

The conflicting role of SIRT3 as therapeutic target in cancer

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Abstract

Mitochondria are increasingly recognized as key factors in cancer, affecting a multitude of tumor hallmarks. Likewise, sirtuin 3, a master regulator of mitochondrial function, has gained attention as a therapeutic target in cancer. As a main mediator of calorie restriction, sirtuin 3 inhibits anabolic reactions and cell proliferation, acting as a tumor suppressor. At the same time, sirtuin 3 protects the cell during nutrient stress by regulating cell death and DNA repair, thereby acting as an oncogene. Here we discuss this conflicting role of sirtuin 3 in cancer and evaluate the therapeutic potential of sirtuin 3 activators and inhibitors in different cancers. **Keywords:** Sirtuin, SIRT3, Cancer, Mitochondria

Introduction

The lifetime risk of developing cancer is greater than 35% in the United States, and cancer is continuously among the three most common causes of death worldwide (1, 2). While tumors are very heterogeneous in their phenotype and underlying molecular changes, there are common characteristics that result in uncontrolled proliferation and malignancy. These hallmarks include proliferative signaling, genome instability, immune evasion, resistance to cell death and a deregulation of cellular energetics (3, 4).

The preference of tumors for anaerobic metabolism in the presence of oxygen, known as the Warburg effect, was discovered almost 100 years ago (5, 6). However, only within the last decade has a better understanding of this phenotype emerged. While oxidative phosphorylation is the most efficient with respect to ATP production, carbon is oxidized to CO₂ and not available for biomass production. To maintain a high proliferation rate, tumor cells need to use glycolytic and TCA cycle

intermediates such as Acetyl-CoA, amino acids, or ribose for biogenesis at the expense of efficient energy production (7, 8). These insights have resulted in a renewed focus on the role of mitochondria in cancer (9). Mitochondria are not only crucial in providing macromolecular precursors for cell proliferation but are also at the crossroads of many other hallmarks of cancer. Mitochondria are the major source of reactive oxygen species (ROS) in the cell, which can result in oxidative damage and mutations in DNA. Similarly, mitochondria regulate the antioxidative response (10) and DNA repair via the redox status and PARP1 (11), demonstrating a key role of mitochondria in genome stability. With respect to immune evasion, mitochondria were shown to regulate immune cell proliferation (12) and inflammatory response (13), suggesting a central role in the immune system and cancer-associated immune evasion (14, 15). Lastly, mitochondria are well known for their role in apoptotic cell death (16) and a dysregulation of mitochondrial apoptotic signaling was associated with cancer (17, 18). Taken together, mitochondria are a common link

between the hallmarks of cancer. This emphasizes mitochondrial metabolism and its regulators, such as sirtuins, as promising targets for therapeutic intervention in cancer.

Sirtuins, or its homolog Sir-2, were first discovered in yeast and *C. elegans* in response to calorie restriction mediating an extended lifespan (19, 20). Sir-2 was described as a class III histone deacetylase, removing acetyl-groups from lysine residues on histones in an NAD⁺ dependent manner, thereby resulting in gene silencing (21).

In mammalian cells there are 7 sirtuin isoforms (SIRT1-SIRT7). They differ with respect to subcellular localization and substrate specificity. While SIRT1, 2, 6, 7 are predominantly localized in the nucleus or cytoplasm, SIRT3-5 are found mostly in the mitochondria (22). Sirtuins are not confined to histones as substrates but can perform posttranslational modifications on many non-histone proteins, resulting in either activation or inhibition of these enzymes. While deacetylation is the predominant modification mediated by sirtuins, some isoforms such as SIRT6 can remove larger Acyl-groups (23) or are involved in ADP-ribosylation (24).

All sirtuins display two core domains, a Rossmann fold domain common in nucleotide binding enzymes (25) and a zinc binding domain (26). Due to their NAD⁺ dependency, sirtuins function as cellular energy sensors detecting a low energy state by an increased NAD⁺/NADH ratio (19, 27), thereupon modifying gene expression or enzyme activity. Sirtuin activation generally results in a downstream induction of catabolism along with a reduction in anabolic reactions. In addition to their function as energy sensors and metabolic regulators (28), sirtuins were shown to be involved in cellular stress (29), the antioxidative response (22, 30), inflammation (31, 32) and DNA repair (33, 34). Taken together, sirtuins are suggested to be a central hub for mitochondrial-nuclear

interactions and for regulating cellular metabolism.

Dysregulation of the sirtuins has been associated with many disorders, such as aging (20, 22, 35), type II diabetes (36, 37), cardiovascular disease (38-40), neurodegeneration (41, 42), and cancer (43, 44). With respect to cancer, it was demonstrated that several sirtuin knockout mice were more prone to develop tumors (45-47) suggesting sirtuin activation as a promising therapeutic target in cancer. However, recent evidence indicates a more conflicting role of sirtuins in tumorigenesis (48, 49) with some tumors showing an upregulation of sirtuin expression (50, 51). Given the crucial role of mitochondria in cancer, SIRT3 is of paramount interest since it is the predominant mitochondrial sirtuin. In this review we focus on SIRT3 aiming to unravel its dichotomous role in cancer, and evaluate activators and inhibitors of SIRT3 as therapeutic interventions in different malignancies.

