Cell. Mol. Life Sci. 65 (2008) 4000 – 4018
1420-682X/08/244000-19
DOI 10.1007/s00018-008-8357-y

Cellular and Molecular Life Sciences

Review

Biological and Potential Therapeutic Roles of Sirtuin Deacetylases

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Received 25 June 2008; received after revision 20 August 2008; accepted 29 August 2008
Online First 27 September 2008

Abstract. Sirtuins comprise a unique class of nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylases that target multiple protein substrates to execute diverse biological functions. These enzymes are key regulators of clinically important cellular and organismal processes, including metabolism, cell division and aging. The desire to understand the important determinants of human health and lifespan has resulted in a firestorm of work on the seven mammalian sirtuins in less than a decade. The implication of sirtuins in medically important areas such as diabetes, cancer, cardiovascular dysfunction and neurodegenerative disease has further catapulted them to a prominent status as potential targets for nutritional and therapeutic development. Here, we present a review of published results on sirtuin biology and its relevance to human disease.

Keywords. Sirtuin, deacetylase, longevity, human disease, therapeutics.

Introduction

The biological function of most proteins relies on reversible post-translational modification. Recent years have linked regulation of nearly every cellular signaling pathway to phosphorylation, acetylation, methylation, O-GlcNacylation, and/or ubiquitination of one or many of its contributors. Although crosstalk between post-translational modifications can regulate multiple aspects of a particular biological pathway, a singular modification, when applied to a crucial mediator, can lead to dramatic effects that modify health at the organism level [1]. For this reason, as well as the fact that enzymes are among the most tractable targets for pharmaceutical intervention, disease-related research has placed a great emphasis on the study of post-translational modification cascades.

The post-translational addition of an acetyl moiety to the ε-amino group of a lysine residue, known as protein acetylation, can have varying effects on protein function [2]. The most prominently studied substrates are histones, whose deacetylation typically results in decreased gene expression [2]. Nonetheless, numerous other proteins such as transcription factors, cytoskeletal proteins, metabolic enzymes and other signaling mediators can also be modified by acetylation. Historically, enzymes that perform acetylation have been known as histone acetyltransferases (HATs), whereas enzymes providing the counterbalancing activity are known as histone deacetylases (HDACs). This nomenclature remains in common use, despite the fact that histones are not exclusive substrates for HDAC enzymes [3].

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Enzymes belonging to the HDAC superfamily play critical roles in the regulation of cellular metabolism, and constitute promising drug targets for treatment of a broad range of human diseases. The classical HDACs are grouped into three subfamilies (termed class I, II, and IV), comprised of eleven enzymes that share sequence homology and require Zn^{2+} for deacetylase activity [2]. Although the sirtuins (SIRTs) nominally comprise the class III HDACs, they possess unique NAD^+-dependent enzymatic activities and share no sequence similarity with the classical enzymes [4]. The present review will focus on the class III HDACs, summarizing current knowledge of the biology of the mammalian sirtuins and highlighting their potential utility as therapeutic targets.

Sirtuin family homologs and orthologs

The first known members of the sirtuin family were discovered in yeast. Among these was the nucleolar *S. cerevisiae* protein Sir2p, which was shown to interact with histones and effect transcriptional silencing at telomeres [5–8]. Although early studies showed that overexpression of Sir2p resulted in histone deacetylation [9], this enzymatic activity was not immediately attributed to Sir2p itself. In 1995, a mutation in the gene encoding the Sir2p interactor Sir4p was shown to extend replicative lifespan in *S. cerevisiae* [10], reinforcing an earlier hypotheses that transcriptional control and telomere maintenance are crucial regulators of aging [11]. Further investigation revealed that Sir2p regulates the rate of ribosomal DNA (rDNA) recombination and formation of toxic extrachromosomal rDNA circles (ERCs), which accumulate with replicative age in yeast [12]. Deletion of *SIR2* results in increased ERC levels, thereby reducing replicative lifespan, while overexpression of Sir2p has the expected opposite effect [13].

The discovery that the longevity-enhancing deacetylase activity of Sir2p was dependent on the nutrient NAD^+ sparked interest in a possible relationship with cellular metabolism, especially in light of the previously ascribed benefit of calorie restriction on lifespan [14–16]. Indeed, a 75% reduction in glucose significantly increases the yeast replicative lifespan, and deletion of *SIR2* abrogates this beneficial effect [17]. The intense interest in discovering longevity genes in higher species prompted a search for additional Sir2p homologs and orthologs (Fig. 1). *S. cerevisiae* was found to express five sirtuins: *SIR2* and four homologs termed *HST1–4*. All are implicated in transcriptional silencing at mating type loci and at telomeres [18]. *C. elegans* has four sirtuins [19]; one of these (SIR-2.1) extends lifespan, while limited information exists as to the biological function of the other three [20, 21]. Similarly, increased expression of the well-studied *D. melanogaster* Sir2 has shown a positive effect on fly lifespan, while four other *Drosophila* sirtuins remain largely uncharacterized [20, 22]. Mammals have seven sirtuins, SIRTs1–7 [19, 23], which are described in detail below.

Sirtuin enzymatic activities

The sirtuin-mediated deacetylation reaction involves hydrolysis of one NAD^+ and formation of both nicotinamide and a unique byproduct called *O*-acetyl-ADP-ribose (*O*AADPr) [24]; *O*AADPr is formed by transfer of the removed acetyl group to ADP ribose [25]. Evidence is emerging that *O*AADPr may have a biological function of its own, including delaying cell division [26], gene silencing [27] and regulation of the cationic channel TRPM2 in a manner that could influence cell death [28]. Kinetically, sirtuins bind to the acetylated substrate, resulting in a conformational change and subsequent formation of a ternary complex with NAD^+ [29]. A very detailed mechanism for this reaction is reviewed in [30]. Deacetylation activity has now been demonstrated for six of seven mammalian SIRTs, with evidence of this activity lacking only for SIRT4 [31–37]. Although of lesser-understood biological significance, ADP-ribosyltransferase activity has been demonstrated for all mammalian SIRTs except SIRT5 and SIRT7 [23, 38–41].

Sirtuin enzymatic action depends on steady availability of reduced NAD^+, and the enzyme pyrazinamidase/nicotinamidase 1 (PNC1) is crucial for recycling of NAD^+ in yeast [42]. A protective effect of elevated nicotinamide/nicotinic acid mononucleotide adenylyltransferase (Nmnat1) expression in mouse neurons was attributed to increased NAD^+ biosynthesis and subsequent SIRT1 activation, suggesting an analogous system in mammals [43]. Further studies of this pathway revealed that nicotinamide phosphoribosyltransferase (Nampt) is the rate-limiting enzyme in NAD^+ recycling [44].

