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# The Role of SIRT7 and Targeted Therapeutics in Human Cancer

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## Abstract

SIRT7 is a $NAD^+$-dependent class III histone deacetylases (HDAC III), which predominantly localized in the nucleus where it regulates RNA polymerase I transcription by deacetylating H3K18. SIRT7 has been implicated in multiple cellular functions including hepatic lipid metabolism, mitochondrial homeostasis and adipogenesis by targeting several non-histone proteins including p53, GABP-β, FOXO3 and U3-55k. In addition, emerging evidences have implicated SIRT7 in cancer development and progression. SIRT7 is important for maintaining the fundamental properties of the cancer cell phenotype and high SIRT7 levels are associated with metastatic disease and poor prognosis. Inactivate SIRT7 are shown to decrease cancer proliferation, metastasis and increase chemosensitivity in multiple cancer types which make SIRT7 to be an attractive therapeutic target for human cancer. In this review, we summarized recent advances in the roles of SIRT7 and new discoveries of targeting SIRT7 in human cancer.

**Keywords:** SIRT7, Histone deacetylase, Cancer, Targeted therapy

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## Introduction

SIRT7 is an $NAD^+$-dependent deacetylase that belongs to the human mammalian sirtuin family which is broadly expressed in human organs and cells (1-4). SIRT7 is primarily localized in the nucleolus where it recruited by specific transcription factors (e.g. ETS-like transcription factor 4 (ELK4) and Myc) to regulate RNA polymerase I transcription by deacetylation of H3K18 (5, 6). SIRT7 has been implicated in multiple cellular functions including genomic integrity (7), hepatic lipid metabolism (2), mitochondrial homeostasis(8) and adipogenesis (9) by targeting several non-histone proteins including p53 (10), GABP-β (8), FOXO3 (11) and U3-55k (12). H3K18 deacetylation by SIRT7 is important for maintaining the fundamental properties of the cancer cell phenotype (13). In prostate cancer cells, SIRT7 cooperates with SIRT1 to suppress E-cadherin regulatory genes to promotes Epithelial-Mesenchymal Transition (EMT) and high SIRT7 levels are associated with metastatic disease and poor prognosis (13). In liver cancer, SIRT7 expression is also upregulated in a large cohort of hepatocellular carcinoma patients and we have shown that elevated SIRT7 expression is associated with chemosensitivity by regulating TP53 activity (14). Inactivate SIRT7 are shown to decrease cancer proliferation (15), metastasis (13) and increase chemosensitivity (16) in multiple cancer types. All those resulted indicated that SIRT7 could serve as an attractive therapeutic target for treatment of human cancer. We thus reviewed recent advances in the role of SIRT7 and new discoveries of targeting SIRT7 in human cancer.

## Cellular localization, function and regulation of SIRT7

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The Sir2 protein family, also known as Sirtuins, are $NAD^+$-dependent deacetylases or ADP-ribosyl transferases, which is a family of highly conserved silencing regulatory proteins that regulate epigenetically related genes (17). Sirtuins family have seven members (SIRT1-7) that share a core structural domain (HDAC structural domain) (18, 19), of which SIRT7 is localized in the nucleolus and interacts with the rDNA transcription upstream binding factor UBF and the RNA polymerase (Pol I) subunit PAF53 (polymerase-associated factor 53) to promote Pol I binding to rDNA and activate transcription of rRNA genes (rDNA), the rate-limiting step in ribosome biosynthesis (20-22). SIRT7 encodes a 400 amino acid protein with lower enzymatic activity than SIRT1 and SIRT6, which are also localized in the nucleus (23). One study reported that SIRT7 was detected in the cytoplasm in primary human fibroblasts by immunocytochemical assessment, which provides new insights into nucleolus independent multi functions of SIRT7 (24). The expression level of SIRT7 was variable in different organs and tissues, with high expression in metabolically active organs such as spleen and liver, and low expression in organs such as heart (25).

