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Mouse and Man Differ in Immune Response to Viruses

Patients who were born with a rare and life-threatening susceptibility to certain bacterial infections are revealing idiosyncrasies in their immune system that immunologists never suspected. Those idiosyncrasies do not exist in the laboratory mouse, which is often used as a model for studying the human immune system, showing once again that when it comes to understanding the cause of diseases, there are not only important similarities but also differences between humans and mice.

Howard Hughes Medical Institute (HHMI) international research scholar Jean-Laurent Casanova of the Necker Medical School in Paris, France, along with a postdoctoral fellow in his lab, Kun Yang, and colleagues have studied 18 young patients with an inherited deficiency in IRAK-4, a member of the interleukin-1 receptor-associated kinase (IRAK) family and an important signalling molecule in pathways mediating innate immunity. They report their findings in the November 2005 issue of the journal *Immunity*.

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— Jean-Laurent Casanova

Innate immunity comprises the defenses against pathogens that humans are born with. Adaptive or acquired immunity develops only after the body is exposed to certain antigens—molecules carried by pathogens that stimulate the production of antibodies in the host. While adaptive immunity is thought to be specific to the antigen, innate immunity has always been regarded as a general response that the body mounts to all pathogens—bacteria, viruses, fungi, and parasites.

Casanova's research suggests otherwise. In 2003, his team published a paper in *Science* describing three cases of IRAK-4 deficient children who, though highly susceptible to the type of bacterial infections that create pus and can lead to the formation of abscesses, were otherwise healthy. They explained this susceptibility by the fact that IRAK-4 mediates signalling by antibacterial signalling molecules produced by immune cells, such as interleukin-1. But IRAK-4 is known to be involved in many innate immune signalling pathways, and the prevailing theory suggested that individuals lacking it

would also succumb to severe viral infections.

These patients did not. However, three is a small sample, so Casanova went searching for others to see if the pattern held across other patients with the same inherited deficiency. Two years later, his team has tracked down 18 IRAK-4 deficient children and young adults from 11 unrelated families from all over the world - and the pattern does indeed hold. "They are vulnerable to bacteria, but they are no more vulnerable to viruses than you or me," he said. "That was the first surprise."

The second surprise came when they took blood samples from these patients and incubated their blood cells and fibroblasts with different viruses. "Even though they have IRAK-4 deficiency, their blood cells are able to produce type I interferons, which are potent antiviral cytokines," explained Casanova.

Viruses carry small molecular sequences that bind to toll-like receptors (TLR) in human immune cells, activating them and setting in motion a type I interferon production line. Five of the 10 human TLRs were known to induce type I interferon, but it was not known whether they did this via IRAK-4 signalling. The latest findings suggest that some TLRs act independently of IRAK-4, and not all are necessary for conferring resistance to viruses. Specifically, the researchers found that when they stimulated TLR-7, TLR-8, and TLR-9 by exposing the patients' blood cells to chemicals mimicking viral products, no interferon was produced—yet the patients were resistant to viruses. When TLR-3 and TLR-4 were stimulated, on the other hand, interferon was produced, even though that production could not have been mediated by IRAK-4, since the patients lack that molecule.

"This means that the TLR-7/TLR-8/TLR-9 interferon pathway is redundant, or is not essential for protective immunity to viruses," said Casanova. In contrast, the TLR-3/TLR-4 pathway appears to be intact in IRAK-4 deficient patients, indicating that while this pathway may be responsible for synthesizing the interferon that protects them from viruses, it cannot do so via IRAK-4. That in turn gives important insights into the normal functioning of the human immune system.

While the 2003 study showed the specificity of the innate immune system for certain pathogens, this study shows that this system contains an unsuspected degree of spare capacity. "The implication is that there is a lot of redundancy in the signalling pathways that trigger the production of type I interferon in response to viruses," said Casanova. "This is surprising, because TLR-7/TLR-8/TLR-9 have been proposed to be very important for immunity to viruses. In humans that does not seem to be the case."