

# Sirtuins at a glance

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Sirtuins are NAD-dependent deacetylases that are highly conserved from bacteria to human and SIR2 was originally shown to extend lifespan in budding yeast (Imai et al., 2000; Kaerberlein et al., 1999). Since then, sirtuins have been shown to also regulate longevity in other lower organisms, such as flies and worms (Tissenbaum and Guarente, 2001;

Rogina and Helfand, 2004). In mammals, there are seven sirtuins (SIRT1-7). All mammalian sirtuins contain a conserved NAD-binding and catalytic domain, termed the sirtuin core domain, but differ in their N- and C-terminal domains (Frye, 2000). They have different specific substrates and biological functions, and are found in various cell compartments. The fact that sirtuins require NAD for their enzymatic activity connects metabolism to aging and aging-related diseases. In this Cell Science at a Glance article, we summarize the recent data related to the role of sirtuins in aging and aging-related diseases, and describe the underlying molecular mechanisms.

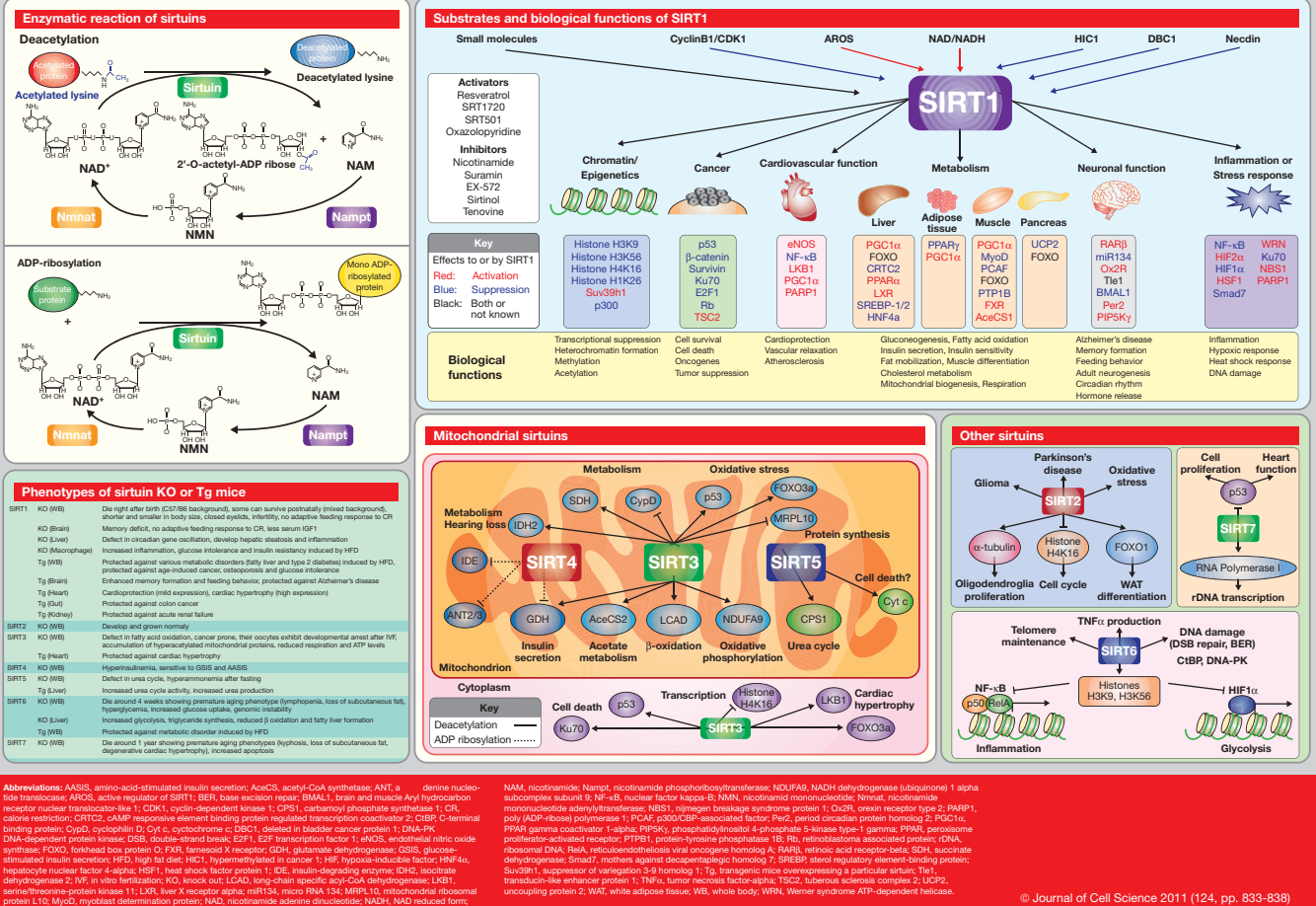
## Enzymatic activity of sirtuins and NAD biosynthesis

