CELL CYCLE
2019, VOL. 18, NO. 18, 2164–2196
https://doi.org/10.1080/15384101.2019.1634953

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REVIEW

The sirtuin family in cancer

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ABSTRACT

Sirtuins are a family of protein deacylases and ADP-ribosyl-transferases, homologs to the yeast SIR2 protein. Seven sirtuin paralogs have been described in mammals, with different subcellular locations, targets, enzymatic activities, and regulatory mechanisms. All sirtuins share NAD^+ as substrate, placing them as central metabolic hubs with strong relevance in lifespan, metabolism, and cancer development. Much effort has been devoted to studying the roles of sirtuins in cancer, providing a wealth of data on sirtuins roles in mouse models and humans. Also, extensive data are available on the effects of pharmacological modulation of sirtuins in cancer development. Here, we present a comprehensive and organized resume of all the existing evidence linking every sirtuin with cancer development. From our analysis, we conclude that sirtuin modulation after tumor initiation results in unpredictable outcomes in most tumor types. On the contrary, all genetic and pharmacological models indicate that sirtuins activation prior to tumor initiation can constitute a powerful preventive strategy.

ARTICLE HISTORY
Received 13 February 2019
Revised 27 May 2019
Accepted 14 June 2019

KEYWORDS
Sirtuins; cancer; cancer therapy; cancer prevention

Introduction

The seven members of the sirtuin family comprise the class III of histone deacetylases (HDACs). They are protein deacylases and ADP-ribosyl-transferases, well conserved from yeast to mammals. All sirtuins share homology to the yeast protein SIR2 (Silent Information Regulator 2), a conserved catalytic domain, and dependence on nicotinamide adenine dinucleotide (NAD^+).

The yeast homolog, *SIR2*, was first identified as one of four complementation groups able to silence mating type loci in *Saccharomyces cerevisiae*, termed *SIR1, SIR2, SIR3,* and *SIR4* after Silent Information Regulator [1–3]. These genes were later also found to silence ribosomal DNA [4] and telomeres [5]. A major breakthrough in the history of the sirtuin family came with the discovery that SIR2, SIR3, and SIR4 could prevent genomic instability and, this way, increase lifespan [6,7]. These results started a long list of works studying the lifespan extension of different organisms overexpressing the homologs of *SIR2*. Overexpression of SIR2.1, the closest homolog to *SIR2* in the nematode *Caenorhabditis elegans*, was shown to extend lifespan [8], although the exact extension is still not clear [9,10]. Similar findings were observed in *Drosophila melanogaster*, where initial extension of lifespan in *sir-2.1* transgenic flies [11] was later under debate [10,12]. As a crucial mechanistic insight, Sir2 was identified as a NAD^+-dependent histone deacetylase [13–15]. In turn, NAD^+ levels increase during calorie restriction (CR), the most robust intervention increasing lifespan in all organisms tested. This effect was mediated at least partly by the induction of the enzyme pyrazinamidase/nicotinamidase 1 (PNC1 in yeast [16] and *C. elegans* [17]; D-NAAM in *Drosophila* [18]), that deaminates nicotinamide and thus activates sirtuins. Sir2 and its different homologs were then proposed to mediate CR-induced lifespan extension. Supporting this notion, Sir2 homologs depletion prevented CR-mediated lifespan extension in several organisms [11,19,20], although this dependence on Sir2 homologs for lifespan extension has also been questioned [10,21]. In mammals, deletion of SIRT1 was also shown to prevent CR-mediated effects in mice [22], although Sirt1-null mice already presented a severe phenotype prior to CR.

Sirtuins in mammalian cancer

Seven sirtuins homologs have been described in mammals (SIRT1-7) with different substrate preferences,

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enzymatic activities, cellular locations, and targets. All sirtuins share a common conserved NAD^+-binding domain but differ in their amino and carboxy-terminal regions that contribute to their catalytic activity and specific locations within the cell [23]. SIRT1 is primarily located in the nucleus but can shuttle between the cytosol and the nucleus depending mainly on the tissue, developmental stage and energetic demands [24]. SIRT2 is mainly located at the cytoplasm but can be found in the nucleus at the G2–M transition during mitosis [25]. SIRT3, SIRT4, and SIRT5 are located at the mitochondria [26]. Finally, SIRT6 and SIRT7 are located in the nucleus [27] and nucleolus [28] respectively.

Valuable revisions have already been written about the description of the sirtuin family, the physiological functions of mammalian sirtuins and their roles during age-related pathologies such as metabolic syndrome, cardiovascular disease or neurological disorders [29–32]. More specifically, there are several revisions on the roles of sirtuins in many cellular and physiological functions relevant to cancer, such as the Warburg effect [33], angiogenesis [34], autophagy [35], genome stability [36], oxidative stress [37,38], and others. In the present revision we will describe all available information about the pro- or anti-tumoral roles of each sirtuin member, grouped by tissue of origin of the tumor, briefly mentioning their most relevant mechanisms of action, when available. All this information is resumed in Table 1.

The main goal of our revision is to establish whether a certain sirtuin can be considered pro- or anti-tumoral in a certain tissue, given the published evidence. Since the amount of data is overwhelming, for the sake of space we have prioritized the inclusion of all published evidence in this regard, rather than to delve into detailed molecular mechanisms. In any case, when available, we have briefly explained the main mechanistic insight of the cited papers, and have summarized them in the section "*Common molecular features of sirtuins in cancer*" and in Table 2.

SIRT1

SIRT1, with 747 amino acids in humans, has been the most studied sirtuin so far. SIRT1 is the closest human homolog of the *S. cerevisiae* SIR2 protein. In addition, it also possesses two nuclear localization signals (NLS) and two nuclear export signals, that allow the shuttling of SIRT1 between the cytoplasm and the nucleus depending on the type of cell or physiological stress [24,39].

Mammalian SIRT1 has been proposed both as an oncogene and as a tumor suppressor. Initial reports suggested an oncogenic role of SIRT1, when it was identified *in vitro* as a regulator of the DNA-damage response by directly deacetylating p53 in the C-terminal lysine 382 residue, resulting in a repressive transcriptional activity and impaired senescence and apoptosis [40–42]. These *in vitro* findings were followed by many other reports showing that SIRT1 repressed several other tumor suppressors, and was repressed by tumor-suppressive regulatory loops (for an excellent revision on these molecular findings, refer to [43]). Most of these molecular mechanisms were described only using cultured tumor cells and have not been further tested in animal models. In contrast, studies using genetic models with moderate overexpression of SIRT1 revealed not only a protective role for this protein in the promotion of healthy aging, metabolic syndrome, and neurodegeneration but also in some types of cancer [44–47]. Given the extensive literature on SIRT1 in cancer, in this revision, we will focus on studies describing human tumor samples or mouse models.

In the liver, SIRT1 has been repeatedly found overexpressed in human hepatocellular carcinoma compared to normal adjacent tissue [48–53], and patients with SIRT1-overexpressing tumors showed worse survival [49,52,54] or higher grade tumors [48]. In contrast, other reports showed a reduction in SIRT1 protein levels in hepatocellular carcinoma compared with normal liver samples [55]. Also, mice overexpressing SIRT1 were protected from developing diethylnitrosamine-induced liver carcinomas by enhancing the DNA-damage response [45].

In the lung, high SIRT1 expression has also been found associated with worse prognosis in non-small cell lung carcinoma [54,56], where it deacetylated and activated the actin-binding oncogene cortactin [56]. Also in NSCLCs, tumors with high SIRT1 expression, low acetyl-p53, and low

Table 1. Summary of the existing evidences for oncogenic [OG] or tumor suppressor [TS] functions of the different sirtuin family members in the indicated tissues.

Tissue	Sirt1	Sirt2	Sirt3	Sirt4	Sirt5	Sirt6	Sirt7
Liver	[OG] Increased in tumors [48–53], associated with worse prognosis [48,49,52,54].	[OG] Upregulated in human tissues of HCC[103,104].			[OG] Increased in HCC, correlated with poorer survival [184].	[OG] Increased in higher-grade HCC, associated with decreased survival [221].	[OG] Increased in higher grade HCC. SIRT7 ablation reduced xenograft growth [251].
	[TS] Reduced in hepatocellular carcinoma [55]. Increased SIRT1 reduced HCC in mice [45].	[TS] Protects from HCC development in mice [100]. Decreased in human HCC [100].	[TS] Downregulated in human HCC [131–134]. Lower levels associated with reduced overall and recurrence free survival [131].	[TS] Decreased in HCC, which correlated with decreased survival. Sirt4-deficiency enhanced HCC in mice [164].	[TS] Decreased SIRT5 in HCC samples is associated with poorer survival [188].	[TS] Suppressed in initial stages [215] or in higher grade HCC [202,217,219,220].	
Lung	[OG] Worse prognosis in NSCLCs [54,56,57].	[OG] Upregulated in human NSCLC samples [111].	[OG] Worse prognosis and survival in NSCLC [135].	[OG] Overexpression in tumors, enhanced aggressiveness in vitro [154].	[OG] High SIRT5 expression in lung tumors, which associated to decreased survival [182,192].		
	[TS] Protects from KRas-driven adenocarcinomas in mice [58].	[TS] Downregulated in NSCLCs [105–107]. Protects from KRAS driven tumors [108,109].		[TS] Spontaneous tumors in *Sirt4*-deficient mice [165]. Decreased in SCLC and LAC [165], correlating with decreased survival [165–167].		[TS] Decreased in NSCLC [224]. Cytoplasmic/inactive SIRT6 correlated with worse prognosis [225].	
Breast	[OG] Increased in tumors, associated to worse prognosis [54,59–61].	[OG] Enhances basal differentiation, stemness and invasion in TNBC [113]. Its inhibition reduces xenograft growth [114].	[OG] Overexpression associated with decreased overall and disease-free survival [141].	[OG] Overexpression in tumors [169].	[OG] High SIRT5 in tumors was associated with increased metastasis and decreased survival [186].	[OG] Increased in aggressive tumors, associated to poorer survival [226].	[OG] Increased in early stage-tumors [252].
	[TS] Decreased in human tumors [55,63]. Its increase inhibited xenograft growth [63].	[TS] Downregulated in human tumors [100].	[TS] Downregulated in all tumor stages [128,130,138]. Ablation induces tumor formation in female mice [130].	[TS] Decreased expression in tumors [163,165]. Lower expression was associated with shorter survival [168].	[TS] Higher SIRT5 is associated to better response to chemotherapy [186].	[TS] Reduced in high-grade tumors [227].	[TS] Decreased in human metastasis; its overexpression inhibits xenograft metastasis [253].
Pancreas	[OG] Increased in tumors [64,65], associated with more metastasis [65].						
	[TS] SIRT1 inhibition enhanced tumor formation in mouse xenografts [67].	[TS] Protects from KRAS driven pancreatic cancer in mice [108,115].	[TS] Downregulation associated with decreased survival [142].			[TS] Low expression in PDACS [214,228], associated to poorer survival [228].	

(*Continued*)

Table 1. (Continued).

Tissue	Sirt1	Sirt2	Sirt3	Sirt4	Sirt5	Sirt6	Sirt7
Colon	[OG] Elevated in MYC-driven human colorectal carcinomas [68,69].		[OG] Higher SIRT3 associated with shorter survival and increased metastasis [143,144].		[OG] Overexpressed in CRC, associated with reduced survival [185,195]. Protects from chemotherapy toxicity [195].		
	[TS] Protects $APC^{min/+}$ mice from tumors [71]. Decreased in high-grade tumors, SIRT1 depletion accelerated xenograft tumors [72].	[TS] Decreased in colorectal carcinoma human samples [116].		[TS] Decreased in tumors, associated with reduced survival [163,170,171].		[TS] Decreased expression is associated with poorer survival in humans and in mice [214,229].	
Immune System	[OG] Increased in AML [74–76], ATL [77], B-cell CLL and CML [78], reduced survival in B-cell lymphoma [73]. Its inhibition prevented CML [78] or Burkitt lymphoma [79] xenografts.	[OG] Increased in AML [118]. Associated with shorter overall and event free survival [119].	[OG] Increased in DLBCL tumors, associated to poorer outcome [146].		[OG] Increased in Waldenström macroglobunemia [183].	[OG] Increased in MM^{233} and AML [231], which correlated with poorer survival by promoting DNA repair and chemotherapy insensitivity.	
	[TS] Accelerated lymphomas in SIRT1-KO mice [55]. Its overexpression protected from lymphoma in p53± mice [80].		[TS] Decreased in mantle cell lymphomas and CLL, associated with worse survival [145].	[TS] Protected from lymphomas in Eμ-Myc mice [173]. Decreased in acute and chronic leukemia [165].			
Prostate	[OG] Overexpressed in high-grade human tumors [81,82]. SIRT1 overexpression enhances tumors in mice [82,83].						[OG] Increased in more aggressive and metastatic tumors [254].
	[TS] Decreased expression in PCA, even lower in metastasis [55].	[TS] Downregulated in human tumors, which associated with worse prognosis [120].	[TS] Downregulated in prostate carcinoma [147]. Lower levels associated with increased metastasis [148].				
Thyroid	[OG] SIRT1-Tg, PTEN-het mice had more tumors [83]. Increased in human tumors [85].					[OG] Overexpressed in PTC, associated with increased nodal metastasis [232].	
			[TS] Downregulated in well-differentiated thyroid carcinoma [149].				
Stomach	[OG] Increased in poor-survival patients [86,87].						[OG] High SIRT7 correlates with decreased survival [255].
	[TS] Decreased in human tumors. Its increase reduced xenograft tumors in mice [88].		[TS] Downregulated in human tumors [150]. Lower SIRT3 associated with decreased survival [151,152].	[TS] Decreased in tumors, associated with reduced prognosis and survival [163,165,174].			

(*Continued*)

Table 1. (Continued).

Tissue	Sirt1	Sirt2	Sirt3	Sirt4	Sirt5	Sirt6	Sirt7
Kidney		[OG] Upregulated in human renal cell carcinoma. Associated with poor prognosis [121].					
				[TS] Decreased in RCC, associated with decreased survival [175].			
Skin/ SCC	[OG] Increased in SCC [89] and melanoma [90].	[OG] Increased in melanoma metastasis [122] and SCC biopsies [89].	[OG] Increased in SCC biopsies [89] and in melanomas [153].	[OG] Increased in SCC biopsies [89].	[OG] Its ablation inhibits melanoma xenograft tumors in mice [256]. Increased in SCC biopsies [89].	[OG] Decreased SIRT6 prevented skin tumors in mice [233]. SIRT6 is increased in human SCC tumors [197,234] and blood [235], and in melanoma [236,237].	[OG] Increased in SCC biopsies [89].
		[TS] Decreased in SCC, Sirt2-KO mice had more aggressive tumors [123]. Reduced in BCC [124].	[TS] Decreased in BCC [124].			[TS] Decreased SIRT6 induced resistance to MAPK inhibitors [238].	
Ovary	[OG] Increased in early-stage tumors [91]. Decreased survival [92].						
	[TS] Decreased in high-grade tumors [91]. Decreased in mucinous, serous and endometrioid carcinoma [55].		[TS] Downregulated in human metastatic cancer [154].	[TS] Downregulated in human ovarian tumors [163,165].		[TS] Decreased in tumors [239].	
Brain	[OG] Increased in medulloblastomas [94].	[OG] SIRT2 inhibition prevented xenograft growth [125].					
	[TS] Decreased in glioblastomas [55].			[TS] Worse prognosis in neuroblastoma with lower SIRT1 [176].	[TS] Higher SIRT5 slowed xenograft growth [196].		

Table 2. Summary of the common molecular features of the different sirtuins in cancer.

Protein	Sirt1	Sirt2	Sirt3	Sirt4	Sirt5	Sirt6	Sirt7
DBC1	[OG] Higher expression of SIRT1 and DBC1 in breast [59,61] and gastric [87] tumors.						
c-MYC	[OG] Increased c-MYC and SIRT1 in colon [68,69], AML [75] and thyroid [83] tumors.	[OG] SIRT2 increases c-MYC stability in breast tumors [114].	[TS] SIRT3 destabilizes c-MYC [147].			[TS] SIRT6 repressed the c-MYC-mediated transcription of the oncogene *Lin28b* in pancreas [228]; and mediated the repression of c-MYC-driven transcription by UCP10 in colon cancer [229].	
p53	[OG] SIRT1 deacetylates at K382 and inhibits p53 [41], and high SIRT1 and low acetyl-p53 correlated with poor survival in lung tumors [57].		[OG] SIRT3 deacetylated at K320 and K382 and destabilized p53 in NSCLC [136].				[OG] SIRT7 deacetylated and inhibited p53 [250].
EMT	[OG] SIRT1 enhances the expression of ZEB1 and EMT in prostate tumors [84].		[TS] SIRT3 inhibits inhibits expression of TWIST in ovarian carcinoma [154] and the Wnt/β-catenin pathway in prostate tumors [148].			[TS] SIRT6 inhibited TWIST expression and EMT in NSCLC [224].	[TS] SIRT7 deacetylated and destabilized the EMT driver SMAD4 in lung metastasis of breast tumors [253]. [OG] SIRT7 promoted EMT in prostate cancer cells [253].
KRas		[TS] SIRT2 deacetylated and inhibited KRas in lung [108,109] and pancreas [108,115] cancer models.					
JMJD2A		[TS] SIRT2 inhibited the expression of the oncogene JMJD2A in lung cancer [105,110].					

(*Continued*)

Table 2. (Continued).

