dismutase 2	Stimulates SIRT3 transcription, leads to SOD2 deacetylation and activation of oxidative stress	Mitochondria	(Chen *et al.*, 2011)
	Binds to peroxisome proliferator-activated receptor co-activator-1α	Stimulates SIRT3 to regulate adaptive thermogenesis, gluconeogenesis, mitochondrial biogenesis, and respiration	Muscle cells and hepatocytes	(Lin *et al.*, 2005; Finck & Kelly, 2006)
Apoptosis	SIRT3 along with SIRT4	Inhibits apoptosis by decreasing NAD+ levels	Somatic cells	(Yang *et al.*, 2007)
	Mitochondrial ribosomal protein L10	Regulates mitochondrial protein synthesis by deacetylation of ribosomal protein MRPL10	Mitochondria	(Yang *et al.*, 2010)
Tumor suppression	Decrease of superoxide dismutase	Depletion of SIRT3 leads to tumor suppression	Mitochondria	(Chen *et al.*, 2011)
	Decrease of superoxide dismutase	Loss of SIRT3 promotes transformation through an increase in chromosomal instability via increased production of ROS and altered intracellular metabolism	Mitochondria	(Kim *et al.*, 2010)
	Human 8-oxoguanine-DNA glycosylase 1	SIRT3 prevents the degradation of protein and repairs mitochondrial DNA damage	Mitochondria	(Cheng *et al.*, 2013)
Muscles	Binds to Ku70 in cardiac muscles	Physically binds and deacetylates Ku70 and promotes interaction of Ku70 with the pro-apoptotic protein Bax	Cardiomyocytes	(Sundaresan *et al.*, 2008)
	CREB phosphorylation in skeletal muscles	Exercise increases SIRT3 expression	Skeletal muscle cells	(Palacios *et al.*, 2009)
	Phospho-activation of AMPK in skeletal muscles	SIRT3 expression increases with fasting and caloric restriction and decreases with high-fat diet. A caloric restriction regimen also leads to phospho-activation of AMPK in muscle	Skeletal muscle cells	(Palacios *et al.*, 2009)
Neurons	LKB1	SIRT3 deacetylates and activates LKB1, augmenting LKB1–AMPK pathway activity, thus protecting against an increase in NAD	Mitochondria	(Miao & St Clair, 2009)
	Activates MnSOD and catalase	Decreases cellular levels of ROS	Mitochondria	(Kawamura *et al.*, 2010)
	Poly (ADP-ribose) polymerase-1 activation or protein transfection of NADase	NAD depletion leads to over-expression of SIRT3, which induces ROS generation, thereby preventing neuronal death	Mitochondria	(Kim *et al.*, 2011)
Caloric restriction	Increase in the deacetylase	Induces the expression of genes involved in mitochondrial biogenesis	Adipocytes	(Shi *et al.*, 2005)
Diabetes	Increase mitochondrial enzyme acetyl-CoA synthetase 2	Increases SIRT3 under ketogenic conditions	Intermembrane space of the mitochondrion	(Schwer *et al.*, 2006)
Metabolism	Activation of acetyl-CoA synthetase 2 and glutamate dehydrogenase	Deacetylates and activates the enzymes to enhance the Krebs cycle and oxidative phosphorylation	Mitochondria	(Hallows *et al.*, 2006; Schlicker *et al.*, 2008)
	Succinate dehydrogenase complex	NAD+-dependent deacetylase, SIRT3 regulates the activity of enzymes	Mitochondria	(Cimen, Han *et al.* 2009)
Thermogenesis	Increase expression of protein PGC-1α, uncoupling protein (UCP1), and a series of mitochondria-related genes in the presence of both ADP and ribosyltransferase	Deacetylates SIRT3	Brown adipose tissue and mitochondrial inner membrane	(Shi *et al.*, 2005)
Fatty acid oxidation	Increase in long-chain acyl-CoA dehydrogenase	Upregulation of SIRT3	Fasting in liver and brown adipose tissues	(Allison & Milner, 2007)

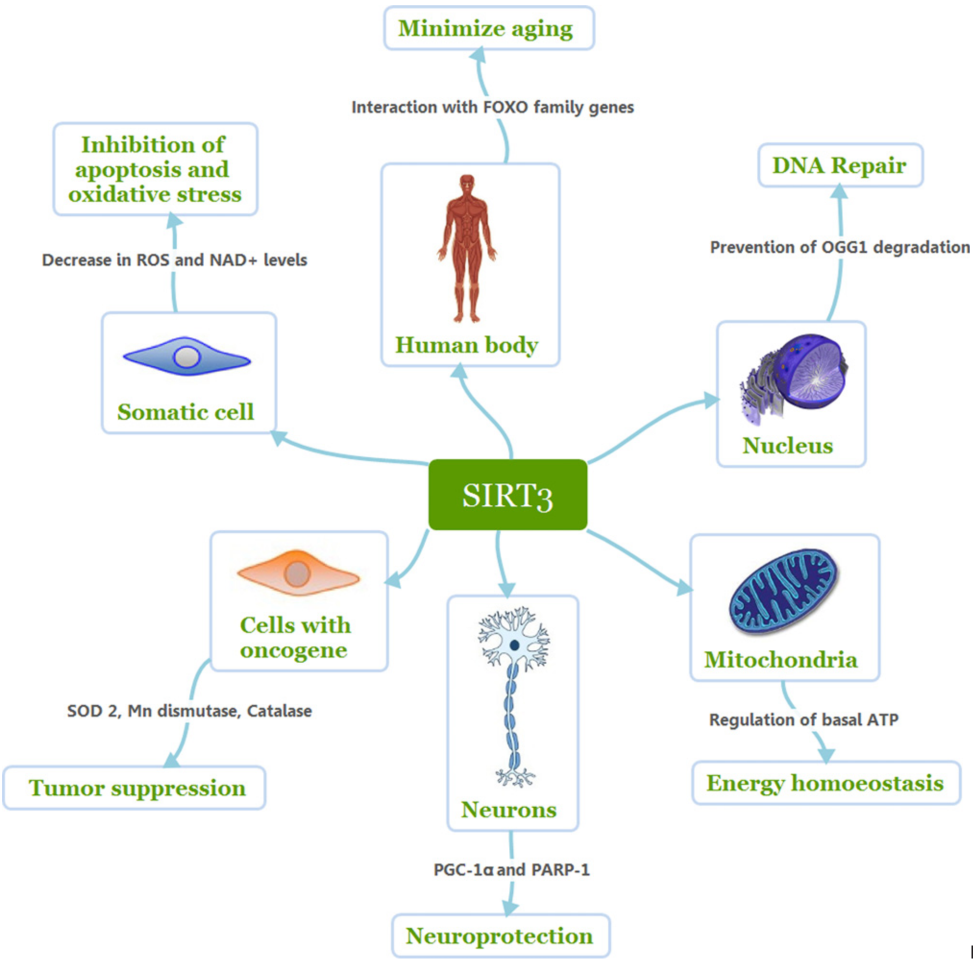

Fig. 1 Molecular functions of SIRT3.

cardiac muscles from hypertrophy (Fig. 3) (Sundaresan *et al.* 2009; Pillai *et al.*, 2015).

In skeletal muscles, SIRT3 responds to both exercise and CREB phosphorylation with PGC-1α upregulation of nutritional signals to coordinate downstream molecular responses (Palacios *et al.*, 2009; Hokari *et al.*, 2010) (Fig. 3). In skeletal muscle, SIRT3 protein level is also sensitive to diet as its expression increases by fasting and caloric restriction and decreases after a high-fat diet. A caloric restriction regimen also leads to the phospho-activation of AMPK in muscle (Palacios *et al.*, 2009). When skeletal muscles were treated with near-infrared light, an increase in oxidative stress was found with increases in the levels of upstream mitochondrial regulatory AMPK, p38, PGC-1α, and SIRT1 proteins along with reduced levels of RIP140; however, mitochondrial regulation/content remained unaltered for SIRT3, Tfam, NRF-1, cytochrome c, and ETC subunits (Nguyen *et al.*, 2014). Consequently, the mechanism underlying such signaling in muscle cells remains unclear.

SIRT3 in DNA repair

SIRT3 is capable of affecting mitochondrial OXPHOS by regulating the function of mitochondrial enzymes (Haigis *et al.*, 2012). Human mitochondrial DNA (mtDNA) contains a number of genes that encode 13 polypeptides, two rRNAs, and 22 tRNA molecules; the 13 polypeptides are known to influence mitochondrial respiration and OXPHOS (Schon, 2000). Mutation of the mitochondrial genome may cause some inherited diseases; remarkable progress has been made from researches in mtDNA mutations with respect to aging and cancer (Taylor & Turnbull, 2005). Moreover, mtDNA is considerably more prone to oxidative damage than the nuclear genome (Richter *et al.*, 1988). Oxygen-free radicals generated by mitochondrial respiration or by exposure to ionizing radiation (or chemicals) are responsible for damaging DNA. Oxidative damage can thus change purine and pyrimidine bases in DNA to 8-oxo-7,8-dihydroguanine (8-oxoG) (Grollman & Moriya, 1993); however, human 8-oxoguanine-DNA glycosylase 1 (OGG1) is a newly identified target protein of SIRT3 that functions in DNA repair by expunging 8-oxoG from damaged genomic DNA (Cheng *et al.*, 2013). SIRT3 becomes physically associated with OGG1 to prevent degradation of the OGG1 protein and controls its incision activity when DNA glycosylase is acetylated. Furthermore, SIRT3 plays a critical role in repairing mitochondrial DNA (mtDNA) damage, protecting mitochondrial integrity, and preventing apoptotic cell death under oxidative stress by regulating the acetylation and turnover of OGG1 (Cheng *et al.*, 2013).