Sirtuins belong to the class III protein deacetylase family, which are the only histone deacetylases (HDACs) that require NAD for their

enzymatic activity (Imai et al., 2000). NAD is an important co-factor for the electron transport chain and is also involved in many enzymatic reactions (Houtkooper et al., 2010). Owing to the characteristic NAD requirement for their enzymatic reaction, the activity of sirtuins is directly linked to the metabolic state in the cell. Initially, yeast SIR2 was discovered as a histone deacetylase, but mammalian sirtuins have also various non-histone protein substrates. The deacetylation reaction of sirtuins consists of two steps. In the first, sirtuins cleave NAD and produce nicotinamide (NAM), and in the second step the acetyl group is transferred from the substrate to the ADP-ribose moiety of NAD to generate O-acetyl-ADP ribose and the deacetylated substrate (Tanner et al., 2000). Although most of sirtuins have deacetylase activity, SIRT4 has been shown to have only ADP-ribosyltransferase activity, whereas SIRT1 and SIRT6 have both deacetylation and a relatively weak ADP-ribosyltransferase activity

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(Haigis et al., 2006; Imai et al., 2000; Liszt et al., 2005; Michishita et al., 2008). Interestingly, the generated NAM is an endogenous inhibitor of sirtuins and is usually converted to nicotinamide mononucleotide (NMN) by the NAD salvage pathway enzyme, nicotinamide phosphoribosyltransferase (Namtpt). Subsequently, nicotinamide mononucleotide adenyltransferase (Nmnat) regenerates NAD from NMN (Houtkooper et al., 2010) (see poster). Recent studies suggest that NAD biosynthesis critically regulates the activity of sirtuins. For example, Nampt-mediated NAD biosynthesis controls SIRT1 activity in several tissues; and SIRT3, SIRT4 and SIRT5 are also regulated by NAD biosynthesis in response to nutrient stress (Nakagawa et al., 2009; Revollo et al., 2007; Yang et al., 2007). Nampt also mediates the production of tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) in a SIRT6 dependent manner (Van Gool et al., 2009). Additionally, NAD biosynthesis is linked to the circadian clock cycle, because Nampt is regulated by a complex consisting of the circadian locomotor output cycles kaput (CLOCK), brain and muscle aryl hydrocarbon receptor nuclear translocator-like 1 (BMAL1) and SIRT1, and in turn regulates SIRT1 activity through NAD (Nakahata et al., 2009; Ramsey et al., 2009).

