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Review Article

ROLES OF SIRT1 IN CANCER/AGEING

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ABSTRACT

Aging and cancer both occur as a result of accumulated cellular damage, and both are related to the regulation of specific genes in the damage response. Recent research has unveiled connections between the mechanisms of aging and cancer, but how to prevent the development of cancer and increase longevity remain unknown. SIRT1 (the mammalian Sir2), which has NAD(+)-dependent class III histone deacetylase activity, may be a key gene linking the modulation of cancer and aging. SIRT1 has broad biological functions in growth regulation, stress response, tumorigenesis, endocrine signaling, and extended lifespan. Here, we focus on the current knowledge regarding the role of SIRT1 in aging and cancer, and discuss the implications of SIRT1 as a therapeutic target for the optimal balance between anti-aging and anti-cancer activities. The sirtuin family has emerged as important regulators of diverse physiological and pathological events, including life-span extension, neurodegeneration, age-related disorders, obesity, heart disease, inflammation, and cancer. In mammals, there are 7 members (SIRT1-SIRT7) in the sirtuin family, with the function of SIRT1 being extensively studied in the past decade. SIRT1 can deacetylate histones and a number of nonhistone substrates, which are involved in multiple signaling pathways. Here, we focus on the current knowledge regarding the role of SIRT1 in aging and cancer, and discuss the implications of SIRT1 as a therapeutic target for the optimal balance between anti-aging and anti-cancer activities. SIRT1 has been considered as a tumor promoter because of its increased expression in some types of cancers and its role in inactivating proteins that are involved in tumor suppression and DNA damage repair. However, recent studies demonstrated that SIRT1 levels are reduced in some other types of cancers, and that SIRT1 deficiency results in genetic instability and tumorigenesis, while overexpression of SIRT1 attenuates cancer formation in mice heterozygous for tumor suppressor p53 or APC. Here, I review these recent findings and discuss the

possibility that activation of SIRT1 both extends lifespan and inhibits cancer formation.

Keywords: SIRT1, sirtuin, cancer, deacetylate, tumorigenesis, NAD

INTRODUCTION

Sirtuins have drawn emerging attention due to their diverse roles in various physiological and pathological events, including life-span extension, neurodegeneration, age-related disorders, obesity, heart disease, inflammation, and cancer. [1] In mammals, there are 7 members (SIRT1-SIRT7) in the sirtuin family, which belong to class III histone deacetylases (HDACs) and show different functions, structure, and localization. [2]

The role of SIRT1 in cancers has been extensively studied in the past decade. However, controversy regarding cancer and sirtuins exists and is still under debate since it could act as either a tumor suppressor or tumor promoter depending on the cellular context or its targets in specific signaling pathways or specific cancers. SIRT1 is a mammalian homolog of yeast silent information regulator 2 (sir2) and is the most extensively studied sirtuin member. [3] This review will highlight the main SIRT1 substrates involved in energy homeostasis, [4] hypoxia response, [5] the PI3K/AKT pathway, [6] the transforming growth factor-β (TGF-β) signaling pathway, [7] the Wnt signaling pathway, [8] and the DNA damage repair pathway, [9] in cancer cells (Table1). Lung cancer is one of the most prevalent and lethal cancers all over the world. It accounts for 28% of all cancer related deaths and 14% of all new cancer cases annually. The process of tumorigenesis is the transformation of normal cells to tumor cells. This process is companied with progressive changes on cells and leads to uncontrolled cell growth and division. Tumor promoter genes function on promoting cell transformation while tumor suppressor genes function to inhibit tumorigenesis. Both tumor promoters and tumor suppressors are important in tumor development. The controversial role of SIRT1 in tumorigenesis with opposite functions underscores the complex regulation of SIRT1 in the process.

Table 1.

