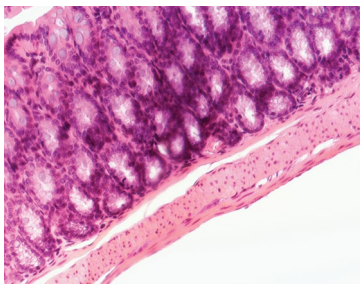
BIOACTIVE LIPIDS

How to irritate your host

Cell Host Microbe **25**, 668–680 (2019)



Credit: Elsevier

Sphingolipids are bioactive signaling lipids that regulate various cellular processes such as inflammation and growth and have been implicated in associated diseases including inflammatory bowel disease (IBD). Sphingolipids are also a substantial component of the membrane of bacteria of the Bacteroidetes phylum, the only human gut commensal known to produce sphingolipids. To determine how Bacteroidetes sphingolipid production affects host metabolism and immunity during IBD, Brown et al. generated a *Bacteroides thetaiotaomicron* strain lacking the sphingolipid biosynthetic enzyme serine palmitoyltransferase (Spt). When introduced into germ-free mice, this sphingolipid-deficient strain led to intestinal inflammation, intestinal barrier dysfunction, and changes in host lipid metabolites (both sphingolipids and those not generated by Spt). Lipidomic analyses of mouse cecal extracts identified 35 unique Spt-dependent *Bacteroides* sphingolipids, including deoxysphinganine and ceramide phosphoinositol, and led the authors to propose an alternate sphingolipid biosynthesis pathway. The authors found that bacterial sphingolipids were inversely correlated with IBD and inflammation in a human cohort. These results define additional lipid products generated by *Bacteroides* Spt and define a role for Spt in both bacterial and host sphingolipid pathways. *MB*

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SYNTHETIC BIOLOGY

The RASER's edge

Science **364**, eaat6982 (2019)

Cancer cells differ from normal cells by the constitutive activation of signaling pathways such as ErbB. However, the ability to selectively modulate or kill cancer cells without altering normal cell activity remains difficult. Chung et al. developed a synthetic circuit called RASER that is selectively activated in cells with constitutive ErbB activity to trigger customizable outputs. The RASER system operates by recruiting two proteins to activated ErbB: the hepatitis C virus (HCV) protease and a cargo protein anchored to the membrane via a protease substrate sequence. Chung et al. showed that cargo was released in cancer cells with elevated ErbB activity, but not in cells with normal ErbB activity even in the presence of the activating ligand EGF. They then used the RASER system to selectively target ErbB-positive cancer cells using the BH3 domain of BID to promote apoptosis or CRISPR–Cas9 domains to alter endogenous gene expression. Finally, delivery of RASER using a non-integrating virus selectively ablated ErbB-positive cancer cells. Overall, the RASER system offers a new way to selectively alter cellular outputs in oncogenic cells for therapeutic or engineering applications. *GM*

https://doi.org/10.1038/s41589-019-0317-3

CHEMICAL ECOLOGY

Come-hither compounds

Science **364**, eaau6389 (2019)

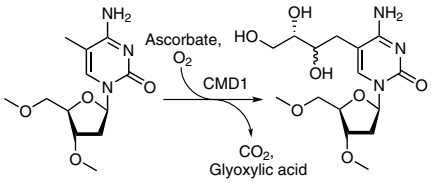
Plants biosynthesize a variety of terpene natural products, many with antimicrobial activities. Seeking to understand an ecological role for these metabolites, Huang and Jiang et al. used heterologous expression, genetic manipulation, and targeted metabolomics to identify a collection of triterpene metabolites in *Arabidopsis thaliana*. They also characterized and assigned functions to multiple previously unknown biosynthetic genes, enabling the elucidation of the intertwined biosynthetic pathways to thalianin, arabidin, and a group of thalianol-derived fatty acid esters. Disruption of thalianin biosynthesis led to the root microbiota being depleted of Deltaproteobacteria and enriched in Bacteroidetes strains, whereas a cocktail of purified triterpene compounds promoted in vitro growth of Proteobacteria strains isolated from *A. thaliana* roots and inhibited growth of Actinobacteria strains. Further investigation of the isolated bacteria also revealed that some contained enzymes for additional modification of thalianol-derived compounds. Together, these results indicate how the plant uses secondary metabolites to tune the composition of its root microbiota. *CD*

https://doi.org/10.1038/s41589-019-0316-4

DNA MODIFICATION

TEThered vitamin C

Nature **569**, 581–585 (2019)



5-Methylcytosine (5mC) is one of the most prevalent DNA modifications and is associated with negative regulation of gene expression. In mammalian cells, 5mC is removed by a series of oxidation reactions mediated by ten–eleven translocation (TET) dioxygenases, which use 2-oxoglutarate (2-OG) as a co-substrate. Xue et al. identified a TET homolog, CMD1, in the green alga *Chlamydomonas reinhardtii* that utilizes vitamin C (ascorbate) as an essential co-substrate instead of 2-OG to convert 5mC to a new DNA modification, 5-glycerylmethylcytosine (5gmC). Depletion of *CMD1* or the key vitamin C synthesis gene *VTC2* reduced the genomic content of 5gmC and increased that of 5mC. Using a luciferase reporter system, the authors revealed that conversion of 5mC to 5gmC reduced downstream gene repression. Functional studies found that loss of CMD1 increased algal sensitivity to light-induced damage by repressing the expression of *LHCSR3*, a key gene for photoprotection, via increasing methylation in its 5′ region. This study identifies a new functional DNA epigenetic marker and expands our understanding of the reaction mechanisms of oxygenases. *YS*

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