It has been suggested recently that increasing sirtuin activities globally by boosting NAD^+ levels could provide one strategy for tapping into the beneficial effects of the SIRTs. However, given that both beneficial and detrimental effects of sirtuin activation can be envisaged (as discussed below), it is difficult to predict whether their manipulation via an upstream cofactor would be successful in achieving only desirable results. Interestingly, the recent description of conditions where increased levels of Nampt may have

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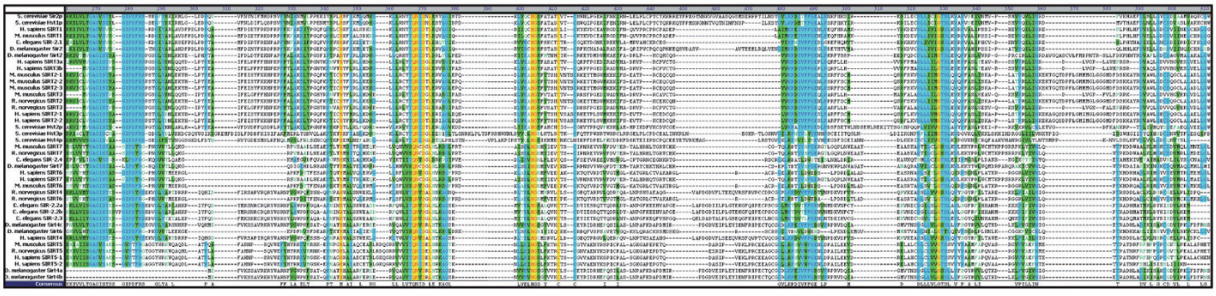

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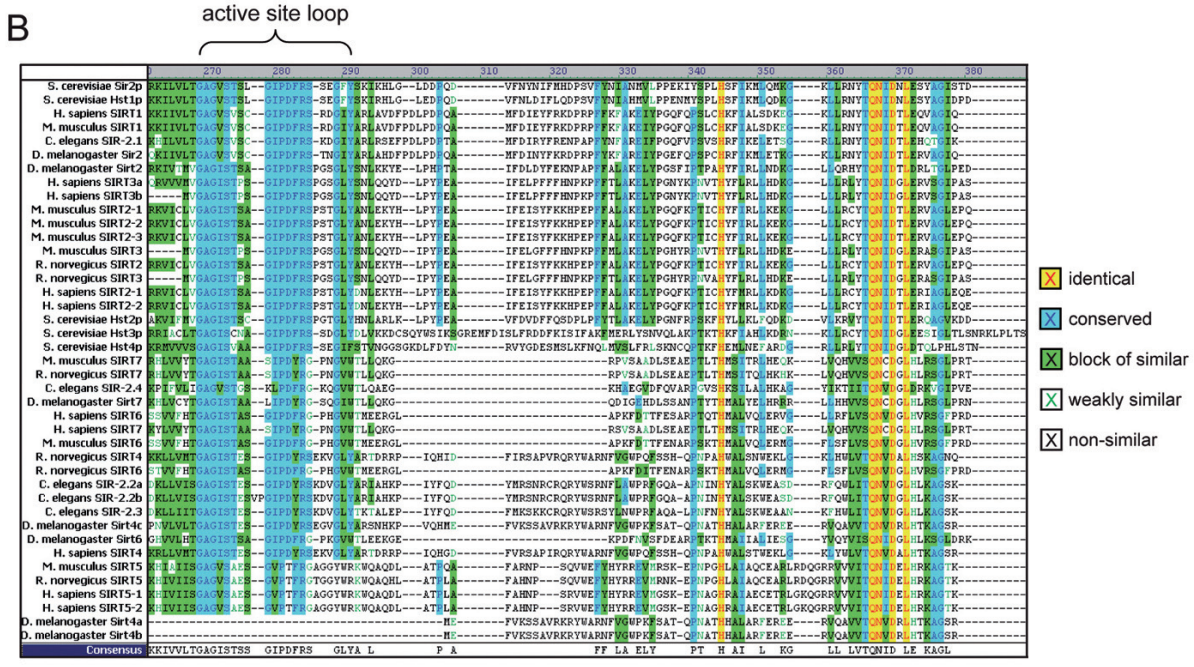

C

Yeast (S. cerevisiae)		Invertebrate (C.elegans)		Invertebrate (D. melanogaster)		Mammalian (H. sapiens)	
Sirtuin	**% homology**	**Sirtuin**	**% homology**	**Sirtuin**	**% homology**	**Sirtuin**	**% homology**
Sir2p	100	SIR-2.1	48	Sir2	46	SIRT1	48
Hst1p	80	SIR-2.2a*	22	Sirt2	42	SIRT2^	40
Hst2p	36	SIR-2.2b*	22	SIRT4a	18	SIRT3^	42
Hst3p	29	SIR-2.3*	22	SIRT4b	18	SIRT4	22
Hst4p	24	SIR-2.4	23	SIRT4c	22	SIRT5^	21
				SIRT6	22	SIRT6	23
				SIRT7	23	SIRT7	23

Figure 1. (*A*) Amino acid sequence alignment of metazoan sirtuins ranked from highest to lowest homology with yeast Sir2p in the conserved sirtuin domain (aa. 255–526). (*B*) Enlarged section of sequence alignment containing the largest active site loop. (*C*) Homology of invertebrate and mammalian sirtuins to yeast Sir2p. Values represent percent amino acid homology. * – hypothetical proteins; ^ – representative of both isoforms.

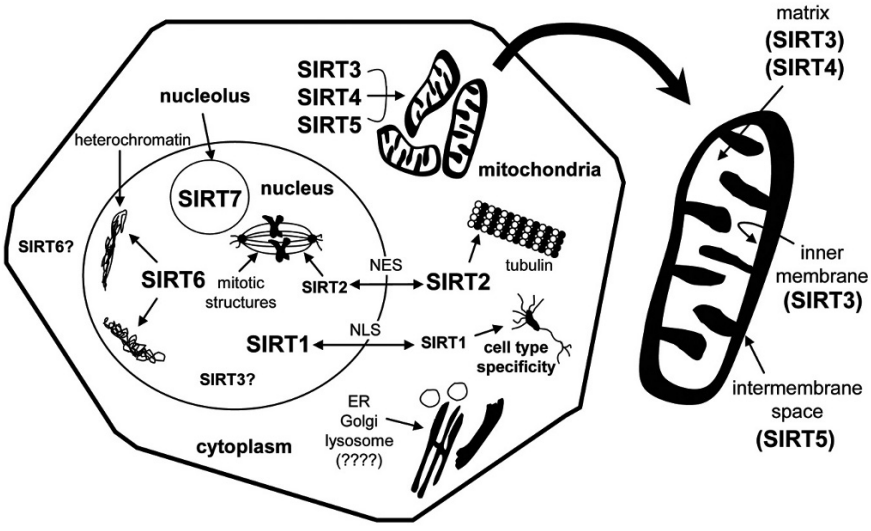

Figure 2. Subcellular localization of mammalian sirtuins.

a negative impact on cellular health reinforces this skepticism [45, 46].

