

## LINKS BETWEEN GUT BACTERIA AND CAVERNOMA FORMATION

***This file contains two reports on a paper published in the scientific journal Nature in May 2017 on the link between gut bacteria and cavernoma formation. The first has a fairly inelegant title, with the benefit of being eye-catching!***

### **Could Poop Pills Be Used to Prevent a Stroke? These Scientists Are Investigating**

[Laura Entis](#)

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The microbiome, or the complex ecosystem of bacteria that resides in the body, is experiencing a renaissance. Once largely ignored by the medical community, scientists have [linked the microbiome to a variety of diseases](#), including obesity, diabetes, and depression. Now a [new study](#) makes the interplay between the microbiome and general health more explicit: bacteria in the gut, it suggests, could cause a brain disorder.

The paper, which was published in *Nature*, traces a connection between the formation of blood-filled bubbles in the brain, called cerebral cavernous malformations, and the presence of a particular strain of bacteria.

Dr. Mark Kahn, one of the study's authors, has studied this disorder, which can lead to serious conditions including seizures and stroke, for nearly a decade. It was only recently, however, that he made the connection between the disease and gut bacteria populations.

Below, he explains how his team of researchers stumbled on the link between cerebral cavernous malformations and the microbiome, and how this revelation could shape our understanding of how we treat a range of disorders. (Spoiler alert: It could involve fecal transplants via poop pills.)

*This interview has been edited for clarity and length.*

#### **How common are cerebral cavernous malformations?**

Pretty common. They occur in up to one in 100 people, although most of this group isn't born with a genetic predisposition. In most cases, there is typically a sudden, single, solitary lesion. But about 20% of patients have what is called a familial form of the disease, which is much more severe. Some present as infants, and experience stroke or seizures. Instead of having one lesion, they can have tens or even hundreds of lesions.

#### **You've previously linked the familial form of the disorder to genetic mutations. How did you discover the microbiome might also be involved in the presentation of the disease?**

When we deleted genes in mice, they developed cerebral cavernous malformations [in humans, this gene is mutated in many CCM patients]. At least at first.

But then our lab moved from one building at the University of Pennsylvania to a different building. When we moved the mice to the new building, they stopped showing lesions. Everything was being done exactly the same as in the building a block away. It was pretty mysterious and it pointed to an environmental influence. We hadn't changed the genetics of these mice; all we had done was put them in a different facility.

This was a huge problem for us, until we came across an important clue. [To delete the relevant gene] we would inject the mice at birth. By putting a needle into an animal's abdomen, occasionally the needle might go through part of the bowel, and cause a bacterial abscess. It's actually pretty common in people too. If bacteria escapes from your gut and

into your belly, it can end up causing a localized infection, which is like a large pimple, but in your abdomen.

Although this was a rare event, the animals that developed these abscesses were also the only animals developing lesions.

### **The bacterial abscesses were somehow causing the lesions?**

Yes. We started to give them infections deliberately and when we did, we found they drove the development of massive numbers of cerebral cavernous malformations.

### **What did this suggest, and how did it relate to the relocation of your lab?**

That a component of bacteria, when it gets into the blood, is what was driving the formation of lesions. This was totally unexpected! Why would a brain vascular malformation come from bacteria?

Once we knew that, we went back to the move in lab locations. If we had animals with the disease in facility A, and not in facility B, maybe that's because when you move to a new place, the bacteria changed.

### **So a change in location can alter the microbiome?**

It happens all the time in science and in human life. I'm in Italy now. If I stayed here for the next five years, I'd probably have a different microbiome than if I stayed in Philadelphia.

When we changed the mice's environment, the bacteria in their guts changed. It wasn't a deliberate experiment, it was serendipitous. But it had a profound effect. When we sequenced the types of bacteria in their gut, we discovered a change in one type of bacteria. They still had the deleted genes, but they weren't developing lesions.

### **How does this apply to human patients?**

In the familial form of the disease, there is an enormous variation in clinical course. There are patients who have the exact same mutation in the same gene, but some of them never develop lesions, and some of them do, as infants.

This is very unusual for a genetic disease. If everyone has same genetic problem, they should all present the same.

### **So it's possible that in humans, as well as mice, gut bacteria could determine whether patients with the same genetic mutation develop lesions?**

It's a huge amount of work to look at the human microbiome. We haven't done it yet. But what we are starting to do is look at several hundred patients in New Mexico who all have the same exact mutation on the CCM1 gene.

### **By collecting fecal samples from these patients, then, you're hoping to make the same connection in humans that you did in mice?**

We haven't proven it. But [previous research in mice suggests] maybe there is a biome that is protective, and a biome that is not.

What we want to do is measure this bacteria [in humans], which requires getting samples and careful analysis. That's exactly the next step.

### **If the microbiome and the development of the disorder *is* linked in humans, how could this lead to new treatments?**

It's not that hard to change someone's biome. You give them antibiotics, which kills off their bacteria. And then you perform a fecal transplant, in which you literally giving them feces from someone else.

In theory, this will seed the gut with new bacteria. If we can prove the biome is as influential in people as it is in mice, we can actually treat people by giving them biomes we believe are protective. This is all still very hypothetical, but I do think we will see some diseases treated this way in the next 10 to 20 years.

### **How big of a deal is this?**

The implications are pretty big. No drugs are without side effects, which makes the microbiome very attractive. If we are right, [i.e. gut bacteria impacts the formation of lesions in people with a familial form of the disorder], by changing a patient's' biome, he can be protected for the duration of his life without taking drugs. It could offer more elegant therapies.

