Researchers find that common stomach pathogen may protect against tuberculosis

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It's been implicated as the bacterium that causes ulcers and the majority of stomach cancers, but studies by researchers at Stanford University, UC Davis, and the University of Pittsburgh have found that *Helicobacter pylori* (*H. pylori*) also may play a protective role - against the worldwide killer, tuberculosis (TB).

In an article appearing online Wednesday in PloS ONE, Jay Solnick, UC Davis professor of medicine and microbiology, and his co-authors report that *H. pylori* infection may enhance immunity against tuberculosis, a disease endemic in many parts of the world, and for which there is no effective vaccine.

"Here is a bacterium that we know is sometimes harmful and that is clearly associated with cancer," Solnick said. "But it's not that simple."

Solnick explains that up until the 20th century, when public health improved and antibiotic use was widespread, virtually everyone was infected with *H. pylori*. That remains the case today in most developing countries, implying that *H. pylori* may have evolved with its human host because it confers some selective benefit.

"These new findings suggest that one such benefit may that *H. pylori* provides protection against tuberculosis, and perhaps other infectious diseases as well," he said.

Tuberculosis is second only to HIV as a cause of death due to a single

infectious agent; an estimated one third of the world population has latent TB infection. But only 30 percent of people exposed to TB ever become infected, and only 10 percent of those infected will develop active tuberculosis disease.

"One explanation may be the presence of chronic infection of the stomach with *H. pylori*," Solnick said. The findings also may eventually aid in managing TB, since *H. pylori* infection may help determine whether someone infected with TB gets a latent, asymptomatic infection or active disease.

The collaborative research effort began with the hypothesis that a person's immune responses to individual infections are modified by the existence of other infections, said Sharon Perry, an epidemiologist at Stanford University, and the study's lead author.

Early studies funded by the National Institutes of Health showed that a patient infected with *H. pylori* had elevated immune responses to TB antigens. Perry's work expanded to test the hypothesis in patients from immigrant populations in Santa Clara County, then in households in Gambia and Pakistan, where TB is prevalent. In the two-year study, they found that individuals exposed to TB who then progressed to active disease were less likely to be infected with *H. pylori* than those who were not infected with *H. pylori*. Protection against tuberculosis may have been a result of enhanced immune responses to TB antigens in those infected with *H. pylori*, since *H. pylori* induces expression of interferon gamma and other cytokines, which are important for immunity against viral and bacterial infections.

At this point, Perry and Stanford University professor Julie Parsonnet wanted to test the theory in non-human primates. They enlisted Solnick at UC Davis, in conjunction with JoAnne Flynn of the Department of Microbiology and Molecular Genetics and Immunology at the University

of Pittsburgh School of Medicine.

With a grant from the Bill and Melinda Gates Foundation, Solnick, Parsonnet, and Flynn looked at the role of *H. pylori* in 41 monkeys challenged with TB. Again, the findings were striking. Of the 30 monkeys that tested positive for *H. pylori*, only 5 developed active TB, but 6 of 11 monkeys that were negative for *H. pylori* developed active disease.

"The one-disease, one-pathogen paradigm doesn't tell the whole story," said Perry. "It is incomplete as an explanation of the clinical outcomes of chronic infection. In fact, the thousands of organisms that live with us play a role in shaping our immune response to specific infections."

Solnick cites the "hygiene hypothesis" as one possible explanation. That theory suggests that a reduction in exposure to infectious diseases can make the immune system less able to fight other challenges. Conversely, exposure to certain pathogens may aid immune response to other infections.

The authors acknowledge the findings are preliminary and propose several follow-up studies. First, Solnick, Parsonnet and Flynn have proposed research to test whether experimental infection of *H. pylori* will protect monkeys from TB, and whether it will enhance the protective effect of immunization. If successful, they will test a recombinant *H. pylori* strain that expresses TB antigens for possible immunization against TB. These studies will be performed in collaboration with Ondek Ltd, founded by Barry Marshall, who was awarded the Nobel Prize in 2005 for the discovery of *H. pylori*.

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