

Molecular Pathways: Emerging Roles of Mammalian Sirtuin SIRT7 in Cancer

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Abstract

SIRT7 belongs to the Sirtuin family of NAD-dependent enzymes, the members of which play diverse roles in aging, metabolism, and disease biology. Increased SIRT7 expression is observed in human cancers and growing evidence suggests important SIRT7 functions in fundamental cellular programs with an impact on oncogenic transformation and tumor biology. SIRT7 associates with chromatin, where it catalyzes selective deacetylation of lysine 18 on histone H3 (H3K18), an emerging epigenetic biomarker of aggressive tumors and poor clinical outcome in patients with cancer. Through H3K18 deacetylation at specific promoters, SIRT7 controls a tumor-suppressive gene expression program that stabilizes the transformed state of cancer cells. SIRT7 also orchestrates several molecular processes, including rRNA and tRNA synthesis, which ultimately promote the increased ribosome biogenesis necessary for tumor cell growth and proliferation. Remarkably, inactivation of SIRT7 can reverse the transformed phenotype of cancer cells and reduce their tumorigenicity *in vivo*. These findings place SIRT7 at the crossroads of chromatin signaling, metabolic, and tumor-regulatory pathways. Thus, SIRT7 is a promising pharmacologic target for epigenetic cancer therapy. The development of SIRT7 modulators may allow new therapeutic strategies that control tumor progression by reprogramming the chromatin landscape and biosynthetic machinery of cancer cells. *Clin Cancer Res*; 20(7); 1741–6. ©2014 AACR.

Background

The founding member of the Sirtuin family of enzymes, *Saccharomyces cerevisiae* Sir2p, is a chromatin silencing factor that prevents genomic instability and cellular senescence by catalyzing the lysine deacetylation of histones (1, 2). Although some Sirtuins have evolved alternative enzymatic activities (3, 4), much work has centered on Sirtuins as class III deacetylase enzymes (5). Sirtuins differ from class I and class II deacetylases in their catalytic mechanisms and pharmacologic sensitivities, and are uniquely dependent on NAD⁺, a molecule whose levels are intimately linked to cellular metabolism (1, 5). Not surprisingly, sirtuins are major players in molecular responses to metabolic stress and cellular homeostasis changes.

The seven mammalian Sirtuins, SIRT1–SIRT7, have distinct biologic functions, enzymatic activities, substrates, and expression patterns (6). SIRT7 is possibly the least understood mammalian sirtuin, but it has several features that suggest that its activity is important for human disease,

particularly cancer. First, SIRT7 is a lysine deacetylase that selectively removes a specific histone mark, acetylated H3K18 (H3K18Ac), depletion of which is associated with highly malignant cancers and poor patient prognosis (7). In addition, SIRT7 is enriched in nucleoli (8), subnuclear sites of ribosome assembly that are increased in size and number in aggressive tumors (9). SIRT7 has an impact on ribosome biogenesis through multiple mechanisms, and may thereby play a major role in supporting the high biosynthetic and metabolic demands of cancer cells. Through these and other functions, SIRT7 is a central coordinator of epigenetic and cellular homeostatic programs that support cancer progression.

Reprogramming tumor-suppressive gene expression by selective H3K18 deacetylation

Cancer cells exhibit epigenetic chromatin alterations in global levels of histone marks and at specific gene regulatory sequences. A study of the genome-wide patterns of 39 histone modifications found that H3K18Ac is one of 17 modifications that form a "back-bone module" that is found at 25% of human promoters and correlate with intermediate levels of gene expression (10). These modifications are proposed to function cooperatively to prepare chromatin for transcriptional activation. However, despite this apparent coregulation of many histone marks, clinicopathologic studies indicate that in multiple tumor tissues, depletion of H3K18Ac in particular is strongly correlated with cancer disease severity. Indeed, in diverse adenocarcinomas (including prostate, lung, and kidney tumors), global hypoacetylation of H3K18 was prognostic of aggressive

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cancer phenotypes and poor patient survival (11–13). Decreased global H3K18Ac levels are also linked to epigenetic reprogramming during oncogenic transformation by viral oncoproteins such as adenoviral E1A (14, 15). Thus, H3K18 hypoacetylation is a potential biomarker for advanced disease in human cancer and changes in the genome-wide distribution of H3K18Ac are proposed to control epigenetic gene expression programs that drive cancer progression (14, 15).

