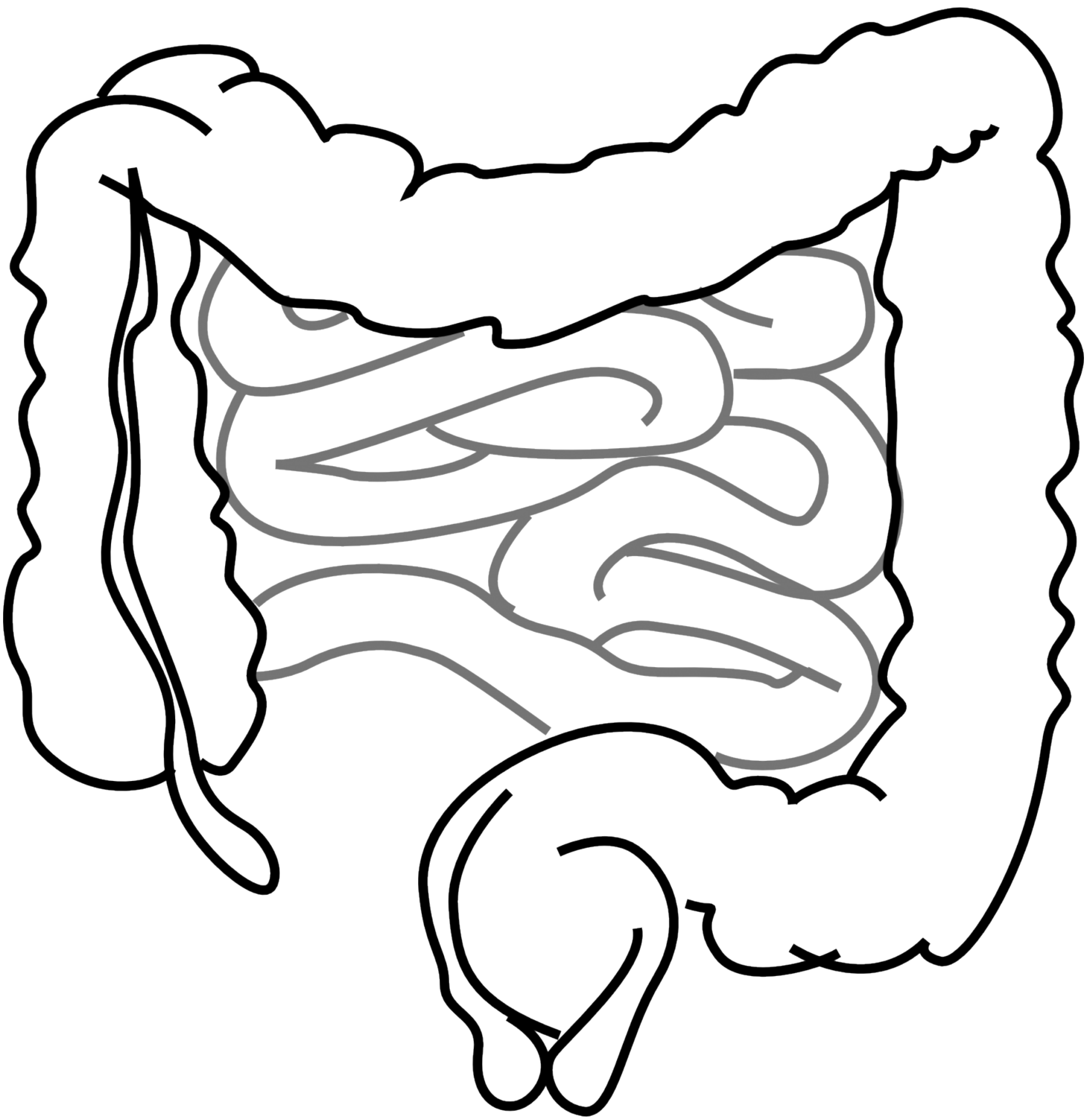
From the bottom of boats to the human gut, this beneficial bacterium has many uses

October 10 2019, by Padma Nagappan



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By scraping tubeworms off the bottom of boats in San Diego Bay to study them, San Diego State University researchers discovered a beneficial bacterium that aids in establishing colonies could also be a boon for human health, because the same process might already take place in the human gut.