SIRT1 Targets in Multiple Signaling Pathways

Signaling pathways	Targets	Reference
Tumor suppressor	p53, p73, and HIC1	13-16
Energy homeostasis	FOXO1, FOXO3a, and FOXO4	17-19
	PGC1α, PPARγ, and AceCS1	22-28
Autophagy	Atg5, Atg7, and Atg8	56
Hypoxia-inducible factors	HIF-1α and HIF-2α	29-31
PI3K/AKT pathway	PTEN	32
TGF-β signaling pathway	Smad3 and Smad7	33, 34
Wnt signaling pathway	β-catenin, DKK1, and Dvls	35, 36, 72
NF-κB signaling	RelA/p65	20, 21, 76
DNA damage repair pathway	Ku70, XPA, XPC, and NBS1	37-40

SIRT1 and aging:

Sirtuins mediate lifespan regulation by CR in organisms as varied as yeast and mammals. [10] CR reduces age-related chronic disorders and extends the lifespan of different organisms. In yeast, Sir2- and NAD+-dependent CR-mediated lowering of glucose concentration extends lifespan [11] Sir2p deacetylates histones at the ribosomal DNA (rDNA) locus, thereby increasing rDNA silencing, which is linked to increased lifespan and repressed production of toxic rDNA circles [12]. Sir-2.1 extends the lifespan of Caenorhabditis elegans by up to 50% and binds to 14-3-3 proteins to activate forkhead transcription factor DAF-16 by down-regulating insulin signaling [13, 14]. the activation of the Sir2 ortholog by resveratrol and other sirtuin activators mimics CR and increases the lifespan in Drosophila melanogaster. [15]

Fig. 1. SIRT1 effects in mammals. CR or cellular stress increases SIRT1 activity. SIRT1 regulation of age-related metabolic changes including fat storage, insulin secretion, glycolysis, neuroprotection, cardioprotection, and cell survival leads to the potentiation of stress resistance and extended longevity.

Therapeutic implications of SIRT1 targeting in cancer chemotherapy:

SIRT1 activators:

Encouraged by these findings, many scientists have spent effort in exploring the therapeutic potential of SIRT1 activators or inhibitors, including natural and nonnatural small molecules, and were considering applying them to clinical practice. Resveratrol, a polyphenolic flavonoid with potent antioxidant properties, is the first reported SIRT1 activator. [16] A number of studies have demonstrated diverse biological effects of resveratrol including anti-inflammatory, antiangiogenic, antioxidant, proapoptotic, antiaging, anticancer, and metabolic modulating properties in mammalian cells. [17] However, it was later found that these effects mediated by resveratrol could only be demonstrated when the substrate was fluorescently tagged, [18] and these compounds (resveratrol, SRT1720, SRT2183, and SRT1460) did not enhance SIRT1 activity when using native peptide or protein substrates. [19] Sirtuins catalyze NAD^+-dependent protein deacetylation and are key regulators of transcription, apoptosis, metabolism, and aging. There are seven human sirtuins (SIRT1–7), and SIRT1 has been proven as a key mediator of the pathways downstream of calorie restriction that has been shown to delay the onset and the incidence of age-related diseases such as type II diabetes. Increasing SIRT1 activity, either by transgenic over expression of the SIRT1 gene in mice or by pharmacological activation by small molecule activator SRT1720, has shown beneficial effects in rodent models of type II diabetes. In this paper, several small molecules were designed and synthesized through a convenient

synthetic procedure. Ten newly synthesized compounds were characterized on the basis of ^{1}H NMR.Therefore, much more specific SIRT1 activators are still needed to be explored for the understanding of sirtuin biology and the treatment of SIRT1-related diseases.