While many lysine deacetylases are relatively promiscuous, SIRT7 stands out in having high selectivity for deacetylating H3K18Ac. SIRT7 is the only known H3K18Ac-specific deacetylase enzyme and plays an essential role in establishing the genome-wide landscape of H3K18Ac (7). SIRT7 deacetylates H3K18Ac at promoters of a network of genes with multiple links to tumor suppression (7). It is directed to a subset of these genes by interacting with the ELK4 transcription factor, which is implicated in prostate and other cancers (16–18). When SIRT7 was inactivated in fibrosarcoma, osteosarcoma, or prostate carcinoma cell lines, H3K18 hyperacetylation led to upregulation of the tumor-suppressive gene network and reversal of important hallmarks of oncogenic transformation, including anchorage independent growth, loss of contact inhibition, and growth factor-independent proliferation. Most strikingly, depletion of SIRT7 dramatically reduced (by more than 75%) the tumorigenicity of multiple cancer cell types (e.g., U251 glioblastoma and Hep3B hepatocellular carcinoma cells) in mouse xenograft assays *in vivo* (7, 19). Thus, SIRT7 plays a fundamental role in epigenetic maintenance of the neoplastic state of cancer cells.

Another major category of SIRT7 target genes consists of ribosomal protein genes, which are transcriptional targets of the oncoprotein MYC (Fig. 1A; refs. 7, 20). By opposing MYC-dependent expression of ribosomal proteins, SIRT7 plays an adaptive role in the Unfolded Protein Response (UPR) to suppress endoplasmic reticulum (ER) stress (20). In the liver, chronic ER stress in SIRT7-deficient mice leads to fatty liver disease. In cancer cells, SIRT7 prevents ER stress-induced apoptosis in a MYC-dependent manner (20). By transiently reducing protein synthesis rates during ER stress, the control of ribosomal protein gene transcription by SIRT7 might be an underlying mechanism that promotes cancer cell survival and tumor progression (21).

It is likely that SIRT7 also regulates other cancer-regulatory gene expression pathways. For instance, MYC coordinates a broad transcriptional program that influences cancer cell proliferation, survival, and metabolism, through many targets (22). SIRT7 might corepress certain MYC functions in such settings, with either tumor-suppressive or oncogenic effects. In addition, MYC is reported to either suppress or promote tumor cell migration and metastasis, depending on the cell type or stage of cancer progression (23–25). It will be important to sort out which of these MYC functions intersect functionally with SIRT7. Other *in vitro* evidence suggests that SIRT7 might directly regulate genes that control cancer cell adaptations to hypoxia through interactions with hypoxia inducible factors HIF-1a and HIF-2a (26).

Finally, SIRT7 is reported to inhibit signaling by the tumor suppressor p53 in mouse cardiomyocytes (Fig. 1C), although there is conflicting data on whether SIRT7 directly deacetylates p53 (7, 8, 27).

In summary, much evidence indicates that SIRT7 plays an important role in the maintenance of epigenetic patterns of H3K18 acetylation in cancer cells, which in turn drive gene expression programs that stabilize the transformed phenotypes of these cells. Future work should uncover additional pathways through which SIRT7 influences cancer cell epigenetics through histone deacetylation at chromatin or novel mechanisms.

