Finding microscopic motors in the gut

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Digestion has a previously unsuspected mechanical dimension: Vanderbilt researchers have discovered that the tiny, hair-like protrusions that line the gut are filled with millions of molecular motors that produce streams of microscopic membrane sacs, called vesicles, containing enzymes for processing nutrients.

For more than 30 years, researchers have known of the existence of these motor proteins, but have assumed that they play a purely structural role.

That never made sense to Matthew Tyska. In 1999, on the first day of his postdoctoral fellowship, Tyska saw an old electron micrograph taken by his mentor, Mark Mooseker, professor of molecular, cellular and developmental biology at Yale University. The image showed the internal structures of a tiny, finger-like protrusion on the surface of an intestinal cell called a microvillus. Microvilli are common features on the epithelial cells that line both the large and small intestines, as well as on many other tissues throughout the body.

At the time, Tyska knew that the core bundle traveling up the center of the microvillus was an array of the structural protein actin and that the ladder-like "rungs" connecting the actin bundle to the cell membrane were composed of a protein called myosin-1a. Although this protein is closely related to the myosin that acts as a molecular motor in muscle cell contraction, digestion researchers believed it had an entirely different function in the microvillus.

They thought the tiny rungs held the membrane in place around the actin bundle, dramatically increasing the contact area between the cellular lining and the liquified nutrients that are pumped through the intestines. This expanded cell surface increases the space available for nutrient-processing enzymes and transporters, resulting in greater nutrient handling capacity.

"The textbook thinking for decades was that microvilli serve as a passive scaffold, a way to amplify the membrane surface area," says Tyska, who is now an assistant professor of cell and developmental biology at Vanderbilt.

"When I looked at that image, the near crystalline arrangement reminded me of actin and myosin in a muscle fiber," says Tyska, who is a molecular motor expert. "I kept returning to the same question: Why would the microvillus have this beautiful structure packed with motor proteins? The concentration of myosin motors in a single microvillus is very high; there's serious force-generating potential there."

So Tyska and Russell McConnell, a graduate student in his laboratory, decided to test the idea that these motor proteins could do more than simply increase cell surface area.

The investigators purified the intestinal "brush border" — the layer of densely packed microvilli — from the intestines of rats or mice, and added ATP, the chemical fuel for myosin-1a. Through the microscope, they watched the cell membrane move toward the tips of the microvilli and pop off the ends in the form of vesicles, tiny bubble-like packets.

Their findings, reported last month in the Journal of Cell Biology with one of their images featured on the issue cover, have implications for nutrient processing and other aspects of gastrointestinal physiology.

"What we're showing is that the microvillus is more than just a scaffold to increase the amount of cell membrane," Tyska says. "It's a little machine that can shed membrane from the tips."

The team confirmed that myosin-1a is the motor that moves membrane up the microvillus. Brush borders isolated from mice lacking the myosin-1a gene shed membrane at only five percent of the level of brush borders from wild-type animals.

The investigators are working now to understand why intestinal cells might launch vesicles from their microvilli. They know from ongoing vesicle sorting and mass spectrometry studies that the vesicles are enriched in nutrient-processing enzymes, like the microvillar membrane.

"One idea is that these vesicles operate remotely to speed nutrient processing, before the nutrients even get to the brush border to be absorbed by the (intestinal epithelial cell)," Tyska says.

The team is exploring other possibilities for the role of membrane shedding: that it offers protection against microbes and pathogens by expelling them from the surface before they can enter the cell; that it provides a mechanism for altering the composition of the microvillar surface to handle changes in "what comes down the pipe"; and that it serves a role in cell-cell communication by launching vesicles that contain signaling proteins.

Tyska and his team also plan to investigate whether myosin-1a is serving a similar membrane-moving role in its other known location, the hair cells of the inner ear, and if other microvilli also use myosin motors to jettison vesicles from their tips.

Source: Vanderbilt University