The organism modifies histones and regulates gene stability and integrity mainly through four modalities: acetylation, methylation, phosphorylation and ubiquitination, which are associated with epigenetic mechanisms and highlight the role of chromatin structural modifications in rRNA gene activity (26, 27). Histones are essential components of chromatin and are associated with transcriptional regulation of genes. Histone hyperacetylation promotes transcriptional activation of genes while

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hypoacetylation inhibits transcription (28). SIRT7 regulates Pol I activity, low SIRT7 expression leads to down-regulation of rDNA transcription and inhibition of cell proliferation (29). Of note, nucleus localization of SIRT7 requires binding to nascent pre-rRNA(30). When the organism undergoes oxidative stress, SIRT7 is released from the nucleolus to the nucleoplasm lead to increased acetylation of PAF53 and U3-55k, resulting in reduced processing and synthesis of pre-rRNA, which causes inhibition of PoI I transcription and ribosome synthesis (12, 30). SIRT7 is known to regulate Pol I and Pol III (8) transcription and SIRT7 knockdown preferentially inhibits protein synthesis rather than rDNA transcription and triggers a decrease in tRNA (31). Interestingly, although both Ras and Akt pathways are capable of increasing rRNA biosynthesis, but under *in vivo* conditions, SIRT7 suppresses the activation of both enzymes (10). SIRT7 also interacts with TFIIIC2 and mTOR which responsible for tRNA transcription and protein synthesis to regulate ribosome and protein biosynthesis and functions (31, 32).

SIRT7 is able to target a variety of non-histone substrates, including p53, GABP-β, DDX21, FOXO3 and U3-55k, to regulate apoptosis, ribosome synthesis and mitochondrial function, and maintain genomic stability (10, 33-35). Interestingly, Functional proteomics suggests that the deacetylase activity of SIRT7 might not important for its interaction with target proteins (36). Nevertheless, SIRT7 is involved in a variety of cellular activities, mediates multiple biological processes through targeting, influences cell proliferation and cancer progression (37), and is a key factor in regulating metabolic transcription (38) and cellular homeostasis (21). SIRT7

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inhibits the transcriptional activity of transcription factors HIF1α and HIF2α in a non-deacetyltransferase-dependent manner and is involved in cellular energy metabolism and oxidative stress (39). In addition, SIRT7 is critical in regulating hepatic lipid metabolism (2) and cellular lifespan (40). The nuclear orphan receptor TAK1/TR4 plays an important role in regulating lipid homeostasis, and SIRT7 activates its target genes by inhibiting TR4 ubiquitination and degradation, which is beneficial for liver accumulated lipids (2, 41). High expression of SIRT7 reverses aging and improves regeneration of hematopoietic stem cells (42, 43). It is worth noting that, in contrast to SIRT proteins that manipulate the lifespan of lower eukaryotes, lifespan in normal human cells is regulated by much more complex networks (23).

SIRT7 is regulated by transcription factors as well as post-translational modifications of itself (33) . The upstream factor X-box binding protein 1 (XBP1) increases SIRT7 levels, while histone deacetylase 3 (HDAC3) and various microRNAs negatively regulate SIRT7 expression. SIRT7 is phosphorylated by the CDK1-CyclinB pathway and AMPK during mitosis and energy stress and the latter promoting SIRT7 degradation(29, 33, 44).

## Sirt7 in Genome Stability

Genome stability and integrity are affected by oxidative stress and genotoxic agents, which can easily induce DNA damage (45). Cellular senescence and genomic stability are closely related, and genomic instability in rDNA repeats ultimately leads

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to cellular aging. Sirtuins are able to inhibit senescence by maintaining genomic integrity and homeostasis and repairing DNA damage under stressful conditions (46, 47). SIRT7 regulates genomic stability by participating in transcriptional regulation, DNA replication and damage repair responses (48). H3K18Ac is associated with genome-wide transcriptional regulation and is directly involved in the DNA damage repair response (7). PARP -dependent SIRT7 mediates H3K12 desuccinylation (49) and H3K18 deacetylation promotes efficient NHEJ repair, thereby regulating the recruitment of DNA damage response factor 53BP1 (p53 binding protein 1) at DSBs and its binding to chromatin, while SIRT7 depletion leads to blocked DNA double-strand break (DSB) repair (7). Homologous recombination (HR) and classical non-homologous end joining (C-NHEJ) are the main pathways for DSB repair, and end resection mismatches lead to chromosomal ectopia, which results in oncogenic transformation (50, 51).