Protein	Sirt1	Sirt2	Sirt3	Sirt4	Sirt5	Sirt6	Sirt7
PKM2		[TS] SIRT2 deacetylated at K305 and activated PKM2, reducing breast tumor growth [112].			[OG] SIRT5 desuccinylated at K311 and K498 and activated PKM2, promoting breast tumor growth [201].	[TS] SIRT6 deacetylated PKM2 at K433, promoting its nuclear export and inhibiting its oncogenic functions [217].	
HIF1α			[TS] SIRT3 destabilizes HIF1a and reduces breast tumor growth [128].			[TS] SIRT6 loss led to stabilization of HIF1α and promoted pancreas tumors [228].	
SOD			[TS] SIRT3 deacetylates and activates SOD2 in B cell malignancies [145].		[TS] SIRT5 desuccinylated and activated SOD1, decreasing lung tumor cell growth [194].		
IDH2			[TS] SIRT3 deacetylates and activates IDH2 in B cell malignancies [145] and in breast cancer [129].				
Notch			[TS] SIRT3 inhibits Notch1 expression and reduces gastric cancer [150].			[TS] SIRT6 inhibited NOTCH3 expression and ovarian cancer cell proliferation [239]	
Glutamine catabolism			[OG] SIRT3 deacetylated and activated GDH, promoting DLBCL [146].	[TS] SIRT4 ADP-rybosylated and inhibited GDH and glutamine metabolism, preventing liver [164], lung [165] and Burkitt B cell lymphoma [173].	[OG] SIRT5 deglutarylated and activated GDH, promoting CRC progression [185]		
SHMT2			[OG] SIRT3 deacetylated at K75 and activated SHMT2 in colon cancer cells [144].		[OG] SIRT5 desuccinylated at K280 and activated SHMT2 in several cancer cell lines [257].		
mTOR			[TS] SIRT3 reduced mTORC1 signaling and breast tumor growth [139].	[TS] SIRT4 inhibited mTOR signaling and liver tumor progression [164]			
miR-34a						[OG] SIRT6 is a target of the tumor suppressor miR-34a in oral SCC [234].	[OG] SIRT7 inhibited the expression of miR34a, promoting stomach tumor growth [255].

levels of the SIRT1 inhibitor HIC1 correlated with decreased overall survival [57]. In contrast, our group recently reported that mice with moderate overexpression of SIRT1 from the germline were protected from mutant KRas-driven lung adenocarcinomas [58].

In breast cancer, SIRT1 expression has been found upregulated in breast tumors compared with normal tissue in several reports, and higher SIRT1 expression correlated with worse prognosis [54,59–61]. Interestingly, in two of these reports increased SIRT1 levels associated with increased expression of Deleted in Breast Cancer 1 (DBC1) [59,61]. Since DBC1 is a SIRT1 inhibitor [62], these histopathological findings could indicate that SIRT1 levels are increased as a compensation to the increased DBC1 expression or vice versa, leaving the open question of which of the two proteins is actually driving tumor development. In contrast, SIRT1 levels were found decreased in breast cancer samples, compared to normal tissue [55]. Also, SIRT1 levels were reduced in BRCA1-mutant breast tumors, and SIRT1 overexpression in BRCA1-mutant breast cancer cell lines inhibited xenograft tumor growth [63].

In the pancreas, increased SIRT1 was found in pancreatic tumors compared to normal nearby tissue [64,65], and it was associated to larger tumor size, lymph node spread and/or distant metastasis [65]. In contrast, mRNA analysis of human pancreatic ductal adenocarcinoma samples revealed no change in *SIRT1* expression between tumoral and normal tissue [66]. Importantly, xenograft tumors in immunodeficient mice from PANC-1 pancreatic cancer cells grew more rapidly when treated with the SIRT1 inhibitor EX527, suggesting a global tumor-suppressor effect of SIRT1 in this setting [67].

In the colon, elevated expression of c-MYC in human colorectal carcinomas correlated with increased SIRT1 protein levels [68], and these increase correlated with malignant transformation in serrated colorectal carcinomas [69]. SIRT1-deficient mice developed the same number and sizes of tumors when crossed with the intestine mutant mouse line $APC^{Min/+}$. [70]. In contrast, in a meta-analysis study, increased SIRT1 expression did not correlate with decreased overall survival in colon cancer patients [54]. Also, intestinal-specific SIRT1 overexpression protected mice from intestinal tumors development in an $APC^{Min/+}$ background by deacetylating and inactivating the tumorigenic nuclear beta-catenin protein, and SIRT1 expression in human intestinal tumors showed an inverse correlation with nuclear beta-catenin [71]. In another report, SIRT1 expression was lower in high-grade colon carcinoma samples, and depletion of SIRT1 in colon carcinoma cell lines accelerated xenograft tumor growth in mice [72].

In tumors of the immune system, SIRT1 overexpression was found to correlate with shorter survival in diffuse large B-cell lymphoma [73]. Primary acute myeloid leukemia (AML) blasts [74–76], adult T-cell leukemia/lymphoma (ATL) [77], B-cell chronic lymphocytic leukemia, and chronic myeloid leukemia [78] showed increased SIRT1 expression, compared with healthy controls. In AML, increased SIRT1 expression was associated with c-MYC-mediated SIRT1 protein stabilization [75] and prevented genotoxic stress-induced p53 activation. Finally, SIRT1 inhibition by cambinol [79] or by Tenovin-6 inhibited the growth of Burkitt lymphoma [79] or chronic myeloid leukemia [78] xenografts in immunodeficient mice, respectively. In contrast, SIRT1-deficient mice showed accelerated development of lymphomas [55], and lymphocyte-specific overexpression of SIRT1 protected from irradiation-mediated lymphoma development in a $p53^{+/-}$ background [80]. Finally, whole-body SIRT1-overexpressing mice developed lymphomas with the same frequency than control wild-type mice [45].

In prostate, SIRT1 was found overexpressed in human prostate carcinomas, compared with normal nearby tissue [81,82], and this increase was more evident in high-grade prostate tumors. In mice, SIRT1 levels were higher in the tumors obtained in the transgenic adenocarcinoma of mouse prostate – TRAMP mouse model, associated with decreased levels of the SIRT1 inhibitor HIC1 [82]. Also, increased SIRT1 levels facilitated the formation of in situ prostate carcinomas in mice heterozygous for PTEN [83]. Finally, deletion of SIRT1 in prostate cancer cell lines reduced their ability to form xenograft tumors in immunodeficient mice by inhibiting the transcription of the

epithelial to mesenchymal transition (EMT) driver ZEB1 [84]. In contrast, analysis of prostate carcinoma samples revealed a decreased expression of SIRT1 compared with normal tissue, and this expression was even lower in metastatic lesions [55].

In the thyroid gland, in accordance with the findings in prostate, SIRT1-overexpressing, PTEN-haploinsufficient mice developed more thyroid carcinomas through a mechanism dependent on the stabilization of the oncoprotein c-MYC [83]. In agreement, SIRT1 levels were found increased in human thyroid tumors, together with reduced expression of the SIRT1 inhibitor HIC1, probably by increased HIC1 promoter methylation [85].

In the stomach, SIRT1 expression was found increased in gastric cancers patients with poor prognostic [86,87]. Interestingly, as discussed above for breast cancer reports, SIRT1 expression in some of these gastric tumors was tightly correlated with the expression of the SIRT1 inhibitor DBC1, again opening the question of which of the two proteins is the driver of the tumor development [87]. In contrast to these reports, SIRT1 levels were found downregulated in gastric tumors compared with their matched normal tissue samples; and xenograft tumor growth was inhibited by overexpression of SIRT1, and enhanced by *Sirt1* knock-down in gastric cancer cell lines inoculated in nude mice [88]. Finally, in the previously cited meta-analysis study by Wang and colleagues, increased SIRT1 expression did not correlate with decreased overall survival in gastric cancer patients [54].

In the skin, SIRT1-deficient mice developed the same number and sizes of tumors in a DMBA-TPA protocol for skin papillomas formation [70]. SIRT1 has been shown overexpressed in SCC [89] and in human melanoma tumors and cell lines, and its inhibition reduced the growth of human melanoma cell lines [90].

In the ovary, SIRT1 levels have been found increased in serous carcinomas in general. However, SIRT1 expression decreased in high-grade serous carcinomas compared with low-grade tumors, and increased expression of SIRT1 in serous ovarian carcinoma correlated with increased overall survival, indicating that SIRT1 would enhance early-stage ovarian serous tumors, but would slow high-grade tumors growth [91]. A different report showed that SIRT1 levels were increased in endometrioid, mucinous, and clear cell carcinomas, but not in serous carcinomas, although the number of tumors analyzed for each case was rather low. Taking all ovarian tumors analyzed, increased SIRT1 expression was a significant predictor of shorter survival [92]. By contrast, SIRT1 levels were found downregulated in ovarian mucinous, serous, and endometrioid adenocarcinomas compared with normal ovary samples [55].

In soft tissues, SIRT1 was found highly expressed in several types of human soft tissue neoplasms, as angiomyolipoma, paraganglioma, leiomyoma, leiomyosarcoma, and rhabdomyosarcoma, although the number of tumors analyzed was rather low [93]. In contrast, whole-body SIRT1-overexpressing mice developed fewer sarcomas compared with wild-type control littermates [45].

In central nervous system tumors, SIRT1 was found overexpressed in all three morphological subtypes of medulloblastomas (large cell/anaplastic cell; classical; and nodular/desmoplastic), compared to tumor-surrounding noncancerous cerebellar tissues [94]. In contrast, analysis of glioblastoma samples revealed a decreased expression of SIRT1 in tumors versus normal tissue [55].

SIRT2

SIRT2, with 389 amino acids in humans, is a human homolog of the yeast SIR2, located mainly in the cytosol [95,96]. In this compartment, SIRT2 colocalizes with the microtubule network, where it targets and directly deacetylates α-tubulin at lysine 40, an important protein in microtubule dynamics [97]. During cell cycle progression, SIRT2 activity can be regulated by the cyclin E-CDK2, cyclin A-CDK2, and p35-CDK5 complexes, that directly phosphorylate and inactivate SIRT2 at serine 331, resulting in impaired migration and adhesion [98]. During mitosis, SIRT2 expression levels increase dramatically [99]. Also, in G2/M phase a G2/M phase transition, SIRT2 is shuttled to the nucleus where it deacetylates histone H4 at lysine 16 and promotes proper mitotic progression [25].

Studies with *Sirt2* knock-out mouse models highlighted the importance of this sirtuin in mitosis and genomic stability *in vivo*. In these models, SIRT2 was shown to work as a positive regulator of the anaphase-promoting complex/cyclosome (APC/C) through the deacetylation and activation of CDH1 and CDC20, improving genomic stability and proper mitotic progression. In agreement, SIRT2-deficient mice developed gender-specific tumors [100]. Supporting these findings, another study found that the APC/C complex can be activated through SIRT2-mediated deacetylation of BUBR1 at lysine 250 [101]. SIRT2 was found to increase the deposition of H4K20 methylation, through a mechanism dependent on the deacetylation of H4K16 [102]. Taken together these studies elucidated an important role for this protein in the regulation of proper mitotic progression and genomic stability *in vivo*, suggesting a possible role for SIRT2 in the process of tumorigenesis.

In the liver, SIRT2 deficiency in mice was reported to increase the formation of hepatocellular carcinomas (HCC) in males. The same work found that human HCC samples showed decreased expression levels of SIRT2 compared to non-tumorigenic tissue [100]. By contrast, other studies with HCC cell lines revealed that depletion of SIRT2 inhibited mobility, invasiveness, and epithelial to mesenchymal transition through a mechanism dependent on the deacetylation and activation of protein kinase B (PKB) [103], and phosphoenolpyruvate carboxykinase 1 and glutaminase [104]. These two reports also found that SIRT2 is upregulated in human tissues from patients with HCC [103,104].

In the lung, SIRT2 was reported to be downregulated in NSCLC samples compared to paired non-invasive lung tissue [105–107]. Mechanistically, several SIRT2 targets have been identified in lung tumor models. Using *in vitro* and mouse xenograft models revealed that SIRT2 bound to the promoter region of *JMJD2A* and inhibited lung tumor formation [105]. Also, SIRT2 deacetylated and induced the degradation of SKP2, resulting in increased levels of p27 and NSCLC growth suppression [106]. Finally, SIRT2 was shown to be protective in the context of KRAS-driven tumorigenesis by a mechanism dependent on the direct deacetylation and inactivation of KRAS [108,109]. Increased expression of miR150 reduced SIRT2 levels, increasing JMJD2A and enhancing proliferation of several NSCLC cell lines [110]. By contrast, SIRT2 levels were found upregulated in human NSCLC samples compared to normal lung, which associated with decreased levels of the SIRT2 inhibitor SPOP, although the number of samples analyzed was rather low [111].

In breast, histological studies found downregulation of SIRT2 in human breast tumors when compared to normal tissue [100]. Mechanistically, one study showed that SIRT2 inhibited glycolysis through deacetylation and activation of pyruvate kinase isoform M2 (PKM2) at lysine 305. Ectopic overexpression of a constitutively deacetylated a PKM2 mutant was the one that reduced glucose metabolism and inhibited tumor growth in SIRT2-deficient mammary tumor cells [112]. Although these reports prompted the hypothesis that SIRT2 could work as a tumor suppressor in breast cancer, in the context of triple negative breast cancer (TNBC) the role of SIRT2 seems to be the opposite. For instance, SIRT2 is responsible for the deacetylation and stabilization of SLUG in a basal like-breast cancer cell line, a model for TNBC, enhancing basal differentiation, stemness, and invasion [113]. Immunohistochemistry studies revealed that SIRT2 levels were significantly higher in human TNBCs when compared to non-TNBCs. This increase was more pronounced in invasive ductal carcinomas (IDC) than in invasive lobular carcinomas (IDC) [113]. In accordance, other report revealed that pharmacological inhibition of SIRT2 decreased c-MYC stability and reduced tumor growth in TNBC xenografts [114].

In the pancreas, SIRT2-deficient mice developed more pancreatic tumors in a mutant KRAS background [108]. Interestingly, SIRT2-deficient mice developed enhanced pancreatic inflammation and spontaneous KRAS mutations after exposure to caerulein, an inducer of pancreatic inflammation [115].

In the colon, SIRT2 expression was reduced in colorectal carcinoma samples, and this reduction was even higher in metastatic tumors. In accordance, the anti-tumor effects of shikonin were shown to be mediated by SIRT2 overexpression [116]. In KRAS-driven colon cancer cell lines, loss of SIRT2 was associated with increased resistance to MEK inhibitors [117].

In immune cells, SIRT2 was shown to sustain cell proliferation in AML cell models. Mechanistically, SIRT2 deacetylated and activated G6PD at lysine 403, promoting NADPH production and supporting biosynthesis of macromolecules to sustain cell proliferation. More importantly, the same study found SIRT2 overexpression and increased G6PD catalytic activity in samples from patients with AML [118]. Another independent study found that elevated SIRT2 expression in human AML samples was associated with shorter overall survival and event-free survival [119]. These findings suggest a tumor promoter role for SIRT2 in the context of AML. In agreement, inhibition of SIRT2 reduced the growth of Burkitt lymphoma [79] or adult T-cell leukemia/lymphoma cells [79].

In the prostate, histological studies revealed that SIRT2 was downregulated in human tumors, and low SIRT2 was associated with higher grade tumors and worse prognosis [120].

In the kidney, SIRT2 was found to be upregulated in human renal cell carcinoma samples, and this increase was associated with poor prognosis [121]. SIRT2 overexpression increased stem cell growth and resistance to fluorouracil-induced apoptosis in renal carcinoma cell lines, and enhanced tumor growth in mouse xenografts [121].

In the skin, SIRT2 expression was not altered in primary melanoma tumors compared with benign nevi controls, but higher SIRT2 expression was found in lymph node metastases, although the number of samples was rather low [122]. By contrast, loss of SIRT2 in B-RAF melanoma cell lines was associated with increased resistance to BRAF inhibitors [117]. In SCC, higher SIRT2 transcription was found in human SCC biopsies [89], although a conflicting report showed decreased SIRT2 protein expression in human SCC samples, and Sirt2-deficient mice showed increased stemness markers and proliferation [123]. In BCC, SIRT2 mRNA was significantly reduced in tumor samples [124].

In the brain, SIRT2 was shown to be responsible for the development of glioblastoma cells. *Sirt2* knock-down and pharmacological inactivation by AGK2 (a SIRT2 specific-inactivator) inhibited cell growth and tumorigeneses in this model both *in vitro* and *in vivo*. The mechanism was dependent on SIRT2 deacetylation of p73 and inactivation of its transcriptional activity [125].

SIRT3

SIRT3, with 399 amino acids in humans, is one of the three sirtuins localized in the mitochondria, along with SIRT4 and SIRT5 [126]. Much smaller than SIRT1 and located in the mitochondrial matrix, SIRT3 has been repeatedly shown to deacetylate key proteins required for proper mitochondrial function under stress conditions [127]. Early studies using *Sirt3* knock-out MEFs revealed that SIRT3 loss led to the stabilization of HIF1α [128] and to the inhibition of isocitrate dehydrogenase 2 (IDH2) enzymatic activity [129], triggering metabolic adaptations towards glycolysis.

Sirt3 knock-out MEFs showed increased superoxide formation, chromosomal instability and decreased mitochondrial integrity when exposed to c-MYC and/or RAS overexpression, were more prone to transformation and showed increased aneuploidy when compared to *Sirt3* wild-type MEFs [130].

In the liver, both SIRT3 mRNA and protein levels were found significantly downregulated in tissues from patients with HCC [131–134] and HCC tumor cell lines [131,134]. Lower levels of SIRT3 were also associated with reduced overall and recurrence-free survival, reduced tumor differentiation, more tumors in advanced stages, higher serum alpha-fetoprotein levels, and multiple tumor numbers [134]. In HepG2 cells, SIRT3 overexpression suppressed cell growth, invasion, and apoptosis [131,132], and SIRT3 upregulation induced the expression of MnSOD, p53, BAX, and FAS [132].

In the lung, increased SIRT3 mRNA and protein expression were associated with worse prognostic and reduced survival in NSCLC patients [135]. Using H520 and SW90 cells, the same study found that SIRT3 colocalized and increased AKT phosphorylation [135]. A further study from the same group found that SIRT3 levels were upregulated in human PTEN-deficient lung tumors, which closely correlated with decreased p53 levels. In the NSCLC cell line H520, SIRT3 deacetylated p53 at lysine 320 and 382, which

decreased p53 stability through ubiquitin-mediated proteasomal degradation [136]. One additional study found that SIRT3 interacted with and deacetylated nicotinamide mononucleotide adenylyltransferase 2 (NMNAT2) to promote mitotic entry and cell proliferation in A549 cells [137]. Taken together these findings highlight an oncogenic role for SIRT3 in lung cancer.