SIRT3

SIRT3 is the major mitochondrial sirtuin and plays a key role in regulating mitochondrial enzymes via acetylation (52, 53). It is found in most cell types and tissues with the highest levels in kidney, brain, heart, and liver (54). It is expressed as a 44kDa cytosolic protein containing an N-terminal mitochondrial targeting sequence. Proteolytic processing by the mitochondrial processing peptidase removes 101 amino acids on the N-terminus thereby resulting in activation of SIRT3 in the mitochondria. It is debated whether SIRT3 is exclusively found in the mitochondria (55) or if it translocates from the nucleus to the mitochondria upon cell stress (56). It appears clear that SIRT3 mainly plays a role in mitochondrial adaptation to stress (57).

Regulation of SIRT3

Different stressors are known to regulate SIRT3 such as metabolic, oxidative, or genotoxic stress (58). Transcriptionally, an antioxidant response element upstream of SIRT3 was reported to regulate SIRT3 expression via the Nrf2-Keap axis in response to metabolic stress (59). On the protein level, it was suggested that SIRT3 can be targeted for degradation by the E3 ligase in response to DNA damage (60). In addition, PARP1 activation can deplete SIRT3 of NAD⁺ given a much lower K_m of PARP1 for NAD⁺ (61, 62). It is well known that NAD⁺ levels play an important role in stimulating SIRT3 activity (63). Conversely, nicotinamide, a product of the sirtuin reaction, was shown to mediate a feedback inhibition by binding to the C-pocket (64). There is some controversy with respect to sirtuin sensitivity for NADH and whether sirtuins sense the NAD⁺/nicotinamide ratio or the NAD⁺/NADH ratio (65). Interestingly, while sirtuin activity is stimulated by NAD⁺, sirtuin expression correlates with a low NAD⁺/NADH ratio (66). This suggests a differential effect of nuclear versus mitochondrial NAD⁺/NADH redox state on SIRT3 expression and activity respectively.

Physiological Function and Substrates of SIRT3

The main function of SIRT3 is the regulation of mitochondrial energy metabolism. SIRT3 deacetylates and thereby activates several enzymes of the TCA cycle such as pyruvate dehydrogenase (67), isocitrate dehydrogenase (IDH) (68) or Acetyl-CoA synthetase 2 (69).

Additionally, it activates the mitochondrial electron transport system directly by deacetylating NDUFA9, a complex I subunit (70), and succinate dehydrogenase (71), complex II of the electron transport chain. Given the role of SIRT3 in metabolic adaptation to nutrient deprivation, SIRT3 stimulates fatty acid oxidation by activating long acyl chain dehydrogenases (57) and ketogenesis by activating the rate limiting enzyme 3-hydroxy-3-methylglutaryl-CoA synthase (72). Similarly, amino acid oxidation (73) and the associated urea cycle are activated by SIRT3 (74). At the same time, SIRT3 helps to preserve nutrient availability by limiting glucose uptake via Cyclophilin D (CYP-D) activation and subsequent dissociation of hexokinase 2 from the mitochondria (75). Taken together, SIRT3 stimulates catabolism and mediates a metabolic switch from glycolysis to oxidative phosphorylation.

Cell and nutrient stress as well as increased activity of the electron transport system are associated with increased ROS production. SIRT3 promotes the antioxidant response by activating Manganese Superoxide Dismutase (MnSOD) directly via deacetylation (76) and indirectly via FOXO3a-mediated upregulation (77). In addition, it stimulates NADPH production by IDH (68) and inactivates glutamic-oxaloacetic transaminase 2 (GOT2), thereby blocking the malate-aspartate shuttle (78). This maintains reducing equivalents in the cytosol, boosting the glutathione antioxidant system.