### SIRT1

#### Roles in chromatin and epigenetics

As well as yeast SIR2, its mammalian homolog SIRT1 was shown to be able to deacetylate histones and preferentially deacetylates lysine (K) residue 9 of histone 3 (H3K9) and lysine 16 of histone 4 (H4K16) in vitro (Imai et al., 2000; Vaquero et al., 2004). SIRT1-deficient mouse embryonic fibroblasts (MEFs) also accumulate hyperacetylated histones, thereby promoting heterochromatin formation and transcription repression (Vaquero et al., 2007; Wang et al., 2008). SIRT1 deletion in MEFs also leads to histone H3K9 hypomethylation (Vaquero et al., 2007). SIRT1 directly binds to the histone methyltransferase Suv39h1 and upregulates its methyltransferase activity by deacetylating lysine residue 266, which resides in the SET domain of Suv39h1. SIRT1 also interacts with linker histone H1b and deacetylates its lysine 26 (H1K26) (Vaquero et al., 2004). In response to oxidative stress, SIRT1 is redistributed and so binds to acetylated histone H1K26, which leads to the repression of various set of genes. Interestingly, the transcriptional repression pattern is similar to that observed in the mouse brain with aging (Oberdoerffer et al., 2008). Thus, it can be speculated that SIRT1 is responsible for aging-dependent global transcriptional changes through chromatin modification.

#### Roles in metabolism pathways and metabolic diseases

SIRT1 regulates various metabolic processes that allow the cell to adapt to nutrient stress and has a pivotal role in aging-related metabolic diseases. In response to fasting, SIRT1 modulates gluconeogenesis in the liver through deacetylation of important factors, such as peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 $\alpha$ ), forkhead box protein O1 (FOXO1) and cAMP response element-binding (CREB)-regulated transcription coactivator 2 (CRTC2) (Brunet et al., 2004; Liu et al., 2008; Motta et al., 2004; Rodgers et al., 2005). In the early phase of fasting, CRTC2 is activated through its acetylation by the co-activator CBP/p300, which then promotes transcription of gluconeogenic genes. If fasting is prolonged, SIRT1 deacetylates both CRTC2 and FOXO1, which leads to a switch from activation of early gluconeogenic genes through CRTC2 to the activation of genes involved in the late phase of gluconeogenesis through FOXO1 (Liu et al., 2008). Deacetylation of PGC-1 $\alpha$  by SIRT1 not only controls gluconeogenesis, but also fatty acid oxidation in coordination with peroxisome proliferator-activated receptor alpha (PPAR $\alpha$ ) (Purushotham et al., 2009). PGC1 $\alpha$  also regulates mitochondria biogenesis and oxidative phosphorylation, and it has been proposed that these effects are mediated through the AMP-activated protein kinase (AMPK)-SIRT1-PGC1 $\alpha$  pathway (Canto et al., 2009; Iwabu et al., 2010). SIRT1 also targets other nuclear receptors, such as the liver X receptor LXR $\alpha$  and the farnesoid X receptor (FXR), which regulate hepatic metabolic processes (Kemper et al., 2009; Li et al., 2007b). SIRT1 deacetylates LXR $\alpha$  and promotes its ubiquitylation, which results in its activation and induction of cholesterol efflux (Li et al., 2007b). In white adipose tissue, SIRT1 regulates fat mobilization through the repression of peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) by binding to its cofactors, the nuclear receptor co-repressor (NCoR) and silencing mediator of retinoid and thyroid hormone receptors (SMRT) (Picard et al., 2004). In pancreatic  $\beta$  cells, SIRT1 regulates glucose-stimulated insulin secretion through the synthesis of uncoupling protein 2 (UCP2) (Bordone et al., 2006; Moynihan et al., 2005). Transgenic mice that specifically overexpress SIRT1 in pancreatic  $\beta$  cells (the so-called BESTO mice) have improved glucose tolerance when fed with a high fat diet (HFD) (Moynihan et al., 2005). In addition, mice that overexpress SIRT1 from a bacterial artificial chromosome (BAC) construct (the so-called SIRT1 BAC mice) are also protected against HFD-induced type 2 diabetes (Banks et al.,

2008; Pfluger et al., 2008). Consistent with these results, compounds that are able to activate SIRT1, such as resveratrol and SRT1720, protect mice from HFD-induced metabolic disorders (Baur et al., 2006; Feige et al., 2008; Lagouge et al., 2006; Milne et al., 2007). In humans, genetic variation in *SIRT1* was shown to be correlated with obesity and type 2 diabetes in studies of Dutch populations (Zillikens et al., 2009b; Zillikens et al., 2009a). Taken together, these findings provide strong evidence that SIRT1 has significant roles in metabolic diseases, such as type 2 diabetes and obesity, and controlling SIRT1 activity with nutrients or small molecules could be a valuable treatment strategy.

