

A new understanding of how cells defend themselves against bacterial pore-forming toxins

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Biologists at the EPFL (Ecole Polytechnique Federale de Lausanne) have unveiled a new twist in a metabolic pathway that cells use to defend themselves against toxins made by disease-causing bacteria.

The discovery of this pathway, published in the September 22 issue of the journal *Cell*, advances our understanding of how cells mount a survival response when attacked by bacteria and parasites and also gives insight into the more general process of cell membrane biogenesis.

Bacteria and parasites often use special toxins to perforate the membranes of target cells. These pore-forming toxins are a key weapon in the attack arsenal of some common and virulent bacteria, such as *Staphylococcus aureus*, well-known for its role in hospital-acquired infections, *Streptococcus pneumoniae*, responsible for middle ear infections and pneumonia, and *Helicobacter pylori*, implicated in ulcers. Pore-forming toxins compose about a quarter of all known protein toxins that increase the infectivity and severity of bacterial diseases.

Once the toxin perforates the host membrane, ions begin to leak out of the cell. Sensing a drop in its potassium concentration, the cell reacts by forming a multi-protein complex known as an inflammasome. Scientists know that inflammasomes act like a sort of roving security force inside the cell, detecting a variety of danger signals such as bacterial RNA or bits of bacterial flagellin. The inflammasomes join together and activate

a protein, caspase-1, that in turn triggers an inflammatory response.

Van der Goot and her colleagues found that in addition to its normal role as a signal for inflammatory response, caspase-1 also triggers the cell's central regulators for membrane synthesis, launching a bout of lipid metabolism. This previously undetected part of the response pathway has important implications for cell survival.

The Swiss team studied the pathway by using RNA interference to silence genes involved. Interrupting the pathway at any point, either by silencing the genes responsible for the inflammasome formation or the gene for caspase-1, resulted in increased cell death.

“We don't yet know the details of the mechanism by which lipid metabolism leads to cell survival,” she says. The lipids are probably used to repair the cell membrane, stopping the potassium leak, which itself can kill the cell, and also protecting the cell from additional toxic substances lurking outside.

“This result is important, because it also explains so much in terms of basic cell physiology,” notes Van der Goot. If a cell absorbs too much water, for example, this pathway would be triggered. The lipids formed in the metabolic pathway would enable the cell to enlarge its membrane to accommodate the extra water.

“Toxins have co-evolved with their hosts for a long time,” says Van der Goot. “That makes them good tools with which to study normal cell physiology. This study is a case in point – using a toxin, we have the first step in an understanding of how cells can regulate their membranes in order to maintain a particular ion concentration.”

The research focused on epithelial cells, the cells that line the gut and blood vessels. Van der Goot explains that because they form a protective

layer, it's critical for the organism that these cells survive, even if they don't function correctly. If the cell dies, it leaves the underlying tissue exposed. She hypothesizes that the toxin response pathway may be different for other types of cells. Immune cells, for example, may be better off committing suicide if their membranes are penetrated, because they could become deadly if their function is compromised.

Van der Goot adds that a better understanding of the biochemical pathway that allows epithelial cells to survive an invasion by a pore-forming toxin will prove valuable as biomedical researchers try to develop drugs to fight antibiotic-resistant strains of bacteria that use these toxins as part of their hijacking strategy.

Source: Ecole Polytechnique Federale de Lausanne

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