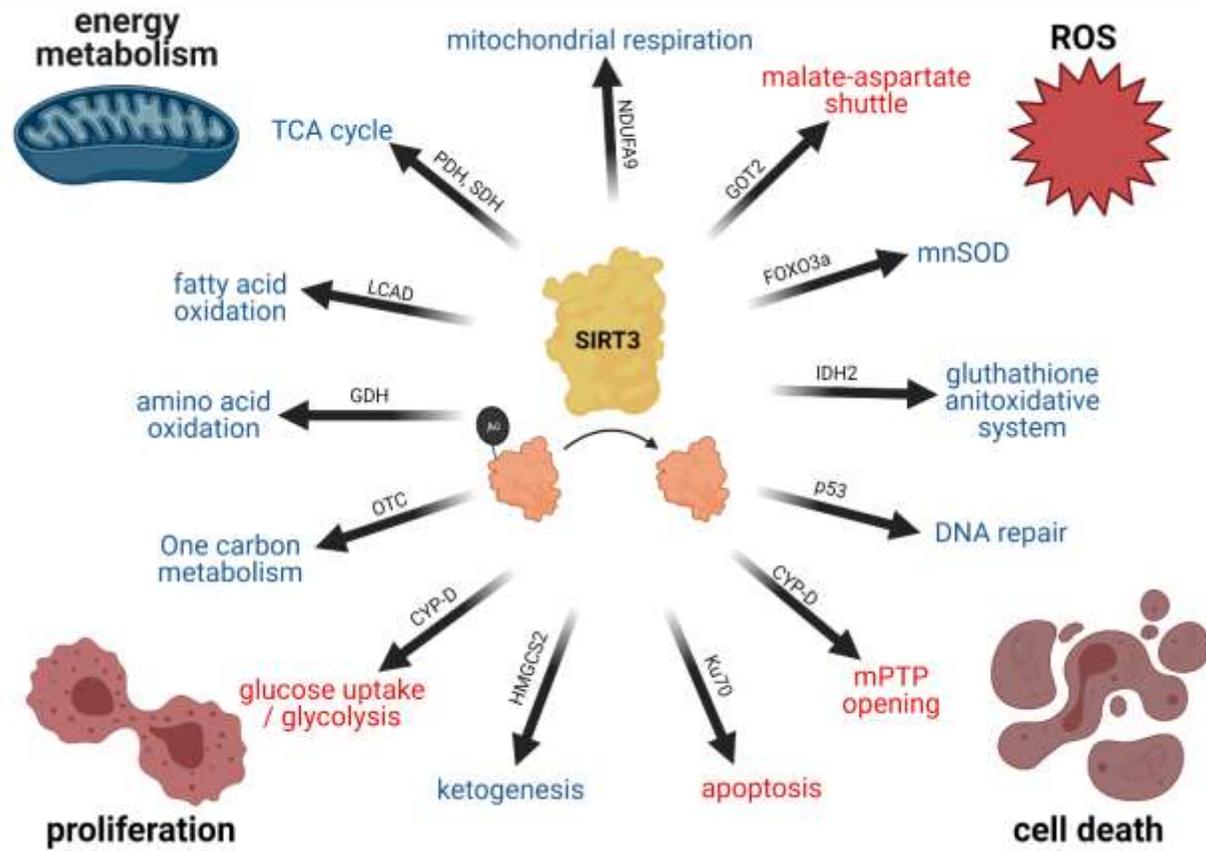


Figure 1: SIRT3 regulates Cell Metabolism and Health

SIRT3 deacetylates many mitochondrial proteins, thereby regulating a multitude of cellular functions. The functional cornerstones are an upregulation (indicated by blue) of mitochondrial energy metabolism, a downregulation (indicated by red) of reactive oxygen species, prevention of cell death and an inhibition of proliferation. Selected deacetylation targets mediating the physiological functions of SIRT3 are indicated on the arrows. Created with BioRender.com.

SIRT3 also plays a role in regulating DNA damage and cell death. SIRT3 was reported to deacetylate p53, which promotes its proteasomal degradation (79). Conversely, SIRT3 prevents degradation of 8-oxoguanine-DNA glycosylase 1 (80), a crucial enzyme in mitochondrial DNA repair. With respect to cell death, it was reported that SIRT3 activates Ku70, which subsequently binds Bax and prevents stress-induced cell death (81). Similarly, opening of the mitochondrial transition pore by CYP-D inactivation is reduced (82) preventing cell death due to mitochondrial calcium overload.

In summary, SIRT3 orchestrates the adaptation of mitochondrial energy metabolism. Upon sensing a low energy state via the redox ratio, it stimulates catabolic reactions and mitochondrial energy production. At the same time, it downregulates cell growth/replication but also protects the cell from ROS, DNA damage, or cell death (Figure 1).

SIRT3 in Cancer

Cancer cells can be distinguished from normal cells based on several key characteristics such as insensitivity to growth inhibitory signals and cell death resistance mechanisms, increased

proliferative signaling, sustained angiogenesis, deregulation of metabolic pathways, genomic instability, increased inflammation, and tumor cell mobility (4). As such, deregulation of several physiological functions mediated by SIRT3 implicate a role for the mitochondrial sirtuin in cancer development. This association was underlined by an early study in SIRT3 knockout mice that demonstrated increased development

of ER/PR-positive mammary tumors (45). SIRT3 deregulation has further been observed across several tumor subtypes. Mitochondrial SIRT3 can act as a tumor promoter or suppressor depending on the tumor profile and distinct molecular signatures of the cancer cells (Figure 2).