SIRT3 in aging

One of the most interesting attributes of SIRT3 is its potential to promote the extension of lifespan (Rose *et al.*, 2003; Halaschek-Wiener *et al.*, 2009). A VNTR polymorphism prevails in the *SIRT3* gene as a potential regulator of SIRT3 expression. In light of the high abundance of SIRT3 in

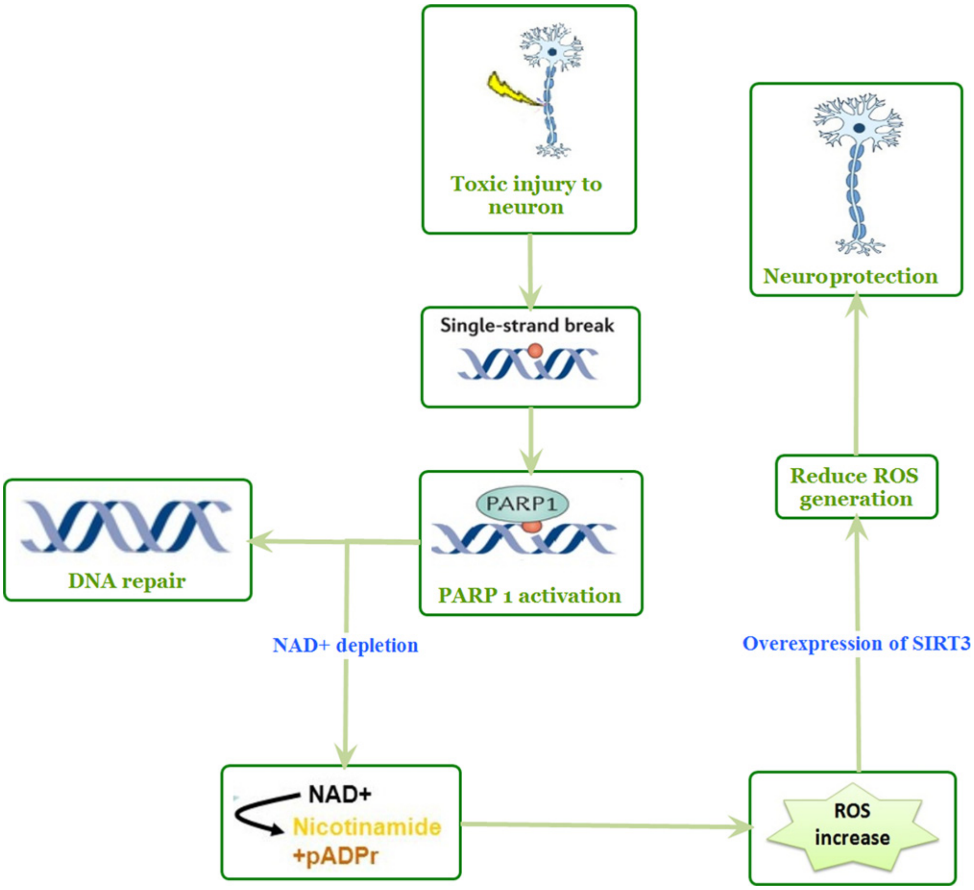

Fig. 2 SIRT3 protect neurons during cellular stress.

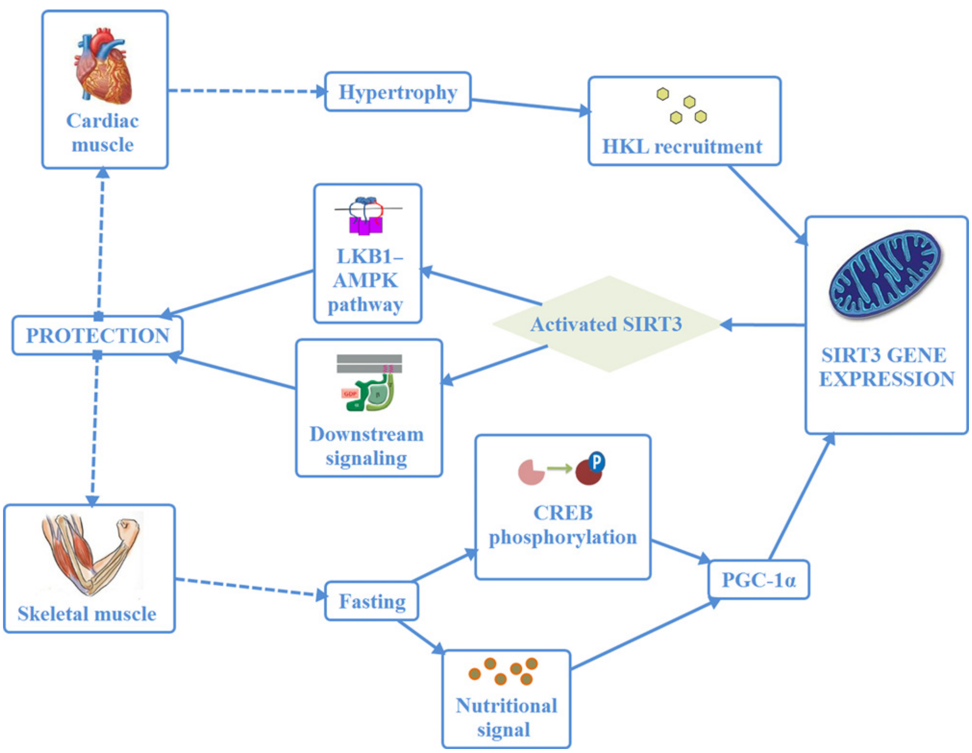

Fig. 3 SIRT3-mediated protection of cardiac and skeletal muscle during hypertrophy and fasting, respectively.

long-lived individuals, a potential link was suggested between SIRT3 and longevity (Bellizzi *et al.*, 2005). A better understanding on SIRT3-dependence of expanded lifespan will indeed help broaden the spectrum of research in this field. The *FOXO1, FOXO3a, FOXO4,* and *FOXO6* genes encode the FOXO family of transcription factors and are human homologs of the *daf-16* gene in *Caenorhabditis elegans*, the product of which contributes to the regulation of nematode lifespan (Shi *et al.*, 2005). FOXO transcription factors appear to regulate a wide variety of intracellular processes such as cellular resistance to oxidative stress and general metabolism (Burgering & Kops, 2002; Accili & Arden, 2004). It is also acknowledged that nuclear sirtuins interact with the activity of FOXO family proteins under specific cellular conditions, as FOXO3a is known to physically interact with SIRT3 in mitochondria (Fig. 4) (Wang *et al.*, 2007; Guarente, 2008). Human colon carcinoma (HCT116) cells were used to overexpress wild-type and/or a catalytically inactive dominant species of negative *SIRT3* (Jacobs *et al.*, 2008). Overexpression of the wild-type *SIRT3* gene increases FOXO3a DNA-binding activity and FOXO3a-dependent gene expression. Biochemical analysis of HCT116 cells overexpressing a deacetylation mutant demonstrates an overall oxidized intracellular environment compared to overexpression of the wild-type *SIRT3* gene, as monitored by increases in intracellular superoxide and oxidized glutathione levels (Wang *et al.*, 2007). As such, both SIRT3 and FOXO3a follow a cascade response pathway for mitochondrial signaling (Jacobs *et al.*, 2008). Tissue fibrosis caused by aging was reported to be mediated by an enzyme called glycogen synthase kinase 3β (GSK3β) (Frame & Cohen, 2001). The deacetylation of GSK3β by SIRT3 can thus potentially block aging process associated tissue fibrosis (Sundaresan *et al.*, 2016).

SIRT3 can also interact with the mitochondrial acetyl-coA synthetase known as AceCS2 (Allison & Milner, 2007). SIRT3/AceCS2 is required for G1 arrest that is induced by the loss of Bcl-2 in a specific type of noncancer epithelial cells (ARPE19 cells). This event suggests a role of SIRT3/AceCS2 in apoptosis and growth regulation under certain environmental conditions (Allison & Milner, 2007). Although the molecular basis for lifespan extension is not yet clear, up-to-date knowledge on SIRT3 can stimulate scientists to seek exciting therapeutic solutions for aging.

SIRT3 in energy homoeostasis

SIRT3 is an important regulator of basal ATP and controls overall energy homeostasis. Some tissues such as the heart, kidney, and liver normally express high levels of SIRT3, leading to a marked reduction in ATP in the absence of the deacetylase (Ahn *et al.*, 2008). However, SIRT3 is capable of boosting the level of ATP in mitochondria due to the acetylation process. As mammalian mitochondrial ribosomal proteins are all nucleus-encoded, some of them have been mapped to regions associated with disorders of mitochondrial energy metabolism (O'Brien *et al.*, 2005). Alterations in the expression level and mutations in the genes encoding these ribosomal proteins can affect mitochondrial protein synthesis, cell growth, and apoptosis (Miller *et al.*, 2004; Chintharlapalli *et al.*, 2005; Yoo *et al.*, 2005). Mitochondrial ribosomal protein L10 (MRPL10) is the major acetylated protein identified in the mitochondrial ribosome. Ribosome-associated SIRT3 was thus found to be responsible for the NAD-dependent deacetylation of MRPL10 (Yang *et al.*, 2010). Mitochondrial biogenesis is also mandatory for oocyte development (John *et al.*, 2010). *In vitro* maturation technique with metaphase II oocytes disclosed the developmental efficiency of SIRT3 by which mitochondrial energy homoeostasis and subsequent oocyte maturation are regulated. Hence, SiRNA-induced SIRT3 knockdown precludes the biogenesis (Zhao *et al.*, 2016).

