Opening a Door into Cells

Research shows how ultrasound can deliver therapeutic molecules into living cells.

BY JOHN TOON

Researchers have shown how ultrasound energy can briefly "open a door" in the protective outer membranes of living cells to allow entry of drugs and other therapeutic molecules — and how the cells themselves can then quickly close the door. Understanding this mechanism could advance the use of ultrasound for delivering gene therapies, targeting chemotherapy and administering large-molecule drugs that cannot readily move through cell membranes.

Using five different microscopy techniques, the researchers showed that the violent collapse of bubbles — an effect caused by the ultrasound — creates enough force to open holes in the membranes of cells suspended in a liquid medium. The holes, which are closed by the cells in a matter of minutes, allow entry of therapeutic molecules as large as 50 nanometers in diameter — larger than most proteins and similar in size to the DNA used for gene therapy.

"The holes are made by mechanical interaction with the collapsing bubbles," says Mark Prausnitz, an associate professor in the School of Chemical and Biomolecular Engineering at the Georgia Institute of Technology. "The bubbles oscillate in the ultrasound field and collapse, causing a shock wave to be released. Fluid movement associated with the resulting shock wave opens holes in the cell membranes, which allow molecules from the outside to enter. The cells then respond to the creation of the holes by mobilizing intracellular vesicles to patch the holes within minutes."

Done by scientists at Georgia Tech and Emory University in Atlanta, the research was reported in the journal *Ultrasound in Medicine and Biology* (Vol. 32, No. 6). The National Institutes of Health and the National Science Foundation supported the work.

Ultrasound is the same type of energy already widely used for diagnostic imaging. Drug delivery employs higher power levels and different frequencies, and bubbles may be introduced to enhance the effect.

Ultrasound drug delivery could be particularly attractive for gene therapy, which has successfully used viruses to insert genetic material into cells — but with side effects. It could also be used for more targeted delivery of chemotherapy agents.

"One of the great benefits of ultrasound is that it is noninvasive," Prausnitz says. "You could give a chemotherapeutic drug locally or throughout the body, then focus the ultrasound only on areas where tumors exist. That would increase the cell permeability and drug uptake only in the targeted cells and avoid affecting healthy cells elsewhere."

Prausnitz and collaborators Robyn Schlicher, Harish Radhakrisha, Timothy Tolentino, Vladimir Zarnitsyn of Georgia Tech and the late Robert Apkarian of Emory University conducted the research.

Researchers face a number of challenges, including FDA approval, before ultrasound can be used to deliver drugs in humans. Researchers also will have to address safety concerns and optimize the creation of collapsing bubbles — a phenomenon known as cavitation — within bodily tissues.

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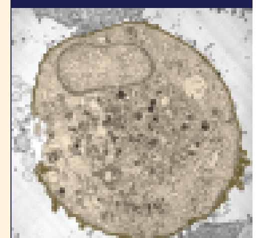

IMAGE COURTESY OF ROBYN SCHLICHER, ROBERT APKARIAN AND MARK BARAN

***ABOVE :** This transmission electron micrograph shows a prostate cancer cell immediately after exposure to ultrasound. The image has been color-enhanced to show the spot where the cell membrane has been removed.*

***BELOW:** Researchers Mark Prausnitz and Robyn Schlicher use a confocal microscope to study cells whose membranes have been opened by the application of ultrasound.*

PHOTO BY GARY MEEK