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RESEARCH HIGHLIGHT

The controversial role of Sirtuins in tumorigenesis – SIRT7 joins the debate

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Sirtuins are NAD-dependent deacetylases that are conserved from yeast to mammals. A new report sheds light on the function of SIRT7, the least understood member of the Sirtuin family by identifying its locus-specific H3K18 deacetylase activity, and linking it to maintenance of cellular transformation in malignancies.

Sirtuins are NAD-dependent deacetylases that have been linked to longevity and genomic stability in yeast [1]. Sirtuins deacetylate histones and non-histone proteins, and are highly conserved from lower organisms to mammals. Seven Sirtuin family members are recognized (SIRT1-7). Sirtuins regulate numerous cellular processes including aging, DNA repair, cell cycle, metabolism, and survival under stress conditions [1]. Although there has been considerable interest in the role of Sirtuins in tumorigenesis [1], studies have provided contradictory results with both tumor promoter and tumor suppressor roles reported [2]. It appears likely that the different effects are related to the specific tissue or tumor type studied, and the models and assay systems used.

Amongst the seven Sirtuins, the function of SIRT7 is the least well understood so far. SIRT7 lacks conserved amino acids within the catalytic domain associated with deacetylase activity, and although suggested to deacetylate the tumor suppressor p53 (Figure 1) [3], has generally been considered to have weak or undetectable deacetylase activity [4, 5]. There is evidence that SIRT7 can mediate protein interactions regulating the RNA Pol I machinery [6]. SIRT7 is most prominently expressed in hematopoietic cells, especially myeloid progenitor cells [4], and is localized on chromosome 17q25.3, a region frequently altered in acute leukemia and lymphomas [4]. In a new report in *Nature*, Barber *et al.* [7] conclusively demonstrate that SIRT7 is an NAD-dependent deacetylase with high selectivity for the H3K18 acetylation (Ac) mark that functions to maintain the transformed phenotype of cancer cells.

The studies of Barber *et al.* show that SIRT7 is almost exclusively localized to chromatin, and that it deacetylates peptides containing H3K18Ac, without activity on 12 other histone acetylation sites. SIRT7 deacetylase activity was abolished by substitution of a conserved histidine residue in the predicted catalytic domain, or by the Sirtuin inhibitor nicotinamide. Conversely, SIRT7 overexpression induced depletion of H3K18Ac in cells with negligible changes in other acetylation marks. Thus, SIRT7 is the first deacetylase with selectivity for the H3K18Ac modification. Low levels of H3K18Ac were previously shown to predict a higher risk of prostate cancer recurrence, and poor prognosis in lung, kidney and pancreatic cancers [8]. Using chromatin immunoprecipitation sequencing to study the genome-wide localization of SIRT7, Barber *et al.* found that SIRT7 is enriched at promoters for a select set of genes, including the ribosomal protein genes *RPS20*, *RPS7*, and *RPS14*, and the tumor suppressor genes, *NME1* and *COPS2*. SIRT7 depletion increased H3K18Ac at these gene promoters, and increased transcription of target genes. Although SIRT7 lacks a sequence-specific DNA binding motif, it is able to form a complex at the promoters of target genes by associating with the ETS protein ELK4. ELK4-mediated stabilization appears to be particularly important for gene repression in the setting of elevated SIRT7 expression, as is seen in cancer. Consistent with these results, lower H3K18Ac levels are associated with overexpression of ELK4 and SIRT7 in prostate cancer [9]. Finally, this study shows that SIRT7 is necessary for maintenance of abnormal growth properties characteristic of cancer cells, including anchorage-independent growth and growth in low serum conditions, and for tumor formation in xenograft assays. Importantly, in the setting of adenoviral E1A oncoprotein-induced transforma-