SIRT3 in oxidative stress

SIRT3 also plays a significant function in the regulation of ROS levels by influencing different enzymes like SOD2, manganese dismutase, and catalase (Miao & St Clair, 2009; Merksamer *et al.*, 2013). As increases in ROS levels can stimulate *SIRT3* transcription, it may ultimately lead to

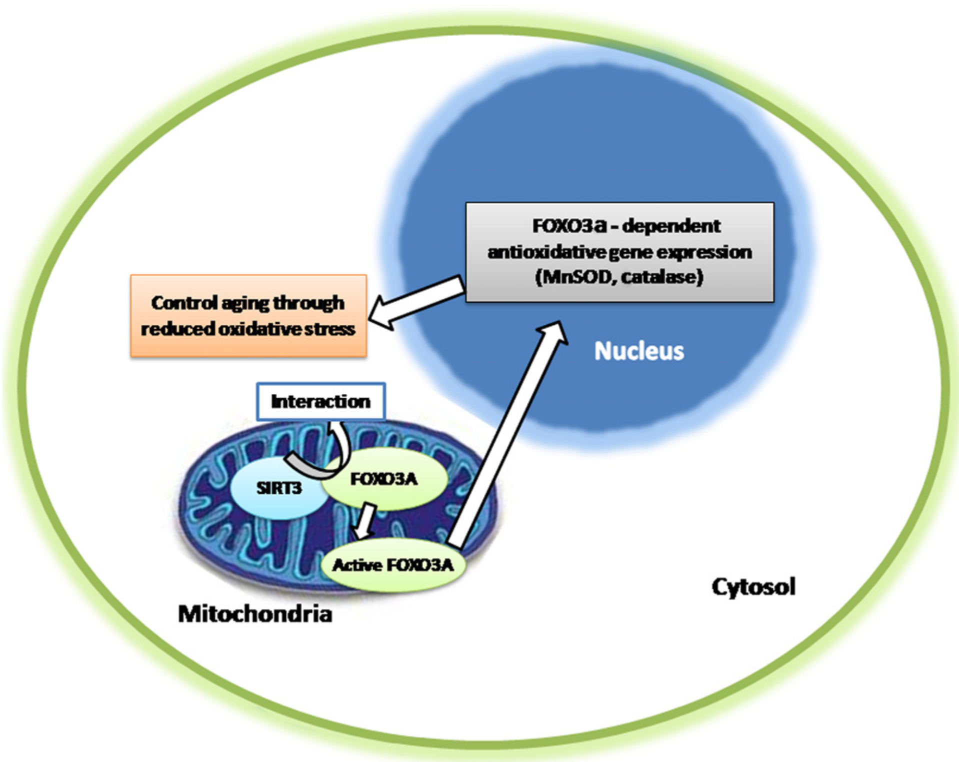

Fig. 4 SIRT3 regulates aging by interacting with FOXO.

deacetylation of SOD2 with the activation of oxidative stress (Chen *et al.*, 2011); however, PGC-1α plays a vital role in adaptive thermogenesis, gluconeogenesis, mitochondrial biogenesis, and respiration to induce ROS-detoxifying enzymes (Lin *et al.*, 2005; Finck & Kelly, 2006). Nonetheless, the molecular mechanism underlying this phenomenon is not yet fully understood. PGC-1α and nuclear ERRα are known to strongly stimulate gene expression of mouse *SIRT3* in hepatocytes and muscle cells (Lin *et al.*, 2005; Giralt and Villarroya, 2012).

SIRT3 in stress-related gene expression

Human SIRT3 exists in a full-length (FL) form that is processed to a distinct short form to localize specifically to the mitochondria; hence, only the short form of human SIRT3 is active as an NAD+-dependent deacetylase (Schwer *et al.*, 2002). It was reported that FL SIRT3 may also be present in the nucleus and is capable of activating histone deacetylase (HDAC) against acetylated histone H3 Lys 9 (H3K9ac) and H4K16ac *in vivo* (Scher *et al.*, 2007; Nakamura *et al.*, 2008; Sundaresan *et al.*, 2008). Such HDAC activity is believed to be associated with transcriptional repression when artificially recruited to a transgenic reporter (Tao *et al.*, 2010). As nuclear FL SIRT3 is subject to cellular stress conditions (e.g., oxidative stress and UV irradiation), it can lead to rapid degradation without affecting the mitochondrial SIRT3 short form. Therefore, the rapid removal of SIRT3 from chromatin could induce genes required for the stress response. Binding of FL SIRT3 to chromatin could also suppress neighboring genes and mediate the deacetylation of H4K16 by activating ubiquitination and proteasome degradation (Iwahara *et al.*, 2012). However, there have been some contradictions about the localization of SIRT3. Many reports nonetheless claimed that SIRT3 should be exclusively located at mitochondria (Michishita *et al.*, 2005; Lombard *et al.*, 2007; Cooper & Spelbrink, 2008).

SIRT3 in thermogenesis

SIRT3 is also expressed in brown adipose tissue (BAT), where it is localized to the inner membranes of mitochondria (Shi *et al.*, 2005). Caloric restriction activates SIRT3 expression in both BAT and brown adipose tissue (WAT). Unlike BAT, *SIRT3* gene expression does not occur in WAT upon cold exposure. In HIB1B brown adipocytes, an imposed expression of SIRT3 augments the expression of PGC-1α, uncoupling protein 1 (UCP1), and a series of mitochondria-related genes in the presence of both ADP-ribosyltransferase and the deacetylase activity of SIRT3 (Shi *et al.*, 2005). A SIRT3 deacetylase mutant has a synergistic effect with PGC-1α to activate UCP1 expression in the mitochondrial inner membrane to mediate the process of adaptive thermogenesis. In addition, SIRT3 stimulates CREB phosphorylation to directly activate the PGC-1α promoter. Sustained expression of SIRT3 decreases ROS production and membrane potential, while causing increased cellular respiration. *SIRT3* and other genes controlling mitochondrial function are downregulated in the BAT of several genetically obese mice (Shi *et al.*, 2005). In the absence of SIRT3, high levels of fatty acid oxidation intermediate products and triglycerides are formed, while long-chain acyl-CoA dehydrogenase (LCAD) is hyperacetylated at Lys 42. LCAD can also be deacetylated under fasting conditions by SIRT3 as hyperacetylation of LCAD reduces its enzymatic activity (Allison & Milner, 2007; Hirschey *et al.*, 2010).

SIRT3 in tumor suppression

To date, the most remarkable feature of SIRT3 is its ability to suppress tumors and/or cancer. As a key regulator of different cancers, SIRT3 detoxifies ROS to act as a tumor suppressor (Schumacker, 2010; Tanno *et al.*, 2012; Tseng *et al.*, 2013). Under such conditions, mitochondrial MnSOD is an important antioxidant enzyme that is primarily regulated by transcriptional activation (Miao & St Clair, 2009). Decrease in enzymatic activity is caused by acetylation at Lys 68; however, mitochondrial deacetylase SIRT3 is able to bind and deacetylate for its activation. Increase in ROS levels also stimulates *SIRT3* transcription, leading to SOD deacetylation and activation. Thus, SOD-mediated ROS reduction is synergistically increased by SIRT3 co-expression, although it can be negated by SIRT3 depletion. As a result, a mechanism involving post-translational regulation of SOD activity was revealed by elaborating the effect to oxidative stress on acetylation and SIRT3-dependent deacetylation (Chen *et al.*, 2011). However, deletion of *SIRT3* removes the requirement for the loss of a tumor suppressor for transformation of primary cells with an oncogene (Kim *et al.*, 2010). SIRT3 KO mouse embryonic fibroblast (SIRT3$^{-/-}$ MEF) demonstrates genomic instability as well as aberrant mitochondrial physiology. Single oncogenic expression (Myc or Ras) alters intracellular metabolism which is recovered by SOD (Kim *et al.*, 2010). Contribution of SIRT3 in cancer genetics is discussed extensively in the following segment.

The role of SIRT3 in cancer

The role of SIRT3 in human cancer has been studied intensively to validate its effect on the disease state. SIRT3 has the ability to reprogram cellular metabolism. In tumor cells, glycolysis occurs at a high rate even in the presence of O_2, which is known as the Warburg effect (Haigis *et al.*, 2012). Warburg effect helps tumor cells by supplementing with biomass-generating substrates (Finley *et al.*, 2011a). SIRT3 regulates the Warburg effect by decreasing the high glycolysis rate in tumor cells. Restricting tumorous cells from gaining substrates and/or biomass is achieved by the decreased level of glycolysis (Finley *et al.* 2011). Some of the important activities of SIRT3 in different cancers are discussed here and are overviewed in Table 2 and Fig. 5.

Oral cancer

According to a tissue microarray analysis, SIRT3 was overexpressed in oral squamous cell carcinoma (OSCC) relative to normal human oral keratinocytes cell lines (Alhazzazi *et al.*, 2011a). Cell growth and proliferation are inhibited by a downregulation of SIRT3, while OSCC cell sensitivity increases with radiation and cisplatin treatments *in vitro*. SIRT3 downregulation reduces tumor burden *in vivo* (Alhazzazi *et al.*, 2011a); however, significant decreases in SIRT3 mRNA and protein level were due to the effect of (-)-epigallocatechin-3-gallate, an antioxidative catechin commonly found in green tea (Tao & Lambert, 2014).

