Sirt1 is a type III histone deacetylase implicated in a wide range of physiological and pathophysiological roles. Acting though a myriad of non-histone substrates, Sirt1 modulates transcriptional regulation of energy metabolism and stress response, with important consequences on cell survival and a myriad of human pathologies. Sirt1 has an apparent (albeit context- and tissue type-dependent) role in tumorigenesis, acting particularly through its deacetylation of tumor suppressor gene products such as p53 and Rb. Recent works have now revealed that cortactin, an F-actin binding protein with established roles in protrusive actin dynamics, is a Sirt1 substrate. Cortactin could be acetylated by the acetyltransferase p300, and its deacetylation by Sirt1, either directly or indirectly, retards cell migration. In conjunction with deacetylation of other oncogenic targets, Sirt1’s modulation of cell migration and invasion may be an important additional aspect of its tumorigenic activity.

Introduction

The sirtuin family proteins are nicotinamide adenine dinucleotide (NAD)-dependent class III histone deacetylases conserved in eukaryotes.\(^1\)\(^2\) The mammalian genome harbors seven sirtuin paralogues, and Sirt1 has the highest homology to Saccharomyces cerevisiae Sir2, a gene famous for its putative role in lifespan extension in several model organisms.\(^3\) Sirt1 has been linked to multiple physiological functions and pathological roles. It deacetylates histones, but it also has a wide range of non-histone substrates. Sirt1’s activity on peroxisome proliferator-activated receptor-γ (PPARγ)\(^4\) and its transcriptional co-activator PPARγ coactivator-1α (PGC-1α)\(^5\)\(^6\) regulates metabolic homeostasis in energy intensive tissues, providing adaptive transcriptional changes to nutrient availability and environmental stimuli. Sirt1’s deacetylation of members of the forkhead box class O (FOXO) family\(^7\) and nuclear factor κB (NFκB)\(^8\) regulates key aspects of cellular stress response and survival.

Another prominent activity of Sirt1 is one associated with cancer. Sirt1 may either be oncogenic or tumor-suppressive, depending on the type of malignancy and the context of analysis.\(^9\)\(^10\) Earlier studies have shown that Sirt1 deacetylates Lys382 of p53, thereby repressing its transcriptional activity and attenuating p53-mediated cell cycle arrest and apoptosis.\(^11\) Sirt1 expression is in fact negatively regulated by several transcription factors with tumor suppressor activities, including p53, Hypermethylated in cancer 1 (Hic1),\(^12\) and Deleted in breast cancer 1 (Dbc1).\(^13\)\(^14\) Human cancers manifesting an inactivation of any of these tumor suppressor genes could therefore enhance Sirt1 expression. Elevated Sirt1 expression is indeed found in several human cancers,\(^10\) and Sirt1 silencing could often sensitize cells to apoptosis.\(^15\)\(^16\) Sirt1 also binds to the cell cycle regulator E2F1 and could inhibit its apoptotic activity during DNA damage response.\(^17\) Furthermore, Sirt1 activity may enhance cancer cell resistance to chemotherapy via its induction of the multidrug resistance gene Mdr1.\(^18\)

On the other hand, emerging evidence also suggests that Sirt1 could be tumor suppressive. Sirt1’s deacetylation of lys310 of the RelA/p65 subunit of NFκB could sensitized cells to tumor necrosis factor...
α (TNFα)-induced apoptosis, and its deacetylation by histone deacetylase 6 (HDAC6) influences actin-dependent cell motility. As discussed below, Zhang and colleagues have now showed that cortactin could also be deacetylated by Sirt1, and this hypoacetylation of cortactin is associated with an increase in cell motility.

**Sirt1 Interacts with and Deacetylates Cortactin**

The deacetylation reaction catalyzed by sirtuins is coupled to cleavage of NAD into 1-O-acetyl-ADP ribose and nicotinamide, and the latter is a rather specific inhibitor of sirtuins’ deacetylase activity (but not other HDACs). Zhang and colleagues have previously observed that nicotinamide treatment increased the level of cortactin deacetylation. The authors surmised that other than HDAC6, cortactin may also be deacetylated by a member of the sirtuin family. To address this possibility, the authors performed an affinity pull-down with recombinant cortactin fused to glutathione S-transferase (GST) with lysates of 293T cells transfected with the Flag-tagged forms of all seven mammalian sirtuins. Of all the mammalian sirtuins, only Sirt1 detectably associates with GST-cortactin. Overexpressed cortactin co-immunoprecipitated with GST-Cortactin. Overexpressed cortactin co-immunoprecipitated with endogenous cortactin and Sirt1 could be demonstrated using lysates of S13, an ovarian cancer line expressing high levels of both proteins. Molecular dissection of the interactions domains indicated that Sirt1, like HDAC6, binds to cortactin’s repeat region.

The authors have previously shown that the p300/CBP-associated factor (P/CAF) co-activator complex, which is an acetyltransferase, is responsible for the acetylation of lysine residues in cortactin’s repeat region. P/CAF is the major, if not the sole acetyltransferase responsible for cortactin acetylation in vivo. Transfected p300, but not other acetyltransferases such as Tip60 and HBO, efficiently acetylates co-transfected cortactin. The acetylation level of cortactin is increased in many of the cancerous tissues. However, corresponding increases...
in the acetylated pool of cortactin were not apparent. When normalized against total cortactin expressed, cortactin in five of eight of the cancerous tissues were hypoacetylated compared to benign controls. Of these five samples, Sirt1 is overexpressed in four of them, and its expression is therefore inversely correlated with cortactin acetylation. These results, taken together, suggest that elevation of Sirt1 levels in cancer tissues could result in decreased cortactin acetylation, which in turn promotes cancer cell motility.

