Researchers Uncover a Secret of the Black Death

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Yersinia pestis, the bacteria that causes plague, is a sneaky little intruder with a remarkable ability to evade the body's immune system. Upon entering an organism, Y. pestis employs a variety of strategies to slip below the radar of the innate immune response—the body's front line of defense against invading pathogens—and in many cases kills the host before its more specific antibacterial response can develop.

It is this stealth and virulence that has made plague one of the most feared diseases in human history, blamed for more than 200 million deaths. While human cases of plague in the United States are now rare, a few thousands worldwide are infected each year and with the potential of intentional misuse of Y. pestis, the efforts to develop better treatments and a vaccine are now no less important than they were when the bacterium was first identified.

Researchers at the University of Massachusetts Medical School have made a significant breakthrough in the field, modifying Y. pestis with a gene found in another commonly known bacterium, effectively rendering it unable to cause plague. In "Virulence factors of Yersinia pestis are overcome by a strong LPS response," to be published in the October issue of *Nature Immunology*, Egil Lien, PhD, assistant professor of medicine and molecular genetics & microbiology, Jon D. Goguen, PhD, associate professor of molecular genetics and microbiology, graduate student Sara Montminy and colleagues, also describe the effectiveness of the modified bacteria as a vaccine.

Innate immunity—the precursor to the adaptive immune system in mammals—acts as the first line of defense against a range of pathogens. Prior to the adaptive immune response that involves the body's production of antibodies that precisely target and combat the invader, the innate immune system reacts immediately upon infection. Recent research has described an important class of sensor molecules, collectively known as Toll-like receptors (TLRs) that recognize pathogens right away, activating the critical signaling pathways that stimulate this initial immune response. Activation of the TLRs also improves the adaptive immune response; in fact, many vaccines include ingredients known as adjuvants that stimulate the innate immune response.

Intriguingly, the bacteria Y. pestis has an unusual temperature-dependent ability to evade this system. Lipopolysaccharide, or LPS, is a major component of the membrane of this type of bacteria, contributing to structural integrity but also typically provoking a strong response from the immune system. When at human body temperature (37ºC), Y. pestis produces an LPS with a poor ability to activate TLR4, one of the major mammalian innate immunity toll-like receptors; at lower temperatures, for example that of a flea that transmits the disease (26º), the LPS produced was distinctly more potent and thus triggered TLR4.

Recognizing that this difference was not found in E. coli, a common bacterium with some similarities to Y. pestis, Lien identified an E. coli gene that was important for the production of LPS but that was missing in Y. pestis. Using this gene to generate new strains of Y. pestis, researchers produced Y. pestis strains that were recognized much more easily by innate immunity and TLR4 at both temperatures. Importantly, the investigators found that the new strains were unable to cause plague and mortality in normal mice; the strains were at least a million times less virulent than the wild type bacteria.

“Our findings describe one of the secrets of the Black Death,” Lien said. “These results suggest that the production of surface lipids with poor ability to activate innate immunity is essential for Y. pestis to be so deadly, and, in fact, for the ability of the bacteria to cause plague. We expect this strategy to also be important for various other human bacterial pathogens.”

“This result is quite surprising, in part because plague research has focused on many active things that the bacteria do to protect themselves from host defenses, including injecting toxins directly into cells of the immune system that try to engulf them," notes Goguen. “Apparently all of this is useless unless the bugs can also hide from TLR4. Stealth is important.”

Significantly, Lien and colleagues also determined that these new harmless strains of Y. pestis could serve as vaccines. After vaccinating mice with the modified strain of Y. pestis, the investigators re-introduced the virulent strain after 30 days and found that all of the animals were protected from developing plague. These findings show that the production of avirulent bacterial strains with enhanced ability to stimulate the immune system could constitute a new general method for generating effective vaccines.

Source: University of Massachusetts Medical School