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# Disarming Antibiotic-Resistant Bacteria That Prevent Healing in Chronic Wounds

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*Credit: Alex Raths/Getty Images*

An international team of scientists, headed by a team at Nanyang Technological University, Singapore (NTU Singapore), has discovered a new way that could speed up the healing of chronic wounds infected by antibiotic-resistant bacteria.

Collaborating with researchers at the University of Geneva, the team's preclinical study showed how a common bacterium, *Enterococcus faecalis,* actively prevents wound healing. The results of their collective studies in mice and in human cells showed that, unlike other bacteria, which produce toxins when they infect wounds, *E. faecalis* produces reactive oxygen species (ROS), which impairs the healing process of human skin cells.

The team identified extracellular electron transport (EET) as a previously unrecognized mechanism by which *E. faecalis* generates ROS, which, in turn, activates the unfolded protein response (UPR) in epithelial cells and impedes their migration following wounding. The study also demonstrated how neutralizing this biological process can allow skin cells to recover and close wounds.

Establishing a direct link between bacterial metabolism and host cell dysfunction, the study points to a potential new therapeutic strategy for chronic wounds. Co-senior and co-corresponding author, NTU associate professor Guillaume Thibault, PhD, at the School of Biological Sciences, and colleagues reported on their findings in *Science Advances*, in a paper titled "*Enterococcus faecalis* redox metabolism activates the

unfolded protein response to impair wound healing," in which they concluded, "Our findings establish EET as a virulence mechanism that links bacterial redox metabolism to host cell stress and impaired repair, offering new avenues for therapeutic intervention in chronic infections."

The study was headed by Thibault and co-senior author Kimberly Kline, PhD, a professor from the University of Geneva, who is a visiting professor at the NTU Singapore Centre for Environmental Life Sciences and Engineering. The paper's first author is NTU Research Fellow Aaron Tan, PhD.

Worldwide, chronic wounds represent a major health challenge, with an estimated 18.6 million people developing diabetic foot ulcers each year, according to figures cited by the NTU. Such wounds are a leading cause of lower-limb amputations and are frequently complicated by persistent infections that prevent healing. In Singapore, chronic wounds, including diabetic foot ulcers, pressure injuries, and venous leg ulcers, are increasingly common, with over 16,000 cases annually, particularly among older adults and people with diabetes.

*(From right) NTU associate professor Guillaume Thibault, PhD; research fellow Aaron Tan, PhD, who is holding an image of a microbial biofilm; and SCELSE visiting professor Kimberly Kline, PhD, from the University of Geneva. [NTU Singapore]*

*E. faecalis* is an opportunistic pathogen frequently found in chronic infections such as diabetic foot ulcers. These wounds are difficult to treat and often fail to heal, increasing the risk of complications and amputation. "*Enterococcus faecalis* is a gut commensal and opportunistic pathogen that causes difficult-to-treat biofilm-associated infections, including catheter-associated urinary tract infection, infective endocarditis, and chronic wound infections," the authors wrote. "We previously showed that *E. faecalis* infection impairs wound healing."

Antibiotic resistance is also an increasing concern in *E. faecalis*, with some strains resistant to several commonly used antibiotics, making certain infections difficult to treat. While such infections are known to delay healing, the biological mechanism behind this disruption has remained unclear to doctors and scientists. "… the extent to which *E. faecalis* metabolism actively interferes with host repair mechanisms is poorly understood," the team further noted.

Through their newly reported research, Thibault and colleagues found that in *E. faecalis*, a metabolic process known as extracellular electron transport continuously produces hydrogen peroxide, a highly reactive oxygen species that can damage living tissue. Laboratory experiments showed that oxidative stress triggers a cellular defense mechanism known as the unfolded protein response (UPR) in keratinocyte skin cells, which are responsible for skin repair.

The unfolded protein response is normally used by cells to cope with damage by slowing down protein production and other vital activities, so that they can recover. Once activated, the stress response effectively paralyses the cells, preventing them

from migrating to close the wound. "*E. faecalis* is the first example, to our knowledge, where a defined EET system is shown to drive ROS production that directly alters host stress signaling and function," the scientists commented.

The researchers showed that a strain of *E. faecalis* genetically modified to lack the EET pathway produced significantly less hydrogen peroxide and was unable to block wound healing. This confirmed that the metabolic pathway was central to the bacterium's ability to disrupt skin repair.

The team then tested whether neutralizing the hydrogen peroxide could reverse the damage. By treating affected skin cells with catalase, a naturally occurring antioxidant enzyme that breaks down hydrogen peroxide, the researchers reduced cellular stress and restored the cells' ability to migrate and heal.

This, they suggest, offers a potential approach to tackle antibiotic-resistant *E. faecalis* strains other than trying to kill or inhibit them with antibiotics. In their paper, they concluded, "These findings not only establish a role for EET in ROS generation but also, through its interaction with the host UPR, establish it as a metabolic virulence mechanism by which *E. faecalis* disrupts epithelial repair, thereby presenting new opportunities for targeting chronic *E. faecalis*-driven pathologies."

Added Thibault, who is also the assistant dean, international engagement, at the College of Science, "Our findings show that the bacteria's metabolism itself is the weapon, which was a surprise finding previously unknown to scientists. Instead of focusing on killing the bacteria with antibiotics, which is becoming increasingly difficult and leads to future antibiotic resistance, we can now neutralize it by blocking the harmful products it generates and restoring wound healing. Instead of targeting the source, we neutralize the actual cause of the chronic wounds—the reactive oxygen species."

As the study used human skin cells to demonstrate the mechanism, the findings are relevant to human physiology and may pave the way for new treatments for patients with non-healing wounds. The researchers suggest that wound dressings infused with antioxidants such as catalase could be an effective treatment in the future.

Because antioxidants such as catalase are already widely used and well understood, the scientists believe this strategy could shorten the path from laboratory research to clinical application, compared with developing a new drug. The team aims to move toward human clinical trials after determining the most effective way to deliver antioxidants through ongoing studies in animal models.

In their paper, the scientists suggested, "Future studies should examine the role of EET *in vivo*, its regulation and contribution within polymicrobial settings, and the potential for targeting redox metabolism to mitigate *E. faecalis* infections that are increasingly recalcitrant to antibiotic therapy."

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