

Emerging role of sirtuins in non-small cell lung cancer (Review)

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Abstract. Non-small cell lung cancer (NSCLC) is a highly prevalent lung malignancy characterized by insidious onset, rapid progression and advanced stage at the time of diagnosis, making radical surgery impossible. Sirtuin (SIRT) is a histone deacetylase that relies on NAD⁺ for its function, regulating the aging process through modifications in protein activity and stability. It is intricately linked to various processes, including glycolipid metabolism, inflammation, lifespan regulation, tumor formation and stress response. An increasing number of studies indicate that SIRT significantly contribute to the progression of NSCLC by regulating pathophysiological processes such as energy metabolism, autophagy and apoptosis in tumor cells through the deacetylation of histones or non-histone proteins. The present review elaborates on the roles of different SIRTs and their mechanisms in NSCLC, while also summarizing novel therapeutic agents based on SIRTs. It aims to present new ideas and a theoretical basis for NSCLC treatment.

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1. Introduction

Sirtuins (SIRT) are members of a highly conserved protein family characterized by adenosine monophosphate

(AMP)-transferring enzyme activity and histone deacetylase (HDAC) function, both of which are dependent on NAD⁺ (1). As of now, seven SIRTs (SIRT1 to SIRT7) have been identified in human cells, each located in different subcellular compartments, collectively comprising the class III HDACs (2). SIRT1, SIRT6 and SIRT7 are situated within the nucleus, while SIRT3, SIRT4 and SIRT5 are found in the mitochondria and SIRT2 is localized in the cytoplasm but can translocate to the nucleus to participate in certain functions when needed (3,4). Mammalian SIRTs rely on their enzymatic activities and post-translationally modify a variety of proteins, including both histones and non-histone proteins. The modification can either initiate or inhibit the expression of downstream target proteins, which are involved in a variety of physiological mechanisms, including adenosine triphosphate synthesis, DNA repair, fatty acid metabolism, glucose metabolism, insulin secretion and regulation of the cell cycle. When an organism is subjected to endogenous or exogenous stimuli, SIRTs participate in a variety of pathological processes including apoptosis, cellular autophagy, oxidative stress and inflammatory responses (5). Lately, multiple studies have recognized the association of the SIRT family with the pathophysiology of various diseases, encompassing Alzheimer's disease, cancer, diabetes and obesity, as well as cardiovascular, inflammatory and neurodegenerative diseases. Lung cancer stands as the most prevalent cancer worldwide and it is the leading cause of cancer-related death. Lung cancer is categorized into small cell lung cancer (SCLC) and non-SCLC (NSCLC) on the basis of clinical and histopathologic features. Among them, NSCLC is a common type of lung cancer, encompassing lung adenocarcinoma, large-cell lung cancer and squamous cell carcinoma, collectively accounting for ~85% of lung cancer cases. Due to its high invasiveness and the lack of effective early screening markers, 70% of patients with NSCLC are diagnosed at advanced stages (6). The current study revealed differentially expressed SIRTs among patients of different sexes and lung cancer types. These SIRTs exhibit dual roles as either tumor promoters or tumor suppressors, influencing various pathophysiological processes within tumor cells, such as autophagy, apoptosis and energy metabolism. Consequently, they play a crucial role in regulating NSCLC, thus emerging as prognostic biomarkers and potential therapeutic targets for NSCLC (7,8).

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2. Relationship between SIRTs and NSCLC

SIRT1 and NSCLC. SIRT1 is the most comprehensively studied member of the SIRT family and exhibits dual roles by acting

both as a promoter and an inhibitor of NSCLC progression (9). The findings of a meta-analysis indicated a notable association between SIRT1 overexpression and survival in patients with lung cancer, suggesting that elevated SIRT1 levels predict an unfavorable prognosis for individuals with solid cancers (10). Chen *et al* (9) and Li and Zhong (11) observed a substantial upregulation of SIRT1 expression in A549 and H1299 cells compared to non-cancerous cells. Furthermore, they demonstrated that inhibition of SIRT1 attenuates the invasion and proliferation of NSCLC cells while inducing apoptosis in tumor cells. Ahmad *et al* (12) identified that SIRT1 directly interacts with cytoplasm through the activation of IGF-1 to increase cell migration, invasion and metastasis, thereby promoting tumor progression. Xie *et al* (13) observed that SIRT1 promotes endothelial cell branching and proliferation, increases vascular density and facilitates lung tumor growth by delta-like canonical Notch ligand 4/NOTCH signaling pathway downregulation and N1IC deacetylation. Lung adenocarcinoma ranks among the most prevalent and lethal types of cancer. Elevated expression of SIRT1 protein is associated with recurrence and an unfavorable prognosis in patients diagnosed with lung adenocarcinoma (14). Han *et al* (15) found that SIRT1 exhibits high expression levels in NSCLC brain metastatic tissues compared to NSCLC tissues, and knockdown of SIRT1 significantly and specifically inhibits A549 migration. However, another study reported that SIRT1 expression is significantly reduced in NSCLC tissues or cells, and SIRT1 overexpression inhibits NSCLC progression (16). For instance, Hosseninia *et al* (17) discovered that serum SIRT1 levels were lower in patients with lung cancer, with significantly lower levels observed in patients with adenocarcinoma relative to those with SCLC and squamous carcinoma. Costa-Machado *et al* (18) found that oncogenic K-RAS in human lung adenocarcinoma cell lines downregulates SIRT1 in a manner dependent on MEK and PI3K. Furthermore, overexpression of SIRT1 delayed the appearance of lung adenocarcinoma driven by K-Ras (18). Li *et al* (19) discovered that SIRT1 overexpression protects NSCLC cells from NF- κ B acetylation and epithelial-mesenchymal transition induced by osteoblasts. In addition, it attenuates cell proliferation, migration and invasion, thereby inhibiting NSCLC progression (19). Circular RNA (Circ)-SIRT1 has been found to be downregulated in NSCLC. Furthermore, the expression of circ-SIRT1 is associated with the staging of tumor size and tumor lymph node metastasis in patients with NSCLC. Elevated circ-SIRT1 inhibits NSCLC cellular activity and glycolysis, and knockdown of circ-SIRT1 promotes the malignant behavior of NSCLC cells. Circ-SIRT1 inhibits the malignant progression of NSCLC cells by targeting SMAD7 via microRNA (miR)-510-5p, suggesting its potential as a therapeutic target for NSCLC therapy (20). Grbesa *et al* (21) revealed that SIRT1 protein expression is notably elevated in NSCLC cell lines and primary lung tumors compared to normal cells and tissues. They also found that this expression is more pronounced in adenocarcinoma. Of note, high SIRT1 expression levels in patients with NSCLC are associated with short recurrence-free survival (21).

