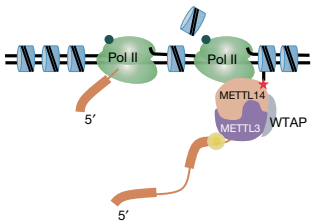
RNA MODIFICATION

Marking histones

Nature **567**, 414–419 (2019)



N^6-methyladenosine (m^6A) is installed in transcriptomes by the methyltransferase complex (MTC) and plays important roles in mRNA stability. To determine how m^6A modification is preferentially deposited to particular transcript regions, Huang et al. used an integrated analysis of ChIP-seq and m^6A-seq to compare the distribution of histone and m^6A modifications, detecting a strong overlap of H3K36me3 and m^6A. METTL14, a critical component of the MTC that is responsible for m^6A deposition, directly interacts with H3K36me3 and associates with active Pol II, suggesting that H3K36me3 recruits the MTC to methylate nascent RNAs during Pol II–mediated transcription elongation. Loss of histone methyltransferase SETD2 activity in mouse embryonic stem cells decreased the level of H3K36me3, prevented deposition of m^6A, stabilized pluripotency genes, and inhibited cell differentiation. This study reveals the instructive role of histone modification in regulating RNA methylation. *YS*

https://doi.org/10.1038/s41589-019-0283-9

CANCER REDOX BIOLOGY

Under pressure

Cell Metab. https://doi.org/10.1016/j.cmet.2019.01.020 (2019)

Glutamate–cysteine ligase (GCL)-mediated production of glutathione (GSH) mitigates oxidative stress in cells. Blocking GSH production through use of L-buthionine sulfoximine (BSO), an inhibitor of the catalytic subunit of GCL (GCLC), has been proposed as a cancer therapy strategy. However, it is not clear whether this approach is applicable to all types of cancer cells. Harris et al. performed a systematic analysis of CRISPR–Cas9 screening data on 300 different cancer cell lines and found that GCLC did not score as a dependency in these cell lines. However, long-term treatment with BSO revealed clusters of highly sensitive and resistant cell lines. A CRISPR–Cas9 screen on a BSO-resistant cancer cell line combined with a small-molecule screen to identify modulators of BSO resistance revealed that inhibition of deubiquitinases (DUBs) sensitized cells to GSH depletion. Combined inhibition of DUBs and GSH increased proteotoxic and ER stress, resulting in cell death. Finally, an additional CRISPR–Cas9 screen to identify modifiers of BSO/DUB inhibitor treatment revealed the anti-apoptotic protein XIAP and mTOR signaling as regulators of sensitivity. Overall, the combination of DUB and GSH inhibition reveals a new mechanism of cancer vulnerability. *GM*

https://doi.org/10.1038/s41589-019-0282-x

CANCER SIGNALING

Avoiding the dumpster

Science **363**, 1226–1230 (2019)

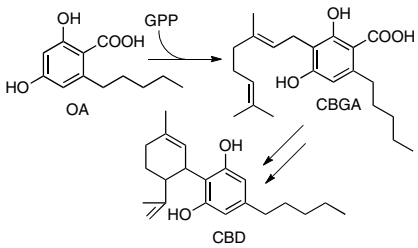
RIT1 is a Ras-related small GTPase, and mutations in RIT1 at the switch II region have been identified in lung adenocarcinoma and Noonan syndrome resulting in increased growth factor signaling and RIT1 protein levels. Given that RIT1 oncogenic mutations were not found in the traditional GTPase hotspots that alter GDP/GTP exchange, it was speculated that RIT1 might undergo a distinct form of regulation. Castel et al. utilized a mass spectrometry approach and identified the leucine-zipper-like transcription regulator 1 (LZTR1), an adaptor for the CUL3 ubiquitin ligase complex, as a binding partner specifically for the GDP-bound form of RIT1. LZTR1–RIT1 interactions resulted in CUL3-mediated ubiquitination and degradation of RIT1. LZTR1 knockdown or RIT1 oncogenic mutations block degradation, resulting in increased RIT1 protein levels and growth factor signaling. Overall, these findings reveal a new form of GTPase regulation by proteasome degradation. *GM*

https://doi.org/10.1038/s41589-019-0281-y

METABOLIC ENGINEERING

Cannabinoids on the rise

Nature **567**, 123–126 (2019)



Cannabinoids, such as Δ^9-tetrahydrocannbinol (THC) and cannabidiol (CBD), are of potential pharmaceutical interest, but they are produced at relatively low levels by their native plant hosts. To address this limitation, Luo and Reiter et al. engineered yeast strains to produce multiple advanced cannabinoids from galactose. The intermediate olivetolic acid (OA) was first produced via the expression of a hexanoyl-CoA biosynthetic pathway, a tetraketide synthase, and an olivetolic acid cyclase. Upregulation of the mevalonate pathway and screening of candidate prenyltransferases then enabled the biosynthesis of cannabigerolic acid (CBGA) from OA and geranyl pyrophosphate (GPP). Finally, the inclusion of a cannabinoid synthase, followed by heat-induced decarboxylation, produced the mature THC or CBD. Capitalizing on the promiscuity of certain enzymes, supplying alternate fatty acids enabled the production of additional cannabinoid analogs with varied acyl chains. The establishment of this cannabinoid expression platform enables the facile production of both natural and synthetic cannabinoids for potential future medicinal studies. *CD*

https://doi.org/10.1038/s41589-019-0280-z

Caitlin Deane, Grant Miura and Yiyun Song