Metabolomic Study Finds Microbe Metabolites in Mammalian Blood

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By Andrea Anderson

NEW YORK (GenomeWeb News) – Gut microbes can influence mammalian metabolism, according to a new metabolomic study that found bacterial metabolites circulating in the mouse bloodstream.

In a study scheduled to appear online this week in the *Proceedings of the National Academy of Sciences*, researchers from The Scripps Research Institute and the Genome Institute of the Novartis Research Foundation used chromatography and mass spectrometry-based approaches to compare the blood metabolites of germ-free and typical mice. They found that the presence of microbes tripled the number of unique metabolites in mouse blood. And the specific compounds detected are providing new clues about microbe-host interactions.

"One of the very surprising things that we found is just the number and magnitude of the changes" that the microbiome conveys, lead author William Wikoff, post-doctoral researcher in Gary Siuzdak's lab at the Scripps Research Institute's Center for Mass Spectrometry, told *GenomeWeb Daily News*.

There are roughly a hundred times more microbial than human genes in the human body. Consequently, the microbiome has been implicated in everything from human health and metabolism to disease pathology and immune response. But efforts to understand the microbiome and its interactions with host biology have been difficult, since many microbes cannot be isolated and cultured in the laboratory.

Along with metagenomic studies that catalogue microbes, the burgeoning field of metabolomics is providing researchers with a window into the complex interactions between microbes and their mammalian hosts. Although researchers and physicians have been measuring specific metabolites, such as blood sugars for a long time, metabolomics now lets researchers look at dozens, hundreds, or even thousands of molecules in a single experiment, Wikoff explained.

In an effort to explore interactions between mammalian host and microbial metabolism, the researchers used an Agilent 6510 quadrupole time of flight LC/MS/MS to characterize the metabolites in blood samples — which represent a snapshot of overall metabolism — from ten germ-free and ten normal mice that had been fed sterilized food.

The team's results suggest there are hundreds of metabolite changes depending on whether mice are colonized by microbes or not. While thousands of metabolites were present in both types of mice, almost 150 were identified exclusively in wild type mice — roughly three times as many unique metabolites as the researchers as they detected in the germ-free mice only.

The team speculated that the differences may be due to a combination of microbial metabolites and differences in the conversion of host metabolites in the presence of these bugs. And while Wikoff said the researchers can't entirely rule out contributions from other bacteria, he and his colleagues believe the effect is primarily due to gut microbes.

One molecule in particular caught the researchers' attention: indole-3-propionic acid, or IPA, an antioxidant that's currently being pursued as an experimental Alzheimer's treatment. The researchers found just one bug producing this compound, *Clostridium sporogenes*. As expected, when they threw *C. sporogenes* into the germ-free mice the team was subsequently able to detect IPA in the mouse bloodstream.

Such work may have implications for understanding and designing effective probiotics, Wikoff said, though he believes it's still "pretty early" to be trying to use certain microbes to improve health. He argued that probiotic development should rely on more studies such as this one, aimed at understanding the compounds that specific microbes produce in the host.

The researchers were also surprised to see that one or more "phase II" metabolic

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Crijns et al., *PLoS Medicine*
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pathways — normally associated with clearing drugs or foreign molecules — were active in the presence of microbes. "We think of these as pathways for clearing drugs," Wikoff said.

He and his colleagues speculate that the phase II activity in wild type but not germ-free mice suggests these pathways may have initially evolved as a method for dealing with microbial interlopers. "We think this provides some additional evidence that phase II molecular pathways evolved from the need to clear these microbial metabolites from the blood," Wikoff explained.

In the future, Wikoff plans to continue colonizing germ-free mice with specific types of bacteria to determine how these microbes influence the metabolites in mouse blood and urine. Though he said it is more complicated to explore microbial metabolomics in humans, he noted that looking at a large sample of individuals from different populations could provide clues to metabolic interactions between humans and their microbiome.

Science

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