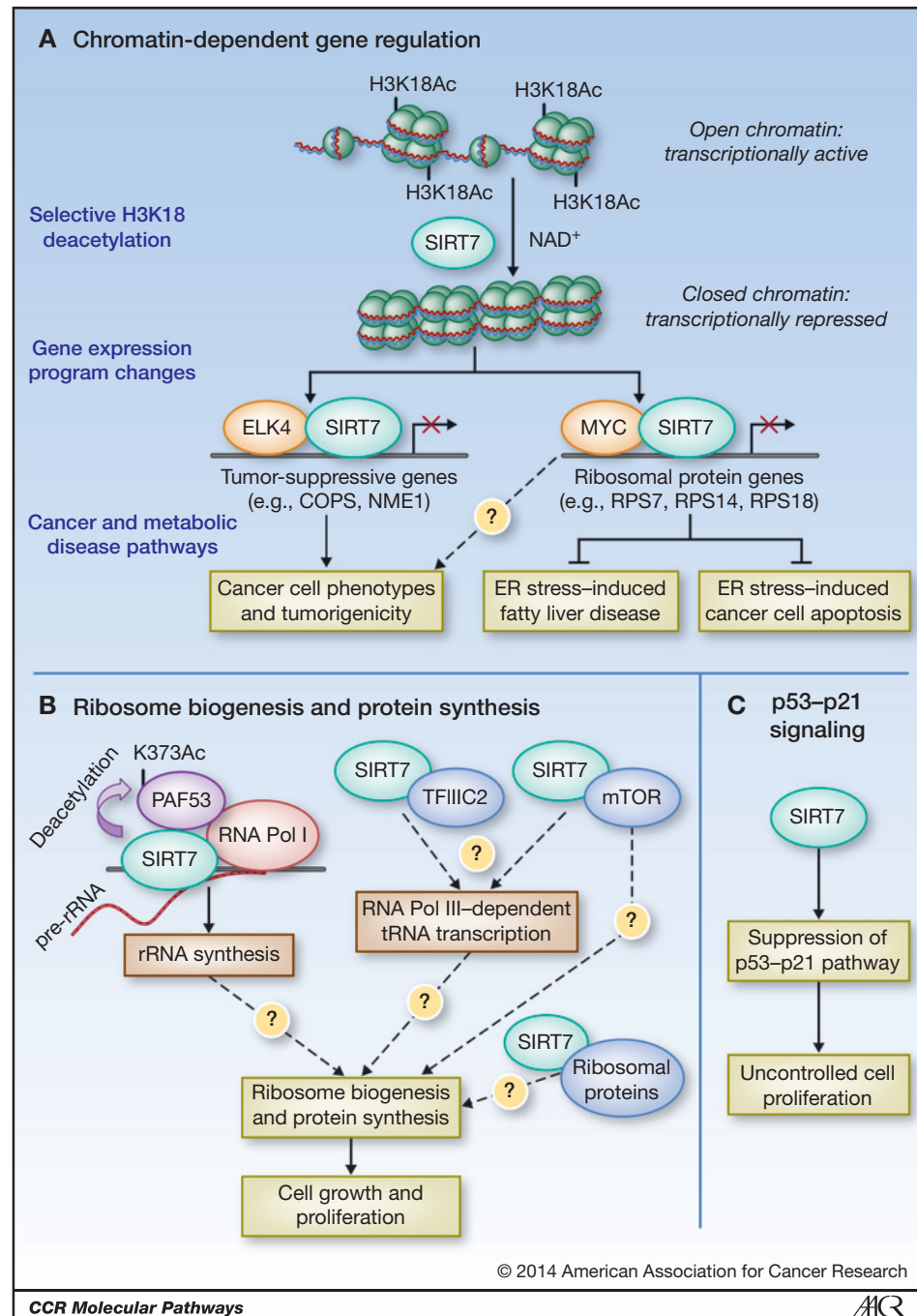
Nucleolar guardian of ribosome biogenesis and protein homeostasis

Nucleoli are factories where ribosomal RNA (rRNA) is expressed and assembled with ribosomal proteins into ribosomal complexes. Metabolically active tumor cells show dramatically increased nucleolar size and number, which support the increased protein synthesis requirements of these cells (9). Indeed, enhanced rRNA synthesis is now proposed to be an essential hallmark of cancer cells (28). Early studies showed that SIRT7 is enriched in nucleoli, where it associates with POLI and rDNA sequences (Fig. 1B; refs. 8, 29). This finding was intriguing, because yeast Sir2p also localizes to rDNA in nucleoli, and one of its central functions is to suppress rDNA transcription by histone deacetylation (1). It is surprising, however, that SIRT7 was found to activate, not repress, rDNA transcription (29). Moreover, reduced rRNA synthesis in SIRT7-depleted cancer cells was associated with decreased cell viability and proliferation (29). This observation suggested that increased SIRT7 activity in cancer cells might fuel tumor growth by promoting rRNA synthesis and ribosome biogenesis.

