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PROTEIN MODIFICATION

Remove to move

Reversible acetylation of the cytoplasmic protein α -tubulin has been implicated in the regulation of microtubule stability and function, and the enzymes that are responsible for the addition and removal of this modification have remained elusive. But now, in *Nature*, Yao and co-workers report that a member of the histone deacetylase family — HDAC6 — is a tubulin deacetylase, and that the HDAC6-mediated deacetylation of tubulin can increase cell movement.

Yao and colleagues wanted to investigate whether acetylation has cellular functions other than its previously established roles in transcriptional regulation and histone metabolism. So they focused on HDAC6 — a member of the histone deacetylase family that is exclusively located in the cytoplasm.

Using immunostaining, the authors found that endogenous HDAC6 localizes to punctate perinuclear structures and to the leading edge of the cell. This pattern was previously seen for the protein p150^{glued}, which is found in the dynein–dynactin microtubule motor complex. As they observed that HDAC6 and p150^{glued} co-localize in these regions, and that nocodazole — which collapses microtubule networks — alters this distribution, they proposed that HDAC6 associates with microtubules.

Acetylation of α -tubulin is an important post-translational modifi-



cation of the microtubule network, so Yao and co-workers investigated whether HDAC6 can act as a tubulin deacetylase *in vivo*. When they overexpressed HDAC6 in NIH-3T3 cells — which usually express low levels of this protein — they found a specific reduction in the acetylation levels of α -tubulin. They did not observe this effect in cells that overexpress either the class I histone deacetylase HDAC1 or a catalytically inactive form of HDAC6.

The authors then tested HDAC6 specificity *in vivo*. HDAC6 is uniquely resistant to two potent HDAC inhibitors, and the authors found that neither of these inhibitors could block α -tubulin deacetylation. They showed, however, that trichostatin A — an inhibitor of all HDACs, including HDAC6 — did block this deacetylation.

The authors were surprised to find that HDAC6 showed no deacetylase activity towards free, acetylated α/β -tubulin dimers *in vitro*. They reasoned that this might be because

polymerized microtubules are the substrate of choice, and found that purified HDAC6 could potently deacetylate α -tubulin in assembled microtubules *in vitro*.

Acetylated microtubules — which represent a stable microtubule population — are absent from the leading edge of fibroblasts (a highly dynamic structure that is involved in cell motility), and HDAC6 is enriched in this region. The authors showed that HDAC6-overexpressing NIH-3T3 cells have greater motility than control cells, and therefore provided evidence that reversible acetylation has important roles beyond those in transcriptional regulation and histone metabolism.

Rachel Smallridge

References and links

ORIGINAL RESEARCH PAPER Hubbert, C. *et al.* HDAC6 is a microtubule-associated deacetylase. *Nature* **417**, 455–458 (2002)

FURTHER READING Kouzarides, T. Acetylation: a regulatory modification to rival phosphorylation? *EMBO J.* **19**, 1176–1179 (2000)

WEB SITE

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<http://pharmacology.mc.duke.edu/viewresearch.asp?id=63>