Cell 'Caves' Harbor Clues to Diseases

Lisanti *et al.*/J. CELL BIOL.

Transmission electron microscopy reveals caveolae (arrows).

Just as the probing of a new cave's mineral deposits can yield discoveries richer than the finding of the cave itself, the identification of the chemicals inside cellular chambers called caveolae is proving a mother lode for researchers.

Last year, cell biologists for the first time isolated these "tiny caves" from the surfaces of cells (SN: 8/28/93, p.143). At the time, not everyone was sure these membranous vesicles were true subcellular compartments, or organelles. But now, using two methods and two types of tissue, two research teams have reached similar conclusions. "This *is* an organelle, and it has a lot of interesting proteins," says Richard G.W. Anderson, who heads one team at the University of Texas Southwestern Medical Center at Dallas.

The protein that forms these vesicles—caveolin—is just one of many biologically important molecules found there, adds Michael P. Lisanti, who led the second group, based at the Whitehead Institute for Biomedical Research in Cambridge, Mass.

Lisanti and his colleagues have demonstrated that caveolae contain molecules implicated in the abnormal buildup of fatlike substances along blood vessels. Other constituents of caveolae play a role in tissue damage related to diabetes and in the disintegration of muscle in Duchenne muscular dystrophy, they report in the July 1 JOURNAL OF CELL BIOLOGY.

For their studies, Lisanti and his colleagues refined their initial purification procedures so they could isolate larger quantities of caveolae, this time from lung tissue rather than from cells grown in the laboratory. As a result, the group could systematically identify the protein components of these compartments, Lisanti explains.

Typically, scientists studying new organelles expect to find novel proteins inside them. "But we found what others had found in a different context, molecules important to the development of major human diseases," says Lisanti.

For example, other scientists had determined that CD36, a docking site for oxidized low-density lipoproteins, can lead to the unwanted cholesterol plaques that clog arteries. CD36 is concentrated inside caveolae, Lisanti's group reports. Also, in diabetics, the accumulation of substances altered by prolonged exposure to blood sugar can damage kidneys, the retina, and other tissues. These harmful substances also deposit inside caveolae, Lisanti says.

In the same journal, Anderson's group reports finding at least 30 proteins concentrated in caveolae. Using a biochemical approach, they purified caveolae from smooth muscle cells of chicken gizzards. These chambers were rich in proteins that use a specific chemical anchor (called glycosylphosphatidylinositol or GPI) to stick to the cell membrane, the Dallas researchers note.

It seems that caveolae can open, take in molecules from outside the cell, then close. They may move, process, or finally release those substances or their by-products. Thus, caveolae may help distribute proteins throughout the cell. At other times, these tiny caves may sequester molecules, Anderson says.

Some of those molecules are known cellular signals; others are suspected of carrying particular messages. "It suggests that caveolae are a central place for processing signals," says Lisanti.

One enzyme, protein kinase C, seems to help regulate the uptake of small molecules by caveolae, Anderson and Lisanti say. If researchers can eventually control the opening and closing of caveolae and the passage of substances into these chambers and thus into cells, the two scientists expect caveolae will prove valuable gateways for new drugs.

Toward that end, Douglas M. Lublin of Washington University School of Medicine in St. Louis has begun to elaborate what determines whether proteins enter caveolae. He finds that the GPI anchor is sufficient for some proteins to gain access, while others need to append two fatty-acid side chains to their structures. His work will appear in the July 15 JOURNAL OF CELL BIOLOGY. — *E. Pennisi*

UV damage: Some surprises under the sun

Ozone depletion and the concomitant strengthening of ultraviolet radiation can harm natural ecosystems in unanticipated ways, according to Canadian ecologists who tested how river organisms react to various types of light.

When researchers from the National Hydrology Research Institute in Saskatoon, Saskatchewan, started their study, they presumed that abundant single-celled plants in the river would grow slower when exposed to UV radiation—an effect previously documented in studies of algae removed from oceans and lakes. But algal communities in the intact river ecosystem actually fared better when subjected to UV radiation.

It was the more complex — and supposedly more resilient—organisms that suffered in the experiment.

"This was quite unexpected. There is nothing in the literature to suggest we would get these results," says Max L. Bothwell, who discussed the team's findings in the July 1 SCIENCE.

Bothwell and his colleagues pumped river water through sets of open conduits, which they shaded with mylar, acrylic, and other materials. Some of the coverings let through all wavelengths of solar radiation; others selectively blocked low-energy ultraviolet (UVA), mid-energy ultraviolet (UVB), or both. Thinning of the ozone layer will boost levels of UVB, but not UVA, striking Earth.

Over several weeks, the researchers analyzed how well algae and midge larvae grew under various conditions. While UV radiation did slow algal growth, the light hurt the algae-eating larvae even more, leading to overall algal increases in the river experiments.

In the past, ecologists presumed that increases in UV light would hit single-celled organisms such as algae hardest because they lack protective layers of cells. But the river experiments yielded the opposite result.

Because the algae-eating larvae form an important link in the food chain, their sensitivity to increasing levels of UV light could send ripples moving up the chain toward larger animals. "The effect of UVB at the ecosystem level is probably magnified higher in the food chain than it is at lower levels in the food chain," Bothwell says.

Deneb Karentz of the University of California, San Francisco, lauds the Canadian team for focusing on the interactions between different ecosystem levels. Karentz, who studies how UV light damages ocean algae, says the well-designed experiment leaves little room for criticism. — *R. Monastersky*