Studying fish to learn about fat

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In mammals, most lipids (such as fatty acids and cholesterol) are absorbed into the body via the small intestine. The complexity of the cells and fluids that inhabit this organ make it very difficult to study in a laboratory setting. New research from Carnegie's Steven Farber, James Walters and Jennifer Anderson reveals a technique that allows scientists to watch lipid metabolism in live zebrafish. This method enabled them to describe new aspects of lipid absorption that could have broad applications for human health. Their work is published in *Chemistry & Biology*.

The small intestine is composed of multiple cell types. It is also the site of microorganisms, bile and mucus that help digest and absorb food. In this environment, dietary lipids are digested by enzymes and bile so that the body, via the absorptive cells of the intestine called enterocytes, can take in critical nutrients.

One type of lipid, cholesterol, is known to impact a number of highly prevalent human diseases and is absorbed by enterocytes. In zebrafish and humans, newly absorbed cholesterol combines with proteins to form lipoproteins, vehicles destined for the lymphatic system for subsequent distribution throughout the body. In humans, a protein called NPC1L1 (short for Niemann-Pick disease, type C1, gene-like 1) plays an important role in absorption by the enterocytes , but how this protein facilitates cholesterol's journey through the cell is poorly understood.

Another lipid metabolic product, called fatty acids, are absorbed by these same cells. Despite years of study, the physiological process by

which proteins mediate the initial steps of fatty acid uptake is unclear. Once absorbed, the fatty acids are converted to triacyglycerides (fat) and either prepared to be transported out of the cell or transformed into droplets of stored fat. How these fat droplets form inside intestinal cells is not well understood.

These processes involving fatty acids, triacyglycerides and cholesterol influence each other in poorly understood ways. For example, it has long been known that the presence of dietary fat increases dietary cholesterol absorption, but the mechanism by which this occurs has not been determined.

Enter Farber and his team's new research tool.

They developed a method for using fluorescently glowing forms of lipids to observe fat and cholesterol absorption in the small intestines of live zebrafish. Using this tool, they were able to demonstrate the following:

- The physiological processes regulating fatty acid absorption and cholesterol absorption are linked, as was first suggested by studies involving rats in the 1960s.
- A fatty acid called oleic acid can greatly increase the uptake of dietary cholesterol.
- The subcellular location of the human protein NPC1L1, suspected to regulate cholesterol absorption, is modulated by the presence of oleic acid. (Farber's team inserted the human NPC1L1 protein, fused to a red fluorescent protein, into the zebrafish.)
- In the presence of an abundance of dietary triacyglycerides, absorbed fatty acids were rapidly stored as lipid droplets. In contrast, cholesterol was stored in special structures, called endosomes,which are distinct from lipid droplets in zebrafish

intestines.

"Historically, the zebrafish has been used in the field of embryology and development and we felt that it had been underutilized for studies of whole-animal physiology," Farber said. "Using the zebrafish in this novel way allowed us to be the first to observe cholesterol absorption in a living vertebrate system."

Zebrafish studies may enable a better understanding of human fat and cholesterol metabolism and contribute to ongoing efforts to reduce the impact of diseases associated with altered lipid metabolism, such as diabetes, obesity, and cardiovascular disease.

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