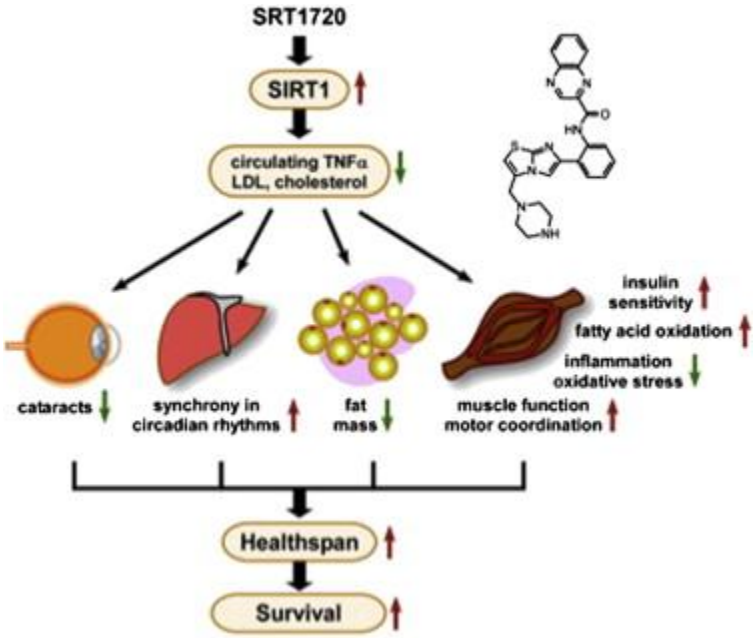
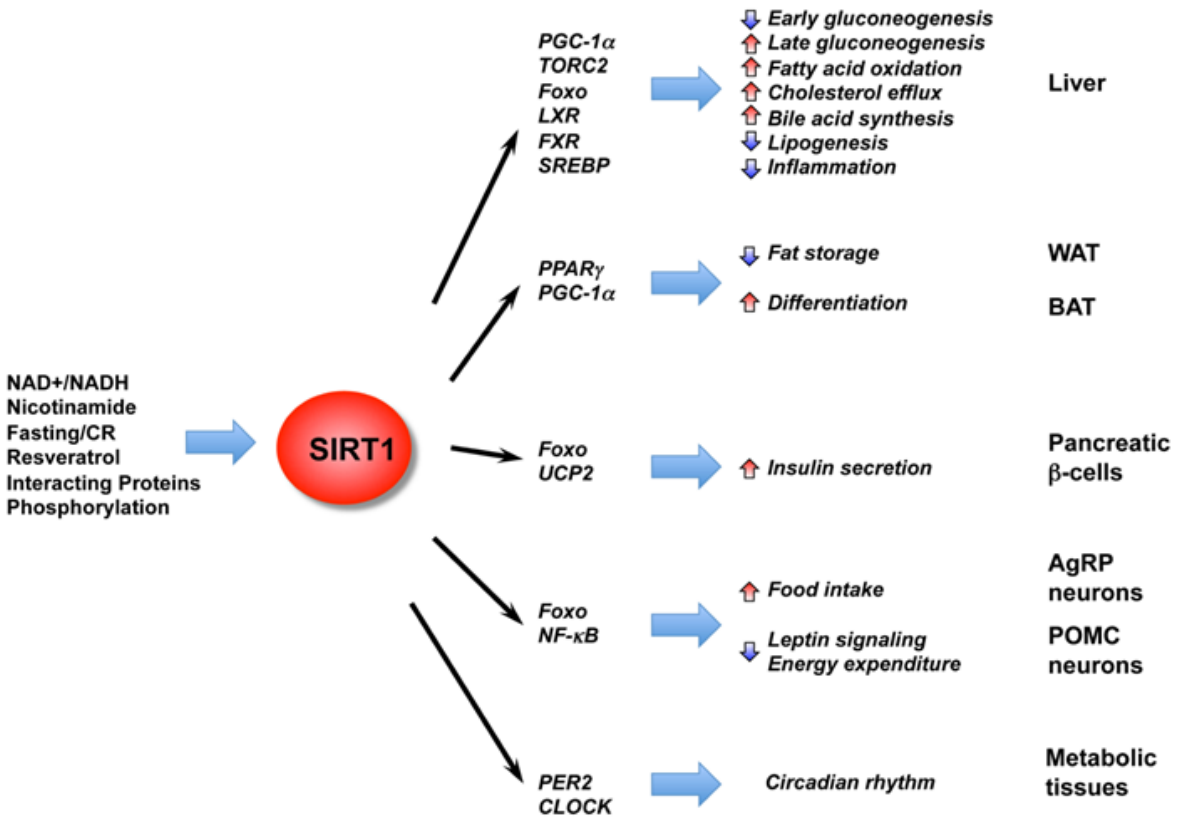