In breast, SIRT3 was found to be downregulated in all breast tumor stages, and this decrease was associated with poor clinical prognosis [128,130,138]. One additional report found that SIRT3 levels were also lower in breast cancer luminal B compared to luminal A, which associated with increased acetylation of IDH2 at lysine 413 [129]. In *Sirt3* knock-out mouse models, females were more prone to develop mammary gland tumors with characteristics of invasive ductal carcinoma. These tumors developed spontaneously after 12 months, were well differentiated and were estrogen and progesterone receptor positive [130]. In mouse xenografts with MDA-MB -231 cells, SIRT3 overexpression was able to inhibit tumor growth through suppression of the mTORC1 pathway [139]. In cellular models of breast cancer, SIRT3 was able to inhibit cell growth, glycolytic phenotype [128] and increase the susceptibility to hyperoxic treatments [140]. By contrast, one report found that higher expression of SIRT3 in human breast cancer was associated with decreased overall and disease-free survival. This report also found that genetic inhibition of *SIRT3* by RNA interference in MDA-MB -231 and BT-549 cells inhibited cell proliferation, migration, and invasion [141]. Of note, different technical approaches were used to study the effect of SIRT3 in MDA-MB-231 cells in both reports, that may explain their divergent results: in Finley et al. this model was used in 3D culture and mouse xenografts [128], whereas in the report from He et al. the study was conducted using cells in monolayer [141].

In the pancreas, one report found SIRT3 levels downregulated in human pancreatic cancers, which associated with decreased overall survival [142].

In the colon, SIRT3 increased expression was associated with decreased survival, increased lymph node metastasis and disease progression [143]. In SW480 and DLD-1 colon carcinoma cell lines, SIRT3 overexpression increased proliferation, migration, and invasion [143]. More recently, SIRT3 was found to bind and deacetylate the serine hydroxymethyltransferase 2 (SHMT2) at lysine 75, a protein frequently increased in tumors. Acetylated SHMT2 was shown to be more stable and active, promoting colon cancer cells proliferation [144]. In human colon cancer samples, higher SIRT3 expression levels were associated with decreased SHMT2 acetylation and global levels of expression, and correlated with decreased overall survival [144]. These results strongly support the hypothesis that SIRT3 works as an oncogene in the context of human colon cancer.

Decreased SIRT3 was found in several B cell malignancies, such as mantle cell lymphomas and chronic lymphocytic leukemia, which was associated with worse overall survival. Mechanistically, SIRT3 was found to deacetylate and activate IDH2 and SOD2 [145]. In contrast, increased SIRT3 expression was found in tumor cells from four independent clinically annotated patient cohorts of diffuse large B-cell lymphoma (DLBCL), and this increase was linked to worse outcome. Mechanistically, SIRT3 was necessary for proper TCA cycle functioning by deacetylating and hyper-activating mitochondrial glutamate dehydrogenase (GDH), and SIRT3 ablation or pharmacological inhibition produced a growth arrest by collapsing the TCA and inducing autophagy in DLBCL cells [146].

In prostate, SIRT3 was found downregulated in human samples of prostate carcinoma but not in prostatic intraepithelial neoplasia [147]. In addition, one different study showed that lower SIRT3 levels were associated with increased metastasis [148]. Both studies concluded that SIRT3 overexpression was able to inhibit tumor growth in mouse xenografts and cell lines of prostate cancer [147,148]. Mechanistically, SIRT3 overexpression in cells suppressed AKT phosphorylation, induced the ubiquitination and destabilization of c-MYC [147] and suppressed EMT through the inhibition of the WNT/ β-catenin pathway and the activation of FOXO3a [148].

In the thyroid gland, one report described that SIRT3 was downregulated in human samples of well-differentiated thyroid carcinoma [149].

In the stomach, SIRT3 was found to be downregulated in human gastric cancer tissues and cell lines, at least partly by inhibiting NOTCH-1 and suppressing cancer cell growth [150]. In addition, SIRT3 decrease was associated with shorter overall and disease-free survival in gastric cancer patients [151,152].

In the skin, higher SIRT3 transcription was found in human SCC biopsies [89]. SIRT3 was also increased in human melanoma samples, and *SIRT3* knockdown induced cell cycle arrest and senescence, and reduced xenograft tumor growth [153]. In contrast, in BCC, *SIRT3* mRNA was significantly reduced in tumor samples [124].

In the ovary, SIRT3 was found downregulated in human samples from metastatic ovarian cancer and cell lines, and overexpression of SIRT3 in ovarian cell lines decreased EMT through the inhibition of TWIST [154]. Indirect pharmacological activation of the STAT3/SIRT3 pathway with the STAT3 inhibitor cryptotanshinone was able to inhibit glycolysis and cell growth in ovarian cancer cell lines (Hey and A2870 cells) and mouse xenografts [155]. Finally, another study found that overexpression of SIRT3 increased the sensitivity of ovarian cancer cell lines (A2870, SKOV3, and HO8910) to metformin-induced apoptosis [156].

SIRT4

Like SIRT3 and SIRT5, SIRT4, with 314 amino acids in humans, is primarily located in the mitochondria [157]. SIRT4 has been shown to ADP-ribosylate [158], deacetylate [159], deacylate [160] or delipoylate [161] different targets including glutamate dehydrogenase, malonyl CoA decarboxylase or pyruvate dehydrogenase, affecting crucial metabolic pathways. The variety of its enzymatic activities, however, has hampered the physiological knowledge of SIRT4 [162].

Interestingly, initial reports showed that *Sirt4*-overexpressing MEFs produced smaller tumors in a mouse xenograft model, indicating a tumor-suppressive role of SIRT4 [163].

In the liver, SIRT4 was found downregulated in HCC, which associated with decreased disease-free survival; and *Sirt4*-deficiency enhanced liver tumor development and lung metastasis in xenografts and KO mice. Mechanistically, SIRT4 deletion augmented mTOR signaling by inactivating glutamine catabolism and AMPKα [164].

In the lung, *Sirt4* knock-out mice showed deficient DNA repair and spontaneously developed lung tumors [165]. Mechanistically, SIRT4 was shown to increase after DNA damage and to inhibit glutamine metabolism by ADP-ribosylating glutamate dehydrogenase, which blocked cell proliferation and enhanced DNA repair [165]. SIRT4 was found downregulated in small cell lung carcinoma (SCLC) and lung adenocarcinoma (LAD), where lower levels of SIRT4 were also associated with decreased overall survival [165]. Other studies found that SIRT4 inhibits the ERK-DRP1 pathway, which in turn results in less mitochondrial fission, tumor growth, and invasion in NSCLC cell models; in agreement, SIRT4 was lower in human NSCLCs than in control lung tissue [166], and low SIRT4 correlated with decreased overall survival [166,167].

In breast, some studies found decreased expression of SIRT4 in breast tumors compared with normal tissue [163,165]. Another report found that SIRT4 was decreased in breast tumors compared with normal tissue, and lower expression of SIRT4 was associated with shorter overall survival [168]. In contrast, another report found overexpression of SIRT4 in breast tumors, and enhanced proliferation, migration, and invasion in SIRT4-overexpressing breast cancer in culture [169].

In the colon, studies with human colorectal cancer tissues showed that SIRT4 is downregulated in these tumors when compared to normal tissue, which was associated with worse pathological differentiation and reduced postoperative overall survival [163,170,171]. SIRT4 overexpression in colon cancer cell models suppressed cell proliferation, migration, and invasion [170,171]. In addition, loss of SIRT4 induced resistance to 5-fluoruracil treatment in colon cancer cell models [170,172].

In immune cells, SIRT4 was found to inhibit c-MYC driven Burkitt B cell lymphomas in Eμ-Myc transgenic mice. Tumors in these mice were highly dependent on glutamine metabolism, which was suppressed by SIRT4 through the inhibition of glutamate dehydrogenase (GDH) [173]. Also, SIRT4 levels were lower in acute and chronic leukemia samples compared with normal cells [165].

SIRT4 was also found to be downregulated in human samples of gastric cancer, and this decrease was related to poor prognosis and survival [163,165,174]. In cell models, genetic ablation of *SIRT4* induced cell growth and invasion in MKN-45 and HGC-27 gastric cancer cells [174].

In the kidney, SIRT4 levels were decreased in human samples of renal clear cell carcinoma, and lower SIRT4 was associated with decreased average survival [175].

In the skin, higher SIRT4 transcription was found in human SCC biopsies [89].

In the brain, SIRT4 levels were decreased in human neuroblastoma samples compared to nearby healthy tissue, and this decreased expression was correlated with higher stage, lymph node metastasis, and shorter overall survival [176].

Finally, lower SIRT4 expression compared with normal tissue was found in bladder, ovarian, and thyroid tumors [163,165].

SIRT5

SIRT5, another mitochondrial sirtuin with 310 amino acids in humans, removes acyl groups (succinate, malonate, and glutarate) from lysine residues in different mitochondrial enzymes [177,178]. Much less known than its other mitochondrial siblings, it has been shown to modify proteins involved in the urea cycle [179], glycolysis [180], β-oxidation or ketogenesis [181].

These posttranslational modifications have been shown to exert pro- or anti-tumoral effects, depending on the context. *SIRT5* mRNA or protein have been found upregulated in non-small cell lung cancers (NSCLC) [182], Waldenström macroglobulinemia [183], hepatocellular carcinoma (HCC) [184], colorectal carcinoma 185, and breast cancer [186,187]. In turn, *SIRT5* mRNA or protein levels were shown to be downregulated in HCC [188], endometrium [189] or head and neck squamous carcinomas [190].

In the liver, reports are controversial: in Chang et al., SIRT5 levels were increased in HCC samples, and higher SIRT5 expression in HCCs correlated with poorer overall survival [184]. Mechanistically, SIRT5 was shown to reduce the levels of E2F1, that is proposed to function as a tumor suppressor in HCC [184]. However, the role of E2F1 in this tumor type is still a question of debate, since E2F1 can function as a proapoptotic or as a pro-proliferative factor in HCC [191]. In a contrasting report, SIRT5 expression was found to be decreased in HCC samples, and decreased SIRT5 expression was associated with poorer overall survival and increased probability of recurrence. Mechanistically, SIRT5 is shown to keep oxidative damage under toxic levels by locating to the peroxisome. Here, it desuccinylates desuccinylates and inhibits acyl-CoA oxidase 1 (ACOX1), the rate-limiting enzyme in peroxisomal β-oxidation, whose activity produces H_2O_2 and oxidative DNA damage in HCC [188].

In the lung, SIRT5 has been shown to promote tumor development by different mechanisms: SIRT5 reduced the expression of SUN2, a member of the linker of nucleoskeleton and cytoskeleton (LINC) complex. SUN2 expression was reduced in samples of different types of lung cancer, and this downregulation by SIRT5 was shown to induce the expression of LDHA and GLUT1 and facilitate the Warburg effect in lung cancer cell lines. Accordingly, lung cancer patients with high SIRT5 expression showed shortened progression-free survival [192]. SIRT5 was also shown to facilitate NSCLC progression by increasing the expression of NRF2, a transcription factor that keeps oxidative damage under a toxic threshold and thus helps promoting cancer progression [193]. *Sirt5* knock-down in NSCLC cell lines reduced the levels of expression of NRF2 and many of its targets, as well as cell proliferation. In accordance, *SIRT5* mRNA was shown to be upregulated in NCSLC samples, and high levels of *SIRT5* mRNA were correlated with decreased overall and disease-free survival [182]. In contrast, SIRT5 was found to reduce ROS levels by desuccinylating and activating superoxide dismutase 1 (SOD1) in lung tumor cells, and a succinylation-resistant mutant of SOD1 K123R exhibited reduced proliferation *in vitro* [194].

In breast cancer, higher *SIRT5* expression was associated with increased metastasis risk and lower 1-year survival. In turn, the same report showed that breast cancer patients expressing higher levels of SIRT5 responded better to the standard chemotherapy epirubicin/cyclophosphamide-docetaxel [186].

In colorectal carcinoma (CRC), SIRT5 was found overexpressed in CRC cells compared with adjacent normal tissue, and high SIRT5 was associated with reduced overall survival [185]. Mechanistically, SIRT5 in CRC cell lines sustained glutamine incorporation into the TCA cycle by deglutarylating and activating glutamate dehydrogenase 1 (GLUD1), that converts glutamate to α-ketoglutarate (α-KG), a metabolic pathway that was shown to be essential for tumor cell growth *in vitro* and in tumor xenografts [185]. Another recent report found that SIRT5 was significantly overexpressed in CRC with wild-type *KRas*, and higher levels of SIRT5 expression in these types of CRCs correlated with more frequent recurrence and poorer overall survival [195]. SIRT5 overexpression on KRas-WT CRC cell lines protected them from chemotherapy . Mechanistically, SIRT5 acted in two ways: first, it was found to demalonylate and inactivate succinate dehydrogenase A (SDHA) leading to succinate accumulation, that in turn was shown to activate the ROS scavenger enzyme thioredoxin reductase 2 (TrxR2). This way, SIRT5 kept oxidative damage below a toxic threshold [195]. Secondly, succinate accumulation increased the succinate/α-KG ratio, inhibiting α-KG-dependent dioxygenases that are critical for chemotherapy resistance [195].

Knock-down of *Sirt5* in melanoma cells *in vitro* strongly reduced their proliferative potential, increased their apoptotic index and reduced their ability to form xenograft tumors in mice. This effect was rescued by PDK1 overexpression or supplementation with non-essential amino acids or treatment with dimethyl α-KG[256]. Also, higher SIRT5 transcription was found in human SCC biopsies [89].

Gliomas harboring R132C IDH1 mutations accumulated the oncometabolite R-2-hydroxyglutarate that acted as a competitive inhibitor of SDH. In these cells, accumulation of succinate in the mitochondria provoked general hypersuccinylation of mitochondrial proteins and mitochondrial dysfunction that triggered the accumulation of the anti-apoptotic protein BCL2 and apoptosis resistance of tumor cells. SIRT5 overexpression reduced mitochondrial protein succinylation levels, reduced BCL2 accumulation and slowed xenografts growth [196].

SIRT5 has been shown to act on other cancer-relevant pathways. For example, SIRT5 was shown to act in U2OS and HCT116 cell lines on the folate pathway (a target of several anti-cancer strategies), by desuccinylating and activating the oncogene serine hydroxymethyltransferase (SHMT2) at K280[257]. SHMT2 is a mitochondrial enzyme that catalyzes the conversion of serine and tetrahydrofolate into glycine and 5,10-methylene tetrahydrofolate, essential for the purine synthesis pathway, and has been shown associated with poor prognosis in intrahepatic cholangiocarcinoma [197] and breast cancer [198], and to promote glioma cell survival [199]. Also, SIRT5 was shown to desuccinylate the glycolytic enzyme pyruvate kinase M2 (PKM2) at two residues, K498 and K311. Desuccinylation by SIRT5 of PKM2 at K498 was shown to reduce its activity, leading to an accumulation of glycolytic intermediates and NADPH that fueled tumor growth and kept oxidative damage under a toxic threshold, promoting tumor development [200]. In another report, Wang and colleagues showed that SIRT5 desuccinylated PKM2 at K311 in HEK293 and in macrophages, increasing PKM2 pyruvate kinase activity but reducing the reportedly oncogenic nuclear PKM2 protein kinase activity. However, the role of SIRT5-mediated PKM2 K311 desuccinylation in cancer was not described [201]. SIRT5, along with SIRT1, was also shown to bind and deacetylate PML, sensitizing HeLa cells to H_2O_2-mediated death [202].

SIRT6

SIRT6, with 355 amino acids in humans, is a nuclear sirtuin displaying several enzymatic activities: it deacetylates Histone 3 (H3) at several residues: H3K9 [203] and H3K56 at telomeres [204], H3K18 at pericentric chromatin [205] and other metabolically relevant regions [206]. In both cases, SIRT6 acts as a transcription repressor and genomic stability guardian. SIRT6 also interacts with several components of the DNA repair machinery: it mono ADP-ribosylates and activates PARP1 [207], and deacetylates and activates C-terminal binding protein (CtBP) interacting protein (CtIP) [208]. Also, SIRT6 promotes the localization to double strand breaks (DSB) of

DNA-PKc [209] and SHF2H [210], both enzymes necessary to maintain genomic stability. The activity of SIRT6 is closely linked to fatty acids in two ways: the presence of fatty acids was shown to induce SIRT6 otherwise weak deacetylase activity [211]; and SIRT6 has been shown to remove long-chain fatty acids from other proteins, such as TNFα [211–213]. Also, SIRT6 has been shown to be a corepressor of MYC signal, by deacetylating H3K9 at the DNA binding sites of MYC, more specifically in ribosomal genes [214].

The first report linking SIRT6 with tumor progression showed that ablation of *SIRT6* in mouse embryo fibroblasts (MEFs) led to glycolysis and MYC-dependent transformation without the requirement of any other oncogene [214].

In the liver, *SIRT6* was found to be a direct transcriptional target of c-FOS. In turn, SIRT6 deacetylated H3K9Ac at the promoter of the anti-apoptotic gene *survivin*, thus counter-acting the pro-tumorigenic role of c-JUN. This tumor-suppressor role of the C-FOS/SIRT6 axis was only found in initiating dysplastic liver nodules, not in advanced HCC, indicating that SIRT6 tumor suppression ability was restricted to the initial stages of HCC formation [215]. SIRT6 was also shown to interact with and deacetylate the glycolytic enzyme PKM2 at K433, promoting PKM2 nuclear export into the cytosol and reducing PKM2 nuclear oncogenic functions [216–218]. Accordingly, SIRT6 levels were decreased in higher grade human HCCs, and this decrease was associated with increased levels of AcK433-PKM2 [217]. Similar findings were shown by Zhang et al.: SIRT6 expression was reduced in HCC human samples, and overexpression of SIRT6 in HepG2 cells reduced proliferation, ROS and ERK1/2 signals [219]. In another report using the HCC cell line HepG2, the oncogenic ubiquitin ligase UBE3A was shown to ubiquitylate SIRT6 at K160. Decreased SIRT6 led to hyperacetylation of H3K9 at the promoter of the oncogene ANXA2 and to its increased expression. Consistently, higher expression of UBE3A and ANXA2 and lower expression of SIRT6 were found in HCC of higher grades [220]. All the previous reports on SIRT6 roles in HCC indicated a tumor-suppressor role of SIRT6; however, some reports also found an oncogenic activity of SIRT6 in the liver: SIRT6 was found upregulated in HCC tumors, and higher SIRT6 expression was associated to shorter overall survival. Overexpression of SIRT6 in HCC cell lines enhanced their proliferation and suppressed apoptosis by deacetylating AcH3K9 at the promoter of BCL2-associated protein (BAX), inhibiting binding of p53 and E2F-1 to *BAx* promoter and decreasing *BAX* transcription [221]. Also in liver, Feng and colleagues showed that TGFβ1 and ROS species (H_2O_2 and HOCl) upregulated SIRT6 expression and ERK signaling in HCC cell lines. These upregulations were shown to act as amechanism to avoid a cellular senescence response to their downstream effectors NFkB, SMAD or p38 MAPK, and to promote HCC development in mouse xenograft models [222]. Finally, miR-122 was shown to inhibit SIRT6 expression, and in turn, SIRT6 inhibited miR-122 transcription by binding to its promoter and deacetylating AcH3K56, which led to an overexpression of several miR-122 target genes. Accordingly, HCC patients displaying strong negative correlation of SIRT6 and miR-122 expressions showed decreased overall survival [223].

