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Scientists identify critical cell in fighting E. coli infection

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Despite ongoing public health efforts, *E. coli* outbreaks continue to infiltrate the food supply, annually causing significant sickness and death throughout the world. But the research community is gaining ground. In a major finding, published today in the scientific journal *Nature*, researchers from the La Jolla Institute for Allergy & Immunology have discovered a molecule's previously unknown role in fighting off *E. coli* and other bacterial infections, a discovery that could lead to new ways to protect people from these dangerous microorganisms.

"We've found that a certain molecule, known as HVEM, expressed by the cells lining the surface of the lung and intestine, is critical to protecting the body from *E. coli*, pneumococcus and other bacterial infections that enter our bodies through the lining of our respiratory or intestinal tracts," said Mitchell Kronenberg, Ph.D., La Jolla Institute's president and chief scientific officer, who led the research team. "We discovered that HVEM acts in these cells like a border guard that responds to the presence of invasive bacteria and signals the immune system to send in more troops. Without its involvement as part of the epithelial protective barrier, the body could be overrun by certain disease causing bacteria," said Dr. Kronenberg, adding that he is hopeful the discovery will advance efforts toward developing new treatments or vaccines against bacterial infections.

"People knew that epithelial cells protect the body's mucosal borders from infection," said Dr. Kronenberg. "But what wasn't known was that HVEM is critically important in turning on the epithelial cell anti-

bacterial response." Epithelial cells line the body's mucosal borders, which include the mouth, nose, intestines and lungs and are the most common entry points for infectious pathogens. "We found that HVEM and another receptor (the receptor for IL-22) have to act together in the epithelial cells to trigger immune protection. Without these two receptors acting in concert, the body couldn't withstand the infection," said Dr. Kronenberg.

Richard S. Blumberg, M.D., a professor of medicine at Harvard Medical School and chief of the division of Gastroenteroogy, Hepatology and Endoscopy at Brigham and Women's Hospital, called the finding important on many levels. "It is of great biological interest because it shows how this very novel pathway has an important role to play in the management of infections at the epithelial boundaries, which is the entry point for the vast majority of infectious diseases," he said. "At the most fundamental levels, it gives us new insights into the way in which our host immune response engages and enables protection mechanisms at that portal of entry. From a therapeutic standpoint, better understanding of these pathways will enable researchers to explore ways to therapeutically manipulate the immune response to prevent and eradicate infectious pathogens at these critical body sites."

While the study, "HVEM signaling at mucosal barriers provides host defense against pathogenic bacteria," focused on *E. coli* and pneumococcus (also known as Streptococcus pneumoniae), Dr. Kronenberg said the HVEM mechanism is likely involved in protecting the body from many other dangerous bacteria and other microorganisms. In fact, HVEM stands for herpes virus entry mediator, and it is a protein that herpes virus uses to enter cells.

In the study, the researchers used mice genetically engineered not to have HVEM. When these mice were exposed to pneumococcus or a mouse pathogen very similar to *E. coli*, the HVEM deficiency led to a

much greater susceptibility to infection, higher bacterial burdens and significantly compromised the mucosal barrier. "It is striking how similar the responses in the lung and the intestine were," said Dr. Kronenberg. "The mice without HVEM were unable to respond effectively at either site, and the deficit was not only major but also nearly immediate, within two days of exposure to the microorganisms."

"In the present era of ever increasing antibiotic resistance, innovative approaches to treatment of bacterial infections are urgently needed," commented Victor Nizet, M.D., a professor of Pediatrics and Pharmaceutical Sciences at the University of California San Diego. "These importantly include new approaches to strengthen immune resistance to infection, and the discovery by the La Jolla Institute scientists reveals HVEM as a candidate drug target with relevance to multiple pathogens and multiple sites of infection."

Pneumococcus is the most common cause of bacterial pneumonia and meningitis in children. According to the World Health Organization, pneumonia is the single largest cause of death in children worldwide, annually killing an estimated 1.4 million children under the age of five. While cases among U.S. children have declined significantly due to the introduction of a pneumococcal vaccine in 2000, the bacteria remains a significant problem, particularly among U.S. children under two years, the elderly and throughout the developing world.

Escherichia coli (abbreviated as *E. coli*) are a large and diverse family of bacteria. Although most strains of *E. coli* are harmless, some can be deadly. *E. coli* creeps into the food supply through contamination by tiny (usually invisible) amounts of human or animal feces. Many people may develop mild symptoms, but some suffer severe complications that can lead to kidney failure and death. In 2011, an *E. coli* outbreak centered in Germany sickened more than 4,000 people, ultimately killing 50 people in 15 countries. The outbreak was eventually traced to contaminated

bean sprouts.

Provided by La Jolla Institute for Allergy and Immunology