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# Multiplying madly: Deacetylases take charge of centrosome duplication and amplification

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In this volume of *Cell Cycle*, Ling et al. discovered acetylation-based control of centrosome duplication and amplification.[1] The centrosome is primarily recognized as a microtubule-organizing center (MTOC), capable of nucleating and anchoring microtubules. At the $G_1$/S transition of the cell cycle, centrosome duplication is initiated, and by $G_2$/M, the process is complete. Normally, vertebrate centrosomes duplicate once and only once during the cell cycle and contribute to the formation of the two spindle poles during mitosis.

Aberrant centrosome duplication can result in centrosome amplification, a condition found in many cancers. This can lead to multipolar spindles and, in turn, chromosome segregation errors, loss of tumor suppressor function and aggressive malignancies.[2,3] Centrosome duplication must be tightly controlled to prevent centrosome amplification and to couple it with DNA replication.

Several mechanisms can contribute to centrosome/MTOC amplification in tumor cells, including cytokinetic failure, centrosome overduplication, centriole pair splitting and acentriolar MTOC formation.[2,4] Certain tumor-derived cell lines undergo multiple rounds of centrosome duplication when DNA replication is blocked, delaying S phase.[2] Centrosome duplication is under cell cycle regulator control, which controls DNA replication and thereby coordinates the two events. Phosphorylation also contributes to centrosome duplication, but little is known about the role of other post-translational modifications in this process.[1] In this study by Ling et al., the authors addressed this question. They unexpectedly found that centrosome number is controlled by deacetylases in both normal and tumor cells.

Histone acetylation is a common form of acetylation, but non-histone acetylation is also significant and plays a major role in mRNA and protein stability, protein interactions and protein localization.[5] In this study, the authors unexpectedly found that several centrosome proteins are acetylated (centrin, Plk2 and SEPT7). They also made the surprising discovery that several deacetylases localize to centrosomes (8/18) and suppress centrosome amplification following expression above endogenous levels (7/8). In contrast, only 3/10 non-centrosomal deacetylases suppressed centrosome amplification, suggesting a role for acetylation/deacetylation in centrosome number control.

The authors next identified a subset of deacetylases with the highest centrosome amplification suppression activity (HDAC1, HDAC5, SIRT1). They showed that the deacetylase activity of HDAC1 and SIRT1 was required to suppress centrosome amplification, but not for HDAC5. In contrast, HDAC5 phosphorylation was required for suppression activity, suggesting that posttranslational events localize HDAC5 to centrosomes suppressing centrosome amplification. More work is required to understand this differential localization, as well as the mechanism of deacetylase action, possible links to the cell cycle and how deacetylases are regulated.

In a previous study, Fukasawa et al. found that cyclin A was required for centrosome reduplication in cells arrested in late S/$G_2$ phase.[6] Here, they found that HDAC1 overexpression suppressed cyclin A transcription.[1] Following completion of centrosome duplication, we speculate that the centrosomal localization of HDAC1 suppresses cyclin A expression, or that low cyclin A levels permit centrosome localization of HDAC1. Consistent with this model is a previous study showing that HDAC1 localizes to centrosomes in metaphase[7] when centrosomes are not replicating and cyclin A expression is low.

Does this work have significance for the etiology of cancer and in therapeutic strategies? Centrosome amplification has become a hallmark of carcinomas and other cancers. The finding that many deacetylases suppress centrosome amplification is inconsistent with the described increase in deacetylase expression in cancer cells.[8] Moreover, deacetylase inhibitors have anticancer effects.[8] However, it is unclear if the deacetylase inhibitors used in the cancer studies affect deacetylase localization to centrosomes. Additional studies will shed light on the roles of deacetylases/acetylases in centrosome duplication and amplification. For example, it is likely that these enzymes function in duplication control, but they could also participate in the many steps of centrosome assembly that have been uncovered over the last several years.[9]

This paper provides novel insights into regulation of centrosome duplication/amplification through the identification of new contributors to this process, acetylases/deacetylases. Moreover, the discovery of acetylated centrosome proteins establishes new frontiers to understanding how post-translational modifications regulate centrosome function. Based on the profound changes in centrosome numbers induced by the perturbation of deacetylases, it is clear that this new area of centrosome biology has high potential to yield important insights into centrosome duplication and, perhaps, into other aspects of centrosome biology for years to come.

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