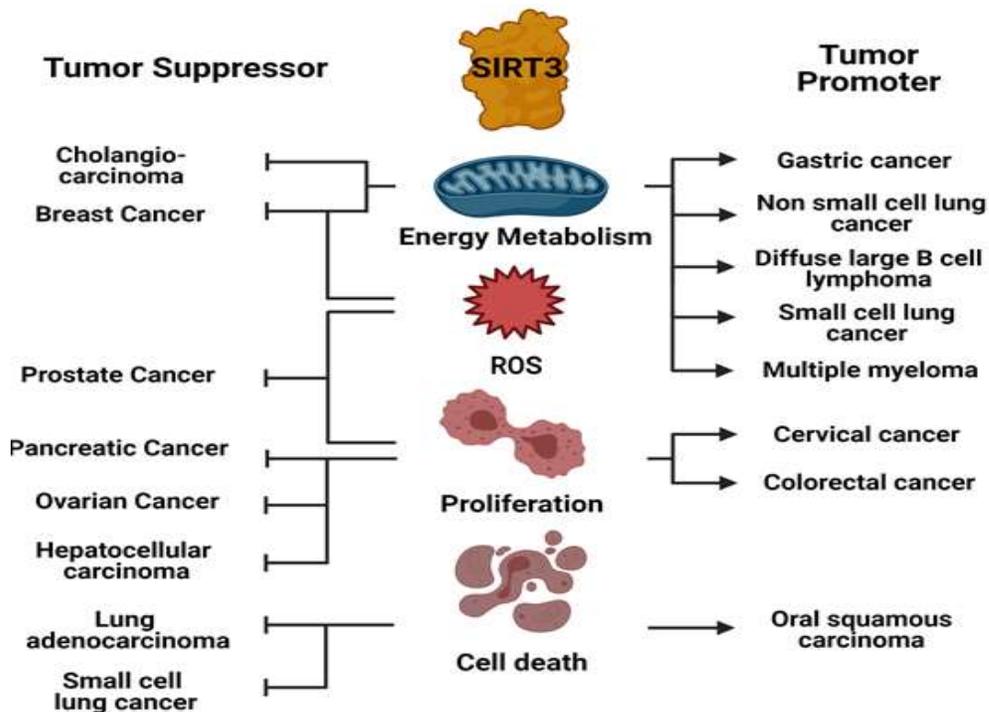


Figure 2: SIRT3 as Tumor Suppressor or Oncogene in different Tumors

SIRT3 mediates its tumor suppressor or oncogenic function by modulating cellular physiology differentially in a variety of tumors. Created with BioRender.com.

SIRT3 as Tumor Suppressor

A strong reliance on glycolytic energy metabolism to produce substrates for anabolic reactions is a hallmark of many tumors. SIRT3, in contrast, promotes a switch towards oxidative phosphorylation, thereby acting as a tumor suppressor. For example, in breast carcinoma SIRT3 inhibits glycolysis by deacetylating cyclophilin D, which leads to the dissociation of hexokinase II from the outer mitochondrial

membrane protein voltage-dependent anion channel (83). Additionally, SIRT3-mediated stabilization of p53 via PTEN and MDM2 was shown to inhibit glycolysis and tumor cell proliferation by positive transcriptional regulation of genes involved in mitochondrial oxidative phosphorylation (84-86). A recent study in cholangiocarcinoma cells demonstrates the anti-Warburg effect of SIRT3 by inhibition of the hypoxia inducible factor 1 α (HIF-1 α)/pyruvate dehydrogenase kinase 1 (PDK1)

pathway (87). SIRT3-mediated ROS depletion is also known to promote tumor inhibition. A study in SIRT3 knockout primary mouse embryonic fibroblasts demonstrated increased activation of HIF-1 α , which is involved in transcriptional regulation of several glycolytic genes known to promote tumorigenesis (88, 89). Activation of prolyl hydroxylases by SIRT3 was found to be responsible for destabilization of HIF-1 α and mitigated its tumor promoting effects (90, 91). Moreover, studies in prostate cancer reported that ROS depletion by SIRT3 could suppress the PI3K/Akt pathway resulting in ubiquitination and degradation of oncoprotein c-Myc, thus inhibiting tumor progression (92).

SIRT3 does not only influence proliferation via the abundance of glycolytic intermediates, but also regulates multiple pathways associated with proliferation, cell migration, and renewal. Given the role of SIRT3 in caloric restriction and downregulation of anabolic reactions a tumor suppressor role would be expected. SIRT3 mediated inactivation of glutamate oxaloacetate transaminase 2 in pancreatic cancer was shown to arrest proliferation and tumor growth (78). Deactivation of the proto-oncogene F-box protein S-phase kinase associated protein 2 by SIRT3 could also inhibit cancer cell progression and migration (93). SIRT3 was found to prevent hyperacetylation of enoyl-CoA hydratase 1 (ECHS1) in cancer, thereby inhibiting mTOR regulated proliferation (94). Furthermore, modulation of ROS signaling by SIRT3 was found to be relevant to tumor cell migration. Depletion of ROS levels by SIRT3 demonstrated diminished focal adhesion kinase (FAK) phosphorylation, which is required for breast cancer metastasis (95). SIRT3 was also shown to inhibit epithelial-to-mesenchymal transition (EMT) and metastasis in ovarian cancer cells by downregulation of Twist (96). Upregulated levels of SIRT3 in metastatic prostate cancer were shown to induce the inhibition of Wnt/ β -catenin pathway, a central regulator of EMT and tumor

metastasis (97). Additionally, SIRT3 mediated inhibition of cellular migration and metastasis have been demonstrated in hepatocellular carcinoma (98) and pancreatic ductal cell carcinoma (99).

