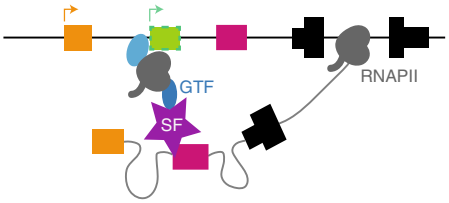
RNA SPLICING

New beginnings

Cell **179**, 1551–1565 (2019)



Credit: Cell Press

Alternative RNA splicing regulates gene expression by varying the inclusion of exons and introns in mRNAs. Fiszbein et al. have now defined a phenomenon called exon-mediated activation of transcription starts (EMATS), which reveals an association between exon splicing and transcriptional start. By comparing RNA transcripts from different species, the authors found that the inclusion of mouse-specific evolutionarily new exons is positively correlated with gene expression and gain of transcription start sites (TSSs). Repressing the splicing of new exons with morpholino antisense oligonucleotides or CRISPR–Cas9 mutations decreased exon inclusion and the expression levels of their parent genes. The proximal upstream TSS exhibited altered association with core transcription machinery, and further studies found that both 5′ and 3′ splice sites are essential for this mode of gene upregulation. These results suggest that new exons promote the creation of new promoters in the proximal upstream region. More importantly, the authors found that similar rules can also be generally applied to thousands of genes with skipped exons (SE); inclusion of SE promotes the usage of a weak proximal TSS. This study provides a good example of finding new insights based on known databases and new ideas for regulating gene expression. *YS*

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TRANSCRIPTOMICS

Noise reduction

Science **367**, 45–51 (2019)

Transcriptomic profiling of single cells treated with small molecules mitigates cell–cell variability in cellular responses, but existing single-cell transcriptome sequencing (scRNA-seq) methods remain costly. The use of cellular barcoding with antibodies or lipid-modified oligonucleotides enables distinction of cells from different samples, but issues with scalability remain. Srivatsan et al. developed sci-Plex, which uses polyadenylated ssDNA oligonucleotides to barcode nuclei before pooling and scRNA-seq. From a single experiment with three cancer cell lines exposed to 188 compounds, the authors identified consistent transcriptional responses for particular HDAC inhibitors with alterations in genes involved in cell cycle arrest and cellular metabolism, such as enzymes for acetyl-CoA and citrate production. The authors found that the combination of HDAC inhibition and supplemented acetyl-CoA precursors reduced the extent of HDAC inhibitor-mediated transcriptional changes, while treatment with inhibitors of acetyl-CoA generation enhanced the changes. Overall, sci-Plex offers the ability to detect small-molecule-induced transcriptomic changes in single cells with high resolution. *GM*

https://doi.org/10.1038/s41589-020-0464-6

NATURAL PRODUCTS

Spying on the microbiome

Science **366**, eaax9176 (2019)

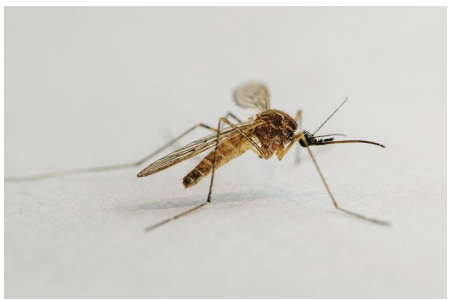
The human microbiome consists of thousands of bacterial species, many of whose interactions among themselves and with their host are likely mediated by small molecules. However, identifying these natural products has so far been limited to culturable strains and those with assembled genomes. To expand the search to full metagenomic samples, in which biosynthetic genes may be in low abundance and sequence reads fragmented, Sugimoto and Camacho et al. developed a bioinformatics algorithm, MetaBGC, which enables detection of biosynthetic gene clusters (BGCs) de novo from metagenomic sequencing data. MetaBGC is built upon segmented profile hidden Markov models, a variation of the method used for detecting protein homologs that works with relatively short 30-amino acid segments. Using MetaBGC, the authors looked for type II polyketide synthase BGCs among human-derived metagenomic samples from diverse sources, which in turn enabled the discovery of five novel polyketide natural products. Though the physiological function of these compounds is not yet known, MetaBGC paves the way for the discovery of more untold microbiome-derived natural products and studies of their function in microbe–microbe and microbe–host interactions. *CD*

https://doi.org/10.1038/s41589-020-0463-7

VIRUS-HOST INTERACTIONS

Lipid hijacking

PLoS. Pathog. **15**, e1008199 (2019)



Credit: Frederic Cerez / EyeEm / Getty

As an enveloped virus, the dengue virus (DENV) relies on the lipid membrane of its host cells, either humans or *Aedes Aegypti* mosquitoes, and the virus reconfigures the lipidome in mosquito cells and midgut (where DENV first enters mosquitoes). To examine more closely how DENV alters lipids, Vial et al. used high-resolution mass spectrometry to monitor polar and non-polar *Ae. Aegypti* metabolites in midguts in whole mosquitoes and in an *Ae. Aegypti* cell line at post-infection time points representing the onset of replication through systemic infection. Of the various metabolite classes, the profiling showed that phospholipids (PL) were highly regulated throughout the DENV lifecycle, with aminophospholipids (aminoPL) and lysophospholipids specifically increased at the beginning of the life cycle and reduced at the end. Next, the authors found that the DENV-induced reconfiguration of the phospholipidome was associated with downregulation of AGPAT1, a rate-limiting enzyme for PL biosynthesis. AGPAT1 and AGPAT2 depletion in cells each caused unique increases in the levels of specific aminoPLs. In the case of AGPAT1 and its associated lipid changes, this caused an increase in DENV production. These findings suggest that DENV promotes increased aminoPL levels via AGPAT1 to support its own life cycle. *MB*

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