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Host Genetics Plays Unexpected Role in Dance With Pathogen

A new study suggests that differences in the host's genetics can make a big difference in susceptibility bacterial infection. In a study in the February 2011 Infection and Immunity, Virginia L. Miller of the University of North Carolina, Chapel Hill, and her collaborators show that the virulence of a strain of Yersinia pestis, notable for causing bubonic plague, varies drastically among mice strains with different genetic backgrounds. These findings carry major implications for vaccine development, says Miller.

A number of earlier reports dating back 20 years had suggested that removing this bacterium's capsule--an envelope of a loose protein gel surrounding the bacterial cell -- had no effect on its virulence. Then, Miller and her collaborators performed the same experiment, with opposite results.

Searching for an explanation for the conflicting results, the only difference in the experiments that Miller could find was in the strains of mice, and so it occurred to her that their susceptibilities might be different. Her team tested that hypothesis by infecting two different strains of mice with *Y. pestis* in which the capsule had been removed. In one strain, the bacteria were nearly normally virulent, while in the other, they were relatively impotent.

This research made sense of the earlier experiments, "while highlighting the importance that host genetics can play in the dance between host and pathogen, and how it can influence the phenotype of a potential virulence factor," says Miller.

Moreover, these findings "demonstrate for the first time that the capsule is a *Y. pestis* virulence factor in a mouse infection model," says James Bliska of Stony Brook University, New York. "It had already been shown that [the capsule] is important for flea transmission, and therefore it was clear why [the capsule] was conserved in *Y. pestis*."

The research is critical for the development of a vaccine against both bubonic and pneumonic plague, also caused by *Y. pestis*, because considerable effort has been invested in establishing Caf1, an antigen within the capsule, as a protective antigen in vaccines against plague. But all the papers showing that removing the capsule had no effect on virulence had gradually undermined the case for using the capsule antigen in a vaccine, when it had been a major target for vaccine development. But now, "This paper may revive hope that Caf1 in conjunction with other antigens would be a useful component of a multivalent vaccine," says Eric Krukonis of the University of Michigan, Ann Arbor.

Developing such vaccines is important because "*Y. pestis* is still a major threat to humans, due to endemic pockets of *Y. pestis*-infected animals and fleas and potential bioterrorism use," Miller and her collaborators note. "A greater understanding of the requirement of the capsule for *Y. pestis* to cause disease is required. It is particularly important to investigate if natural capsule mutants are able to cause disease and in what contexts, as the current vaccine potentially would not protect against these strains."

Source: E. H. Weening, J. S. Cathelyn, G. Kaufman, M. B. Lawrenz, P. Price, W. E. Goldman, V. L. Miller. The Dependence of the *Yersinia pestis* Capsule on Pathogenesis Is Influenced by the Mouse Background. *Infection and Immunity*, 2010; 79 (2): 644 DOI: 10.1128/IAI.00981-10