Tumor-modulating effects of SIRT3 can also be attributed to its regulation of DNA repair and programmed cell death. As a tumor suppressor SIRT3 works to promote apoptosis. In HepG2 cells SIRT3 was found to induce Bax and Fas regulated apoptosis. This was mechanistically shown to be an effect of SIRT3-mediated upregulation of p53 and MnSOD (100). SIRT3 was also found to induce apoptosis in hepatocellular carcinoma by deacetylation of glycogen synthase kinase-3 β , which further resulted in increased expression and mitochondrial translocation of Bax (101). Additionally, downregulation of Bcl-2 and JNK2 by SIRT3 was shown to contribute to apoptosis in hepatocellular carcinoma (102). In human lung adenocarcinoma tissue upregulated levels of SIRT3 results in increased translocation of apoptosis inducing factor (AIF) to the nucleus with higher levels of p53, p21, and depletion of ROS. This ultimately results in increased apoptosis (103). A recent study in small-cell lung cancer demonstrated that SIRT3 can inhibit tumor progression by promoting apoptosis and necroptosis via modulation of ubiquitination-mediated proteasomal degradation of mutant p53 protein (104). Ovarian cancer cell lines with increased expression of SIRT3 have also demonstrated increased sensitivity to metformin-induced apoptosis (105).

SIRT3 as Oncogene

Numerous studies over the past decade have also demonstrated the tumor promoting effects of SIRT3 across different cancers (Figure 2). This controversial role of SIRT3 as an oncogene likely arises from differential regulation of SIRT3-mediated cellular pathways in certain tumor settings. For example, increased protein and

mRNA levels of SIRT3 were reported in non-small cell lung cancer tissues, and SIRT3 was found to regulate the activation of Akt promoting tumor malignancy (106). PTEN-deficient lung tissues have also demonstrated increased levels of SIRT3, which correlate with depleted p53 levels. SIRT3 was found to be responsible for ubiquitination and proteasomal degradation of p53 (79). SIRT3 was reported to activate lactate dehydrogenase in gastric cancer cells resulting in glycolysis and promotion of tumorigenesis (107). Hematological cancers that depend on oxidative phosphorylation also demonstrate an oncogenic role for SIRT3 (108). SIRT3 was found to promote lymphomagenesis in diffuse large B cell lymphomas by regulating TCA cycle via glutamate dehydrogenase (109). SIRT3 was further shown to deacetylate IDH2, a critical enzyme participating in forward Krebs cycle. The activation of IDH2 by SIRT3 promotes carcinogenesis in multiple myeloma cell lines (110).

SIRT3 can also participate in stimulation of proliferative signaling pathways and promote tumorigenesis. For example, SIRT3-mediated activation of nicotinamide mononucleotide adenylyl transferase 2 (NMNAT2) was shown to result in increased cellular proliferation and glycolytic flux (111). Similarly, SIRT3 activates the pyrroline-5-carboxylate reductase 1 (PYCR1) thereby stimulating proliferation (112). An increased expression of SIRT3 in lymph node positive breast cancer metastasis is also believed to contribute to the survival of aggressive cancer phenotypes. SIRT3-mediated deacetylation of serine hydroxymethyl-transferase 2 (SHMT2) was demonstrated to inhibit its lysosome-dependent degradation and contributed to colorectal cancer development (113). Other studies in colorectal cancer have demonstrated that SIRT3 activates the Akt/PTEN pathway, regulates transcription of metastatic genes like EGFR and BRAF, and promotes cancer cell migration and proliferation (114). Likewise, a

study in cervical cancer cells revealed that SIRT3 deacetylated Acetyl-CoA carboxylase and reprogrammed fatty acid metabolism to promote migration and invasion (115).

As a central mitochondrial deacetylase, SIRT3 can respond to metabolic and genotoxic stress and protect cancer cells from apoptosis. SIRT3 was shown to deacetylate and bind with Ku70, which augmented Ku70-Bax interactions and prevented translocation of Bax to the mitochondria. This resulted in inhibition of apoptosis in HeLa cells (81). Overexpression of SIRT3 in oral squamous carcinoma cells is also shown to correlate with anoikis, apoptosis triggered by loss of extracellular matrix, and cell survival. Increased expression of SIRT3 in anoikis-resistant oral cancer was found to be accompanied by lower expression of receptor interacting protein, which can act as a negative regulator of SIRT3 (116). SIRT3-mediated deacetylation of histone H3 was also found to promote nonhomologous end joining repair. Histone H3 is known to be involved in the response to DNA damage and is found to be colocalized with γ H2AX implicating a role for SIRT3 in maintenance of genomic stability in tumors (117). Likewise, another study reported that SIRT3 modulates the activity of human 8-oxoguanine-DNA glycosylase 1, a DNA repair enzyme, and assists in the response to mitochondrial DNA damage preventing stress mediated apoptosis (80).

Taken together, SIRT3 can act as a tumor suppressor or oncogene dependent on the specific tumor by regulating important tumor hallmarks such as energy metabolism, ROS, apoptosis, and proliferation.

Therapeutic targeting of SIRT3 in Cancer

As SIRT3 is implicated in the pathogenesis of cancer and other diseases, numerous compounds have been identified and studied for their activity on SIRT3. These molecules can

regulate the activity of SIRT3 by either influencing its expression or by modulating its deacetylation function (118). Based on their effect, SIRT3 modulators can be broadly classified as SIRT3 activators or inhibitors (Table 1) (119).