Functional classes of sirtuin substrates

The enzymatic activities of the sirtuins are executed on a variety of substrates with a broad spectrum of cellular functions (Table 1). Deacetylation of their hallmark substrates, histones, alters gene expression via silencing of chromatin to maintain energy homeostasis under glucose deprivation conditions [47]. However, gene regulatory mechanisms of the SIRTs are not limited to histone deacetylation, but also extend to various transcription factor and co-regulator substrates, whose activities can be either augmented or repressed. These targets include multiple forkhead box, class O (FOXO) transcription factors [48–50] that regulate metabolic, cell cycle and cell death-related pathways [51, 52]. Other prominent cell cycle and cell death-related substrates include the signal transduction mediator NF-κB [53] and the tumor suppressor p53 [32, 33]. Additional actions of sirtuins through deacetylation of p53, histones, and Ku70 include regulation of complexes involved in DNA repair and DNA damage-induced apoptosis [54, 55]. Regulation of endothelial nitric oxide synthase (eNOS) [56], and transcriptional regulatory proteins such as myocyte enhancer factor 2 (MEF2) [57] and the human immunodeficiency virus (HIV) transactivator of transcription (Tat) protein [58], suggest additional roles for sirtuins in other important tissue- and disease-specific functions.

Critical regulators of metabolism comprise another major subcategory of sirtuin substrates. These include the fatty acid synthesis enzymes acetyl-coenzyme A synthases 1 and 2 [59], and the PGC-1α [41, 60] and LXR [61] transcriptional co-regulators, all of which play central roles in cellular lipid and carbohydrate metabolism. Regulation of PGC-1α function is also an important determinant of mitochondrial energetics and biogenesis [41, 60, 62].

Autophagy-related proteins Atg5, Atg7, and Atg8 [63] comprise a new category of sirtuin substrates. Regulation of autophagy may have important implications for protein clearance as well as aging or cell death-related pathways.

The structural protein alpha-tubulin is an important substrate for the cytoskeletal and cell differentiation effects of SIRT2 and its interacting protein HDAC6 [37]. Histone and/or additional unknown substrates may underlie SIRT2-dependent regulation of cytokinesis [64].

Non-substrate sirtuin interactors have also been shown to serve key functions in SIRT-dependent biological effects. For example, the binding of SIR-2.1 to the mediator 14-3-3 is required for activation of the forkhead family transcription factor DAF-16 and extension of lifespan in *C. elegans* [65]. Another example is SIRT1's inhibitory interaction with the silencing mediator for retinoid and thyroid hormone receptor (SMRT) and the nuclear receptor corepressor (NCoR), which are essential for peroxisome proliferator-activated receptor γ (PPARγ)-mediated gene expression and adipogenesis [66].

As additional substrates and interactors of sirtuins become known, the mechanisms behind the widespread and profound effects of these proteins at the organism level will become increasingly clear.

Table 1. Summary of known sirtuin enzymatic activities, substrates and biological functions. Yeast Sir2p substrate references include: [181–183]. C. elegans SIR-2.1 references include: [20,21]. Drosophila Sir2 substrate references include: [184]. SIRT1 substrate references include: [32, 33, 41, 48–50, 53, 56–61, 63, 76, 77, 136, 139, 141, 185–191]. SIRT2 substrate references include: [37, 91, 100, 143, 192]. SIRT3 substrate references include: [59, 93, 192]. SIRT4 substrate references include: [31, 39]. SIRT5 substrate references include: [37, 193, 194]. SIRT6 substrate references include: [36]. SIRT7 substrate references include: [35].

Sirtuin	Activity	Known Substrate(s)	Biological Function(s)
Yeast Sir2p	deacetylase ADP-ribosyltransferase	histone H3 (K9,K14,K56) histone H4 (K12,K16)	cellular metabolism regulation maintenance of genome stability aging
C. elegans SIR-2.1	none described interaction with 14-3-3	?	neuroprotection repression of ER stress genes aging
Drosophila Sir2	deacetylase	histone H2B (K5,K20) histone H3 (K9,K14,K18,K23) histone H4 (K5,K8,K12,K16)	aging
Human SIRT1	deacetylase ADP-ribosyltransferase	AceCS1, Atg5, Atg7, Atg8, BCL6, β-catenin, FOXO1, FOXO3a, FOXO4, HES-1, HEY-1, HIC1, histone H1 (K26), histone H3 (K9,K14), histone H4 (K16), H2A.z, HIV Tat protein, Ku70, LXR, MEF2 MyoD, NF-κB, p300/CBP, p53, p73, PCAF, PGC-1α, Rb, TAF_I68	cellular metabolism regulation (glucose homeostasis) (augment insulin secretion by glucose) (increase skeletal muscle mito. function) neuroprotection anti-inflammatory cardioprotection anti-/pro-cancer? stimulates HIV transcription anti-oxidant regulation of autophagy cell survival/aging
Human SIRT2	deacetylase ADP-ribosyltransferase	α-tubulin FOXO1, FOXO3a histone H3 (K14) histone H4 (K16) p53	mitotic exit from cell cycle early mitotic checkpoint tumor suppression (glioma) myelinogenesis adipocyte differentiation regulation of cellular stress inhibits cell adhesion and migration inhibits neurite outgrowth inhibits growth cone collapse
Human SIRT3	deacetylase ADP-ribosyltransferase	AceCS2 GDH histone H4 (K16)	mitochondrial lysine deacetylation mitochondrial NAD(+) salvage thermogenesis cellular metabolism regulation apoptosis cell survival/aging
Human SIRT4	ADP-ribosyltransferase	GDH BSA, histones?	regulation of insulin secretion mitochondrial NAD(+) salvage
Human SIRT5	deacetylase	cytochrome c, histone H4, p53	unknown (acceleration of neuronal aging?)
Human SIRT6	deacetylase ADP-ribosyltransferase	histone H3 (K9)	regulation of metabolism telomere maintenance cell survival/aging base excision repair?
Human SIRT7	deacetylase	p53	RNA polymerase I activation cardiac stress resistance cell survival/aging

Cell biology of the mammalian SIRTs

An obvious complexity in the roles of the mammalian SIRTs is evidenced by their heterogenous subcellular compartmentalizations (Fig. 2). The current consensus suggests that mammalian sirtuins consist of two nuclear (SIRT1, 6), one cytoplasmic (SIRT2), three mitochondrial (SIRT3, 4, and 5) and one nucleolar (SIRT7) protein [67]. However, these behaviors are still based on a relatively limited number of studies, conditions and cell types, suggesting that classification by these localizations may be premature. Although SIRT1 is largely nuclear and SIRT2 cytoplasmic, both have been demonstrated to undergo nucleo-cytoplas-

