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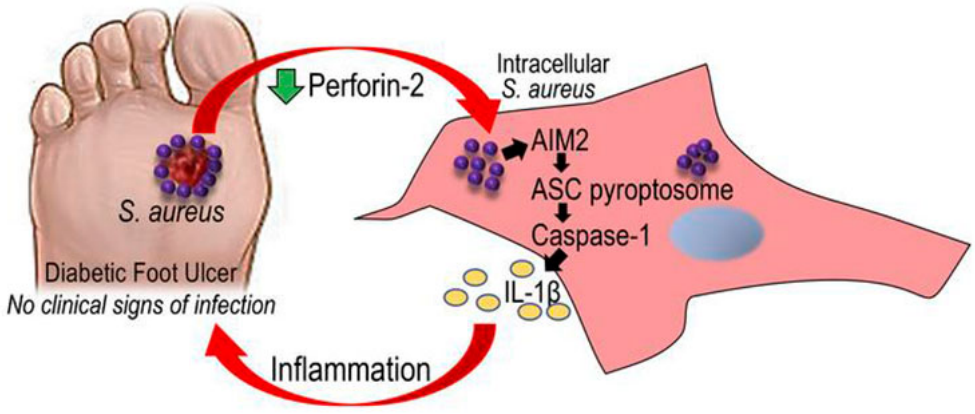
December 8, 2021

Miller Researchers Discover ‘Hiding’ Bacteria Orchestrate Non-Healing Diabetic Foot Ulcers

Researchers at the University of Miami Miller School of Medicine discovered a new way that bacterial infections can cause people with diabetes to develop chronic foot ulcers resistant to treatment and healing. The novel findings could identify people at high risk before they develop these debilitating wounds and could lead to effective treatments if they do.



It’s the story of a bad actor (the pathogenic bacteria *Staphylococcus aureus*), a good actor (the antimicrobial protein Perforin-2), and a violent ending for skin cells, including ‘death by inflammation.’

“Wound infections are one of the leading causes of impaired wound healing. Particularly in diabetic patients, wound

infection, its recurrence, and frequent resistance to antibiotic treatment represent a major clinical challenge and are a leading cause of lower limb amputations," senior study author Marjana Tomic-Canic, Ph.D., professor, vice chair of research and the William H. Eaglstein Chair in Wound Healing in the Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery at the Miller School.

Dr. Tomic-Canic and her colleagues from dermatology, microbiology and immunology collaborated on the research animals and human cells that revealed this mechanism for the first time. Their findings were published November 2, 2021 in *The Journal of Clinical Investigation.*

How Bacteria Hide

It's an inside job.

"We discovered a novel mechanism by which bacteria can evade our defense system, 'hide' inside the cell, causing further tissue damage and inhibiting healing," said Dr. Tomic-Canic, who is also Director of the Wound Healing and Regenerative Medicine Research Program. "Understanding such a mechanism provides new insights into a very complex disease – diabetic foot ulcers – and identifies new targets for potential therapeutic interventions."

Once inside, *S. aureus* is out of reach of antibiotics, and the foot ulcers do not show signs of infection. However, it doesn't mean the bacteria are benign. In a process known as pyroptosis, or cell death, the bacteria cause pores to form in the membrane, cell contents to swell, and cell material to leak out. Inflammation then ensues.

This *S. aureus*-driven 'death by inflammation' is associated with persistent infection and perpetual inflammation, hallmarks of non-healing diabetic wounds, Dr. Tomic-Canic said.

A Team Effort

Making such discoveries takes collaboration.

"This is a multidisciplinary team effort that builds on major strength of our institution: the premier wound healing clinical and translational research program at Frost Department of Dermatology and legacy of discovery of perforin-2 by the Microbiology and Immunology Department," she added.

"Only such an approach can pave the way to first understand such complex clinical problem and develop solutions for new therapeutics," Dr. Tomic-Canic said.

The current findings build on previous research by Dr. Tomic-Canic and colleagues.

Years of Discovery

"It took years of research and dedicated team effort for this discovery addressing important clinical problem of diabetic foot infection," said first author Irena Pastar, Ph.D., research associate professor.

Despite focusing on molecular events, the investigators remain committed to the big picture. "We will continue working on this project with the goal to improve lives," Dr. Pastar said. "It is well known that nearly half of all diabetic foot ulcers will become infected, and unfortunately infection strongly

correlates with subsequent amputation and increased mortality."

Future research could focus on ways to target pathways deregulated due to Perforin-2 suppression and consequent accumulation of intracellular bacteria. For example, increasing Perforin-2 levels could decrease intracellular bacterial load and pyroptosis. Another promising avenue involves developing biomarkers to predict diabetic foot infection prior to its clinical manifestations.

Other Miller School Miller faculty involved in the study include Natasa Strbo, M.D., Ph.D., Tongyu Cao Wikamanayake, Ph.D., Rivka C. Stone, M.D., Ph.D., Ivan Jozic, Ph.D., Robert S. Kirsner, M.D., Ph.D., and Hadar lev-Tov, M.D.

The work is dedicated to their late colleague, Eckhard Podack, Ph.D., who made seminal discoveries regarding the antimicrobial protein domain Perforin-2.

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