A Room of Their Own

Finding the place where immune cells process undesirable proteins

By ELIZABETH PENNISI

Talk about a high-stress job. Twenty-four hours a day, 365 days a year the body's white cells must be on the lookout for harmful bacteria, viruses, and other pathogens. What's more, these undesirables don't look very different, biochemically, from most of the normal molecules white cells encounter in the blood. Yet a mistake by these immune cells can leave the body vulnerable to infection.

Fortunately, the immune system has evolved an exquisite mechanism — antibodies — for distinguishing the body's own molecular debris from potentially harmful material. Antibodies are Y-shaped molecules that bind to specific foreign proteins, or pieces of protein, called antigens. If the immune system mistakenly identifies the body's own proteins as foreign, an autoimmune disorder can result.

When antibodies on the surface of a B cell, a type of white cell, snag an undesirable protein, both disappear inside the cell. Eventually, a bit of the foreign protein may reemerge, this time handcuffed to an MHC class II molecule. The pair acts as a red flag to other white cells, called T cells, which set off an aggressive immune response.

Until now, scientists did not know where the cell chopped up this undesirable protein and attached it to the MHC.

But last week, four research teams announced the discovery of a special compartment, or organelle, inside cells where this processing occurs. Using sophisticated biochemical and immunological techniques, they independently determined that both MHC and the antibody-protein complex wind up in this new compartment, says Ira Mellman, who heads the Yale University group reporting the discovery in the May 12 NATURE. "Here is where all the action is," he says.

Typically, a cell swallows proteins and the molecules that snag them by forming indentations that bud off from the cell membrane. Organelles called endosomes then split off from these buds. Eventually, the cell may spit out these proteins or degrade them in other organelles called lysosomes.

Antigens avoid this fate. "One of the paradoxes is that [the protein] must come far enough in the pathway to be broken down, but then it must be rescued and a fragment retained with the MHC," explains cell biologist Colin Watts of the University of Dundee in Scotland.

The antibody-protein pair starts out in an endosome but gets waylaid into a special compartment, Watts and his colleagues also report in the May 12 NATURE. His group determined this, in part, by getting rid of known compartments in the cell while leaving the cell intact.

In the newly discovered compartment that remained, enzymes began to break down the antigen, probably with an MHC molecule standing by to grab the fragment it wants. "There's a key handover that's going on here," Watts says.

The MHC molecule receiving this handoff comes from an organelle called the Golgi body as a complex of three MHC molecules. Each has an alpha, beta, and invariant peptide chain. The invariant chain shepherds MHC, keeping it from attaching to just any protein that floats by. But at some point the invariant chain falls off, enabling the MHC molecule to link with an antigen.

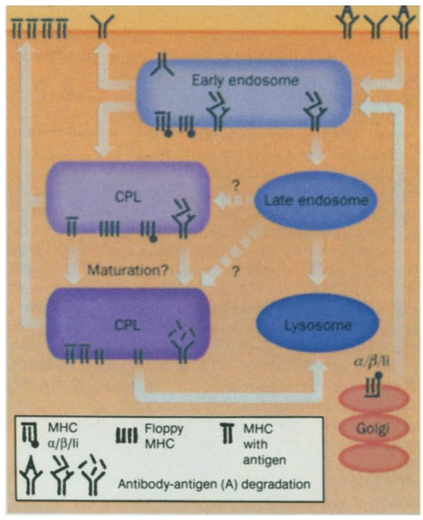
Scientists had thought that this processing occurred in an organelle but could not track it to any known one. Peter J. Peters of the University of Utrecht in the Netherlands caught a glimpse of a compartment full of MHC in 1991, but not until now have researchers been able to confirm this.

"The whole purpose [of this new compartment], I think, is to create a reaction vessel with everything you need in it and [that] keeps most other things out," Mellman explains.

This discovery, coupled with recent findings of atypical organelles in neurons and a few other cells, indicates that cells can modify compartments for their own purposes. "What these studies indicate is there is greater specialization than was anticipated," says Eric O. Long of the National Institute of Allergy and Infectious Diseases in Bethesda, Md.

In the same issue of NATURE, another team reached similar conclusions after studying skin cancer cells grown in the laboratory. These melanoma cells possess and present MHC II molecules just as B cells do, says Jean Pieters of the Netherlands Cancer Institute in Amsterdam. Working with Hidde L. Ploegh at the Massachusetts Institute of Technology, Pieters' group used density gradient electrophoresis to separate various cell components and find this new one.

"The characterization of a specialized vesicle is an important step," says Pieters. "It allows us to understand the trafficking events and defines the intracellular event of antigen processing."



Schmid and M.R. Jackson/NATURE

Diagram shows role of new compartment (CPL).

Other results, from Northwestern University in Evanston, Ill., indicate that two compartments may be involved, one with a floppy form of MHC and one with a compact form. There, experiments by Susan K. Pierce and her colleagues showed that in one chamber, the cell readies MHC for linking to an antigen by removing invariant chains. Even though this chamber contains invariant chains (which may account for the floppiness), at least some of those chains have dropped off, leaving a few alpha and beta components ready to attach to an antigen, she explains. The compartment's constituents do not activate T cells by themselves, they activate them when provided with antigens, the group reports in the May JOURNAL OF CELL BIOLOGY.

But in the cell, "no peptide ever gets to them," Pierce told SCIENCE NEWS.

Readied MHC must proceed to a second compartment, where protein breakdown occurs, she suspects. Her team has observed in that chamber compact MHC — that is, MHC molecules bound to protein fragments. The researchers expect that the MHC there ensures that pieces of the foreign protein will be protected for later presentation to T cells.

Not everyone agrees with Pierce's interpretation, however. It may be that she is viewing the same compartments at different stages in the process, says Sandra L. Schmid of the Scripps Research Institute in La Jolla, Calif.

Indeed, all the teams involved agree that finding this compartment is just a first step. But they are optimistic about making rapid progress because they can now replicate in a test tube how cells process and present antigens. "You can pick apart each of the individual events that take place and begin to ask why some antigens are processed one way and why other antigens are processed another way," says Mellman. □