Potential drug target for dangerous E. coli infections identified

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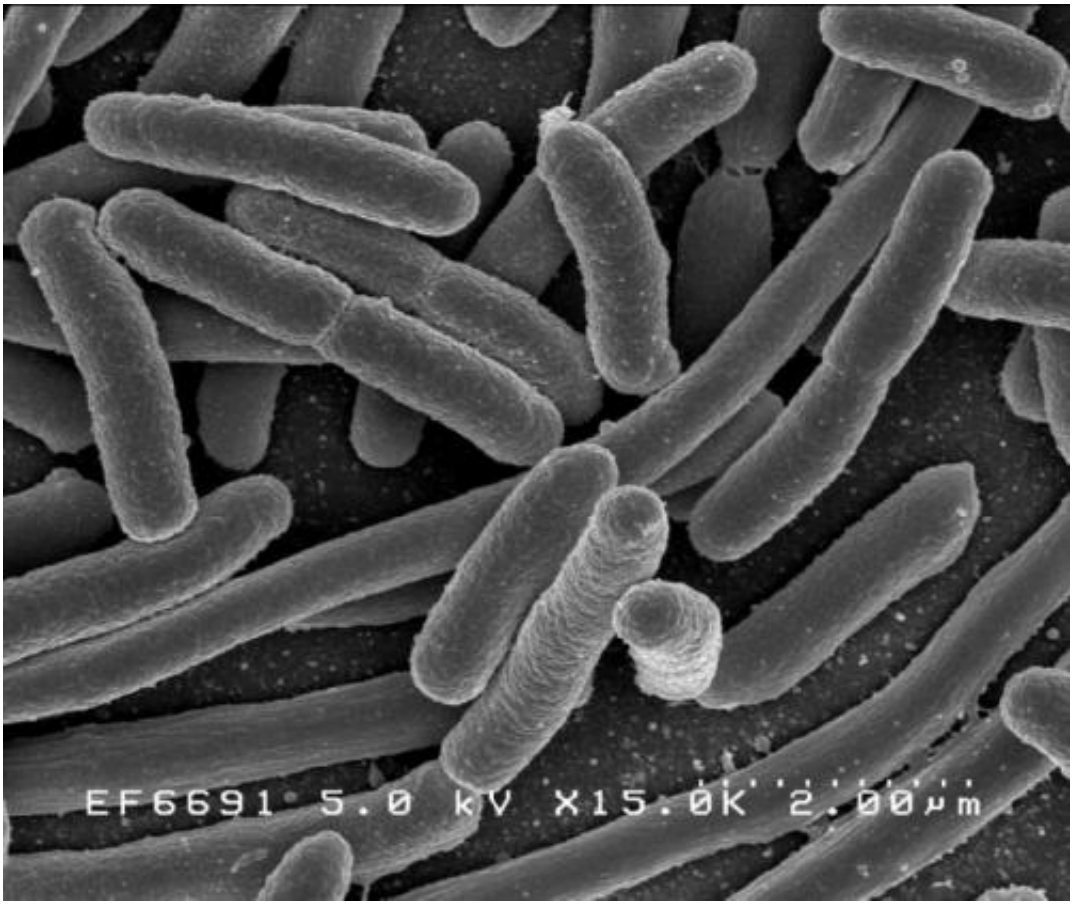

Escherichia coli. Credit: Rocky Mountain Laboratories, NIAID, NIH

Escherichia coli, known as E. coli, are bacteria which many people associate with causing mild food poisoning, but some types of E. coli can be fatal.

UNSW Science microbiologists studied an E. coli strain that causes a severe intestinal infection in humans: enterohemorrhagic E. coli (EHEC). Their findings were published this week in the *Proceedings of the National Academy of Sciences*.

EHEC is a food-borne pathogen that releases Shiga toxins during infection, resulting in kidney and neurological damage.

Dr. Jai Tree, the study's senior author, said the researchers' discovery of a new molecular pathway that controls Shiga toxin production was important because there was no commercially available treatment for EHEC infections.

"Antibiotic treatment of these infections is generally not recommended because antibiotics stimulate production of the Shiga toxin, leading to an increased risk of kidney failure, neurological damage, and death," Dr. Tree said.