Breast cancer

Tamoxifen (Tam) is commonly used as an adjuvant therapy during the management of breast cancer as it acts as an antagonist to the related selective estrogen receptor, that is, estrogen receptor-positive (ER+). A study of the Tam-resistant human breast cancer cell line (MTR-3) revealed significant upregulation of SIRT3 at both the mRNA and protein levels (Zhang *et al.*, 2013b). The above cell line was derived from the standard MCF-7 cell line through a selective culture process in the presence of 1 mM Tam. SIRT3 level also rapidly increases in MCF-7 cells after exposure to Tam. When the *SIRT3* gene is overexpressed in MCF-7 cells, a decrease in cellular sensitivity to Tam is accompanied by a blockage in Tam-induced apoptosis. Furthermore, cells are susceptible to

Table 2 Function of SIRT3 in different cancers

Type of cancer	Type of cells used	Activity of SIRT3	References
Oral cancer	Oral squamous cell carcinoma cell line	Cell growth and proliferation are inhibited by SIRT3 downregulation	(Alhazzazi *et al.*, 2011a,b)
Breast cancer	MCF-7 cell line produced through continuous selective culture in the presence of Tamoxifen	SIRT3 decreases apoptosis and decreases cellular sensitivity to Tamoxifen	(Zhang *et al.*, 2013b)
Hepatocellular carcinoma	Hepatoma cells	Overexpression of SIRT3 leads to JNK activation and resulting apoptosis	(Zhang & Zhou, 2012)
Esophageal cancer	Patients with esophageal cancer	Increase in SIRT3 decreases ROS levels, prolonging survival rate	(Zhao *et al.*, 2013)
Lung cancer	Nonsmall cell lung carcinoma	Low SIRT3 decreases cancer cell growth	(Li *et al.*, 2013)
Gastric cancer	MGC-803 gastric cancer cells	Presence of SIRT3 decreases cancer	(Huang *et al.*, 2014)
Bladder cancer	p53 bladder carcinoma cells	SIRT3 prevents cancer cells from spreading	(Li *et al.*, 2010)

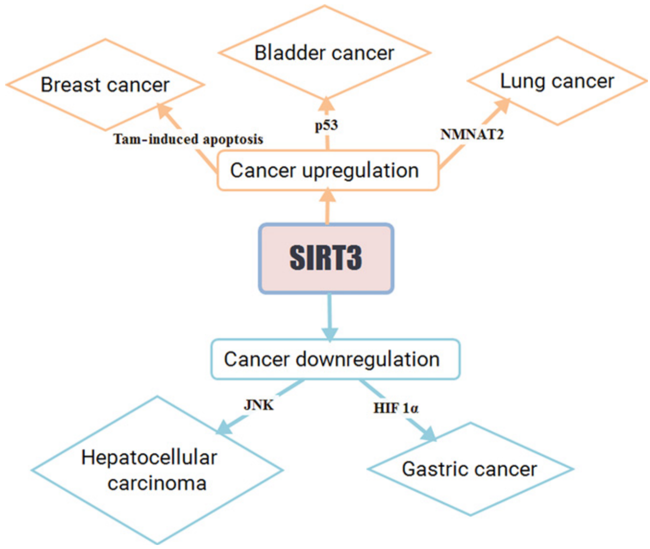

Fig. 5 SIRT3 has both oncogenic and tumor suppressive activities.

Tam and apoptotic cell death when SIRT3 expression is knocked down in MTR-3 cells. These MTR-3 cells also showed increases in the mitochondrial content of ERb, ROS levels, and apoptosis (Zhang *et al.*, 2013b). In addition to ER+ breast cancer, low SIRT3 expression is also associated with survival in the ER−, HER2+, and basal breast cancer subtypes. These results imply that SIRT3 can be used as a molecular biomarker to diagnose patients with high-risk breast cancer (Desouki *et al.*, 2014). Although some other sirtuin molecules like SIRT7 have impacts on breast cancer (Ashraf *et al.*, 2006), little is known about the contribution of SIRT3. A form of human cancer known as luminal B breast cancer is suspected to have certain linkage with the inefficiency of SIRT3. SIRT3 KO murine models are found to develop tumors with similar characteristics of human luminal B breast cancer due probably to acetylation of MnSOD. In contrast, wild-type mice did not show such symptoms, while MnSOD was deacetylated by SIRT3 (Zou *et al.*, 2016).

Hepatocellular carcinoma

SIRT3 protein expression in hepatocellular carcinoma (HCC) is associated with the degree of differentiation, pathological features, and complications with portal vein tumor thrombus. It is known that relative SIRT3 protein expression gradually decreases with the increases in differentiation between hepatoma cells and between the deterioration and progression of hepatocellular cells (Zhang *et al.*, 2013a). The SIRT3 mechanism should thus be related to ROS levels in the mitochondria (Chen *et al.*, 2011; Park *et al.*, 2011; Schumacker, 2011); however, low SIRT3 expression was reported to act as a poor independent prognostic factor of survival in patients with postsurgical hepatocellular carcinoma (Zhang *et al.*, 2012). The results of other research have provided evidence of increased recurrence with a decrease in SIRT3 level in HCC (Wang *et al.*, 2014a). In hepatocellular carcinoma cells, overexpression of SIRT3 facilitated the activation of the JNK signaling pathway, resulting in apoptosis (Zhang & Zhou, 2012); however, low SIRT3 expression is associated with a markedly shorter period of clinical recurrence.

Esophageal cancer

A number of studies have analyzed the clinical significance of SIRT3 expression in esophageal squamous cell carcinoma (ESCC). High SIRT3 expression levels in ESCC tissues were previously reported to occur more frequently than in adjacent nonmalignant esophageal mucosa tissues (Yan *et al.*, 2014). The 5-year postoperational survival rate of patients with esophageal cancer was examined in relation with the SIRT3 expression (Zhao *et al.*, 2013). Accordingly, high expression of SIRT3 was related to a shorter survival time in patients with esophageal cancer, which might be due to the suppression of apoptosis signals that prolonged the survival rate of esophageal cancer. Moreover, tumors with high SIRT3 level might lead to genomic or signaling deregulation, taking advantage of SIRT3 overexpression to prolong survival by decreasing ROS levels (Zhao *et al.*, 2013). Presumably, an overexpression of SIRT3 may help cancer cells divide and grow further. In addition, a reduction in cellular ROS is suggested to activate anti-apoptotic proteins like Bcl-2 and Bcl-xL (Li *et al.*, 2004).

Lung cancer

Nonsmall cell lung carcinoma (NSCLC) is the most common lung cancer subtype encompassing approximately 85% of all such cases. Most of these patients have locally advanced or distant metastatic disease (stage III/IV) from the onset of symptoms. A 5-year survival rate of NSCLC was reported to be less than 10% and 5% in male and female patients, respectively (Reungwetwattana *et al.*, 2012). It was found that SIRT3 interacted with the full-length nicotinamide mononucleotide adenylyl transferase 2 (*NMNAT2*) gene, causing its deacetylation to promote mitotic entry, growth, and proliferation of cultured cells *in vitro* and *in vivo*. Moreover, downregulation of SIRT3 apparently inhibited the acetylation of *NMNAT2* and NAD+ synthesis enzyme activity (Yan *et al.*, 2010). However, a lack of SIRT3 expression caused the inhibition of mitotic entry, growth, and proliferation of a NSCLC cell line, leading to apoptosis. This is actually related to energy metabolism involved in the interaction between SIRT3 and *NMNAT2* (Li *et al.*, 2013) (Fig. 6). *NMNAT2* is a promising therapeutic target in lung cancer treatment.

Gastric cancer

SIRT3 also plays a role in gastric cancer (GC); however, its role in the pathogenesis of GC remains unclear. It has been reported that SIRT3 expression level is inversely correlated with such factors as tumor infiltration, tumor differentiation, and tumor stage. *In vitro* experiments showed that the absence of SIRT3 in MGC-803 GC cells significantly increased the expression of HIF-1a (Yang *et al.*, 2014); therefore, aberrantly decreased expression of SIRT3 was seen in patients with GC. SIRT3 is likely to function as a mitochondrial tumor suppressor in GC to affect the progression of patients with GC by exerting direct control on HIF-1a. However, it is unclear whether the aberrant expression of SIRT3 in patients with GC is a causal factor, a subsequent effect of tumor progression, or if other mutations play a role in GC (Wang *et al.*, 2015). The Notch family of proteins substantially contributes to cell behavior including cell proliferation, differentiation, and apoptosis (Vallejo *et al.*, 2011). Notch-1 is also overexpressed in GC, suggesting its critical role in the disease (Du *et al.*, 2014). SIRT3 suppresses the proliferation of GC cells through the downregulation of Notch-1, which suggests a novel therapeutic target in GC therapy (Wang *et al.*, 2015). Previously, it was observed that GC patients with SIRT3 expression have better prognosis than those without it. SIRT3 expression is an independent prognostic marker of survival to act as a tumor suppressor in GC (Huang *et al.*, 2014).

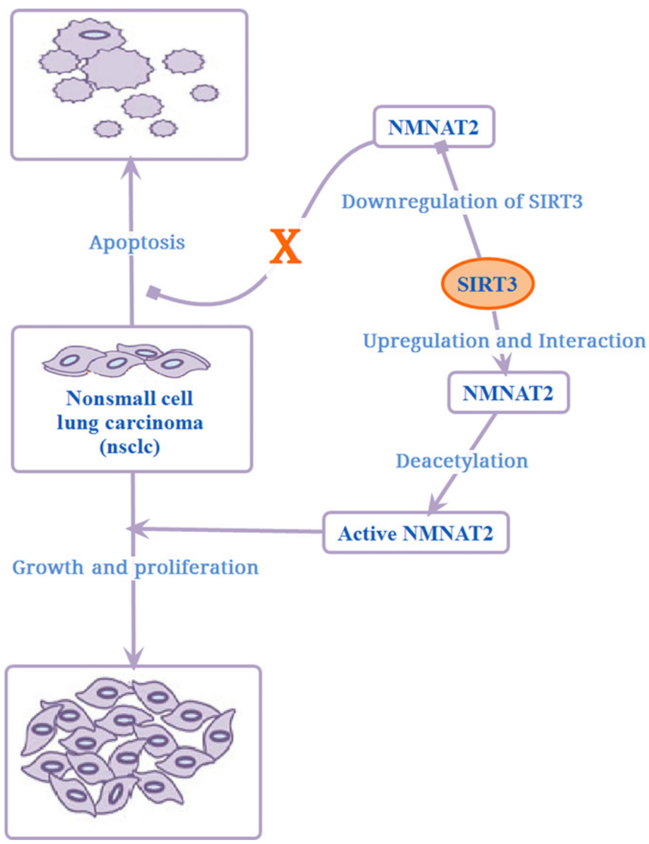

Fig. 6 Function of SIRT3 in lung cancer.