While examining this bacterium that causes metamorphosis in the humble tubeworm, marine microbiologist Nicholas Shikuma discovered that the nanoscale syringe-like structures produced by it—a structure nicknamed the Death Star for the effect it has—could be used in the future to deliver novel therapeutics or vaccines to targeted cells and tissues in humans.

Tubeworms (Hydroides elegans) are tiny marine creatures with hard shells that cause a lot of trouble and economic loss for boat and ship owners. They stick to the bottoms of boats and form inches-thick crusty layers, and also attract other invertebrates like barnacles that then form on top of them. This process, called 'biofouling,' leads to additional weight and higher fuel consumption. That's why the shipping and boat building industry, and the U.S. Navy, are interested in finding out how they do this and what can be done to prevent it from happening.

Marine research led to significant discovery

"We've been studying tubeworms for several years with students in my lab to understand exactly why they are drawn to certain places in the ocean where they establish colonies," Shikuma said.

Previous research by others showed that like coral reefs, sea urchins and sea squirts, the tubeworms also needed a conducive environment to reproduce, so they typically gravitated to areas with healthy populations of bacteria like Pseudoalteromonas luteoviolacea, a beneficial bacterium. Shikuma discovered the bacterium has Metamorphosis Associated Contractile structures (MACs) – syringe-like structures that inject content into the larvae of tubeworm, helping transform it into juvenile worms.

What he and fellow scientists did not know was if the MACs were injecting a biochemical into the tubeworm to cause metamorphosis and to enable it to stick to boat hulls. Shikuma's lab used cryo-electron tomography imaging to study the structures and found arrays of spherical death star shaped injection systems, which are released by the bacterium.

They discovered the syringe structures contained a novel effector protein, Mif1, that regulates biological activity in the tubeworm host, and it's this protein that's responsible for causing metamorphosis.

It was Ph.D candidate Kyle Malter's job to figure out how the protein was causing metamorphosis.

"We accomplished this by creating the protein separately from the MACs complex and added it directly to the worms," Malter said.

He used electroporation—a microbiology technique in which an electrical pulse is applied to create temporary pores in cell membranes—in the tubeworm's cells so the protein was able to enter inside.

Stealing syringes from phages, but for good cause

"Lots of pathogens produce these syringe structures that typically cause disease," Shikuma said. "But this is the first time we discovered bacteria that use the syringe for a symbiotic purpose."

The MACs resemble similar syringe structures found on bacteriophages—viruses that infect bacteria—and with evolution, the bacteria have 'stolen' this structure from the phages, and have put it to good use.

"Phage typically attack bacteria with these structures, but instead of using it to infect other bacteria, the Pseudoalteromonas now uses it to interact with other animals, such as tubeworms, insects, and mouse cells," Shikuma said.

"MACs are created when the bacteria undergo cell lysis—when the cells blow themselves up—and the bacteria that do this die afterwards, so it's almost like altruism because it benefits the rest of the bacterial population."

Not every bacterium in this strain produces the MACs—only about one out of 50 do so –but since we can produce trillions of these bacteria, supply will not be an issue and more of them can be engineered to produce MACs, he explained.

Post-doctoral scholar Giselle Cavalcanti focused on genetic manipulation and testing of the bacterium.

"As this fascinating interaction happens between relatively simple model systems, some of their features are helping us reveal how environmental bacteria shape animal development in the ocean," Cavalcanti said. "We could identify the molecules underlying this bacterial-animal interaction due to our ability to grow and manipulate both the bacteria and the tubeworm in the laboratory."

The findings were published in *eLife* journal, and follow on the heels of a recent study from Shikuma's lab that was published in *Cell Reports* in June this year which looked at how this bacterium interacts in vitro with insect and mouse cells. That paper showed how the microscopic syringe structures could be modified as payloads that could potentially carry therapeutics or vaccines. Shikuma has obtained a provisional patent for the findings in both papers, on how to use the MACs to deliver modified proteins.

As a next step, current research in his lab involves mining data from the Human Microbiome Project to see if we humans have this same bacterial syringe structure in our guts that can be harnessed for therapeutics.

Provided by San Diego State University