



GLADSTONE INSTITUTE OF CARDIOVASCULAR DISEASE NEWS

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To coincide with publication in the *Proceedings of the National Academy of Sciences USA*

CHEMOKINE RECEPTOR GENE CRUCIAL IN THE CONTROL OF TUBERCULOSIS, GLADSTONE/UCSF RESEARCHERS FIND

Controlling a tuberculosis infection requires precise interactions between a number of different immune cells. Researchers are showing for the first time that the absence of the gene for CCR2, a receptor on white blood cells known to be important for cell migration, can have fatal consequences in this setting. The study is a joint collaboration between the Gladstone Institute of Cardiovascular Disease and the UCSF Division of Infectious Diseases.

When proteins known as chemokines bind to white cells they initiate a cascade of events that results in the accumulation of specific groups of cells at the site of infection or inflammation. This failed to happen in the lungs of CCR2 deficient mice after infection with *Mycobacterium tuberculosis*, and they quickly succumbed. At autopsy, the mice had 100 times more bacteria in their lungs than the normal mice that had the receptor.

“It was unexpected that CCR2 would be so important in resistance to TB,” said lead author Wendy Peters, PhD, a postdoctoral fellow in the laboratory of Israel F. Charo, MD-PhD, at Gladstone. Dr. Charo is a senior investigator at Gladstone and UCSF professor of medicine.

Published in the July 3rd issue of the *Proceedings of the National Academy of Sciences USA*, the discovery also provides a possible explanation for why some people are more susceptible to tuberculosis than others, said co-author Joel D. Ernst, MD, UCSF professor of medicine in the division of infectious diseases.

In 90 percent of people infected, the immune system permanently controls the bacterium. But not in the remaining 10 percent, who go on to suffer the ravages of the disease. Some of these people could have a variant of the CCR2 gene that’s not as effective, Ernst speculated. Roughly one-third of the world’s population is infected with tuberculosis.

“What this study shows is that a failure of recruiting the crucial cells can lead to disease, and CCR2 is necessary for this to happen,” Ernst said.

The study also sends a message to pharmaceutical companies who are trying to find a drug that blocks CCR2. Two years ago Gladstone scientists found that mice that lacked CCR2 were protected from developing atherosclerotic plaques. The current finding sounds

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the alert “that drugs that block CCR2, may predispose patients to tuberculosis,” said Charo, whose laboratory initially discovered CCR2.

Other co-authors of this study include Holly M. Scott, graduate student, and JoAnne L. Flynn, PhD, associate professor, both of the University of Pittsburgh School of Medicine department of molecular genetics and biochemistry; and Henry F. Chambers, MD, UCSF professor of medicine at San Francisco General Hospital Medical Center.

This study was funded by grants from the National Institutes of Health and the Sandler Family Foundation.

The Gladstone Institute of Cardiovascular Disease is one of three research institutes that comprise The J. David Gladstone Institutes, a private biomedical research institution affiliated with UCSF. The institution is named for a prominent real estate developer who died in 1971. His will created a testamentary trust that reflects his long-standing personal interest in medical education and research.

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