

# The emerging and diverse roles of sirtuins in cancer: a clinical perspective

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**Abstract:** Sirtuins are a highly conserved family of nicotinamide adenine dinucleotide (NAD<sup>+</sup>)-dependent protein lysine modifying enzymes with deacetylase, adenosine diphosphate-ribosyltransferase and other deacylase activities. Mammals have seven sirtuins, namely SIRT1-7. They are key regulators for a wide variety of cellular and physiological processes such as cell proliferation, differentiation, DNA damage and stress response, genome stability, cell survival, metabolism, energy homeostasis, organ development, aging, and cancer. Here we present an extensive literature review of the roles of mammalian sirtuins, particularly SIRT1 as that is the most studied sirtuin, in human epithelial, neuronal, hematopoietic, and mesenchymal malignancies, covering breast, prostate, lung, thyroid, liver, colon, gastric, pancreatic, ovarian, and cervical cancers, tumors of the central nervous system, leukemia and lymphoma, and soft tissue sarcomas. Collective evidence suggests sirtuins are involved in both promoting and suppressing tumorigenesis depending on cellular and molecular contexts. We discuss the potential use of sirtuin modulators, especially sirtuin inhibitors, in cancer treatment.

**Keywords:** sirtuin, cancer, sirtuin modulator, deacetylation, acetylation

## Introduction

The sirtuins are a family of proteins homologous to yeast silent information regulator 2 (Sir2) that was cloned and characterized in 1984 as a gene required for maintaining silent chromatin in yeast.<sup>1</sup> The discovery of the longevity-promoting effect of Sir2 in yeast in 1999<sup>2</sup> and subsequently in higher eukaryotes nematode worm in 2001<sup>3</sup> and fruit fly in 2004<sup>4</sup> has stimulated extensive research interest in the biology of sirtuins. Although the effect of Sir2 and the most-studied mammalian Sir2 homolog, SIRT1, on longevity has recently been questioned,<sup>5-9</sup> sirtuin family proteins appear to play important roles in many physiological and pathological processes.

There are seven sirtuin genes, *SIRT1-7*, in mammals.<sup>10,11</sup> Biochemically, they are a class of proteins that possess nicotinamide adenine dinucleotide (NAD<sup>+</sup>)-dependent lysine deacetylase (SIRT1, SIRT2, SIRT3, SIRT5, SIRT6, and SIRT7) and mono-ribosyltransferase (SIRT4 and SIRT6) activities.<sup>12-19</sup> Recently, SIRT5 was shown to be a NAD<sup>+</sup>-dependent protein lysine demalonylase and desuccinylase.<sup>20</sup> Sirtuin family members share a conserved NAD<sup>+</sup>-binding and catalytic core domain. Sirtuins are also known as class III histone deacetylases (HDACs), and their unique NAD<sup>+</sup>-dependency distinguishes sirtuins from other (classes I, II, and IV) HDACs.

## Brief overview of physiological functions of sirtuins

SIRT1 is primarily a nuclear deacetylase.<sup>21</sup> It contains at least two nuclear localization signals and two nuclear export signals, and can shuttle between the nucleus and

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cytoplasm under certain conditions.<sup>22</sup> SIRT1 removes the acetyl group from the  $\epsilon$ -amino group of lysine residues in histones and non-histone proteins, and regulates target gene expression and protein activities that control various cellular processes such as cell proliferation, differentiation, apoptosis, metabolism, DNA damage and stress response, genome stability, and cell survival in complex matters (Table 1). SIRT1<sup>-/-</sup> mice in C57/B6 background typically die within 1 month after birth, but in some other background they may survive through adulthood with smaller body size, closed eyelids, infertility, and autoimmune-like conditions.<sup>23–26</sup>

SIRT2 is mainly localized to the cytoplasm, but can shuttle to the nucleus during mitosis.<sup>21,27,28</sup> It deacetylates many substrates such as histone H4K16, H3K56,  $\alpha$ -tubulin, PR-Set7, phosphoenolpyruvate carboxykinase 1, NF- $\kappa$ B subunit p65, FOXO, and RIP1 (receptor-interacting protein 1) (Table 2). SIRT2 regulates several cell functions including cell cycle progression, cell death, and stress response. SIRT2 knockout female mice develop mammary tumors, whereas males develop hepatic and intestinal tumors.<sup>29</sup>

SIRT3 is present in mitochondria,<sup>21,30,31</sup> but is also detected in the nucleus.<sup>32,33</sup> It is a major protein deacetylase within the mitochondrial matrix,<sup>34</sup> and plays a crucial role in cellular energy metabolism and redox regulation by deacetylating key mitochondrial proteins, including acetyl-coenzyme A synthetase 2, isocitrate dehydrogenase 2 (IDH2), glutamate dehydrogenase (GDH), manganese superoxide dismutase (MnSOD) (Table 3). SIRT3-null mice exhibit reduction of respiration and adenosine triphosphate levels, defect of fatty acid oxidation, metabolic syndrome, and development of mammary tumors.<sup>35–37</sup>

SIRT4 is localized to mitochondria,<sup>21</sup> and is a NAD<sup>+</sup>-dependent protein adenosine diphosphate (ADP)-ribosyl transferase, which catalyzes the transfer of ADP-ribosyl groups onto target proteins, such as GDH.<sup>16</sup> SIRT4 regulates cellular metabolic functions like insulin secretion and fatty acid oxidation.<sup>16,38–40</sup> Following genotoxic stress, SIRT4 has also exhibited an anti-apoptotic function by maintaining mitochondrial NAD<sup>+</sup> levels together with SIRT3.<sup>41</sup> SIRT4-depleted mice develop hyperinsulinemia and lung tumors.<sup>16,40</sup>

SIRT5 is also localized to mitochondria.<sup>21</sup> It can deacetylate carbamoyl phosphate synthetase 1 and activate its catalytic activity in the initial step of the urea cycle for ammonia detoxification and disposal.<sup>42</sup> It also possesses NAD<sup>+</sup>-dependent lysine demalonylase and desuccinylase activities that remove malonyl and succinyl groups on target proteins including GDH, carbamoyl phosphate synthetase 1, pyruvate dehydrogenase, succinate dehydrogenase, and many other

substrates impacting diverse metabolic pathways.<sup>20,43,44</sup> Interestingly, a proteomics study by Park et al<sup>44</sup> showed significant cytoplasmic activity of SIRT5, in line with a previous study by Matsushita et al<sup>45</sup> showing that there are two isoforms of human SIRT5 differing in the C-terminal sequence, with the shorter isoform (SIRT5<sup>iso2</sup>) mainly localized in mitochondria and the longer form (SIRT5<sup>iso1</sup>) localized in both cytoplasm and mitochondria. SIRT5-null mice exhibit urea cycle defect and hyperammonemia after fasting.<sup>42</sup>

SIRT6 is a nuclear protein having both deacetylase and ADP-ribosyltransferase activity.<sup>17,46</sup> Recently SIRT6 was shown to be able to remove long-chain fatty acyl group from lysine to regulate tumor necrosis factors (TNF)- $\alpha$  secretion.<sup>47</sup> SIRT6 has been implicated in the regulation of transcription, genome stability, metabolism, and lifespan. Its substrates include histone H3K9, H3K56, C-terminal binding protein interacting protein, poly(ADP-ribose) polymerase 1, DNA-dependent protein kinase, and GCN5 (Table 4). SIRT6 deficient mice die around 4 weeks after birth, showing premature aging phenotypes, hypoglycemia, increased glucose uptake, cardiac hypertrophy and heart failure, hypersensitivity to DNA damage, and genomic instability. The observed lethal hypoglycemia directly results from its histone H3K9 deacetylase function that controls the expression of glycolytic genes.<sup>48–62</sup>

SIRT7 is localized to the nucleolus.<sup>21</sup> It exhibits high selectivity for histone H3K18, and functions to maintain the transformed phenotypes of cancer cells.<sup>18</sup> SIRT7 is a positive regulator of RNA polymerase I transcription and therefore ribosome biogenesis, and its knockdown induces apoptosis in human cells, indicating that SIRT7 is required for cell survival.<sup>63,64</sup> SIRT7-deficient mice die around 1 year, showing premature aging phenotypes (kyphosis and loss of subcutaneous fat), and enhanced inflammatory cardiomyopathy as well as enhanced cardiomyocyte apoptosis.<sup>65</sup> Some available mouse models for sirtuin research are summarized in Table 5.

