New "Omics" Technique Taps into Unknown Metabolome

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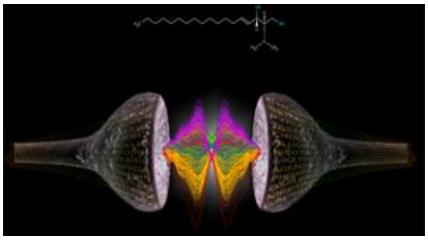
Researchers using untargeted metabolomics identify a new candidate therapeutic target for chronic pain.

A novel potential drug target for the treatment of chronic pain has been revealed by a newcomer to the "omics" family: untargeted metabolomics.

The newly characterized metabolite—N,N-dimethylsphingosine (DMS)—induces long-lasting pain responses to normally harmless physical stimulation when injected into rats, according to a study published in *Nature Chemical Biology.* Previously, the biological role of DMS remained largely unknown, and its involvement in pain sensation had not been determined.

"We wouldn't have been able to pull the DMS compound out using the targeted metabolomics approach because we never would have thought to look at this particular compound," said study author Gary Patti, a biochemist at Washington University. "This study really highlights the value of doing untargeted metabolomics to find compounds that have biological importance that previously wouldn't have been associated with a particular condition of interest."



Bioinformatics analysis superimposed on synapse between neurons. The analysis revealed N,N-dimethylsphingosine (DMS, above) as a naturally occurring metabolite and an active molecule in chronic pain. Source: Gary Siuzdak

In contrast to most metabolomics studies that focus on a limited number of preselected biomarkers of disease states or other molecules of interest, untargeted metabolomics allows scientists to analyze thousands of metabolites in an unbiased manner. As scientists realize that the number of metabolites in biological systems is much larger than previously thought, the usefulness of this approach is becoming increasingly clearer.

"Targeted metabolomics made a lot of sense because we thought we really had our finger on the pulse of all of the important metabolic pathways," he said. "But what we're seeing with the increasing sensitivity of mass spectrometers is actually there are many more metabolites than we can account for with those canonical pathways, and so using untargeted metabolomics is important because it allows us to tap into that unknown space."

To search for pain-related molecules in the new study, Patti and his collaborators analyzed metabolites in rats experiencing chronic pain after a surgical procedure in which one of their leg nerves was cut. When the researchers compared these metabolites to those in rats that did not undergo this procedure, they found that the vast majority of pain-associated metabolites were located in the spinal cord.

"We were surprised to see that almost all the metabolites that were changing significantly were so far removed from the site of injury," Patti said.

Through mass spectrometry analysis of these molecules, the researchers found that DMS was more prevalent in the spinal cords of rats experiencing pain three weeks after surgery than in control rats. Healthy rats injected with DMS remained abnormally sensitive to nylon filaments pressed against their hindpaw for at least three days. In vitro studies revealed that DMS may elicit pain by causing cells called astrocytes to release proteins that promote inflammation, a biological

response that normally protects the body from harmful substances.

DMS probably plays an analogous role in rats and humans because they share similar metabolic pathways and processes related to DMS production, Patti said. He and his collaborators plan to test this possibility, look for enzymes that synthesize DMS and could be candidate drug targets, and use untargeted metabolomics to study biochemical pathways involved in autoimmune diseases and viral infections.

References

1. Patti, G.J., O. Yanes, L. Shriver, J.-P. Courade, R. Tautenhahn, M. Manchester and G. Siuzdak. 2012. Metabolomics implicates altered sphingolipids in chronic pain of neuropathic origin. Nature Chemical Biology **VOL: XXX-XXX**.

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