The effect of SIRT7 on rRNA synthesis depends on an intact SIRT7 catalytic domain, but the molecular substrate of SIRT7 in this context was not initially clear. Indeed, histone deacetylation by SIRT7 would have the opposite effect on rDNA transcription. Recent findings now reveal that SIRT7 can control transcription of rDNA through deacetylation of a new substrate, the PAF53 subunit of POLI, which facilitates recruitment of POLI to rDNA sequences (Fig. 1B; ref. 30). Additional protein interactions of SIRT7 with several nucleolar chromatin-remodeling complexes with rDNA regulatory activities (e.g., NoRC, B-WICH) might also affect rDNA transcription (31).

Recent studies provide direct evidence that SIRT7 is important for efficient protein translation and implicate additional molecular mechanisms (Fig. 1B). SIRT7-depleted cells have substantially reduced rates of protein synthesis and a functional network analysis of the SIRT7 interactome identified several SIRT7-enriched factors with tight links to ribosome dynamics and protein translation (32). For example, SIRT7 interacts with mTOR and the TFIIC2 transcription factor, which control POLIII-mediated synthesis of transfer RNA (tRNA). In addition, SIRT7 interacts with multiple ribosomal proteins, which might directly influence ribosome function. The effects of SIRT7 on alleviating

Figure 1. Molecular pathways of SIRT7 and their known or predicted effects on cancer cell biology. **A**, chromatin-dependent gene regulation: SIRT7 deacetylates H3K18 to promote formation of transcriptionally repressive chromatin at specific gene promoters. SIRT7 represses expression of an ELK4-dependent tumor-suppressive gene network, leading to stabilization of the transformed phenotype of cancer cells. SIRT7 also represses Myc-dependent ribosomal protein genes, which alleviates ER stress and prevents fatty liver disease. In cancer cells, SIRT7 opposes Myc function in ER stress-induced apoptosis, allowing cancer cell survival and proliferation. SIRT7 might also affect cancer cell phenotypes and tumorigenicity by regulating other functions of Myc in cancer cells. **B**, ribosome biogenesis and protein synthesis: SIRT7 is implicated in multiple pathways that ultimately promote ribosome biogenesis and increased protein translation. At rDNA, SIRT7 deacetylates the PAF53 subunit of RNA polymerase I to activate rRNA transcription, the rate-limiting step in ribosome biogenesis. SIRT7 also interacts with TFIIC2 and mTOR, factors that promote tRNA transcription and protein synthesis. In addition, SIRT7 interacts with ribosomal protein subunits, and might directly regulate ribosome function through such interactions. High levels of ribosome biogenesis fuel cancer cell proliferation and survival. **C**, p53-p21 signaling: SIRT7 is implicated in repressing the tumor-suppressive p53-p21 pathway, with potential effects on cancer cell proliferation and survival. The molecular mechanisms are still unclear but might involve effects on p53 acetylation or nucleolar dysfunction. Question marks indicate connections that are predicted but not yet demonstrated experimentally.



ER stress during the UPR, described above, may also contribute to promoting efficient protein translation. Indeed, a reduction in active polysomal ribosomes is characteristic of ER stress (33), and is observed in SIRT7-deficient cells (20).

Together, this body of work has identified SIRT7 as a global regulator of diverse aspects of ribosome biogenesis and protein translation. Reprogramming of cellular metabolism and biosynthetic machinery towards anabolic processes is crucial to fuel the unlimited cell growth and division of cancer cells (34). Increased ribosome biogenesis

and rates of protein synthesis are required for the elevated levels of cell proliferation in cancer and this likely constitutes one general paradigm through which SIRT7 has an impact on cancer biology (21).

