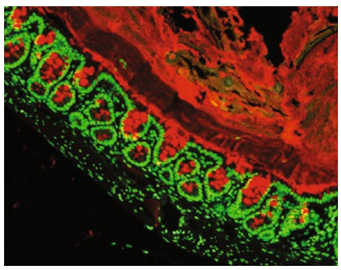
HOST-MICROBIOTA INTERACTIONS

A NAMe-tag for ALS

Nature **572**, 474–480 (2019)



Credit: Nature

The neurodegenerative disease ALS has been shown to be modulated by environmental factors, which could include gut bacteria. Given that gut bacteria are known to affect the pathogenesis of other neurological disorders, Blacher et al. tested the interface between the gut microbiome and the host in the context of ALS. They used mouse models of ALS and found that antibiotic treatment exacerbated the motor-function defects associated with the disease and led to increased motor-neuron cell death and brain atrophy. There were significant differences in compositions of the fecal microbiome of ALS mice compared to those of wild-type (WT) mice even before the appearance of motor-neuron dysfunction. In particular, they identified four strains that exacerbated ALS disease, survival, and brain atrophy, and one, *Akkermansia muciniphila* (AM), that improved them. Untargeted metabolomics and a scoring algorithm identified AM-induced nicotinamide (NAM) as being synthesized by the WT, but not the ALS microbiota. NAM supplementation mimicked the effects of AM on motor function. Finally, results from a small human study suggested different AM levels and aberrant metabolism of NAM in some patients with ALS, highlighting the involvement of the microbiota in modulating ALS. *MB*

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NATURAL PRODUCTS

Colibactin comes to light

Science https://doi.org/10.1126/science.aax2685 (2019)

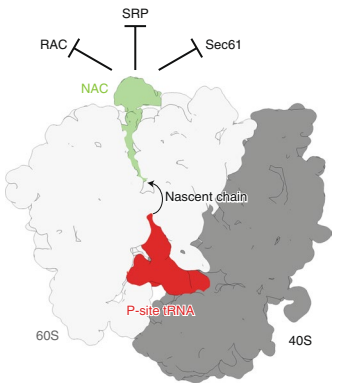
Colibactin is a secondary metabolite produced by certain gut bacteria associated with colorectal cancer. Despite many studies characterizing colibactin precursors (precolibactins) and derivatives, their biosynthetic steps, and their DNA-alkylating activity, colibactin has eluded isolation and its structure has remained incompletely defined. Using a combination of mass spectrometry, isotope labeling, and biosynthetic logic, Xue and Kim et al. determined the structure of a colibactin–diadenine adduct that results from two DNA alkylation events. Building upon that adduct, the authors predicted the full structure of colibactin, identified the metabolite in cultures of *Escherichia coli* Nissle 1917, and confirmed the structural prediction by chemical synthesis. These data, together with the characterization of a new advanced intermediate (precolibactin 1489) and the accumulated data from previous studies, enabled the proposal of a complete biosynthetic pathway for colibactin incorporating all of the biosynthetic enzymes encoded in the gene cluster. This structure of mature colibactin both enables further studies of its genotoxic effects and illustrates the power of a multipronged approach to the structural elucidation of natural products that are recalcitrant to isolation. *CD*

https://doi.org/10.1038/s41589-019-0373-8

TRANSLATION

First contact

Mol. Cell https://doi.org/10.1016/j.molcel.2019.06.030 (2019)



Credit: Elsevier

Ribosomes interact with various factors to enable the biogenesis of newly synthesized polypeptides, including the nascent polypeptide-associated complex (NAC) and the translocon Sec61. It's generally thought that these ribosome-associated protein biogenesis factors don't interact with nascent polypeptides until they exit the ribosome tunnel. However, a new study by Gamerdinger et al. challenges the concept. Through structural analysis of the reconstituted *Caenorhabditis elegans* NAC-60S ribosomal complex and site-specific crosslinking experiments, the authors revealed that the N terminus of the β subunit of NAC (N-βNAC) inserts deeply into the ribosomal tunnel to contact nascent peptide chains upon their synthesis and are then pushed out of the ribosome tunnel together. A NAC mutant with GFP fused to the N terminus of βNAC that has lost the ability to insert into the channel fails to rescue the embryonic lethal phenotype induced by loss of NAC, suggesting that the tunnel-sensing activity of N-βNAC is essential for its biological function. This study suggests a new type of co-translational regulatory event and lays a foundation for further investigation into the ribosome-associated protein networks. *YS*

https://doi.org/10.1038/s41589-019-0375-6

PLANT SIGNALING

The root of the cause

Mol. Cell https://doi.org/10.1016/j.molcel.2019.06.044 (2019)

Auxin is a phytohormone that regulates root development and growth through transcriptional regulation, mediated by the members of the auxin response factor (ARF) family. ARF7 and ARF19 proteins exhibit elevated auxin transcriptional responsiveness near the growing root tip but are diminished in mature roots. Powers et al. observed that ARF7/19 proteins were organized as cytoplasmic protein complexes or condensates made up of higher order oligomers in mature root cells but were present as nuclear-localized monomers at the growing root tip. Formation of the ARF19 complex required the intrinsically disordered MR domain and the PB1 domain, which is necessary for mediating endogenous ARF–ARF interactions. The formation of these oligomeric complexes corresponded to diminished auxin transcriptional activity. Mutation of a critical lysine (K962) in the PB1 domain reduced ARF19 complex formation, resulting in constitutive nuclear localization and enhanced auxin-mediated transcription. Although future studies will be needed to reveal how the ARF7/19 condensate is resolved into a monomer in high auxin-responsive tissues, the findings from Powers et al. reveal a new regulatory mechanism that controls auxin responsiveness. *GM*

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