SIRT1 is regulated by different factors and deacetylates regulatory histones and non-histone proteins, thereby influencing tumor progression. MiR-124 and miR-142 inhibit

autophagy by directly targeting SIRT1 and enhancing cisplatin sensitivity in NSCLC cells (22). MiR-133a-3p promotes tumor growth and metastasis after incomplete microwave ablation by decreasing SIRT1 expression and increasing viability, migratory invasiveness and proliferation of NSCLC cells (23). MiR-22 directly targets fibroblast growth factor receptor 1 and SIRT1 in endothelial cells and inhibits all key angiogenic activities in endothelial cells. This inhibition leads to inactivation of the AKT/mammalian target of rapamycin (mTOR) pathway, thus suppressing NSCLC growth (24). MiR-217 inhibits NSCLC cell invasion and proliferation while inducing tumor cell apoptosis by targeting SIRT1 and inhibiting the SIRT1-mediated AMP-activated protein kinase (AMPK)/mTOR signaling pathway (11). MiR-326 inhibits SIRT1 by suppressing hypoxia-inducible factor (HIF)-1 α expression, thereby inhibiting chemoresistance and proliferation and promoting apoptosis in NSCLC cells (25). Low expression levels of small nucleolar RNA host gene 10 (SNHG10) predict poor survival in patients with NSCLC. Overexpression of SNHG10 leads to upregulation of SIRT1, a downstream target of miR-543, and overexpression of SIRT1 results in reduced proliferation of NSCLC cells. Conversely, elevated expression of miR-543 reduces the effects of SNHG10 and SIRT1 overexpression, suggesting that SNHG10 inhibits tumor cell proliferation by regulating miR-543 upregulation of tumor-suppressive SIRT1 (26). CircRNA hsa_circ_0001946 facilitates the growth of lung adenocarcinoma cells by modulating miR-135a-5p/SIRT1 consequently inhibiting NSCLC growth (27). Hsa-miR-217 along with its target gene SIRT1 serve as a metastasis suppressor and initiator genes, respectively, in NSCLC. The hsa-miR-217/SIRT1/P53/CD82 metastasis regulatory pathway exhibits a key influence in NSCLC brain metastasis (28). Deacetylation of K-Ras by SIRT1 increases the conversion of Ras-GTP to Ras-GDP and promotes ERK1/2 downstream activation. In turn, the Ras/ERK pathway regulates SIRT1 transcription (29). Inhibition of SIRT1 results in the acetylation of heat shock protein family A (Hsp70) member 5 (HSPA5), leading to the activation of activating transcription factor 4 (ATF4) and DNA damage inducible transcript 4 (DDIT4), which induces autophagy. This process ultimately suppresses the mTOR signaling pathway in NSCLC cells (30). SIRT1 may induce pro-apoptotic effects by transcription factor deacetylation in A549/CADD cells (31). In the NSCLC microenvironment, SIRT1 participates in the molecular metabolic mechanism underlying hypoxia-induced chemoresistance by regulating the peroxisome proliferator activated receptor γ (PPARG) coactivator 1 (PGC-1 α)/PPAR- γ signaling pathway (32).

SIRT2 and NSCLC. A cross-sectional analysis by the Cancer Genome Atlas Program demonstrated that the SIRT2 gene is amplified in ~4% of patients with NSCLC, suggesting that it has a bifacial role in NSCLC (33). For instance, Li *et al* (34) observed significant downregulation of SIRT2 expression in tumor tissues. Furthermore, they found that SIRT2 overexpression inhibits cell proliferation and induction of apoptosis, leading to cell cycle arrest and increased sensitivity to cisplatin treatment. Further investigation revealed that overexpression of SIRT2 increases the production of reactive oxygen species (ROS) and p27 levels (34). In addition, research uncovered

that SIRT2 levels are notably reduced in lung cancer cell lines and SIRT2 overexpression promotes deacetylation and degradation of S-phase kinase-associated protein 2 (Skp2), consequently increasing p27 levels and inhibiting NSCLC cell growth. By contrast, SIRT2 knockdown restrains deacetylation and degradation of Skp2, leading to decreased p27 levels and elevated NSCLC cell growth (35). Xu *et al* (36) discovered that SIRT2 could suppress KDM4A expression by binding to the promoter region of the KDM4A gene. This action inhibits the clone formation, proliferation and tumor growth of NSCLC cells (36). However, research demonstrated that SIRT2 has an oncogenic role in NSCLC. For instance, Gao *et al* (37) identified that the median survival time of patients exhibiting high SIRT2 expression was substantially lower compared to those with low SIRT2 expression. They proposed that SIRT2 may serve as a distinct prognostic biomarker for non-metastatic lung adenocarcinoma (37). Hoffmann *et al* (38) found that AEM1 and AEM2, the selective inhibitors of SIRT2, sensitize NSCLC cell lines to etoposide-induced apoptosis by increased p53 activation resulting from decreased SIRT2-dependent p53 deacetylation. Xu *et al* (39) demonstrated that SIRT2 deacetylates and promotes the activation of the K100 residue of phosphoglycerate-converting enzyme, which enhances NADPH production and accelerates tumor growth. Tang *et al* (40) depicted the involvement of SIRT2 in the induction of a protective autophagy mechanism in HL60/A cells, which is closely related to drug resistance in patients. However, conflicting studies indicate that SIRT2 expression is downregulated in NSCLC and that SIRT2 inhibits tumor growth (41).

SIRT2 contributes to NSCLC progression by modulating acetylated protein levels. Inhibition of SIRT2 in cancer cells increases forkhead box (FOX)O1 acetylation, promotes interactions of FOXO1 related to autophagy and ultimately induces autophagy. Of note, autophagic processes are negatively correlated with tumor progression (42). Deacetylation of aldo-keto reductase family 1 member C1 (AKR1C1) by SIRT2 inhibits the binding of AKR1C1 to STAT3, thereby reducing the transcriptional activity of STAT3 and suppressing the migration of NSCLC cells (43). Inhibition of SIRT2 triggers autophagy in human NSCLC cells by preventing the mTOR signaling pathway through increased acetylation of HSPA5 and upregulation of the expression levels of ATF4 and DDIT4. SIRT2 binds directly to the transcription factor EB and regulates apoptosis induced by acute shear stress through autophagy modulation and exosome release, thereby inhibiting NSCLC onset and metastasis (30). SIRT2 overexpression induces the deacetylation and rapid degradation of Skp2, eliminating the impact of Skp2 on p27, leading to an increase in the p27 expression level and subsequent inhibition of NSCLC cell growth (35). ATP citrate lyase (ACLY) displays oncogenic functions in NSCLC, and SIRT2 deacetylates and promotes the degradation of ACLY, leading to a reduction in fatty acid synthesis and delaying tumor growth in NSCLC cells. SIRT2 acts as a primary HDAC for ACLY in NSCLC cells, thereby attenuating the oncogenic activity of ACLY (44). SIRT2 deacetylates AKR1C1 and inhibits the transactivation of STAT3 target genes, thereby inhibiting cell migration. The acetylation on Lysines 185 and 201 of AKR1C1 determines its potential to promote metastasis both *in vitro* and *in vivo*.