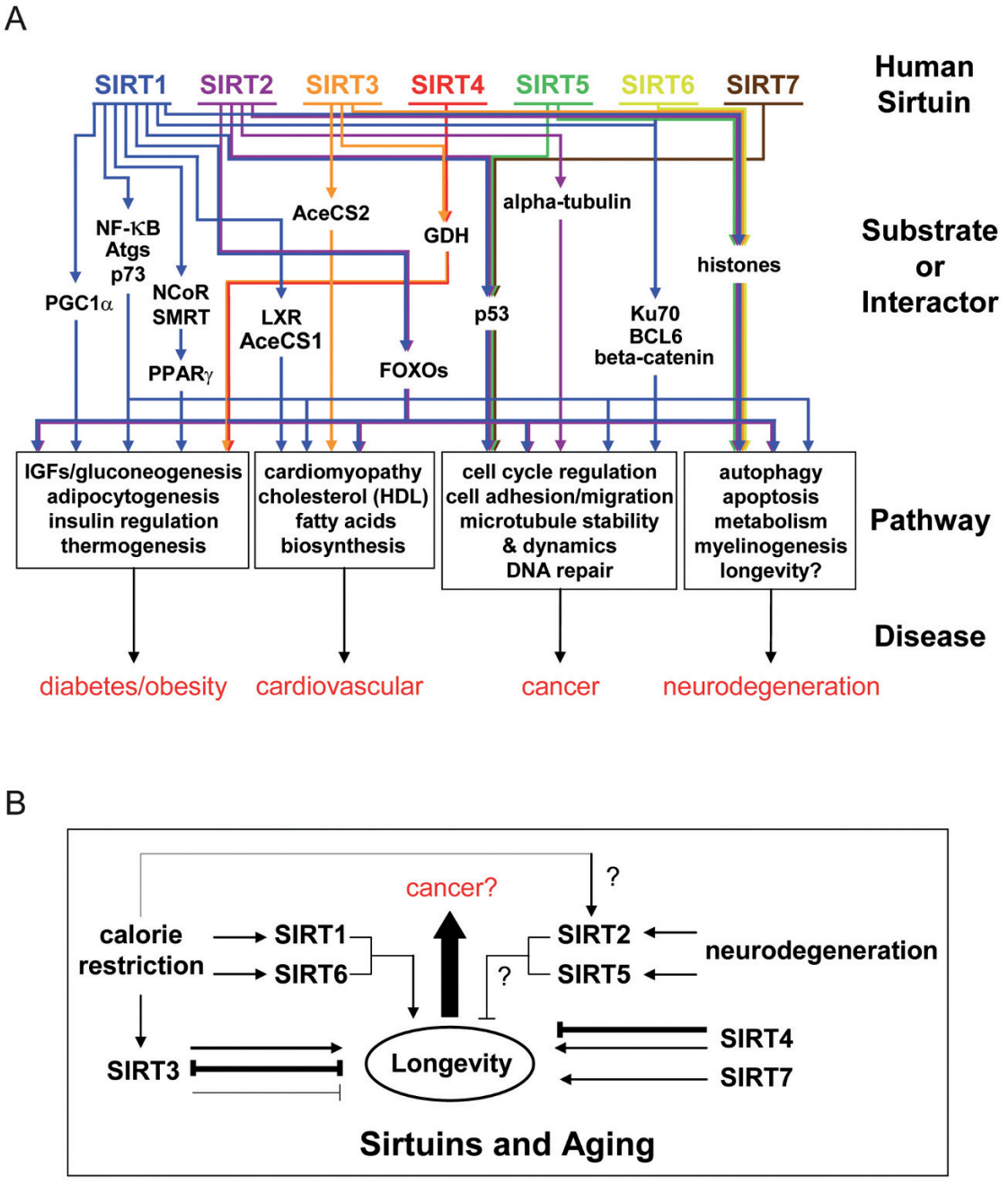

Figure 3. Impact of sirtuins on biological and pathological pathways. (*A*) A map of currently identified sirtuin substrates with corresponding diseases where alteration of their activity may demonstrate an effect. (*B*) Present knowledge of mammalian sirtuin influence on aging. Line thickness represents an influence with greater supporting evidence with respect to corresponding thinner counterparts. Arrow ends represent enhancement, blunted ends represent repression. Double blunted ends indicate no effect on longevity.

mic shuttling [68]. Interestingly, unlike normally dividing cells, postmitotic neurons appear to have considerable levels of nuclear SIRT2 [69, 70, A. Kazantsev, B. Woodman, G. Bates unpublished observations]. The mitochondrial SIRTs appear to be localized in distinct subcompartments, which may imply non-redundant, organelle-specific functions [71]. Human SIRT3 has been localized to the mitochondrial matrix [72], while murine SIRT3 has been shown to reside on the mitochondrial inner membrane [40, 71], or in the matrix [73]. Human and murine SIRT3 have also been localized to the nucleus under certain conditions [71, 74]. SIRT7 is the only mammalian sirtuin that is localized to the nucleolus, as is the yeast Sir2p [75].

Table 2. Summary of transgenic and knockout mouse phenotypes for mammalian sirtuins. References include: SIRT1 KO [196, 197], SIRT1 Tg [82], SIRT1 gut villi-specific [195], heart-specific [150], beta cell-specific [84], neuron-specific [78], SIRT3 KO [73], SIRT4 KO [39, 73], SIRT5 KO [73], SIRT6 KO [107], SIRT7 KO [35].

Sirtuin	Knockout (KO) or Transgenic (Tg)	Phenotype
SIRT1	KO	- reduced size, sterile, shorter snout - delayed eyelid opening - developmental defects of retina and heart - frequent prenatal, early postnatal death - sporadic exencephaly - frequent lung infection, pancreatic defects - no reduced mean telomere length - p53 hyperacetylation - loss of calorie restriction-induced increase in physical activity
	Tg	- lean, increased metabolic activity - reduced blood cholesterol, adipokines, insulin, fasted glucose - improved rotarod performance - delayed reproduction - no longevity data reported yet
	tissue-specific expression	- suppression of intestinal tumorigenesis (gut villi-specific) - cardiac protection via induction of myosin heavy chain α (heart-specific) - improved glucose tolerance - enhanced insulin secretion by glucose (beta cell-specific – BESTO) - increased α-secretase activity (neuron-specific)
SIRT2	KO	- forthcoming unpublished (H.L. Cheng and F.W. Alt)
SIRT3	KO	- viable, fertile (reported at one year) - no gross phenotypic abnormalities - mitochondrial hyperacetylation - metabolically unremarkable (fed or fasted) - normal adaptive thermogenesis
SIRT4	KO	- viable, fertile - no gross phenotypic abnormalities - increased pancreatic glutamate dehydrogenase activity - opposite insulin regulatory profile from calorie restriction - no mitochondrial hyperacetylation
SIRT5	KO	- viable, fertile - no gross phenotypic abnormalities - increased pancreatic glutamate dehydrogenase activity - opposite insulin regulatory profile from calorie restriction - no mitochondrial hyperacetylation
SIRT6	KO	- reduced size - lymphopenia, fat loss, lordokyphosis - severe metabolic defects - premature death
SIRT7	KO	- decreased mean and median lifespan - heart hypertrophy, inflammatory cardiomyopathy

