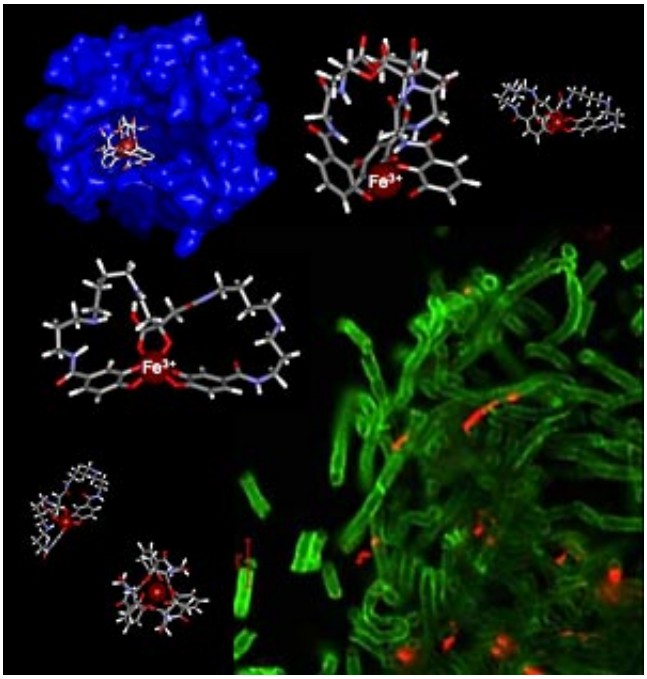
New finding points way to foiling anthrax's tricks

November 30 2006



Anthrax bacteria (green) secrete two iron-scavenging molecules, the siderophores bacillibactin and petrobactin, represented by ball-and-stick structures with a red iron atom inside. One of these, bacillibactin (top right), is intercepted by the protein siderocalin (blue) produced by the human immune system, but the second, petrobactin (lower left), slips through the body's defenses. (Raymond lab/UC Berkeley)

University of California, Berkeley, chemists have discovered a trick that anthrax bacteria use to make an end run around the body's defenses, but which may turn out to be their Achilles' heel.

The UC Berkeley scientists, working with colleagues at the University of Mississippi Medical Center in Jackson and the Fred Hutchinson Cancer Research Center in Seattle, uncovered the trick while studying how these deadly bacteria steal iron from their human hosts to grow and reproduce.

"Humans make a protein called siderocalin to defend against bacteria in the continual arms race between pathogen and host. This is the first example of a protein produced by the human immune system that disrupts bacteria's iron scavenging system," said Ken Raymond, UC Berkeley professor of chemistry and faculty scientist at Lawrence Berkeley National Laboratory.

Anthrax bacteria are known to produce two small molecules - bacillibactin and petrobactin - that snatch iron away from the human body's iron transporter molecules, called transferrin. These scavengers, or "siderophores," are essential to anthrax's ability to grow rapidly, especially after the spores are inhaled, though why the bacteria need two siderophores to do the job has been an enigma.

The new study shows why anthrax bacteria require two siderophores working by two different mechanisms. Siderocalin, the human immune protein, binds bacillibactin and effectively sidelines it, the researchers found. Apparently, anthrax fielded a second "stealth" iron scavenger, petrobactin, to get around the human defense against the first scavenger. Petrobactin is not bound by siderocalin.

As far as is known, the human immune system has yet to launch a successful counterattack against the stealth siderophore, but that doesn't mean humans can't design one of their own, according to Raymond. His UC Berkeley team and the Seattle team are now exploring how their discovery could be used to diagnose or treat anthrax.

The researchers published their findings Nov. 28 in the online edition of

the *Proceedings of the National Academy of Sciences*. Their paper will appear in the Dec. 5 print edition.

Many bacteria, including the benign Escherichia coli in our gut, make small molecules called siderophores that snatch iron from the tissues of their host so that the bacteria can reproduce. Some strains of E. coli produce more than one kind of siderophore, apparently attacking on several fronts to get the iron they need.

The discovery of a similar strategy in anthrax, Bacillus anthracis, suggests that producing more than one siderophore is a general strategy of bad as well as benign bacteria, according to the researchers. To date, however, only the pathogenic forms of E. coli and Bacillus have been found to produce a siderophore not bound by siderocalin; the non-pathogenic forms that produce more than one siderophore base them on the same molecular structure to which siderocalin binds.

Anthrax is a potential bioweapon because it is nearly always fatal when inhaled. Its long-lived spores grow rapidly in the lungs, leading to breathing problems and shock within days. While a vaccine is available, there is no effective treatment.

The bacteria succeed by forming capsules that invade lung cells, then capturing iron in order to reproduce, and finally, manufacturing a toxin that kills the cells and releases thousands of new spores into the bloodstream.

Because the iron-capture stage is critical to growth, it has become a recent focus of attention as a possible drug target. Raymond, who has studied bacterial siderophores that capture iron for 35 years, recently teamed up with Roland Strong of the Seattle cancer center to study siderocalin, a human protein Strong had found that appeared to interfere with the siderophores secreted by anthrax bacteria.

To study the role of this protein, Raymond and UC Berkeley graduate students Rebecca J. Abergel and Trisha M. Hoette approached an anthrax research laboratory run by B. Rowe Byers, professor of microbiology at the University of Mississippi Medical Center, to obtain samples of anthrax siderophores. Because bacteria secrete siderophores, these molecules can be separated from the bacteria and studied without danger of infection.

Using these anthrax bacteria extracts, Abergel and Hoette isolated the two siderophores, bacillibactin and petrobactin, and showed that siderocalin tightly binds bacillibactin, preventing it from capturing iron from human cells. However, siderocalin does not prevent petrobactin from binding iron.

Interestingly, bacillibactin is very similar to siderophores in other bacteria, including enterobactin, which is produced by several pathogenic bacteria that live in the gut, such as Salmonella enterica and pathogenic strains of E. coli. These two bacteria also contain a second siderophore, aerobactin, with a molecular structure similar to petrobactin.

The researchers suggest that producing a second, stealth siderophore - petrobactin or aerobactin - that has a different molecular structure than bacillibactin and enterobactin may be a common response by bacteria to the human body's production of siderocalin.

The research could lead to anti-anthrax drugs that target petrobactin synthesis or iron-uptake, or to anthrax sensors that detect petrobactin, which is not known to occur in any other pathogenic bacteria.

Source: UC Berkeley