SIRT3 Activators

Given the tumor suppressive function of SIRT3 across several cancer types, SIRT3 activation can prove to be an effective strategy. Endogenous regulators like nicotinamide riboside or nicotinamide mononucleotide can boost the intracellular levels of NAD⁺ and thereby stimulate SIRT3 (120). For example, it has been shown that nicotinamide mononucleotide can inhibit tumor growth and metastasis in mice (121). However, these endogenous regulators are not specific to SIRT3 but activate all sirtuins and directly affect cellular energy metabolism independent of the sirtuins.

Among the other compounds studied for specific SIRT3 activation, Honokiol, isolated from the bark of *Magnolia officinalis*, has shown great efficacy in the activation of SIRT3 (122). In vitro and in vivo studies with Honokiol in cancers of the breast, colon, prostate, liver, and squamous cell lung carcinomas have demonstrated promising results. However, most of its anti-cancer activity is attributed to its effects on other molecular targets such as NF- κ b, STAT3, EGFR, mTOR, β -catenin and HIF1 α , which are also known to be involved in pathways of cell survival, proliferation, and metabolism (123-128). Similarly, Silybin demonstrates weak SIRT3 activation (129, 130) and has been found to suppress tumor growth (131, 132), however a connection between both functions of Silybin have not yet been established. Resveratrol (119, 133, 134) and Piceatannol (133, 135, 136) were found to activate most sirtuins but there are controversial reports of activation or inhibition of SIRT3 (137, 138) and conclusive evidence supporting their role in SIRT3 mediated anti-

cancer activity is lacking. More research into the discovery of synthetic, specific SIRT3 activators is needed to reveal a comprehensive overview of the potential of SIRT3 activation in different cancers as current activators lack specificity.

SIRT3 Inhibitors

On the contrary, improved understanding of the deacetylation process and identification of the crystal structure of SIRT3 has prompted research into the development of SIRT3 inhibitors. Using high throughput and in silico screening, several molecules with a wide range of core structures have been identified for SIRT3 inhibition. Of the numerous strategies employed, catalytic mechanism-based inhibition of SIRT3 has been widely studied. Nicotinamide serves as a natural sirtuin inhibitory molecule by binding to a conserved region in the sirtuin catalytic site and promoting a reverse base-exchange reaction instead of the deacetylation reaction (139). The chemo-preventive potential of nicotinamide was also demonstrated in keratinocyte cancers (140). However, the non-specific inhibition of all sirtuin isoforms and its rapid conversion to NAD⁺ limit the potential of nicotinamide for use in the treatment of cancer and other diseases. Thus, nicotinamide analogues have been developed for possible sirtuin inhibition. 3-TYP is a highly specific SIRT3 inhibitor (141), whereas Selisistat (or EX-527), a SIRT1, SIRT2 and SIRT3 inhibitor, has shown to work synergistically with Wee1 in lung cancer cells to promote growth inhibition and apoptosis (142-144).

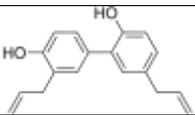
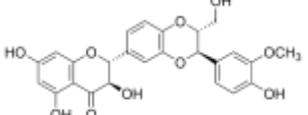
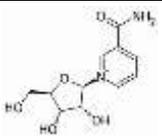
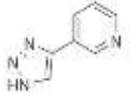
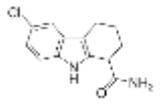
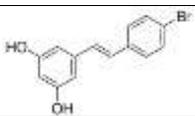
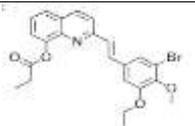
Another strategy for the development of sirtuin inhibitors employs substrate specific competition. 4'-bromo resveratrol, an analogue of Resveratrol, was found to suppress SIRT1 and SIRT3 in melanoma where the targeted sirtuins had a proliferative role (145, 146). It was observed that this dual inhibition of SIRT1 and SIRT3 was accompanied by induction of caspase-dependent apoptosis, inhibition of migratory potential, arrest in G1 phase, and ablation of

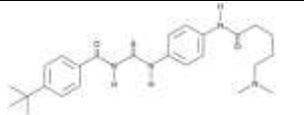
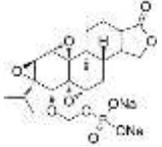
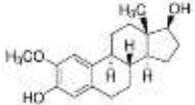
aerobic glycolysis (146). Several SIRT3 inhibitors have been developed using a SIRT3-structure based approach but their biological activity has not been reported (147).

Chemical library screening-based development of SIRT3 inhibitors is another efficient strategy to identify novel SIRT3 inhibitors. A study utilizing self-assembled monolayer desorption/ionization mass spectrometry (SAMDI-MS) was used to screen small molecules for SIRT3 inhibition activity. This led to the discovery of SDX-437, which has an IC₅₀ of 700nM and is one of the

strongest SIRT3 inhibitors identified so far but has not yet been tested for potential anti-cancer activity (148). In contrast, Tenovin-6, a p53 activator and non-competitive inhibitor of SIRT3, has shown anti-tumor activity mostly through regulation of SIRT1, SIRT2 and to a lesser extent through SIRT3 (149, 150). Minnelide, a water-soluble prodrug for diterpene tri-epoxide triptolide, was shown to inhibit the expression of SIRT3 in p53-deficient cancer cells and promoted mitochondrial dysfunction and upregulation of pro-apoptotic genes via mitigation of NF- κ B signaling (151, 152).

