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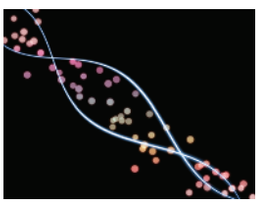
Epigenetics

Major finding: Decreased extracellular pH induces sustained global histone deacetylation.

Mechanism: Acetate released by histone deacetylation is coexported with protons to buffer intracellular pH.

Impact: An alternate mechanism of HDAC inhibitor activity may involve disruption of pH-buffering capacity.

GLOBAL HISTONE ACETYLATION IS LINKED TO pH



Global alterations in histone acetylation levels have been observed in both normal and cancer cells and can be prognostic of clinical outcome. However, unlike site-specific acetylation changes that can affect transcription of particular genes, the reason for genome-wide changes has been less clear. Because acetyl-coA molecules required for histone acetylation and acetate anions generated by histone deacetylation are required for many metabolic processes, McBrian and colleagues hypothesized that metabolic or physiologic cues might affect global histone acetylation levels. Systematic testing of the effects of culture medium components on histone acetylation revealed that decreased sodium bicarbonate concentrations resulting in lowered extracellular and intracellular pH led to a rapid, marked reduction in total levels of histone H3 and H4 acetylation at multiple lysine residues. These pH-dependent changes were specific to histone acetylation, as histone methylation was unaffected and required histone deacetylase (HDAC) activity. Chromatin immunoprecipitation sequencing analysis showed that a decrease in extracellular pH led to an extreme redistribution and decreased overall levels of histone H4 lysine 16 acetylation, although these changes were not correlated with changes in gene expression. Export of acetate anions released by histone deacetylation increased as extracellular pH decreased and was dependent on monocarboxylate transporters (MCT), which bidirectionally cotransport acetate with protons. In this manner, continual histone deacetylation can promote proton efflux to buffer against further reduction of intracellular pH. Under conditions of low extracellular pH, HDAC inhibition prevented acetate release and proton efflux and reduced intracellular pH, showing that both HDACs and MCTs are necessary for cellular pH-buffering capacity. In addition to establishing a role for chromatin as an intracellular pH buffer, these findings raise the possibility that HDAC inhibitors may have an alternative mechanism of action as cancer therapeutics involving deregulation of intracellular pH control. ■

McBrian MA, Behbahan IS, Ferrari R, Su T, Huang TW, Li K, et al. Histone acetylation regulates intracellular pH. Mol Cell 2012 Nov 29 [Epub ahead of print].

Drug Resistance

Major finding: MED12 loss confers resistance to targeted therapies through activation of TGF-β signaling.

Mechanism: Loss of cytoplasmic MED12 activity promotes TGF-βR2 maturation and induces a partial EMT.

Impact: MED12 may represent a general biomarker of drug response in multiple cancer types.

MED12 IS A GENERAL DETERMINANT OF DRUG RESPONSE

Targeted therapies can elicit dramatic responses, but resistance often rapidly develops. Known mechanisms include secondary mutations of the drug target, activating downstream mutations, and activation of parallel pathways, but resistance often cannot be explained by such events. Huang and colleagues uncovered a distinct, broadly acting drug resistance mechanism through a large-scale RNA interference (RNAi) screen for genes required for ALK inhibitor sensitivity in a non–small cell lung cancer (NSCLC) cell line that identified *MED12*, encoding a subunit of the MEDIATOR transcriptional adaptor complex. MED12 loss also conferred resistance to EGFR, BRAF, and MEK inhibitors and cytotoxic agents in various cancer cell types. A second kinome library RNAi screen showed that knockdown of TGF-β receptor 2 (TGF-βR2) restored ALK inhibitor sensitivity in MED12-deficient NSCLC cells, and TGF-βR2 overexpression or TGF-β treatment was sufficient to confer resistance to targeted and cytotoxic therapies in the cell types in which MED12 knockdown also induced resistance. MED12 knockdown led to TGF-β target gene upregulation, but not through transcriptional activation of *TGFBR2*, an unexpected finding given the role of MED12 in the MEDIATOR complex. Surprisingly, a proportion of cellular MED12 was bound to TGF-βR2 in the cytoplasm independently of other MEDIATOR subunits and suppressed TGF-βR2 maturation and cell surface expression. Consistent with a role for MED12 in TGF-β regulation, the MED12-knockdown gene signature was suggestive of a partial epithelial–mesenchymal transition (EMT) and a TGF-βR inhibitor synergized with targeted agents to suppress growth of drug-resistant MED12-deficient cells. Together with the observation that the MED12-knockdown signature was predictive of poor outcome in several clinical contexts, these findings suggest that MED12 expression may be a broadly useful biomarker of drug response and provide a rationale for testing whether TGF-βR inhibitors reverse drug resistance associated with MED12 loss and EMT induction. ■

Huang S, Hölzel M, Knijnenburg T, Schlicker A, Roepman P, McDermott U, et al. MED12 controls the response to multiple cancer drugs through regulation of TGF-β receptor signaling. Cell 2012;151:937–50.

AACR American Association for Cancer Research

CANCER DISCOVERY

Global Histone Acetylation Is Linked to pH

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