## Roles of sirtuins in cancer

All mammalian sirtuins except SIRT5 have been reported to be involved in tumorigenesis. But the roles of sirtuins in cancer are complex and may contribute to either tumor promotion or suppression depending on cellular and molecular contexts as reviewed recently.<sup>66</sup>

## SIRT1 in cancer

In the past decade, numerous substrates of SIRT1 have been identified, including many important regulators for cancer cell proliferation, DNA damage repair, and survival under various stress conditions (Table 1). SIRT1 plays a dual role

**Table 1** Examples of SIRT1 substrates and functions

SIRT1 substrates	SIRT1 functions
AceCSI	Promotes AceCSI activity and metabolism <sup>183</sup>
Akt, PDK1	Enhances their PIP <sub>3</sub> binding and membrane localization during tumorigenesis and cardiac hypertrophy <sup>184</sup>
Androgen receptor	Represses dihydrotestosterone-induced androgen receptor signaling <sup>185</sup>
APEI	Promotes base excision repair activity <sup>186</sup>
ATG (autophagy genes Atg5, Atg7, and Atg8)	Promotes autophagy <sup>187</sup>
β-catenin	Suppresses its ability to activate transcription and to drive cell proliferation <sup>125</sup>
BMAL1	Modulates CLOCK-mediated chromatin remodeling and circadian control <sup>188</sup>
CIITA (class II transactivator)	Augments MHC II transcription by shielding CIITA from proteasomal degradation and promoting nuclear accumulation and target binding <sup>189</sup>
c-MYC	Stabilizes <sup>89,190</sup> or destabilizes c-MYC oncoprotein <sup>132</sup>
CRTC1 (CREB-regulated transcription coactivator I, or TORC1)	Activates TORC1 by promoting its dephosphorylation and its interaction with CREB for neuroprotection <sup>191</sup>
CRTC2 (TORC2)	Attenuates CRTC2 activity and glucose output during fasting <sup>192</sup>
DNMT1	Deacetylation of different lysines on DNMT1 has different effects on the activities for DNA methylation <sup>193</sup>
EVII	Triggers EVII degradation <sup>194</sup>
eNOS	Stimulates eNOS activity, increases endothelial nitric oxide, promotes endothelium-dependent vascular relaxation <sup>195</sup>
ERα	Represses its DNA binding and transcriptional activity <sup>196</sup>
FOXO1	Potentiates FOXO1-mediated transcription through its deacetylase activity <sup>197</sup>
FOXO3	Increases FOXO3's ability to induce cell cycle arrest and resistance to oxidative stress but inhibits FOXO3's ability to induce cell death <sup>198,199</sup>
FOXp3	Promotes its degradation, inhibits Treg functionality <sup>200</sup>
FXR (nuclear bile acid receptor)	Decreases its stability but enhances transactivation activity in lipid and glucose metabolism regulation <sup>201</sup>
HIF1α	Inactivates HIF-1 alpha under hypoxia <sup>130</sup>
HIF2α	Promotes HIF-2 signaling during hypoxia <sup>202</sup>
Histone H1 (K26), H3(K9, K56), H4(K16)	Transcription regulation and chromatin function <sup>12</sup>
HSF1	Prolongs HSF1 binding to the heat shock promoter Hsp70 <sup>203</sup>
Ku70	Promotes DNA repair activity <sup>204</sup>
LXR (Liver X receptor)	Positively regulates its function for cholesterol and lipid homeostasis <sup>205</sup>
MeCP2 (Methyl-CpG binding protein 2)	Promotes MeCP2-mediated BDNF expression <sup>206</sup>
MMP2	Enhances MMP2 protein stability <sup>81</sup>
MyoD	Inhibits myogenesis <sup>207</sup>
NBS1	Maintains NBS1 in a hypoacetylated state, which is required for ionizing radiation-induced NBS1 Ser343 phosphorylation <sup>208</sup>
NF-κB p65	Reduces NF-κB transcriptional activity, augments apoptosis in response to TNFα <sup>209</sup>
NHLH2	Activates MAO-A to mediate anxiety and exploratory drive <sup>210</sup>
N-MYC	Promotes protein stability <sup>111</sup>
NoRC	Leads to enhanced promoter-associated RNA binding and an increase in heterochromatic histone marks <sup>211</sup>
NICD (Notch I intracellular domain)	Acts as a negative modulator of Notch signaling in endothelial cells <sup>212</sup>
p300	Represses its transactivation activity <sup>213</sup>
p53	Promotes cell survival under stress <sup>214,215</sup>
PARP1	Promotes cell survival under stress <sup>216</sup>
PER2	Promotes PER2 degradation to regulate circadian clock gene expression <sup>217</sup>
PGC1α	Positively and negatively controls gene expression for glucose homeostasis <sup>218</sup>
PIP5 Kγ	Regulates thyroid-stimulating hormone release by enhancing PIP5 Kgamma activity <sup>219</sup>
PTEN	Modulates PTEN interaction with PDZ domain-containing proteins <sup>220</sup>
RARβ	Activates alpha-secretase gene <i>ADAM10</i> , suppresses beta-amyloid production <sup>221</sup>
Rb (Retinoblastoma tumor suppressor protein)	Inactivates retinoblastoma tumor suppressor protein <sup>222</sup>
Smad7	Inhibits transforming growth factor beta-induced apoptosis in glomerular mesangial cells <sup>223</sup>
SREBP-1C	Inhibits SREBP-1C activity in regulation of hepatic lipid metabolism <sup>224</sup>
STAT3	Suppresses the inhibitory effect of STAT3 on gluconeogenesis <sup>225</sup>
Survivin	Suppresses survivin thus inhibits cell survival <sup>226</sup>
SUV39H1	Increases SUV39H1 activity during heterochromatin formation <sup>227</sup>
Tat	Facilitates the recycling of Tat <sup>228</sup>

(Continued)

**Table 1** (Continued)

SIRT1 substrates	SIRT1 functions
Tip60, hMOF WRN	Inhibits their acetyltransferase activity and promotes their degradation in DNA damage response <sup>229</sup> Increases its helicase and exonuclease activities, promotes its translocation from nucleoplasm to nucleoli after DNA damage <sup>230</sup>
XBPIs	Inhibits its transcriptional activity <sup>231</sup>
Xpa, Xpc	Promotes nucleotide excision repair activity <sup>232,233</sup>

**Abbreviations:** AceCSI, acetyl-coenzyme A synthetase I; APEI, apurinic/aprimidinic endonuclease-I; ATG, autophagy genes; BDNF, brain-derived neurotrophic factor; CREB, cyclic adenosine monophosphate response element-binding protein; DNMT1, DNA methyltransferase I; eNOS, endothelial nitric oxide synthase; ER $\alpha$ , estrogen receptor alpha; EVI1, ecotropic viral integration site I; FOXO1, forkhead box protein O1; FOXO3, forkhead box protein O3; FOXp3, forkhead box P3; HIF1 $\alpha$ , hypoxia-inducible factor 1-alpha; HIF2 $\alpha$ , hypoxia-inducible factor 2-alpha; HSF1, heat shock factor protein 1; LXR, liver X receptor; MAO-A, monoamine oxidase A; MeCP2, methyl-CpG binding protein 2; MHC II, major histocompatibility complex class II; MMP2, matrix metalloproteinase-2; NBS1, nijmegen breakage syndrome protein 1; NF- $\kappa$ B, nuclear factor kappa-light-chain-enhancer of activated B cells; NICD, Notch I intracellular domain; NoRC, nitric oxide reductase; PARP1, poly(adenosine diphosphate ribose) polymerase I; PDK1, phosphoinositide-dependent kinase-I; PGC1 $\alpha$ , peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PIP<sub>3</sub>, phosphatidylinositol (3,4,5)-triphosphate; PTEN, phosphatase and tensin homolog; RAR $\beta$ , retinoic acid receptor beta; SREBP-1C, sterol regulatory element-binding protein; STAT3, signal transducer and activator of transcription 3; TNF, tumor necrosis factor; WRN, Werner syndrome; XBPI, X-box binding protein I; Xpa, xeroderma pigmentosum group A; Xpc, xeroderma pigmentosum group C.

in cancer promotion and suppression, depending on tissue contexts and the temporal and spatial distribution of SIRT1 upstream and downstream factors (Figure 1). This section will review SIRT1 functions in several types of cancer.

