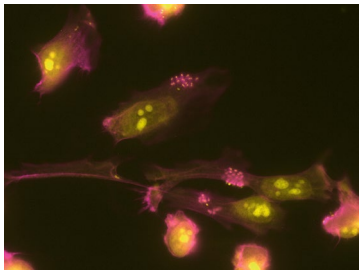
BACTERIA-HOST INTERACTIONS

Modulating the microbiota

Cell Host Microbe **28**, 41–53 (2020)



Credit: Cell Press

Bacteria in the gastrointestinal (GI) tract can impact neurological function, and, conversely, host-derived neurotransmitters can affect bacterial virulence. To understand the interplay between the neurotransmitter serotonin, which is mainly synthesized in the GI tract, and bacterial virulence, Kumar et al. studied the human enteric pathogen EHEC and found that serotonin decreased virulence gene expression in EHEC, including that of genes in the locus of enterocyte effacement (LEE) required for lesion formation by the bacteria. Transcriptomic analysis showed changes in expression of both virulence genes and a histidine sensor kinase, CpxA, which has been shown to sense the structurally similar bacteria-generated compound indole and similarly decreases LEE gene expression in EHEC. Biochemical and knockout studies indicated that CpxA can act as a receptor for serotonin on EHEC and is required for its virulence. Serotonin also required CpxA to decrease LEE gene expression in the murine pathogen *Citrobacter rodentium*. In vivo work using genetic and pharmacologic modulators of serotonin levels found that intestinal serotonin decreases virulence gene expression in *C. rodentium*, leading to decreased host susceptibility to the pathogen. These results suggest an important role for the microbiota–gut–brain axis in host and pathogen physiology. *MB*

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METALS

Histones do double duty

Science **369**, 59–64 (2020)

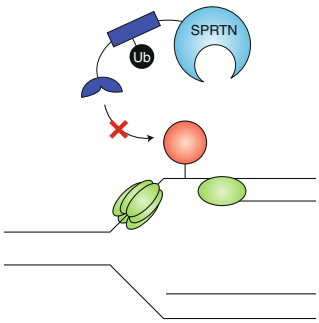
The eukaryotic histone H3–H4 tetramer contains conserved residues at the dimerization interface reminiscent of copper-binding sites in other proteins, but the functional implications of this site have been a mystery. Now, Attar et al. have demonstrated that in addition to binding copper ions, the H3–H4 tetramer also has an active role in maintaining cellular metal homeostasis. In vitro, purified *Xenopus laevis* H3–H4 tetramers exhibit cupric reductase activity (reducing Cu^{2+} to Cu^{+}), involving two key residues in histone H3, Cys110 and His113. Wild-type yeast H3 lacks the Cys110 residue but retains cupric reductase activity, which is increased by installation of an A110C mutation. In yeast cells, substitution of His113 with alanine was lethal, while substitution with asparagine or tyrosine caused growth defects, impaired mitochondrial respiration, and decreased superoxide dismutase activity due to decreased Cu^{+} abundance. The characterization of an additional function for the histone tetramer identifies a new player in eukaryotic metal homeostasis and hints at the activities of related archaeal proteins that lack a known epigenetic role. *CD*

https://doi.org/10.1038/s41589-020-0633-7

POST TRANSLATIONAL MODIFICATIONS

Repair switches

Mol. Cell https://doi.org/10.1016/j.molcel.2020.06.027 (2020)



Credit: Cell Press

DNA–protein crosslinks (DPCs) impede regular cellular processes, including DNA duplication and transcription, and induce genome instability. SPRTN is a DNA-dependent metalloprotease that translocates to the chromatin to repair DPCs when monoubiquitin is removed. However, the identities of the enzymes that remove ubiquitin were not known. By screening a panel of deubiquitinating enzymes (DUBs), followed by biochemical characterization and mutagenesis, Huang et al. identified VCPIP1 as a DUB of SPRTN that directly binds to ubiquitinated SPRTN and recruits acetylation enzymes. Acetylation of SPRTN is essential for promoting chromatin translocation of SPRTN and the subsequent DPC repair. Knockdown of VCPIP1 or replacement of the wild type with a catalytic inactive mutant decreases SPRTN acetylation, suppresses the chromatin translocation of SPRTN, and increases DPC accumulation and sensitivity to DPC-inducing agents. The DUB activity of VCPIP1 is dependent on its phosphorylation, which is mediated by DNA-damage-responsive kinases upon DPC induction. This study depicts a detailed early picture of DPC repair and promotes an understanding of the concerted regulatory roles of PTMs in controlling protein activities. *YS*

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DNA METHYLATION

Peaking at the right time

Nature **583**, 625–630 (2020)

N^6-Methyladenine (N^6-mA) is a DNA epigenetic mark present during early embryogenesis that can be removed by ALKBH1, a demethylase that prefers unpairing DNA substrates (SIDD). Given that *Alkbh1*-deficient mice exhibit extraembryonic defects particularly in the trophoblast, Li et al. examined the role of N^6-mA during trophoblast development using an inducible embryonic stem cell system that transitions to trophoblast stem cell-like cells (TSC-LCs) and then differentiates into mature trophoblasts. N^6-mA levels were elevated in TSC-LCs in which DNA exhibited unpairing (SIDD regions) and then declined in mature trophoblasts. The authors focused on the SIDD-binding protein SATB1 as a potential regulator of N^6-mA, as SATB1 is highly upregulated during trophoblast stem cell development. Biochemical experiments demonstrated that SATB1 binding to DNA was blocked in the presence of N^6-mA-modified DNA. ChIP-seq analysis showed that SATB1 DNA binding was reduced in regions in which N^6-mA levels were enriched, while overexpression of ALKBH1 increased SATB1 binding. The competition between SATB1 and N^6-mA regulates trophoblast cell fate, as overexpression of *Alkbh1* increases TSC-LC differentiation whereas *Satb1* deficiency blocks differentiation. Further work is needed to explore the function of this antagonistic relationship in other developmental and adult tissues. *GM*

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