A new weapon in the fight against superbugs

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The ever-increasing threat from "superbugs"—strains of pathogenic bacteria that are impervious to the antibiotics that subdued their predecessor generations—has forced the medical community to look for bactericidal weapons outside the realm of traditional drugs. One promising candidate is the antimicrobial peptide (AMP), one of Mother Nature's lesser-known defenses against infections, that kills a pathogen by creating, then expanding, nanometer-sized pores in the cell membrane until it bursts. However, before this phenomenon can be exploited as a medical therapy, researchers need a better understanding of how AMPs and membranes interact at the molecular level.

Using a novel imaging technique, a research team led by the United Kingdom's National Physical Laboratory (NPL) is helping acquire much-needed insight into the fundamental physical and chemical processes that occur when AMPs bind with membranes and form pores in them. Team leader Paulina D. Rakowska will discuss the latest aspects of this work during the AVS 60th International Symposium & Exhibition, which will be held Oct. 27-Nov. 1, 2013, in Long Beach, Calif.

Observing the formation of pores in live cell membranes by naturally occurring AMPs is difficult because researchers have no control over the steps in the complex process. In many cases, the membranes of the target cell leak, swell and rupture before individual pores can expand enough to be examined. Rakowska and her colleagues have overcome this obstacle by combining nanoscale imaging via two different systems, computer simulation, a made-from-scratch (de novo) AMP, and lipid bilayers fixed to a solid surface (known as a supported lipid bilayer or SLB).

With the ability to specifically test where and how the de novo peptide binds to the SLB, the pore formation process is opened up to direct observation. Atomic force microscopy (AFM) provides topographical (structural) imaging of the peptide-treated membrane while chemical analysis is done with high-resolution nanoscale secondary ion mass spectroscopy (NanoSIMS).

"Data from the AFM images suggests that membranes change as a result of peptide action and pore formation," Rakowska says. "NanoSIMS imaging performed on the same samples reveal the precise location of peptide molecules within the membranes."

Rakowska says that these observations provide the first-ever physical and visual evidence of antimicrobial pore expansion from nano-to-micrometer scale to the point of complete membrane disintegration. "We can now postulate the mechanism by which this occurs," she explains. "We believe that the first AMPs binding with the membrane actively 'recruit' others to do the same, resulting in the formation of numerous small pores. As these pores expand, they eventually lead to membrane disintegration and cell death."

The research team includes scientists from the NPL, the London Centre for Nanotechnology, University College London, the University of Oxford, the University of Edinburgh, Freie University Berlin and IBM. The team's latest publication, "Nanoscale imaging reveals laterally expanding antimicrobial pores in lipid bilayers," recently appeared in the Proceedings of the National Academy of Sciences USA.

More information: Presentation BI+AS+BA+NS+SS-ThA3, "Nanoscale Imaging of Peptide-Membrane Interactions," is at 2:40 p.m. Pacific Time on Thursday, Oct. 31, 2013.

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