Expanding database enables discoveries in emerging field of metabolomics

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LA JOLLA, CA – September 10, 2012 – Over the last decade, metabolomics has emerged as the newest of the "omic" sciences (following genomics and proteomics) to provide comprehensive biochemical information about cellular metabolism. This new field has revealed that many of the chemicals involved in or produced through metabolism are currently unknown, but may play vital and previously unappreciated roles in human health and disease.

A major hurdle in profiling both unknown and known metabolic compounds ("metabolites") has been the scarce amount of reference data. But a team from The Scripps Research Institute has developed a massive, searchable online metabolite database that is transforming the field and being widely used in research on countless conditions including cancer and chronic pain.

The researchers describe the newly expanded database, called METLIN, and its potential benefits in the September issue of the journal *Nature Biotechnology*.

Getting Off the Beaten Path

Scientists once focused on only the major metabolic highways, well-known pathways such as glycolysis and the Krebs Cycle. New metabolomic studies have shown that other pathways and metabolites, however, also play critical roles in fundamental biological processes and the progression of disease.

"For decades biochemical studies have targeted only a handful of canonical metabolites, and comprehensive profiling has been mostly limited to genes and proteins," said Gary Patti, a former postdoctoral fellow at Scripps Research now an assistant professor at Washington University in St. Louis who helped develop the database. But now he says the new field of metabolomics has emerged with huge promise for medical and other advancements. "I think it's a really exciting time because the insights being provided by metabolomics are in some cases affecting the way in which we think about fundamental biochemistry," he said.

The sheer number and complexity of metabolites offer scientists a colossal challenge. While DNA studies of genes that code for proteins offer clues about how many proteins there are and their functions, there's no such map for metabolites—which include a huge range of chemical types, from amino acids, carbohydrates, and steroids to large, complex fatty acids. No one knows how many metabolites there are in humans, though the number may well be over 100,000, and other organisms may have their own unique arrays.

Digging In

Metabolites can be isolated and analyzed from almost any biological specimen, including tissues, blood, urine, and tumors. The most sensitive technique for analyzing metabolites is mass spectrometry. By using cutting-edge mass spectrometric technologies, the molecular weight of thousands of metabolites can be measured within a few minutes. Previously, researchers might spend days combing databases and other sources of information to identify just one metabolite of interest.

"If you don't have a database like METLIN, the value of metabomic data would be very limited because each study would require manual searches and ultimately fail to culminate in enough reference data to arrive at conclusive metabolite identifications," said team leader Gary Siuzdak, a metabolomics expert at Scripps Research.

It was against this landscape that Siuzdak's group recognized the need for a consolidated and expanded metabolite database to meet the group's own needs as it struggled to understand key metabolic processes. Efforts to build such a resource began in 2004 and the database they dubbed METLIN was initially built upon slowly. Information was scarce and entered manually, sometimes after curating chemistry books manually for new structural information. Researchers in the lab would compete to see who could add the most in a week. Simultaneously, the lab also began cataloging experimental tandem mass spectrometry data on these compounds and established the first of such resources to provide structural information on metabolites that can be used to identify metabolites.

Over the past few years, determined to accelerate their work, group members gained major momentum largely by partnering with companies like Sigma, Cayman, ChromaDex, as well as labs at Scripps Research (Boger), University of California, San Diego (Gerwick), the Joint BioEnergy Institute (Berkeley), and now Washington University (Patti) to facilitate acquisition of more molecules on which to generate tandem mass spectrometry data.

More than 10,000 Metabolites

Now METLIN includes more than 60,000 compounds with detailed, high-resolution tandem mass spectrometry information on more than 10,000 metabolites, by far the largest in the world. And the Siuzdak group is far from done. "METLIN is still growing as we speak," said Ralf Tautenhahn, a senior research associate in Siuzdak's lab and first author of the paper. "It's a key tool for all our projects." Once a metabolite is identified, researchers can begin working out how it functions in the body and in disease.

A key benefit of the database is that it goes beyond basic molecular weight—which might be the same for a range of different compounds. The tandem mass spectrometry data allows for a higher level of confidence in

identifying these molecules from biological systems. This involves bombarding individual compounds with gas molecules, which causes them to break apart in unique ways. The weights of the resulting molecular fragments offer a sort of chemical signature for each metabolite that researchers can use to match unknowns more precisely.

Though you can search METLIN manually, the Scripps Research team has also developed software called XCMS Online that performs detailed automated searches. Users can input their own data and the coupled XCMS-METLIN system will come back with precise matches, or if there's no direct match, it will identify structurally similar metabolites. "It really does accelerate the whole process of discovering new molecules associated with diseases and research in many different areas," said Siuzdak.

Tapping the Potential

The Siuzdak team has already had major successes using the database. The researchers recently identified a metabolite that is associated with chronic pain when found in higher than normal levels. Finding ways to break down this metabolite or to prevent it from forming might lead to new treatment options for chronic pain sufferers.

Other projects are focused on cancer. While some researchers are looking for metabolites that might be present in the bloodstream as early indicators of cancer, Siuzdak's group is identifying metabolites involved in cancer's progression that might offer targets for new therapies. Patti's lab at Washington University is further investigating the role of metabolism in chronic pain and is also looking into metabolite roles in aging and drug addiction.

But public access means METLIN's reach stretches far beyond Scripps Research. "When we first started doing this, I was expecting a couple of hundred people in the world to use it," said Siuzdak. Instead, he and his colleagues were shocked to find users by the thousands exploring a huge range of topics. Some researchers are looking for metabolites produced after ingestion of drugs to aid in forensics work; others are interested in ways to detect signs of pesticide ingestion.

"What's really exciting about this is seeing that something we created is being so widely used," said Siuzdak, "It definitely makes us feel good to think that we've accelerated the progress of science and allowed a lot of other scientists to do things they wouldn't have been able to do otherwise."

Source: **Scripps Research Institute**

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