### Breast cancer

The expression of SIRT1 protein was seen in most human breast cancer specimens, and its expression was significantly associated with distant metastasis and poor prognosis.<sup>67–69</sup>

**Table 2** Examples of SIRT2 substrates and functions

SIRT2 substrates	SIRT2 functions
Alpha-tubulin	Abrogates resistance to axonal degeneration <sup>14,234</sup>
CDHI, CDC20	Promotes their degradation and cell cycle exit <sup>29</sup>
FOXO1 FOXO3a	Inhibits adipocyte differentiation <sup>235</sup> Leads to Skp2-mediated FOXO3 ubiquitination and degradation <sup>76</sup>
Histone H3K56	Inhibits its assembly into chromatin in response to DNA damage <sup>157</sup>
Histone H4K16 Keratin 8 (K207)	Promotes cell cycle G2/M transition <sup>28</sup> Increases its solubility <sup>236</sup>
NF- $\kappa$ B p65 (K310)	Suppresses NF- $\kappa$ B dependent gene expression <sup>237</sup>
p300	Restores its binding to the pre-initiation complex, thereby promoting transcription <sup>238</sup>
PAR-3	Decreases the activity of the polarity complex signaling component atypical protein kinase C, thereby regulating myelin formation <sup>239</sup>
PEPCK I (Phosphoenolpyruvate carboxykinase I)	Stabilizes PEPCK I for gluconeogenesis <sup>240</sup>
PR-Set7	Increases its chromatin localization <sup>241</sup>
RIP1	Is required for programmed necrosis <sup>242</sup>

**Abbreviations:** FOXO1, forkhead box protein O1; FOXO3a, forkhead box protein O3a; NF- $\kappa$ B, nuclear factor kappa-light-chain-enhancer of activated B cells; PEPCK I, phosphoenolpyruvate carboxykinase I; RIP1, receptor-interacting protein 1; PAR-3, protease-activated receptor-3.

SIRT1 upregulation in breast cancer cells is associated with inactivation of tumor suppressor hypermethylated in cancer 1 (HIC1) by DNA hypermethylation.<sup>70</sup> SIRT1 promotes cell survival after DNA damage through inactivation of the p53 pathway. SIRT1 upregulation is also associated with decreased miR-200a in breast cancer samples, which targets the three prime untranslated region of SIRT1 messenger RNA (mRNA) and promotes epithelial–mesenchymal transition (EMT)-like transformation in mammary epithelial cells.<sup>71</sup> SIRT1 is essential for oncogenic signaling of estrogen/estrogen receptor  $\alpha$  (ER $\alpha$ ) in breast cancer. SIRT1 inactivation suppresses estrogen/ER $\alpha$ -induced cell growth and tumor development, and induces apoptosis. Compared to adjacent normal tissue, SIRT1 is found to be significantly upregulated in the invasive ductal carcinoma, and positively regulates the expression of aromatase, an enzyme responsible for a key step in the biosynthesis of estrogen in breast cancer.<sup>72</sup> In addition, SIRT1 can promote cell migration by directly interacting and deacetylating cortactin,<sup>73</sup> and promote the expression of multidrug resistance-associated protein 2 in tamoxifen-resistant breast cancer cells for chemoresistance by deacetylating FOXO1.<sup>74</sup> SIRT1 activator SIRT1720 promotes the migration and pulmonary metastasis of subcutaneously-implanted breast cancer cells in mice, further supporting the cancer promoting effect of SIRT1 in breast cancer.<sup>75</sup>

### Prostate cancer

SIRT1 is significantly overexpressed in human prostate cancer cell lines and tissues, compared with normal prostate epithelial cells and adjacent normal prostate tissues. SIRT1 inhibition via nicotinamide, sirtinol, short hairpin RNAs, or mutation of the 25 amino acid C-terminal SIRT1 activator sequence, results in a significant inhibition in the cell growth, viability, and chemoresistance.<sup>76–80</sup> SIRT1 is highly expressed in

**Table 3** Examples of mitochondrial sirtuin substrates and functions

Sirtuins	Sirtuin substrates	Sirtuin functions
SIRT3	AceCS2	Promotes AceCS2 activity <sup>183,243</sup>
	Cyclophilin D	Induces dissociation of hexokinase II from the mitochondria, <sup>244</sup> and suppresses age-related cardiac hypertrophy <sup>245</sup>
	FOXO3a	Promotes its nuclear localization and mitochondrial biogenesis <sup>246</sup>
	GDH	Increases its activity <sup>34,247</sup>
	Histone H4K16	Gene transcription <sup>33</sup>
	IDH2	Activates its activity, protects cells from oxidative stress, prevents age-related hearing loss under caloric restriction <sup>146,147,247</sup>
	Ku70	Protects cells from stress-mediated cell death <sup>248</sup>
	LCAD	Increases its enzymatic activity <sup>249</sup>
	LKBI	Activates LKBI, thus augmenting the activity of the LKBI-AMPK pathway <sup>250</sup>
	HMGCS2	Enhances its enzymatic activity <sup>251</sup>
	MnSOD	Enhances its enzymatic activity <sup>252</sup>
	MRPL10	Suppresses translational activity of mitochondrial ribosomes <sup>253</sup>
	NDUFA9	Augments complex I activity of the electron transport chain <sup>254</sup>
	OTC	Stimulates its activity <sup>255</sup>
	SDH (Succinate dehydrogenase)	Promotes its enzyme activity <sup>256,257</sup>
SIRT4	GDH	Mono-ADP-ribosylates it, reduces GDH activity <sup>16</sup>
	MCD	Deacetylates and inhibits the activity of MCD <sup>258</sup>
SIRT5	CPS I	Deacetylates and upregulates its activity to regulate the urea cycle <sup>42</sup>
	Pyruvate dehydrogenase and succinate dehydrogenase	Desuccinylates and represses their biochemical activity and thus cellular respiration <sup>44</sup>

**Notes:** There are a large and growing number of mitochondrial sirtuin substrates. The list only shows some examples that have been studied in more detail.