In the lung, SIRT6 was found downregulated in NSCLC tumor samples, and overexpression of SIRT6 impaired proliferation of NSCLC cell lines and reduced the expression of TWIST1, a pro-tumorogenic transcription factor [224]. In another report, patients with high cytoplasmic expression and low nuclear expression of SIRT6 (a pattern of expression that could indicate inactive SIRT6) had more aggressive cancer, shorter overall survival, and shorter recurrence-free survival than did patients with different SIRT6 expression profiles. Downregulation of SIRT6 in NSCLC cell lines increased their sensitivity to chemotherapy, although the mechanism was not described [225].

In breast cancer, there are conflicting results. First, SIRT6 was shown to be overexpressed in aggressive breast tumors, and higher SIRT6 expression, specially in the nucleus, was associated with shorter overall survival. Mechanistically, SIRT6 was found to be phosphorylated and activated by the oncogenic casein kinase 2α 1 (CSNK2A1), and to induce oncogenic nuclear β-catenin location [226]. In contrast, in another report, SIRT6 expression was found reduced in breast tumors of higher grade, inversely to

RUNX2 expression. Mechanistically, SIRT6 was found repressed at the transcriptional and post-transcriptional level by RUNX2, and this repression reduced mitochondrial respiration and enhanced glycolysis [227].

In the pancreas, *SIRT6* locus was found deleted in a high percentage of pancreatic tumor cell lines, and SIRT6 protein expression was lower in pancreatic ductal adenocarcinoma (PDACs) samples than in healthy samples [214,228]. Importantly, PDAC patients with low expression of SIRT6 had a decreased overall survival than patients with high SIRT6 expression [228]. SIRT6 loss in PDAC cell lines induced HIF1α target glycolytic genes, but SIRT6-deficient PDAC cell lines were not more sensitive to glycolysis inhibition than SIRT6-WT cells. Instead, SIRT6 was found to repress the MYC-driven transcription of the oncofetal RNA-binding protein LIN28b by deacetylation of AcH3K9 and AcH3K56 at the promoter of LIN28b. LIN28b is a well-known repressor of the let-7 miRNA family, and, accordingly, SIRT6-low PDAC cell lines and tumors showed increased levels of LIN28b and of several pro-tumoral let-7 target genes, as *IGF2BP2, IGF2BP3* or *HMGA2*, all of which were associated with poorer PDAC survival [228].

In the colon, SIRT6 was shown to be downregulated in colorectal carcinomas (CRCs), and lower expression of SIRT6 was associated to decreased disease-free survival in aggressive colorectal carcinoma patients (node-positive and C-Reactive Protein-positive tumors) [214]. In this same report, specific deletion of *SIRT6* in intestines of $APC^{Min/+}$ mice produced a remarkable increase in the number, size, and grade of adenomas. This effect was reduced treating mice with the PDK1 inhibitor dichloroacetate, stressing the dependence of SIRT6-deficient intestinal tumors on glycolysis. In another report, SIRT6 was shown to interact with the protein USP10, that suppressed the ubiquitination and subsequent degradation of SIRT6 and p53. By the stabilization of these two partners, USP10 blunted c-MYC-mediated transcription and tumor progression. Accordingly, the USP10-SIRT6 tandem was found downregulated in colon cancer tissues compared to normal colon samples [229].

Two reports by the same authors investigate the role of SIRT6 in hematologic malignancies: SIRT6 was shown to be overexpressed in multiple myeloma (MM) [230] and acute myeloid leukemia (AML) [231] cells, and high SIRT6 expression correlated with shorter overall survival in both tumor types. Mechanistically, in MM SIRT6 bound to the promoters of several members of the MAPK family, most notably ERK2, and to the binding sites of the transcription factor ELK1, a target of ERK2. SIRT6 deacetylated AcH3K9 at ELK1 binding sites and inhibited the expression of ELK1 target genes, reducing cell proliferation, DNA damage, and tumor growth in xenograft models [230]. In AML cells, *SIRT6* knock-down increased cell proliferation, similar to what was described in MM, although no mechanistic explanation was given [231]. On the other hand, SIRT6 improved the DNA-damage response of MM and AML cells: in MM, SIRT6 deacetylated AcH3K56 at the DNA-damage sites, and this effect protected MM cells from doxorubicin treatment *in vitro* and *in vivo*. In AML, SIRT6 enhanced DNA stability at least partly by deacetylating DNA-PKCs and CtIP. In both cases, as suggested before with lung cancer [225], authors concluded that improved DNA stability in SIRT6-overexpressing tumors protected them from different DNA damaging therapies, which explained the worse prognosis of MM and AML patients expressing high levels of SIRT6, and suggested that inhibition of SIRT6 could constitute a therapeutic opportunity for these tumor types [230,231].

SIRT6 has also been investigated in papillary thyroid carcinoma (PTC): SIRT6 was found overexpressed in PTC samples compared to normal tissue, and higher SIRT6 expression was associated to increased nodal metastasis, although no significant association was found between SIRT6 and survival. *In vitro*, SIRT6 stimulated proliferation and invasion [232].

Sirt6 deletion in skin led to a decrease in the frequency and number of papillomas in a DMBA/TPA protocol and to a decreased UVB irradiation induced hyperplasia and proliferative index, indicating that SIRT6 was promoting tumor development. Mechanistically, UVB irradiation-induced SIRT6 expression, which in turn inhibited *COX-2* mRNA stability by downregulating the AMPK pathway [233]. In agreement, another report showed that

the pro-differentiation miR-34a expression was downregulated, and the expression of SIRT6, a target of miR-34a, was upregulated in oral SCC samples versus normal epidermis by methylation of miR-34a promoter. These results imply that SIRT6 might be associated with SCC development, although no functional effects of SIRT6 levels in SCC development were assayed in this report [234]. In accordance, higher SIRT6 transcription was found in human SCC biopsies [89]. Finally, SIRT6 and SIRT7 expression in PBMCs from head and neck squamous cell carcinomas (HNSCC) patients were higher in preoperative blood samples, compared to postoperative blood samples [235]. In melanomas, SIRT6 was found overexpressed in tumor samples and cell lines [236], and ablation in melanoma cell lines significantly reduced cell growth. Two additional reports on SIRT6 confer additional complexity to the role of this sirtuin in melanoma: in one of them, SIRT6 was found downregulated in initial melanoma but increased in metastatic lesions [237]. In another report, haploinsufficiency of SIRT6 induced resistance to MAPK inhibitors in $BRAF^{V600E}$ melanomas cell lines suggesting that modulation of SIRT6 might be therapeutically detrimental [238].

In ovaries, expression of SIRT6 was found downregulated in ovarian cancer tissues compared to normal ovary. SIRT6 inhibited ovarian cancer cell lines proliferation, at least partly by inhibiting NOTCH3 expression [239].

Finally, expression of SIRT6 has been shown to be downregulated by E2F1, that bound to *SIRT6* promoter and inhibited its transcription, in bladder and prostate cancer cell lines [240].

SIRT7

SIRT7, with 400 amino acids in humans, was initially found in the nucleolus, where it facilitated transcription of rDNA by deacetylating and activating the subunit of Pol I PAF53 [241]. Also, SIRT7 promoted the processing of pre-rRNA by deacetylating and activating U3-55k, a core component of the U3 small nucleolar ribonucleoprotein complex (snoRNP) [242]. Later, SIRT7 has also been shown to reside in other nuclear regions and to deacetylate various other targets, as members of the chromatin remodeling complexes B-WICH, that facilitates rDNA transcription by interacting with Pol I; the nucleolar remodeling complex (NoRC); or SWI/SNF [243]. SIRT7 also enhances Pol III-mediated transcription of tRNAs [244], deacetylates AcH3K18 and represses transcription of ELK4 and MYC, promoting tumor formation [245] or preventing hepatic steatosis [246]; and deacetylates and activates the master regulator of nuclear-encoded mitochondrial genes GABPβ1 [247]. Importantly, SIRT7 also desuccinylates H3K122 at double-strand breaks, promoting genomic stability [248]. In agreement with this, *Sirt7*-deficient mice age prematurely and display genomic instability [249]. SIRT7 has been proposed to deacetylate and inhibit p53 [250], although these findings have been questioned by other reports [245].

Regarding cancer, SIRT7 is generally considered an oncogene: in HCC; SIRT7 was found upregulated in human HCC samples and its expression increased with tumor grade. In mice, *Sirt7* knock-down reduced xenograft tumor growth. Both miR-125a-5p and miR-125b were found downregulated in HCC, and these miRNAs were shown to target and inhibit SIRT7, enhancing xenograft growth [251].

In breast cancer, *SIRT7* mRNA was found upregulated in tumor samples, more specifically in tumors at their earlier stages, but not in the most advanced tumors [252]. In contrast, in a later report SIRT7 was found strongly repressed in human node and breast cancer lung metastases. In addition, SIRT7 overexpression in xenografts reduced lung metastasis in mice. SIRT7 deacetylated SMAD4 at K428 and destabilized it, impairing TGF-β signaling and EMT *in vitro*. Importantly, resveratrol treatment destabilized SMAD4 and reduced EMT and lung metastasis in mice, implicating SIRT7 in the anti-tumorogenic roles of resveratrol [253].

In prostate adenocarcinomas, SIRT7 was overexpressed specially in the most aggressive and metastatic tumors [254]. In this same report, SIRT7 promoted EMT in cell lines from several tumor types [254].

In the stomach, high SIRT7 expression was found in gastric tumors and correlated with shorter overall and disease-free survival. Mechanistically, SIRT7 deacetylated AcH3K18 at the promoter of the tumor-suppressor miR-34a and inhibited its expression, inducing proliferation and reducing apoptosis in gastric cancer cells [255].

In the skin, higher *SIRT4* transcription was found in human SCC biopsies [89].

SIRT7 was shown to be upregulated in ovarian [258] and NSCLC [259] cell lines compared with normal cells of the corresponding tissues, and *SIRT7* knock-down [258] or interference with miR-3666 [259] reduced cell growth and induced apoptosis.

Common molecular features of sirtuins in cancer

In this section, we will put together the molecular features described in the papers reviewed above, when available. We will focus on the features that are common to different sirtuins or to the same sirtuin in different tumors or in independent reports. All these data have been summarized in Table 2:

- SIRT1: higher expression of SIRT1 and its inhibitor, DBC1, were found in breast [59,61] and gastric [87] tumors. Also, increased c-MYC and SIRT1 protein levels were found in the colon [68,69], AML [75] and thyroid [83] tumors, indicating that there is a functional interaction between these two proteins in several tumor types. These findings establish the MYC oncogene as a common functional target with SIRT2, SIRT3, and SIRT6. SIRT1 was found to deacetylate at K382 and inhibit p53 [41], a target common to SIRT3 [132, 136], SIRT6 [221], and SIRT7 [250]. Indeed, high SIRT1 and low acetyl-p53 correlated with poor survival in lung tumors [57]. Finally, SIRT1 was found to induce EMT by enhancing the expression of ZEB1 in prostate tumors [84].
- SIRT2 was found to counteract KRas oncogenic role in lung [108,109] and pancreas [108,115] tumor models. In some cases, SIRT2 was found to deacetylate and inhibit KRas [108,109], indicating a very close functional interaction between these two proteins. Interestingly, as found with SIRT1, SIRT2 enhanced c-MYC stability in breast tumors [114]. SIRT2 inhibited the expression of the oncogene JMJD2A in two independent reports on lung cancer [105,110]. Finally, SIRT2 shared PKM2 as a target with SIRT5 and SIRT6, although at different residues: SIRT2 deacetylated at K305 and activated PKM2, reducing breast tumor growth [112].
- SIRT3 shares HIF1α as a target with SIRT6: SIRT3 deficiency led to the stabilization of HIF1α, promoting breast tumor growth [128]. Interestingly, as described for SIRT1 and SIRT7, SIRT3 deacetylated p53 (in this case, at K320 and K382), decreasing p53 stability in NSCLC [136]. Similar to SIRT5, SIRT3 was found to deacetylate, induce the expression and activate SOD2 in B cell malignancies [145]. SIRT3 has been found to deacetylate and activate IDH2 in several models: in MEFs, breast cancer 129, and CLL [145]. Also, SIRT3 overexpression led to the destabilization of the MYC oncogene [147], contrary to what was described for SIRT1 and SIRT2. As SIRT6, SIRT3 reduced Notch signaling, in this case by inhibiting the expression of NOTCH1, which reduced gastric cancer growth [150]. SIRT3 also prevented EMT by inhibiting the expression of TWIST in ovarian carcinoma [154] and the Wnt/ β-catenin pathway in prostate tumors [148]. In contrast to SIRT4, SIRT3 deacetylated and activated GDH, favoring glutamine metabolism into the Krebs cycle and promoting DLBCL tumor progression [146]. Similar to SIRT5, SIRT3 deacetylated at K75 and activated the tumor-promoting enzyme serine hydroxymethyltransferase 2 (SHMT2) in colon cancer cells [144]. Finally, SIRT3 also reduced mTORC1 signaling and breast tumor progression [139].
- In contrast to SIRT3 and SIRT5, SIRT4 inhibited glutamine metabolism, at least in part by ADP-ribosylating and inhibiting GDH. This function prevented tumor progression in liver (via mTOR inhibition) [164], lung [165] and in Burkitt B-cell lymphoma [173].
- SIRT5 desuccinylated and activated PKM2 at K311 and K498, promoting tumor growth [200,201]. In parallel to SIRT3, SIRT5 desuccinylated and activated SOD1, reducing the growth of lung tumor cells [194], and serine hydroxymethyltransferase 2 (SHMT2) at K280 in several cancer cell lines [257]. In contrast to SIRT4, and in common to

SIRT3, SIRT5 deglutarylated and activated GDH, promoting CRC progression [185].

- SIRT6 deacetylated PKM2 at K433, promoting its nuclear export and inhibiting PKM2 oncogenic functions [217]. As happened with SIRT3, SIRT6 loss led to stabilization of HIF1α in pancreas tumors [228], to the inhibition of Notch signaling and ovarian cancer cells proliferation by decreasing NOTCH3 expression [239], and prevented EMT by inhibiting TWIST expression in NSCLC [224]. Also, SIRT6 shares MYC as a functional target with SIRT1 and SIRT2, but in contrast with them, SIRT6 was found to repress MYC-driven transcription of the oncogene LIN28b in pancreatic cancer [228], and to inhibit c-MYC-driven transcription by its interaction with USP10 [229]. Interestingly, SIRT6 was described as a target in oral SCC of the tumor-suppressor miR-34a [234], which in turn was found to be repressed by SIRT7 [255].
- SIRT7 has been shown to deacetylate and inhibit p53 [250], as happened with SIRT1, SIRT3 and SIRT6. SIRT7 inhibited the expression of the tumor-suppressor miR-34a in stomach tumor cells, promoting their growth [255]; in turn, as described above, miR-34a was shown to target and inhibit SIRT6 in oral SCCs [234]. SIRT7, as SIRT1 and SIRT3, has been shown to regulate EMT: in lung metastasis from breast tumors, SIRT7 deacetylated at K428 and destabilized the EMT-driver SMAD4 [253]; in contrast, SIRT7 promoted EMT in several prostate cancer cell lines [253].

Therapeutic interventions based on sirtuins modulators

Sirtuin activators

The first sirtuin-activating compounds (STACs) were described for SIRT1 in 2003, being resveratrol the most potent compound in this first screening [260]. Since then, thousands of new STACs have been described, including more than a dozen chemical families such as stilbenes (for example, resveratrol), chalcones (for example, butein), flavones (for example, quercetin) from plants [260], or synthetic, such as imidazothiazoles (for example, SRT1720) [261], thiazolopyridines (for example, STAC-2) [262], benzimidazoles (for example, STAC-5) [262] and urea-based scaffolds (for example, STAC-9) [263]. Interestingly, metformin, the frontline treatment against type 2 diabetes, has also been shown to activate SIRT1 [264]. After a strong debate about the ability of STACs to specifically activate SIRT1, it was shown that SIRT1 activity strongly depended on the amino acid residues positioned nearby the deacetylated lysine, a confounding factor that can strongly compromise STACs identification [262,265].

Several reports have shown that treatment of mouse models of cancer with STACs can reduce tumor growth. Firstly, and even before it was described as a SIRT1 activator, topical treatment with resveratrol prevented the development of skin papillomas in a DMBA-TPA protocol with mice [266], at least partly by reducing reactive oxidant species and c-fos [267], and this protective effect of resveratrol was lost in Sirt1-KO mice [70]. Resveratrol has been shown to reduce the proliferation of many cell lines from different origins *in vitro* (reviewed by Aggarwal and colleagues [268]). Treatment with resveratrol in mice or rats also delayed formation of tumors in several other *in vivo* models: in mice orthotopically inoculated with the murine liver cell line H22 [269]; in mammary duct adenocarcinomas induced by the carcinogen DMBA in rats [270]; or in azoxymethane-induced colon carcinoma in rats [271]. Also, treatment of immunocompetent mice bearing orthotopic melanoma (B16F10) or colon carcinoma (CT26) tumors with resveratrol or metformin reduced tumor growth [272]; mechanistically, SIRT1 deacetylated and inhibited STAT3, that could no longer induce the transcription of *Rorc*, a master regulator of the pro-tumoral Th17 T-cells [272]. In contrast, treatment with resveratrol had no effect on lung tumors induced by tobacco smoke carcinogens [273] or in the $APC^{Min/+}$ intestinal tumor formation mouse model [270]. In one report, prepubertal treatment with resveratrol in rats enhanced the development of MNU-induced mammary carcinomas [274].

Other STACs, as SRT1720, SRT1460, and SRT3025, were found to reduce the growth of pancreatic [275] and breast [276] cancer cells-xenografts in athymic mice through a lysosome-

dependent mechanism. In contrast, Suzuki and colleagues showed that treatment with SRT1720 reduced cisplatin cytotoxic effects and enhanced xenograft lung metastasis of breast cancer cells [277]. Butein, a plant-derived STAC, has also been shown to suppress the growth of breast [278,279] and cervical [280] cancer cells *in vitro*, although the proposed mechanisms (reactive oxygen species production) were not associated with SIRT1 activity.