Table 1: Activators and Inhibitors of SIRT3

Compound	Chemical Structure	Mechanism/Specificity	Applications
SIRT3 Activators			
Honokiol		Increased SIRT3 levels and activity (122) Not sirtuin-specific (123)	Cardiomyopathy (122) Multiple cancers (123)
Silybin		Increased SIRT3 expression Not sirtuin-specific (129)	Acute kidney injury (129) Liver disease (130) Cancer (131, 132)
Nicotinamide Riboside		Boosts NAD ⁺ levels Activates all sirtuins alters energy metabolism	Neurodegeneration Cancer Mitochondrial disorders (120)
SIRT3 Inhibitors			
Nicotinamide		Feedback inhibition (139)	Multiple cancers (140)
3-TYP		NAD ⁺ competitive SIRT3 inhibitor (141)	Acute myeloid leukemia (156)
Selisistat		Occupies NAD ⁺ binding pocket, Inhibitor of SIRT1, SIRT2, SIRT3 (143)	Lung Cancer (142) Huntington's disease (144)
4-Bromo-Resveratrol		Substrate competitive SIRT1 and SIRT3 inhibitor (145)	Melanoma (146)
SDX-437		Inhibitor of SIRT3 > SIRT1	-

Tenovin-6		SIRT1, SIRT2 > SIRT3 inhibitor (149)	Gastric cancer (150)
Minnelide		Regulates SIRT3 expression and proteasomal degradation (152)	Non-small cell lung carcinoma (151)
2-Methoxy-estradiol		Binds to canonical and allosteric inhibitor binding sites of SIRT3 (153)	Osteosarcoma (153)

2-Methoxyestradiol, a natural derivative of 17β -estradiol was also found to inhibit the activity of SIRT3 by binding to both the canonical and allosteric inhibitor binding sites ultimately causing inhibition of mitochondrial biogenesis in osteosarcoma cancer cell model (153).

The use of Encoded library technology for screening of DNA encoded small molecules identified pan-inhibitors of SIRT1/2/3 such as carboxamides, which block the nicotinamide binding site (154). Additionally, the application of techniques such as DNA encoded Dynamic combinatorial library has led to the discovery of more selective and potent SIRT3 inhibitory ligands compared to the pan-sirtuin inhibitors (155). However, most of these compounds have yet to be evaluated for their efficacy in experimental models of cancer.

Taken together, the discovery of new and improved compounds targeting SIRT3 activity for therapeutic benefit is highly desired. Application of scientific drug design strategies will be particularly important to achieve this.

Perspective

SIRT3 is a crucial conductor of mitochondrial activity and cell metabolism thereby regulating important hallmarks of cancer. Alterations in SIRT3 and its downstream pathways have been found in many tumors emphasizing its involvement in cancer. However, SIRT3 cannot

be pinpointed as a universal tumor suppressor or oncogene (48). One future challenge will be to elucidate the role of SIRT3 in different types and stages of tumors and to identify molecular tumor profiles that determine the divergent role of SIRT3. For example, SIRT3 generally acts more as a tumor suppressor in tumors that heavily rely on glycolysis as opposed to its oncogenic role in lymphomas, which rely more on oxidative energy metabolism. It could also be hypothesized that SIRT3 activation might work well preventing tumor growth in early stages due to its antiproliferative effect but is less effective in later stages because of its protective effect on cell stress. Future studies correlating the function of SIRT3 in specific tumors with their metabolic or expression profile will shed light on potential applications for SIRT3 modulators as cancer therapeutics in a personalized medicine approach (Figure 3).

Given the complex role of SIRT3 in cancer, application of SIRT3 activators or inhibitors needs to be carefully evaluated depending on the type and location of cancer. Application of SIRT3 activators might lead to increased carcinogenesis, whereas SIRT3 inhibition could culminate into multiple organ toxicities. As such, the development and application of targeted drug delivery systems might help overcome drawbacks associated with nonspecific effects of SIRT3 modulation. Similarly, combination of SIRT3 modulators with chemotherapeutics

might be a promising approach given that SIRT3 can confer chemoresistance in some tumors (156). Despite the identification of several SIRT3 modulators, none have been approved for therapeutic use. Hence, an improved

understanding of the contextual role of SIRT3 will be required for successful development and application of SIRT3 modulators as therapeutic anti-cancer drugs