The restoration of SIRT2 acetylation offers a potential therapeutic target for the treatment of patients with metastatic NSCLC who exhibit elevated AKR1C1 expression (43). SIRT2 regulates histone and non-histone activities by acetylation and is regulated by upstream factors. For instance, miR-150 impacts NSCLC cell viability and mobility by regulating the SIRT2/JMJD2A pathway (36,45); synoviolin 1 (SYVN1) stimulates pathological processes such as tumor cell growth, ontogeny and migration by regulating SIRT2 (41). The level of speckle type BTB/POZ protein (SPOP) is significantly reduced and the level of SIRT2 is significantly increased in NSCLC cell lines; mutations in NSCLC suppress the ability of SPOP to degrade SIRT2 and inhibit NSCLC cell growth (46). In addition, some somatic mutations within SIRT2 have been identified in NSCLC that alter SIRT2 protein levels (47).

The involvement of SIRT2 in cancer is complex and controversial, with evidence supporting both tumor-suppressive and oncogenic roles. Initially, SIRT2 was proposed as a tumor suppressor due to its regulatory effects on the mitotic checkpoint and its deacetylase activity on histone H3K56, a modification frequently observed in cancer cells (48,49). Genetic experiments further supported this role, showing that mice deficient in SIRT2 had a higher incidence of tumors (50). Conversely, SIRT2 has been shown to promote tumor growth by deacetylating p53, leading to decreased p53 transcriptional activity (51). In addition, SIRT2 deacetylates lactate dehydrogenase A at K5, increasing its activity and protein levels, thereby accelerating glycolysis and lactate production, which enhances cancer cell proliferation and migration (52). Furthermore, the broad anticancer activity observed with SIRT2 inhibitors (53,54) suggests their potential as therapeutic agents in cancer treatment. These findings underscore the dual nature of SIRT2 in cancer, highlighting its complex and multifaceted role in tumor biology.

SIRT3 and NSCLC. SIRT3, the most important mitochondrial SIRT, is widely studied and exhibits a dual role in NSCLC, promoting both tumor progression and exerting antitumor effects. The findings of meta-analysis and systematic review indicate that SIRT3 is linked with poor prognosis in NSCLC (55). Yang *et al* (56) discovered that SIRT3 expression is notably elevated in NSCLC tissues. Furthermore, the levels of SIRT3 were identified as an independent factor in the prognosis of patients with NSCLC (56). The findings of Ahmed *et al* (57) reveal that SIRT3 exhibits oncogenic properties in high-fat diet (HFD)-induced tumorigenesis, and inhibition of SIRT3 may attenuate the pro-carcinogenic effects of HFD. Radiotherapy is an indispensable therapeutic tool for the treatment of NSCLC; however, the resistance of tumor cells against ionizing radiation often leads to treatment failure. Cao *et al* (58) found that expression of SIRT3 is upregulated in lung cancer tissues and NSCLC cell lines. They noted that SIRT3 knockdown significantly increases cell cycle arrest and radiation-induced apoptosis. Conversely, SIRT3 overexpression promotes radioresistance in lung cancer cells, which is linked to the activation of the ATM-checkpoint kinase 2 pathway following irradiation (58). However, Tao *et al* (59) found that SIRT3 mRNA and protein levels are significantly reduced in lung cancer tissues and serum samples. They observed a negative association between SIRT3 expression and

tumor size, tumor lymph node metastasis stage and metastasis. Furthermore, they revealed that the serum levels of SIRT3 are able to differentiate between patients with lung cancer and healthy individuals with high sensitivity and specificity. These findings suggest that SIRT3 may serve as a biomarker for early diagnosis of lung cancer (59). Xiao *et al* (60) revealed down-regulated expression of SIRT3 in human lung adenocarcinoma tissues. Furthermore, they observed that overexpression of SIRT3 substantially suppresses the proliferation of the A549 lung adenocarcinoma cell line, increases the ratio of Bax/Bcl-2 and Bad/Bcl-xL, as well as upregulates the protein levels of p21 and p53, ultimately inducing cell apoptosis (60). Cisplatin resistance poses a significant challenge in chemotherapy treatment for patients with lung cancer. Cao *et al* (61) revealed that the expression of chromatin licensing and DNA replication factor 1 (CDT1), FOXO3 and SIRT3 is inhibited in both cells and tissues of lung cancer. They found that FOXO3 positively regulates the expression of CDT1. In addition, they observed that elevated levels of SIRT3 suppress FOXO3 through acetylation, consequently enhancing FOXO3 expression. Elevated levels of CDT1, FOXO3 or SIRT3 inhibit cisplatin resistance and diminish *in vitro* survival, invasion, and proliferation of lung cancer cells. It was further demonstrated that SIRT3 deletion elevates Ki-67 and VEGFA levels, while the overexpression of SIRT3 increases the expression of the FOXO3a/CDT1 axis, thereby enhancing the sensitivity of lung cancer cells (61). Geoghegan *et al* (62) found that decreased SIRT3 expression reduces oxidative metabolism, decreases mitochondrial abundance and increases glycolytic flux and ROS production in H1299 lung large cell carcinoma cells with acquired cisplatin-resistance.

