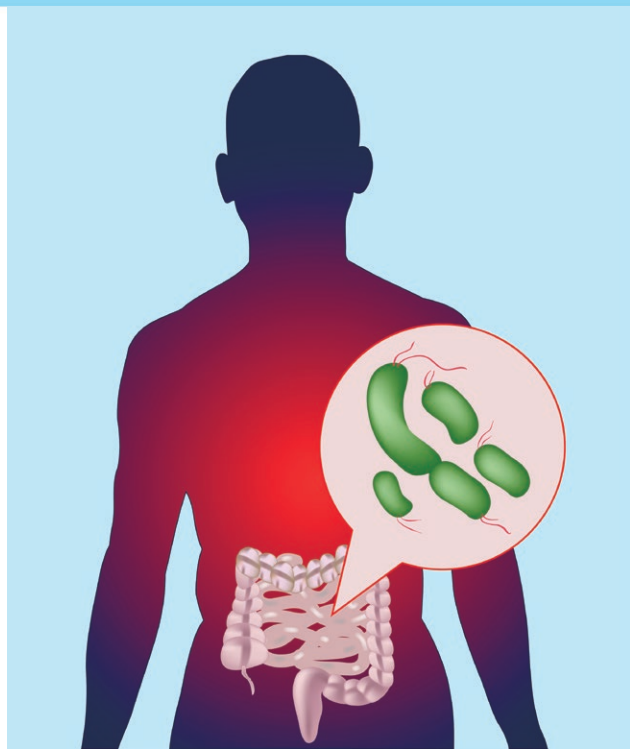
METABOLON®

UNLOCKING MICROBIOTA FUNCTION



Metabolomics as a Rosetta Stone for Understanding the "Bugs" Living Within Us

A wave of publications continues to cascade from top scientific journals illustrating that the "bugs" (bacteria) that live on and within us have an important influence on our health. The collection of bacteria is referred to as the microbiota or microbiome, and their breadth of influence on our health is astonishing.

Bacteria can dictate how drugs or metabolites interact with our brain, make us susceptible to infectious diseases, and affect a host of conditions including cardiovascular disease and cancer. Since they have cohabitated with humans throughout evolution, it's not surprising that they play such an important role. For better or worse, we're in this together.

While many recent publications associate different bacteria to certain diseases, they have often been criticized for failing to clarify how the microbiota functionally influences disease. In fact, the discussion sections of many of publications from the past few years reveal a need to move beyond "description" and into "function or mechanism."

It's All About Function

Function is where metabolites come in. The language and currency of microbial communities throughout nature are small molecules—metabolites. This is not lost on microbiota researchers. Many studies conduct some form of metabolite profiling, which often provides a key element to bringing more functional insight to the research. However, most microbiome studies have focused primarily on determining the type of microbes present and sometimes the collection of genes they contribute.

Now, there is a palpable shift among many key opinion leaders in the microbiome field, who have started promoting metabolomics as a way forward in assigning function more directly to the microbiota. For a good example of this, see "Specialized Metabolites from the Microbiome in Health and Disease," *Cell Metabolism,* 2014.

Small Molecules Reveal More About Host-Microbiota Interaction

Metabolomics can take on many forms, each providing different levels of insight; the type of information you get from a technology that profiles 40 metabolites, such as NMR, is distinct from the information you get from a technology that measures 1,000 or more metabolites, such as LC/MS.

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We believe that to effectively address the complexity of the microbiota's influence on human health, you must employ a technology that is capable of surveying host metabolism, xenobiotics, dietary metabolites and novel metabolites produced by the microbiota. This is what Metabolon's Precision Metabolomics™ platform does: it offers a very precise, systematic surveillance of the metabolome, which may include novel, bacterially-produced compounds.

Combining metabolomics with traditional microbiome genetic research tools has resulted in some pretty exciting findings in gut microbiome research. We are pleased to work with many top labs in the field as they embrace a more comprehensive approach to capturing the small molecule complement of the host-microbiota interaction.

- Using our metabolomics platform, Sarkis Mazmanian's group at Caltech discovered that 4-ethylphenylsulfate was altered with behavior in a mouse model of autism. They developed a probiotic strategy that led to the reduction of 4-EPS and a reduction in the behavioral phenotype.[1]
- Function is also being explored in pathogenic Clostridium difficile infection (CDI). Susceptibility to CDI can arise after treatment with broad-spectrum antibiotics and is linked to 14,000 American deaths each year. Our work with Vincent Young's lab at the University of Michigan illuminated specific metabolites that create a favorable environment for CDI, thus providing insights on targeted approaches to prevention.[2]
- Many people struggle with repeated weight gain and loss known as the "yo-yo effect." Investigators at the Weizmann Institute of Science used microbiome profiling and metabolomics to show that several plant metabolites metabolized by the microbiome were involved in this effect.[3]
- The ultimate prize for combining metabolomics and microbiome research is human health. We are excited about the collaboration we have with Craig Venter's company, Human Longevity, Inc., to dovetail genomic, microbiome analysis with metabolomics data.

Supporting References

1. Hsiao, E.Y. et al. "Microbiota Modulate Behavioral and Physiological Abnormalities Associated with Neurodevelopmental Disorders." *Cell* **155**, 1451-1463 (2013).
2. Theriot, C.M. et al. "Antibiotic-Induced Shifts in the Mouse Gut Microbiome and Metabolome Increase Susceptibility to Clostridium difficile Infection." *Nature Communications* **5** (2014).
3. Thaiss, C.A. et al. "Persistent Microbiome Alterations Modulate the Rate of Post-Dieting Weight Regain." *Nature* **540**.7634 (2016): 544-551.

Making Sense Out of Skin Microbiota

We believe this is an opportune time for applying metabolomics to another dimension of the human microbiota—the skin. Like the gut, our skin contains an entire ecosystem of microorganisms that are not just important in dermatological conditions such as acne, psoriasis and rosacea, but also in immune function. The skin is a major barrier to infection, and the microbes that live upon it are a front line of defense.

Microbiota research in the skin field is at an earlier stage compared to the gut. The first waves of basic characterization of the microbes that colonize the skin are completed, but studies probing associations with various conditions and diseases are few, relative to gut microbiome research. By using metabolomic technology as a first-line tool, skin researchers can bypass the criticisms, like not assigning enough "function" to studies.

Realizing the importance of metabolomics in understanding skin biology, we have invested a tremendous effort in methods and tools for skin research. In addition to our metabolomics platform and accompanying methods for skin biopsies and tape strips, we have focused panels directed at lipids, a metabolite class of high importance in skin biology, in specific skin regions—the sebum and stratum corneum.

We envision that this arsenal of tools will not only promote better understanding of the basic principles governing skin biology, but also become a frontline approach for understanding the complex interaction between the host and microbiota that govern skin health.

Cracking the Functional Code

Much as the Rosetta Stone was vital to deciphering a previously untranslated ancient language, metabolomics may hold the key to unlocking the secrets of the microbiota. Microbiota research has outlined an important landscape for human health. Combining metabolomics with existing research tools will help populate this landscape with functional detail.

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