"The new pathway that we have found reduces toxin production and is not expected to be stimulated by antibiotic treatment. So, our results identify a potential new target for the development of drugs that can suppress Shiga toxin production during EHEC infection. It's still early days, however, and we need to conduct a lot more research to understand if our findings apply to a broad range of clinical EHEC isolates and to both types of Shiga toxins produced by human EHEC isolates."

How EHEC infections start

Dr. Tree said there were several ways in which people could become infected with EHEC.

"EHEC is mainly found in the feces of cows and sheep and people can become infected through contact with farm animals and their feces, or

via person-to-person infection if people come into contact with tiny amounts of feces from a sick person—for example, directly or indirectly by touching contaminated surfaces," he said.

"This strain of E. coli can also spread through ingesting the bacteria by eating undercooked minced meat (for example, in hamburgers), eating contaminated fresh produce like salad vegetables, or drinking contaminated water or unpasteurised milk. Children under five years old and older people are at greatest risk of developing an EHEC infection."

EHEC outbreaks less common but deadly

Dr. Tree said while the prevalence of EHEC was low compared to other foodborne pathogens, the disease could be very severe or even fatal. EHEC is a type of STEC (Shiga toxin-producing Escherichia coli).

"EHEC outbreaks occur sporadically in Australia and worldwide. The most significant outbreak occurred in South Australia in 1995 and was caused by contaminated mettwurst, a semi-dry fermented sausage made from raw minced pork preserved by curing and smoking," he said.

"In that outbreak, 143 people were infected—23 of them suffered kidney and neurological damage. Many of these severe cases were in infants who suffered permanent kidney damage and later required kidney transplants. A four-year-old girl suffered multiple strokes and died three days after admission to hospital. This episode triggered a major food safety investigation and outbreaks since 1995 have been smaller."

Dr. Tree said globally, Shiga toxin-producing E. coli was still a major food safety concern after a large outbreak in Germany in 2011.

"The strain in Germany was spread mostly via consumption of

contaminated sprouts and in several cases, from close contact with an infected person," he said.

"During this outbreak more than 4000 people were infected and 50 people died."

New pathway hiding in plain sight

Dr. Tree said the UNSW research was the first discovery of a new pathway that controls the Shiga toxins in almost 20 years.

"In 2001, researchers at Tufts and Harvard universities first showed how production of the Shiga toxin was controlled by a bacterial virus, known as a bacteriophage, within the genome. This has been the only known pathway that controls Shiga toxin production for almost two decades," he said.

"We have extended that work to show a new mechanism of toxin control that is, surprisingly, buried within the start of the DNA sequence that encodes the Shiga-toxin messenger RNA—a working copy of the gene. We discovered a very short piece of the toxin messenger RNA is made into a regulatory non-coding RNA that silences the toxin and promotes growth of the pathogen."

Dr. Tree said their findings were a surprise because Shiga toxin genes have been well studied, with almost 7,000 published studies in the past 40 years.

"Only recently have we been able use advances in RNA sequencing technology to detect the presence of the new regulatory non-coding RNA embedded within the Shiga toxin messenger RNA," he said.

"This new regulatory non-coding RNA had been hiding in plain sight for

almost 20 years."

Implications for treating EHEC infections

Dr. Tree said the researchers' findings opened up new possibilities for the treatment of EHEC infections.

"Patients largely receive supportive care to manage disease symptoms and to reduce the effects of the toxin on the kidneys," he said.

"Our work shows a new mechanism for controlling toxin production that may be amenable to new RNA-based therapeutics to inhibit toxin production during an infection. We anticipate this would expand intervention options and potentially allow use of antibiotics that are currently not recommended because they stimulate Shiga toxin production. New treatments could therefore reduce the risk of kidney damage, neurological complications and death. We look forward to testing these new interventions in the next stage of our research."

More information: Brandon M. Sy et al. Early termination of the Shiga toxin transcript generates a regulatory small RNA, *Proceedings of the National Academy of Sciences* (2020). DOI: 10.1073/pnas.2006730117

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