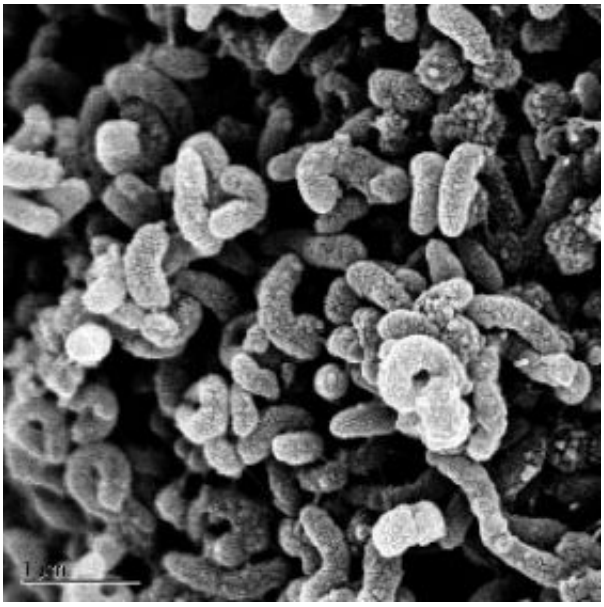
Rapid escalation characterizes virus/host arms race

May 22 2008



A scanning electron microscope image of a piece of biofilm shows that these microbial communities comprise a very tight association of microbial cells. The bacteria, archaea and viruses in the biofilm grow hundreds of feet underground in the absence of light. (Clara Chan/UC Berkeley)

The interaction between a virus and its host is often portrayed as an arms race, with each new viral attack parried by the host and each new defense by the host one-upped by the virus.

University of California, Berkeley, researchers have for the first time documented this arms race within the genes of both the virus and its

host.

In the May 23 issue of *Science*, the researchers confirm that a sophisticated microbial "immune system" spits out bits of RNA to silence viral genes, and they also report the viruses' counterstrategy - to shuffle their DNA until their genome sequences becomes scrambled enough to evade the RNA silencers.

This snapshot of a community of bacteria, archaea and viruses sheds light on the constant warfare between viruses and microbes going on all around us and inside us - in our mouths, guts, organs and skin, said Jill Banfield, professor of earth and planetary science and of environmental science, policy and management at UC Berkeley.

"Viruses play a critical role in all ecosystems, but because they can lower the fitness of, or kill, cells, cells had to find a way around the viruses, leading both to evolve to arm themselves against one another," Banfield said.

Virus-microbe wars also have an economic impact. Vats of microbe cultures are used increasingly today to produce products like drugs, food additives and now biofuels, not to mention cheese, yogurt, wine and beer. All of these communities are in constant warfare with viruses.

"Any biological system will be prone to crash if viruses get too successful," a catastrophe which can happen in industrial-scale cultures of nearly identical microbes, Banfield said.

Virus-microbe interactions are notoriously hard to investigate, however.

"There are billions of viruses in a community, each slightly different, and it is generally difficult to determine which virus goes with which host," she said. "This is one of the first studies to link viruses with their

hosts and to show a major component of how the virus responds."

Viruses are relatively simple, consisting of naked DNA or RNA and a protein coat - the bare essentials for invading a cell. Bacteria and archaea are more complex than viruses and provide the machinery for viral reproduction. Viruses have probably been invading cells and using their enzymes to reproduce for 3-4 billion years.

But how do bacteria and archaea protect themselves? And how do viruses, which contain only a few dozen genes, outwit them?

The newest chapter of this story was written a year ago, when scientists with Danisco, a company that makes live bacterial cultures for yogurt and cheese, discovered a bacterial immune system that silences viral genes that threaten the bacteria. This discovery came out of Danisco's efforts to engineer virus-resistant bacteria for its cultures.

The Danisco scientists reported in the March 23, 2007, issue of *Science* that a peculiar strand of DNA found in the genomes of most bacteria and archaea actually includes DNA bits captured from invading viruses. The DNA region, called a "clustered regularly interspaced short palindromic repeats" (CRISPR), consists of several dozen to more than 100 short snippets of DNA strung together like beads on a string.

These researchers showed with the common yogurt bacteria Streptococcus thermophilus that when a particular virus infected the bacteria, a piece of that virus's DNA appeared in the CRISPR region, making that particular strain of bacteria resistant to that particular virus. They concluded that bacteria typically snip up invading viruses and stick these bits in the CRISPR area of their genome, using these so-called "spacers" to produce RNA to silence similar viruses. This is very similar to a scheme called RNA interference (RNAi) used by humans and others to silence genes. The interfering RNA binds with a complementary

messenger RNA and prevents it from being used to make a protein.

"The microbial system may be the evolutionary precursor of our RNA interference system," Banfield said.

Working in a radically different system - a biological film on the surface of acidic mine waste - UC Berkeley's Banfield and former post-doctoral fellow Anders F. Andersson noted a similar correlation between CRISPR snippets and viral genomes, but also discovered viruses' more primitive counterstrategy. Viruses shuffle their genome frequently, leading to rapid rearrangement of their DNA, evidently gambling that one of the mutated genomes will contain a mismatch with the interfering RNA. Because RNA interference works only if the spacer RNA exactly matches a virus's messenger RNA, a single base pair difference can neutralize RNA silencing.

Because genome shuffling could incapacitate critical genes, "a lot of viruses probably die," Banfield said. "But all it takes is one virus to succeed, and it can take over because the microbe is no longer resistant."

Several years ago, a team led by Banfield had sequenced all organisms in the biofilm - a community of bacteria, archaea and viruses - and had reconstructed the genomes of seven different bacteria and eight different archaea. For the work reported this week in Science, the researchers used the DNA spacers in these microbes' CRISPR regions to fish out of the community genome the viruses afflicting each one.

Andersson and Banfield found that some viruses target one bacterial, or archaeal, host, while others target more than one host. All the microbes were afflicted with more than one virus. In all, the two researchers report the reconstruction of five virus populations in four archaea and one bacteria. The spacers in these microbes ranged in length from 28 to 54 base pairs each, representing a very small part of a viral genome, which

in this community ranged in length from 4,000 to 60,000 base pairs.

When the researchers sampled the biofilm population again seven months later, only one CRISPR spacer from the earlier sample was still there. Evidently, each microbe had shed spacers that no longer protected against viruses and picked up new ones created by viral genome shuffling.

"These populations are dynamic," Banfield said. "Potentially, a microbe may add one or more spacers per division cycle, which makes for a very fast arms race and perhaps a complete turnover of spacers in just a few months' time. If this is true, it means that bacterial and archaeal populations are not clonal," that is, identical copies of one another.

The implication for microbial cultures, ranging from the oceans to biofuel reactors, is that diversity probably is the key to a sustained healthy population, she added. Monocultures of microbes can be wiped out by a single virus, whereas a diversity of microbes - what Banfield calls a "cloud" - has the ability to survive against a cloud of competing viruses.

"If you have one host and one virus and the virus gets too virulent, it could either kill off the host or make it sick and uncompetitive," she said. "Biological diversity is significant in a natural population precisely because it allows cloud versus cloud competition."

Banfield and her UC Berkeley team continue to sample the mine waste biofilm to see how rapidly evolution operates in microbe-virus communities.

Source: UC Berkeley