### Sirt1’s Expanded Role in Tumorigenesis

The work of Zhang and colleagues points to a novel aspect of Sirt1’s role in human malignancy, namely cancer cell migration and invasion. Many important and interesting issues remained unexplored. Cortactin deacetylation by both HDAC6 and Sirt1 likely affects its interaction with F-actin, as well as actin-modifying factors such as cofilin. Whether the acetylation of cortactin affects its other important post-transcriptional modification, namely phosphorylation, remains to be investigated. Another question is how Sirt1 may act in conjunction with HDAC6 in terms of cortactin deacetylation. Both deacetylases appear to bind to and act on residues within the repeat region of cortactin, and presumably the extent to which each deacetylase is involved in modulating cortactin deacetylation in a given cell or tissue would depend on their relative levels and activity. Both HDAC6 and Sirt1 are fairly ubiquitously expressed, but their relative activities in different types of tissue malignancies are likely to be different. Another point that is of interest and needs to be further clarified is the role of another sirtuin, Sirt2, in cortactin deacetylation. The author have previously shown that Sirt2 and cortactin acetylation. Interestingly, both HDAC6 and Sirt2 are also tubulin deacetylases that could modulate microtubule-dependent cell motility. These two proteins could also interact with each other in vivo. Although whether Sirt1 has deacetylation activity on tubulin is unknown, the HDACs could potentially enhance cell migration and invasion via coordinated modulation of actin filaments and microtubule dynamics. This coordination may have physiological or developmental roles, and its aberrant regulation would contribute to cancer invasion and metastasis.

Finally, it is worth exploring to what extent does Sirt1-mediated deacetylation promote migration and invasion of the myriad of human cancers. In other words, would Sirt1 be an effective clinical target in attenuating cancer cell invasion and metastasis? Sirt1 inhibitors (and activators) are already being tested as cancer therapeutics, and their effects on cancer invasion and metastasis would be an additional important clinical efficacy parameter to watch out for.

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### References

1. Blander G, Guarente L. The Sir2 family of protein deacetylases. Annu Rev Biochem 2004; 73:47-92.
2. Deniz JM. The Sir 2 family of protein deacetylases. Curr Opin Chem Biol 2005; 9:431-40.
3. Haigis MC, Guarente L. Mammalian sirtuins: emerging roles in physiology aging and calorie restriction. Genes Dev 2006; 20:2913-21.
4. Picard F, Kurrett M, Chung N, Topark-Ngarm A, Senawong T, Machado De Oliveira R, et al. Sirt1 promotes fat mobilization in white adipocytes by repressing PPARGamma. Nature 2004; 429:771-6.
5. Nemoto S, Ferguson MM, Finkel T. SIRT1 functionally interacts with the metabolic regulator and transcriptional coactivator PGC-1-alpha. J Biol Chem 2005; 280:16456-60.
6. Rodgers JT, Lerin C, Haas W, Gygi SP, Spiegelman BM, Puigserver P, et al. Modulation of NFkappaB-dependent transcription and cell survival by the SIRT1 deacetylase. EMBO J 2004; 23:2369-80.
7. Firestein R, Blander G, Michan S, Oberdoerffer P, Ogino S, Campbell J, et al. The SIRT1 deacetylase suppresses intestinal tumorigenesis and colon cancer growth. PloS One 2008; 3:2020.
8. Kabra N, Li Z, Chen L, Li B, Zhang X, Wang C, et al. Sirt1 is an inhibitor of proliferation and tumor formation in colon cancer. J Biol Chem 2009; 284:18210-7.
9. Wang RH, Sengupta K, Li C, Kim HS, Cao L, Xiao C, et al. Impaired DNA damage response, genome instability and tumorigenesis in SIRT1 mutant mice. Cancer Cell 2008; 14:312-23.
10. Wang RH, Zheng Y, Kim HS, Xu X, Cao L, Luhasen T, et al. Interplay among BRCA1, SIRT1 and Survivin during BRCA1-associated tumorigenesis. Mol Cell 2008; 32:11-20.
11. Yamaguchi H, Condeelis J. Regulation of the actin cytoskeleton in cancer cell migration and invasion. Biochim Biophys Acta 2007; 1773:642-52.
12. Buday L, Downward J. Roles of cortactin in tumor pathogenesis. Biochim Biophys Acta 2007; 1775:263-73.
13. Ren G, Crompton MS, Yap AS. Cortactin: Coordinating adhesion and the actin cytoskeleton at cellular protrusions. Cell Motil Cytoskeleton 2009; 66:865-73.
14. Oser M, Yamaguchi H, Mader CC, Bravo-Cordero JJ, Arias M, Chen X, et al. Cortactin regulates cofilin and N-WASP activities to control the stages of invadopodium assembly and maturation. J Cell Biol 2009; 186:571-87.
15. Zhang X, Yuan Z, Zhang Y, Yong S, Salas-Burgos A, Koomen J, et al. HDAC6 modulates cell motility by altering the acetylation level of cortactin. Mol Cell 2007; 27:197-213.
16. Zhang Y, Zhang M, Dong H, Yong S, Li X, Olalwang N, et al. Deacetylation of cortactin by SIRT1 promotes cell migration. Oncogene 2009; 28:445-60.
17. Hubbert C, Guardiola A, Shao R, Kawaguchi Y, Ito A, Nixon A, et al. HDAC6 is a microtubule-associated deacetylase. Nature 2002; 417:455-8.
18. North BJ, Marshall BL, Borra MT, Denu JM, Verdin E. The human Sir2 ortholog, SIRT2, is an NAD+-dependent tubulin deacetylase. Mol Cell 2003; 11:437-44.