Genomic instability due to excessive DNA damage increases the susceptibility of the body to cancer, and normal cells rely on multiple pathways to repair DNA damage, while defects in DNA repair pathways in cancer cells promote the development of their aggressive phenotype (52, 53). The DNA damage response (DDR) is tightly regulated and severe damage will activate the apoptotic pathway. In addition, cell cycle arrest and senescence are also part of the DNA damage response, and the above pathways are mediated by the non-histone substrate p53 of SIRT7, which inhibits cancer cell proliferation and metastasis (54). SIRT7 reduces p53 accumulation to mitigate DNA damage and maintain genomic stability (55). Studies have also shown

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that the activated tumor suppressor p53 regulates apoptosis or induces cell cycle arrest and can respond to external stimuli by affecting specific gene expression (56).

SIRT7 induces inactivation of ataxia-telangiectasia mutated (ATM) deacetylation both *in vitro* and *in vivo*, SIRT7 depletion leads to sustained activation of ATM and inhibition of DNA damage repair and cell survival (57). SIRT7 depletion was also associated with accelerated senescence and multi-organ dysfunction (8, 10, 58). *In vitro* experiments showed that SIRT7 knockdown not only significantly reduces the proliferative of HT1080 cells and increases the number of senescence markers, but also severely inhibited adenovirus E1A oncoprotein-dependent H3K18 deacetylation, indicating that SIRT7 deficiency increases the susceptibility of cells to DNA damage caused by external stimuli and influences on carcinogenic transformation(5, 7, 59). In consistent with this, SIRT7 knockout mice shows higher frequency of mutation and embryonic lethal phenotype (46).

## Sirt7 in cancer

Elevated SIRT7 levels are observed in numeral cancer types including human hepatocellular carcinoma (14), cholangiocarcinoma (60), colorectal cancer (61), ovarian cancer(62), cervical cancer (63), breast cancer(64) and non-small cell lung cancer (65), which provides a potential basis for exploring the cancer-promoting function of SIRT7. A growing number of studies also suggest that high SIRT7 expression associate with tumor aggressiveness as lower levels of overall histone modifications, including H3K18, predict a more aggressive cancer phenotype,

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increasing the risk of recurrence and reducing survival in cancer patients (61, 66, 67). SIRT7 also regulate the metastatic phenotype in epithelial and mesenchymal tumors by promoting EMT which (13). By inducing H3K18 deacetylation, SIRT7 inhibits the transcription of oncogene-related target genes and contributes to transformation phenotype of cancer cells and enhances tumorigenic capacity (5). SIRT7 also inhibit miR-34a expression to promote gastric cancer development by catalyzing tumor suppressor genes p53 deacetylation and inhibits apoptosis (10, 68).

The oncogenic potential of SIRT7 has been mainly attributed to it function of inducing H3K18 deacetylation to regulate transcription of specific genes, in particular, oncogenes (5). SIRT7 directly interacts with the ELK4 to forma complex that induces H3K18ac deacetylation (7, 69). In pancreatic cancer cells, SIRT7 O-GlcNAcylation promotes H3K18 deacetylation and oncogenic transformation by stabilizing SIRT7 protein (70). SIRT7 is also associated with cancer risk. SIRT7 binds to DBC1 to inhibit SIRT1 transcription and increases SIRT1 interaction with Akt and p70S6K1 thereby promoting their phosphorylation and increasing the risk of thyroid cancer (71). In addition, SIRT7 significantly promoted prostate cancer cell proliferation, metastasis and autophagy by indirectly inhibiting AR signaling pathway through reducing SMAD4 protein levels, SIRT7 depletion reduces metastasis of cancer cells both *in vivo* and *in vitro* (15). We and others report that the expression level of SIRT7 in liver is higher than that in normal tissues, and it correlates with cancer progression and poor clinic outcomes(14, 16). Inactive SIRT7 sensitize liver cancer cells to chemodrugs including doxorubicin and sorafenib by alternate p53 dependent NOXA