Sirtuin inhibitors

Due to the oncogenic role of many sirtuins in different tumor types, a strong effort was devoted to identify robust inhibitors that could be used as new clinically relevant anticancer therapeutic agents. At present, there are several sirtuin inhibitors described with different selectivity for SIRT1, SIRT2, SIRT3, SIRT5, and SIRT6. One of the first inhibitors described was Sirtinol, a molecule that belongs to the family of the β-naphthol-containing compounds. Sirtinol was first identified as an inhibitor of the deacetylating activity of SIRT2 and its yeast homolog Sir2p [281]. In prostate cancer (PCa) cell lines, sirtinol treatment increased FOXO1 acetylation and decreased cell growth and viability with no apparent effect in normal epithelial cells [81]. In breast (MCF7) and lung (H1299) tumor cells, sirtinol-induced senescence-like growth arrest through a mechanism dependent on the inhibition of the MAPK pathway [282].

Other sirtinol analogs have been developed: JGB1741, a specific inhibitor of SIRT1 when compared to SIRT2 and SIRT3, induced cytochrome c release and PARP cleavage-dependent apoptosis in MDA-MB 231 breast cancer cell lines [283].

Salermide, an inhibitor of SIRT1 and SIRT2, proved to be efficient at inducing apoptosis in leukemia (MOLT4, KG1A, and K562), lymphoma (Raji), colon (SW480) and breast (MDA-MB-231 and MCF7) cell models but not in non-tumorigenic MRC5 cells [284–286].

Another commonly used sirtuin inhibitor is nicotinamide, first identified in an in silico screening for its ability to inhibit SIRT2 (IC50 = 100μM) [287]. Further reports have found that nicotinamide has a pan-sirtuin inhibitory capacity inhibiting SIRT1 (IC50 = 70μM) [288], SIRT3 (IC50 = 37μM) [288] and SIRT6 (IC50 = 184μM) [289]. Nicotinamide proved to be effective at inhibiting cell growth in chronic lymphocytic leukemia (CLL cells) through a mechanism dependent on SIRT1 inhibition and p53 and caspase-3 activation [290].

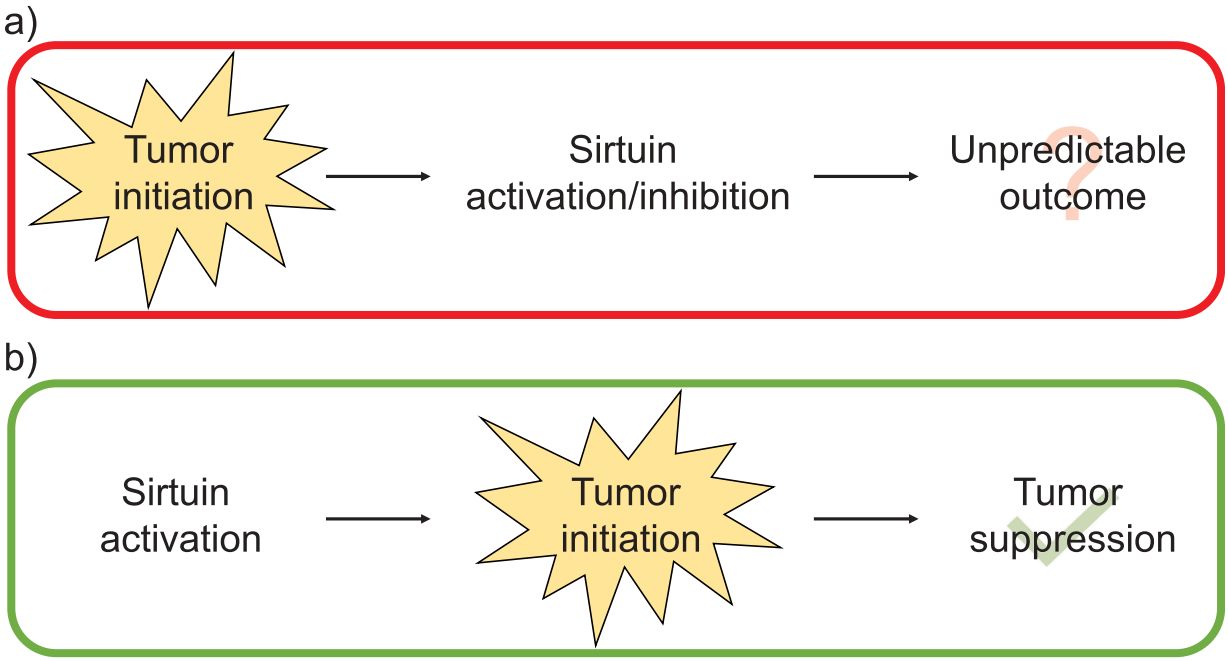

Figure 1. Therapeutic strategies using sirtuin modulators. Sirtuin modulation after tumor onset (a) has shown to lead to unpredictable outcomes, due to the heterogeneous response of all seven sirtuin members in different tissues. In contrast, sirtuin activation prior to tumor appearance (b) has consistently shown to prevent or delay cancer appea.rance.

In PCa cells, nicotinamide was also able to reduce cell growth and viability [81].

Niacinamide, a derivative of vitamin B3 (niacin), is another pan-sirtuin inhibitor that binds and inhibits the sirtuin catalytic domain. Interestingly, treatment of lymphoma human patients or mouse models with niacinamide combined with other drugs showed promising results [291].

Although these compounds revealed to be efficient at inhibiting sirtuin activity, their specificity is not limited to one specific sirtuin. For this reason, much effort was devoted to identify new compounds with increased specificity. In the case of SIRT1, one of the strongest and most specific SIRT1 inhibitors reported so far is the indole derivative EX527, efficient at inhibiting SIRT1 catalytic activity at nanomolar concentrations (IC50 ~100nM compared to 20μM and 48μM for SIRT2 and SIRT3, respectively) [292]. In leukemia cell lines, treatment with EX527 increased apoptosis when combined with HDAC inhibitors through a mechanism dependent on BAX upregulation [293], and also stalked the growth of chemoresistant stem-like cells from human chronic myeloid leukemia [294]. In cervical cancer cells, EX527 was able to inhibit growth in the cervical tumor SiHa cells but not in the immortalized counterpart HaCaT cells [295]. In the pancreas, reports were more controversial: *in vitro*, EX527 had a synergistic effect when combined with gemcitabine in PANC-1 and ASPC-1 cells [296]. By contrast, treatment of PANC-1 xenografts with EX527 increased tumor formation and no synergistic effect was observed when combined with gemcitabine [67].

Another highly specific and promising compound is thiomyristoyl lysine compound (TM). This compound had a high specificity for SIRT2 (IC50 = 28nM) when compared to SIRT1 (IC50 = 98μM) and SIRT3 (IC50 = 200μM), and showed no effect on SIRT5, SIRT6 or SIRT7 enzymatic activities. TM displayed a strong anticancer activity through a mechanism dependent on the ubiquitination and destabilization of c-MYC. *In vivo*, TM inhibited tumor growth in mouse xenografts of breast cancer (MDA-MD-231) and increased survival in MMTV-PyMT female mice [114]. In addition, other specific compounds were developed for SIRT2, that include AGK2 [297], SirReal2 [298], AK-7 [299], AC-93253 [300]. AGK2, for instance, induced cell cycle arrest and apoptosis in 3D cell models of glioblastoma (GB2, GB4, GB11, and GB16 spheres); and AK-7 was able to inhibit glioblastoma tumor formation *in vivo*. Both compounds worked through a mechanism dependent on the deacetylation of p73 [125].

One of the strongest SIRT3 inhibitors described to date is SDX-437 which, when compared to SIRT1, exhibited a 100 higher selectivity for this sirtuin [301]. Another family of SIRT3 inhibitors is the 5-amino-2-phenyl-benzoxazole derivates, that were identified in a virtual drug screening reported to inhibit SIRT3 in a specific manner, when compared to SIRT1 and SIRT2 [302]. Although these compounds proved to be highly specific at inhibiting SIRT3, their efficiency in cancer models has not been addressed.

APO866, and inhibitor of nicotinamide phosphoribosyltransferase (NMPRTase), blocks the NAD^+ synthesis pathway and thus acts as a global sirtuin inhibitor. Interestingly, treatment of several leukemia and lymphoma cell lines and mouse tumor models with this compound induced mitochondria- and autophagy-mediated apoptosis and tumor recurrence [303].

Conclusions

After all the data presented above, we can draw the general conclusion that modulation of sirtuins activity by genetic or pharmacological approaches once tumors are formed leads to unpredictable outcomes (Figure 1(a)). On one hand, a certain sirtuin can have pro- or anti-tumoral functions in the same or in different tissues. Therefore, even when the effects of modulating that sirtuin would seem positive for that precise tumor type, they could have deleterious effects in a different tissue. On the other hand, most STACS and sirtuins inhibitors have only been studied for their activity on a subset of sirtuins, but thorough studies on the effects of a precise STAC or sirtuin inhibitor in all the sirtuin family members, or in other enzymes, are still lacking. In fact, several reports have shown that some of the most

widely used sirtuin activators (resveratrol, SRT1720, SRT2183 or SRT1460) are actually not direct SIRT1 activators, displaying off-target effects that had not been extensively studied [304,305]. These findings, most probably, can also apply to other sirtuins modulators, whose specificity has not been thoroughly checked. Also, given the pleiotropic, and often opposite, functions of the different sirtuin family members in cancer development described above, special consideration should be taken before proposing the use of sirtuins modulators as anti-cancer agents (Figure 1(a)). Measuring the activity of other sirtuin family members during the treatment with these modulators, and paying special attention to the tissues where pro- or anti-tumoral effects of sirtuins have been described would constitute a sensible safeguard for any future therapeutic strategy.

Most sirtuins modulators have been studied for their anti-cancer therapeutic potential, that is: their effects on already transformed cells and tumors. By contrast, the preventive potential of the use of sirtuins modulators has received much less attention. Mouse models of overexpression or ablation prior to tumor onset for different sirtuin family members have shown that, in general, germline sirtuin overexpression prevents tumors appearance; or that germline sirtuin ablation promotes tumor development. This has been shown when SIRT1 overexpression prevented hepatocarcinoma [45], $APC^{Min/+}$-driven intestinal tumors [71], and lung adenocarcinoma [58] development; Sirt2-KO mice developed spontaneous breast (females) and liver (males) tumors [100]; Sirt3-KO mice developed spontaneous mammary tumors [130]; Sirt4-KO mice spontaneously developed lung tumors [165]; Sirt6-specific deletion in intestine sensitized to $APC^{Min/+}$-driven intestinal tumors [214]; or Sirt7-KO mice showed compromised genomic integrity [249]. On the contrary, only a few reports have shown that increased activation of sirtuins can increase tumor development, as with Sirt1-Tg mice enhancing PTEN-driven thyroid carcinomas [83]. However, in this last model, one copy of PTEN is already lost at germline, and therefore there is oncogenic stress from the embryonic stage. All these *in vivo* data suggest that, in general, global sirtuins activation when there is a healthy basal state can constitute a powerful preventive strategy against cancer development (Figure 1(b)).

Acknowledgments

Work in the laboratory of P.J.F.-M. was funded by the IMDEA Food, the Spanish Association Against Cancer – AECC (SIRTBIO), the Ramon Areces (CIVP18A3891) Foundation, the Ramon y Cajal Program (RYC-2017-22335) and the MICINN (SAF2017-85766-R). L.F.C-M. was supported by a PhD Fellowship from the Portuguese Foundation for Science and Technology (FCT-MCTES, SFRH/BD/124022/2016).

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by the Fundación Científica Asociación Española Contra el Cáncer [SIRTBIO]; Fundación Ramón Areces [CIVP18A3891]; Ministerio de Economía, Industria y Competitividad, Gobierno de España [SAF2017-85766-R]; Ministerio de Economía, Industria y Competitividad, Gobierno de España [RYC-2017-22335]; fundaçao para a ciencia e a tecnologia [FCT-MCTES, SFRH/BD/124022/2016].

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References

[1] Rine J, Strathern JN, Hicks JB, et al. A suppressor of mating-type locus mutations in saccharomyces cerevisiae: evidence for and identification of cryptic mating-type loci. Genetics. 1979;93:877–901.
[2] Nasmyth KA. The regulation of yeast mating-type chromatin structure by SIR: an action at a distance affecting both transcription and transposition. Cell. 1982;30:567–578.
[3] Klar AJ, Strathern JN, Broach JR, et al. Regulation of transcription in expressed and unexpressed mating type cassettes of yeast. Nature. 1981;289:239–244.
[4] Gottlieb S, Esposito RE. A new role for a yeast transcriptional silencer gene, SIR2, in regulation of

recombination in ribosomal DNA. Cell. 1989;56:771–776.
[5] Aparicio OM, Billington BL, Gottschling DE. Modifiers of position effect are shared between telomeric and silent mating-type loci in S. cerevisiae. Cell. 1991;66:1279–1287.
[6] Kaeberlein M, McVey M, Guarente L. The SIR2/3/4 complex and SIR2 alone promote longevity in saccharomyces cerevisiae by two different mechanisms. Genes Dev. 1999;13:2570–2580.
[7] Sinclair DA, Guarente L. Extrachromosomal rDNA circles–a cause of aging in yeast. Cell. 1997;91:1033–1042.
[8] Tissenbaum HA, Guarente L. Increased dosage of a sir-2 gene extends lifespan in Caenorhabditis elegans. Nature. 2001;410:227–230.
[9] Schmeisser K, Mansfeld J, Kuhlow D, et al. Role of sirtuins in lifespan regulation is linked to methylation of nicotinamide. Nat Chem Biol. 2013;9:693–700.
[10] Burnett C, Valentini S, Cabreiro F, et al. Absence of effects of Sir2 overexpression on lifespan in C. elegans and Drosophila. Nature. 2011;477:482–485.
[11] Rogina B, Helfand SL. Sir2 mediates longevity in the fly through a pathway related to calorie restriction. Proc Natl Acad Sci. 2004;101:15998–16003.
[12] Hoffmann J, Romey R, Fink C, et al. Overexpression of Sir2 in the adult fat body is sufficient to extend lifespan of male and female Drosophila. Aging (Albany NY). 2013;5:315–327.
[13] Smith JS, Brachmann CB, Celic I, et al. A phylogenetically conserved NAD+-dependent protein deacetylase activity in the Sir2 protein family. Proc Natl Acad Sci U S A. 2000;97:6658–6663.
[14] Landry J, Sutton A, Tafrov ST, et al. The silencing protein SIR2 and its homologs are NAD-dependent protein deacetylases. Proc Natl Acad Sci. 2000;97:5807–5811.
[15] Imai S, Armstrong CM, Kaeberlein M, et al. Transcriptional silencing and longevity protein Sir2 is an NAD-dependent histone deacetylase. Nature. 2000;403:795–800.
[16] Anderson RM, Bitterman KJ, Wood JG, et al. Nicotinamide and PNC1 govern lifespan extension by calorie restriction in Saccharomyces cerevisiae. Nature. 2003;423:181–185.
[17] van der Horst A, Schavemaker JM, Pellis-van Berkel W, et al. The Caenorhabditis elegans nicotinamidase PNC-1 enhances survival. Mech Ageing Dev. 2007;128:346–349.
[18] Balan V, Miller GS, Kaplun L, et al. Life span extension and neuronal cell protection by *Drosophila* nicotinamidase. J Biol Chem. 2008;283:27810–27819.
[19] Banerjee KK, Ayyub C, Ali SZ, et al. dSir2 in the adult fat body, but not in muscles, regulates life span in a diet-dependent manner. Cell Rep. 2012;2:1485–1491.
[20] Lin SJ, Defossez PA, Guarente L. Requirement of NAD and SIR2 for life-span extension by calorie restriction in Saccharomyces cerevisiae. Science. 2000;289:2126–2128.
[21] Kaeberlein M, Kirkland KT, Fields S, et al. Sir2-independent life span extension by calorie restriction in yeast. PLoS Biol. 2004;2:e296.
[22] Boily G, Seifert EL, Bevilacqua L, et al. SirT1 regulates energy metabolism and response to caloric restriction in mice. PLoS One. 2008;3:e1759.
[23] Chalkiadaki A, Guarente L. The multifaceted functions of sirtuins in cancer. Nat Rev Cancer. 2015;15:608.
[24] Tanno M, Sakamoto J, Miura T, et al. Nucleocytoplasmic shuttling of the NAD+-dependent histone deacetylase SIRT1. J Biol Chem. 2007;282:6823–6832.
[25] Vaquero A, Scher MB, Lee DH, et al. SirT2 is a histone deacetylase with preference for histone H4 Lys 16 during mitosis. Genes Dev. 2006;20:1256–1261.
[26] Huang J-Y, Hirschey MD, Shimazu T, et al. Mitochondrial sirtuins. Biochim Biophys Acta. 2010;1804:1645–1651.
[27] Mostoslavsky R, Chua KF, Lombard DB, et al. Genomic instability and aging-like phenotype in the absence of mammalian SIRT6. Cell. 2006;124:315–329.
[28] Ford E, Voit R, Liszt G, et al. Mammalian Sir2 homolog SIRT7 is an activator of RNA polymerase I transcription. Genes Dev. 2006;20:1075–1080.
[29] Imai S-I, Guarente L. It takes two to tango: NAD+ and sirtuins in aging/longevity control. NPJ Aging Mech Dis. 2016;2:16017.
[30] Houtkooper RH, Pirinen E, Auwerx J. Sirtuins as regulators of metabolism and healthspan. Nat Rev Mol Cell Biol. 2012;13:225.
[31] Herskovits AZ, Guarente L. Sirtuin deacetylases in neurodegenerative diseases of aging. Cell Res. 2013;23:746–758.
[32] Hall JA, Dominy JE, Lee Y, et al. The sirtuin family's role in aging and age-associated pathologies. J Clin Invest. 2013;123:973–979.
[33] Guarente L. The many faces of sirtuins: sirtuins and the Warburg effect. Nat Med. 2014;20:24–25.
[34] Oellerich MF, Potente M. FOXOs and sirtuins in vascular growth, maintenance, and aging. Circ Res. 2012;110:1238–1251.
[35] Ng F, Tang BL. Sirtuins' modulation of autophagy. J Cell Physiol. 2013;228:2262–2270.
[36] Jeong SM, Haigis MC. Sirtuins in cancer: a balancing act between genome stability and metabolism. Mol Cells. 2015;38:750.
[37] Singh CK, Chhabra G, Ndiaye MA, et al. The role of sirtuins in antioxidant and redox signaling. Antioxid Redox Signal. 2018;28:643–661.
[38] Merksamer PI, Liu Y, He W, et al. The sirtuins, oxidative stress and aging: an emerging link. Aging (Albany NY). 2013;5:144–150.
[39] Jin Q, Yan T, Ge X, et al. Cytoplasm-localized SIRT1 enhances apoptosis. J Cell Physiol. 2007;213:88–97.

