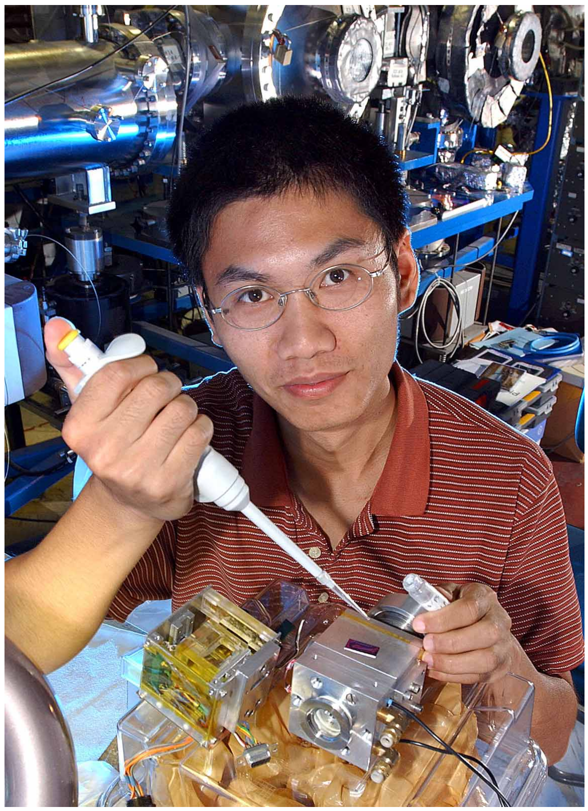
Biological Serendipity: Molecular Details of Cell Membrane Fusion Revealed

For the first time, scientists have observed the molecular details of biological cells fusing together, a fleeting event never before observed at this scale. This research, which could lead to more efficient drug delivery processes and gene therapy techniques, was performed on NSLS beamline X21 and Rice University. The results appear in the September 13, 2002 issue of *Science*.

Cellular membrane fusion is well known to scientists and is one of the most common ways for molecules to enter or exit cells, in processes such as fertilization and viral infection. When two cells fuse together, their membranes come together at one location and create a connection between the cells that allows the exchange of material between them. Eventually, the two membranes form one single, continuous membrane surrounding the contents of both cells.

"We have now confirmed the existence of a temporary structure that occurs during membrane fusion and that has been postulated by scientists for a long time," says Lin Yang, a postdoctoral physicist at the NSLS and the lead author of the study. Yang and coauthor Huey Huang, professor of physics and astronomy at Rice University in Houston, with whom Yang did his doctoral studies, made their observation by serendipity while studying how certain small proteins kill bacteria by digging holes into bacterial membranes.



Lin Yang

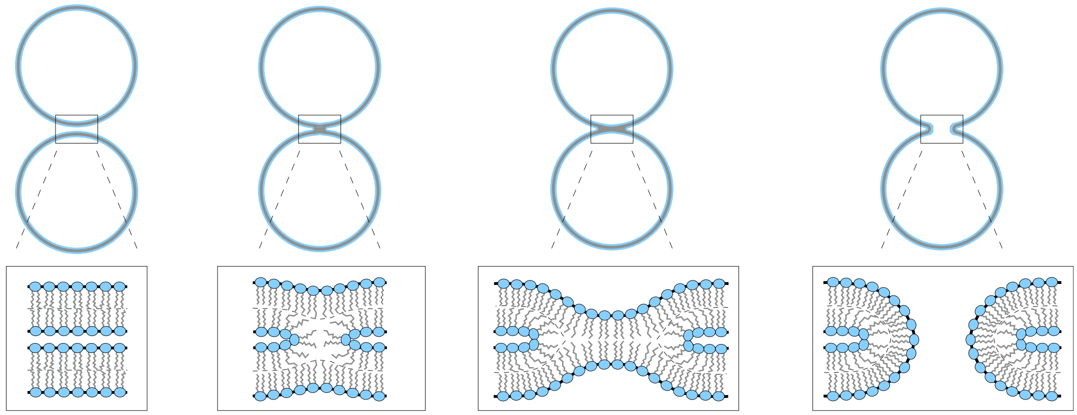
"We were trying to understand how changes in humidity and temperature affect the properties of a certain type of cell membrane," Yang says, "when, amid our results, we observed this structure that nobody had ever seen. That was pretty exciting."

To reveal the structure of the fused cell membranes, the scientists used a method called x-ray diffraction. They first produced small crystals composed of stacks of membranes made of phospholipids. Then, they projected x-rays produced by the NSLS toward the crystals. By looking at how the x-rays scattered off the crystals, Yang and Huang measured a pattern of points with varying intensities, called a diffraction pattern, which represents a map of the atomic structure of the phospholipid layers in the membranes.

"We noticed that by changing the humidity, we could significantly alter the structure of the membrane," Yang says. For certain humidity values, the scientists noticed that, instead of displaying a single line of regularly spaced points, the diffraction pattern revealed many more points at other positions. By studying these diffraction patterns more closely, the scientists realized that these patterns were those of two membranes caught in the act of fusing.

The diffraction pattern showed that, when the two membranes fuse, they form an hourglass-shaped structure called a stalk, confirming theoretical predictions. When the stalk stretches further, it creates a connecting bridge between the membranes. This connection then enlarges, and the two membranes ultimately become one single membrane.

Huang comments that the membrane considered in this study is relatively simple and does not reflect the complexity of more common natural membranes, which are made of phospholipids and proteins. "What is truly exciting is that we now have, for the first time, a model system that can provide clues about how more complicated membranes work," he says.



A simple representation of the fusion of two cells, with close-up views of the changes that the cellular membranes undergo. Each membrane is made of a double layer of phospholipids which intermingle to create a passage between the cells. (Each phospholipid is represented with a head and two tails.)

Understanding cell fusion may be key to preventing viral infection or designing new drug delivery methods, the scientists say. "Understanding the details of membrane fusion may help scientists find the appropriate conditions for preventing viruses such as HIV from fusing to and thereby infecting human cells," Yang says. "This knowledge could also lead to the design of systems in which a drug or a piece of DNA is enclosed in a membrane known to fuse with specific cells in our body, thus facilitating drug delivery or improving gene therapy."

— Patrice Pages

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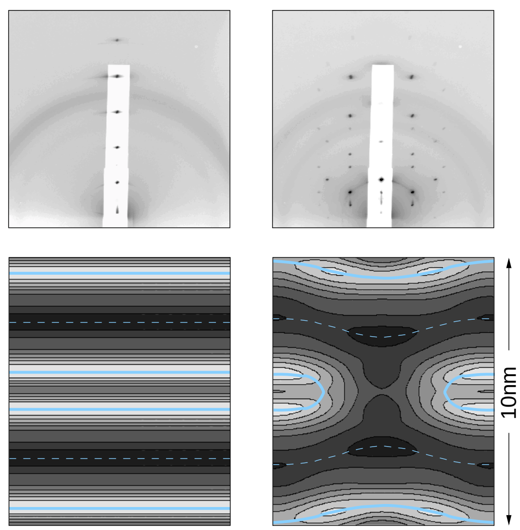

(Top) Diffraction patterns of two cell membranes before (left) and during (right) fusion. (Bottom) Three-dimensional representation of the membranes before (left) and during (right) fusion.