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expression (14). All those data suggesting that SIRT7 would be served as a biomarker in disease progression and drug sensitivity in human liver cancer (72).

Ubiquitin specific protease 39 (USP39) is associated with gene transcription, and SIRT7 deacetylation of USP39 inhibits hepatocellular carcinoma cell proliferation and tumor formation (73). Moreover, the transcriptional response element C/EBP recruits HDAC3 to regulate SIRT7 transcription, and both play a synergistic role in hepatocellular carcinoma by occupying the upstream promoter region of SIRT7 and suppressing SIRT7 expression (74). Ras pathway is closely associated with lung cancer development. Ras-ERK1/2 activation promotes lung cancer phenotypic transformation by upregulating MDM2 to degrade GCN5 and thereby decreasing the acetylation level of H3K18, while endogenous Myc is a key factor in Ras-driven lung cancer cell survival and proliferation (75, 76). In the presence of SIRT7 inactivation, Myc induces apoptosis in cancer cells via endoplasmic reticulum stress (ER stress) (77), suggesting that Myc, which is deprived of SIRT7 regulation, may act as a suppressor of precancerous cells in the early stages of carcinogenesis(6). Conversely, SIRT7 suppresses ER stress in a Myc-dependent manner and maintains tumor cell survival and proliferation (6). The contradictory results suggest that the effect of Myc on cancer cells may be two-sided in relation to cancer stage or cell type (32). SIRT7 expression levels in bladder cancer show different trends. Low SIRT7 expression promotes the transformation of bladder cancer cells to a more aggressive phenotype and EMT, resulting in lower overall survival in bladder cancer patients (78). Interestingly, two studies showed opposite results, while one study shows that SIRT7

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overexpression promotes an aggressive phenotype and focal metastasis in colorectal cancer and facilitates oncogenic transformation(61), but the other study indicates that SIRT7 acts as a cancer inhibitor to maintains intestinal homeostasis and genetic stability, and that deficiency leads to impaired DNA repair and increases the malignancy of colorectal cancer (43).

## Targeting Sirt7 in human cancer

Inactive SIRT7 have aroused great interests in treatment of human cancer and emerging evidences showed attractive effects (32). In breast cancer, AMPK coordinates with GSK3β to ensure the stability of SIRT7 to inhibit AKT activity, combination of doxorubicin and trametinib enhances GSK3β activity, which in turn phosphorylates SIRT7 to reduce its ubiquitinated degradation and block oncogenic signaling (79). In addition, it has been elucidated that IRF5 and PD1 in the breast cancer lumen are positively correlated with high SIRT7 expression, and both serve as markers suggesting that SIRT7 increases M1 macrophage infiltration and causes T-cell failure (80). The PD1/PDL1 axis plays an essential role in tumor escape as an immunosuppressive molecule (81). In liver cancer, it has been shown that interferon gamma, myocyte enhancer factor 2D (MEF2D) increases PD-L1 expression on the surface of hepatocellular carcinoma cells, and SIRT7 deacetylated MEF2D thereby decreasing PD-L1 expression as well as enhancing anti-tumor immunity, suggesting that SIRT7 not only promotes hepatocellular carcinoma proliferation but also has potential roles in regulating immunotherapeutic efficacy (82).

