

Protein controls acid in cells by direct detection of volume changes, study finds

DALLAS – July 5, 2004 – A protein responsible for regulating acid levels within cells – and pumping out acid accumulated in cardiac cells after a heart attack – activates in direct response to changes in a cell’s volume, according to a new study by researchers at UT Southwestern Medical Center at Dallas.

Their findings show that the protein NHE1, which is found in the membranes of nearly all cells and is especially active in cancer cells, is regulated by the stretch and pull of the membrane as a cell changes volume. The study appears in the *Proceedings of the National Academy of Sciences* and is available online.

NHE1, which is called a transporter protein, oscillates its shape rapidly in a cell’s membrane. This allows sodium from the outside to come in and protons – positively charged particles – from inside the cell to escape and lower the cell’s acidity. The fewer protons in a cell, the less acidic it is.

“The acidity in the cell is a huge signal for the cell,” said [Dr. Donald Hilgemann](#), professor of physiology at UT Southwestern and senior author of the study. “The control of acidity regulates cell growth and proliferation.”

Hormones and many other signals that control cell growth and proliferation act on NHE1, he said.

“Our study shows that as cell volume increases, this transporter turns off. If volume decreases, it turns on by directly sensing mechanical changes in the membrane,” continued Dr. Hilgemann.

The NHE1 transporter is a protein of much interest to drug developers investigating ways to prevent cell death, which often accompanies heart attacks and strokes. In ischemia, where the blood supply is cut off

to cardiac cells or brain cells, cells become very acidic. As the body's normal metabolism gets going again, the NHE1 system starts pumping out the accumulated acid, exchanging the acid for sodium.

"It's such an active system that you can overload the cell with sodium," Dr. Hilgemann said. "Too much sodium is a major mechanism of cell death in ischemic episodes. Virtually every study that has been done (on inhibiting NHE1) has shown that if you block this transporter, you can prevent this type of cell death from ischemia."

Previous studies have suggested that NHE1 plays a role in cancer cells that are trying to spread, or metastasize, to different parts of the body. As cancer cells move, they must change their volume, protruding at one end and retracting on the other. Dr. Hilgemann said other researchers speculate that NHE1 is at the head of the cell as it is moving, and is always rearranging itself to be at the cell's head.

"While the cancer applications are very speculative, understanding this system can be very important for many aspects of cell biology," he said.

The new study also compares NHE1 to another, very similar transporter called NHE3, which is found only in the kidneys.

"We found there are very specific differences in the way these two systems respond to changes in the cell," Dr. Hilgemann said. "For example, the one in the kidney is involved in reabsorbing sodium, but it is not regulated at all by changes in cell volume."

Dr. Hilgemann and his colleagues improved upon an existing experimental technique in order to study the NHE transporters and how acidity changes within a cell. The existing method involves skewering a single cell on a tiny, hollow needle called a pipette. Dr. Hilgemann's group made their pipette larger to make a larger hole in the cell, which allowed them better control over what was inside and outside of the cell.

They also optimized the use of tiny sensors that can measure exactly the movement of protons across the cell membrane. "This tells us how the acidity is changing," Dr. Hilgemann said. "Our advancements allow us to better show and study how these systems are working."

Other UT Southwestern researchers who contributed to the study are Dr. Daniel Fuster, a postdoctoral researcher in internal medicine, and [Dr. Orson Moe](#), director of the Charles and Jane Pak Center for Mineral Metabolism and Clinical Research.

The research was funded by the National Institutes of Health and the Department of Veterans Affairs Research Service.

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