Bladder cancer

Extracellular/intracellular stress may lead to cell cycle arrest, apoptosis, and cellular senescence in bladder cancer (Li *et al.*, 2012). Accordingly, tumor protein p53 functions to regulate the transcriptional program in the related events of above cellular stress. The mitochondrial p53 gene has an antiproliferative function, although it is normally expressed in the nucleus (Talos *et al.*, 2005). In the absence of p53, an EJ bladder carcinoma cell line maintained growth arrest until p53 was introduced (Sugrue *et al.*, 1997). Endogenous p53 can be independently partitioned with mitochondrial and nuclear proteins, as it is capable of promoting senescence. SIRT3 thus rescued p53-EJ cells from induced p53-mediated growth arrest and partially nullified the ability of p53 to enact growth arrest and senescence; however, after the introduction of the chaperone protein BAG-2, SIRT3 targeting of p53-mediated senescence was averted (Li *et al.*, 2010).

The role of SIRT3 in other diseases

Although SIRT3 has a potential role in cancer, it can also exert important control on other diseases. The most notable aspects of these diseases are described below.

Alzheimer's disease

ROS marker analysis revealed the prevalence of oxidative stress in Alzheimer's disease (AD). This analysis was carried out by determining oxidized biomolecules generated by ROS (Wang *et al.*, 2014b). Oxidative stress is engaged in a spiral interaction with mitochondrial dysfunction. Thus, it poses a major threat by producing ROS that are critical for the pathogenesis of AD as well as a number of other neurodegenerative diseases (Lin & Beal, 2006). Recent studies revealed that SIRT3 expression has been increasing in both human and mouse AD pathology. Apolipoprotein E_4 ($APOE_4$) is a major genetic factor in late-onset AD, and SIRT3 is known to be downregulated in the frontal cortices of human brain $APOE_4$ carriers compared to noncarriers. Analysis of SIRT3 level may aid in the diagnosis of AD (Yin *et al.*, 2015). In addition, SIRT3 level may increase in response to increased ROS synthesis. In an experiment with primary neuronal cultures, the occurrence of such SIRT3 upregulation indicated a possibility for an increased oxidative stress-oriented mitochondrial response in AD. An increase in LF SIRT3 could well extend the neuronal lifespan under mitochondrial oxidative stress (Weir *et al.*, 2012).

Huntington's disease

Huntington's disease (HD) as a progressive and autosomal dominant neurodegenerative disorder develops with psychiatric manifestations, cognitive decline, and movement abnormalities (Harper, 1996). HD is caused by abnormal polyglutamine expression in the Huntingtin (Htt) protein (Naia & Rego, 2015). To date, there is no cure for HD. Nonetheless, as energy-demanding neurons are particularly susceptible to energy deficits and oxidative stress, mitochondrial dysfunction might be a mediating factor for the mutant Htt-induced neurotoxicity (Fu *et al.*, 2012). It was previously reported that cells expressing mutant Htt displayed reduced SIRT3 levels, and mutant Htt-induced depletion of

SIRT3 protected cells from mutant Htt. The natural product viniferin and other semisynthetic stilbenic compounds can also decrease ROS levels; as such, they will decrease deacetylase activity along with a reduction in cellular NAD+ levels and mitochondrial biogenesis in cells. Viniferin also activates AMP-activated kinase while enhancing mitochondrial biogenesis. On the other hand, a knockdown significantly inhibited viniferin-mediated AMP-activated kinase activation with diminished neuroprotective effects (Fu *et al.*, 2012). Thus, SIRT3 is suggested to mediate the neuroprotection of viniferin (Fu *et al.*, 2012).

Amyotrophic lateral sclerosis

The ALS disease shows an increase in fragmented mitochondria along with defects to bi-directional axonal transport with increased cell death. In a model of amyotrophic lateral sclerosis (ALS), SIRT3 is able to prevent mitochondrial fragmentation of spinal cord motor neurons transfected with SOD1^{G93A}. Interestingly, co-expression with either SIRT3 or PGC-1α is able to rescue SOD1^{G93A}-induced mitochondrial fragmentation to improve cell survival (Song *et al.*, 2013). SIRT3 regulates ketone body production by deacetylation of mitochondrial 3-hydroxy-3-methylglutaryl CoA synthase 2 (HMGCS2), indicating its potential for neuroprotection in the SOD1^{G93A} model (Pasinetti *et al.*, 2013).

Age-related hearing loss

Age-related hearing loss (AHL) is frequently explained in association with oxidative stress. In mice, oxidative stress causes damage to hair cells and spiral ganglia neurons of the cochlea, which results in hearing loss in about 12 months. Calorie restriction induces SIRT3, which prevents or delays age-related hearing loss by protecting cochlear neurons from oxidative damage (Someya *et al.*, 2010; Bell & Guarente, 2011). Mitochondria can maintain oxidative stress by the glutathione antioxidant system that is mediated by increased levels of NADPH, which is achieved by direct deacetylation of mitochondrial isocitrate dehydrogenase 2 (IDH2) by SIRT3 (Someya *et al.*, 2010; Jing *et al.*, 2011).

Conclusion

SIRT3 is a NAD+-dependent protein deacetylase. It is a noble protein with numerous roles that are essential in human physiology. Starting with energy homeostasis and metabolism, SIRT3 impacts nuclear and muscular function, reduces the effects of aging, and mediates several genetic diseases. Moreover, it has the ability to repair DNA, regulate thermogenesis, and fight against oxidative stress. SIRT3 has been noted extensively for its role in different types of cancer such as oral cancer, breast cancer, esophageal cancer, lung cancer, gastric cancer, and hepatocellular carcinoma and also in other diseases such as AD, HD, ALS, and AHL. Perceptual research in the field of SIRT3 is continually increasing our knowledge. Both *in vitro* and *in vivo* studies can be used to acquire information regarding the potential of different SIRT3 activators and the pharmacological applications of this protein. In summary, SIRT3 is a clinically novel target for various complications of human physiology.

Acknowledgments

The corresponding author acknowledges support from a National Research Foundation of Korea (NRF) grant funded by the Ministry of Education, Science and Technology (MEST) (No. 2006-0093848).

Conflict of Interest

The authors have no conflict of interests to declare.

References

Accili D, Arden KC (2004) FoxOs at the crossroads of cellular metabolism, differentiation, and transformation. *Cell* **117**, 421–426.

Ahn B-H, Kim H-S, Song S, Lee IH, Liu J, Vassilopoulos A, Deng C-X, Finkel T (2008) A role for the mitochondrial deacetylase Sirt3 in regulating energy homeostasis. *Proc. Natl. Acad. Sci. USA* **105**, 14447–14452.

Alano CC, Ying W, Swanson RA (2004) Poly (ADP-ribose) polymerase-1-mediated cell death in astrocytes requires NAD+ depletion and mitochondrial permeability transition. *J. Biol. Chem.* **279**, 18895–18902.

Alano CC, Garnier P, Ying W, Higashi Y, Kauppinen TM, Swanson RA (2010) NAD+ depletion is necessary and sufficient for poly (ADP-Ribose) polymerase-1-mediated neuronal death. *J. Neurosci.* **30**, 2967–2978.

Alhazzazi TY, Kamarajan P, Joo N, Huang JY, Verdin E, D'Silva NJ, Kapila YL (2011a) Sirtuin-3 (SIRT3), a novel potential therapeutic target for oral cancer. *Cancer* **117**, 1670–1678.

Alhazzazi TY, Kamarajan P, Verdin E, Kapila YL (2011b). SIRT3 and cancer: tumor promoter or suppressor? *Biochim. Biophys. Acta*. **1816**, 80–88.

Allison SJ, Milner J (2007) SIRT3 is pro-apoptotic and participates in distinct basal apoptotic pathways. *Cell Cycle* **6**, 2669–2677.

Ashraf N, Zino S, Macintyre A, Kingsmore D, Payne A, George W, Shiels P (2006) Altered sirtuin expression is associated with node-positive breast cancer. *Br. J. Cancer* **95**, 1056–1061.

Battistini S, Giannini F, Greco G, Bibbò G, Ferrera L, Marini V, Causarano R, Casula M, Lando G, Patrosso MC (2005) SOD1 mutations in amyotrophic lateral sclerosis. *J. Neurol.* **252**, 782–788.

Bause AS, Matsui MS, Haigis MC (2013) The protein deacetylase SIRT3 prevents oxidative stress-induced keratinocyte differentiation. *J. Biol. Chem.* **288**, 36484–36491.

Bell EL, Guarente L (2011) The SirT3 divining rod points to oxidative stress. *Mol. Cell* **42**, 561–568.

Bellizzi D, Rose G, Cavalcante P, Covello G, Dato S, De Rango F, Greco V, Maggiolini M, Feraco E, Mari V, Franceschi C, Passarino G, De Benedictis G (2005) A novel VNTR enhancer within the SIRT3 gene, a human homologue of SIR2, is associated with survival at oldest ages. *Genomics* **85**, 258–263.

Bellizzi D, Covello G, Di Cianni F, Tong Q, De Benedictis G (2009) Identification of GATA2 and AP-1 Activator elements within the enhancer VNTR occurring in intron 5 of the human SIRT3 gene. *Mol. Cells* **28**, 87–92.