### **What are the potential drawbacks?**

We are just starting to learn about the microbiome. There are almost no diseases right now for which altering the microbiome is an accepted therapy. This is all very new.

### **There's been a lot of research linking the microbiome to a host of disorders, including obesity, diabetes, and ADHD. Is it possible fecal transplants could inadvertently cause new problems, even as they solve old ones?**

You know, there's no free lunch: whenever you alter something, you maybe get some good, but you are probably going to get some bad. We're at the very beginning of this era of medicine and biology, and we don't know what the answers are yet.

### **Are there any general takeaways you think your study reveals?**

We've worked on this disease for almost a decade. We never imagined in our wildest flights of idea that it could be affected by bacteria in the gut. The gut is in no obvious way connected to the brain.

What this really tells you is that the biology in the body is complicated—there are so many things going on that we are not aware of yet.

## Researchers connect brain blood vessel lesions to intestinal bacteria

Thursday, May 18, 2017

**NIH-funded pre-clinical study links gut microbes and the immune system to a genetic disorder that can cause stroke and seizures**

**A study in mice and humans suggests that bacteria in the gut can influence the structure of the brain's blood vessels, and may be responsible for producing malformations that can lead to stroke or epilepsy. The research, published in Nature, adds to an emerging picture that connects intestinal microbes and disorders of the nervous system. The study was funded by the National Institute of Neurological Disorders and Stroke (NINDS), a part of the National Institutes of Health (NIH).**

**Cerebral cavernous malformations (CCMs) are clusters of dilated, thin-walled blood vessels that can lead to seizures or stroke when blood leaks into the surrounding brain tissue. A team of scientists at the University of Pennsylvania investigated the mechanisms that cause CCM lesions to form in genetically engineered mice and discovered an unexpected link to bacteria in the gut. When bacteria were eliminated the number of lesions was greatly diminished.**

**"This study is exciting because it shows that changes within the body can affect the progression of a disorder caused by a genetic mutation," said Jim I. Koenig, Ph.D., program director at NINDS.**

**The researchers were studying a well-established mouse model that forms a significant number of CCMs following the injection of a drug to induce gene deletion. However, when the animals were relocated to a new facility, the frequency of lesion formation decreased to almost zero.**

**"It was a complete mystery. Suddenly, our normally reliable mouse model was no longer forming the lesions that we expected," said Mark L. Kahn, M.D., professor of medicine at the University of Pennsylvania, and senior author of the study. "What's interesting is that this variability in lesion formation is also seen in humans, where patients with the same genetic mutation often have dramatically different disease courses."**

**While investigating the cause of this sudden variability, Alan Tang, a graduate student in Dr. Kahn's lab, noticed that the few mice that continued to form lesions had developed bacterial abscesses in their abdomens—infections that most likely arose due to the abdominal drug injections. The abscesses contained Gram-negative bacteria, and when similar bacterial infections were deliberately induced in the CCM model animals, about half of them developed significant CCMs.**

**"The mice that formed CCMs also had abscesses in their spleens, which meant that the bacteria had entered the bloodstream from the initial abscess site," said Tang. "This suggested a connection between the spread of a specific type of bacteria through the bloodstream and the formation of these blood vascular lesions in the brain."**

**The question remained as to how bacteria in the blood could influence blood vessel behavior in the brain. Gram-negative bacteria produce molecules called lipopolysaccharides (LPS) that are potent activators of innate immune signaling. When the mice received injections of LPS alone, they formed numerous large CCMs, similar to those produced by bacterial infection. Conversely, when the LPS receptor, TLR4, was genetically removed from these mice they no longer formed CCM lesions. The researchers also found that, in humans, genetic mutations causing an**

increase in TLR4 expression were associated with a greater risk of forming CCMs.

“We knew that lesion formation could be driven by Gram-negative bacteria in the body through LPS signaling,” said Kahn. “Our next question was whether we could prevent lesions by changing the bacteria in the body.”

The researchers explored changes to the body’s bacteria (microbiome) in two ways. **First, newborn CCM mice were raised in either normal housing or under germ-free conditions.** Second, these mice were given a course of antibiotics to “reset” their microbiome. **In both the germ-free conditions and following the course of antibiotics, the number of lesions was significantly reduced, indicating that both the quantity and quality of the gut microbiome could affect CCM formation.** Finally, a drug that specifically blocks TLR4 also produced a significant decrease in lesion formation. **This drug has been tested in clinical trials for the treatment of sepsis, and these findings suggest a therapeutic potential for the drug in the treatment of CCMs, although considerable research remains to be done.**

“These results show that we can take findings in the mouse and possibly apply them at the human patient population,” said Koenig. “The drug used to block TLR4 has already been tested in patients for other conditions, and it may show therapeutic potential in the treatment of CCMs, although considerable research still remains to be done.”

Kahn and his colleagues plan to continue to study the relationship between the microbiome and CCM formation, particularly as it relates to human disease. **Although specific gene mutations have been identified in humans that can cause CCMs to form, the size and number varies widely among patients with the same mutations.** The group next aims to test the hypothesis that differences in the patients’ microbiomes could explain this variability in lesion number.

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- by Carl P. Wonders, Ph.D.

Article:

Tang et al. Endothelial TLR4 and the microbiome drive cerebral cavernous malformations. Nature. May 10, 2017.

Learn More:

[Cerebral Cavernous Malformation Information Page](#)

[www.ninds.nih.gov](http://www.ninds.nih.gov)

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