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Probing a Chink in the Immunological Armor

Herpes simplex virus is a common pathogen - infecting about eight out of every 10 adults. Most people who are infected develop nothing more than a bothersome cold sore. But for some, infection with the virus can develop into herpes simplex encephalitis, which can lead to mental retardation, epilepsy and possibly death.

According to new research by Howard Hughes Medical Institute (HHMI) international research scholar Jean-Laurent Casanova, a person's ability to tamp down herpes simplex virus infection depends on the fitness of their innate immune system — which provides immediate defense against infection.

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— **Jean-Laurent Casanova**

Casanova and colleagues have now shown that individual variability in innate immunity may leave some people dangerously exposed to common pathogens such as herpes simplex virus. Reporting in the September 14, 2007, issue of the journal *Science*, Casanova and his colleagues describe a newly identified genetic mutation that predisposes carriers to herpes simplex encephalitis (HSE), a potentially lethal complication of herpes simplex virus infection.

The mutation is the second primary immunodeficiency that Casanova, Shen-Ying Zhang and other colleagues at the Necker Medical School in Paris, France, have found that confers susceptibility to HSE. In 2006, the group reported that primary immunodeficiency to HSE arises in people who cannot manufacture the protein UNC-93B. In the new report in *Science*, the researchers identified a mutation in a gene encoding toll-like receptor 3 (TLR3) that predisposes people to HSE.

The researchers found the mutation in the *TLR3* gene in two unrelated French children who had survived HSE, but whose brains had been damaged by the virus. As with the children in the 2006 study, the TLR3-deficient children

were normal in the sense that their immune systems could fend off bacteria, parasites and fungi as well as the rest of the population. But the TLR3 deficiency left them with a narrow chink in their immunological armor, which the herpes simplex virus was able to penetrate.

There is one important difference between the two immunological defects identified by Casanova. The TLR3 deficiency is autosomal dominant, meaning a single copy of the mutated gene is enough to make children susceptible to HSE. UNC-93B deficiency, in contrast, is recessive, meaning that patients need two copies of the faulty gene to have the condition. One corollary to this difference is that UNC-93B-deficient children are more likely to come from families where the parents are blood relatives. This increases a child's chances of inheriting two copies of the faulty gene. Not so with TLR3 deficiency. Because it's dominant, it can strike virtually any child on Earth, said Casanova.

Casanova said this is the first primary immunodeficiency to be reported in any of the 10 human TLRs that have been identified to date. TLRs have been shown in mice to be critical for immunity to infection, but their role in human host defense is unclear. Until you identify mutations in any of the TLRs and look at the consequences for the affected individual, there is uncertainty as to whether individual TLRs are necessary or redundant in host defense, said Casanova. We have now shown that TLR3 is critical for protective immunity to herpes simplex infection in the central nervous system, and that it's redundant for immunity to most other micro-organisms.

TLR3 is known to recognize viral infections by binding to the double-stranded RNAs (dsRNAs) that some viruses generate during their life cycle. In doing so, TLR3 triggers the activation of type 1 interferon, a molecule that interferes with viral replication. UNC-93B is involved in the same pathway, and both UNC-93B- and TLR3-deficient patients are unable to produce type 1 interferon in response to dsRNA. Casanova has filed an application with his hospital's institutional review board to conduct a small clinical trial that will treat patients with HSE with type 1 interferon as well as the standard antiviral acyclovir. The protocol calls for treatment to be initiated as soon as the patients have been diagnosed with HSE.

Casanova believes there are still undiscovered primary immunodeficiencies that predispose people to HSE infection—which may bring the total to at least four and possibly as many as 10, he said. The findings also suggest that although the mouse remains the best model for studying viruses that infect humans, important differences have arisen in the two species' host defenses over the course of evolution.

According to Grant McFadden, an HHMI international research scholar at the University of Western Ontario and the Robarts Institute and a visiting scientist at the University of Florida, this is one reason why no single pathogen has succeeded in wiping out all vertebrates. The nice thing about Casanova's work is that it is probing the human pathway, said McFadden. He added that the implications of the work go beyond HSE. All viruses are either

susceptible to TLRs or have learned to circumvent them, so in that sense it will be relevant to all viruses.