SIRT3 is regulated by different factors and deacetylates regulatory histones and non-histone proteins, thereby affecting tumor progression. For instance, Zhang *et al* (63) found that cancer-associated fibroblasts (CAF) induce endothelial cell angiogenesis and enhance the malignant phenotype of NSCLC cells through the establishment of a CAF-NSCLC co-culture model. MiR-224 targets the 3'-untranslated region of SIRT3 mRNA, consequently suppressing SIRT3/AMPK, while activating mTOR/HIF-1 α . Forced overexpression of SIRT3 leads to the upregulation of AMPK and inactivation of the mTOR/HIF-1 α signaling pathway. Conversely, suppression of HIF-1 α notably enhances SIRT3/AMPK levels and decreases mTOR phosphorylation. It is noteworthy that both the overexpression of SIRT3 and the inhibition of HIF-1 α result in a reduction of miR-224 levels and NSCLC promotion facilitated by miR-224. This observation suggests the existence of a positive feedback loop involving the miR-224-SIRT3/AMPK/mTOR/HIF-1 α axis in the regulation of NSCLC carcinogenesis induced by CAF (63). Xiong *et al* (64) identified that circRNA Rac GTPase activating protein 1 (circRACGAP1) exhibits elevated expression in NSCLC. Deficiency of circRACGAP1 led to the inhibition of epithelial-mesenchymal transition, metastasis and stemness of stem cells. CircRACGAP1 enhances SIRT3 stability and expression by recruiting associated proteins, which subsequently leads to deacetylation of replication timing regulatory factor 1 (RIF1) and activates the Wnt/ β -catenin pathway. Overexpression of circRACGAP1 counteracts SIRT3 or RIF1 knockdown-mediated inhibition of NSCLC cell stemness and

metastasis. The absence of circRACGAP1 impedes tumor development and metastasis *in vivo*, suggesting its role in promoting SIRT3-mediated deacetylation of RIF1 through the recruitment of related proteins, thereby promoting differentiation and metastasis of NSCLC cells (64). Xiong *et al* (65) found that SIRT3 expression is significantly increased and P53 expression is almost negative in clinical samples of phosphatase and tensin homologue-deficient NSCLC. Furthermore, they demonstrated that SIRT3 promotes P53 degradation by deacetylating P53 at lysines 320 and 382.

SIRT5 and NSCLC. SIRT5 exhibits a dual role in cancer, functioning as a tumor suppressor in certain cancers while acting as an oncogene in others. Of note, the expression of SIRT5 is not specific but rather significantly dependent on the cellular environment. SIRT5, as a tumor suppressor, prevents the Warburg effect, enhances protection against ROS, and decreases cell proliferation and metastasis. However, as an oncogene, it exhibits opposing effects by increasing resistance to chemotherapeutic agents and/or radiotherapy (66,67). Mendelian randomization analysis reveals that SIRT5 acts as a protective factor and is causally associated with lung squamous cell carcinoma (64). However, most studies concluded that SIRT5 has an oncogenic role in NSCLC. For instance, one study reported upregulated SIRT5 expression in tumor tissues from certain patients with NSCLC, with the higher SIRT5 levels correlating with poorer clinical prognosis (68). Deng *et al* (69) identified that hsa_circ_0081664 enhances the expression of SIRT5 by adsorbing miR-507, which promotes cisplatin resistance in NSCLC cells, silences SIRT5 to inhibit tumor cell proliferation, reduces cell invasion and migration, and promotes cell apoptosis. Lu *et al* (70) were the first to find in A549 lung cancer cells that SIRT5 binds to pyruvate kinase isoform M2 (PKM2) and desuccinates its K498 residue, which inhibits its activity, reduces ROS production, and promotes tumor growth and cell proliferation. In addition, Ye *et al* (68) found that PKM2 desuccinylation mediated by SIRT5 favors tumor cell growth and promotes cell survival and proliferation, and that suppression of SIRT5 inhibits tumor cell proliferation by PKM2 K498 desuccinylation. Li *et al* (71) found that SIRT5 facilitates the onset and progression of NSCLC by decreasing the acetylation level of fatty acid binding protein 4. Wu *et al* (72) discovered that in HCC827 and PC9 lung adenocarcinoma cells, APC down-regulated 1 like-antisense 1, a long non-coding RNA, positively regulates SIRT5 expression with the sponge miR-1322/miR-1972/miR-324-3pin. This regulation suppresses autophagic degradation of epidermal growth factor receptor, thereby inducing resistance to imatinib (72).

SIRT6 and NSCLC. SIRT6 demonstrates both pro- and anti-tumor effects in NSCLC in multiple ways. For instance, Azuma *et al* (73) identified that enhanced SIRT6 expression is associated with T and N staging in tumors of patients with NSCLC. Furthermore, its overexpression facilitates metastasis and chemoresistance of NSCLC cells, leading to poor prognosis. Bai *et al* (74) were the first to demonstrate that SIRT6 is upregulated in NSCLC. Furthermore, they found that its overexpression enhances extracellular signal-regulated kinase 1/2 phosphorylation, activates

matrix metalloproteinase 9, and promotes tumor cell invasion and migration (74). Subramani *et al* (75) found that SIRT6 functions as an oncogene in NSCLC, and SIRT6 silencing suppresses NSCLC cell proliferation and induces apoptosis. The NOTCH signaling pathway plays a crucial role in cell survival and modulates both cell proliferation and differentiation. SIRT6 silencing substantially facilitates and stabilizes the acetylation state of DNA methyltransferase 1, which then translocates into the nucleus and methylates the Notch receptor 1 (NOTCH1) promoter region, leading to the blockage of NOTCH1-mediated NOTCH signaling (75). Krishnamoorthy *et al* (76) found that SIRT6 expression is significantly increased in A549, NCI-H460 and NCI-H520. The small interfering RNA-mediated silencing of SIRT6 activates p53/p21-induced suppression of cell proliferation, resulting in apoptosis induction and cell cycle arrest. This suggests that SIRT6 is a tumor promoter in the ontogeny, progression and regulation of NSCLC, and thus, SIRT6 silencing is expected to be a new approach for lung cancer treatment (76). Furthermore, Kim *et al* (77) identified that decreased expression of SIRT6 mediates the enhancement of apoptosis induced by radiation through cAMP signaling in lung cancer cells. However, SIRT6 functions as a tumor suppressor involved in NSCLC progression (78). SIRT6 increases the radiosensitivity of NSCLC and protects against lung injury induced by radiation. Wang *et al* (79) found that the alveolar wall of the radiotherapy group was significantly thickened and a large amount of proliferative fibrous tissue could be observed in the alveolar interstitium, while the thickness of the alveolar wall and interstitial fibrosis were substantially decreased in the SIRT6 overexpression group, and the level of inflammatory factors was significantly reduced so that SIRT6 could inhibit inflammation and reduce radiation pneumonitis and lung injury (79). SIRT6 expression inhibits HIF-1 α and VEGF expression and promotes egl-9 family HIF-1 expression, thereby inhibiting angiogenesis and tumor growth (80).