Figure 1

SIRT1 inhibitors:

Based on cell culture systems, many studies show that SIRT1 can inhibit apoptosis and senescence, [20] suggesting that SIRT1 inhibition may be beneficial for treating certain types of cancer. [21] EX527 was initially reported as a SIRT1 inhibitor, which was shown to increase p53 acetylation in the presence of etoposide. [22] However, it had no effect on the expression of p53 target genes, cell viability, and proliferation in various tumor lines. Followed by this, many other SIRT inhibitors such as cambinol, [23] sirtinol, [24] salermide, [25] JGB1741, [26] suramin analogs, [27] and the tenovins [28] are found and are effective in inducing cancer cell apoptosis. Inhibition of both SIRT1 and SIRT2 induced apoptosis in MCF-7 breast cancer cells, whereas knockdown of the individual proteins was ineffective, [29] suggesting a possible functional redundancy between SIRT1 and SIRT2 in certain types of cancer. Consistent with this finding, both sirtinol and salermide, dual SIRT1/2 inhibitors, but not EX527, enhanced p53 acetylation and stabilization in MCF-7 cells. These observations remind us that dual SIRT1/2 inhibition or broad-spectrum sirtuin inhibitors may provide therapeutic benefits in cancer. However, the efficacy and safety of these inhibitors need to be fully assessed. There is still a long way to go for combating SIRT1-related diseases such as cancer.



SIRT1 ageing and cancer:

As cancer is an aging-related disease, several investigations have implicated SIRT1 in the epigenetic regulation of gene expression in cancer cells. In many cancers, SIRT1 localizes to the promoters of several aberrantly silenced tumor suppressor genes whose DNA is hypermethylated. [30] Furthermore, the inhibition of SIRT1 increases H4-K16 and H3-K9 acetylation at endogenous promoters and suffices to induce gene re-expression in breast and colon cancer cells. [31] SIRT1 also regulates heterochromatin formation via deacetylation of histone H1-K26 and promotes the loss of H3K79me2, a marker associated with transcriptionally active chromatin. SIRT1 binds directly to and deacetylates SUV39H1, and contributes to elevated SUV39H1 activity that results in increased levels of H3K9me3 modification. [32] These reports have speculated that SIRT1 has a role associated with the epigenetic hallmarks of cancer. It has been shown that SIRT1 is significantly elevated in human prostate cancer, acute myeloid leukemia, and primary colon cancer. Hida et al. examined SIRT1 protein levels in several different types of skin cancer by immunohistochemical analysis. Overexpression of SIRT1 was frequently observed in all kinds of non-melanoma skin cancers including squamous cell carcinoma, basal cell carcinoma, Bowen's disease, and actinic keratosis. Based on the elevated levels of SIRT1 in cancers, it was hypothesized that SIRT1 serves as a tumor promoter. However it does not rule out a possibility that increased expression of SIRT1 is a consequence, rather than a cause, of

tumorigenesis. In contrast, Wang et al. analyzed a public database and found that SIRT1 expression was reduced in many other types of cancers, including glioblastoma, bladder carcinoma, prostate carcinoma and ovarian cancers as compared to the corresponding normal tissues. Their further analysis of 44 breast cancer and 263 hepatic carcinoma cases also revealed reduced expression of SIRT1 in these tumors. These data suggest that SIRT1 acts as a tumor suppressor rather than a promoter in these tissues.

