Factor key to severity of community-associated methicillin-resistant staph infections identified

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Newly described proteins in drug-resistant strains of the Staphylococcus aureus bacterium attract and then destroy protective human white blood cells—a key process ensuring that S. aureus survives and causes severe disease, according to scientists at the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health.

S. aureus disease is a global public health concern because some strains, including community-associated methicillin resistant S. aureus (CA-MRSA), have developed resistance to existing antibiotics. The NIAID scientists hope to use this finding to advance development of new therapeutic treatments.

In a study published online in *Nature Medicine*, Michael Otto, Ph.D., and his colleagues at NIAID's Rocky Mountain Laboratories (RML) describe how novel members of the phenol-soluble modulin (PSM) protein family help determine disease severity and eliminate immune defense mechanisms against CA-MRSA.

"This elegant work helps reveal the complex strategy that S. aureus has developed to evade our normal immune defenses," says Anthony S. Fauci, M.D., NIAID director. "Understanding what makes the infections caused by these new strains so severe and developing new drugs to treat them are urgent public health priorities."

Up until a year ago, most scientists studying S. aureus believed they had narrowed their search for the cause of severe CA-MRSA infections, focusing on the Panton-Valentine leukocidin (PVL) toxin produced by certain strains. But then last year, Dr. Otto and his RML colleagues published a study indicating that PVL does not play a major role in CA-MRSA infections.

Given the scope of the problem in the United States, Dr. Otto's group continued its search to understand why the CA-MRSA strains cause widespread and often severe infections in otherwise healthy people. Until now, no one had examined what role PSMs have in Staphylococcus infection.

The RML group identified previously unknown PSMs secreted by S. aureus and identified the genes that encode those PSM proteins. They then compared PSM production between CA-MRSA and the most prominent hospital-associated MRSA strains. The research team found PSM genes in all MRSA strains, but production of the proteins was typically higher in CA-MRSA strains known for severe virulence, according to Dr. Otto.

To determine whether PSMs contribute to virulence, the scientists developed test strains using the most widespread isolates of CA-MRSA, called USA300 and USA400. Each test strain had a certain combination of PSM-encoding genes removed so the researchers could ascertain whether those genes affected virulence. The scientists then observed how laboratory mice responded to the test strains. By doing so, they pinpointed the psm-alpha gene cluster (which makes PSM-alpha protein) as playing an essential role in determining CA-MRSA virulence and, ultimately, disease severity.

To understand how PSMs contribute to virulence, Dr. Otto and colleagues next examined the role of the molecules in S. aureus evasion

of human immune defenses. They observed that the psm-alpha genes generated the most resistance activity and the PSM-alpha proteins were best at destroying most immune cells that help protect against infection and disease. In all instances, the PSM-alpha molecules caused the greatest destruction of white blood cells, an effect that occurred rapidly.

What was remarkable, says Dr. Otto, is that a specific sensing mechanism likely enabled S. aureus to secrete PSMs at the ideal time when host immune cells were weakest and most vulnerable to destruction. Likewise, PSM production slowed when the bacterial survival was most jeopardized.

“We’re not saying the psm-alpha gene cluster is the only element contributing to the virulence and survival of CA-MRSA, but it is a major factor,” says Dr. Otto.

Next, he and his RML colleagues will examine whether the simple presence of the psm-alpha genes create havoc with the immune system, or whether some unknown trigger causes these genes to be expressed in a harmful way. Dr. Otto’s group also is continuing to study the molecular details of how PSMs function. Ultimately they hope to identify new candidate therapeutics for CA-MRSA by studying the roles of the different PSM genes.

Source: National Institute of Allergy and Infectious Diseases