# Immune Cells Gain Wider Recognition

Researchers always thought the T cell, a crucial cellular component of the immune system, exhibited an exquisitely discriminating attitude. The thousands of key receptors each T cell sports on its surface, which activate the cells' immune response, seemed to accept only small protein fragments called peptides.

That immunological paradigm is now crumbling. Last year, a group led by Michael B. Brenner of Brigham and Women's Hospital in Boston reported that a small subset of T cells snubs peptides in favor of mycolic acids, a class of lipids. These fatty molecules are unique to the cell walls of mycobacteria, the bacteria most notable for causing tuberculosis and leprosy.

Now, Brenner's group has collaborated with a research team headed by Barry R. Bloom, of the Howard Hughes Medical Institute at the Albert Einstein College of Medicine in New York, to demonstrate that the T cell receptors (TCRs) of a more common class of immune cells also recognize nonpeptides.

These two efforts, and similar work now in progress at other laboratories, suggest that the immune system harbors a greater variety of methods to spot foreign objects than researchers had realized.

"It makes a lot of sense for the immune system to do this. These are fascinating insights that will lead into the next generation of immunology," says Jonathan W. Yewdell at the National Institute for Allergy and Infectious Diseases (NIAID) in Bethesda, Md.

"A whole new realm of chemistry may be open to the T cells," Bloom adds. He and Brenner report their research in the May 11 NATURE.

The standard line in immunology has held that specialized cells, so-called antigen-presenting cells, engulf viruses and bacteria and chop them into pieces. They then attach bacterial or viral peptides, the antigens, to molecules called MHC proteins for a return trip to the surface of the cells.

A patrolling T cell might then encounter one of these antigen-presenting cells. Its TCR, actually a collection of proteins usually dominated by two chains of peptides known as the alpha and beta chains, could then bind to a specific MHC-peptide complex and trigger an immune response.

But the T cells studied by Brenner and Bloom are different. Instead of the alpha and beta chains, their TCRs depend on peptide chains called gamma and delta. Rare in humans, making up only 5 percent of all T cells, these unusual cells are often more prevalent in other mammals.

A few lines of evidence suggest that gamma-delta T cells defend mammals from mycobacteria. But what these T cells recognize and how they function remained largely a mystery. "They've been known about for a long time, but nobody really knows what they do," says Peter Linsley of Bristol Myers Squibb Pharmaceutical Research Institute in Seattle.

Probing that question, Brenner, Bloom, and their colleagues synthesized nonpeptide antigens until they found compounds that activated human gamma-delta T cells. They then discovered that various mycobacteria make natural counterparts of the synthetic antigens.

One natural compound that gamma-delta T cells recognize is isopentenyl pyrophosphate, a small organic molecule with a few phosphate groups attached, the researchers report. Mycobacteria use the molecule and its derivatives in a variety of ways; they even secrete one form of it.

To further establish that gamma-delta T cells defend against mycobacteria, the Brenner-Bloom team cites in its NATURE article some completed research not yet submitted for peer review. The researchers infected normal mice and a strain unable to assemble the TCR delta chain with the tuberculosis bacterium. The normal mice survived; the animals without functioning gamma-delta T cells died.

Mammalian cells also use isopentenyl pyrophosphate, raising questions of whether gamma-delta T cells generate autoimmune responses. These immune cells do recognize and kill certain tumor cells, Bloom notes .

While immunologists describe this latest study of gamma-delta T cells as an "important advance," they're even more thrilled by the general message that T cell recognition goes beyond MHC-peptide complexes.

"The big, exciting conceptual breakthrough was the paper of Brenner's last year. This area is now exploding," says Ronald H. Schwartz, chief of the Laboratory of Cellular and Molecular Immunology at NIAID. — *J. Travis*

## New wrinkle on California's raisins

*California produces 425,000 tons of raisins — 99 percent of the nation's annual yield — with a market value of $560 million. A big business, producing raisins is also an unpredictable one. Early rains can rot the grapes as they dry on trays in the field for up to 4 weeks. And growers find it increasingly difficult to locate enough handpickers.*

Agricultural Research Service, USDA

*To get around these problems, David W. Ramming and his coworkers at the U.S. Department of Agriculture's Horticultural Crops Research Laboratory in Fresno — raisin country — have spent the past 12 years developing DOVine. Named for its ability to dry on the vine, it's the first commercial grape resulting from a cross between two seedless varieties.*

*Growers can mechanically harvest DOVine's raisins off trellised canes. Moreover, Ramming notes, dried-on-the-vine raisins (such as the predecessor of DOVine pictured at right) are less vulnerable to rot and to the burned flavor that can develop when unseasonable heat caramelizes the sugar in tray-dried grapes.*

*Because vine drying takes longer than tray drying under equivalent sunlight, grapes to be vine-dried must ripen earlier to beat the fall rains. DOVine does. And Ramming's team reports that the quality of its raisins "is the same as or better than [that of] Thompson Seedless" — the variety now used for 99 percent of California raisins.*

*Key to producing the new grape was a technique known as "embryo rescue," developed in Ramming's laboratory. Seedless grapes initially develop a seed that later aborts. His team excised that seed from 6-week-old grapes and nurtured its embryo. This shaved 5 years off DOVine's development time, Ramming says, and eliminated the unwanted traits a true-seeded parent would have contributed.* — J. Raloff