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## Solved: The Mystery of Flesh-Eating Bacteria's Relentless Attack

A Howard Hughes Medical Institute (HHMI) international research scholar in Israel has discovered one reason why so-called flesh-eating bacteria are so hard to stop.

Emanuel Hanski, a microbiologist at Hebrew University in Jerusalem, and colleagues have found that the success of group A *Streptococcus* is due in part to a protein that blocks the immune system's distress calls. The findings, published in the October 4, 2006, issue of the *EMBO Journal*, could lead to new strategies for treating necrotizing fasciitis and halting its rapid destruction of tissue. The paper was published in advance online.

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— Emanuel Hanski

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The bacterium, group A *Streptococcus*, wreaks destruction on muscle and skin tissue in the form of necrotizing fasciitis, which kills roughly 30 percent of its victims and leaves the rest disfigured. Antibiotics and surgical interventions, the known treatments, often fail. Necrotizing fasciitis is a serious but rare infection of the skin and the tissues beneath it.

The work began two years ago, when Hanski developed a mouse model for necrotizing fasciitis. After injecting the mice with a virulent strain of *Streptococcus* of a type known as M14, isolated from a necrotizing fasciitis patient, the team noticed that unlike most strep infections, in which white blood cells swarm invading bacteria to clear them from the body, few white blood cells appeared at the M14 infection site. A similar phenomenon had been observed in patients with necrotizing fasciitis but did not receive sufficient attention at the time.

"We knew that the pathology of the disease in people was typified by various degrees of a lack of white blood cells," said Hanski. After publishing their findings in the British medical journal *The Lancet* in 2004, the team began to search for the factor that blocked the recruitment of white blood cells during M14 infection.

They focused on the gene for a *Streptococcus* peptide called SilCR, after finding that the gene product was turned off in the M14 strain. This gene is supposed to produce a peptide that acts as a signaling molecule that the *Streptococcus* bacteria use to communicate with each other, said Hanski. Since the bacteria were not producing the peptide, we decided to synthesize it ourselves and give it to mice infected with M14.

The mice receiving this peptide survived at a much higher rate than mice that did not receive it. The team also observed many white blood cells at the infection site in mice receiving the peptide.

Next, the team turned its attention to an important human immune system signaling molecule, interleukin-8. In healthy people, an infection triggers the production of interleukin-8 (IL-8), which acts as a distress call. When the body senses an infection, it creates interleukin-8 to recruit white blood cells to the infection, said Hanski.

In a laboratory culture, the M14 strain of *Streptococcus* destroyed IL-8. But when the team added the SilCR protein to the growing bacteria, the IL-8 survived.

The amount of IL-8 that survives is inversely related to how much SilCR there is in the culture, said Hanski. This may be one reason why some strains are less virulent than others; they might make more SilCR. It would be interesting to study the amount of SilCR produced by the other strains and to determine their degree of tissue invasiveness, said Hanski.

The link between SilCR and a healthy immune response still did not explain the underlying mechanism. The team knew that SilCR itself did not degrade IL-8, so they began to search for the missing link in the chain of events. They expected to find an enzyme that degrades IL-8. Drawing on a database of enzymes and using advanced techniques that measure the levels of gene transcription products in a cell, they soon identified the culprit: an enzyme called ScpC.

The team then created a mutant variation of the M14 strain of *Streptococcus* that could not produce ScpC. As expected, this strain was much less virulent than the original M14. Only three of 28 mice receiving the mutant strain succumbed to infection, a death rate much lower than that of mice who received the original strain. Mice receiving the original bacteria developed lesions that grew until the mice died; while mice receiving the mutant strain developed only small lesions that spontaneously healed.

The experiments show that SilCR down-regulates the production of ScpC, and ScpC is what destroys the IL-8, said Hanski. In our strain, M14, SilCR is missing completely, which explains why it is so virulent.

He said the work points to more effective strategies for treating *Streptococcus* infection. There are different avenues you could explore for treatment, all based on reducing the amount of ScpC the bacteria produces, Hanski said. You could look for a specific inhibitor of ScpC, or you could explore the

activity of SilCR more fully and try to boost its action.