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Cholesterol rafts deliver drugs inside cancer cells

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DNA, siRNA and miRNA can reprogram cancer cells – that is, if these nucleic acids could cross through the cell membrane. A University of Colorado Cancer Center study published today in the journal *Therapeutic Delivery* shows that cholesterol "rafts" can shepherd genetic payloads into cancer cells.

"There are many promising therapeutic applications for nucleic acids, but because they can't diffuse across cell membranes on their own, delivery to cancer cells has been a major challenge. Our method is a promising way to get these drugs inside cancer cells where they can do their work," says Tom Anchordoquy, PhD, investigator at the CU Cancer Center and professor at the Skaggs School of Pharmacy and Pharmaceutical Sciences.

The technology works by exploiting a relatively new understanding of what cell membranes look like.

"It used to be that we thought about membrane proteins floating around in a disorganized two-dimensional soup. Now we know that different functions are clustered into domains we call rafts," Anchordoquy says. Imagine these rafts like continents of the Earth, each presenting its own plant species. Perhaps a raft with palm trees but not spruce unlocks passage into a cancer cell?

Anchordoquy and colleagues aren't the first to imagine particle-payload delivery systems, but when you engineer and introduce a non-rafted

particle into the blood, it quickly becomes coated with all sorts of blood proteins that can cover the membrane proteins ("palm trees") needed to unlock passage into cancer cells. However, blood proteins don't bind to rafts and so particles with rafts continue to present the engineered bits rather than being silted over by the body's proteins. Anchordoquy and colleagues make these rafts by boosting the concentration of cholesterol while forming particles for drug delivery.

"See, rafts are made of 30-50 percent cholesterol, about five times the level in the surrounding lipid. We'd shown in earlier experiments that rafts create more delivery of payload materials into cancer cells, but there was always the outside chance that the benefit was due simply to higher levels of cholesterol and not to the action of the rafts, themselves," Anchordoquy says.

The current study found an elegant fix: with longer tails on lipid molecules, particles will form rafts at lower cholesterol concentrations. The team used long-tailed lipids to form their particles, allowing them to keep cholesterol concentration low while showing the same benefit in delivering genes into cancer cells. This demonstrates that it is indeed the raft that facilitates delivery.

"We've used these synthetic rafts to deliver a gene inside these cells that makes the cells fluoresce," Anchordoquy says. "That way we can see how much payload went in. But because we're talking particles and not just individual molecules, in the future we can send other cargo like microRNA's that can reprogram a cell's gene expression."

Anchordoquy is working with colleagues at the CU Cancer Center to match his delivery system with a potent payload, and welcomes collaboration outside the center as well.

Provided by University of Colorado Denver