radial position of some features in Saturn's B ring and the outer edge of the Cassini division.

Many more details of ring behavior should become apparent as the Voyager observations of the two stellar occultations come under close scrutiny. During the encounter Lane reported that the epsilon ring, whose circumference is eight times that of Earth's equator, is at most 25 to 30 meters thick. Its width as detected during stellar occultations observed from Earth varies from 12 to 60 kilometers, but its edges are so sharp that Voyager found the transition from apparently empty space to dense ring occurs over only 30 to 40 meters.

According to Larry Esposito of the University of Colorado, another photopolarimeter team member, the five broad variations in opacity across epsilon detected from Earth split into about two dozen features in the Voyager occultation data. Most of these features were stable enough to also be detected 120 degrees around the ring during the star's passage back to the outside of the rings. On the other hand, the single strand of the delta ring seen as the star crossed the ring inbound was split into three strands when the star crossed outbound. Some of the patterns of opacity variations in epsilon remind Esposito of the F ring or the edges of Saturn's Encke gap, which holds at least one shepherd. There is even a regular pattern of undulations that bears some resemblance to a spiral density wave, the watch spring–shaped wave of particle compression responsible for much of the structure in Saturn's A ring. ■

RICHARD A. KERR

ADDITIONAL READING

N. Borderies, P. Goldreich, S. Tremaine, "A granular flow model for dense planetary rings," *Icarus* **63**, 406 (1985).

J. A. Burns *et al.*, "Lorentz resonances and the structure of the Jovian ring," *Nature (London)* **316**, 115 (1985).

R. G. French, J. A. Kangas, J. L. Elliot, "What perturbs the γ and δ rings of Uranus?" *Science* **231**, 480 (1986).

Ubiquitin Moves to the Cell Surface

The varied activities of the protein ubiquitin now extend from the cell nucleus to the cytoplasm to the outer membrane

THE protein ubiquitin has two characteristics that are sure to draw the attention of cell biologists. Its distribution is . . . ubiquitous; it is found in all the cells of higher organisms and perhaps also in bacteria. Moreover, ubiquitin's structure has changed very little during the course of evolutionary history. Such characteristics generally indicate a protein that has a fundamental role in the life of the cell. "Ubiquitin is everywhere and is probably functional everywhere," says Alexander Varshavsky of the Massachusetts Institute of Technology.

Best established is its function as a marker for proteins that are destined for degradation. As such it helps to destroy the normally short-lived proteins of the cell, a category that is likely to include many of those involved in regulating gene expression and other cellular activities. Ubiquitin addition may also tag for destruction damaged or abnormal proteins, which could harm the cell if they accumulated. In this capacity, the ubiquitin system may be part of the cell's defenses against heat shock and other stresses.

All these activities take place in the nucleus and cytoplasm. New evidence now extends the possible sphere of ubiquitin's influence to the outer membrane of the cell. In two papers in this issue of *Science* (pp. 823 and 845), Irving Weissman and his colleagues at Stanford University School of Medicine present evidence suggesting that the protein is part of the receptor by which lymphocytes home in on and enter the lymph nodes, an activity that is necessary for normal immune responses.

Once lymphocytes, both of the T and B types, have reached a stage of maturity in which they are capable of responding to antigens, they begin shuttling around the body. During this time, they periodicially move into one or another of the lymphoid organs, which include the lymph nodes, the spleen, and the Peyer's patches found in and around the intestines. This system helps to ensure that a lymphocyte of appropriate specificity will be available no matter where a foreign antigen enters the body.

About 20 years ago, James Gowans, who was then at the University of Oxford in England, showed that lymphocytes enter the lymphoid organs through specialized blood vessels called postcapillary high endothelial venules. Results from Weissman and his Stanford colleagues Eugene Butcher and W. Michael Gallatin indicate that lymphocytes bind to the cells lining the vessels by means of specific receptors, which they call homing receptors. They find, among other things, that lymphocytes have a strong, although not absolute, preference for binding to venules from the lymph organ from which they were originally isolated.