#### Roles in inflammation and stress response

A number of studies have revealed that SIRT1 mediates different stress responses, including inflammation, hypoxic stress, heat shock and genotoxic stress, and inflammation in particular is a highly important cause of aging and aging related diseases. SIRT1 can suppress inflammation through its effect on nuclear factor- $\kappa$ B (NF- $\kappa$ B) (Yeung et al., 2004); it physically interacts with its RelA subunit and deacetylates lysine 310, which inactivates NF- $\kappa$ B, thereby inhibiting the expression of its target genes. By contrast, during hypoxic condition, SIRT1 activates hypoxia inducible factor 2 alpha (HIF2 $\alpha$ ) through its deacetylation and thus initiates hypoxic stress responses (Dioum et al., 2009). However, SIRT1 also deacetylates HIF1 $\alpha$  at lysine 647 – which, in this case, inhibits its activity – to control glycolysis in response to hypoxic conditions (Lim et al., 2010). During hypoxia, NAD level gradually decrease and, subsequently, SIRT1 is deactivated. Therefore, it has been speculated that SIRT1 triggers a switch from HIF2 $\alpha$  to HIF1 $\alpha$  activation to coordinate metabolism, vascular formation and hypoxic stress responses (Lim et al., 2010).

SIRT1 is also involved in the transmission of the heat shock response through the heat shock factor protein1 (HSF1) (Westerheide et al., 2009). Upon protein-damage stress that is associated with the accumulation of misfolded proteins, SIRT1 deacetylates and, thereby, positively regulates HSF1 activity, which promotes the transcription of heat shock response genes (Westerheide et al., 2009). Thus, SIRT1 acts as a sensor of various stresses and organizes the survival signals in response to these stresses.

#### Roles in cardiovascular disease

Cardiovascular diseases increase with aging and are also closely influenced by the metabolism.

Several lines of evidence show that SIRT1 has pivotal roles in cardiovascular functions. For example, transgenic mice that overexpress SIRT1 in the heart, are protected against age-related cardiac hypertrophy as well as ischemia or reperfusion injury (Alcendor et al., 2007; Hsu et al., 2010). SIRT1 also regulates vascular endothelial cell functions through deacetylation of endothelial nitric oxide synthase (eNOS) (Mattagajasingh et al., 2007). In addition, activation of SIRT1 with resveratrol can ameliorate heart ischemia or reperfusion injury and also improve vascular functions (Orallo et al., 2002). SIRT1 also functions in reactive oxygen species (ROS)-mediated cell death through deacetylation of poly (ADP-ribose) polymerase 1 (PARP1) and, furthermore, deletion of SIRT1 results in the promotion of cardiomyocytes cell death during heart failure (Pillai et al., 2005; Kolthur-Seetharam et al., 2006).

#### Roles in cancer

The role of SIRT1 in tumor progression is controversial, as SIRT1 might have dual functions as an oncogene and tumor suppressor. The initial evidence that SIRT1 might function as an oncogene was the observation that it deacetylates lysine residue 383 of p53, thereby repressing its transcriptional activity (Luo et al., 2001; Vaziri et al., 2001). As p53 is a key tumor suppressor, its downregulation by SIRT1 could drive cells to tumorigenesis. In addition, two other tumor suppressors, deleted in bladder cancer 1 (DBC1) and hypermethylated in cancer 1 (HIC1) have been found to affect SIRT1. DBC1 binds to the N-terminus of SIRT1 and inhibits its enzymatic activity (Kim et al., 2008; Zhao et al., 2008), whereas HIC1 binds to the promoter region of the SIRT1 gene and represses its expression (Chen et al., 2005). As DBC1 and HIC1 are silenced in certain types of cancer cell, it has been speculated that they indirectly promote tumorigenesis – at least in part – through the resulting activation of SIRT1.