Sirtuin effects at the organism level and implications for human disease

The number of proteins that are regulated by acetylation is vast [4]. Given that mammalian sirtuins are localized in several cellular compartments, the potential number of substrates and subsequently affected pathways is also considerable. To date, much of our knowledge of mammalian SIRT functions is derived from the phenotypes of genetically modified rodents (Table 2). These experiments, in conjunction with functional experiments in cultured cells, have demonstrated that mammalian sirtuins may protect (or harm) cells through their regulation of multiple pathways including cell cycle, cell death, oxidative stress and metabolism (Fig. 3).

Metabolic pathways. The initial link between calorie restriction and sirtuin activation hinted at their prominent role in regulating mammalian metabolism

[76]. The influence of sirtuins on mammalian longevity is still not fully understood, yet their ability to regulate metabolism is well defined.

SIRT1 is upregulated and activated in many tissues after fasting or calorie restriction in rodents [76–78], and increased SIRT1 protein stabilization appears to contribute to diet-related increases in SIRT1 activity [79]. Dietary manipulations such as calorie restriction appear to have widespread effects on metabolism with primary sites of action in the liver, pancreas, muscle and adipose tissue.

Deacetylation of PGC-1α by SIRT1 modulates lipid and cholesterol homeostasis, initiates gluconeogenic gene induction, increases hepatic glucose output [80], and regulates mitochondrial fatty acid oxidation in skeletal muscle [81]. In addition, SIRT1-dependent modulation of PGC-1α stimulates mitochondrial biogenesis and induction of oxidative phosphorylation genes in muscle tissue [62]. Liver X receptors (LXR) are also positively regulated by SIRT1 deacetylation, thereby leading to the induction of lipid metabolism genes, including those that regulate HDL biogenesis [61].

Pre-longevity studies of mice in which SIRT1 is mildly overexpressed (two to three times endogenous levels), reveal decreased blood cholesterol, insulin, and fasting glucose levels. These mice are also leaner and more metabolically active than wild-type [82]. The powerful effects of SIRT1 on metabolism were confirmed when potent small molecule activators of SIRT1 were shown to ameliorate symptomatic conditions in diet- and genetically-induced obese mice, as well as in an obese rat model of diabetes [83]. The profound effects on insulin sensitivity and whole body glucose homeostasis suggest that SIRT1 activators are excellent candidates for therapeutic intervention in Type 2 diabetes.

Targeted overexpression of SIRT1 in the pancreatic beta cells of mice increases glucose-triggered insulin secretion and improves glucose tolerance, thereby reversing age-related decreases in insulin sensitivity [84]. These studies suggest that the observed improvement in beta cell function may be due to SIRT1-mediated repression of uncoupling protein 2 (UCP2), a mitochondrial protein that affects ATP production [85]. Further, SIR-2.1 of *C. elegans* acts upstream of the forkhead family transcription factor DAF-16, which regulates the insulin pathway to promote health and longevity [21, 86]. SIRT1-dependent regulation of insulin and insulin-like growth factor 1 (IGF-1) signaling also appears to involve mammalian FOXOs [87]. In addition to coordinately regulating beta cell function, SIRT1 and FOXO1 also appear to function together in regulating adipocyte metabolism [88], via the induction of the specialized hormone adiponectin [89, 90]. SIRT1 function in adipocytes also involves repression of PPARγ, via interaction with the cofactors NCoR and SMRT, thereby repressing adipogenesis and reducing lipolysis and fatty acid mobilization [66].

A few reports have linked SIRT2 activity to regulation of metabolism. Knockdown of SIRT2 in adipocytes causes upregulation of CCAAT box enhancer binding protein α (C/EBPα) and PPARγ, and promotes adipogenesis through a FOXO1-mediated effect [91]. SIRT2 has also been shown to be upregulated in diabetic myocytes [92].

SIRT3 was first linked to metabolism when it was discovered that this enzyme could deacetylate and enhance activity of acetyl-CoA synthase 2 [93]. Acetyl-CoA is involved in numerous intermediary metabolic pathways, implicating SIRT3 in the regulation of carbohydrate, amino acid and fat metabolism, and in the tricarboxylic acid (TCA) cycle [59]. A recent study demonstrated *in vivo* deacetylation of mitochondrial glutamate dehydrogenase (GDH) by SIRT3 and further suggested that SIRT3 may regulate global mitochondrial lysine acetylation, implying a role for this sirtuin in an even broader range of metabolic processes [73]. Furthermore, like SIRT1, SIRT3 is upregulated following calorie restriction, which suggests the triggering of compensatory mechanisms through these pathways in times of limited food intake [40].

SIRT4 null-mutant mice revealed that SIRT4 catalyzes the ADP-ribosylation of GDH [39]. This reaction leads to GDH inactivation and reduces both ATP production and insulin secretion in response to glucose. Consequently, SIRT4 knockout mice exhibit an upregulation of the insulin response in a manner that mimics calorie-restricted mice. However, no mitochondrial hyperacetylation is associated with SIRT4 deletion [39, 73]. SIRT4 also interacts with the insulin degrading enzyme and two ADP/ATP carrier proteins [31].

Targeting sirtuins implicated in the regulation of glucose homeostasis and adipogenesis may be beneficial for the development of treatments for diabetes and obesity, respectively. In addition, targeting sirtuin-dependent regulation of cholesterol biosynthesis and transport may potentially lead to effective therapies for hyperlipidemias and cardiovascular diseases (see also below).

Aging. Medical and cosmetically utilizable anti-aging effects of mammalian sirtuins are currently being sought with great enthusiasm. There are nonetheless fewer data to support such an effect than might have originally been anticipated based on sirtuin manipulations in lower organisms. In addition to regulating

metabolic activities (as described above), anti-oxidant and lysosomal clearance mechanisms have been invoked to account for potential anti-aging activities. There have been conflicting reports as to the effect of SIRT1 overexpression on cellular senescence. For example, it has been shown to both retard senescence [94] and have no effect [67] in diploid human fibroblasts. Decreased levels of SIRT1 correlate with withdrawal from the cell cycle and reduced longevity of cultured cells and mouse tissues (thymus, testis), whereas expression levels are maintained in long-lived growth hormone knockout mice [95]. In surprisingly strong support of an anti-aging activity, strict control of maternal diet during weaning of infant rats was reported to yield elevated SIRT1 levels and extend lifespan in these offspring [96]. The direct influence of elevated SIRT1 expression on rodent lifespan has not yet been demonstrated, although a premortem battery of tests in such mice was promising [82].