SIRT4 as well as SIRT7 and NSCLC. SIRT4 is a mitochondrial SIRT and research on its functions related to NSCLC is currently scarce. Fu *et al* (81) found reduced expression of SIRT4 in 70 out of 133 NSCLC cases through immunohistochemistry. They noted that a low expression level of SIRT4 was associated with the metastatic stage of tumor lymph nodes, the histological type of the tumor, lymph node status, Ki-67 and poor overall survival. A further study revealed that SIRT4 suppresses lung cancer cell proliferation by regulating mitochondrial dynamics through the ERK-dynamin-related protein 1 pathway. Furthermore, SIRT4 blocks the cell cycle, and suppresses cell invasion and migration, suggesting its crucial role as an important anti-tumor protein in NSCLC (81). Autophagy is one of the processes leading to the increasingly prevalent resistance to cytotoxic chemotherapy. Jiang *et al* (82) discovered that SIRT7 protein levels are significantly elevated after treatment with gemcitabine, an antimetabolite drug. Furthermore, they observed that SIRT7 deficiency promotes gemcitabine-induced cell death and enhances the antitumor activity of gemcitabine. These findings suggest that SIRT7 inhibition can enhance the effectiveness of antimetabolite therapy in NSCLC cells (82).

3. Mechanisms of SIRT6 in NSCLC

SIRT-targeted therapies in NSCLC involve manipulating the functions of SIRT proteins to inhibit tumor growth and enhance the effectiveness of existing cancer treatments. The mechanisms through which SIRT6 influence NSCLC can be broadly categorized based on their roles in cellular metabolism, DNA repair and regulation of gene expression.

DNA repair and genomic stability. SIRT6 plays a crucial role in DNA repair and cells lacking SIRT6 (knockout) exhibit genomic instability and heightened sensitivity to DNA damage. In response to DNA double-strand breaks (DSBs), SIRT6 dynamically associates with chromatin and significantly reduces overall H3K9 acetylation in cells. This action facilitates the formation of a macromolecular complex with the DNA DSB repair factor DNA-dependent protein kinase, enhancing the repair of DNA DSBs. Furthermore, SIRT6 recruits the chromatin remodeling factor SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 5 homolog to the DSB sites and is essential for deacetylating H3K56, which opens up the chromatin—an early step in the DNA damage response (83). Recent studies have also observed that c-Jun N-terminal kinase phosphorylates SIRT6 to stimulate DNA DSB repair in response to oxidative stress (84). Following this post-translational modification, SIRT6 recruits poly(ADP-ribose) polymerase 1 to DNA breaks and activates it through mono-ADP-ribosylation, thereby promoting homologous recombination and non-homologous end joining, and enhancing the repair of DNA breaks. By boosting SIRT6 activity, the sensitivity of cancer cells to DNA-damaging agents used in chemotherapy can be increased, thereby improving therapeutic outcomes.

Regulation of apoptosis and cell survival. SIRT1 is an NAD-dependent deacetylase that plays a crucial role in transcription, DNA replication and repair. p53 was identified as the first non-histone substrate of SIRT1, with its acetylation levels being regulated by the activity of SIRT1 (85,86). SIRT1 induces deacetylation of p53 at its C-terminal residues in an NAD-dependent manner, which suppresses its transcriptional activation ability and ultimately inhibits p53-mediated transcription-dependent apoptosis (86). Studies have shown that dysfunction of the SIRT1-p53 axis is closely associated with various cancers (87-89). In preclinical studies, compounds targeting the SIRT1-p53 axis have proven to be effective cancer therapies. These findings suggest that the SIRT1-p53 pathway may be a promising therapeutic target for cancer treatment.

In addition, SIRT3 deacetylates and activates superoxide dismutase 2 (SOD2); S-glutathionylation-induced inactivation of SIRT3 leads to hyperacetylation of SOD2 and exacerbates hypertension in angiotensin II-induced SIRT3 knockout and SOD2-depleted mice (90). The activity of SIRT3 is also regulated by mitochondrial function and matrix pH. A reduction in membrane potential decreases SIRT3 activity, shifting substrate utilization from carbohydrate oxidation to lactate production. This shift increases the NADH/NAD⁺ ratio and raises the levels of acetyl-CoA, thereby reducing SIRT3 activity (91). As a mitochondrial SIRT, SIRT3 primarily promotes apoptosis in cancer cells by enhancing mitochondrial

function and increasing oxidative stress. Enhancing SIRT3 activity could exploit mitochondrial vulnerabilities in cancer cells, leading to their death.

Metabolic regulation. Han *et al* (92) found that SIRT6 is reduced in human NSCLC tissues and cell lines. Overexpression of SIRT6 can inhibit the proliferation of NSCLC cells, while knockout of SIRT6 promotes their proliferation. Further studies revealed that SIRT6 suppresses the expression of twist family bHLH transcription factor 1 at both mRNA and protein levels in NSCLC cells. Therefore, SIRT6 regulates numerous glycolytic genes in NSCLC, and its deficiency promotes tumor growth by enhancing glycolysis (73). Overexpression of SIRT6 may decrease the expression of HIF-1 α and VEGF, and promote the expression of prolyl hydroxylase-2, thus inhibiting angiogenesis and tumor growth. Other enzymes such as PKM, lactate dehydrogenase A and hexokinase have also been shown to be downregulated in A549 cells to inhibit glycolysis, leading to cell cycle arrest in G0/G1 phase and apoptosis (80). SIRT6 can target glycolytic enzymes and reduce their activity, depriving cancer cells of their primary energy source. In addition, multiple studies have indicated that SIRT6 may inhibit gluconeogenesis, a function that can lead to reduced blood glucose levels (93-96). SIRT6 can interact with and modify the acetyltransferase GCN5 to enhance its activity. This enhancement may increase the acetylation of PGC-1 α , a key mediator of gluconeogenesis gene transcription, leading to the suppression of gluconeogenesis gene expression and hepatic glucose production. Thus, enhancing the expression or activity of SIRT6 could be an effective strategy to disrupt the metabolic pathways relied upon by NSCLC cells, ultimately inhibiting their proliferation.

Drug resistance. In ~20% of patients with NSCLC, an association between SIRT2 and resistance mutations in EGFR has been observed. EGFR tyrosine kinase inhibitors are currently the standard treatment for patients with NSCLC with EGFR mutations. However, resistance remains a major factor impacting the efficacy of cancer treatments. Bajpe *et al* (97) demonstrated through extensive screening that the absence of SIRT2 confers resistance to EGFR inhibitors in NSCLC and colorectal cancer. SIRT2 deacetylates MEK1 and inhibits its activation. The absence of SIRT2 leads to increased acetylation and phosphorylation levels of MEK1, potentially causing cancer relapse due to enhanced activation of MEK1 and subsequent phosphorylation of downstream ERK. Similarly, the lack of SIRT2 also results in resistance to B-Raf proto-oncogene, serine/threonine kinase (BRAF) and MEK inhibitors in melanoma with BRAF mutations and colorectal cancer with Kras mutations (98). Conversely, increased levels of SIRT2 expression may induce multidrug resistance in acute myeloid leukemia by activating the ERK1/2 signaling pathway (99). Furthermore, SIRT2 exerts a protective role against chemotherapy-induced peripheral neuropathy in a subcutaneous lung cancer mouse model, a common reason for the reduction and discontinuation of chemotherapy dosages. Cisplatin induces the nuclear accumulation of SIRT2 in dorsal root ganglion neurons, allowing SIRT2 to participate in the repair of DNA damage caused by cisplatin (100). Multiple studies suggest that SIRT2 contributes to the stemness of cancer stem cells,

providing further links between SIRT2 and chemoresistance in NSCLC (101).