Boillée S, Vande Velde C, Cleveland DW (2006) ALS: a disease of motor neurons and their nonneuronal neighbors. *Neuron* **52**, 39–59.

Bose A, Teh M-T, Hutchison IL, Wan H, Leigh IM, Waseem A (2012) Two mechanisms regulate keratin K15 expression in keratinocytes: role of PKC/AP-1 and FOXM1 mediated signalling. *PLoS One* **7**, e38599.

Brown K, Xie S, Qiu X, Mohrin M, Shin J, Liu Y, Zhang D, Scadden DT, Chen D (2013) SIRT3 reverses aging-associated degeneration. *Cell Rep.* **3**, 319–327.

Bruijn LI, Miller TM, Cleveland DW (2004) Unraveling the mechanisms involved in motor neuron degeneration in ALS. *Annu. Rev. Neurosci.* **27**, 723–749.

Burgering BM, Kops GJ (2002) Cell cycle and death control: long live Forkheads. *Trends Biochem. Sci.* **27**, 352–360.

Chen Y, Zhang J, Lin Y, Lei Q, Guan KL, Zhao S, Xiong Y (2011) Tumour suppressor SIRT35 deacetylates and activates manganese superoxide dismutase to scavenge ROS. *EMBO Rep.* **12**, 534–541.

Chen I, Chiang WF, Chen PF, Chiang HC (2014) STRESS-responsive deacetylase SIRT3 is up-regulated by areca nut extract-induced oxidative stress in human oral keratinocytes. *J. Cell. Biochem.* **115**, 328–339.

Cheng Y, Ren X, Gowda AS, Shan Y, Zhang L, Yuan Y, Patel R, Wu H, Huber-Keener K, Yang J (2013) Interaction of Sirt3 with OGG1 contributes to repair of mitochondrial DNA and protects from apoptotic cell death under oxidative stress. *Cell Death Dis.* **4**, e731.

Cheng A, Yang Y, Zhou Y, Maharana C, Lu D, Peng W, Liu Y, Wan R, Marosi K, Misiak M (2016) Mitochondrial SIRT3 mediates adaptive responses of neurons to exercise and metabolic and excitatory challenges. *Cell Metab.* **23**, 128–142.

Chintharlapalli SR, Jasti M, Malladi S, Parsa KV, Ballestero RP, González-García M (2005) BMRP is a Bcl-2 binding protein that induces apoptosis. *J. Cell. Biochem.* **94**, 611–626.

Choudhury M, Jonscher KR, Friedman JE (2011) Reduced mitochondrial function in obesity-associated fatty liver: SIRT3 takes on the fat. *Aging (Albany NY)* **3**, 175–178.

Cimen H, Han MJ, Yang Y, Tong Q, Koc H, Koc EC (2009) Regulation of succinate dehydrogenase activity by SIRT3 in mammalian mitochondria. *Biochemistry* **49**, 304–311.

Cooper HM, Spelbrink JN (2008) The human SIRT3 protein deacetylase is exclusively mitochondrial. *Biochemical J.* **411**, 279–285.

Desouki MM, Doubinskaia I, Gius D, Abdulkadir SA (2014) Decreased mitochondrial SIRT3 expression is a potential molecular biomarker associated with poor outcome in breast cancer. *Hum. Pathol.* **45**, 1071–1077.

Du X, Cheng Z, Wang Y-H, Guo Z-H, Zhang S-Q, Hu J-K, Zhou Z-G (2014) Role of Notch signaling pathway in gastric cancer: a meta-analysis of the literature. *World J. Gastroenterol.* **20**, 9191.

Falkenberg M, Gaspari M, Rantanen A, Trifunovic A, Larsson N-G, Gustafsson CM (2002) Mitochondrial transcription factors B1 and B2 activate transcription of human mtDNA. *Nat. Genet.* **31**, 289–294.

Finck BN, Kelly DP (2006) PGC-1 coactivators: inducible regulators of energy metabolism in health and disease. *J. Clin. Investig.* **116**, 615–622.

Finley LW, Carracedo A, Lee J, Souza A, Egia A, Zhang J, Teruya-Feldstein J, Moreira PI, Cardoso SM, Clish CB, Pandolfi PP, Haigis MC (2011) SIRT3 opposes reprogramming of cancer cell metabolism through HIF1α destabilization. *Cancer Cell* **19**, 416–428.

Frame S, Cohen P (2001) GSK3 takes centre stage more than 20 years after its discovery. *Biochemical J.* **359**, 1–16.

Fu J, Jin J, Cichewicz RH, Hageman SA, Ellis TK, Xiang L, Peng Q, Jiang M, Arbez N, Hotaling K (2012) trans-(−)-ε-Viniferin increases mitochondrial sirtuin 3 (SIRT3), activates AMP-activated protein kinase (AMPK), and protects cells in models of Huntington Disease. *J. Biol. Chem.* **287**, 24460–24472.

Giralt A, Villarroya F (2012) SIRT3, a pivotal actor in mitochondrial functions: metabolism, cell death and aging. *Biochemical J.* **444**, 1–10.

Giralt A, Hondares E, Villena JA, Ribas F, Díaz-Delfín J, Giralt M, Iglesias R, Villarroya F (2011) Peroxisome proliferator-activated receptor-γ coactivator-1α controls transcription of the Sirt3 gene, an essential component of the thermogenic brown adipocyte phenotype. *J. Biol. Chem.* **286**, 16958–16966.

Gleyzer N, Vercauteren K, Scarpulla RC (2005) Control of mitochondrial transcription specificity factors (TFB1M and TFB2M) by nuclear respiratory factors (NRF-1 and NRF-2) and PGC-1 family coactivators. *Mol. Cell. Biol.* **25**, 1354–1366.

Grollman AP, Moriya M (1993) Mutagenesis by 8-oxoguanine: an enemy within. *Trends Genet.* **9**, 246–249.

Guarente L (2008) Mitochondria—a nexus for aging, calorie restriction, and sirtuins? *Cell* **132**, 171–176.

Hafner AV, Dai J, Gomes AP, Xiao C-Y, Palmeira CM, Rosenzweig A, Sinclair DA (2010) Regulation of the mPTP by SIRT3-mediated deacetylation of CypD at lysine 166 suppresses age-related cardiac hypertrophy. *Aging (Albany NY)* **2**, 914–923.

Haigis MC, Deng C-X, Finley LW, Kim H-S, Gius D (2012) SIRT3 is a mitochondrial tumor suppressor: a scientific tale that connects aberrant cellular ROS, the Warburg effect, and carcinogenesis. *Cancer Res.* **72**, 2468–2472.

Halaschek-Wiener J, Amirabbasi-Beik M, Monfared N, Pieczyk M, Sailer C, Kollar A, Thomas R, Agalaridis G, Yamada S, Oliveira L (2009) Genetic variation in healthy oldest-old. *PLoS One* **4**, e6641.

Hallows WC, Lee S, Denu JM (2006) Sirtuins deacetylate and activate mammalian acetyl-CoA synthetases. *Proc. Natl. Acad. Sci. USA* **103**, 10230–10235.

Harper PS (1996) New genes for old diseases: the molecular basis of myotonic dystrophy and Huntington's disease: The Lumbeian Lecture 1995. *J. R. Coll. Physicians Lond.* **30**, 221–231.

Hirschey MD, Shimazu T, Goetzman E, Jing E, Schwer B, Lombard DB, Grueter CA, Harris C, Biddinger S, Ilkayeva OR (2010) SIRT3 regulates mitochondrial fatty-acid oxidation by reversible enzyme deacetylation. *Nature* **464**, 121–125.

Hirschey MD, Shimazu T, Jing E, Grueter CA, Collins AM, Aouizerat B, Stančáková A, Goetzman E, Lam MM, Schwer B (2011) SIRT3 deficiency and mitochondrial protein hyperacetylation accelerate the development of the metabolic syndrome. *Mol. Cell* **44**, 177–190.

Hokari F, Kawasaki E, Sakai A, Koshinaka K, Sakuma K, Kawanaka K (2010) Muscle contractile activity regulates Sirt3 protein expression in rat skeletal muscles. *J. Appl. Physiol.* **109**, 332–340.

Huang K-H, Hsu C-C, Fang W-L, Chi C-W, Sung M-T, Kao H-L, Li AF-Y, Yin P-H, Yang M-H, Lee H-C (2014) SIRT3 expression as a biomarker for better prognosis in gastric cancer. *World J. Surg.* **38**, 910–917.

Iwahara T, Bonasio R, Narendra V, Reinberg D (2012) SIRT3 functions in the nucleus in the control of stress-related gene expression. *Mol. Cell. Biol.* **32**, 5022–5034.

Jacobs KM, Pennington JD, Bisht KS, Aykin-Burns N, Kim H-S, Mishra M, Sun L, Nguyen P, Ahn B-H, Leclerc J (2008) SIRT3 interacts with the daf-16 homolog FOXO3a in the mitochondria, as well as increases FOXO3a dependent gene expression. *Int. J. Biol. Sci.* **4**, 291.

Jing E, Emanuelli B, Hirschey MD, Boucher J, Lee KY, Lombard D, Verdin EM, Kahn CR (2011) Sirtuin-3 (Sirt3) regulates skeletal muscle metabolism and insulin signaling via altered mitochondrial oxidation and reactive oxygen species production. *Proc. Natl. Acad. Sci. USA* **108**, 14608–14613.

John JCS, Facucho-Oliveira J, Jiang Y, Kelly R, Salah R (2010) Mitochondrial DNA transmission, replication and inheritance: a journey from the gamete through the embryo and into offspring and embryonic stem cells. *Hum. Reprod. Update* **16**, 488–509.