Clinical-Translational Advances

SIRT7 modulation for epigenetic cancer therapy

Genome-wide loss of epigenetic stability is a common feature of diverse tumors and plays a significant role in cancer development (35), but unlike DNA mutations,

which are permanent, epigenetic changes are potentially reversible. Because of its effects on the chromatin landscape and malignant phenotypes of cancer cells, SIRT7 is a promising target for epigenetic cancer therapy. Moreover, elevated SIRT7 expression has been observed in multiple human cancer tissues, including prostate, hepatocellular, breast, thyroid, and other carcinomas (7, 19, 36, 37). Analysis of large hepatocellular carcinoma patient cohorts revealed that SIRT7 is overexpressed by >1.8 fold ($P < 0.0001$) in cancer tissues compared with normal controls (19), and in microarray analyses, relative SIRT7 expression increased, 2-, 3.5-, and 4.5-fold in tumors of increasing grade (G1–3), respectively, compared with premalignant samples ($P < 0.05$, 0.001, 0.001; ref. 19). These observations strongly suggest that upregulation of SIRT7 in cancer cells may contribute to the malignant phenotype of human patient tumors.

On the other hand, it will be important for future translational studies to determine whether pleiotropic and potentially cell type-specific functions of SIRT7 might influence overall cancer incidence and tumor progression in unexpected ways. For example, the impact of SIRT7 on the process of oncogenic transformation itself remains unclear. Indeed, in early stages of cancer initiation in premalignant cells, it is possible that SIRT7 might have tumor-suppressive effects. This could occur through its repression of oncogenic MYC-dependent genes (20) or other SIRT7 gene targets that have not yet been identified. The tools are now available to ask how SIRT7 activity influences both the efficiency of oncogenic transformation of primary human cells and the chromatin landscape of H3K18Ac and gene expression programs in these cells both before and during induction of cellular transformation.

We also speculate that SIRT7 might have differential effects depending on the particular genetic elements that underlie neoplastic transformation in specific tumors, and this can be modeled in preclinical studies using cellular transformation assays in primary human cells and mouse tumor models (38). For example, given its functional interplay with MYC-, ELK4-, and E1A-dependent epigenetic programs (7, 14, 20), SIRT7 activity might be particularly important for neoplastic transformation programs and tumors associated with these factors. Finally, the effects of SIRT7 on spontaneous tumor development in mice are not yet known. SIRT7-deficient mice have been reported to die from causes unrelated to cancer at 7 months of age (27), precluding analysis of long-term tumor incidence. However, a different SIRT7-mutant mouse strain does not show this premature lethality (20), and these mice should be studied for tumor development and survival.

SIRT7 activity and disease: a double-edged sword?

The possibility of SIRT7 inactivation as a pharmacologic strategy in cancer therapy is complicated by evidence that SIRT7 might have beneficial effects on human health. Knockout mice lacking SIRT7 develop degenerative pathologies associated with aging, such as kyphosis, loss of subcutaneous fat, and degenerative cardiac hypertrophy (27). Moreover, the increased ER stress in SIRT7-deficient mice

leads to fatty liver pathology, which in humans, predisposes to cirrhosis and hepatocellular carcinoma (20). ER stress is also implicated in other disease processes, from pancreatic beta cell failure and insulin resistance to neurodegeneration (39, 40). It will be important to determine whether SIRT7 activity influences the spontaneous or induced development of these or other pathologies in mice, and to ask whether SIRT7 levels or mutations are associated with metabolic or neurodegenerative disease in human patients. In addition, the transcriptional programs that are regulated by SIRT7 in the context of normal human physiology have not yet been examined systematically. An important goal for future work will be to carry out genomic studies of the chromatin landscape of SIRT7 binding in non-cancer cells and mammalian tissues, and the effects of SIRT7 activity on H3K18Ac patterns and gene expression. Finally, it might be possible to "dial down" SIRT7 activity pharmacologically to levels that might attenuate cancer progression, without being sufficient to induce the disease processes observed in mice completely lacking SIRT7. Thus, development of compounds that can modulate SIRT7 activity will be instrumental in examining these questions.