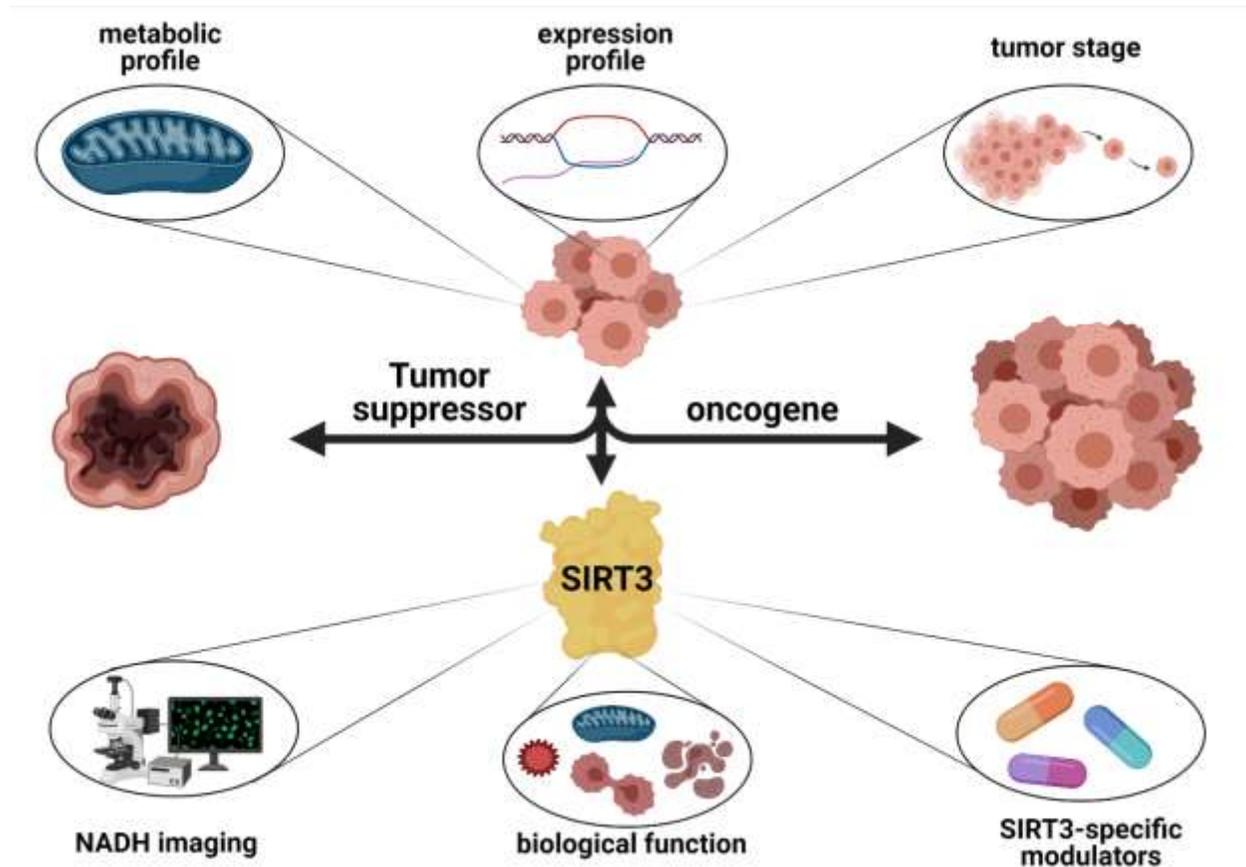


Figure 3: SIRT3 as potential therapeutic Target in Cancer

SIRT3 can act as either a tumor suppressor or oncogene. Combining the knowledge of molecular tumor signatures with a better understanding of SIRT3 biological function, regulation and the availability of SIRT3-specific compounds will allow evaluation of SIRT3 as therapeutic tumor target in future studies. Created with BioRender.com.

In addition to increasing our understanding of tumor modalities that favor SIRT3 modulation, more work is needed to understand the function and regulation of SIRT3. For example, there is still debate as to whether SIRT3 is regulated by NAD^+ content, the NAD^+/NA ratio or rather the $NAD/NADH$ redox ratio (119). Given that SIRT3 is mostly located in the mitochondria, cytoplasmic and mitochondrial redox state might have differential effects on SIRT3. NADH imaging

allows for assessing the redox state with subcellular resolution (157, 158) and future studies combining this powerful technology with SIRT3 expression and activity promise crucial insights into SIRT3 regulation. This is especially important given the current limitation on SIRT3 activators. Most evidence is related to usage of nonspecific drugs, such as NAD^+ boosting compounds, whose effects are only partially mediated through SIRT3. A better understanding

of SIRT3 regulation could open new approaches for its activation. In addition, development of more specific, synthetic activators and inhibitors is essential to allow for targeted SIRT3 modulation in different tumor settings.

Taken together, SIRT3 demonstrates a high functional relevance in tumor biology but a better understanding of suitable tumor profiles and more specific compounds are necessary to fully evaluate the potential of SIRT3 modulation as a cancer therapeutic.

Disclosures

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Summary

- Sirtuins are deacylases involved in epigenetic and posttranslational regulation
- Sirtuin 3 is a key regulator of mitochondrial function
- Sirtuin 3 is involved in tumor pathogenesis by regulating energy metabolism, ROS levels, proliferation and apoptosis
- Sirtuin 3 can act as tumor suppressor or oncogene dependent on the tumor
- Sirtuin 3 is a promising therapeutic target in personalized tumor therapy upon development of more specific activators and inhibitors.

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