In summary, SIRT proteins, particularly SIRT1, SIRT3 and SIRT6, exhibit complex and context-dependent roles in NSCLC, functioning both as promoters and suppressors of tumor growth based on specific conditions and interactions within the cellular and tumor environments. SIRT1 can promote NSCLC progression by inhibiting the tumor suppressor p53, reducing apoptosis and allowing cancer cell proliferation. However, under different conditions, SIRT1 also enhances the action of chemotherapeutic drugs by acetylating p53, thereby promoting its tumor-suppressive functions. Similarly, while SIRT3 generally acts as a tumor suppressor by improving mitochondrial function and increasing oxidative stress that can lead to cancer cell death, it may also support cancer cell survival under certain metabolic conditions by enhancing energy production. SIRT6 mainly exhibits tumor-suppressive properties in NSCLC by maintaining genomic stability through DNA repair and chromatin remodeling, and by suppressing glycolysis, a key metabolic pathway heavily relied upon by cancer cells. SIRT6's ability to repress the expression of glycolytic genes diminishes a critical energy source for tumor cells, thereby inhibiting their growth and survival. These SIRT family members' roles are significantly influenced by the tumor microenvironment, genetic variations and differential expression levels, which can shift their function from tumor-promoting to tumor-suppressing. This dual functionality makes SIRTs valuable targets for NSCLC therapy, highlighting the need for precise targeting in therapeutic strategies to exploit their cancer-regulating capabilities effectively. Clinical trials and preclinical studies suggest that modulating SIRT activity, either through small molecule inhibitors or gene therapy, could enhance the response to standard chemotherapies and provide a broader strategy for managing resistance. So far, the exploration of SIRT proteins in NSCLC has highlighted their potential as both biomarkers and therapeutic targets, reflecting their complex roles in tumor biology. Continued research is essential to fully understand and harness these proteins' capabilities to improve NSCLC treatment outcomes.

4. SIRT-based treatment

Inhibitors and agonists of SIRT. SIRTinol is a specific inhibitor of SIRT1 and SIRT2 and a novel anticancer drug. SIRTinol chelates iron in NSCLC cells, leading to a substantial reduction in unstable iron and a cell lineage-specific adaptive response (66). SIRTinol potentially suppresses the proliferation of NSCLC cells and induces apoptosis by modulating the AKT- β -catenin-FOXO3a axis (102). The combination of SIRTinol and AGK2 with sodium dichloroacetate leads to elevated lysine acetylation and reduced serine phosphorylation of pyruvate dehydrogenase α 1, resulting in synergistic therapeutic effects (103). Inauhizin is an inhibitor of SIRT1 and a P53 activator. It prevents MDM2-mediated p53 degradation, induces p53 activation and inhibits the activity of SIRT1 to indirectly interrupt the negative feedback loop of MDM2-p53. Subsequently, this action enhances p53 acetylation, thus making Inauhizin a promising new strategy for anticancer therapy (104). Doxorubicin and Trifolium

Table I. Therapeutic drugs based on sirtuins and their mechanisms of action.

First author, year	Compound	Target	Mechanism of action	(Refs.)
Fong, 2014	Sirtinol	SIRT1,	Regulates the AKT- β -catenin-FOXO3a axis, inhibits NSCLC cell proliferation, induces apoptosis.	(102)
Ma, 2018		SIRT2	Combines with AGK2 and sodium dichloroacetate to increase lysine acetylation of pyruvate dehydrogenase α 1, reduce serine phosphorylation.	(103)
Zhang, 2012	Inauhizin	SIRT1	Inhibits MDM2-mediated p53 degradation, induces p53 activation, inhibits SIRT1 activity, disrupts MDM2-p53 negative feedback loop, enhances p53 acetylation.	(104)
Akbaribazm, 2020	Resveratrol	SIRT1	Increases SIRT1 expression, reduces serum levels of inflammatory cytokines, inhibits tumor growth and distant metastasis.	(105)
Shang, 2021	MDL-800	SIRT6	<ul style="list-style-type: none"> Induces histone H3 deacetylation in NSCLC cell lines, inhibits NSCLC cell proliferation; knockdown of SIRT6 significantly weakens its antiproliferative effect. Inhibits MAPK pathway, enhances the antiproliferative effect of epidermal growth factor receptor tyrosine kinase inhibitors. Enhances SIRT6-dependent histone H3 deacetylation, reduces tumor tissue levels of p-MEK and p-ERK, inhibits tumor growth. 	(106)
Feng, 2023	Isoquercitrin	SIRT6	Activates the SIRT6/NRF2/GPX4 signaling pathway to promote iron sinking in lung cancer; reverses resistance.	(107)
Fang, 2021	α -Hederin	SIRT6	Activates SIRT6 expression, inhibits glycolytic protein expression, slows lung cancer cell growth.	(108)
Dai, 2017	Astragaloside	SIRT6	Regulates SIRT6 to enhance tumor cell sensitivity to gefitinib; inhibits NSCLC cell proliferation.	(109)
Iskandar, 2013	β -Cryptoxanthin	SIRT1	Increases SIRT1 levels, inhibits diversity and volume of lung tumors, improves survival rate.	(110)
You, 2018	Baicalin	SIRT1	Activates SIRT1/AMPK and mTOR signaling targets, inhibits NSCLC cell viability, migration and invasion; increases apoptosis.	(111)
Chen, 2021	Melatonin	SIRT3	Stimulates SIRT3 to increase the activity of the pyruvate dehydrogenase complex, enhances mitochondrial energy metabolism, reverses the Warburg effect.	(112)
Li, 2021	Metformin	SIRT1	<ul style="list-style-type: none"> Regulates the NRF2/HO-1 pathway activated by gallic acid through SIRT1-dependent NRF2 deacetylation, enhances the antitumor effect of gallic acid ester. Upregulates partial expression of SIRT1 via the NF-κB pathway. 	(113)
Lee, 2019			Combined with tenovin-6, it enhances the antitumor effect in NSCLC cells through LKB1-independent downregulation of SIRT1.	(114)
Cha, 2016	Celecoxib and Sulindac	SIRT1	Inhibits TGF- β 1-induced EMT, suppresses migration and invasion of lung cancer cells through downregulation of SIRT1. Overexpression of SIRT1 is a potential therapeutic target to reverse TGF- β 1-induced EMT and block migration and invasion of lung cancer cells.	(115)
Hwang, 2015	Pemetrexed	SIRT1	Induces apoptosis in NSCLC cells through ROS accumulation and downregulation of SIRT1-mediated mitochondrial dysfunction.	(116)
Lai, 2022	Pentoxifylline	SIRT1	Inhibits the key regulatory factor of mitochondrial biogenesis, the SIRT1/PGC-1 α axis.	(117)

Table I. Continued.