**Abbreviations:** AceCS2, acetyl-coenzyme A synthetase 2; ADP, adenosine diphosphate; AMPK, adenosine monophosphate-activated protein kinase; CPSI, carbamoyl phosphate synthetase I; FOXO3a, forkhead box protein O3a; FOXp3, forkhead box P3; GDH, glutamate dehydrogenase; HMGCS2, mitochondrial 3-hydroxy-3-methylglutaryl coenzyme A synthase 2; IDH2, isocitrate dehydrogenase 2; LCAD, long-chain acyl coenzyme A dehydrogenase; LKBI, liver kinase B1; MCD, malonyl coenzyme A decarboxylase; MnSOD, manganese superoxide dismutase; MRPL10, mitochondrial ribosomal protein L10; NDUFA9, nicotinamide adenine dinucleotide dehydrogenase [ubiquinone] I alpha subcomplex subunit 9, mitochondrial; OTC, ornithine transcarbamoylase; SDH, succinate dehydrogenase.

advanced prostate cancer tissues and could promote prostate cancer cell invasion, migration, and metastasis through matrix metalloproteinase-2,<sup>81</sup> EMT inducing transcription factor ZEB1,<sup>82</sup> and cortactin.<sup>73,83</sup> In the transgenic mouse model, SIRT1 expression promotes murine prostate carcinogenesis initiated by phosphatase and tensin homolog deficiency.<sup>84</sup>

**Table 4** Examples of nuclear SIRT6 and SIRT7 substrates and functions

Sirtuins	Sirtuin substrates	Sirtuin functions
SIRT6	CtIP	Deacetylates it to promote DNA end resection <sup>53</sup>
	DNA-PK	Deacetylates and stabilizes it at chromatin for DNA double-strand break repair <sup>52</sup>
	GCN5	Interacts with and modifies GCN5, enhancing GCN5's activity to acetylate PGC1 $\alpha$ and suppresses hepatic glucose production <sup>59</sup>
	Histone H3K56	Deacetylates H3K56 to promote genomic stability <sup>19,156</sup>
	Histone H3K9	Deacetylates H3K9: maintains telomeric chromatin; <sup>46,57</sup> represses NF- $\kappa$ B <sup>50</sup> and HIF1 $\alpha$ <sup>51,60</sup> dependent gene expression; attenuates IGF-Akt signaling <sup>58</sup>
	PARP1	Mono-ADP-ribosylates it, thereby stimulating its poly-ADP-ribosylase activity and enhancing DSB repair under oxidative stress <sup>56</sup>
SIRT7	TNF- $\alpha$	Removes the fatty acyl modification on K19 and K20 of TNF- $\alpha$ to promote its secretion <sup>47</sup>
	Histone H3K18	Maintains the transformation phenotype of cancer cells <sup>18</sup>

**Abbreviations:** ADP, adenosine diphosphate; CtIP, C-terminal binding protein interacting protein; DNA-PK, DNA-dependent protein kinase; HIF1 $\alpha$ , hypoxia-inducible factor 1-alpha; IGF, insulin-like growth; NF- $\kappa$ B, nuclear factor kappa-light-chain-enhancer of activated B cells; PARP1, poly(adenosine diphosphate ribose) polymerase I; PGC1 $\alpha$ , peroxisome proliferator-activated receptor gamma coactivator 1-alpha; TNF, tumor necrosis factor.

### Lung cancer

Positive SIRT1 and cortactin expression was observed in 67% (96 of 144) and 58% (84 of 144) of patients with invasive non-small-cell lung cancer, respectively.<sup>85</sup> SIRT1 and cortactin expression are significantly associated with unfavorable clinical factors, including high pathological T stage, lymph node metastasis, and advanced tumor invasion.<sup>85</sup> Deregulation of the HIC1-SIRT1-p53 regulation loop was confirmed in 118 non-small-cell lung cancer patients. The patients with low p53 acetylation and high SIRT1 expression mostly showed low HIC1 expression and worse prognosis compared to other patients.<sup>86</sup> SIRT1 could facilitate endothelial cell branching and proliferation to increase vessel density and promote lung tumor growth through downregulation of DLL4/Notch signaling and deacetylation of Notch1 intracellular domain.<sup>87</sup> Conversely, SIRT1/2 inhibition by short interfering RNA (siRNA) or a small molecule inhibitor Salermide, causes apoptosis in human non-small-cell lung cancer cells by upregulating death receptor 5 expression.<sup>88</sup>

**Table 5** Available mouse models for sirtuins research

Sirtuin	Mouse models	Phenotypes
SIRT1	KO (whole body)	In C57/B6 background, mice die within 1 month after birth. In BALB/c background or mixed background, mice can survive through adulthood with smaller body size, closed eyelids, infertility, and autoimmune-like conditions
	KO (brain)	Memory defect, no adaptive feeding response to calorie restriction, less serum insulin-like growth factor I
	KO (liver)	Defect in circadian gene oscillation, develop hepatic steatosis and inflammation
	KO (macrophage)	Increased inflammation, glucose intolerance and insulin resistance induced by high fat diet
	Tg (whole body)	Protected against various metabolic disorders (fatty liver and type 2 diabetes) induced by high fat diet, protected against age-induced cancer, osteoporosis and glucose intolerance
	Tg (brain)	Enhanced memory formation and feeding behavior, protected against Alzheimer's disease
	Tg (heart)	Cardioprotection (mild expression), cardiac hypertrophy (high expression)
	Tg (gut)	Protected against colon cancer
	Tg (kidney)	Protected against acute renal failure
SIRT2	KO (whole body)	SIRT2 knockout female mice develop mammary tumors, whereas males develop liver and intestinal tumors
SIRT3	KO (whole body)	Defect in fatty acid oxidation, cancer prone, their oocytes exhibit developmental arrest after in vitro fertilization, accumulation of hyperacetylated mitochondrial proteins, reduced respiration and adenosine triphosphate levels
	Tg (heart)	Protected against cardiac hypertrophy
SIRT4	KO (whole body)	Developed hyperinsulinemia and lung tumors
SIRT5	KO (whole body)	Defect in urea cycle, hyperammonemia after fasting
	Tg (liver)	Increased urea cycle activity, increased urea production
SIRT6	KO (whole body)	Died around 4 weeks showing premature aging phenotype (lymphopenia, loss of subcutaneous fat), hypoglycemia, increased glucose uptake, genomic instability
	KO (liver)	Increased glycolysis, triglyceride synthesis, reduced $\beta$ oxidation and fatty liver formation
	Tg (whole body)	Protected against metabolic disorder induced by high fat diet
SIRT7	KO (whole body)	Died around 1 year showing premature aging phenotypes (kyphosis, loss of subcutaneous fat, degenerative cardiac hypertrophy), increased apoptosis

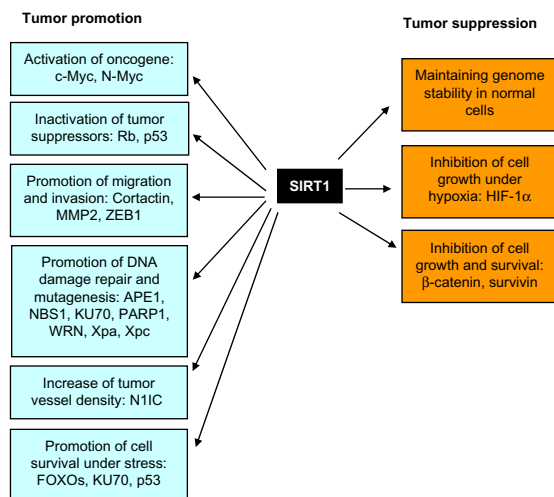
**Note:** Adapted with permission from *J Cell Sci.* 2011;124(Pt 6):833–838. Nakagawa T, Guarente L. Sirtuins at a glance.<sup>259</sup>

**Abbreviations:** KO, knockout; Tg, transgenic.

## Colon cancer

Highly-expressed c-MYC correlates with increased SIRT1 protein level in colorectal cancer.<sup>89</sup> c-MYC, nicotinamide phosphoribosyltransferase, deleted in breast cancer protein 1, and SIRT1 form a positive feedback regulatory loop.<sup>89</sup> In

121 colorectal serrated lesions, the higher expression of c-MYC and SIRT1 proteins is strongly associated with higher grades of malignancy.<sup>90</sup> In another study with a total of 485 colorectal cancer patients, SIRT1 overexpression was detected in 180 (37%) tumors.<sup>91</sup> SIRT1 expression is associated with microsatellite instability and CpG island methylator phenotype, although not patient prognosis.<sup>91</sup> Reduced expression of miR-34a, a negative regulator of SIRT1 mRNA, is observed in drug-resistant DLD-1 colon cancer cells, and introduction of miR-34a induces apoptosis by downregulating SIRT1.<sup>92</sup>



**Figure 1** Bifurcated roles of SIRT1 in tumor promotion and suppression.

**Abbreviations:** APE1, apurinic/apyrimidinic endonuclease-1; FOXO, forkhead box protein O; HIF-1 $\alpha$ , hypoxia-inducible factor 1-alpha; MMP2, matrix metalloproteinase-2; NBS1, nijmegen breakage syndrome protein 1; NIIC, Notch1 intracellular domain; PARP1, poly(adenosine diphosphate ribose) polymerase 1; WRN, Werner syndrome; Xpa, xeroderma pigmentosum group A; Xpc, xeroderma pigmentosum group C; ZEB1, zinc finger E-box-binding homeobox 1.