SIRT1 negatively regulates p53-dependent apoptosis by deacetylation of p53 in response to cellular damage and localizes to promyelocytic leukemia bodies to inhibit p53-dependent cellular senescence. Other substrates of SIRT1 including DNA repair protein Ku70, FOXO family proteins, and nuclear factor kappa B are also involved in stress response and apoptosis. Tumor suppressor HIC1 binds directly to the SIRT1 promoter and attenuates its transcription, modulating p53-dependent DNA damage responses. The level of SIRT1 is also highly elevated in several cancer cell types. SIRT1 binds to and deacetylates the androgen receptor and represses dihydrotestosterone-induced androgen receptor signaling in human prostate cancer, and SIRT1 silencing induces growth arrest and/or apoptosis in human epithelial cancer cells. The ectopic induction of SIRT1 in a β-catenin-driven mouse model of colon cancer significantly reduces tumor formation, proliferation, and animal morbidity. It is interesting to note that most of the murine experiments by Di Sante et al were performed in 7-month-old mice. When 3-month-old mice were tested for mitophagy markers, the findings were reversed, indicating that the role of SIRT1 as a tumor suppressor could be age-dependent. This is not surprising considering that SIRT1 has been shown to play a role in aging through its impact on cellular metabolism. The possibility that SIRT1 plays an oncogenic role in younger mice and a tumor suppressor role in older mice could be an important finding for the prevention and treatment of age-related diseases such as prostate cancer.

However, a contradictory view supporting the role of *Sirt1* as an oncogene in aging mice was previously reported by Chen et al and more recently summarized by Deng. Briefly, hypermethylated in cancer-1 (HIC1) is a natural suppressor of SIRT1 transcription in the cell. SIRT1's deacetylation target TP53 transactivates HIC1, forming a regulatory feedback loop among the three proteins. As cells age, *Hic1* becomes silenced through hypermethylation resulting in the up-regulation of SIRT1 in cancer cells. Again, the overexpression of SIRT1 in cancer cells in aging mice does not necessarily mean that this overexpression is responsible for the cancer formation but likely also depends on the status of proteins which interact with SIRT1. If *Hic1* were to be silenced in tissue with a PTEN deficiency for example, the resultant overexpression of SIRT1 could induce oncogenic events. Thus, the tumor suppressive effects of SIRT1 in aging mice could also be dependent on other factors and not necessarily the case in all genetic backgrounds.