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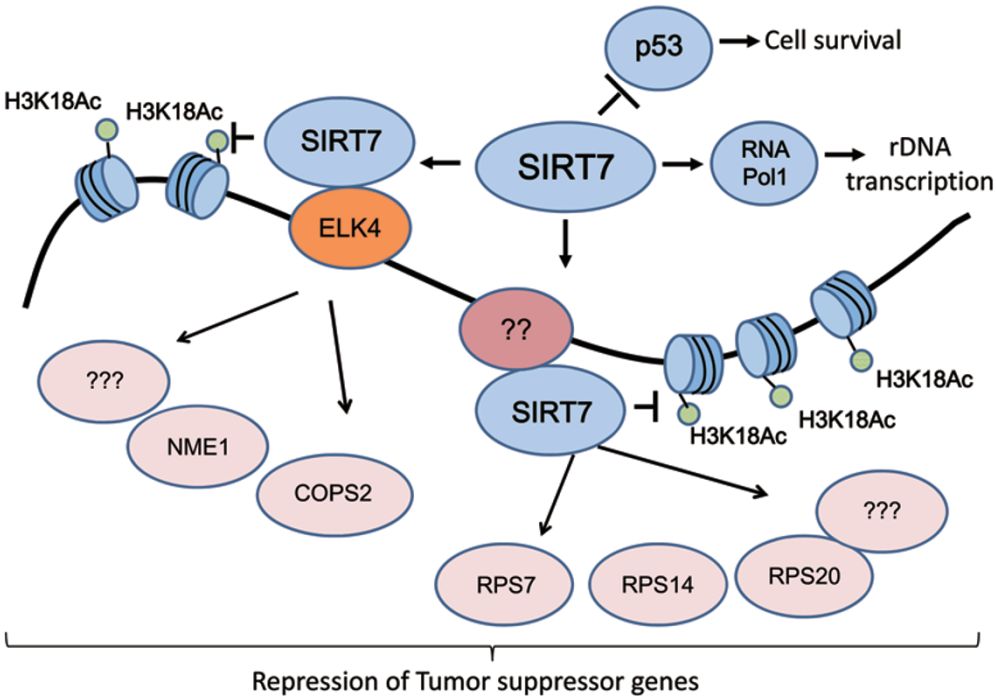

Figure 1 SIRT7 suppresses expression of tumor suppressor genes by locus-specific deacetylation of H3K18Ac at promoter regions. SIRT7 complexes with ELK4 to deacetylate H3K18 at the promoters of a select set of tumor suppressor genes, such as *NME1*, *COPS2*, thus repressing target gene expression. SIRT7 may also complex with other as yet undetermined transcriptional proteins (shown as "??") to deacetylate histone H3K18Ac at promoters of the ribosomal protein gene, *RPS7*, *RPS14*, *RPS20*, which can function as tumor suppressor genes in hematopoietic malignancy, and repress their gene expression. Previously described effects of SIRT7 are also represented. SIRT7 can connect chromatin remodeling complexes with the RNA Pol I machinery required for rDNA driving ribosome biogenesis in dividing cells [6]. SIRT7 is also reported to deacetylate p53, and promote cell survival [3], although this effect needs further confirmation.

tion, associated with H3K18 deacetylation, enhanced cell cycle entry and escape from contact inhibition, SIRT7 knockdown restores H3K18Ac and abolishes the transformed phenotype. SIRT7 overexpression and SIRT7 gene amplification are seen in several tumors, and these results support the importance of selective H3K18Ac deacetylation by SIRT7 in maintaining transformation of cancer cells.

The results of this study also raise several questions, which will be avenues for additional investigation in future. Since H3K18Ac appears to be a general mark of active transcription [10], it will be of interest to determine the interactions between H3K18Ac deacetylation by SIRT7 and by HDACs in epigenetic regulation. ELK4 knockdown leads to elevated H3K18Ac levels at some locations, such as the *NME1* and *COPS2* promoters, but not at others, such as the *RPS20* promoter. Loss of function mutations in ribosomal protein genes have been linked to hematopoietic malignancies [11], and it will be of interest to identify transcriptional regulatory proteins other than ELK4 that can target SIRT7 to specific promoters for H3K18 deacetylation. The current studies were carried out using cell lines, and it will be important to extend these studies to understand the role of SIRT7 in transformation of primary tumors, and in the setting of expression of oncogenes other than the adenovirus E1A protein. In contrast to its role in maintaining tumor transformation, overexpression of SIRT7 did not lead to oncogenic transformation of immortalized mouse or human fibroblasts, suggesting that SIRT7 may not initiate cellular transformation by itself. However, studies evaluating the role of SIRT7 in tumor initiation in cell lines and fibroblasts need to be extended to *in vivo* evaluation of primary tissues. Finally, development of mice bearing SIRT7 mutant genes will be very helpful in defining its role in epigenetic regulation, stress response, and tumor susceptibility, in addition to tumor maintenance as shown here.

In summary, the studies of Barber *et al.* represent a major advance in our understanding of the role of Sirtuins in cancer, by demonstrating a novel activity of SIRT7 in deacetylating H3K18Ac at promoter regions of specific tumor suppressor genes, inhibiting transcription of target genes, and maintaining the malignant phenotype of tumor cells. This new work supports explora-

tion of a potential therapeutic role for restoration of H3K18Ac by targeting SIRT7. The role of Sirtuins in cancer has been the subject of controversy, because of its complexity and context dependence. Together with other recent Sirtuin research [12], the present work supports an important role for Sirtuins in maintenance of tumorigenic properties of cancer cells and on the front line of cancer research.

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