Kawamura Y, Uchijima Y, Horike N, Tonami K, Nishiyama K, Amano T, Asano T, Kurihara Y, Kurihara H (2010) Sirt3 protects in vitro-fertilized mouse preimplantation embryos against oxidative stress-induced p53-mediated developmental arrest. *J. Clin. Invest.* **120**, 2817–2828.

Kendrick AA, Choudhury M, Rahman SM, McCurdy CE, Friederich M, Van Hove JL, Watson PA, Birdsey N, Bao J, Gius D (2011) Fatty liver is associated with reduced SIRT3 activity and mitochondrial protein hyperacetylation. *Biochemical J.* **433**, 505–514.

Kim SC, Sprung R, Chen Y, Xu Y, Ball H, Pei J, Cheng T, Kho Y, Xiao H, Xiao L (2006) Substrate and functional diversity of lysine acetylation revealed by a proteomics survey. *Mol. Cell* **23**, 607–618.

Kim H-S, Patel K, Muldoon-Jacobs K, Bisht KS, Aykin-Burns N, Pennington JD, van der Meer R, Nguyen P, Savage J, Owens KM (2010) SIRT3 is a mitochondria-localized tumor suppressor required for maintenance of mitochondrial integrity and metabolism during stress. *Cancer Cell* **17**, 41–52.

Kim SH, Lu HF, Alano CC (2011) Neuronal Sirt3 protects against excitotoxic injury in mouse cortical neuron culture. *PLoS One* **6**, e14731.

Kincaid B, Bossy-Wetzel E (2013) Forever young: SIRT3 a shield against mitochondrial meltdown, aging, and neurodegeneration. *Front. Aging Neurosci.* **5**, 1–13.

Kong X, Wang R, Xue Y, Liu X, Zhang H, Chen Y, Fang F, Chang Y (2010) Sirtuin 3, a new target of PGC-1α, plays an important role in the suppression of ROS and mitochondrial biogenesis. *PLoS One* **5**, e11707.

Li D, Ueta E, Kimura T, Yamamoto T, Osaki T (2004) Reactive oxygen species (ROS) control the expression of Bcl-2 family proteins by regulating their phosphorylation and ubiquitination. *Cancer Sci.* **95**, 644–650.

Li S, Banck M, Mujtaba S, Zhou M-M, Sugrue MM, Walsh MJ (2010) p53-induced growth arrest is regulated by the mitochondrial SirT3 deacetylase. *PLoS One* **5**, e10486.

Li T, Kon N, Jiang L, Tan M, Ludwig T, Zhao Y, Baer R, Gu W (2012) Tumor suppression in the absence of p53-mediated cell-cycle arrest, apoptosis, and senescence. *Cell* **149**, 1269–1283.

Li H, Feng Z, Wu W, Li J, Zhang J, Xia T (2013) SIRT3 regulates cell proliferation and apoptosis related to energy metabolism in non-small cell lung cancer cells through deacetylation of *NMNAT2*. *Int. J. Oncol.* **43**, 1420–1430.

Lin MT, Beal MF (2006) Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature* **443**, 787–795.

Lin J, Handschin C, Spiegelman BM (2005) Metabolic control through the PGC-1 family of transcription coactivators. *Cell Metab.* **1**, 361–370.

Lombard DB, Alt FW, Cheng H-L, Bunkenborg J, Streeper RS, Mostoslavsky R, Kim J, Yancopoulos G, Valenzuela D, Murphy A (2007) Mammalian Sir2 homolog SIRT3 regulates global mitochondrial lysine acetylation. *Mol. Cell. Biol.* **27**, 8807–8814.

Merksamer PI, Liu Y, He W, Hirschey MD, Chen D, Verdin E (2013) The sirtuins, oxidative stress and aging: an emerging link. *Aging (Albany NY)* **5**, 144.

Miao L, St Clair DK (2009) Regulation of superoxide dismutase genes: implications in disease. *Free Radic. Biol. Med.* **47**, 344–356.

Michishita E, Park JY, Burneskis JM, Barrett JC, Horikawa I (2005) Evolutionarily conserved and nonconserved cellular localizations and functions of human SIRT proteins. *Mol. Biol. Cell* **16**, 4623–4635.

Miller C, Saada A, Shaul N, Shabtai N, Ben-Shalom E, Shaag A, Hershkovitz E, Elpeleg O (2004) Defective mitochondrial translation caused by a ribosomal protein (MRPS16) mutation. *Ann. Neurol.* **56**, 734–738.

Morigi M, Perico L, Rota C, Longaretti L, Conti S, Rottoli D, Novelli R, Remuzzi G, Benigni A (2015) Sirtuin 3–dependent mitochondrial dynamic improvements protect against acute kidney injury. *J. Clin. Investig.* **125**, 715.

Naia L, Rego AC (2015) Sirtuins: double players in Huntington's disease. *Biochim. Biophys. Acta* **1852**, 2183–2194.

Nakamura Y, Ogura M, Tanaka D, Inagaki N (2008) Localization of mouse mitochondrial SIRT proteins: shift of SIRT3 to nucleus by co-expression with SIRT5. *Biochem. Biophys. Res. Commun.* **366**, 174–179.

Nguyen LMD, Malamo AG, Larkin-Kaiser KA, Borsa PA, Adhihetty PJ (2014) Effect of near-infrared light exposure on mitochondrial signaling in C2C12 muscle cells. *Mitochondrion* **14**, 42–48.

O'Brien TW, O'Brien BJ, Norman RA (2005) Nuclear MRP genes and mitochondrial disease. *Gene* **354**, 147–151.

Palacios OM, Carmona JJ, Michan S, Chen KY, Manabe Y, Ward Iii JL, Goodyear LJ, Tong Q (2009) Diet and exercise signals regulate SIRT3 and activate AMPK and PGC-1α in skeletal muscle. *Aging (Albany NY)* **1**, 771.

Park S-H, Ozden O, Jiang H, Cha YI, Pennington JD, Aykin-Burns N, Spitz DR, Gius D, Kim H-S (2011) Sirt3, mitochondrial ROS, ageing, and carcinogenesis. *Int. J. Mol. Sci.* **12**, 6226–6239.

Pasinetti GM, Bilski AE, Zhao W (2013) Sirtuins as therapeutic targets of ALS. *Cell Res.* **23**, 1073–1074.

Paulin R, Dromparis P, Sutendra G, Gurtu V, Zervopoulos S, Bowers L, Haromy A, Webster L, Provencher S, Bonnet S, Michelakis ED (2014) Sirtuin 3 deficiency is associated with inhibited mitochondrial function and pulmonary arterial hypertension in rodents and humans. *Cell Metab.* **20**, 827–839.

Pillai VB, Sundaresan NR, Jeevanandam V, Gupta MP (2010) Mitochondrial SIRT3 and heart disease. *Cardiovasc. Res.* **88**, 250–256.

Pillai VB, Samant S, Sundaresan NR, Raghuraman H, Kim G, Bonner MY, Arbiser JL, Walker DI, Jones DP, Gius D (2015) Honokiol blocks and reverses cardiac hypertrophy in mice by activating mitochondrial Sirt3. *Nat. Commun.* **6**, 1–16.

Qiu X, Brown K, Hirschey MD, Verdin E, Chen D (2010) Calorie restriction reduces oxidative stress by SIRT3-mediated SOD2 activation. *Cell Metab.* **12**, 662–667.

Reungwetwattana T, Weroha SJ, Molina JR (2012) Oncogenic pathways, molecularly targeted therapies, and highlighted clinical trials in non–small-cell lung cancer (NSCLC). *Clin. Lung Cancer* **13**, 252–266.

Richter C, Park J-W, Ames BN (1988) Normal oxidative damage to mitochondrial and nuclear DNA is extensive. *Proc. Natl Acad. Sci. USA* **85**, 6465–6467.

Rose G, Dato S, Altomare K, Bellizzi D, Garasto S, Greco V, Passarino G, Feraco E, Mari V, Barbi C (2003) Variability of the SIRT3 gene, human silent information regulator Sir2 homologue, and survivorship in the elderly. *Exp. Gerontol.* **38**, 1065–1070.

Rutberg S, Saez E, Glick A, Dlugosz A, Spiegelman B, Yuspa S (1996) Differentiation of mouse keratinocytes is accompanied by PKC-dependent changes in AP-1 proteins. *Oncogene* **13**, 167–176.

Satterstrom FK, Swindell WR, Laurent G, Vyas S, Bulyk ML, Haigis MC (2015) Nuclear respiratory factor 2 induces SIRT3 expression. *Aging Cell* **14**, 818–825.

Scher MB, Vaquero A, Reinberg D (2007) SirT3 is a nuclear NAD+-dependent histone deacetylase that translocates to the mitochondria upon cellular stress. *Genes Dev.* **21**, 920–928.

Schlicker C, Gertz M, Papatheodorou P, Kachholz B, Becker CF, Steegborn C (2008) Substrates and regulation mechanisms for the human mitochondrial sirtuins Sirt3 and Sirt5. *J. Mol. Biol.* **382**, 790–801.

Schon EA (2000) Mitochondrial genetics and disease. *Trends Biochem. Sci.* **25**, 555–560.

Schreiber V, Dantzer F, Ame J-C, De Murcia G (2006) Poly (ADP-ribose): novel functions for an old molecule. *Nat. Rev. Mol. Cell Biol.* **7**, 517–528.

Schumacker PT (2010) A tumor suppressor SIRTainty. *Cancer Cell* **17**, 5–6.

Schumacker PT (2011) SIRT3 controls cancer metabolic reprogramming by regulating ROS and HIF. *Cancer Cell* **19**, 299–300.

Schwer B, North BJ, Frye RA, Ott M, Verdin E (2002) The human silent information regulator (Sir) 2 homologue hSIRT3 is a mitochondrial nicotinamide adenine dinucleotide-dependent deacetylase. *J. Cell Biol.* **158**, 647–657.