First author, year	Compound	Target	Mechanism of action	(Refs.)
Tae, 2018	Cyclopentenone PG	SIRT1	Reduces the expression of SIRT1 in LUADC cells, promotes early apoptosis of tumor cells, inhibits cell cycle, proliferation and migration.	(119)
Hwang, 2021	Salinomycin	SIRT1	Activates the AMPK/SIRT1 pathway to downregulate MMP-2 and MMP-9, inhibits TGF- β 1-induced EMT, suppresses migration and invasion of lung cancer cells.	(120)

SIRT, sirtuin; AKT, protein kinase B; FOXO3a, Forkhead box O3; p-MEK, phosphorylated mitogen-activated protein kinase/extracellular signal-regulated kinase; p-ERK, phosphorylated extracellular signal-regulated kinase; NRF2, nuclear factor erythroid 2-related factor 2; GPX4, glutathione peroxidase 4; HO-1, heme oxygenase-1; LKB1, liver kinase B1; TGF- β 1, transforming growth factor β 1; PGC-1 α , peroxisome proliferator-activated receptor γ coactivator 1 α ; LUADC, lung adenocarcinoma; MMP, matrix metalloproteinase; NSCLC, non-small cell lung cancer; AMPK, AMP-activated protein kinase; EMT, epithelial-mesenchymal transition.

pratense L. (Red clover) extract, when combined, have been shown to reduce serum levels of inflammatory cytokines, increase SIRT1 expression, and inhibit tumor growth and distant metastasis (105). MDL-800, a constitutive activator of SIRT6, dose-dependently induces histone H3 deacetylation in NSCLC cell lines and inhibits NSCLC cell proliferation. Its antiproliferative effect is significantly attenuated after the knockdown of SIRT6. MDL-800 enhances the antiproliferative effect of EGFR tyrosine kinase inhibitor and inhibits the MAPK pathway in osimertinib-resistant cells and patient-derived primary tumor cells. Furthermore, intraperitoneal injection of MDL-800 in nude mice xenografted from HCC827 cells significantly inhibits tumor growth, enhances SIRT6-dependent histone H3 deacetylation and reduces phosphorylated (p-)ERK and p-MEK in tumor tissues, suggesting that MDL-800 may be a potential compound for the treatment of NSCLC (106).

Plant extracts. Feng *et al* (107) observed that co-treatment with isoorientin and cisplatin leads to a notable reduction in the viability of drug-resistant cells and a significant rise in intracellular iron, malondialdehyde and ROS concentrations, along with a significant reduction in glutathione concentrations, as well as ferroptosis of the cells. Furthermore, they demonstrated that isoorientin can promote ferritin sedimentation in lung cancer cells via the SIRT6/nuclear factor E2-related factor 2 (NRF2)/glutathione peroxidase 4 signaling pathway, consequently reversing drug resistance (107). α -Hederin is a potent biologically active compound found in *Pulsatilla chinensis* (Bunge) Regel. Fang *et al* (108) discovered that α -hederin activates SIRT6 expression, inhibits glycolytic protein expression and slows lung cancer cell growth. Astragaloside IV, an active ingredient of *Astragalus membranaceus*, possesses anti-tumor biological effects. It can inhibit the proliferation of NSCLC cells by sensitizing tumor cells to gefitinib through modulation of SIRT6 (109). β -cryptoxanthin is an oxygenated carotenoid. A meta-analysis reported that β -cryptoxanthin intake is linked with a lower risk of lung cancer in smokers. Iskandar *et al* (110) further found that supplementation of β -cryptoxanthin suppresses lung tumor diversity and tumor volume, restores SIRT1 levels and improves survival rates. Astragalin, an herbal flavonoid, has been found to activate SIRT1/AMPK and mTOR in A549 and H1299 cells in a dose-dependent manner. This activation leads to the inhibition of NSCLC cell viability, migration and invasion, as well as an increase in apoptosis. Importantly, silencing of SIRT1 and AMPK reduces the impacts of astragalin on cell proliferation and migration (111).

Melatonin. Melatonin is an endogenous molecule produced by the pineal gland, affecting circadian rhythms and cellular redox status. In addition, melatonin serves as an important immunomodulatory molecule, exhibiting inhibitory effects on the growth of certain tumors. Initially, melatonin was found to inhibit lung cancer growth and suppress NSCLC cell proliferation in a Lewis lung carcinoma mouse model. This inhibition was associated with metabolic reprogramming of cancer cells, characterized by a shift from aerobic glycolysis in the cytoplasm to oxidative phosphorylation.