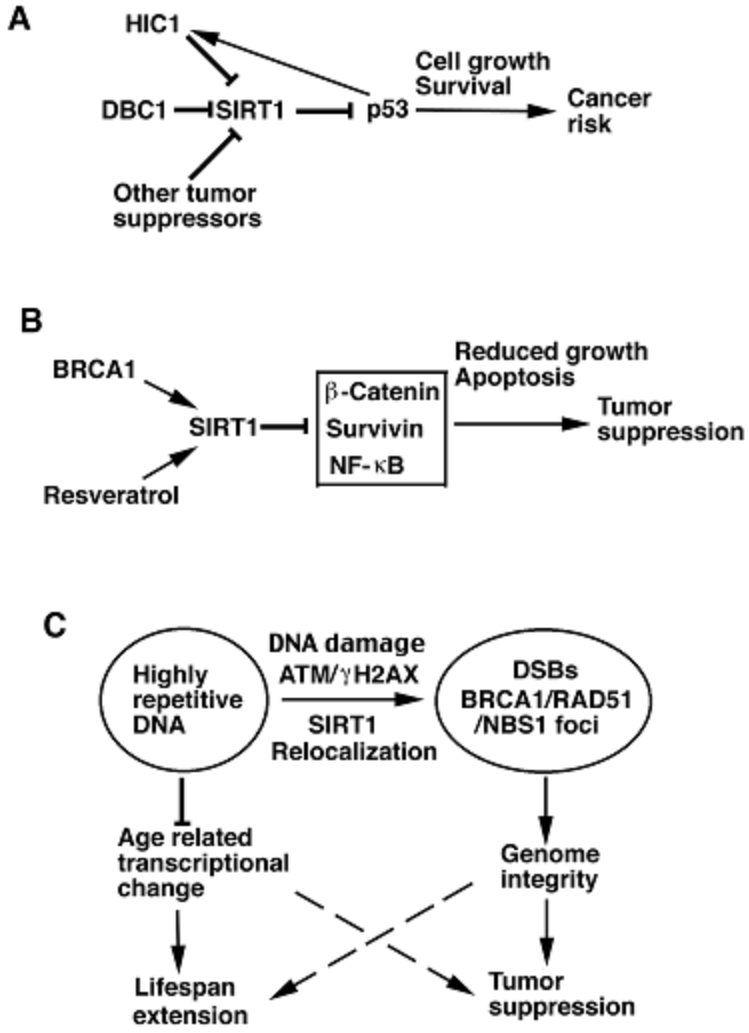


Figure 3

Models illustrating possible functions of SIRT1 in tumor promotion or suppression. A. SIRT1 deacetylates and inactivates p53, leading to down regulation of p53-mediated growth arrest and apoptosis. This may result in increased risk of cancer. Transcription and activity of SIRT1 are also negatively regulated by many tumor suppressor genes, including DBC1, HIC1, and p53, which may regulate SIRT1 through HIC1. B. BRCA1 and resveratrol can positively regulate SIRT1 transcription and activity, respectively. Increased SIRT1, in turn, inhibits expression and/or activity of several oncogenes, leading to reduced cell proliferation, increased apoptosis, and tumor suppression. C. In response to DNA damage, SIRT1 dissociates from highly repetitive DNA and relocalizes to DSBs to promote repair and maintain genome integrity. ATM and γH2AX are required for the efficient recruitment of SIRT1 to DSBs. Moreover, SIRT1 deficiency impaired BRCA1, RAD51 and NBS1 foci formation, suggesting direct or indirect interactions of these proteins in the DNA damage foci.

SIRT1 overexpression suppresses the age-related transcriptional changes and tumor formation, suggesting a possibility to extend lifespan and inhibit tumor formation through activation of SIRT1.

DISCUSSION

Cigarette smoke and vehicle exhaust contain a high concentration of B[***a***]P that has been proved to be associated with lung cancer. Although there are many cytokines contributing to lung cancer development and progression, the underlying molecular mechanisms is not well understood.

SIRT1, the founding member of the class III HDACs, uses NAD^+ to mediate the deacetylation of histone and non-histone proteins. SIRT1 plays a dual role in cancer development and progression. The SIRT1 expression is significantly downregulated in human head and neck squamous cell carcinoma (HNSCC). And the high SIRT1 expression is associated with a good prognosis. [37] SIRT1 transgenic mice exhibit reduced susceptibility to carcinogen-induced liver cancer [38]. SIRT1 overexpression in ApcMin/+ mice induces beta-catenin deacetylation, reducing colon tumor formation [39]. On the other hand, it recently has been implicated in the initiation and progression of various malignancies [40]. SIRT1 can promote cell migration and metastasis by directly interacting and deacetylating cortactin in breast cancer [41]. SIRT1 could stimulate tumor growth by increasing vessel density and downregulating DLL4/Notch signaling in lung cancer [42].

It has been reported that many transcription factors could bind to the TNF-α promoter, such as NF-κB and AP1. In this work, we found that β-catenin was up-regulated at the transcription level in a SIRT1-dependent way. XAV939, a Wnt/beta-catenin specifice inhibitor, reduced the mRNA levels of TNF-α, while β-catenin stimulated the promotor activity of TNF-α. On the other hand, silencing TNF-α by shRNA inhibited the expression of β-catenin. It indicated that there was a positive feedback between the TNF-α and Wnt/β-catenin signaling pathways and amplified the effect of B[a]. Epithelial-mesenchymal transition (EMT) is a key step toward cancer progression, invasion and metastasis. A common hallmark of EMT is the breakdown of E-cadherin expression or function. Therefore, we surmised that SIRT1 could drive EMT to tumorgenesis.

