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From Metagenomes to Molecules: Innovations in Functional Metagenomics Unlock Hidden Chemistry in the Human Microbiome

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Cite This: https://dx.doi.org/10.1021/acs.biochem.0c00033 Read Online

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Once in a while, a conceptual or technical breakthrough changes the way we approach science. In microbiology, Leeuwenhoek's lenses, Koch's solid growth medium, Fleming's penicillin, and Woese's recognition of the 16S rRNA sequence as a universal chronometer all changed the way discoveries were made, each providing a new way to study or understand microbial life. Following Woese's groundbreaking insight, Pace applied the polymerase chain reaction to the 16S rRNA gene, making it possible to characterize the molecular diversity of microorganisms in natural environments without culturing bias.[1] The cascade of publications that followed made it clear that microbiologists were ignorant about the staggering diversity that had eluded detection by the culture-based methods that had dominated microbiology research since Koch's 19th century innovation. Also made clear was the fact that many of the as-yet unculturable organisms were deeply divergent from those known from culture, presenting an opportunity to redefine the limits of microbial life. Pace then proposed that it was time to extract and clone DNA directly from environmental samples to conduct genomic analysis on the cornucopia of organisms that could not be cultured. This approach eventually became known as metagenomics—the analysis of collective genomes extracted from an environment. For the past 20 years, metagenomics research has primarily focused on sequence-based information and only a small proportion has been dedicated to functional metagenomics, which involves expressing DNA extracted from an environmental sample in a surrogate host to discover new metabolites and proteins.[2−4] Functional metagenomics has been plagued by the hurdle of heterologous gene expression, and consequently, progress has been slow. Recently, Sugimoto et al.[5] presented a game-changing approach to functional metagenomics that has the potential to revolutionize discovery.

Sugimoto et al. offer two innovations in the search for gene function and new secondary metabolites encoded in microbial genomes. First, they present a major step forward in the characterization of biosynthetic pathways directly from sequencing reads, rather than from metagenomic assemblies, allowing them to avoid the fragmentation that often arises from variable coverage of shotgun community sequencing. Working directly with sequencing reads also allowed them to explore new taxonomic and functional genomic space and mitigated the uneven sampling of previously sequenced or culturable organisms (biased toward the Western, heathy human gut). Their new algorithm, designated MetaBGC, identifies biosynthetic gene cluster (BGC) reads from shotgun metagenomes with systematically tested and tuned sequence-scoring models that work in read-length sized chunks. Reads are binned for targeted assembly enabling reconstitution of entire pathways. The authors first focus on pathways containing type II polyketide synthases (T2PKSs) from a variety of human microbiome databases and show impressive results, even at very low coverage and abundance. Importantly, their method facilitates easy separation of true-positive and false-positive BGC bins. Looking across 3203 human metagenome samples from all major human body sites, the authors identify many new T2PKS BGCs, many from organisms not found in reference databases. BGC abundance was then correlated to body site, taxonomy of the organism of origin, and metatranscriptome information to provide further insight into the diversity and distribution of chemistry in the human microbiome.

Sugimoto et al. focus on two novel BGC pathways for expression and chemical structure elucidation. The first, BGC3 from the oral microbiome, was found in a strain that had not yet been cultured. Another innovation in the work is that the authors opted to synthesize the entire BGC, inserting strong promoters and optimizing codon usage for expression in *Streptomyces*, and expressed the pathway in the heterologous host *Staphylococcus albus*. The resulting suite of molecules, dubbed metamycins, show strong inhibitory activity against Gram-positive isolates, especially those isolated from the human oral cavity (Figure 1). Transcriptomics analysis showed that the metamycin BGC is expressed under physiological conditions in human plaque during early biofilm formation. A second novel pathway, BGC6 from the gut microbiome, was also found in a cultured isolate. The authors amplified the BGC from *Blautia wexlerae* and expressed it in *Bacillus subtilis* to discover wexrubicin, a tetracyclic anthracycline. Unlike other anthracyclines (e.g., doxyrubicin), wexrubicin displays no toxicity in human cell assays.

The discoveries reported by Sugimoto et al. advance natural products chemistry and drug discovery from uncultured organisms to a new level by making it more routine to access

Received: January 10, 2020

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https://dx.doi.org/10.1021/acs.biochem.0c00033
Biochemistry XXXX, XXX, XXX−XXX