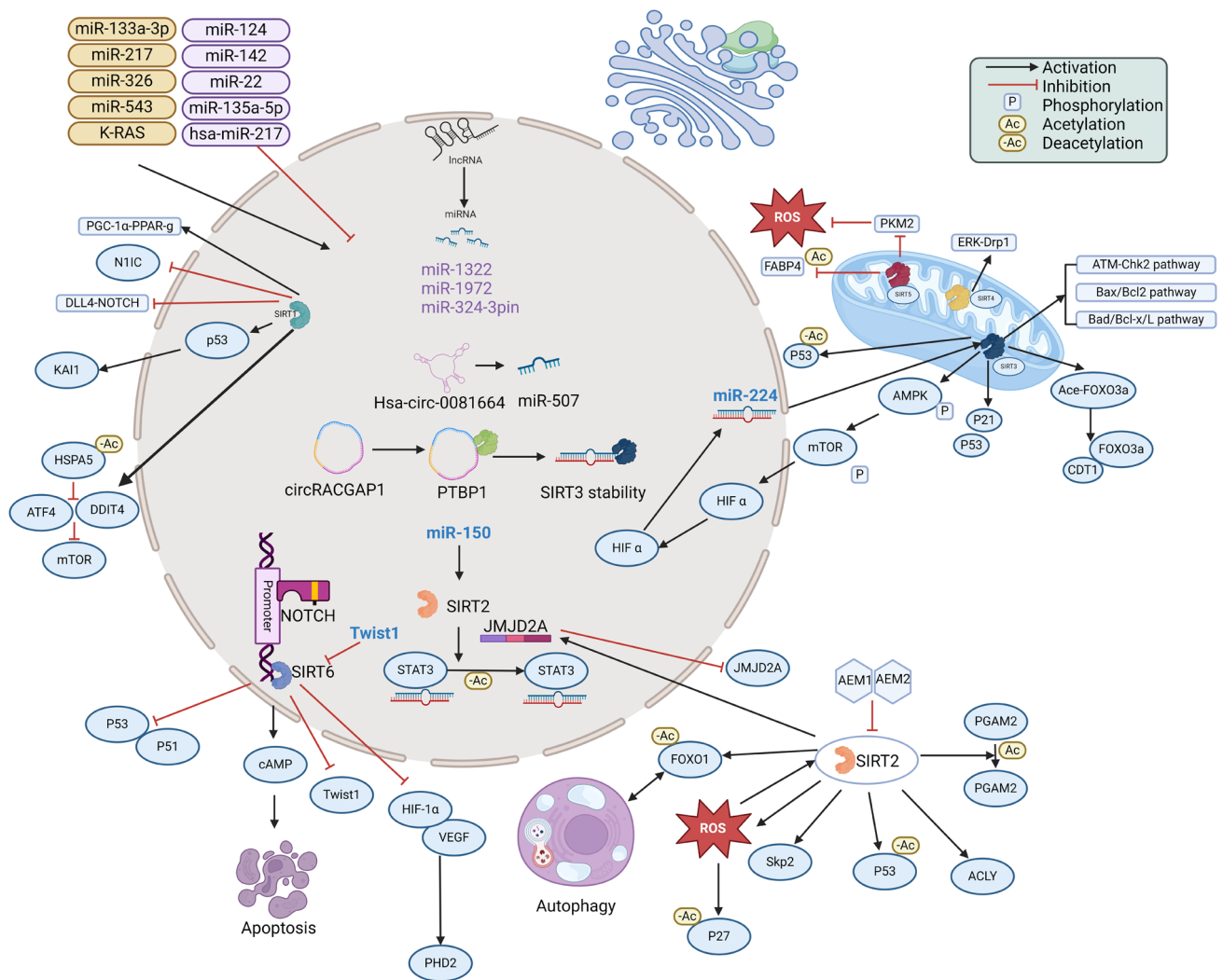


Figure 1. Summary of the roles of different SIRTs in non-small-cell lung carcinoma. SIRT, sirtuin; lncRNA, long non-coding RNA; miRNA, microRNA; AMPK, AMP-activated protein kinase; EMT, epithelial-mesenchymal transition; ROS, reactive oxygen species; HIF, hypoxia-inducible factor; AC, acetylation; VEGF, vascular endothelial growth factor.

These metabolic changes were accompanied by higher ATP production, elevated coupled oxygen consumption by ATP production, higher levels of ROS, higher mitochondrial ROS levels and lower lactate secretion. A further study revealed that melatonin significantly enhances mitochondrial energy metabolism by stimulating SIRT3 to increase the recombination activity of pyruvate dehydrogenase, thereby reversing the Warburg effect (112). It has also been found that melatonin combined with local radiofrequency ablation suppresses the progression of multiple lung nodules in the unablated region, thereby reducing patient trauma and tumor recurrence (113).

Others. Metformin is a typical anti-diabetic drug. Li *et al* (113) revealed that metformin enhances the antitumor effect of gallate ester by regulating the gallic acid-activated NRF2/heme oxygenase-1 pathway through SIRT1-dependent NRF2 deacetylation. It is further confirmed that metformin partially upregulates the expression of SIRT1 through the NF-κB signaling (113). Furthermore, metformin combined with tenovin-6 enhances antitumor effects in NSCLC cells through serine/threonine kinase 11-independent

SIRT1 downregulation (114). Celecoxib and sulindac inhibit epithelial-mesenchymal transition (EMT) induced by TGF-β1 and suppress lung cancer cell migration and invasion by downregulation of SIRT1. Overexpression of SIRT1 is a potential therapeutic target for reversing EMT induced by TGF-β1 and blocking lung cancer cell migration and invasion (115). Pemetrexed, a multi-targeted antifolate drug, induces apoptosis in A549 NSCLC cells through ROS accumulation and SIRT1 downregulation, which in turn mediates mitochondrial dysfunction (116). The foundation of cancer cell growth lies in energy metabolism. As a result of rapid cell proliferation, the energy dependence gets stronger. Penfluridol treatment of lung cancer cells (A549 and HCC827) lead to a substantial reduction in total ATP, a decrease in the mitochondrial number and membrane integrity, and an increase in glycolysis-associated proteins. A mechanistic study suggests that the energy reduction mediated by penfluridol is attributed to the inhibition of SIRT1/PGC a key regulator of mitochondrial biogenesis, along the SIRT1/PGC-1α axis. Upregulation of the SIRT1/PGC-1α axis reverses the inhibitory effects of penfluridol on cell viability and mitochondrial biogenesis (117).

Cyclopentenone prostaglandins (cyPGs) possess antioxidant, anti-cancer and anti-inflammatory characteristics and are involved in various physiological processes including apoptosis, anti-inflammation, cell growth, cytoskeletal dysfunction, differentiation, protein conversions and redox alterations. Slanovc *et al* (118) found that cyPGs promote early apoptosis and inhibit the cell cycle, migration and proliferation of tumor cells by decreasing SIRT1 expression in lung adenocarcinoma cells. Salinomycin is an antitumor drug. It was found that salinomycin inhibits TGF- β 1-induced EMT through the downregulation of MMP-2 and MMP-9 via the AMPK/SIRT1 pathway, ultimately suppressing the invasion and migration of lung cancer cells (119). The SIRT-related treatment methods are summarized in Table I.

5. Conclusions and prospects

SIRT6 exert dual roles as either tumor promoters or suppressors in NSCLC, influencing a variety of pathophysiological processes such as autophagy, apoptosis and energy metabolism within tumor cells (Fig. 1). Their involvement contributes to the regulation of various biological properties of NSCLC cells, such as growth, invasion, migration and proliferation. SIRT6 regulate the activity of related proteins at the acetylation level and are regulated by multiple upstream factors, thus affecting lung cancer progression. Although SIRT1, SIRT3 and SIRT6 have been studied in NSCLC, investigations on SIRT2, SIRT4 and SIRT7 are still scarce and SIRT6 are understudied in SCLC. Therefore, further exploration is needed to explore the potential mechanisms of SIRT6 in lung cancer and to identify novel antitumor agents.

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Authors' contributions

RFL and MZ conceived and designed the study and wrote and revised the manuscript. MZ and LW performed the initial literature search and prepared the manuscript. RFL and LW reviewed and revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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