## Thyroid cancer

SIRT1 is overexpressed in human thyroid cancers and it is positively correlated with c-MYC protein levels. Transgenic SIRT1 expression promotes murine thyroid carcinogenesis initiated by phosphatase and tensin homolog deficiency. SIRT1 increases c-MYC transcription and stabilizes c-MYC protein in thyroid cancers from SIRT1 transgenic mice or cultured thyroid cancer cells.<sup>84</sup>

## Gastric cancer

SIRT1 protein expression in gastric cardiac carcinoma is significantly higher than that in normal gastric cardiac tissues and is associated with lymphatic metastasis, TNM (the extent

of tumor [T], the extent of spread to lymph nodes [N], and the presence of distant metastasis [M]) stage, survival rate, and mean survival time.<sup>93</sup> In another study, positive expression of SIRT1 was seen in 73% (130 of 177) of gastric cancer patients.<sup>94</sup> SIRT1 expression is also significantly associated with shorter overall survival and relapse-free survival.<sup>94</sup> SIRT1 is required for activating-transcription-factor-4-induced multidrug resistance in gastric cancer cells. Activating transcription factor 4 facilitates multidrug resistance in gastric cancer cells through direct binding to SIRT1 promoter and activating SIRT1 expression. Significantly, inhibition of SIRT1 by RNA interference or a specific inhibitor (EX-527) sensitizes gastric cancer cells to therapeutic treatment.<sup>95</sup>

### Liver cancer

SIRT1 expression is significantly elevated in hepatocellular carcinoma (HCC) compared to non-tumor tissues, and the expression levels correlate with tumor grades and predict poor prognosis. SIRT1 promotes tumorigenesis and chemoresistance in HCC, and inhibition of SIRT1 consistently suppresses the proliferation of HCC cells in vitro or in vivo via the induction of cellular senescence or apoptosis.<sup>96–100</sup> SIRT1 expression also positively correlates with c-MYC levels in HCC. SIRT1 and c-MYC regulate each other via a positive feedback loop and act synergistically to promote cell proliferation of both mouse and human liver tumor cells.<sup>101</sup> Accordingly, expression of microRNA (miRNA)-34a is reduced in HCC, and the reduced expression of miRNA-34a is associated with worse outcome of HCC patients. Treatment of established HCC xenograft with miR-34a-expressing adenovirus in a mouse model results in complete tumor regression without recurrence.<sup>102</sup> In addition, miRNA-29c also functions as a tumor suppressor by directly targeting oncogenic SIRT1 in HCC.<sup>103</sup>

### Pancreatic cancer

SIRT1 overexpression was observed in pancreatic cancer tissues at both mRNA and protein levels.<sup>104</sup> Increased SIRT1 positivity is associated with patients' age (over 60 years old), larger tumor size (larger than 4 cm), and higher TNM stage. SIRT1 knockdown induces apoptosis and senescence, inhibits invasion and enhances chemosensitivity in pancreatic cancer cells.<sup>104,105</sup> In pancreatic cancer, SIRT1 regulates acinar-to-ductal metaplasia and supports cancer cell viability through deacetylating pancreatic transcription factor-1a and  $\beta$ -catenin. Inhibition of SIRT1 is effective in suppression of acinar-to-ductal metaplasia and in reducing cell viability in established pancreatic ductal adenocarcinoma.<sup>106</sup> In addition,

SIRT1 promotes EMT ability as well as invasion of pancreatic cancer cells by forming a complex with Twist and MBD1, thus suppressing E-cadherin transcription activity.<sup>107</sup>

### Ovarian and cervical cancers

Expression of SIRT1 protein was significantly increased in 90 cases of malignant ovarian epithelial tumors compared to 40 cases of benign and 36 cases of borderline epithelial tumors.<sup>108</sup> In granulosa cells, SIRT1 suppresses the activity of transcriptional factor FOXL2 on targets involved in cell cycle and DNA repair. Conversely, inhibition of SIRT1 by nicotinamide limits granulosa cell proliferation by increasing FOXL2 expression.<sup>109</sup> In human SiHa cervical cancer cells, SIRT1 is upregulated by oncogenic viral protein human papillomavirus E7, and may mediate the pro-survival function of human papillomavirus E7 through attenuating p53 activity.<sup>110</sup>

### Tumors of the central nervous system

SIRT1 and N-MYC form a positive feedback regulation loop during the tumorigenesis of neuroblastoma, and preventive treatment with the SIRT1 inhibitor Cambinol significantly reduces tumorigenesis in *N-MYC* transgenic mice.<sup>111</sup> SIRT1 regulates tyrosine hydroxylase expression and differentiation of neuroblastoma cells via FOXO3a. SIRT1 inhibition by siRNA or nicotinamide inhibits all trans-retinoic acid induced upregulation of tyrosine hydroxylase and differentiation.<sup>112</sup> In glioblastoma, SIRT1 is highly expressed in tumor-derived CD133<sup>+</sup> progenitor cells compared to CD133<sup>-</sup> cells and knockdown of SIRT1 expression enhances the radio-sensitivity and radiation-induced apoptosis in the CD133<sup>+</sup> cells in vitro and in vivo.<sup>113</sup> Also, casein kinase-2 inhibitors could sensitize glioblastoma cells to TNF- $\alpha$ -induced apoptosis through a mechanism involving SIRT1 inhibition.<sup>114</sup> SIRT1 is also frequently expressed (64.2%, 77/120 patients) in human medulloblastomas relative to surrounding noncancerous cerebellar tissues and its expression is correlated with the formation and prognosis of medulloblastomas. Inhibition of SIRT1 by siRNA or nicotinamide arrests medulloblastoma cell UW228-3 in the G1 phase and induces apoptosis, suggesting SIRT1 as a potential therapeutic target in this type of tumor.<sup>115</sup>

### Lymphoma and leukemia

In adult T-cell leukemia cells, overexpression of SIRT1 was observed and its inhibition by sirtinol induced apoptosis.<sup>116</sup> In 104 diffuse large B-cell lymphoma patients, positive expression of SIRT1 protein was seen in 74% (77/104)

of patients, and was significantly associated with shorter overall survival.<sup>117</sup> SIRT1 is also overexpressed (greater than two-fold) in acute myelogenous leukemia (AML) samples.<sup>118</sup> Increased SIRT1 expression appears critical for cell survival. Inhibition of SIRT1/2 by Cambinol induces apoptosis in Burkitt lymphoma cells.<sup>119</sup> In a large cohort of primary AML (n=12) and B-cell chronic lymphocytic leukemia (n=36) samples and leukemia cell lines, a combination of sirtuin inhibitors such as sirtinol, cambinol, or EX-527 with HDAC inhibitors led to a synergistic anti-leukemic effect.<sup>120</sup>

