Evolution of virulence regulation in Staphylococcus aureus

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Scientists have gained insight into the complex mechanisms that control bacterial pathogenesis and, as a result, have developed new theories about how independent mechanisms may have become intertwined during evolution. The research, published by Cell Press in the October 10th issue of the journal *Molecular Cell,* may lead to strategies for developing more effective therapeutics against the human pathogen responsible for most of the antibiotic-resistant infections contracted in the community.

Bacteria have evolved mechanisms called quorum-sensing systems that allow for rapid communication between cells. "In pathogenic bacteria, these systems were first described as virulence regulators, whereas it has been shown more recently that quorum-sensing control is also aimed to respond to changing environmental conditions via metabolic adaptations," explains lead study author Dr. Michael Otto from the Laboratory of Human Bacterial Pathogenesis at Rock Mountain Laboratories.

Dr. Otto and colleagues studied *S. aureus,* a major human pathogen that is the most common cause of bacterial infections in the community and the hospital. Many strains are resistant to a wide spectrum of antibiotics, including methicillin (methicillin-resistant *S. aureus,* MRSA). "Recent outbreaks of MRSA in the community form a novel major challenge for the public health system," says Dr. Otto. "It is thought that drugs which interfere with quorum-sensing regulators may prevent production of several virulence factors and be less likely to lead to resistance that drugs

which directly kill bacteria."

The accessory gene regulator (agr) system is a pivotal regulator of virulence factor expression and a potential therapeutic target. The agr system initiates rapid target gene expression when bacterial cell density reaches a threshold level, exerting its effect through RNAIII. Phenol-soluble modulins (PSMs), which play an important role in the ability of *S. aureus* to evade the host immune system, are also controlled by agr but the molecular mechanisms of PSM regulation are not well understood.

The researchers examined the role of RNAIII within the agr regulatory system, with an emphasis on PSM regulation. They found that there are two distinct subsets of agr target gene regulation, an RNAIII-independent circuit that regulates metabolic genes and an RNAIII-dependent circuit controlling virulence. They went on to demonstrate that agr-dependent regulation of the PSM gene family is achieved by direct binding of a key agr response regulator protein.

The researchers concluded that control of virulence factors by RNAIII and quorum-sensing control of metabolism may have once been separate regulatory circuits. The circuits may have evolved a connection in order to allow for quick cell density-dependent change of virulence factor expression during infection as regulation by an RNA is thought to have a shorter response time than regulation by a protein.

"By discovering RNAIII-independent regulation of agr target genes, our findings establish a novel mechanism of target gene control by quorum-sensing in S. aureus and give insight into the evolution of quorum-sensing systems with regard to the connection of metabolism and virulence gene regulation," offers Dr. Otto.

Source: Cell Press