Schwer B, Bunkenborg J, Verdin RO, Andersen JS, Verdin E (2006) Reversible lysine acetylation controls the activity of the mitochondrial enzyme acetyl-CoA synthetase 2. *Proc. Natl Acad. Sci. USA* **103**, 10224–10229.

Shi T, Wang F, Stieren E, Tong Q (2005) SIRT3, a mitochondrial sirtuin deacetylase, regulates mitochondrial function and thermogenesis in brown adipocytes. *J. Biol. Chem.* **280**, 13560–13567.

Smith BC, Hallows WC, Denu JM (2008) Mechanisms and molecular probes of sirtuins. *Chem. Biol.* **15**, 1002–1013.

Someya S, Yu W, Hallows WC, Xu J, Vann JM, Leeuwenburgh C, Tanokura M, Denu JM, Prolla TA (2010) Sirt3 mediates reduction of oxidative damage and prevention of age-related hearing loss under caloric restriction. *Cell* **143**, 802–812.

Song W, Song Y, Kincaid B, Bossy B, Bossy-Wetzel E (2013) Mutant SOD1 G93A triggers mitochondrial fragmentation in spinal cord motor neurons: neuroprotection by SIRT3 and PGC-1α. *Neurobiol. Dis.* **51**, 72–81.

Sugrue MM, Shin DY, Lee SW, Aaronson SA (1997) Wild-type p53 triggers a rapid senescence program in human tumor cells lacking functional p53. *Proc. Natl Acad. Sci. USA* **94**, 9648–9653.

Sundaresan NR, Samant SA, Pillai VB, Rajamohan SB, Gupta MP (2008) SIRT3 is a stress-responsive deacetylase in cardiomyocytes that protects cells from stress-mediated cell death by deacetylation of Ku70. *Mol. Cell. Biol.* **28**, 6384–6401.

Sundaresan NR, Gupta M, Kim G, Rajamohan SB, Isbatan A, Gupta MP (2009) Sirt3 blocks the cardiac hypertrophic response by augmenting Foxo3a-dependent antioxidant defense mechanisms in mice. *J. Clin. Investig.* **119**, 2758–2771.

Sundaresan NR, Bindu S, Pillai VB, Samant S, Pan Y, Huang J-Y, Gupta M, Nagalingam RS, Wolfgeher D, Verdin E (2016) SIRT3 blocks aging-associated tissue fibrosis in mice by deacetylating and activating glycogen synthase kinase 3β. *Mol. Cell. Biol.* **36**, 678–692.

Talos F, Petrenko O, Mena P, Moll UM (2005) Mitochondrially targeted p53 has tumor suppressor activities in vivo. *Cancer Res.* **65**, 9971–9981.

Tanno M, Kuno A, Horio Y, Miura T (2012) Emerging beneficial roles of sirtuins in heart failure. *Basic Res. Cardiol.* **107**, 1–14.

Tao L, Lambert J (2014) The role of sirtuin 3 in the differential pro-oxidant effects of (-)-epigallocatechin-3-gallate in oral cells (261.4). *FASEB J.* **28**(261), 264.

Tao R, Coleman MC, Pennington JD, Ozden O, Park S-H, Jiang H, Kim H-S, Flynn CR, Hill S, Hayes McDonald W (2010) Sirt3-mediated deacetylation of evolutionarily conserved lysine 122 regulates MnSOD activity in response to stress. *Mol. Cell* **40**, 893–904.

Taylor RW, Turnbull DM (2005) Mitochondrial DNA mutations in human disease. *Nat. Rev. Genet.* **6**, 389–402.

Tseng AH, Shieh S-S, Wang DL (2013) SIRT3 deacetylates FOXO3 to protect mitochondria against oxidative damage. *Free Radic. Biol. Med.* **63**, 222–234.

Vallejo DM, Caparros E, Dominguez M (2011) Targeting Notch signalling by the conserved miR-8/200 microRNA family in development and cancer cells. *EMBO J.* **30**, 756–769.

Virág L, Szabó C (2002) The therapeutic potential of poly (ADP-ribose) polymerase inhibitors. *Pharmacol. Rev.* **54**, 375–429.

Wang F, Nguyen M, Qin F, Tong Q (2007) SIRT2 deacetylates FOXO3a in response to oxidative stress and caloric restriction. *Aging Cell* **6**, 505–514.

Wang J-X, Yi Y, Li Y-W, Cai X-Y, He H-W, Ni X-C, Zhou J, Cheng Y-F, Jin J-J, Fan J (2014a) Down-regulation of sirtuin 3 is associated with poor prognosis in hepatocellular carcinoma after resection. *BMC Cancer* **14**, 297.

Wang X, Wang W, Li L, Perry G, H-g Lee, Zhu X (2014b) Oxidative stress and mitochondrial dysfunction in Alzheimer's disease. *Biochim. Biophys. Acta* **1842**, 1240–1247.

Wang L, Wang W-Y, Cao L-P (2015) SIRT3 inhibits cell proliferation in human gastric cancer through down-regulation of Notch-1. *Int. J. Clin. Exp. Med.* **8**, 5263.

Weir HJ, Murray TK, Kehoe PG, Love S, Verdin EM, O'Neill MJ, Lane JD, Balthasar N (2012) CNS SIRT3 expression is altered by reactive oxygen species and in Alzheimer's disease. *PLoS One* **7**, e48225.

Winnik S, Gaul DS, Siciliani G, Lohmann C, Pasterk L, Calatayud N, Weber J, Eriksson U, Auwerx J, van Tits LJ (2016) Mild endothelial dysfunction in Sirt3 knockout mice fed a high-cholesterol diet: protective role of a novel C/EBP-β-dependent feedback regulation of SOD2. *Basic Res. Cardiol.* **111**, 1–15.

Yan T, Feng Y, Zheng J, Ge X, Zhang Y, Wu D, Zhao J, Zhai Q (2010) Nmnat2 delays axon degeneration in superior cervical ganglia dependent on its NAD synthesis activity. *Neurochem. Int.* **56**, 101–106.

Yan S-M, Han X, Han P-J, Chen H-M, Huang L-Y, Li Y (2014) SIRT3 is a novel prognostic biomarker for esophageal squamous cell carcinoma. *Med. Oncol.* **31**, 1–8.

Yang H, Yang T, Baur JA, Perez E, Matsui T, Carmona JJ, Lamming DW, Souza-Pinto NC, Bohr VA, Rosenzweig A, de Cabo R, Sauve AA, Sinclair DA (2007) Nutrient-sensitive mitochondrial NAD+ levels dictate cell survival. *Cell* **130**, 1095–1107.

Yang Y, Cimen H, Han M-J, Shi T, Deng J-H, Koc H, Palacios OM, Montier L, Bai Y, Tong Q (2010) NAD+-dependent deacetylase SIRT3 regulates mitochondrial protein synthesis by deacetylation of the ribosomal protein MRPL10. *J. Biol. Chem.* **285**, 7417–7429.

Yang B, Fu X, Shao L, Ding Y, Zeng D (2014) Aberrant expression of SIRT3 is conversely correlated with the progression and prognosis of human gastric cancer. *Biochem. Biophys. Res. Commun.* **443**, 156–160.

Yin J, Han PC, Caselli R, Beach T, Serrano G, Reiman E, Shi J (2015) Sirtuin 3 is down-regulated in Apolipoprotein E4 carriers with Alzheimer's disease (P5. 011). *Neurology* **84**, P5.011.

Yoo YA, Kim MJ, Park JK, Chung YM, Lee JH, Chi S-G, Kim JS, Do Yoo Y (2005) Mitochondrial ribosomal protein L41 suppresses cell growth in association with p53 and p27Kip1. *Mol. Cell. Biol.* **25**, 6603–6616.

Zhang Y-Y, Zhou L-M (2012) Sirt3 inhibits hepatocellular carcinoma cell growth through reducing Mdm2-mediated p53 degradation. *Biochem. Biophys. Res. Commun.* **423**, 26–31.

Zhang CZ, Liu L, Cai M, Pan Y, Fu J, Cao Y, Yun J (2012) Low SIRT3 expression correlates with poor differentiation and unfavorable prognosis in primary hepatocellular carcinoma. *PLoS One* **7**, e51703.

Zhang B, Qin L, Zhou C-J, Liu Y-L, Qian H-X, He S-B (2013a) SIRT3 expression in hepatocellular carcinoma and its impact on proliferation and invasion of hepatoma cells. *Asian Pac. J. Trop. Med.* **6**, 649–652.

Zhang L, Ren X, Cheng Y, Huber-Keener K, Liu X, Zhang Y, Yuan Y-S, Yang JW, Liu C-G, Yang J-M (2013b) Identification of Sirtuin 3, a mitochondrial protein deacetylase, as a new contributor to tamoxifen resistance in breast cancer cells. *Biochem. Pharmacol.* **86**, 726–733.

Zhao Y, Yang H, Wang X, Zhang R, Wang C, Guo Z (2013) Sirtuin-3 (SIRT3) expression is associated with overall survival in esophageal cancer. *Ann. Diagn. Pathol.* **17**, 483–485.

Zhao H-C, Ding T, Ren Y, Li T-J, Li R, Fan Y, Yan J, Zhao Y, Li M, Yu Y (2016) Role of Sirt3 in mitochondrial biogenesis and developmental competence of human in vitro matured oocytes. *Hum. Reprod.* **31**, 607–622.

Zou X, Santa-Maria C, O'Brien J, Gius D, Zhu Y (2016) MnSOD acetylation and dysregulation, due to loss of SIRT3 activity, promotes a Luminal B-like breast carcinogenic permissive phenotype. *Antioxid. Redox Signal.* **25**, 326–336.