Global metabolomic initiative announced: Scientists set sail on the uncharted waters of the metabolome

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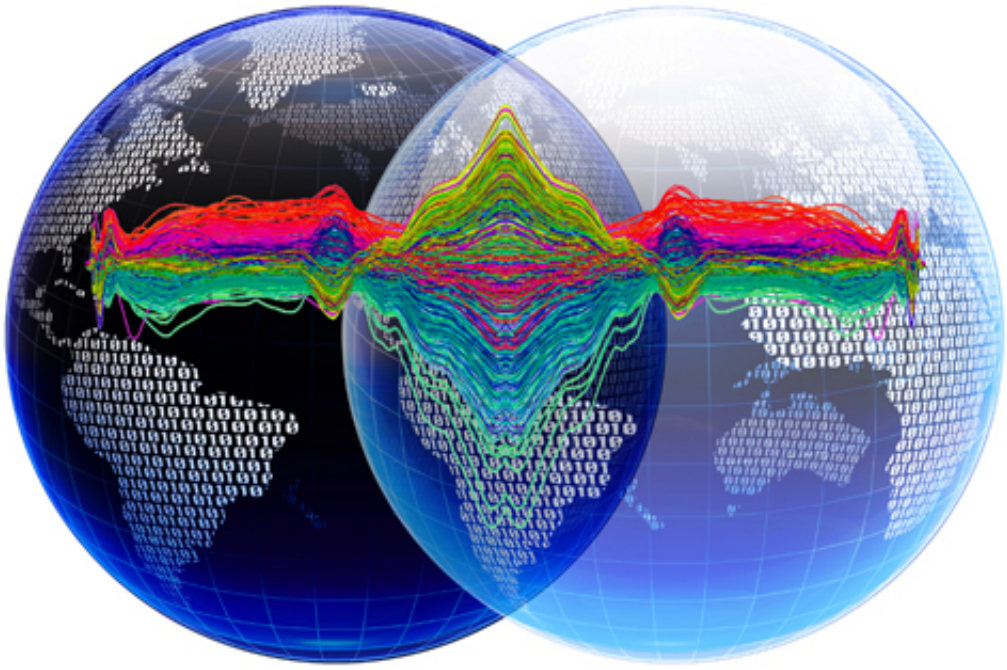

Credit: Patti/Suizdal

Investigators at Washington University and The Scripps Research Institute have announced the launch of a "Global Metabolomic Initiative" to facilitate meta-analyses on studies of the metabolism of bacteria, yeast, plants, animals and people.

The announcement of the Global Metabolomic Initiative was sent to

more than 1,600 registered XCMS Online users who have uploaded a total of more than 35,000 files of metabolomic data to a web-based processing platform called XCMS Online.

XCMS Online is a public resource developed by Gary Siuzdak and colleagues at The Scripps Research Institute. Siuzdak, PhD, director of the Scripps Center for Metabolomics, is a pioneer in the systematic study of metabolites (metabolomics).

The goal of metabolomics is to take a urine, blood or tissue sample, analyze it with an instrument called a mass spectrometer, and acquire a complete profile of all of the small molecules in the sample. The profile might reveal whether the sample donor is ill, at risk of developing a disease, has been exposed to a toxin, or is unable to tolerate a drug therapy.

Gary J. Patti, assistant professor of chemistry, genetics and medicine at Washington University in St. Louis, who is co-leading the XCMS Online meta-study, predicts that many groundbreaking discoveries will emerge from these analyses.

"A lot of people suddenly are excited about metabolism again," Patti says. "People are seeing that metabolism provides a downstream signature of disease states which is complementary to that provided by genes and proteins. As a result, there has been a huge resurgence of interest in this area."

Why is metabolomics interesting?

Patti has good reason for his optimism. Metabolomics has existed as a discipline for only about a decade. But there have already been many examples of "studies in which metabolomics has provided unparalleled insight into disease," Patti says.

He describes studies underway in his laboratory focusing on chronic pain. "We identified a molecule that, prior to our studies, was not known to be a naturally occurring compound. We have demonstrated that this molecule is an important player in mediating chronic pain, and this has opened up new avenues for therapies that could help millions of people," he says.

He emphasizes that the molecule (dimethylsphingosine) was found in what is called an untargeted search that compared thousands of metabolites in rats suffering from chronic pain to those that were healthy. "If we had performed a targeted analysis of only those molecules thought to be relevant in pain biology, we would never have identified dimethylsphingosine as an important player," he explains.

Targeted studies of metabolites, whose power is boosted by the sensitivity and throughput of modern day mass spectrometers, have also achieved important insights, he says. For example, targeted metabolic screening has recently revealed that branched-chain amino acids (the building blocks of protein) are more strongly associated with insulin resistance than many common lipids (fats).

But untargeted searches are voyages of discovery into unknown territory that may have completely unforeseen results.

An untargeted study by Stanley Hazen of the Cleveland Clinic, for example, showed an unexpected link between microbes in our guts and the risk of cardiovascular disease. Levels of a metabolite known as TMAO, a by-product made when gut bacteria break down dietary fat, have proved to be a strong predictor of heart disease, Patti explains.

"Even though we're just getting started, the success of the field has already been pretty extraordinary," he says.

Where meta-analysis comes in

"When they hear the word metabolism, most people think of glycolysis, or the Krebs cycle. But the compounds on those pathways represent only a small fraction of the peaks that we are detecting in untargeted metabolomics," Patti explains.

In fact, Patti said, only about half of the compounds that his laboratory routinely detects in biological samples actually match metabolites in biochemistry textbooks, publications, databases, etc.

Nobody really knows how many metabolites there are. "Some think it's just a few thousand, others argue that it's substantially more. We don't know," Patti says.

"The key is to find the metabolites that are physiologically important in health and disease. One way to find them is by comparing the results of large numbers of studies. We can do this by harnessing the statistical power of thousands of studies from the Global Metabolomic Initiative," Patti says.

"Not only will we be able to make improved disease associations, but we will be able to average out potential artifact signals that may be complicating our analyses," he says.

Additionally, Patti explained, the scientists hope to find biochemical pathways common to organisms with different evolutionary histories. Patti's colleague and collaborator Tim Schedl, professor of genetics at Washington University, refers to this as "metabolic homology" by analogy with more familiar sequence and anatomical homologs, such as the similarity of the bones in the forelimbs of a bat, seal, cat and human.

Integrating metabolomics and genetics

As this borrowing suggests, Patti and his colleagues seek to integrate genetic and metabolic information. "It turns out that it is harder to correlate genes with phenotype than was originally expected," Patti says. "So we've started to leverage new technologies, and one of the new technologies is metabolomics, which has already proven to be clinically diagnostic."

"By integrating global metabolomic and genomic data, we hope to get the best of both worlds," says Patti. He explains that the ultimate objective is to connect genotype to phenotype by integrating metabolomics into the already successful Genome Technology Access Center (GTAC) at the School of Medicine.

Since the announcement of the Global Metabolomic Initiative was sent to XCMS Online users, hundreds of research groups have agreed to participate. Patti is betting his career that many startling discoveries will soon follow.

Provided by Washington University in St. Louis

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