A link between autophagy and longevity has been described for years [97]. Recently, additional direct connections to both calorie restriction [98] and SIRT1 [63] have emerged. Overexpression of SIRT1 stimulates basal levels of autophagy, while calorie restriction cannot activate autophagy in SIRT1 null mice. SIRT1 appears to form a complex with several autophagy components (Atgs), whereby their deacetylation triggers activation of the catabolic process [63]. However, there is also evidence that sirtuin-independent rapamycin (TOR) signaling is the true mediator of calorie restriction-related lifespan extension [99]. Other potential mechanisms for regulation of cell survival by SIRT1 include improved resistance to cell stress and anti-apoptotic functions as mediated through the previously described substrates FOXO4 [50], p53 [32, 33], and Ku70 [54, 76].

As for SIRT1, a protective function for SIRT2 against oxidative stress has been described. Upregulation of SIRT2 after treatment with hydrogen peroxide correlates with deacetylation of FOXO3a and increased transcription of protective genes such as MnSOD and Bim [100]. However, the efficacy of SIRT2 inhibitors in diseases of aging (neurodegenerative) has suggested a new "pro-aging" function for this protein [101]. Interestingly, a similar function may potentially be attributed to SIRT5 [102]. The biological roles of SIRT2 and SIRT5 in neurons are discussed in greater detail below.

Prior to its characterization as a mitochondrial NAD-dependent deacetylase, SIRT3 was linked to aging. A VNTR repeat polymorphism with enhancer activity was found consistently in the SIRT3 genes of males who surpassed 90 years of age [103]. This is particularly interesting given that two similar studies failed to associate SNPs in SIRT1 with long lifespan [104, 105].

In contrast, SIRT4 expression appears to promote aging from a metabolic standpoint. Its antagonism of insulin secretion is the opposite effect of both SIRT1 overexpression and calorie restriction [39]. However, the characterization of SIRT4 as 'negative' with regard to cellular health and longevity was recently challenged by evidence that SIRT4 (along with SIRT3) is required *in vivo* for protection against cell death, due to its role in the mitochondrial NAD^+ salvage pathway [106].

SIRT6 has been most recently described as a critical factor in mammalian aging, as its absence creates a remarkable phenotype in rodents that includes metabolic defects, lymphopenia, loss of subcutaneous fat, and premature death at approximately four weeks [107]. A compelling follow-up study has now demonstrated that knockdown of SIRT6 in cells results in markedly premature senescence and that SIRT6 acts to prevent dysfunction of telomeres through deacetylation of histone 3 during S phase [36]. Prior to these studies, SIRT6 was thought to have only ADP-ribosyltransferase activity [38]. Hypoacetylated telomeric chromatin adopts a specialized state that permits interaction with factors including WRN, which are crucial to normal telomere function. A link between SIRT6 and the protein governing Werner's syndrome is not surprising, given the premature aging phenotype of SIRT6 knockout mice. In addition, like SIRTs 1, 2 and 3, cellular SIRT6 levels are increased in calorie restriction conditions, although for SIRT6 this increase appears to result from protein stabilization rather than augmented gene expression [108].

SIRT7 exhibits nucleolar localization and association with active rDNA genes; common features with yeast Sir2p [109]. SIRT7 knockout mice exhibit reduced mean and maximum lifespan, implicating it as a pro-survival sirtuin [35]. Its depletion also halts cellular proliferation and triggers apoptosis via hyperacetylated p53. This increase in p53 acetylation suggests that SIRT7 may in fact possess NAD^+-dependent deacetylase activity, although such activity has not yet been demonstrated directly [35].

The NAD^+ dependence for sirtuin deacetylase activity has led to speculation that efficient regulation of NAD^+ availability could have more profound effects on longevity than overexpression of a single sirtuin [110]. Nampt is upregulated with calorie restriction and stress, which may explain increased sirtuin enzymatic activity under these conditions [106]. In addition, aged human cells have a marked decline in Nampt levels [111]. That Nampt expression can regulate insulin secretion [112], protect cells against

genotoxic stress [106] and delay senescence in human cells [111], suggests that transgenic Nampt mice may play a critical role in our understanding of mammalian sirtuins' effect on longevity as a whole.

Neurodegenerative diseases. The influence of sirtuins on aging immediately aroused interest in their ability to combat neurodegenerative diseases. This interest was heightened by studies describing reduced synaptic plasticity and cognition, in correlation with decreased sirtuin expression, in rodents fed a diet that was high in sugar and saturated fat [113].

Both calorie restriction and small-molecule sirtuin activators have demonstrated protective effects in rodent models of neurodegenerative disease. Resveratrol, the first identified SIRT1 activator, has proven effective against excitotoxicity [114], ischemia-reperfusion [115], chemically induced cognitive impairment [116], inflammation-related neurotoxicity stimulated by activated microglia [117] or expression of toxic, aggregate-prone proteins [118]. Accordingly, calorie restriction has shown protective effects in several studies, including a striking improvement in locomotor activity and striatal dopamine preservation in an MPTP-treated primate model of Parkinson's disease [119]. Although the extent to which each of the sirtuins contributes to the beneficial effects of resveratrol and calorie restriction remains unknown, there is considerable evidence that SIRT1 plays an important role [20, 53, 62, 66, 87, 94, 120–124].

The first major study to implicate SIRT1 directly showed that the protection against transection-induced axonal degeneration exhibited by Wallerian degeneration slow Wld(S) mice is due to augmented SIRT1 activation in these animals [43]. More recent studies demonstrated that SIRT1 is protective *in vitro* against the cytotoxic effects of a mutant superoxide dismutase 1 (SOD1) that causes familial amyotrophic lateral sclerosis [123]. Increased *sir-2.1* dosage also rescued early neuronal dysfunction in a *C. elegans* model of Huntington's disease [124]. In addition, lentiviral-mediated overexpression of SIRT1 significantly reduced hippocampal degeneration in a transgenic mouse model of Alzheimer's disease [123]. Potential mechanisms of neuroprotection in this model include inhibition of p53-regulated cell death pathways and increased alpha-secretase activity, which promotes production of non-toxic beta amyloid species [78, 123].