Moreover, many lines of cloned lymphoma cells are extremely specific, binding either to lymph node or Peyer's patch venules, but not to both. By making monoclonal antibodies against the lymph-node specific lymphoma cells the Stanford workers were able to produce an antibody, which they called MEL-14, that recognizes the lymph node homing receptor.

Weissman, Thomas St. John, also of Stanford, and their colleagues then used the MEL-14 antibody in an attempt to identify the gene coding for the lymph node homing receptor protein. Three DNA clones yielded protein products that were recognized by the antibody. At this point the research took an unexpected turn. "We sequenced the genes and found they all encoded ubiquitin," Weissman says. "We were surprised and disappointed." Not only was ubiquitin not thought to occur on the cell surface, but the protein would not seem to provide any basis for the specificity required by a receptor.

For one, its structure is highly conserved, having the same sequence of 76 amino acids in species as diverse as the toad *Xenopus laevis*, the chicken, and the human. Even yeast ubiquitin differs in only three amino acids from the human version, according to Varshavsky and his MIT colleagues Daniel Finley and Engin Ozkaynak. "Currently it is the most conserved of all eukaryotic proteins," Varshavsky says.

For another, ubiquitin is made in all cells, not just the subgroup of lymphocytes that carry the lymph node homing receptor. Specificity could therefore not be attained by restricting production of ubiquitin to a particular cell type.

All this left Weissman and his colleagues

asking whether the identification of the ubiquitin clones was merely an artifact. Perhaps the ubiquitin structure just resembled that of the antigen recognized by MEL-14.

The Weissman group was encouraged when experiments performed in collaboration with Victor Fried of St. Jude Children's Research Hospital in Memphis indicated that antibodies recognize ubiquitin-containing determinants on the cell surface. More direct evidence came when Weissman, Mark Siegelman, also of Stanford, and their colleagues isolated the lymphocyte protein with which MEL-14 reacts. This turned out to be a single, sugar-containing polypeptide with a molecular weight of 90,000. Determination of a partial amino acid sequence for the molecule revealed that it has a branched structure with two amino terminals—one of which corresponds to the ubiquitin sequence.

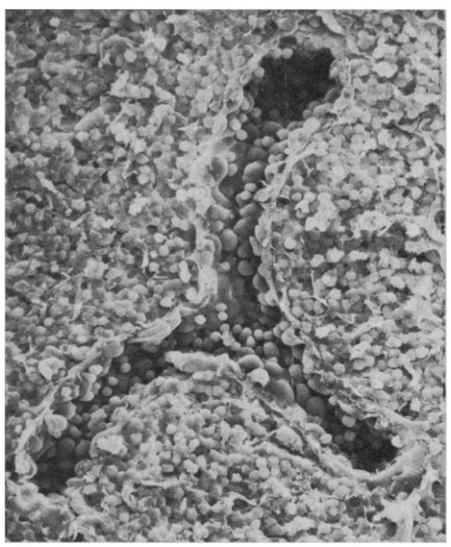
This structure is similar to one identified several years ago by Harris Busch of Baylor College of Medicine, who showed that ubiquitin attaches to a nuclear protein, histone 2A, to form a branched molecule. In the case of the histone, which is associated with the DNA in chromatin, ubiquitin attachment may be involved in regulating gene expression. Varshavsky and his colleagues have found that the ubiquitin-histone complexes tend to be localized in regions where genes are being actively transcribed. They postulate that attachment of ubiquitin to histone 2A might contribute to the chromatin unfolding that is needed for gene expression.

What ubiquitin is doing on the lymph node homing receptor is currently unclear. One possible explanation is that it might act to mark the membrane protein for degradation. Work by Avram Hershko of the Faculty of Medicine of the Technicon-Israel Institute of Technology in Haifa and Irwin Rose of the Fox Chase Cancer Center in Philadelphia has established that ubiquitin attachment to cytoplasmic proteins leads to their degradation. This is part of the normal pathway for removing proteins that have relatively short half-lives.

However, ubiquitinated proteins are not necessarily destined for destruction. For example, histones that have undergone the modification do not appear to undergo rapid degradation.