[40] Cheng H-L, Mostoslavsky R, Saito S, et al. Developmental defects and p53 hyperacetylation in Sir2 homolog (SIRT1)-deficient mice. Proc Natl Acad Sci U S A. 2003;100:10794–10799.
[41] Langley E, Pearson M, Faretta M, et al. Human SIR2 deacetylates p53 and antagonizes PML/p53-induced cellular senescence. Embo J. 2002;21:2383–2396.
[42] Vaziri H, Dessain SK, Ng Eaton E, et al. hSIR2(SIRT1) functions as an NAD-dependent p53 deacetylase. Cell. 2001;107:149–159.
[43] Lin Z, Fang D. The roles of SIRT1 in cancer. Genes Cancer. 2013;4:97–104.
[44] Pfluger PT, Herranz D, Velasco-Miguel S, et al. Sirt1 protects against high-fat diet-induced metabolic damage. Proc Natl Acad Sci U S A. 2008;105:9793–9798.
[45] Herranz D, Muñoz-Martin M, Cañamero M, et al. Sirt1 improves healthy ageing and protects from metabolic syndrome-associated cancer. Nat Commun. 2010;1:3.
[46] Banks AS, Kon N, Knight C, et al. SirT1 gain of function increases energy efficiency and prevents diabetes in mice. Cell Metab. 2008;8:333–341.
[47] Kim D, Nguyen MD, Dobbin MM, et al. SIRT1 deacetylase protects against neurodegeneration in models for Alzheimer's disease and amyotrophic lateral sclerosis. Embo J. 2007;26:3169–3179.
[48] Chen J, Zhang B, Wong N, et al. Sirtuin 1 is upregulated in a subset of hepatocellular carcinomas where it is essential for telomere maintenance and tumor cell growth. Cancer Res. 2011;71:4138–4149.
[49] Jang KY, Noh SJ, Lehwald N, et al. SIRT1 and c-Myc promote liver tumor cell survival and predict poor survival of human hepatocellular carcinomas. PLoS One. 2012;7:e45119.
[50] Portmann S, Fahrner R, Lechleiter A, et al. Antitumor effect of SIRT1 inhibition in human HCC tumor models in vitro and in vivo. Mol Cancer Ther. 2013;12:499–508.
[51] Moon W, Bae JS, Jamiyandorj U, et al. Expression and role of SIRT1 in hepatocellular carcinoma. Oncol Rep. 2011;26:503–510.
[52] Chen H-C, Jeng Y-M, Yuan R-H, et al. SIRT1 promotes tumorigenesis and resistance to chemotherapy in hepatocellular carcinoma and its expression predicts poor prognosis. Ann Surg Oncol. 2012;19:2011–2019.
[53] Bae HJ, Noh JH, Kim JK, et al. MicroRNA-29c functions as a tumor suppressor by direct targeting oncogenic SIRT1 in hepatocellular carcinoma. Oncogene. 2014;33:2557–2567.
[54] Wang C, Yang W, Dong F, et al. The prognostic role of Sirt1 expression in solid malignancies: a meta-analysis. Oncotarget. 2017;8:66343–66351.
[55] Wang R-H, Sengupta K, Li C, et al. Impaired DNA damage response, genome instability, and tumorigenesis in SIRT1 mutant mice. Cancer Cell. 2008;14:312–323.
[56] Zhang Y, Zhang M, Dong H, et al. Deacetylation of cortactin by SIRT1 promotes cell migration. Oncogene. 2009;28:445–460.
[57] Tseng R-C, Lee -C-C, Hsu H-S, et al. Distinct HIC1-SIRT1-p53 loop deregulation in lung squamous carcinoma and adenocarcinoma patients. Neoplasia. 2009;11:763–770.
[58] Costa-Machado LF, Martin-Hernandez R, Sanchez-Luengo MA, et al. Sirt1 protects from K-Ras-driven lung carcinogenesis. EMBO Rep. 2018;19.
[59] HIRAIKE H, WADA-HIRAIKE O, NAKAGAWA S, et al. Expression of DBC1 is associated with nuclear grade and HER2 expression in breast cancer. Exp Ther Med. 2011;2:1105–1109.
[60] Wu M, Wei W, Xiao X, et al. Expression of SIRT1 is associated with lymph node metastasis and poor prognosis in both operable triple-negative and non-triple-negative breast cancer. Med Oncol. 2012;29:3240–3249.
[61] Lee H, Kim KR, Noh SJ, et al. Expression of DBC1 and SIRT1 is associated with poor prognosis for breast carcinoma. Hum Pathol. 2011;42:204–213.
[62] Kim J-E, Chen J, Lou Z. DBC1 is a negative regulator of SIRT1. Nature. 2008;451:583–586.
[63] Wang R-H, Zheng Y, Kim H-S, et al. Interplay among BRCA1, SIRT1, and survivin during BRCA1-associated tumorigenesis. Mol Cell. 2008;32:11–20.
[64] Jin J, Chu Z, Ma P, et al. SIRT1 promotes the proliferation and metastasis of human pancreatic cancer cells. Tumor Biol. 2017;39:101042831769118.
[65] Zhao G, Cui J, Zhang J-G, et al. SIRT1 RNAi knockdown induces apoptosis and senescence, inhibits invasion and enhances chemosensitivity in pancreatic cancer cells. Gene Ther. 2011;18:920–928.
[66] Wauters E, Lobo VJS-A, Pinho AV, et al. Sirtuin-1 regulates acinar-to-ductal metaplasia and supports cancer cell viability in pancreatic cancer. Cancer Res. 2013;73:2357–2367.
[67] Oon CE, Strell C, Yeong KY, et al. SIRT1 inhibition in pancreatic cancer models: contrasting effects in vitro and in vivo. Eur J Pharmacol. 2015;757:59–67.
[68] Menssen A, Hydbring P, Kapelle K, et al. The c-MYC oncoprotein, the NAMPT enzyme, the SIRT1-inhibitor DBC1, and the SIRT1 deacetylase form a positive feedback loop. Proc Natl Acad Sci. 2012;109:E187–96.
[69] Kriegl L, Vieth M, Kirchner T, et al. Up-regulation of c-MYC and SIRT1 expression correlates with malignant transformation in the serrated route to colorectal cancer. Oncotarget. 2012;3:1182–1193.
[70] Boily G, He XH, Pearce B, et al. SirT1-null mice develop tumors at normal rates but are poorly protected by resveratrol. Oncogene. 2009;28:2882–2893.
[71] Firestein R, Blander G, Michan S, et al. The SIRT1 deacetylase suppresses intestinal tumorigenesis and colon cancer growth. PLoS One. 2008;3:e2020.
[72] Kabra N, Li Z, Chen L, et al. SirT1 is an inhibitor of proliferation and tumor formation in colon cancer. J Biol Chem. 2009;284:18210–18217.

[73] Jang KY, Hwang SH, Kwon KS, et al. SIRT1 expression is associated with poor prognosis of diffuse large B-cell lymphoma. Am J Surg Pathol. 2008;32:1523–1531.
[74] Sasca D, Hähnel PS, Szybinski J, et al. SIRT1 prevents genotoxic stress-induced p53 activation in acute myeloid leukemia. Blood. 2014;124:121–133.
[75] Li L, Osdal T, Ho Y, et al. SIRT1 activation by a c-MYC oncogenic network promotes the maintenance and drug resistance of human FLT3-ITD acute myeloid leukemia stem cells. Cell Stem Cell. 2014;15:431–446.
[76] Bradbury CA, Khanim FL, Hayden R, et al. Histone deacetylases in acute myeloid leukaemia show a distinctive pattern of expression that changes selectively in response to deacetylase inhibitors. Leukemia. 2005;19:1751–1759.
[77] Kozako T, Aikawa A, Shoji T, et al. High expression of the longevity gene product SIRT1 and apoptosis induction by sirtinol in adult T-cell leukemia cells. Int J Cancer. 2012;131:2044–2055.
[78] Li L, Wang L, Li L, et al. Activation of p53 by SIRT1 inhibition enhances elimination of CML leukemia stem cells in combination with imatinib. Cancer Cell. 2012;21:266–281.
[79] Heltweg B, Gatbonton T, Schuler AD, et al. Antitumor activity of a small-molecule inhibitor of human silent information regulator 2 enzymes. Cancer Res. 2006;66:4368–4377.
[80] Oberdoerffer P, Michan S, McVay M, et al. SIRT1 redistribution on chromatin promotes genomic stability but alters gene expression during aging. Cell. 2008;135:907–918.
[81] Jung-Hynes B, Nihal M, Zhong W, et al. Role of sirtuin histone deacetylase SIRT1 in prostate cancer. A target for prostate cancer management via its inhibition? J Biol Chem. 2009;284:3823–3832.
[82] Huffman DM, Grizzle WE, Bamman MM, et al. SIRT1 is significantly elevated in mouse and human prostate cancer. Cancer Res. 2007;67:6612–6618.
[83] Herranz D, Maraver A, Canamero M, et al. SIRT1 promotes thyroid carcinogenesis driven by PTEN deficiency. Oncogene. 2013;32:4052–4056.
[84] Byles V, Zhu L, Lovaas JD, et al. SIRT1 induces EMT by cooperating with EMT transcription factors and enhances prostate cancer cell migration and metastasis. Oncogene. 2012;31:4619–4629.
[85] Wu W, Zhang L, Lin J, et al. Hypermethylation of the HIC1 promoter and aberrant expression of HIC1/SIRT1 contribute to the development of thyroid papillary carcinoma. Oncotarget. 2016;7:84416–84427.
[86] Feng AN, Zhang LH, Fan XS, et al. Expression of SIRT1 in gastric cardiac cancer and its clinicopathologic significance. Int J Surg Pathol. 2011;19:743–750.
[87] Cha EJ, Noh SJ, Kwon KS, et al. Expression of DBC1 and SIRT1 is associated with poor prognosis of gastric carcinoma. Clin Cancer Res. 2009;15:4453–4459.
[88] Yang Q, Wang B, Gao W, et al. SIRT1 is downregulated in gastric cancer and leads to G1-phase arrest via NF-kappaB/cyclin D1 signaling. Mol Cancer Res. 2013;11:1497–1507.
[89] Benavente CA, Schnell SA, Jacobson EL. Effects of niacin restriction on sirtuin and PARP responses to photodamage in human skin. PLoS One. 2012;7:e42276.
[90] Wilking MJ, Singh C, Nihal M, et al. SIRT1 deacetylase is overexpressed in human melanoma and its small molecule inhibition imparts anti-proliferative response via p53 activation. Arch Biochem Biophys. 2014;563:94–100.
[91] Jang KY, Kim KS, Hwang SH, et al. Expression and prognostic significance of SIRT1 in ovarian epithelial tumours. Pathology. 2009;41:366–371.
[92] Mvunta DH, Miyamoto T, Asaka R, et al. Overexpression of Sirt1 is associated with poor outcomes in patients with ovarian carcinoma. Appl Immunohistochem amp. 2017;25:415–421.
[93] Dickson BC, Riddle ND, Brooks JS, et al. Sirtuin 1 (SIRT1): a potential immunohistochemical marker and therapeutic target in soft tissue neoplasms with myoid differentiation. Hum Pathol. 2013;44:1125–1130.
[94] Ma J-X, Li H, Chen X-M, et al. Expression patterns and potential roles of SIRT1 in human medulloblastoma cells *in vivo* and *in vitro*. Neuropathology. 2013;33:7–16.
[95] Afshar G, Murnane JP. Characterization of a human gene with sequence homology to Saccharomyces cerevisiae SIR2. Gene. 1999;234:161–168.
[96] Perrod S, Cockell MM, Laroche T, et al. A cytosolic NAD-dependent deacetylase, Hst2p, can modulate nucleolar and telomeric silencing in yeast. Embo J. 2001;20:197–209.
[97] North BJ, Marshall BL, Borra MT, et al. The human Sir2 ortholog, SIRT2, is an NAD+-dependent tubulin deacetylase. Mol Cell. 2003;11:437–444.
[98] Pandithage R, Lilischkis R, Harting K, et al. The regulation of SIRT2 function by cyclin-dependent kinases affects cell motility. J Cell Biol. 2008;180:915–929.
[99] Dryden SC, Nahhas FA, Nowak JE, et al. Role for human SIRT2 NAD-dependent deacetylase activity in control of mitotic exit in the cell cycle. Mol Cell Biol. 2003;23:3173–3185.
[100] Kim H-S, Vassilopoulos A, Wang R-H, et al. SIRT2 maintains genome integrity and suppresses tumorigenesis through regulating APC/C activity. Cancer Cell. 2011;20:487–499.
[101] Suematsu T, Li Y, Kojima H, et al. Deacetylation of the mitotic checkpoint protein BubR1 at lysine 250 by SIRT2 and subsequent effects on BubR1 degradation during the prometaphase/anaphase transition. Biochem Biophys Res Commun. 2014;453:588–594.
[102] Serrano L, Martinez-Redondo P, Marazuela-Duque A, et al. The tumor suppressor SirT2 regulates cell cycle progression and genome stability by modulating the

mitotic deposition of H4K20 methylation. Genes Dev. 2013;27:639–653.
[103] Chen J, Chan AWH, To K-F, et al. SIRT2 overexpression in hepatocellular carcinoma mediates epithelial to mesenchymal transition by protein kinase B/glycogen synthase kinase-3beta/beta-catenin signaling. Hepatology. 2013;57:2287–2298.
[104] Huang S, Zhao Z, Tang D, et al. Downregulation of SIRT2 inhibits invasion of hepatocellular carcinoma by inhibiting energy metabolism. Transl Oncol. 2017;10:917–927.
[105] Xu W, Jiang K, Shen M, et al. SIRT2 suppresses non-small cell lung cancer growth by targeting JMJD2A. Biol Chem. 2015;396:929–936.
[106] Li Z, Huang J, Yuan H, et al. SIRT2 inhibits non-small cell lung cancer cell growth through impairing Skp2-mediated p27 degradation. Oncotarget. 2016;7:18927–18939.
[107] Li Z, Xie QR, Chen Z, et al. Regulation of SIRT2 levels for human non-small cell lung cancer therapy. Lung Cancer. 2013;82:9–15.
[108] Song HY, Biancucci M, Kang H-J, et al. SIRT2 deletion enhances KRAS-induced tumorigenesis in vivo by regulating K147 acetylation status. Oncotarget. 2016;7:80336–80349.
[109] Yang MH, Laurent G, Bause AS, et al. HDAC6 and SIRT2 regulate the acetylation state and oncogenic activity of mutant K-RAS. Mol Cancer Res. 2013;11:1072–1077.
[110] Jiang K, Shen M, Chen Y, et al. miR-150 promotes the proliferation and migration of non-small cell lung cancer cells by regulating the SIRT2/JMJD2A signaling pathway. Oncol Rep. 2018;40:943–951.
[111] Luo J, Bao Y, Ji X, et al. SPOP promotes SIRT2 degradation and suppresses non-small cell lung cancer cell growth. Biochem Biophys Res Commun. 2017;483:880–884.
[112] Park S-H, Ozden O, Liu G, et al. SIRT2-mediated deacetylation and tetramerization of pyruvate kinase directs glycolysis and tumor growth. Cancer Res. 2016;76:3802–3812.
[113] Zhou W, Ni TK, Wronski A, et al. The SIRT2 deacetylase stabilizes slug to control malignancy of basal-like breast cancer. Cell Rep. 2016;17:1302–1317.
[114] Jing H, Hu J, He B, et al. A SIRT2-selective inhibitor promotes c-Myc oncoprotein degradation and exhibits broad anticancer activity. Cancer Cell. 2016;29:607.
[115] Quan S, Principe DR, Dean AE, et al. Loss of Sirt2 increases and prolongs a caerulein-induced pancreatitis permissive phenotype and induces spontaneous oncogenic Kras mutations in mice. Sci Rep. 2018;8:16501.
[116] Zhang -L-L, Zhan L, Jin Y-D, et al. SIRT2 mediated antitumor effects of shikonin on metastatic colorectal cancer. Eur J Pharmacol. 2017;797:1–8.
[117] Bajpe PK, Prahallad A, Horlings H, et al. A chromatin modifier genetic screen identifies SIRT2 as a modulator of response to targeted therapies through the regulation of MEK kinase activity. Oncogene. 2015;34:531–536.
[118] Xu S-N, Wang T-S, Li X, et al. SIRT2 activates G6PD to enhance NADPH production and promote leukaemia cell proliferation. Sci Rep. 2016;6:32734.
[119] Deng A, Ning Q, Zhou L, et al. SIRT2 is an unfavorable prognostic biomarker in patients with acute myeloid leukemia. Sci Rep. 2016;6:27694.
[120] Damodaran S, Damaschke N, Gawdzik J, et al. Dysregulation of sirtuin 2 (SIRT2) and histone H3K18 acetylation pathways associates with adverse prostate cancer outcomes. BMC Cancer. 2017;17:874.
[121] Wei R, He D, Zhang X. Role of SIRT2 in regulation of stemness of cancer stem-like cells in renal cell carcinoma. Cell Physiol Biochem. 2018;49:2348–2357.
[122] Wilking-Busch MJ, Ndiaye MA, Huang W, et al. Expression profile of SIRT2 in human melanoma and implications for sirtuin-based chemotherapy. Cell Cycle. 2017;16:574–577.
[123] Ming M, Qiang L, Zhao B, et al. Mammalian SIRT2 inhibits keratin 19 expression and is a tumor suppressor in skin. Exp Dermatol. 2014;23:207–209.
[124] Temel M, Koç MN, Ulutaş S, et al. The expression levels of the sirtuins in patients with BCC. Tumour Biol. 2016;37:6429–6435.
[125] Funato K, Hayashi T, Echizen K, et al. SIRT2-mediated inactivation of p73 is required for glioblastoma tumorigenicity. EMBO Rep. 2018;19:e45587.
[126] Onyango P, Celic I, McCaffery JM, et al. SIRT3, a human SIR2 homologue, is an NAD-dependent deacetylase localized to mitochondria. Proc Natl Acad Sci U S A. 2002;99:13653–13658.
[127] Verdin E, Hirschey MD, Finley LWS, et al. Sirtuin regulation of mitochondria: energy production, apoptosis, and signaling. Trends Biochem Sci. 2010;35:669–675.
[128] Finley LWS, Carracedo A, Lee J, et al. SIRT3 opposes reprogramming of cancer cell metabolism through HIF1alpha destabilization. Cancer Cell. 2011;19:416–428.
[129] Zou X, Zhu Y, Park S-H, et al. SIRT3-mediated dimerization of IDH2 directs cancer cell metabolism and tumor growth. Cancer Res. 2017;77:3990–3999.
[130] Kim H-S, Patel K, Muldoon-Jacobs K, et al. SIRT3 is a mitochondria-localized tumor suppressor required for maintenance of mitochondrial integrity and metabolism during stress. Cancer Cell. 2010;17:41–52.
[131] Zeng X, Wang N, Zhai H, et al. SIRT3 functions as a tumor suppressor in hepatocellular carcinoma. Tumour Biol. 2017;39:1010428317691178.
[132] Liu Y, Liu Y-L, Cheng W, et al. The expression of SIRT3 in primary hepatocellular carcinoma and the mechanism of its tumor suppressing effects. Eur Rev Med Pharmacol Sci. 2017;21:978–998.
[133] Zhang B, Qin L, Zhou C-J, et al. SIRT3 expression in hepatocellular carcinoma and its impact on