In chronic myelogenous leukemia (CML), a crucial role of SIRT1 in CML development and chemoresistance has recently been demonstrated.<sup>121–123</sup> SIRT1 is activated by oncogenic breakpoint-cluster region-Abelson-murine-leukemia (BCR-ABL) in part via STAT5 signaling in hematopoietic progenitor cells. SIRT1 inhibition efficiently impairs the growth of human CML cells and sensitizes leukemia stem cells to the BCR-ABL inhibitor imatinib both in vitro and in vivo. SIRT1 knockout robustly inhibits BCR-ABL-mediated transformation of mouse bone marrow cells and development of CML-like myeloproliferative disease. Moreover, in a CML chemoresistance model that faithfully recapitulates many features of human CML response to imatinib treatment, SIRT1 inhibition prevents BCR-ABL mutagenesis through inhibiting Ku70-mediated DNA repair pathway and blocks CML cell relapse upon imatinib treatment.<sup>121–123</sup>

### Soft tissue sarcomas

SIRT1 is frequently expressed in soft tissue neoplasms with myoid differentiation including angiomyolipoma (four out of five patients), glomus tumor (five out of five patients), leiomyoma (nine out of ten patients), leiomyosarcoma (76.5% of 51 patients), and rhabdomyosarcoma (87% of 24 patients), and thus could be a potential immunohistochemical marker and therapeutic target in these tumors.<sup>124</sup>

### SIRT1 in tumor suppression

The above studies support roles of SIRT1 in cancer promotion; however, there is also a body of evidence, particularly from mouse model studies, pointing to a tumor suppressor role of SIRT1. SIRT1 transgenic mice exhibit a reduced incidence of spontaneous carcinomas and sarcomas, and a reduced susceptibility to carcinogen-induced liver cancer.<sup>6</sup> Ectopic induction of SIRT1 in an APC<sup>min/+</sup> (adenomatous polyposis coli) mouse colon cancer model reduces tumor formation and proliferation.<sup>125</sup> SIRT1<sup>+/-</sup>p53<sup>+/-</sup> mice have a higher incidence of tumors than wild-type, SIRT1<sup>+/-</sup> and p53<sup>+/-</sup> mice.<sup>126</sup>

SIRT1 expression is significantly downregulated in human head and neck squamous cell carcinoma (HNSCC). High SIRT1 expression is associated with good prognosis for HNSCC patients.<sup>127</sup> In colorectal adenocarcinoma, SIRT1 overexpression was observed in approximately 25% of stage I/II/III tumors but rarely in advanced stage IV tumors and approximately 30% of carcinomas showed lower SIRT1 expression than normal tissues.<sup>128</sup> In another clinical observation, SIRT1 protein expression gradually decreased during the normal-adenoma-adenocarcinoma-metastasis sequence in colorectal cancers, with positivity of 100%, 80.8%, 41.9%, and 35.7%, respectively.<sup>129</sup>

SIRT1 may suppress tumor growth through distinct mechanisms. SIRT1 deacetylates and inactivates hypoxia-inducible factor 1 $\alpha$ , thus inhibits the expression of genes targeted by hypoxia-inducible factor 1 $\alpha$  in certain tumors.<sup>130</sup> In HMLER breast cancer cells, SIRT1 was found to suppress EMT, and reduced SIRT1 expression increases metastasis of these cells in nude mice.<sup>131</sup> In one study, it was shown that although c-MYC induces SIRT1 expression, SIRT1 deacetylates c-MYC to reduce c-MYC protein stability and thus cellular transformation.<sup>132</sup> SIRT1 inhibits proliferation of pancreatic cancer cells expressing oncogenic pancreatic adenocarcinoma upregulated factor, by suppression of  $\beta$ -catenin and cyclin-D1.<sup>133</sup> In hepatitis-B-virus-X-protein-overexpressed Hep3B hepatocellular carcinoma cells, SIRT1 inhibits proliferation and enhances the sensitivity of the cells to doxorubicin or oxidative stress through destabilization of  $\beta$ -catenin or inhibition of c-Jun N-terminal kinase, respectively.<sup>134,135</sup> These studies further underline the distinct roles of SIRT1 in cancer cells under different conditions.

### SIRT2 in cancer

Similar to SIRT1, SIRT2 may have both tumor suppression and promotion function. SIRT2 expression is reduced in gliomas, and SIRT2 inhibits colony formation of glioma cell lines.<sup>136</sup> SIRT2 expression is also reduced in esophageal adenocarcinomas, gastric adenocarcinomas, and HNSCC.<sup>137</sup> The direct evidence that SIRT2 may act as a tumor suppressor came from a SIRT2 knockout mouse study.<sup>29</sup> SIRT2 deficient male mice develop HCC whereas females develop mammary tumors.<sup>29</sup> Mechanistically, SIRT2 regulates the anaphase-promoting complex/cyclosome activity through deacetylation of its coactivators, anaphase-promoting complex (CDH1) and CDC20. SIRT2 deficiency causes increased levels of mitotic regulators, including Aurora-A and Aurora-B that direct centrosome amplification, aneuploidy, and mitotic cell



death. Moreover, SIRT2 level is reduced in human breast cancer and HCC.<sup>29</sup>

On the other hand, SIRT2 knockdown leads to both necrotic and apoptotic cell death in C6 glioma cells.<sup>138</sup> Similarly, cervical carcinoma HeLa cells undergo apoptosis in response to SIRT2 downregulation.<sup>139</sup> SIRT2 promotes bladder cancer cell migration and invasion by targeting cortactin together with HDAC6.<sup>140</sup> SIRT2 is upregulated in neuroblastoma cells by N-MYC and in pancreatic cancer cells by c-MYC; and in turn, SIRT2 stabilizes N-MYC and c-MYC protein by downregulating ubiquitin-protein ligase NEDD4 expression.<sup>141</sup> In AML cells, SIRT2 and NAD<sup>+</sup> salvage enzyme nicotinamide phosphoribosyltransferase are upregulated and involved in the aberrant proliferation and survival of leukemic cells.<sup>142</sup> The results from these studies indicate a tumor promotion role of SIRT2.

### SIRT3 in cancer

The mitochondrial sirtuin SIRT3 plays crucial roles in metabolism and oxidative stress response, and is considered as a mitochondrial tumor suppressor. SIRT3 levels are reduced in human breast and colon carcinoma,<sup>37</sup> HNSCC,<sup>143</sup> HCC, and osteosarcoma.<sup>144,145</sup> About 20% of all human cancer samples and 40% of breast and ovarian cancer samples contain deletions of SIRT3.<sup>37</sup> Mechanistically, SIRT3 may inhibit tumor growth by reducing production of reactive oxygen species (ROS) through regulating electron transport, superoxide dismutase, mitochondrial IDH2, and FOXO3a.<sup>66</sup> Notably, SIRT3 deacetylates IDH2 at lysine 413 and activates its activity, leading to increased nicotinamide adenine dinucleotide phosphate levels and an increased ratio of reduced-to-oxidized glutathione in mitochondria, and thus reducing ROS.<sup>146,147</sup> SIRT3 promotes antioxidant activity of superoxide dismutase MnSOD via direct deacetylation, and loss of SIRT3 increases acetylation of MnSOD and thereby increases cellular ROS. Increased ROS stabilizes hypoxia-inducible factor (HIF) 1- $\alpha$ , resulting in metabolic reprogramming toward glycolysis and thus facilitating tumor development.<sup>35,37,148</sup> Recently, it has been shown that SIRT3 deacetylates and destabilizes the proto-oncogene product S-phase kinase-associated protein 2 (Skp2), and inactivation of SIRT3 leads to Skp2 acetylation and thereby increased Skp2 stability and cytoplasmic retention, resulting in enhanced cellular proliferation, migration, and tumorigenesis *in vivo*.<sup>149</sup>

