Infection by antibiotic-resistant bacteria is a dangerous complication of broad-spectrum antibiotic therapy. Treatment with antibiotics impairs natural immune defenses in the intestines, allowing antibiotic-resistant microbes to flourish. Now Memorial Sloan Kettering researchers have found a way to restore innate immune defense in the intestines and enhance resistance to vancomycin-resistant Enterococcus (VRE), a potentially harmful antibiotic-resistant bacterium.

Eric G. Pamer

Enterococcus is harmless when it remains in the intestines. However, it can cause life-threatening infections if it traverses the intestinal lining and invades the bloodstream. Enterococcus strains are increasingly resistant to antibiotics, including vancomycin.

Fortunately the intestines are equipped with an innate immune defense, explained Memorial Sloan Kettering immunologist Eric G. Pamer, senior author of the study, which was published in October in Nature. Resident bacteria known as commensals are involved in triggering this defense system. When molecules on their surfaces bind to receptors on the cells of the intestinal lining, the cells start pumping out bacteria-killing proteins, including RegIII*f*ngamma.

Dr. Pamer's team found that antibiotics destroy this defense system by killing commensal bacteria and dampening RegIII*f*ngamma production. Without RegIII*f*ngamma, VRE proliferates in the intestines and invades the bloodstream. "These antibiotics don't just make VRE a predominant organism in the gut," explained Dr. Pamer. "They actually weaken the intestine's immune defenses."

In mice, Dr. Pamer's group restored RegIII*f*ngamma production in antibiotic-treated, VRE-infected animals by adding lipopolysaccharide (LPS), a component of the commensal bacterial membranes, to their drinking water. LPS-treated mice had significantly lower levels of intestinal VRE compared with untreated mice. "By reactivating the host defense systems, we can restore the intestine's natural ability to fight pathogens," explained Dr. Pamer.

Antibiotic-mediated compromise of the intestine's innate defenses is one further reason antibiotics should be used judiciously, observed Dr. Pamer. Therapies that increase RegIIIƒngamma have the potential to protect individuals taking broad-spectrum antibiotics, and while LPS has toxic properties, it may be useful in certain clinical situations.

Co-authors from Memorial Sloan Kettering on this study were Katharina Brandl, George Plitas, Coralia N. Mihu, Carles Ubeda, Ting Jia, Martin Fleisher, and Ronald P. DeMatteo.