Antibiotic Discovery and Global Climate Change in a Day's Work

It's neither plant nor animal, although it has attributes of both. It swims in tidal estuaries and oceans, emitting a chemical that gives oceans their familiar "sea" smell. And it has been blamed for massive fish kills, in Chesapeake Bay and elsewhere.

Its name is *Pfiesteria piscicida*, and it's a species of algae that has led Professor Robert Belas and colleagues at the Center for Marine Biology (COMB) down a highly productive research path, with potentially important applications in commercial aquaculture and implications for the health of global oceans.

Dr. Belas is a marine microbiologist whose attention was drawn to *Pfiesteria* during several toxic algal blooms—vast rafts of multiplying algae—that choked portions of the Bay in the late 1990s. Belas came to the problem from an oblique but fruitful angle: he is an authority on marine bacteria, and specifically, on bacterial chemotaxis, the means by which those tiny, single-celled organisms sense molecules in their environment and respond to them. Bacteria, it turned out, were playing a central role in the life of the Bay-choking algae.

A graduate student in Belas's lab, Todd Miller, isolated a bacterium in a family, or "clade," called *Roseobacter*, that had developed a very close working relationship with *Pfiesteria*. Belas's team discovered that this particular kind of bacterium, given the name *Silicibacter* sp. TM1040 (with the "TM" honoring Miller, its UMBI grad-student discoverer), was hitchhiking on the backs of the harmful algae.

TM1040 was a symbiont—it found a home on the surface of its algal host. This raised the question of whether it did something in return for the favor (not all symbionts are so thoughtful). All that the team knew, after Miller's early experiments, was that TM 1040 was the predominant bacterium in samples of *Pfiesteria* taken from the Bay. The first question was: how did the minuscule bacteria, tumbling around in the currents, locate and attach to their "ride"?

Belas, drawing on his expertise in chemotaxis, knew that *Pfiesteria* emitted a chemical called DMSP to which the bacteria were drawn, like homing pigeons. The "s" in DMSP stands for sulfur, and it is that sulfur which gives the ocean its unmistakable smell. No one is certain why TM1040 are drawn to DMSP, but the effect is clearly observed. Sensing DMSP in the water column, the bacteria use their fine, screwlike "propellers," called flagella, to swim toward their target—the algae—which, like everything in the water column, is also in motion. "It's something like the space shuttle moving in to dock with the International Space Station," Belas says. "Except in this case, the 'radar' is that chemical signal, DMSP, that the bacteria sense. Chemotaxis literally means *movement toward a chemical*, and this is an excellent example."

Within a few hours of latching on to their moving target, the bacteria undergo a remarkable physical transformation. They shed their flagellar paddles and enter a new phase of life. No longer motile creatures, they settle in on the surface of the algae, forming a patchy biofilm on their surface.

It's at this point that the story takes an even more remarkable turn, and it has to do with the hitchhiker's "payment" for a free ride. TM1040, now forming a thin film on the algae, begin to manufacture a chemical called TDA, which has antibiotic properties. Belas believes the bacteria utilize the sulfur in DMSP to manufacture TDA. In turn, TDA "essentially surrounds the algae, and we hypothesize that it protects them from unwanted, potentially harmful bacteria that could colonize their surface and (unlike TM1040) consume them," he explains.

Had Belas stumbled upon a potential means of attacking harmful algal blooms—by disrupting the symbiotic relationship between the algae and its hitchhiking bacterial protector? He suspects not; "We know that *Pfiesteria* and TM1040 have been living together for eons; it's doubtful, although not impossible, that this well-orchestrated symbiosis would have such a weak link in it."

But Belas's probing of this symbiosis is by no means at a dead end. It now appears that the "payoff" of his lab's basic science work concerns the antibiotic TDA, produced by TM1040. "Biochemically, TDA has what we call a tropolone ring, around which seven carbon atoms are attached. Many compounds in nature with this structure have been found valuable, whether as antibacterial, antifungal, antiparasitic, or, in one instance, even a potential anti-HIV agent." Harvesting TDA from precursors in nature—it's found in red cedar, for instance—is inconvenient and costly.

"But we have a bacterium that produces TDA, which could easily be fermented in large quantities. TM1040 is found naturally in sea water. We know it produces TDA when attached to surfaces—*Pfiesteria*, and possibly other algae. We envision it will be most useful in commercial aquaculture. We could modify TM1040 to produce TDA on our command, which, in turn, would be mixed with algae, which would be fed to larval fish. The fish would be nourished while receiving continual dosages of a protective antibiotic."

With a collaborator in Israel, Dr. Eugene Rosenberg, Belas is simultaneously investigating another possibility. "*Roseobacter* are known to be part of the community of bacteria living within the mucous and tissue surrounding healthy coral polyps in the tropical seas," he notes. "Eugene and I have evidence suggesting these bacteria are producing TDA, which may be having a protective effect on the coral."

In recent years a decline of up to 30 percent has been observed in the global extent of coral reefs. Coral "bleaching," caused by abnormally high ocean temperatures, has been blamed. Belas and Rosenberg are testing TDA's activity against strains of bacteria known to consume coral at high ocean temperatures. In TM1040 and other tiny creatures of the *Roseobacter* group, then, they may have found an antibiotic "factory" that can help support the rapidly growing commercial fish market and at the same time help protect the coral reefs that provide a vital habitat for endangered species in our tropical seas.

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