proliferation and invasion of hepatoma cells. Asian Pac J Trop Med. 2013;6:649–652.
[134] Zhang CZ, Liu L, Cai M, et al. Low SIRT3 expression correlates with poor differentiation and unfavorable prognosis in primary hepatocellular carcinoma. PLoS One. 2012;7:e51703.
[135] Xiong Y, Wang M, Zhao J, et al. SIRT3 is correlated with the malignancy of non-small cell lung cancer. Int J Oncol. 2017;50:903–910.
[136] Xiong Y, Wang L, Wang S, et al. SIRT3 deacetylates and promotes degradation of P53 in PTEN-defective non-small cell lung cancer. J Cancer Res Clin Oncol. 2018;144:189–198.
[137] Li H, Feng Z, Wu W, et al. SIRT3 regulates cell proliferation and apoptosis related to energy metabolism in non-small cell lung cancer cells through deacetylation of NMNAT2. Int J Oncol. 2013;43:1420–1430.
[138] Desouki MM, Doubinskaia I, Gius D, et al. Decreased mitochondrial SIRT3 expression is a potential molecular biomarker associated with poor outcome in breast cancer. Hum Pathol. 2014;45:1071–1077.
[139] Gonzalez Herrera KN, Zaganjor E, Ishikawa Y, et al. Small-molecule screen identifies de novo nucleotide synthesis as a vulnerability of cells lacking SIRT3. Cell Rep. 2018;22:1945–1955.
[140] Pinteric M, Podgorski II, Sobocanec S, et al. De novo expression of transfected sirtuin 3 enhances susceptibility of human MCF-7 breast cancer cells to hyperoxia treatment. Free Radic Res. 2018;52:672–684.
[141] He S, He C, Yuan H, et al. The SIRT 3 expression profile is associated with pathological and clinical outcomes in human breast cancer patients. Cell Physiol Biochem. 2014;34:2061–2069.
[142] Huang S, Chen X, Zheng J, et al. Low SIRT3 expression contributes to tumor progression, development and poor prognosis in human pancreatic carcinoma. Pathol Res Pract. 2017;213:1419–1423.
[143] Liu C, Huang Z, Jiang H, et al. The sirtuin 3 expression profile is associated with pathological and clinical outcomes in colon cancer patients. Biomed Res Int. 2014;2014:871263.
[144] Wei Z, Song J, Wang G, et al. Deacetylation of serine hydroxymethyl-transferase 2 by SIRT3 promotes colorectal carcinogenesis. Nat Commun. 2018;9:4468.
[145] Yu W, Denu RA, Krautkramer KA, et al. Loss of SIRT3 provides growth advantage for B cell malignancies. J Biol Chem. 2016;291:3268–3279.
[146] Li M, Chiang Y-L, Lyssiotis C, et al. SIRT3 is a novel metabolic driver of and therapeutic target for chemotherapy resistant Dlbcls. Blood. 2017;130:643.
[147] Quan Y, Wang N, Chen Q, et al. SIRT3 inhibits prostate cancer by destabilizing oncoprotein c-MYC through regulation of the PI3K/Akt pathway. Oncotarget. 2015;6:26494–26507.
[148] Li R, Quan Y, Xia W. SIRT3 inhibits prostate cancer metastasis through regulation of FOXO3A by suppressing Wnt/beta-catenin pathway. Exp Cell Res. 2018;364:143–151.
[149] Shackelford R, Hirsh S, Henry K, et al. Nicotinamide phosphoribosyltransferase and SIRT3 expression are increased in well-differentiated thyroid carcinomas. Anticancer Res. 2013;33:3047–3052.
[150] Wang L, Wang W-Y, Cao L-P. SIRT3 inhibits cell proliferation in human gastric cancer through down-regulation of Notch-1. Int J Clin Exp Med. 2015;8:5263–5271.
[151] Huang K-H, Hsu -C-C, Fang W-L, et al. SIRT3 expression as a biomarker for better prognosis in gastric cancer. World J Surg. 2014;38:910–917.
[152] Yang B, Fu X, Shao L, et al. Aberrant expression of SIRT3 is conversely correlated with the progression and prognosis of human gastric cancer. Biochem Biophys Res Commun. 2014;443:156–160.
[153] George J, Nihal M, Singh CK, et al. Pro-proliferative function of mitochondrial sirtuin deacetylase SIRT3 in human melanoma. J Invest Dermatol. 2016;136:809–818.
[154] Dong X-C, Jing L-M, Wang W-X, et al. Down-regulation of SIRT3 promotes ovarian carcinoma metastasis. Biochem Biophys Res Commun. 2016;475:245–250.
[155] Yang Y, Cao Y, Chen L, et al. Cryptotanshinone suppresses cell proliferation and glucose metabolism via STAT3/SIRT3 signaling pathway in ovarian cancer cells. Cancer Med. 2018;7:4610–4618.
[156] Wu Y, Gao W-N, Xue Y-N, et al. SIRT3 aggravates metformin-induced energy stress and apoptosis in ovarian cancer cells. Exp Cell Res. 2018;367:137–149.
[157] Michishita E, Park JY, Burneskis JM, et al. Evolutionarily conserved and nonconserved cellular localizations and functions of human SIRT proteins. Mol Biol Cell. 2005;16:4623–4635.
[158] Haigis MC, Mostoslavsky R, Haigis KM, et al. SIRT4 inhibits glutamate dehydrogenase and opposes the effects of calorie restriction in pancreatic beta cells. Cell. 2006;126:941–954.
[159] Laurent G, German NJ, Saha AK, et al. SIRT4 coordinates the balance between lipid synthesis and catabolism by repressing malonyl CoA decarboxylase. Mol Cell. 2013;50:686–698.
[160] Anderson KA, Huynh FK, Fisher-Wellman K, et al. SIRT4 is a lysine deacylase that controls leucine metabolism and insulin secretion. Cell Metab. 2017;25:838–855.e15.
[161] Mathias RA, Greco TM, Oberstein A, et al. Sirtuin 4 is a lipoamidase regulating pyruvate dehydrogenase complex activity. Cell. 2014;159:1615–1625.
[162] Li Y, Zhou Y, Wang F, et al. SIRT4 is the last puzzle of mitochondrial sirtuins. Bioorg Med Chem. 2018;26:3861–3865.

[163] Csibi A, Fendt S-M, Li C, et al. The mTORC1 pathway stimulates glutamine metabolism and cell proliferation by repressing SIRT4. Cell. 2013;153:840–854.
[164] Wang Y, Du L, Liang X, et al. SIRT 4 depletion promotes HCC tumorigenesis through regulating AMPK α/mTOR axis. Hepatology. 2019;69(4):1614–1631.
[165] Jeong SM, Xiao C, Finley LWS, et al. SIRT4 has tumor-suppressive activity and regulates the cellular metabolic response to DNA damage by inhibiting mitochondrial glutamine metabolism. Cancer Cell. 2013;23:450–463.
[166] Fu L, Dong Q, He J, et al. SIRT4 inhibits malignancy progression of NSCLCs, through mitochondrial dynamics mediated by the ERK-Drp1 pathway. Oncogene. 2017;36:2724–2736.
[167] Gong J, Wang H, Lou W, et al. Associations of sirtuins with clinicopathological parameters and prognosis in non-small cell lung cancer. Cancer Manag Res. 2018;10:3341–3356.
[168] Shi Q, Liu T, Zhang X, et al. Decreased sirtuin 4 expression is associated with poor prognosis in patients with invasive breast cancer. Oncol Lett. 2016;12:2606–2612.
[169] Huang G, Lin Y, Zhu G. SIRT 4 is upregulated in breast cancer and promotes the proliferation, migration and invasion of breast cancer cells. Int J Clin Exp Pathol. 2017;10(12):11849–11856.
[170] Huang G, Cheng J, Yu F, et al. Clinical and therapeutic significance of sirtuin-4 expression in colorectal cancer. Oncol Rep. 2016;35:2801–2810.
[171] Miyo M, Yamamoto H, Konno M, et al. Tumour-suppressive function of SIRT4 in human colorectal cancer. Br J Cancer. 2015;113:492–499.
[172] Zhu Y, Wang G, Li X, et al. Knockout of SIRT4 decreases chemosensitivity to 5-FU in colorectal cancer cells. Oncol Lett. 2018;16:1675–1681.
[173] Jeong SM, Lee A, Lee J, et al. SIRT4 protein suppresses tumor formation in genetic models of Myc-induced B cell lymphoma. J Biol Chem. 2014;289:4135–4144.
[174] Sun H, Huang D, Liu G, et al. SIRT4 acts as a tumor suppressor in gastric cancer by inhibiting cell proliferation, migration, and invasion. Onco Targets Ther. 2018;11:3959–3968.
[175] Chen Z, Lei T, Zheng L, et al. SIRT4 protein levels are downregulated in kidney renal clear cell carcinoma. Int J Clin Exp Med. 2017;10(9):14022–14029.
[176] Wang Y, Guo Y, Gao J, et al. Tumor-suppressive function of SIRT4 in neuroblastoma through mitochondrial damage. Cancer Manag Res. 2018;10:5591–5603.
[177] Tan M, Peng C, Anderson KA, et al. Lysine glutarylation is a protein posttranslational modification regulated by SIRT5. Cell Metab. 2014;19:605–617.
[178] Du J, Zhou Y, Su X, et al. Sirt5 is a NAD-dependent protein lysine demalonylase and desuccinylase. Science. 2011;334:806–809.
[179] Nakagawa T, Lomb DJ, Haigis MC, et al. SIRT5 deacetylates carbamoyl phosphate synthetase 1 and regulates the urea cycle. Cell. 2009;137:560–570.
[180] Nishida Y, Rardin MJ, Carrico C, et al. SIRT5 regulates both cytosolic and mitochondrial protein malonylation with glycolysis as a major target. Mol Cell. 2015;59:321.
[181] Rardin MJ, He W, Nishida Y, et al. SIRT5 regulates the mitochondrial lysine succinylome and metabolic networks. Cell Metab. 2013;18:920–933.
[182] Lu W, Zuo Y, Feng Y, et al. SIRT5 facilitates cancer cell growth and drug resistance in non-small cell lung cancer. Tumor Biol. 2014;35:10699–10705.
[183] Sun JY, Xu L, Tseng H, et al. Histone deacetylase inhibitors demonstrate significant preclinical activity as single agents, and in combination with bortezomib in waldenström's macroglobulinemia. Clin Lymphoma Myeloma Leuk. 2011;11:152–156.
[184] Chang L, Xi L, Liu Y, et al. SIRT5 promotes cell proliferation and invasion in hepatocellular carcinoma by targeting E2F1. Mol Med Rep. 2018;17:342–349.
[185] Wang Y-Q, Wang H-L, Xu J, et al. Sirtuin5 contributes to colorectal carcinogenesis by enhancing glutaminolysis in a deglutarylation-dependent manner. Nat Commun. 2018;9:545.
[186] Xu L, Che X, Wu Y, et al. SIRT5 as a biomarker for response to anthracycline-taxane-based neoadjuvant chemotherapy in triple-negative breast cancer. Oncol Rep. 2018;39:2315–2323.
[187] Igci M, Kalender ME, Borazan E, et al. High-throughput screening of Sirtuin family of genes in breast cancer. Gene. 2016;586:123–128.
[188] Chen X-F, Tian M-X, Sun R-Q, et al. SIRT5 inhibits peroxisomal ACOX1 to prevent oxidative damage and is downregulated in liver cancer. EMBO Rep. 2018;19:e45124.
[189] Bartosch C, Monteiro-Reis S, Almeida-Rios D, et al. Assessing sirtuin expression in endometrial carcinoma and non-neoplastic endometrium. Oncotarget. 2016;7.
[190] Lai -C-C, Lin P-M, Lin S-F, et al. Altered expression of SIRT gene family in head and neck squamous cell carcinoma. Tumor Biol. 2013;34:1847–1854.
[191] Rossella F, Gabriele G, Federica T, et al. The role of the transcription factor E2F1 in hepatocellular carcinoma. Curr Drug Deliv. 2016;13:1.
[192] Lv X, Liu L, Cheng C, et al. SUN2 exerts tumor suppressor functions by suppressing the Warburg effect in lung cancer. Sci Rep. 2015;5:17940.
[193] Menegon S, Columbano A, Giordano S. The dual roles of NRF2 in cancer. Trends Mol Med. 2016;22:578–593.
[194] Lin Z-F, Xu H-B, Wang J-Y, et al. SIRT5 desuccinylates and activates SOD1 to eliminate ROS. Biochem Biophys Res Commun. 2013;441:191–195.
[195] Du Z, Liu X, Chen T, et al. Targeting a sirt5-positive subpopulation overcomes multidrug resistance in

wild-type kras colorectal carcinomas. Cell Rep. 2018;22:2677–2689.
[196] Li F, He X, Ye D, et al. NADP+-IDH mutations promote hypersuccinylation that impairs mitochondria respiration and induces apoptosis resistance. Mol Cell. 2015;60:661–675.
[197] Ning S, Ma S, Saleh AQ, et al. SHMT2 overexpression predicts poor prognosis in intrahepatic cholangiocarcinoma. Gastroenterol Res Pract. 2018;2018:1–6.
[198] Bernhardt S, Bayerlová M, Vetter M, et al. Proteomic profiling of breast cancer metabolism identifies SHMT2 and ASCT2 as prognostic factors. Breast Cancer Res. 2017;19:112.
[199] Kim D, Fiske BP, Birsoy K, et al. SHMT2 drives glioma cell survival in ischaemia but imposes a dependence on glycine clearance. Nature. 2015;520:363–367.
[200] Xiangyun Y, Xiaomin N, linping G, et al. Desuccinylation of pyruvate kinase M2 by SIRT5 contributes to antioxidant response and tumor growth. Oncotarget. 2017;8:6984–6993.
[201] Wang F, Wang K, Xu W, et al. SIRT5 desuccinylates and activates pyruvate kinase M2 to block macrophage IL-1β production and to prevent DSS-induced colitis in mice. Cell Rep. 2017;19:2331–2344.
[202] Guan D, Lim JH, Peng L, et al. Deacetylation of the tumor suppressor protein PML regulates hydrogen peroxide-induced cell death. Cell Death Dis. 2014;5:e1340.
[203] Michishita E, McCord RA, Berber E, et al. SIRT6 is a histone H3 lysine 9 deacetylase that modulates telomeric chromatin. Nature. 2008;452:492–496.
[204] Michishita E, McCord RA, Boxer LD, et al. Cell cycle-dependent deacetylation of telomeric histone H3 lysine K56 by human SIRT6. Cell Cycle. 2009;8:2664–2666.
[205] Tasselli L, Xi Y, Zheng W, et al. SIRT6 deacetylates H3K18ac at pericentric chromatin to prevent mitotic errors and cellular senescence. Nat Struct Mol Biol. 2016;23:434–440.
[206] Zhong L, D'Urso A, Toiber D, et al. The histone deacetylase sirt6 regulates glucose homeostasis via Hif1α. Cell. 2010;140:280–293.
[207] Mao Z, Hine C, Tian X, et al. SIRT6 promotes DNA repair under stress by activating PARP1. Science. 2011;332:1443–1446.
[208] Kaidi A, Weinert BT, Choudhary C, et al. Human SIRT6 promotes DNA end resection through CtIP deacetylation. Science. 2010;329:1348–1353.
[209] McCord RA, Michishita E, Hong T, et al. SIRT6 stabilizes DNA-dependent protein kinase at chromatin for DNA double-strand break repair. Aging (Albany NY). 2009;1:109–121.
[210] Toiber D, Erdel F, Bouazoune K, et al. SIRT6 recruits SNF2H to DNA break sites, preventing genomic instability through chromatin remodeling. Mol Cell. 2013;51:454–468.
[211] Feldman JL, Baeza J, Denu JM. Activation of the protein deacetylase SIRT6 by long-chain fatty acids and widespread deacylation by mammalian sirtuins. J Biol Chem. 2013;288:31350–31356.
[212] Jiang H, Khan S, Wang Y, et al. SIRT6 regulates TNF-α secretion through hydrolysis of long-chain fatty acyl lysine. Nature. 2013;496:110–113.
[213] Wang WW, Zeng Y, Wu B, et al. A chemical biology approach to reveal sirt6-targeted histone H3 sites in nucleosomes. ACS Chem Biol. 2016;11:1973–1981.
[214] Sebastián C, Zwaans BMM, Silberman DM, et al. The histone deacetylase SIRT6 is a tumor suppressor that controls cancer metabolism. Cell. 2012;151:1185–1199.
[215] Min L, Ji Y, Bakiri L, et al. Liver cancer initiation is controlled by AP-1 through SIRT6-dependent inhibition of survivin. Nat Cell Biol. 2012;14:1203–1211.
[216] Yang W, Xia Y, Hawke D, et al. PKM2 phosphorylates histone H3 and promotes gene transcription and tumorigenesis. Cell. 2012;150:685–696.
[217] Bhardwaj A, Das S. SIRT6 deacetylates PKM2 to suppress its nuclear localization and oncogenic functions. Proc Natl Acad Sci U S A. 2016;113:E538–47.
[218] Yang W, Xia Y, Ji H, et al. Nuclear PKM2 regulates β-catenin transactivation upon EGFR activation. Nature. 2011;478:118–122.
[219] ZHANG Z-G, QIN C-Y. Sirt6 suppresses hepatocellular carcinoma cell growth via inhibiting the extracellular signal-regulated kinase signaling pathway. Mol Med Rep. 2014;9:882–888.
[220] Kohli S, Bhardwaj A, Kumari R, et al. SIRT6 is a target of regulation by UBE3A that contributes to liver tumorigenesis in an ANXA2-dependent manner. Cancer Res. 2018;78:645–658.
[221] Ran L-K, Chen Y, Zhang -Z-Z, et al. SIRT6 overexpression potentiates apoptosis evasion in hepatocellular carcinoma via BCL2-associated x protein-dependent apoptotic pathway. Clin Cancer Res. 2016;22:3372–3382.
[222] Feng -X-X, Luo J, Liu M, et al. Sirtuin 6 promotes transforming growth factor-β1/H2O2/HOCl-mediated enhancement of hepatocellular carcinoma cell tumorigenicity by suppressing cellular senescence. Cancer Sci. 2015;106:559–566.
[223] Elhanati S, Ben-Hamo R, Kanfi Y, et al. Reciprocal regulation between SIRT6 and miR-122 controls liver metabolism and predicts hepatocarcinoma prognosis. Cell Rep. 2016;14:234–242.
[224] Han Z, Liu L, Liu Y, et al. Sirtuin SIRT6 suppresses cell proliferation through inhibition of Twist1 expression in non-small cell lung cancer. Int J Clin Exp Pathol. 2014;7:4774–4781.
[225] Azuma Y, Yokobori T, Mogi A, et al. SIRT6 expression is associated with poor prognosis and chemosensitivity in patients with non-small cell lung cancer. J Surg Oncol. 2015;112:231–237.

