Pinning down T cell death in the thymus

Though an inconspicuous organ located behind the breastbone, the thymus is the place where the immune system makes peace with the rest of the body. Here, white cells called T cells — key soldiers in the body's cellular army — proliferate and mature. But if all these soldiers were allowed to roam free through the blood, they would destroy the body's own tissues as well as foreign invaders. So here many immature T cells also meet their demise, two immunologists have now demonstrated.

A staining technique for marking dying cells made possible this demonstration, says Charles D. Surh of the Scripps Research Institute in La Jolla, Calif. Until now, scientists only suspected that this breeding ground for T cells was also a burial ground, he adds.

Surh and Scripps colleague Jonathan Sprent monitored the thymus for a particular type of disintegration called apoptosis (SN: 1/15/94, p.44), a programmed cell death in which the cell membrane shrivels and its genetic material crumbles.

Throughout the body, cells activate this program when damaged beyond repair or when their particular jobs are done. But in this act of cellular suicide, as with suicide in the traditional sense, outside signals can trigger the process.

Surh, Sprent/Nature

Most of the dying cells (red) cluster in the cortex (cor) of the thymus. A few die later in the medulla (med).

For years, immunologists have tried to determine exactly where in the thymus and why about 95 percent of the T cells there call it quits before ever leaving. In this organ, each immature T cell develops a unique molecular docking site, called a receptor, on its surface. That receptor recognizes a particular MHC (major histocompatibility complex) molecule with a specific protein fragment attached. The thymus keeps the immune system in check by getting rid of T cells that recognize and subsequently react to MHC molecules carrying fragments of the body's own proteins, Surh explains. That's where apoptosis comes in handy.

To "see" apoptosis, Surh and Sprent first injected lots of a particular enzyme into slices of mouse thymus. This enzyme puts a nucleotide building block onto the end of the DNA pieces created early in apoptosis. By then adding antibodies — first some that recognize this building block and then others that carry a different enzyme and link up with the first antibodies — the researchers can mark dying cells in red, Surh explains.

In the part of the thymus called the cortex, positive selection occurs: Only new T cells that recognize and link with MHC molecules seem to avoid apoptosis, Surh says. Then the thymus somehow weeds out and triggers cell death in T cells that would bind to MHC molecules carrying the body's own protein pieces.

Based on the staining patterns observed in the thymuses of mice genetically altered to make no MHC molecules, "we're thinking that most of the [T cell] death occurs for lack of [the] positive selection," Surh says.

Researchers had not seen this massive destruction before, because other immune system cells called macrophages gobble up the dying cells quickly and efficiently, he and Sprent report in the Nov. 3 Nature. They determined this by irradiating thymuses and monitoring them for 24 hours. Within an hour, macrophages had ingested the T cells, disposing of them by the next day, they report. — *E. Pennisi*

Fermat's famous theorem: Proved at last?

A year ago, mathematician Andrew Wiles of Princeton University faced a troubling gap in the logic he had followed to prove Fermat's last theorem. Now, he has apparently found a way to bridge the gap and complete his proof of Fermat's famous conjecture.

Last week, in a move that caught the mathematical community by surprise, Wiles began distributing copies of two new manuscripts addressing the concerns that had been raised about his original argument. The first, lengthy paper announces the revised proof, still following quite closely the strategy Wiles had outlined in his lectures in June 1993 at the University of Cambridge in England (SN: 7/3/93, p.5).

The second, short paper, produced in collaboration with Cambridge mathematician Richard L. Taylor, contains mathematical reasoning justifying a key step in the main proof. Instead of solving the original problem, Wiles and Taylor avoided it by using a different approach to reach the same conclusion.

Both papers have been submitted for publication in the Annals of Mathematics.

"The proof looks really beautiful, but it's too soon to comment in detail [on its validity]," says Fernando Q. Gouvêa of Colby College in Waterville, Maine. "Everybody's being very cautious." Gouvêa has been attending a seminar at Harvard University, where Taylor has been discussing aspects of the proof.

Pierre de Fermat's claim, made more than 350 years ago, was that for each whole number greater than 2, the equation $x^n + y^n = z^n$ has no solutions that are positive whole numbers. Over the centuries that followed, many mathematicians tried to prove Fermat's conjecture but invariably failed.

The attack chosen by Wiles relied on recently discovered links between Fermat's conjecture and the theory of elliptic curves. By assuming that Fermat's last theorem is false, mathematicians could construct a "weird" elliptic curve that they believe, for other mathematical reasons, shouldn't exist.

Moreover, the existence of this strange curve would also contradict the Taniyama-Shimura conjecture, which involves other characteristics of elliptics. Hence, if proving certain aspects of the Taniyama-Shimura conjecture excluded the strange curve, this would establish the validity of Fermat's last theorem.

This is the course that Wiles followed. But his original argument foundered near the end, where he had relied on a powerful new method developed by Viktor A. Kolyvagin of the V.A. Steklov Institute of Mathematics in Russia to serve as a kind of mathematical bookkeeping system. Wiles found a serious flaw in his attempt to construct the so-called Euler system necessary for completing his proof (SN: 12/18&25/93, p.406; 6/25/94, p.406).

To circumvent the problem, Wiles decided to go back to an approach that he had tried several years earlier but abandoned in favor of Euler systems. Helped by Taylor, who had come to Princeton last spring to work on the problem, Wiles succeeded in establishing the conditions he needed to complete the proof. This time, he used mathematical techniques based on Hecke algebras.

"The new approach turns out to be significantly simpler and shorter than the original one," noted Karl Rubin, who is presently visiting Harvard, in a message last week to colleagues at Ohio State University in Columbus. Some mathematicians are already looking into simplifying the proof further, even as they check the work done by Wiles and Taylor.

"While it is wise to be cautious for a little while longer, there is certainly reason for optimism," Rubin adds.

As the manuscripts go into circulation in the mathematical community, many mathematicians are getting a chance to see for themselves. — *I. Peterson*