There is also recent evidence for a role of SIRT1 in neurogenesis, where the redox state of surrounding tissue determines the fate of neural progenitors. SIRT1 is activated under oxidative conditions, causing progenitor cells to differentiate into astrocytes, whereas under reducing conditions they are favored to become neurons [125]. SIRT1-mediated inhibition of the pro-neuronal factor, Mash1, promotes proliferation of astrocytes, but not neurons, in response to various oxidizing CNS insults, revealing a conundrum of SIRT1 activation/inhibition during times of neuronal disease [125].

Perhaps surprisingly, inhibition of sirtuins has also shown neuroprotective effects in some systems. The sirtuin inhibitor nicotinamide protects neurons against anoxic injury [126] and can preserve axonal integrity in colchicine-treated Wld(S) mice [127]. Accordingly, both genetic and chemical inhibition of SIRT2 protect cultured primary neurons against alpha synuclein-mediated toxicity [101], and recent work suggests a similar affect in an *in vitro* model of Huntington's disease [R. Luthi-Carter, O. Gokce, D. Taylor, H. Runne, A. Kazantsev unpublished observations]. Given the interaction between SIRT2 and HDAC6, these results are concordant with an earlier study demonstrating the benefits of trichostatin A against the toxicity of mutant huntingtin [128], and non-specific HDAC inhibitors have also shown neuroprotection in a *Drosophila* model of Huntington's disease [129]. Further, overexpression of SIRT2 causes inhibition of neurite outgrowth and growth cone collapse [69] and blocks the resistance of Wld(S) mice to axonal degeneration [127]. Additional experiments utilizing SIRT2 knockdown or knockout will be necessary to assess its specific role as a target for neuroprotection [130] and to understand why both inhibition and activation of sirtuins can provide a similar outcome [131]

High level expression in oligodendrocytes may also implicate SIRT2 in diseases of myelination, in which deacetylation of tubulin has been shown to prevent oligodendrocyte differentiation and to affect myelin basic protein expression [132]. SIRT2 is virtually absent in the myelin of a mouse model for hereditary spastic paraplegia (SPG-2), which is deficient in proteolipid protein (PLP)/DM20, the factor required for SIRT2 transport into myelin [133].

Until recently, expression of SIRT2 in the central nervous system was considered to be restricted to myelinating cells [132]. However, recent studies have demonstrated a neuronal compartment of SIRT2 expression [69, 70, A. Kazantsev, B. Woodman, G. Bates unpublished observations], and cell-type specific gene expression studies reveal detectable levels of SIRT2 mRNA in neurons (and astrocytes), despite confirming higher levels in oligodendrocytes [A. Kuhn, R. Luthi-Carter unpublished observations].

Although little is known about SIRT5 relative to the other sirtuins, a prominent brain function for SIRT5 is suggested by the discovery that it is the most consistently upregulated gene, even pre-phenotypi-

cally, in mice lacking the serotonin1B receptor. These mice are characterized by motor dysfunction, early markers of brain aging, and reduced longevity [102]. Expression of SIRT6 is very high in mouse brain [38], but at present little is known regarding its function or cell-type distribution. Similarly, the potential function of SIRT3 and SIRT4 in neurons is unknown. SIRT7 expression appears to be low in brain [109].

Cell division & cancer. Given the ability of sirtuins to influence cellular lifespan and cell cycle regulation, it is not surprising that there is considerable interest in their carcinogenic potential. In fact, despite the excitement regarding the potential role of sirtuins in augmenting mammalian health and longevity, even greater efforts been made to understand their relationships with cancer.

SIRT1 levels are markedly elevated in both mouse and human prostate cancer [134], but this may be a compensatory effect, since SIRT1 can also act as a co-repressor of the androgen receptor and thereby enhance the benefits of androgen antagonist treatment [135]. The tumor suppressor hypermethylated in cancer 1 (HIC1) has transcriptional repressor activity that is enhanced through its deacetylation by SIRT1 [136].

Conversely, the fact that the key tumor suppressor p53 is a major target of its deacetylase activity implies a pro-carcinogenic function for SIRT1. Most recently, the protein deleted in breast cancer (DBC) was shown to be an endogenous inhibitor of SIRT1 thereby promoting hyperacetylation/hyperactivation of p53 [137]. Deacetylation of the transcriptional repressor BCL6 by SIRT1 promotes the pathogenesis of B-cell lymphomas [138], which is therapeutically remedied by the SIRT1 inhibitor cambinol [139]. Antisense oligonucleotides directed against SIRT1 induce apoptosis in lung cells, suggesting their therapeutic use in lung cancer [140]. The retinoblastoma tumor suppressor gene can also be deacetylated and inactivated by SIRT1 [141].

Tubulin deacetylation is the most frequently reported function of mammalian SIRT2 [37]. A Crm-dependent nuclear export signal maintains the majority of the protein in the cytoplasm where it interacts with HDAC6 to regulate tubulin cytoskeletal structure [68]. SIRT2 also plays a prominent role in mitosis, where it regulates mitotic exit from the cell cycle [64] via association with the centrosome, mitotic spindle and midbody at different stages of the process [68]. SIRT2 is dramatically downregulated in human gliomas [142], and ectopic overexpression of SIRT2 disrupts the tubulin network in cultured glioma cells, which reduces the number of stable clones, suggesting a function as a tumor suppressor gene [142]. Conversely, others have reported p53 deacetylation and inactivation by SIRT2 after interaction with 14-3-3 [143]. Given its ability to modulate the cell cycle, SIRT2 is increasingly being examined as a target for anti-cancer drugs [144].

Both SIRT3 and SIRT7 expression are increased in node-positive breast cancer [145] and SIRT7 is also overexpressed in thyroid carcinoma cell lines and tissue, where it was originally identified as a cytoplasmic protein called SIRT8 [146]. Depletion of SIRT7 *in vitro* can halt cell proliferation and trigger apoptosis [35, 109]. The participation of SIRT3 has also been implicated in basal apoptotic pathways, albeit in a less prominent way than SIRT1 [147]. SIRT6 has been shown to interact with a GCIP, a possible tumor suppressor [148]. SIRT4 is consistently underexpressed in various acute myeloid leukemia cells [149].

Heart diseases. An abundance of literature supports a protective effect of sirtuins on heart tissue, particularly in prevention of cardiac hypertrophy and subsequent heart failure [35, 150]. In addition, SIRT1 exerts a protective effect on endothelial cells (via FOXO1 deacetylation) [151] and may regulate vasodilation [56, 152] and promote vascular health. The fact that SIRT1 is upregulated with exercise in aged rats provides another link between cardiopulmonary health and physical activity [153]. Interestingly, in transgenic mice, high levels (12.5-fold) of SIRT1 actually increase oxidative stress and stimulate apoptosis leading to cardiomyopathy, whereas low to moderate levels provide stress resistance and reduce cell death [150].