[226] Bae JS, Park S-H, Jamiyandorj U, et al. CK2α/CSNK2A1 phosphorylates SIRT6 and is involved in the progression of breast carcinoma and predicts shorter survival of diagnosed patients. Am J Pathol. 2016;186:3297–3315.
[227] Choe M, Brusgard JL, Chumsri S, et al. The RUNX2 transcription factor negatively regulates SIRT6 expression to alter glucose metabolism in breast cancer cells. J Cell Biochem. 2015;116:2210–2226.
[228] Kugel S, Sebastián C, Fitamant J, et al. SIRT6 Suppresses pancreatic cancer through control of Lin28b. Cell. 2016;165:1401–1415.
[229] Lin Z, Yang H, Tan C, et al. USP10 antagonizes c-Myc transcriptional activation through SIRT6 stabilization to suppress tumor formation. Cell Rep. 2013;5:1639–1649.
[230] Cea M, Cagnetta A, Adamia S, et al. Evidence for a role of the histone deacetylase SIRT6 in DNA damage response of multiple myeloma cells. Blood. 2016;127:1138–1150.
[231] Cagnetta A, Soncini D, Orecchioni S, et al. Depletion of SIRT6 enzymatic activity increases acute myeloid leukemia cells' vulnerability to DNA-damaging agents. Haematologica. 2018;103:80–90.
[232] Qu N, Hu J-Q, Liu L, et al. SIRT6 is upregulated and associated with cancer aggressiveness in papillary thyroid cancer via BRAF/ERK/Mcl-1 pathway. Int J Oncol. 2017;50:1683–1692.
[233] Ming M, Han W, Zhao B, et al. SIRT6 promotes COX-2 expression and acts as an oncogene in skin cancer. Cancer Res. 2014;74:5925–5933.
[234] Lefort K, Brooks Y, Ostano P, et al. A miR-34a-SIRT6 axis in the squamous cell differentiation network. Embo J. 2013;32:2248–2263.
[235] Lu C-T, Hsu C-M, Lin P-M, et al. The potential of SIRT6 and SIRT7 as circulating markers for head and neck squamous cell carcinoma. Anticancer Res. 2014;34:7137–7143.
[236] Garcia-Peterson LM, Ndiaye MA, Singh CK, et al. SIRT6 histone deacetylase functions as a potential oncogene in human melanoma. Genes Cancer. 2017;8:701–712.
[237] Wang L, Guo W, Ma J, et al. Aberrant SIRT6 expression contributes to melanoma growth: role of the autophagy paradox and IGF-AKT signaling. Autophagy. 2018;14:518–533.
[238] Strub T, Ghiraldini FG, Carcamo S, et al. SIRT6 haploinsufficiency induces BRAFV600E melanoma cell resistance to MAPK inhibitors via IGF signalling. Nat Commun. 2018;9:3440.
[239] Zhang J, Yin X-J, Xu C-J, et al. The histone deacetylase SIRT6 inhibits ovarian cancer cell proliferation via down-regulation of notch 3 expression. Eur Rev Med Pharmacol Sci. 2015;19:818–824.
[240] Wu M, Seto E, Zhang J. E2F1 enhances glycolysis through suppressing Sirt6 transcription in cancer cells. Oncotarget. 2015;6:11252–11263.
[241] Chen S, Seiler J, Santiago-Reichelt M, et al. Repression of RNA polymerase I upon stress is caused by inhibition of RNA-dependent deacetylation of PAF53 by SIRT7. Mol Cell. 2013;52:303–313.
[242] Chen S, Blank MF, Iyer A, et al. SIRT7-dependent deacetylation of the U3-55k protein controls pre-rRNA processing. Nat Commun. 2016;7:10734.
[243] Tsai Y-C, Greco TM, Boonmee A, et al. Functional proteomics establishes the interaction of SIRT7 with chromatin remodeling complexes and expands its role in regulation of RNA polymerase I transcription. Mol Cell Proteomics. 2012;11:60–76.
[244] Tsai Y-C, Greco TM, Cristea IM. Sirtuin 7 plays a role in ribosome biogenesis and protein synthesis. Mol Cell Proteomics. 2014;13:73–83.
[245] Barber MF, Michishita-Kioi E, Xi Y, et al. SIRT7 links H3K18 deacetylation to maintenance of oncogenic transformation. Nature. 2012;487:114–118.
[246] Shin J, He M, Liu Y, et al. SIRT7 represses Myc activity to suppress ER stress and prevent fatty liver disease. Cell Rep. 2013;5:654–665.
[247] Ryu D, Jo YS, Lo Sasso G, et al. A SIRT7-dependent acetylation switch of GABPβ1 controls mitochondrial function. Cell Metab. 2014;20:856–869.
[248] Li L, Shi L, Yang S, et al. SIRT7 is a histone desuccinylase that functionally links to chromatin compaction and genome stability. Nat Commun. 2016;7:12235.
[249] Vazquez BN, Thackray JK, Simonet NG, et al. SIRT7 promotes genome integrity and modulates non-homologous end joining DNA repair. Embo J. 2016;35:1488–1503.
[250] Vakhrusheva O, Smolka C, Gajawada P, et al. Sirt7 increases stress resistance of cardiomyocytes and prevents apoptosis and inflammatory cardiomyopathy in mice. Circ Res. 2008;102:703–710.
[251] Kim JK, Noh JH, Jung KH, et al. Sirtuin7 oncogenic potential in human hepatocellular carcinoma and its regulation by the tumor suppressors MiR-125a-5p and MiR-125b. Hepatology. 2013;57:1055–1067.
[252] Aljada A, Saleh AM, Alkathiri M, et al. 7 expression is associated with early stage breast cancer. Breast Cancer (Auckl). 2015;9:3–8.
[253] Tang X, Shi L, Xie N, et al. SIRT7 antagonizes TGF-β signaling and inhibits breast cancer metastasis. Nat Commun. 2017;8:318.
[254] Malik S, Villanova L, Tanaka S, et al. SIRT7 inactivation reverses metastatic phenotypes in epithelial and mesenchymal tumors. Sci Rep. 2015;5:9841.
[255] Zhang S, Chen P, Huang Z, et al. Sirt7 promotes gastric cancer growth and inhibits apoptosis by epigenetically inhibiting miR-34a. Sci Rep. 2015;5:9787.
[256] Park J, Chen K, Park J, et al. Human melanoma cell need SIRT5 to survive. Free Radic Biol Med. 2016;100:S128.
[257] Yang X, Wang Z, Li X, et al. SHMT2 desuccinylation by SIRT5 drives cancer cell proliferation. Cancer Res. 2018;78:372–386.
[258] Wang H-L, Lu R-Q, Xie S-H, et al. SIRT7 exhibits oncogenic potential in human ovarian cancer cells. Asian Pac J Cancer Prev. 2015;16:3573–3577.

[259] Shi H, Ji Y, Zhang D, et al. MicroRNA-3666-induced suppression of SIRT7 inhibits the growth of non-small cell lung cancer cells. Oncol Rep. 2016;36:3051–3057.
[260] Howitz KT, Bitterman KJ, Cohen HY, et al. Small molecule activators of sirtuins extend saccharomyces cerevisiae lifespan. Nature. 2003;425:191–196.
[261] Milne JC, Lambert PD, Schenk S, et al. Small molecule activators of SIRT1 as therapeutics for the treatment of type 2 diabetes. Nature. 2007;450:712–716.
[262] Hubbard BP, Gomes AP, Dai H, et al. Evidence for a common mechanism of SIRT1 regulation by allosteric activators. Science. 2013;339:1216–1219.
[263] Dai H, Kustigian L, Carney D, et al. SIRT1 activation by small molecules: kinetic and biophysical evidence for direct interaction of enzyme and activator. J Biol Chem. 2010;285:32695–32703.
[264] Cuyàs E, Verdura S, Llorach-Parés L, et al. Metformin is a direct SIRT1-activating compound: computational modeling and experimental validation. Front Endocrinol (Lausanne). 2018;9:657.
[265] Lakshminarasimhan M, Rauh D, Schutkowski M, et al. Sirt1 activation by resveratrol is substrate sequence-selective. Aging (Albany NY). 2013;5:151–154.
[266] Jang M, Cai L, Udeani GO, et al. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. Science. 1997;275:218–220.
[267] Jang M, Pezzuto JM. Effects of resveratrol on 12-O-tetradecanoylphorbol-13-acetate-induced oxidative events and gene expression in mouse skin. Cancer Lett. 1998;134:81–89.
[268] Aggarwal BB, Bhardwaj A, Aggarwal RS, et al. Role of resveratrol in prevention and therapy of cancer: preclinical and clinical studies. Anticancer Res. 2004;24:2783–2840.
[269] Yu L, Sun Z-J, Wu S-L, et al. Effect of resveratrol on cell cycle proteins in murine transplantable liver cancer. World J Gastroenterol. 2003;9:2341–2343.
[270] Banerjee S, Bueso-Ramos C, Aggarwal BB. Suppression of 7,12-dimethylbenz(a)anthracene-induced mammary carcinogenesis in rats by resveratrol: role of nuclear factor-kappaB, cyclooxygenase 2, and matrix metalloprotease 9. Cancer Res. 2002;62:4945–4954.
[271] Tessitore L, Davit A, Sarotto I, et al. Resveratrol depresses the growth of colorectal aberrant crypt foci by affecting bax and p21(CIP) expression. Carcinogenesis. 2000;21:1619–1622.
[272] Limagne E, Thibaudin M, Euvrard R, et al. Sirtuin-1 activation controls tumor growth by impeding Th17 differentiation via STAT3 deacetylation. Cell Rep. 2017;19:746–759.
[273] Hecht SS, Kenney PM, Wang M, et al. Evaluation of butylated hydroxyanisole, myo-inositol, curcumin, esculetin, resveratrol and lycopene as inhibitors of benzo[a]pyrene plus 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumorigenesis in A/J mice. Cancer Lett. 1999;137:123–130.
[274] Sato M, Pei RJ, Yuri T, et al. Prepubertal resveratrol exposure accelerates N-methyl-N-nitrosourea-induced mammary carcinoma in female sprague-dawley rats. Cancer Lett. 2003;202:137–145.
[275] Chini CCS, Espindola-Netto JM, Mondal G, et al. SIRT1-Activating Compounds (STAC) negatively regulate pancreatic cancer cell growth and viability through a SIRT1 lysosomal-dependent pathway. Clin Cancer Res. 2016;22(10):2496–2507.
[276] Lahusen TJ, Deng C-X. SRT1720 induces lysosomal-dependent cell death of breast cancer cells. Mol Cancer Ther. 2015;14:183–192.
[277] Hayashi R, Hayashi R, Ichikawa T, et al. SRT1720, a SIRT1 activator, promotes tumor cell migration, and lung metastasis of breast cancer in mice. Oncol Rep. 2012;27:1726–1732.
[278] YANG L-H, HO Y-J, LIN J-F, et al. Butein inhibits the proliferation of breast cancer cells through generation of reactive oxygen species and modulation of ERK and p38 activities. Mol Med Rep. 2012;6:1126–1132.
[279] Cho S-G, Woo S-M, Ko S-G. Butein suppresses breast cancer growth by reducing a production of intracellular reactive oxygen species. J Exp Clin Cancer Res. 2014;33:51.
[280] BAI X, MA Y, ZHANG G. Butein suppresses cervical cancer growth through the PI3K/AKT/mTOR pathway. Oncol Rep. 2015;33:3085–3092.
[281] Grozinger CM, Chao ED, Blackwell HE, et al. Identification of a class of small molecule inhibitors of the sirtuin family of NAD-dependent deacetylases by phenotypic screening. J Biol Chem. 2001;276:38837–38843.
[282] Ota H, Tokunaga E, Chang K, et al. Sirt1 inhibitor, sirtinol, induces senescence-like growth arrest with attenuated Ras–MAPK signaling in human cancer cells. Oncogene. 2005;25:176.
[283] Kalle AM, Mallika A, Badiger J, et al. Inhibition of SIRT1 by a small molecule induces apoptosis in breast cancer cells. Biochem Biophys Res Commun. 2010;401:13–19.
[284] Lara E, Mai A, Calvanese V, et al. Salermide, a sirtuin inhibitor with a strong cancer-specific proapoptotic effect. Oncogene. 2009;28:781–791.
[285] Dastjerdi MN, Salahshoor MR, Mardani M, et al. The apoptotic effects of sirtuin1 inhibitor on the MCF-7 and MRC-5 cell lines. Res Pharm Sci. 2013;8:79–89.
[286] Peck B, Chen C-Y, Ho -K-K, et al. SIRT inhibitors induce cell death and p53 acetylation through targeting both SIRT1 and SIRT2. Mol Cancer Ther. 2010;9:844–855.
[287] Tervo AJ, Kyrylenko S, Niskanen P, et al. An in silico approach to discovering novel inhibitors of human sirtuin type 2. J Med Chem. 2004;47:6292–6298.
[288] Guan X, Lin P, Knoll E, et al. Mechanism of inhibition of the human sirtuin enzyme SIRT3 by nicotinamide: computational and experimental studies. PLoS One. 2014;9:e107729.

[289] Hu J, He B, Bhargava S, et al. A fluorogenic assay for screening Sirt6 modulators. Org Biomol Chem. 2013;11:5213–5216.
[290] Audrito V, Vaisitti T, Rossi D, et al. Nicotinamide blocks proliferation and induces apoptosis of chronic lymphocytic leukemia cells through activation of the p53/miR-34a/SIRT1 tumor suppressor network. Cancer Res. 2011;71:4473–4483.
[291] Amengual JE, Clark-Garvey S, Kalac M, et al. Sirtuin and pan-class I/II deacetylase (DAC) inhibition is synergistic in preclinical models and clinical studies of lymphoma. Blood. 2013;122:2104–2113.
[292] Napper AD, Hixon J, McDonagh T, et al. Discovery of indoles as potent and selective inhibitors of the deacetylase SIRT1. J Med Chem. 2005;48:8045–8054.
[293] Cea M, Soncini D, Fruscione F, et al. Synergistic interactions between HDAC and sirtuin inhibitors in human leukemia cells. PLoS One. 2011;6:e22739.
[294] Kim H-B, Lee S-H, Um J-H, et al. Sensitization of chemo-resistant human chronic myeloid leukemia stem-like cells to Hsp90 inhibitor by SIRT1 inhibition. Int J Biol Sci. 2015;11:923–934.
[295] Singh S, Kumar PU, Thakur S, et al. Expression/localization patterns of sirtuins (SIRT1, SIRT2, and SIRT7) during progression of cervical cancer and effects of sirtuin inhibitors on growth of cervical cancer cells. Tumour Biol. 2015;36:6159–6171.
[296] Zhang J-G, Hong D-F, Zhang C-W, et al. Sirtuin 1 facilitates chemoresistance of pancreatic cancer cells by regulating adaptive response to chemotherapy-induced stress. Cancer Sci. 2014;105:445–454.
[297] Outeiro TF, Kontopoulos E, Altmann SM, et al. Sirtuin 2 inhibitors rescue alpha-synuclein-mediated toxicity in models of parkinson's disease. Science. 2007;317:516–519.
[298] Rumpf T, Schiedel M, Karaman B, et al. Selective Sirt2 inhibition by ligand-induced rearrangement of the active site. Nat Commun. 2015;6:6263.
[299] Taylor DM, Balabadra U, Xiang Z, et al. A brain-permeable small molecule reduces neuronal cholesterol by inhibiting activity of sirtuin 2 deacetylase. ACS Chem Biol. 2011;6:540–546.
[300] Zhang Y, Au Q, Zhang M, et al. Identification of a small molecule SIRT2 inhibitor with selective tumor cytotoxicity. Biochem Biophys Res Commun. 2009;386:729–733.
[301] Patel K, Sherrill J, Mrksich M, et al. Discovery of SIRT3 inhibitors using SAMDI mass spectrometry. J Biomol Screen. 2015;20:842–848.
[302] Salo HS, Laitinen T, Poso A, et al. Identification of novel SIRT3 inhibitor scaffolds by virtual screening. Bioorg Med Chem Lett. 2013;23:2990–2995.
[303] Nahimana A, Attinger A, Aubry D, et al. The NAD biosynthesis inhibitor APO866 has potent antitumor activity against hematologic malignancies. Blood. 2009;113:3276–3286.
[304] Beher D, Wu J, Cumine S, et al. Resveratrol is not a direct activator of SIRT1 enzyme activity. Chem Biol Drug Des. 2009;74:619–624.
[305] Pacholec M, Chrunyk BA, Cunningham D, et al. SRT1720, SRT2183, SRT1460, and resveratrol are not direct activators of SIRT1. J Biol Chem. 2010;285(11):8340–8351.