By contrast, several studies have shown that SIRT1 has also potential tumor suppressor effects. As discussed above, SIRT1 inactivates HIF1 $\alpha$  through deacetylation and so protects against the growth of tumors and vascular formation – prerequisites for tumor progression (Lim et al., 2010). In addition, overexpression of SIRT1 in murine intestines reduces the incidence of cancer and growth in a mouse colon cancer model: SIRT1 was shown to deacetylate  $\beta$ -catenin and inhibit its accumulation in the nucleus, which lead to the hyperactivation of  $\beta$ -catenin and the formation of tumors (Firestein et al., 2008). Another study showed that the SIRT1 activator resveratrol also protects mice that are heterozygous for p53 from cancer (Boily et al.,

2009; Oberdoerffer et al., 2008). Consistent with these results, it was shown that SIRT1 haploinsufficiency facilitates tumorigenesis in these mice by accelerating tumorigenesis (Wang et al., 2008). These data imply that SIRT1 functions as a tumor suppressor in vivo. However, the exact molecular effects of SIRT1 might vary in different tissues and/or cancer types.

#### Roles in neuronal functions and neurodegenerative diseases

Recent accumulating evidence shows that SIRT1 has also crucial roles in neuronal physiology and pathology. One of the most important neuronal functions of SIRT1 is its role in promoting feeding behavior during dietary limited conditions, including calorie restriction (CR) and fasting. Several studies suggest that SIRT1 expression is induced in hypothalamic pro-opiomelanocortin (POMC) expressing neurons, where it regulates various feeding behaviors (Cakir et al., 2009; Ramadori et al., 2010; Satoh et al., 2010). Correspondingly, mice in which *SIRT1* was specifically knocked out in the brain lack the increase of adaptive physical activity in response to CR – a characteristic that is enhanced in mice overexpressing *SIRT1* in their brains (Cohen et al., 2009; Satoh et al., 2010). SIRT1 also controls the central endocrine axes in the hypothalamus and pituitary gland. Mice in which *SIRT1* was specifically knocked out in the brain have lower serum levels of growth hormones (Cohen et al., 2009). SIRT1 also positively regulates the secretion of thyroid-stimulating hormone (TSH) from the pituitary gland by deacetylating phosphatidylinositol 4-phosphate 5-kinase type-1 gamma (PIP5K $\gamma$ ), which has a crucial role in exocytosis of TSH from pituitary cells (Akiyama et al., 2010).

More recently, SIRT1 was found to modulate memory formation and synaptic plasticity (Michan et al., 2010; Gao et al., 2010). Here, SIRT1 promotes CREB expression through repression of the micro RNA 134 (miR134) and induces transcription of brain-derived neurotrophic factor (BDNF), which has crucial roles in normal cognitive function. Indeed, activation of SIRT1 in brain enhances, and its deletion impairs, memory formation and synaptic plasticity in mice (Gao et al., 2010).

Another recent study in mice indicates that SIRT1 is also implicated in Alzheimer's disease (AD) (Donmez et al., 2010). Using an AD mouse model, we have shown that overexpression of *SIRT1* in the brain could prevent the formation of amyloid  $\beta$  (A $\beta$ ) plaques and rescue behavioral deficits. Here, SIRT1 directly activates retinoid acid receptor  $\beta$  (RAR $\beta$ ) through its deacetylation. RAR $\beta$  activation, in turn, promotes transcription of

a disintegrin and metallopeptidase 10 (ADAM10), which encodes for a component of  $\alpha$ -secretase. The resulting increase in  $\alpha$ -secretase activity leads to a reduced processing of toxic amyloid precursor protein (APP) (Donmez et al., 2010). In another AD mice model (mice that overexpress *CDK5 p25*), activation of SIRT1 by genetic or pharmacological means ameliorated neurodegeneration and memory decline (Kim et al., 2007). This study also uncovered a protective role for SIRT1 in amyotrophic lateral sclerosis (ALS) (Kim et al., 2007).