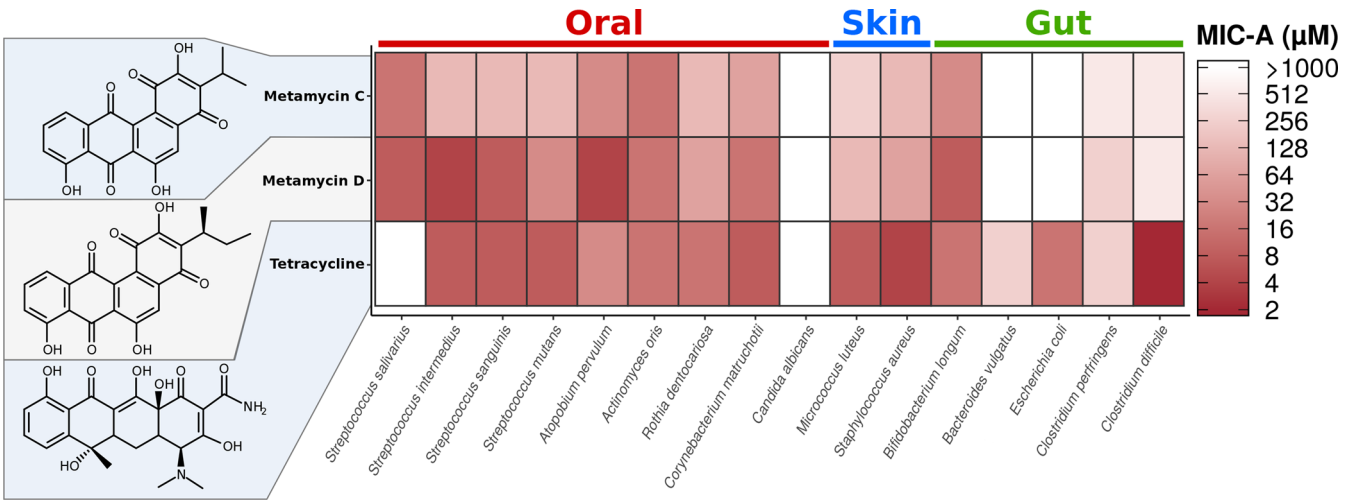

Figure 1. Innovation in metagenomics from Donia and colleagues uncovers new chemical diversity in the microbiome. New molecules, metamycin C and D, are active against bacteria sourced from the human microbiome at levels similar to that of the antibiotic tetracycline. MIC-A is the minimum inhibitory concentration on solid media.

the biosynthetic machinery of the microbiome. But the work is equally impactful on microbial ecology. By returning to the source of the metagenome and examining expression of the pathways discovered in vitro, Sugimoto et al. have been able to propose ecological roles for the newly discovered molecules in the microbiome of origin. The metamycin biosynthetic pathway is expressed in the oral microbiome during initial biofilm formation, and the metamycins target Gram-positive bacteria in the human oral microbiome. The contributions to both chemical discovery and ecology make this research a turning point in understanding the diversity and roles of microbial metabolites in the microbial communities in which they are produced.

Despite advances in molecular biology and sequencing over the past four decades, our understanding of microbiomes and the genes and molecules underlying microbial interaction networks remains in its infancy. The astounding diversity of microbial life begets exponential chemical complexity in the communities that comprise it, inviting microbiologists and chemists to unravel the structures, activities, and ecological roles of the cornucopia of compounds encoded in these communities' metagenomes. We have learned that the intricate networks underpinning microbial community interactions form miniature versions of Darwin's tangled bank, but work has been stymied by the inaccessibility of the tangible products of many functions encoded in metagenomes. Just as microscopy, culturing, antibiotics, and culture-independent analyses of microbes have all revolutionized microbiology, Sugimoto et al.'s advance will accelerate understanding microbiome functions in many biological processes, including global nutrient cycling, agriculture, and human health.

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Funding

The authors are thankful for Army Research Office MURI Grant W911NF1910269.

Notes

The authors declare no competing financial interest.

REFERENCES

(1) Schmidt, T. M., DeLong, E. F., and Pace, N. R. (1991) Analysis of a marine picoplankton community by 16S rRNA gene cloning and sequencing. *J. Bacteriol. 173*, 4371−4378.

(2) Rondon, M. R., August, P. R., Bettermann, A. D., Brady, S. F., Grossman, T. H., Liles, M. R., Loiacono, K. A., Lynch, B. A., MacNeil, I. A., Minor, C., Tiong, C. L., Gilman, M., Osburne, M. S., Clardy, J., Handelsman, J., and Goodman, R. M. (2000) Cloning the Soil Metagenome: a Strategy for Accessing the Genetic and Functional Diversity of Uncultured Microorganisms. *Appl. Environ. Microbiol. 66*, 2541−2547.

(3) Sommer, M. O. A., Dantas, G., and Church, G. M. (2009) Functional Characterization of the Antibiotic Resistance Reservoir in the Human Microflora. *Science 325*, 1128−1131.

(4) Gillespie, D. E., Brady, S. F., Bettermann, A. D., Cianciotto, N. P., Liles, M. R., Rondon, M. R., Clardy, J., Goodman, R. M., and Handelsman, J. (2002) Isolation of Antibiotics Turbomycin A and B from a Metagenomic Library of Soil Microbial DNA. *Appl. Environ. Microbiol. 68*, 4301−4306.

(5) Sugimoto, Y., Camacho, F. R., Wang, S., Chankhamjon, P., Odabas, A., Biswas, A., Jeffrey, P. D., and Donia, M. S. (2019) A metagenomic strategy for harnessing the chemical repertoire of the human microbiome. *Science 366*, eaax9176.

https://dx.doi.org/10.1021/acs.biochem.0c00033
Biochemistry XXXX, XXX, XXX−XXX