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Studies also show that 5-FU treatment enhances interaction between Tat-binding protein 1 (TBP1) and SIRT7 which in turn promotes SIRT7 degradation, resulting in enhances radiosensitivity of colorectal cancer cells (83). The levels of the epithelial markers E-cadherin and β-catenin were upregulated with the introduction of SIRT7 knockdown or ERK inhibitor PD98059, which inhibits cancer cell migration and invasion(61). SIRT7 deficiency activates transforming growth factor beta (TGF-β) signaling to inhibit SMAD4 degradation and enhance EMT, which results in increasing of breast cancer cell metastasis and chemoresistance, while resveratrol directly activates SIRT7 to deacetylate SMAD4 to exert oncogenic effects (84). HDAC8 is a class I HDAC, HDAC8 cooperates with SMAD3/4 to inhibit SIRT7 transcription, and HDAC inhibitor blocks breast cancer lung metastasis and attenuates TGF-β-induced paclitaxel resistance (85). In addition, combination of nortriptyline (NCTD) and chemotherapeutic agent paclitaxel in prostate cancer can effectively inhibit the proliferation and induce apoptosis by regulating SIRT7 expression (86). It is reported that low expression of SIRT7 increases cellular sensitivity to the DNA damaging agent adriamycin, and accelerates the production of senescence markers (24, 55). In addition, p53 regulates the expression of miR-125a-5p, miR-125b(87) and miR-526b (88), endogenous repressors of SIRT7. MicroRNAs operate as tumor suppressors or prognostic factors in hepatocellular carcinoma and cholangiocarcinoma carcinogenesis by inhibiting the oncogenic activity of SIRT7, and their ectopic expression leads to retarded growth of cancer cells and inhibits focal metastasis (60, 88). MiR-3666 and Hsa-miR-125b target SIRT7 to inhibit cancer cell growth and

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metastasis in breast and bladder cancer (89, 90). When miRNA activity is inhibited, it leads to overactivation of SIRT7 and accelerates the oncogenic transformation process. Activation of SIRT7 induces autophagy against apoptosis, reduces the killing effect of the antimetabolite gemcitabine on non-small cell lung cancer cells, and induces cellular drug resistance (91).

By using compounds screening, Kim et al developed compounds reduce the deacetylase activity of SIRT7 in uterine sarcoma cells *in vitro* in a dose-dependent manner without damaging normal cells by enhancing acetylation and stability of p53 (92). A previous study in our laboratory found that the lead compounds 2800Z and 40569Z acted as specific inhibitors of SIRT7 deacetylase activity, blocking proliferation, metastasis and invasion of hepatocellular carcinoma cells *in vitro* and *in vivo* (14). Our results also show that the combination of the above two compounds with sorafenib can promote apoptosis through the SIRT7/p53/NOXA axis, improve sensitivity to sorafenib and reduce drug resistance in hepatocellular carcinoma patients compared to single dosing, which is consistent with the results obtained by knocking down SIRT7 (14, 16). From this it is clear that exploring SIRT7 inhibitors alone or in combination with first-line anti-cancer drugs holds great promise.

## Perspective and Conclusion

SIRT7 is the only member of Sirtuins family selectively deacetylates H3K18 and promotes cancer cell proliferation, metastasis and associates with poor prognosis in various type of cancer. SIRT7 is also involved in maintaining genomic stability which

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protects from dysfunction of DNA repair and tumorigenesis. Inactivate SIRT7 has been shown to reduce cancer proliferation, metastasis and increase chemotherapy as well as immunotherapy sensitivities in a variety of human cancer types. All those data clearly support that targeting SIRT7 potentiates mechanism-based translational therapeutic strategy for human cancer management. Indeed, small molecule inhibitors such as 2800Z and 40569Z showed beneficial effects in the treatment of human liver cancer. Further works focus on optimization of potency and selectivity, anti-cancer effects on other types of cancer and pharmacological implications of these compounds would be of interest. Moreover, future works focus on determine crystal structure of SIRT7 would largely stimulate the development of specific SIRT7 inhibitors.

## Conflict of interest

The authors declare no potential conflicts of interest.

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