#### SIRT2

SIRT2 resides mainly in the cytoplasm but can also shuttle to the nucleus. SIRT2 can function as a  $\alpha$ -tubulin deacetylase and was suggested to have a role in oligodendroglial differentiation (Li et al., 2007a; North et al., 2003). In the nucleus, SIRT2 acts as a H4K16 deacetylase and controls the cell cycle. MEFs, in which *SIRT2* has been knocked out, accumulate H4K16 acetylation during mitosis and exhibit a delay in S-phase entry (Vaquero et al., 2006). SIRT2 also regulates adipocyte differentiation through FOXO1 deacetylation (Jing et al., 2007). Of particular note, a SIRT2-specific inhibitor can ameliorate  $\alpha$ -synuclein-mediated toxicity in a Parkinson's disease model (Outeiro et al., 2007), but the mechanism underlying this effect is remains unknown. Further investigations are required to determine in greater depth the physiological and pathological functions of SIRT2.

#### Mitochondrial sirtuins SIRT3, SIRT4 and SIRT5

SIRT3, SIRT4 and SIRT5 are found in the mitochondrial matrix because they contain mitochondrion-targeting sequences in their N-termini (Haigis et al., 2006; Lombard et al., 2007; Nakagawa et al., 2009). SIRT3 is the best-characterized mitochondrial sirtuin. It interacts with acetyl-CoA synthetase 2 (AceCS2) and deacetylates lysine 642 in vitro and in vivo (Hallows et al., 2006; Schwer et al., 2006), thereby increasing its acetyl-CoA synthesis activity. Interestingly, the bacterial sirtuin CobB also regulates acetyl-CoA synthetase through its deacetylation, and cytoplasmic AceCS1 is regulated by SIRT1 in mammals (Hallows et al., 2006; Starai et al., 2002). Therefore, this mechanism of AceCS regulation appears to be evolutionary conserved. SIRT3 also deacetylates NDUFA9, a component of the OXPHOS complex I, which is involved in regulating cellular ATP levels (Ahn et al., 2008).

A recent study also revealed a new function of SIRT3 in fatty acid oxidation. Here, SIRT3 deacetylates long-chain acyl CoA



dehydrogenase (LCAD) and upregulates its enzymatic activity during fasting (Hirschey et al., 2010). Moreover, *SIRT3*-knockout mice accumulate higher levels of fatty acid oxidation intermediates and have lower ATP levels during fasting (Hirschey et al., 2010).

In contrast to *SIRT3*, *SIRT4* has only ADP-ribosylation but no deacetylation activity. It has been shown that *SIRT4* can ADP-ribosylate glutamate dehydrogenase (GDH) and control insulin secretion in pancreatic  $\beta$ -cells in response to CR (Haigis et al., 2006). GDH is also deacetylated by *SIRT3*, but the physiological significance of this reaction is unknown (Lombard et al., 2007). *SIRT4* also negatively regulates fatty acid oxidation and this effect is dependent on *SIRT1* (Nasrin et al., 2010).

*SIRT5* is also known to have a deacetylase activity. We have recently reported that *SIRT5* has a role in the regulation of the urea cycle (Nakagawa et al., 2009). In this study, we uncovered that *SIRT5* deacetylates and activates carbamoyl phosphate synthetase 1 (CPS1), an enzyme, which catalyzes the first and rate-limiting step of the urea cycle. *SIRT5*-knockout mice fail to upregulate CPS1 activity and are hyperammonemic during fasting, and similar effects were also observed with mice on a high protein diet or undergoing CR (Nakagawa et al., 2009). Conversely, *SIRT5*-overexpressing mice show increased CPS1 activity and urea production (Ogura et al., 2010). Thus, taken together, these findings support the idea that mitochondrial sirtuins directly control the activity of metabolic enzymes and have crucial roles in the metabolic adaptation to dietary conditions, such as calorie restriction and fasting.