SIRT1 as an oncogene or tumor suppressor in cancer:

An overview of the available literature shows that SIRT1 is overexpressed in a variety of human cancer cell lines and tissues. This includes several studies in prostate cancer, which are in agreement with the findings of Di Sante et al. Furthermore, chemical inhibition of SIRT1 in prostate cancer has been shown to reduce cellular growth, viability, and chemoresistance, and a recent analysis of prostate cancer tissues showed SIRT1 to be a reliable biomarker of disease recurrence. It would be logical to conclude from these findings that SIRT1 has a tumor promoter function in prostate cancer. However, Di Sante et al have found that in prostate cancer patients, a low level of SIRT1 is associated with decreased recurrence-free survival,

supporting a tumor suppressor function of SIRT1 in prostate cancer. The data in *Sirt1*$^{-/-}$ mice also support the tumor suppressor role for SIRT1, which could suggest that the increased levels of SIRT1 in prostate cancer tissues are a response to the cancer rather than a cause. However, this does not explain why chemical inhibition of SIRT1 has been shown to have tumor suppressive effects, thus leading to seemingly contradictory theories.

One possibility for this contradiction could be found in the species being studied. The studies referenced in which chemical inhibition of SIRT1 resulted in tumor suppressive effects were conducted in human prostate cancer cell lines. However, Di Sante et al have used murine cells and *Sirt1*$^{-/-}$ mice for their experiments. Similar results have previously been shown in mouse models of other cancers, which could signify a difference in SIRT1 behavior between mice and humans. Alternatively, *Sirt1*$^{-/-}$ mice are also embryonic lethal in many backgrounds, and those that are not frequently have developmental abnormalities such as smaller body size, infertility, and autoimmune deficiencies. It cannot be ruled out that unintended consequences of the *Sirt1*$^{-/-}$ genotype could be contributing to the tumor suppressive phenotype. However, several studies have shown that the overexpression of SIRT1 alone does not increase tumor formation in mice, indicating that either *Sirt1* is not an oncogene, or that additional contributing factors are necessary for the oncogenic function of SIRT1.

CONCLUSION

Over the past decade, SIRT1 has been the most investigated gene involved in diverse cellular functions. The link between SIRT1 and both cancer and aging provide new insight into the therapeutic potential of small molecule activators or specific targets of SIRT1 for the prevention and treatment of cancer and aging. Further investigation into the specific mechanism of SIRT1 is required to realize this potential. The apparent opposite role of SIRT1 seems contradictory at first but the multiple functions of SIRT1 made this possible. SIRT1 can negatively regulate multiple pathways including both tumor suppressors and oncogenic proteins (Survivin, β-catenin, NF-κB). In each specific circumstance, which pathway has been dominantly regulated decided the outcome of tumor suppressing or tumor promoting. Which face that SIRT1 shows up in tumorigenesis may well depends on the temporal and special distribution of different SIRT1 upstream regulators anddownstream targets. Obviously, more intense research is necessary in order to understand the complex role of SIRT1 in tumorigenesis.

In summary, our detailed assessment of the Sirtris series and resveratrol involving several biochemical assays with native substrates and biophysical studies employing NMR, SPR, and ITC demonstrated that these compounds are not direct SIRT1 activators. We also demonstrated that SRT1720 does not show beneficial effects in a rodent diabetes model, which is in contrast to that previously reported. The broad selectivity assessment against over 100 targets including receptors, enzymes, ion channels, and transporters show that the Sirtris series and resveratrol are highly promiscuous and would not serve as

useful pharmacological tools for studying SIRT1 pathways. In the literature, resveratrol has been widely referred to as a SIRT1 activator (for selected recent references. and routinely used to activate SIRT1 in various cellular assays, with only a few questioning the original study that reported its ability to activate SIRT1 in an artificial substrate-based fluorescent assay. Likewise, the Sirtris compounds have been referred to as SIRT1 activators in recent publications. Our present data are significant for the field as we provided strong evidence that neither the Sirtris series nor resveratrol are direct SIRT1 activators.

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