

# Biologists spy on the secret inner life of a cell

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The transportation of antibodies from a mother to her newborn child is vital for the development of that child's nascent immune system. Those antibodies, donated by transfer across the placenta before birth or via breast milk after birth, help shape a baby's response to foreign pathogens and may influence the later occurrence of autoimmune diseases. Images from biologists at the California Institute of Technology (Caltech) have revealed for the first time the complicated process by which these antibodies are shuttled from mother's milk, through her baby's gut, and into the bloodstream, and offer new insight into the mammalian immune system.

Newborns pick up the antibodies with the aid of a protein called the neonatal Fc receptor (FcRn), located in the plasma membrane of intestinal cells. FcRn snatches a maternal antibody molecule as it passes through a newborn's gut; the receptor and antibody are enclosed within a sac, called a vesicle, which pinches off from the membrane. The vesicle is then transported to the other side of the cell, and its contents--the helpful antibody--are deposited into the baby's bloodstream.

Pamela Bjorkman, Max Delbrück Professor of Biology at Caltech and an investigator with the Howard Hughes Medical Institute, and her colleagues were able to watch this process in action using gold-labeled antibodies (which made FcRn visible when it picked up an antibody) and a technique called electron tomography. Electron tomography is an offshoot of electron microscopy, a now-common laboratory technique in which a beam of electrons is used to create images of microscopic objects. In electron tomography, multiple images are snapped while a

sample is tilted at various angles relative to the electron beam. Those images can then be combined to produce a three-dimensional picture, just as cross-sectional X-ray images are collated in a computerized tomography (CT) scan.

"You can get an idea of movement in a series of static images by taking them at different time points," says Bjorkman, whose laboratory studies how the immune system recognizes its targets, work that is offering insight into the processes by which viruses like HIV and human cytomegalovirus invade cells and cause disease.

The electron tomography images revealed that the FcRn/antibody complexes were collected within cells inside large vesicles, called "multivesicular bodies," that contain other small vesicles. The vesicles previously were believed to be responsible only for the disposal of cellular refuse and were not thought to be involved in the transport of vital proteins.

The images offered more surprises. Many vesicles, including multivesicular bodies and other more tubular vesicles, looped around each other into an unexpected "tangled mess," often forming long tubes that then broke off into the small vesicles that carry antibodies through the cell. When those vesicles arrived at the blood-vessel side of the cell, they fused with the cell membrane and delivered the antibody cargo. The vesicles also appeared to include a coat made from a molecule called clathrin, which helps form the outer shell of the vesicles. Researchers previously believed that a vesicle's clathrin cage was completely shed before the vesicle fused with the cell membrane. The new results suggest that only a small section of that coating is sloughed off, which may allow the vesicle to more quickly drop its load and move on for another.

"We are now studying the same receptor in different types of cells in order to see if our findings can be generalized, and are complementing

these studies with fluorescent imaging in live cells," Bjorkman says. "The process of receptor-mediated transport is fundamental to many biological processes, including detection of developmental decisions made in response to the binding of hormones and other proteins, uptake of drugs, signaling in the immune and nervous systems, and more. So understanding how molecules are taken up by and transported within cells is critical for many areas of basic and applied biomedical research," she adds.

The paper, "FcRn-mediated antibody transport across epithelial cells revealed by electron tomography," was published in the September 25 issue of *Nature*.

Source: California Institute of Technology

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