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Bacterial toxin closes gate on immune response

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Researchers at the University of Pennsylvania School of Medicine have demonstrated that a bacterial toxin from the common bacterium Staphylococcus aureus shuts down the control mechanism of the tunnel, called an ion channel, in immune cell membranes. Shutting down ion channels has long been known to suppress the immune response, and the bacteria may use the toxin to neutralize host defenses against bacteria. The study is published in the February 14 issue of *Nature*.

Immune cells, like other cells, have ion channels in their membranes. When the voltage-sensing part of the channel detects an electrical change in the cell membrane, the channel gate opens, allowing small ions such as sodium, potassium, or calcium to flow across the cell membrane. The channels in immune cells called Kv1.3 channels allow only potassium ions to pass, and the activity of these channels is required for triggering an immune response.

“We have provided a key piece of evidence for the hypothesis that the negatively charged phosphate groups of membrane lipids around voltage sensors provide the critical electric balance for some of these positive charges in the sensors,” says Zhe Lu, MD, PhD, of the Department of Physiology at Penn.

The research team, that included Yanping Xu, MD, PhD and Yajamana Ramu, PhD, showed that removal of phosphate head groups from some membrane lipids by the bacterial toxin called sphingomyelinase (SMase) C shuts down the Kv1.3 channel. Therefore if the positive charges are

not properly balanced by negative charges, the electrical sensor cannot move to “open the gate” of the channel. And, if the channel fails to open, the immune response is derailed.

“Our study builds on the efforts of two senior colleagues in the Department,” says Lu. Twenty-five years ago, Professor Clay Armstrong (now emeritus) hypothesized that the positive charges in the electrical sensor must be balanced by negative charges for the sensor to function properly. And a few years later, Professor Carol Deutsch, among others, demonstrated the presence of potassium channels controlled by voltage in immune cells.

SMase C is made by, among other bacteria, S. aureus, a pathogenic bacterium that causes a range of infections from minor skin lesions to toxic shock. “This finding raises the intriguing possibility that the SMase C action against Kv1.3 helps S. aureus to neutralize host defenses,” state the authors in the paper.

The findings of this study suggest the possibility that identifying inhibitors of SMase C may be a way to combat S. aureus infections. One strain of S. aureus is the much-talked-about, MRSA, or methycillin-resistant S. aureus. Specific inhibitors of SMase C may expand the choice of therapies for treating MRSA and other resistant S. aureus infections.

This study was conducted in a common experimental system where frog eggs were engineered to have particular voltage-gated ion channels in their membranes. SMases used in the study were purified from bacteria engineered to produce the enzymes.

This new study follows a 2006 study by the same research team showing that an SMase from the brown recluse spider could activate voltage-gated ion channels. In 2007 the team discovered that SMases from lung-

infecting bacteria inactivate ion channels that conduct chloride ions, which would in turn aggravate lung infection in some cystic fibrosis patients.

Source: University of Pennsylvania