However, potential roles of SIRT3 in tumor promotion have also been reported. SIRT3 expression is higher in human lymph-node-positive breast cancer<sup>150</sup> and oral squamous cell carcinoma (OSCC).<sup>151</sup> Inhibition of SIRT3 in OSCC cells

inhibits cell growth and anoikis (a form of programmed cell death) resistance, lowers tumor burden and incidence, and sensitizes OSCC cells to radiation and cisplatin treatments *in vitro*.<sup>151,152</sup> The tumor suppressor p53 is deacetylated by SIRT3, and SIRT3 rescues p53-induced growth arrest in human bladder-tumor-derived EJ-p53 cells.<sup>153</sup> SIRT3 deacetylates mitochondrial matrix protein IDH2 to protect cells from oxidative stress; but in cancer, IDH2 activation by SIRT3 may have a pro-survival effect on cancer cells. IDH2 activity has been demonstrated to be a major factor in cancer, and as such, SIRT3 is a potential regulator of IDH2-dependent functions in cancer cell metabolism.<sup>147</sup>

### SIRT4 in cancer

The roles of SIRT4 in cancer have been unclear until two recent studies revealing that it is a potential tumor suppressor.<sup>40,154</sup> SIRT4 expression is found to be significantly lower in human bladder, breast, colon, gastric, ovarian, and thyroid carcinomas, relative to normal tissues. In cancer cells, the mammalian target of rapamycin complex 1 pathway promotes glutamine anaplerosis by repressing SIRT4, thus activating GDH. SIRT4 overexpression reduces cell proliferation and transformation, and delays tumor development in a Tsc2<sup>-/-</sup> (tuberous sclerosis complex 2) mouse embryonic fibroblast xenograft model.<sup>154</sup> Consistently, in another study, the loss of SIRT4 led to increased glutamine-dependent cell proliferation and stress-induced genomic instability, resulting in tumorigenic phenotypes.<sup>40</sup> SIRT4 knockout mice spontaneously develop lung tumors.<sup>40</sup> These studies indicate a crucial role of SIRT4 in linking glutamine metabolism with tumorigenesis.

### SIRT6 in cancer

There is a growing body of evidence showing SIRT6 as a tumor suppressor. SIRT6 is downregulated in several human cancers such as pancreatic cancer, colorectal cancer, and HCC, and its expression is associated with clinical outcomes in cancer patients.<sup>51,143,155</sup> SIRT6 deacetylates histones H3K9 and H3K56.<sup>19,46,156</sup> H3K56 has been shown to be hyperacetylated in breast, liver, skin, thyroid, and colon cancers.<sup>157</sup> Loss of SIRT6 leads to transformation of immortalized mouse embryonic fibroblasts, and the transformed SIRT6-deficient cells display increased glycolysis. In a conditional SIRT6 knockout mouse model, SIRT6 deletion increased the number, size, and aggressiveness of tumors.<sup>60</sup> In a genetic mouse model specific for liver cancer initiation, SIRT6 represses Survivin expression by reducing histone H3K9 acetylation and NF- $\kappa$ B activation, and the increased SIRT6 expression at the liver cancer initiation stage markedly impairs liver

cancer development.<sup>158</sup> Overexpression of SIRT6 leads to massive apoptosis in a variety of cancer cell lines but not in non-transformed cells.<sup>159</sup>

However, there is also some evidence inconsistent with its tumor suppression function. Compared to 17 normal volunteer controls, SIRT6 mRNA levels were significantly increased in 32 chronic lymphocytic leukemia patients, although its relationship with clinical prognosis was not clear.<sup>160</sup> SIRT6 protein levels are elevated in paclitaxel- and epirubicin-resistant MCF-7 cells compared to the parental cells. SIRT6 depletion sensitizes cells to both paclitaxel and epirubicin treatment, whereas SIRT6 overexpression leads to increased resistance. Consistently, the stronger immunostaining of SIRT6 in 118 breast cancer patient samples was significantly associated with poorer overall survival.<sup>161</sup> In pancreatic cancer cells, SIRT6 enhances Ca(2+) responses by activating Ca(2+) channel transient receptor potential cation channel, subfamily M, member 2 via modulating levels of ADP-ribose, which increases the expression of proinflammatory cytokines/chemokines, such as interleukin 8 and TNF, and promotes cell migration.<sup>162</sup>

## SIRT7 in cancer

SIRT7 mRNA expression is increased in breast and thyroid cancer, compared to their normal counterparts.<sup>163</sup> SIRT7 knockdown inhibits proliferation and induces apoptosis in U2OS cells.<sup>64</sup> SIRT7 specifically deacetylates histone H3K18, which is necessary for maintaining tumor phenotypes of human cancer cells, including anchorage-independent growth and the escape from contact inhibition.<sup>18</sup> Moreover, SIRT7 depletion markedly reduces the growth of human U251 cancer cell xenografts in mice.<sup>18</sup> Very recently, both mRNA and protein levels of SIRT7 were shown to be increased in HCC, and knockdown of its expression efficiently suppressed tumor growth in vitro and in vivo.<sup>164</sup>

However, in HNSCC, SIRT7 mRNA expression level is lower.<sup>143</sup> An antiproliferative role of SIRT7 has been demonstrated by using SIRT7 knockout or overexpressing cells, and an inverse correlation with tumorigenic potential has been shown in several murine cell lines.<sup>165</sup> In HeLa, Hep3B, MDA-MB-231, and HEK293T cells, a negative transcriptional regulation of HIF1 and HIF2 by SIRT7 was established, suggesting that SIRT7 may function as a tumor suppressor through HIF signaling.<sup>166</sup>

## Potential clinical implications of sirtuins in human malignancies

Apparently, sirtuins have complex roles in human malignancies. Several factors should be taken into consideration

regarding some contradictory laboratory observations.

- 1) Species difference. Mouse studies provide crucial *in vivo* evidence for tumor suppressor functions of several sirtuins. But the tumorigenesis process in mice is not identical to that in humans, in spite of similarity between the two processes.
- 2) Genes crucial for inhibiting tumor initiation may not necessarily play the same role in the later stages of cancer development. In fact, opposing roles of tumor promotion and suppression have been observed for many genes including telomerase reverse transcriptase, transforming growth factor beta, and DNA methyltransferases.<sup>66</sup>
- 3) Tissue difference. Genes may play different roles in different tissues, which in turn affects their functions in cancers of different tissue origins. In-depth understanding of the roles of individual sirtuins in a particular type of cancer would thus be necessary to better guide a therapeutic strategy with sirtuin modulation. Sirtuin modulators could possibly be used as a single agent for cancer treatment if a specific sirtuin is found to be crucial for a specific type of cancer.