A more interesting possibility is that ubiquitin participates directly in the lymphocyte-endothelial cell interaction that is mediated by the homing receptor. According to Weissman, studies with monoclonal antibodies suggest that the ubiquitin moiety may be critical for the interaction. They also indicate that its conformation on the homing receptor is different from the conformation of free ubiquitin or of ubiquitin bound to other proteins. Such conformational changes might enable ubiquitin to contribute to specific receptor interactions.

The extent of ubiquitin addition to membrane proteins is currently unclear, although the Weissman group has evidence it might happen to others besides the lymph node homing receptor. Preliminary evidence from Louis Williams and Jaime Escobedo of the University of California School of Medicine in San Francisco and Fried indicates that the receptor for platelet-derived growth factor may be one of the others. "We feel pretty sure that it [the receptor] is ubiquitinated," Williams says, "but we don't know what it means yet."



Lymphocytes in a high endothelial venule

The scanning electron micrograph shows lymphocytes adhering to the plump endothelial cells of a Y-shaped venule. [*Source: I. L. Weissman, E. C. Butcher, R. V. Rouse, R. G. Scollay, in* Strategies of Immune Regulation, *E. E. Sercarz and A. J. Cunningham, Eds.* (*Academic Press, New York, 1980*), *p. 78*]

How ubiquitin reaches the cell surface is another mystery. It is unlikely to be transported there on its own because it lacks a signal sequence, which is generally considered a prerequisite for membrane targeting. The best bet, Weissman suggests, is that it is added to the receptor protein while this is still being synthesized and would be accessible to ubiquitin in the cytoplasm.

At the same time that ubiquitin's sphere of influence has been expanding to include the outer cellular membrane, evidence has also been accumulating to suggest a broader than expected role for it in the cell interior. The ability to attach ubiquitin to proteins is an essential one. For example, Varshavsky, Finley, and Aaron Ciechanover, also of MIT, have identified the defect in a line of mutant cells that die when the temperature is raised from 32° to 39°C. The temperature increase rapidly inactivates an enzyme needed for ubiquitinating proteins.

This loss might disrupt regulation of gene control or other cell activities by leading to an abnormal buildup of the short-lived proteins that should otherwise be degraded following ubiquitin addition. In addition, the MIT workers propose, the ubiquitin system may contribute to the cell's ability to withstand heat shock and other stresses that can damage proteins. If these are not ubiquitinated and destroyed, they may aggregate and thereby injure the cell by disrupting the filament networks that lace the interior.

Suggestions that ubiquitin may participate in the stress responses are buttressed by the finding of the Varshavsky group and also that of Milton Schlesinger at Washington University School of Medicine that ubiquitin synthesis is stimulated when cells are exposed to high temperatures. It thus resembles synthesis of the "heat shock" proteins, which is also stimulated by stresses such as heat. The heat shock proteins apparently protect cells against the untoward effects of the stresses in ways that are not completely understood. The synthesis of most other proteins stops under similar conditions.

Ubiquitin genes can show an unusual organization, one which may help the cell produce large quantities of the protein in a short time—as may be needed in times of stress, for example. DNA sequence studies in the Varshavsky laboratory and elsewhere reveal that the genes often consist of a variable number of repeated ubiquitin coding elements that are linked head-to-tail and are not separated by introns or other spacer sequences. The protein products are thus "polyubiquitins" that must be precisely split to produce free ubiquitin.

Not all ubiquitin genes show this organization, however. The MIT workers find that the yeast genome contains three additional ubiquitin coding sequences, at least one of which is fused to a sequence encoding an unrelated protein of unknown function. The yeast polyubiquitin gene is turned on by heat shock, Varshavsky notes, whereas these others are not and their role is unclear.

The full complexity of the ubiquitin system has yet to be revealed, much less understood, but it is now certain that the protein's influence extends throughout the cell. ■

JEAN L. MARX

ADDITIONAL READING

D. Finley and A. Varschavsky, "The ubiquitin system: Functions and mechanisms," *Trends Biochem. Sci.* 10, 343 (1985).

S. Munro and H. Pelham, "What turns on heat shock genes?" *Nature (London)* 317, 477 (1985).