Targeting SIRT7: Translating insights from structure and biochemistry

Several features of SIRT7 suggest that chemical modulators of SIRT7 activity could be designed to have relatively high levels of biologic specificity. First, cross-reactivity of SIRT7 modulators with other mammalian sirtuins might be minimized by taking advantage of unique features of SIRT7's structure and enzymatic mechanism. The conserved catalytic domains of sirtuins are flanked by variable N- and C-terminal extensions. Within the conserved domain, SIRT7 is only approximately 40% similar to its closest mammalian family member SIRT6, and <30% similar to the others. In addition, the nonconserved N- and C-terminal regions have been shown in other sirtuins to influence catalytic activity and contain sequences that are bound by endogenous and chemical regulators (41–43). Development of compounds that target these unique regions of SIRT7 might be a promising strategy. Similarly, SIRT7 gene regulatory activity depends on interactions with specific binding partners (e.g., MYC, ELK4; refs. 7, 20), and such interactions might be selectively targeted pharmacologically to enable pathway-specific modulation of SIRT7 function. The identification of distinct substrates of SIRT7 also suggests the possibility of substrate-selective activity modulation, which has recently been demonstrated for SIRT1-activating compounds (STAC; refs. 44, 45).

Finally, there are indications that SIRT6 and SIRT7 are unusual among sirtuins in requiring activation by endogenous regulators for efficient catalytic activity in cells and such regulatory mechanisms might offer additional useful drug targets. This notion is supported by the observations that purified SIRT6 and SIRT7 proteins have relatively weak deacetylase activity on peptide substrates *in vitro*, despite the clear importance of their enzymatic activities for cellular and whole organism physiology (46). For SIRT6,

the efficiency of histone deacetylation can be stimulated approximately 35-fold by certain free fatty acids (FFA; ref. 47). The sensitivity of SIRT6 to FFA activation results from structural features of SIRT6 that may be shared with SIRT7 but not other mammalian sirtuins. For example, the low intrinsic activity of SIRT6 enzyme is proposed reflect an unusually "splayed" conformation that binds acetylated substrate poorly (46). Binding of FFAs to SIRT6 can induce a conformational change to a more enzymatically active structure (47). The unusual conformation of SIRT6 is partly due to its lack of a conserved helix bundle region that forms important structural contacts in most other sirtuins (46). Although the structure of SIRT7 has not yet been characterized, predictions based on sequence comparisons indicate that SIRT7 also lacks this domain (46). It remains to be shown whether SIRT7 requires activation by FFAs, but if so, this regulation would provide a link of SIRT7 activity to metabolic conditions that might be targeted through pharmacologic or dietary regimens. Structural and biochemical studies of SIRT7 in this context should provide invaluable insights into how the binding by FFAs might be exploited for therapeutic strategies.

Perspective

Mammalian sirtuins have been the subject of much excitement as potential therapeutic targets for treating aging-related, metabolic, and neurodegenerative disease. A large effort has focused on STACs, which have numerous beneficial health effects in mice. The selectivity of STACs for SIRT1 highlights the structural differences among sirtuins and the possibility of sirtuin-selective targeting (44, 48, 49). Several chemically diverse small-molecule inhibitors of Sirtuins also have therapeutic potential and varying degrees of specificity (48–50). In contrast to other Sirtuins, SIRT7 has not been amenable to screens for small-molecule mod-

ulators, because it does not efficiently deacetylate the substrates used in such screens and its physiologic substrates were only recently discovered (7, 30). Thus, a major barrier in the field has finally been overcome and it should now be possible to design strategies to screen for SIRT7-specific modulating compounds. Thus, these are early days for conceptualizing the translation of SIRT7 biology into clinical applications. Current findings suggest that pharmacologic inhibition of SIRT7 might allow for simultaneous attack on both the epigenetic programming and metabolic machinery of cancer cells that support tumor progression. However, deeper understanding of SIRT7 biology at the molecular and physiologic levels will be essential for elucidating the potential therapeutic benefits and detrimental side effects of SIRT7 inactivation.

Disclosure of Potential Conflicts of Interest

K.F. Chua reports receiving a commercial research grant from Daiichi Sankyo Company. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: S. Paredes, L. Villanova
Writing, review, and/or revision of the manuscript: S. Paredes, L. Villanova, K.F. Chua

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