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Newly Identified Genetic Deficiency in Children Illuminates Immune System Breakdown

Children with meningitis and other serious infections need swift treatment with antibiotics to survive, but physicians have not been able to figure out why the same microbe causes some children to get seriously ill and not others. Now researchers have identified a genetic defect that makes these children susceptible to attack by a certain type of bacteria, a finding that will speed up the diagnosis and treatment of these sick children.

The discovery is reported by Howard Hughes Medical Institute international research scholar Jean-Laurent Casanova in the August 1, 2008, issue of *Science*. In the last 6 years Casanova has published a series of research articles that establish a genetic pathway essential to immunity to bacteria that cause meningitis, septicemia, and other severe illnesses.

While most people can fight off infections caused by the bacteria *Streptococcus pneumoniae*, some children have a rare genetic mutation that perturbs their immune system, making them unable to defeat this particular type of bacteria. This means they get repeated life-threatening infections. "In the pre-antibiotic era all these patients would have died," says Casanova, a practicing pediatrician and professor in the pediatric hematology-immunology unit at Necker Hospital in Paris, France. "Even today, the success of antibiotics is limited because the children's mild and delayed signs of illness make diagnosis difficult."

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- Jean-Laurent Casanova

Several years ago, Casanova and his lab started looking for genetic differences in children who were particularly vulnerable to *Streptococcus* and other so-called pyogenic bacteria. His laboratory's "working hypothesis is

that primary genetic deficiency makes these children vulnerable to this infectious disease,” he says.

In 2003, the team discovered that children with a defective *IRAK4* gene were highly vulnerable to pyogenic bacteria but were resistant to most other pathogens. So they decided to look for children with intact *IRAK4* genes but whose immune systems were still deficient, possibly due to other genetic abnormalities. IRAK-4 is an important signaling molecule involved in mediating the immune system.

In an international survey, the team found nine infection-prone children with defective or missing copies of the myeloid differentiation primary response gene 88 (*MYD88*). From research in mice, scientists knew that the corresponding MyD88 protein activates immune defenses in the bloodstream just like IRAK-4 does. But because mice with the condition are vulnerable to at least 34 different pathogens including bacteria, viruses, parasites, and fungi, it was not immediately clear whether a MyD88 deficiency could be the culprit for these kids, who have a narrow vulnerability to meningitis and other pyogenic bacterial diseases.

The team found that the MyD88 protein was either entirely missing or found in abnormally low levels in the children's blood cells. The MyD88 protein controls many of the most important immune system receptors that help people fight off a wide range of microorganisms, including Toll-like and interleukin receptors. Based on studies of the blood samples and mouse studies, the team expected that the children also would be vulnerable to a wide range of disease. But they were surprised to find that the children with the *MYD88* defect “have a much more limited spectrum of infections,” Casanova says. They were vulnerable to pyogenic bacteria, but their immune systems were able to fight off most other common infections in an apparently normal way.

The finding suggests that both IRAK-4 and MyD88 are necessary for children to generate an immune response to pyogenic bacteria. “The implication is that there are other pathways for other pathogens” not controlled by the *MYD88* gene, Casanova says. “One of my goals is to discover those genes.”

The study also found that as the children grew older, other receptors began to compensate for the MyD88 deficiency. The six surviving children in the sample were eventually able to naturally fend off pyogenic infections that had required antibiotic intervention before.

Casanova says the unexpectedly poor link between infections in mouse models and humans is probably due to “the difference between experimental infections in mice and natural infections in humans.” He emphasizes that humans are being investigated in their natural settings, rather than in a laboratory, in order to include all possible genetic and environmental effects

in their studies.

The next step is to identify other genetic causes of invasive pneumococcal diseases in children, Casanova says, and link them to receptors essential to defeating each class of disease. “The idea is that children with invasive pneumococcal diseases should be tested for defects in their Toll-like and interleukin receptor pathways,” he adds.

Testing for these immune receptors could become a part of genetic counseling diagnostics, Casanova suggests. If parents and pediatricians know that a child has no natural defenses against certain diseases, they will be better prepared to treat incipient infections aggressively and successfully. They need to be treated with the same antibiotics as anyone else, but earlier, he notes.

“Everybody carries pneumococcus in one's nostrils, but only a few of us end up in the intensive care unit with sepsis,” Casanova says. “MyD88 deficiency is one reason.”