Family Affair

In discovering their shared ancestry, a distantly related animal geneticist and plant pathologist find a common thread in their work on immune receptors.

By Megan Scudellari | April 1, 2011

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At a 2009 meeting at the University of California, Davis, plant pathologist Pamela Ronald and a group of immunologists were talking about the work that led to the identification of the first mammalian innate immune receptor a decade before. Ronald, who isolated the first immune receptor in plants that recognizes a conserved microbial molecule, had heard the story before. This time, however, the name of the mammal paper's lead author—Bruce Beutler—jumped out at her. A branch of her family contained some Beutlers. In fact, she had regularly kept in touch with Käthe Beutler, who occasionally mentioned her geneticist grandson. "Somehow it just clicked," recalls Ronald. Bruce Beutler, chairman of the Department of Genetics at the Scripps Research Institute, was her cousin.

"He isolated the first of these receptors in animals, I isolated the first in plants. It was just such a coincidence," says Ronald. She sent Beutler an e-mail, attaching a *Science* paper she had published on a protein that activated her plant immune receptor (*Science*, 326: 850-53, 2009). Beutler responded by inviting Ronald to La Jolla, California, to speak at Scripps.

Over dinner after her presentation, Ronald and Beutler discussed not only their common ancestors, but what their respective realms of research, plants and animals, have in common—strikingly similar mechanisms for detecting and resisting infection.

Fifteen years ago, immunologists believed that plants, which lack phagocytes, antibodies, and other vital parts of the animal immune system, must use fundamentally different defenses against invading pathogens. But in the 1990s, a string of classical genetic studies in plants and animals changed that assumption.

It began with Ronald and rice. By the early 1990s, scientists had not isolated any of rice's suspected "resistance" genes, which encode proteins that protect the plants from infection. As a young faculty member at UC Davis in 1995, Ronald isolated and identified the gene that conferred broad resistance to rice blight disease, caused by a gram-negative bacterium called *Xanthomonas oryzae.* She dubbed the gene *Xa21* and discovered that it encoded a receptor kinase, a membrane protein characterized in animal cells that was predicted to bind a signal outside a cell and trigger a response inside the cell, but that had yet to be associated with a specific function in plants.

Five years later, scientists isolated a similar gene in *Arabidopsis*. "Now that we have their genome sequences, we can predict that there are hundreds of these [receptors] in rice, and tens of these in Arabidopsis," says Ronald. "They probably all recognize different types of molecules produced by different pathogens."

Meanwhile, Bruce Beutler was making similar breakthroughs in mice. Scientists had identified numerous molecules—such as the bacterial compound endotoxin—that triggered an innate immune response in mammals, but they'd been unable to pin down specific receptors that detected those molecules. Analyzing two mutant strains of mice that were unresponsive to endotoxin, Beutler determined that one gene, *Tlr4*, conferred resistance to the toxic substance. *Tlr4* encodes a Toll-like receptor, a member of a family of proteins first identified in fruit flies, where it is vital for development and for immune responses

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to fungal infection. Some scientists believed that endotoxin simply percolated through cell membranes, so the identification of a specific, familiar transmembrane receptor "came as a great surprise," says Beutler. "It was the most exciting moment of my scientific life."

These days, researchers know that plant, fly, and mouse receptors, including Xa21 and TLR4, have structurally similar binding surfaces that detect microbial molecules. "One thing all immune receptors seem to have are leucine-rich repeats," says Frederick Ausubel, who studies immunity in *Arabidopsis* and *C. elegans* at Massachusetts General Hospital. Leucine-rich repeats are horseshoe-shaped structures containing 20–30 amino acids. "They are good for recognizing a lot of different ligands," he adds.

But the similarities between these immune receptors in plants and animals don't necessarily denote a shared family history. Instead, the resemblance likely resulted from convergent evolution. "People debate that, but generally the thought is that plants and animals came upon the same methods to defend themselves," says Ronald. "There isn't one ancestral organism that had all these components."

Last November Ronald and Beutler gathered details on immune pathways in plants and animals, from their own work and others, for a review article (*Science*, 330:1061-64, 2010). The two dedicated the paper to their great-great-grandparents, the "last common ancestors of the authors," they add in a footnote. And they continue to keep in touch. "Now I have someone I can ask whenever I have a dumb question about animals," laughs Ronald.

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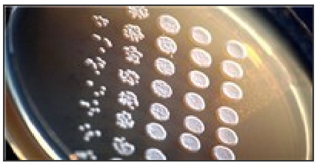

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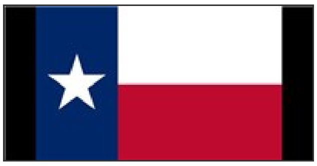

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