### SIRT6

*SIRT6* is a nuclear sirtuin and has roles that differ from those of *SIRT1*. *SIRT6*-knockout mice exhibit aging-like phenotypes, such as lymphopenia, loss of subcutaneous fat and severe hypoglycemia, which lead to their death by 4–5 weeks (Mostoslavsky et al., 2006; Xiao et al., 2010). MEFs and embryonic stem cells that are deficient in *SIRT6* show genomic instability and impaired base-excision repair (Mostoslavsky et al., 2006). *SIRT6* is also involved in DNA double-strand break repair by regulating C-terminal binding protein (CtBP) and DNA protein kinase (McCord et al., 2009; Kaidi et al., 2010). Biochemically, *SIRT6* was shown to have ADP-ribosyltransferase activity, but recent studies suggest that *SIRT6* has also a deacetylase activity, preferentially acting on histone H3K9 and H3K56 (Liszt et al., 2005; Michishita et al., 2008; Michishita et al., 2009).

*SIRT6* also associates with telomeric chromatin and depletion of *SIRT6* results in premature cellular senescence and telomere dysfunction (Michishita et al., 2008). Similarly to *SIRT1*, *SIRT6* also interacts with the RelA subunit of NF- $\kappa$ B and deacetylates histone H3K9 at NF- $\kappa$ B target gene promoters, which leads to their repression (Kawahara et al., 2009). Disruption of the *SIRT6* gene leads to hyperactivation of NF- $\kappa$ B signaling and is, thus, the likely cause for the premature aging phenotype observed in *SIRT6*-knockout mice, as haploinsufficiency of RelA attenuates the lethality and aging-like phenotypes of *SIRT6*-knockout mice. Another recent paper has revealed that *SIRT6* also selectively binds to the promoter regions of HIF1 $\alpha$  target genes, at which it deacetylates histone H3K9 (Zhong et al., 2010). Here, *SIRT6* functions as a co-repressor of HIF1 $\alpha$  and inhibits the transcription of glycolytic genes. Consistent with this notion, MEFs and mice that are deficient in *SIRT6* exhibit amplified HIF1 $\alpha$  activity and increased glycolysis together with diminished mitochondrial respiration, thus providing a possible explanation for the observed hypoglycemia in *SIRT6*-knockout mice. In addition, a recent report shows that liver-specific deletion of *SIRT6* in mice leads to increased glycolysis, triglyceride synthesis, reduced  $\beta$  oxidation, and fatty liver formation (Kim et al., 2010). Taken together, these data suggest that *SIRT6*, similar to *SIRT1*, also has pivotal roles in metabolism.

### SIRT7

Among the sirtuins, *SIRT7* is the least studied. *SIRT7* has been shown to be a positive regulator of RNA polymerase I transcription (Ford et al., 2006), but the enzymatic activity of *SIRT7* remains undetermined thus far. Recently, *SIRT7*-knockout mice were reported to exhibit various signs of aging-related changes, such as kyphosis, loss of subcutaneous fat and premature death (Vakhrusheva et al., 2008), and they also suffer from degenerative heart hypertrophy. However, *SIRT7*-specific substrates have not been reported yet and additional studies are necessary to reveal the biological roles of *SIRT7*.

### Perspectives

Over the last decade, the study of sirtuins has made remarkable progress and expanded our knowledge regarding aging and aging-related diseases. However, our understanding of sirtuin biology is still far from complete and many important questions remain to be answered. For example, it has been shown that activation of *SIRT1* can slow down phenotypes of aging, such as diabetes and bone loss, but an extension of life span has only been demonstrated in mice

that are fed a high-fat diet. It is possible that this crucially important sirtuin turns out to have opposing roles in aging, which might make it a good target for specific aging diseases, but not for life span extension. Moreover, one or several of the other sirtuins (*SIRT2* to *SIRT7*) might need to be modulated in concert with *SIRT1* to be able to extend life span. What has become clear is that sirtuins are required to exert many of the beneficial aspects of calorie restriction. Most recently, *SIRT3* has been shown essential in CR-mediated protection against aging-related hearing loss (Someya et al., 2010).

Finally, it will be extremely important to determine what happens to the activity of sirtuins during aging. There are hints that their activity declines, which provide further rationales to develop drugs that activate sirtuins to combat aging. Thus, to achieve the goal of a therapeutic intervention of aging, it will be important to fully elucidate the functions of all seven sirtuins and in many different tissues.

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