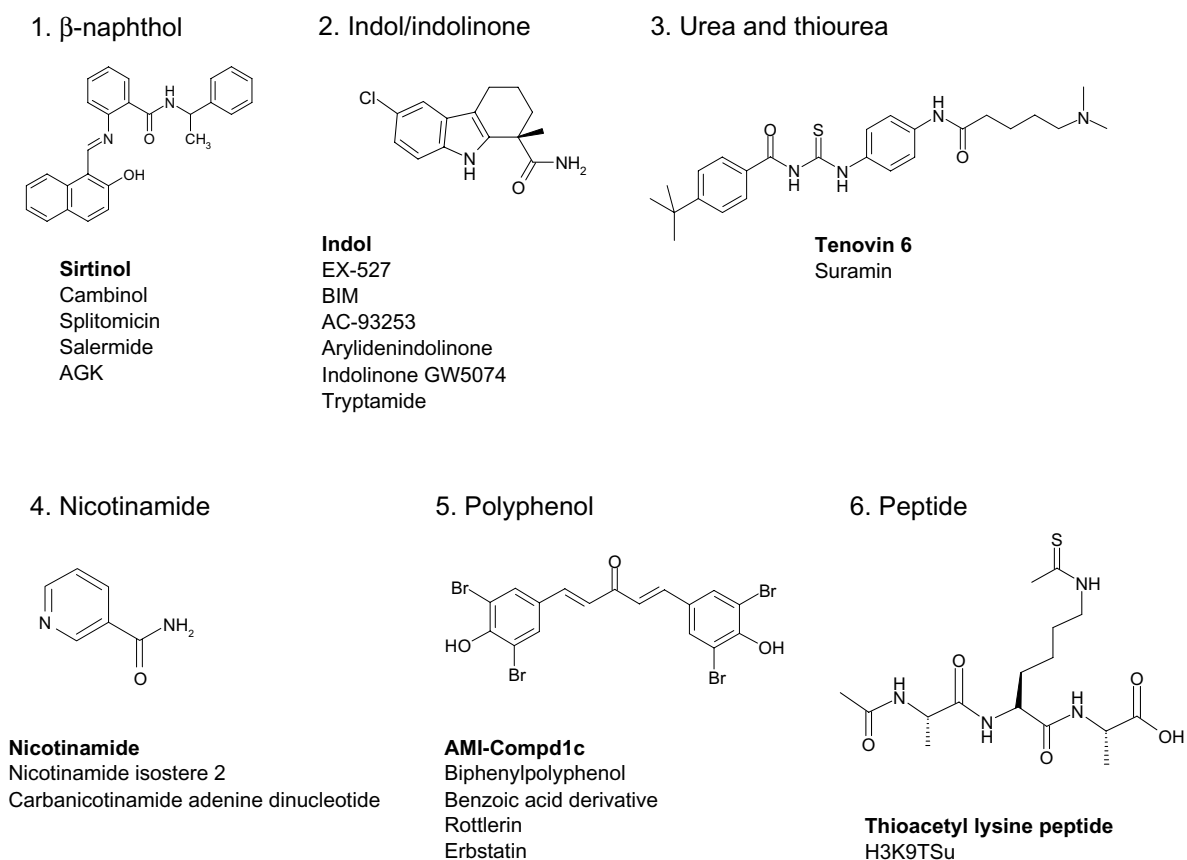
Although much research is still needed to understand SIRT2-7 in human malignancies, a consensus theme has now emerged from SIRT1 studies that it is crucial for cancer drug resistance. SIRT1 mediates multiple aspects of cancer drug resistance, by decreasing drug penetration, conferring proliferation and anti-apoptotic survival advantages to cancer cells, facilitating acquired resistance through genetic mutations, promoting survival of cancer stem cells, and changing the tumor microenvironment for resistance, as described above and in a recent review.<sup>167</sup> Inhibition of SIRT1 in combination with a cancer-cell-specific agent would greatly benefit cancer treatment. For example, SIRT1 inhibition plus a BCR-ABL kinase inhibitor would likely eradicate CML stem cells and prevent them from acquisition of resistant mutations, which may ultimately lead to a cure of the disease. However, there may be potential side effects of SIRT1 inhibition given that SIRT1 has complex roles in regulating a wide variety of cellular and physiological functions. Intriguingly, developmental defects observed in SIRT1 homozygous knockout mice are typically far more severe in inbred mouse strains than in outbred mouse strains.<sup>23</sup> Besides, heterozygous SIRT1 knockout has little impact on mouse development and physiology. Given that human populations are genetically heterogeneous and SIRT1 inhibition by small molecules is unlikely 100% as complete as by homozygous gene knockout, we speculate that SIRT1 inhibition by small molecules might have only mild side effects on humans, in particular, if such drugs would not be intended for life-long use. The side effects could be further reduced in adult patients without risk

of developmental impact. Therefore, SIRT1 is a promising target for cancer treatment.

Numerous SIRT1/sirtuin activators and inhibitors have been developed in the past decade.<sup>168–171</sup> Sirtuin inhibitors have been explored for cancer treatment. These inhibitors have diverse chemical scaffolds (Figure 2) and can be broadly classified into several categories: 1) Naphthol based inhibitors: for example, Sirtinol, Cambinol, Splitomicin, Salermide, AGK2. 2) Indol/indolinone based inhibitors: for example, EX-527, bisindolylmaleimide, tryptamide. 3) Nicotinamide based inhibitors: for example, carbanicotinamide adenine dinucleotide. 4) Urea and thiourea based inhibitors: for example, Tenovin and Suramin. 5) Polyphenol based inhibitors: for example, biphenylpolyphenol, benzoic acid derivative rottlerin, erbstatin. 6) Peptide based inhibitors: for example, thioacetyl-lysine peptides and H3K9TSu peptide 5. Among these inhibitors, tenovin-6<sup>111,121,122,172</sup> and cambinol<sup>108,119</sup> have been shown to have encouraging in vivo effect against cancers in animal studies. In a recent clinical trial, the pan-sirtuin inhibitor niacinamide was reported to improve therapeutic outcome when in combination with HDAC inhibition for treatment of human aggressive B-cell lymphomas.<sup>173</sup>

However, these inhibitors are neither potent enough nor specific enough, and their in vivo effect is also limited.<sup>122</sup> In addition, a specific SIRT1 inhibitor EX-527 is in a Phase II clinical trial for treating Huntington's disease,<sup>174</sup> although its effect on cancer remains unclear. Future efforts will be needed towards developing more selective and potent SIRT1 or other individual sirtuin inhibitors.

Crystal structures of SIRT2,<sup>175</sup> SIRT3,<sup>176</sup> SIRT5,<sup>177</sup> SIRT6,<sup>178</sup> and most recently, the SIRT1 catalytic core<sup>179</sup> have been determined. These crystal structures are expected to facilitate development of a new generation of selective sirtuin inhibitors. The conserved catalytic core of sirtuins consists of three structural parts: an NAD<sup>+</sup> binding domain based on a large Rossmann fold, a small zinc-binding domain, and an extended cleft between the two domains where the substrate binds. Most of current sirtuin inhibitors target either the substrate binding cleft or the NAD<sup>+</sup> binding domain according to docking studies.<sup>169,170</sup> The crystal structure of SIRT5 bound to suramin shows that suramin interacts with both the nicotinamide binding pocket (C-pocket) within the NAD<sup>+</sup> binding domain and the substrate cleft.<sup>177</sup> The C-pocket is also targeted by several other inhibitors such as an analog



**Figure 2** Various scaffolds of known sirtuin inhibitors.

of EX-527 on the SIRT1 catalytic core.<sup>179</sup> Thieno[3,2-d]pyrimidine-6-carboxamides, a new class of sirtuin inhibitors that have been most recently developed using encoded library technology, also bind to the C-pocket of SIRT3 but extend through the substrate cleft on the co-crystal structure.<sup>180</sup> Despite these progresses, certain difficulties remain, particularly for SIRT1, in that long and unstructured N-terminal and C-terminal sequences may influence catalytic core functions.<sup>79,181</sup> A small rigid N-terminal region (amino acids 190–244) appears to mediate the interaction of sirtuin activating compounds with SIRT1.<sup>182</sup> However, the large portions of unstructured sequences may play regulatory roles under cellular settings when SIRT1 is in complex with other proteins, and they may influence the functions of small molecule modulators and add some uncertainty to how the drugs act. A combination of biochemical, structural, and cell-based assays is thus necessary for drug development and will help improve the selectivity and specificity of candidate sirtuin inhibitors.

## Conclusion

Sirtuins have diverse functions in mammalian physiology and research of these genes is continuing to grow rapidly. More research findings are expected in cancer and other age-related diseases, particularly for those less-understood sirtuin members. Future results will not only shed new insight on their biological functions, but also help devise more rational application of sirtuin inhibitors or activators for treatment of cancer and other diseases. Generation of more potent and individual sirtuin-selective inhibitors will further accelerate the endeavor to improve the management of human malignancies.

## Acknowledgments

The authors would like to acknowledge the research support from the National Cancer Institute of the National Institutes of Health under award number R01 CA143421, and the State of California Tobacco Related Disease Research Program (TRDRP) award 20XT-0121 to WenYong Chen. The contents are solely the responsibility of the authors and do not represent the official views of the National Institutes of Health.

## Disclosure

The authors report no conflicts of interest in this work.

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