As mentioned earlier, SIRT7 knockout mice exhibit reduced lifespan and hyperacetylated p53 that stimulates extensive apoptosis. The major defects described in these animals are cardiac hypertrophy and inflammatory cardiomyopathy due to extensive fibrosis, although it appears that the authors did not extensively characterize other tissues [35]. Sirtuin effects on lipid and sterol metabolism (see Metabolism section) are also pertinent targets for preserving cardiovascular health.

HIV. The HIV Tat protein has been identified as a substrate for SIRT1 deacetylation, thereby boosting transactivation of the HIV promoter [58]. Tat is required for efficient HIV replication [154]. More recently, the interaction between Tat and SIRT1 was described to prevent SIRT1 from deacetylating and inactivating NFκB, leading to T-cell hyperactivation in HIV-infected individuals [155]. Further work should clarify whether SIRT1 inhibitors or activators may have efficacy as HIV therapeutics.

Other diseases. Smokers with chronic obstructive pulmonary disease have decreased SIRT1 expression in their lungs, which results in excessive inflammation related to hyperacetylation of NFκB [156]. Accordingly, resveratrol has shown vasoprotective effects in smokers via a SIRT1-mediated mechanism [121]. Reduced inflammation due to NFκB results from SIRT1 deacetylation of the RelA/p65 subunit [53]. An anti-apoptotic effect of SIRT1 in kidney cells may also imply some protection against nephritic diseases [157]. Upregulation of SIRT1 in kidney cells exposed to hydrogen peroxide leads to activation of FOXO3a and subsequent induction of protective levels of catalase [158].

Discovery and development of sirtuin ligands

The implication of the roles for sirtuins in so many human disorders has precipitated intensive interest in small molecule ligands as potential therapeutics. For this reason, an abundance of research has focused on developing pharmacological inhibitors and activators of sirtuins. A high throughput screen using a fluorescent-based sirtuin enzymatic assay yielded a breakthrough discovery, via identification of the natural product resveratrol (along with less potent polyphenols) as a SIRT1 activator [122].

Resveratrol is the hallmark activator of SIRT1 [122]. Originally identified through recognition of the French paradox (a phenomenon where individuals with high-fat diets have low incidence of cardiovascular disease due to regular consumption of red wine) [159], resveratrol has demonstrated effectiveness in models of cardiovascular, metabolic, inflammatory and neurodegenerative diseases, and has also shown chemopreventative activity [120]. One of the earliest and most striking studies revealed anti-cancer effects of resveratrol at each of the three major stages of carcinogenesis [160], although this seems contradictory to the role of SIRT1 in enhancing cellular longevity and its negative implication in many cancers (see above section *Cell division & Cancer).* However, the protective effects observed in the other disease types have all been attributed to SIRT1 activation and in some cases have been corroborated by direct SIRT1 expression. For example, resveratrol treatment improves the health and longevity of mice on a high-calorie diet [161], and many of the described improvements were demonstrated in both SIRT1 transgenic mice [82], as well as in mice treated with potent SIRT1 activating compounds [83]. Resveratrol has also been shown to directly affect aging in non-mammalian organisms [20,122] and to retard cellular senescence in human diploid fibroblasts [94]; however, it does not extend lifespan of normal mice given the compound in their food beginning at midlife (despite their comparatively improved health during later life) [162].

Polyphenols such as resveratrol have apparent liabilities associated with their structures, including extremely poor compound stability *in vivo.* Further, the emerging role of resveratrol in SIRT1-independent activities (for example, activation of Egr-1 [163] and SIRT2 [70]), the questions regarding its potency as an activator [164], and its potential inhibition of SIRT1 under certain conditions [165] has sparked interest in the development of more specific and potent sirtuin activators [166]. In one of the most remarkable pharmacological studies to date, a group at Sirtris Pharmaceuticals Inc. described novel SIRT1 activators, structurally unrelated to resveratrol and 1000 times more potent [83]. As described earlier, the *in vivo* efficacy of these drugs is substantial and was translated into therapeutic benefits in rodent models of diabetes.

In addition to activators, natural inhibitors of SIRT1 have also been identified [167]. The reaction by-product nicotinamide is a potent inhibitor of sirtuins [168] and can mimic deletion of the yeast *SIR2* gene [169]. The pan-sirtuin inhibitor, sirtinol, was identified in a screen of 1600 compounds for inhibitors of yeast Sir2p [170]. In a similar study, a new type of inhibitor, called splitomicin, was shown to compete with acetylated substrate binding [171]. Several splitomicin derivatives have now been tested for increased potency over the original compound [144].

Resolving sirtuin crystal structures has aided the development of 3D models and expedited rational design of specific ligands. The crystallization studies were conducted with unbound protein [172] or complexed with substrates or NAD^+ analogs [173–177]. Structure modeling and virtual screening, where docking of millions compounds in the enzymatic active site are conducted *in silico,* were used to identify SIRT2 inhibitors [178]. A virtual 3D model of SIRT2 was employed to probe the interaction of empirically identified inhibitors with the enzyme's active site [101]. SIRT5 has also been used as a template for understanding the inhibition of NAD^+-dependent deacetylase by suramin [179]. The payoff of these early functional studies is beginning to emerge: a small, water-soluble inhibitor of both SIRT1 and SIRT2 showing considerable *in vivo* activity (called tenovin-6) has recently been described [180].

Discovery of these small molecule probes is critical for further understanding of sirtuin biology and for validation of sirtuins as pharmacological targets in disease models. However, the feasibility of developing sirtuin-based therapies remains to be demonstrated.

The design of potent, selective and bioavailable drug-like small molecules, and the validation of these modalities in animal efficacy studies, are key to the development of human therapeutics. Further, the significant roles of the sirtuins in regulating critically important biological responses and pathways raise questions regarding the safety of sirtuin-based therapy. *A priori,* it can be argued that modulation of sirtuin activities may yield more adverse than beneficial effects. However, this caveat is not specific to sirtuins and applies generally to virtually any candidate drug target. Ultimately, the safety of any therapeutic candidates must be exhaustively tested in animal models prior to application for use in humans.

Future perspectives

To grasp fully the effects of sirtuin manipulation in mammals it will be important to design and generate additional transgenic and knockout mice that permit further investigations into sirtuin biology. These models will be critical to elucidating the relationship between sirtuins, metabolism, and aging. In addition, substantial effort will be necessary to identify and validate new sirtuin protein substrates, which are key to understanding sirtuin regulatory mechanisms and signaling pathways.

Sirtuin-based therapies hold great appeal as potential treatments for diabetes, obesity, cancer, cardiovascular disease and neurodegenerative conditions. Continued pharmacological development of bioactive small molecule ligands is central to validation of the sirtuins as drug targets.

Acknowledgements. We gratefully acknowledge funding from Nestec SA.

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