A drug used to treat HIV might defuse deadly staph infections

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A new study by NYU School of Medicine researchers suggests that an existing HIV drug called maraviroc could be a potential therapy for *Staphylococcus aureus*, a notorious and deadly pathogen linked to hundreds of thousands of hospitalizations each year. Their study is published online this week in *Nature*.

"What are the chances that a drug for HIV could possibly treat a virulent Staph infection?" asks Victor J. Torres, PhD, assistant professor of microbiology, and senior author of the study. "These findings are the result of a fantastic collaboration that we hope will result in significant clinical benefit." Staph causes toxic shock syndrome, pneumonia, and food poisoning, among other illnesses, and is becoming increasingly resistant to antibiotics.

The discovery arose from a serendipitous finding that was a part of a collaborative study between Dr. Torres, a bacteriologist, and immunologist Derya Unutmaz, MD, associate professor of microbiology and pathology and medicine, whose laboratories are adjacent to each other.

They focused on a receptor called CCR5 that dots the surface of immune T cells, macrophages, and dendritic cells. Sixteen years ago, researchers at NYU School of Medicine discovered that CCR5 is the receptor HIV uses to gain entry into T cells in order to replicate, spread, and cause an infection that can progress into AIDS.

That same receptor has now been found to be critical to the ability of certain strains of Staph to specifically target and kill cells with CCR5, which orchestrate an immune response against the bacteria. The scientists discovered that one of the toxins the bacterium releases, called LukED, latches on to CCR5 and subsequently punches holes through the membrane of immune cells, causing them to rapidly die. The LukED toxin belongs to a family of proteins called leukotoxins, encoded and produced by Staph to fight off the immune system's defenses.

This discovery was made after Dr. Torres asked Dr. Unutmaz and fellow HIV researcher Nathaniel Landau, PhD, professor of microbiology, if he might use some of the human immune cells they had collected over the course of their HIV studies. The laboratories of all three scientists are adjacent to each other. Dr. Torres was trying to find out which immune cells were affected by different leukotoxins. Dr. Unutmaz gave him a T cell line, which they were using for their HIV infection studies and had previously engineered to express CCR5, to test the effects of these toxins.

"Within one hour flat, T cells with CCR5 all died when exposed to LukED" says Dr. Torres, whereas a similar T cell line that lacked the receptor was completely resistant to the toxin's effects. This observation quickly led to another set of experiments to determine that the LukED toxin was indeed interacting with the receptor and that its presence on the cell surface was necessary for the toxin to kill the cells.

The investigators then treated cells with CCR5 with maraviroc, a drug on the market that binds to CCR5 and blocks HIV infection, and then exposed the cells to the Staph toxin. The result, the scientists say, was astonishing. "It was remarkable. Maraviroc completely blocked the toxic effects of this leukotoxin at doses similar to those used to inhibit HIV infection" Dr. Unutmaz says.

"The goal in blocking the toxin with maraviroc or similar agents is to give the upper hand to the immune system to better control the infection," Dr. Torres adds. The researchers further corroborated the critical role of CCR5 in Staph infections using a mouse model. When they infected mice susceptible to Staph infection with strains that contain the LukED toxin, almost all the mice died. However, mice that were genetically engineered to lack CCR5 on their cells survived this lethal Staph infection.

Based on these findings, the investigators hope that future human clinical trials will determine whether drugs that block CCR5, such as maraviroc, could help the immune system to control the infection and potentially save lives.

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