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Zebrafish research shows how dietary fat regulates cholesterol absorption

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Buttery shrimp. Fried eggs. Burgers and fries. New research suggests there may be a biological reason why fatty and cholesterol-rich foods are so appealing together.

It has been known for more than 40 years that dietary fat promotes cholesterol uptake, but fundamental aspects of that process remain poorly understood. James Walters, Ph.D., and his colleagues at the Carnegie Institution for Science are using zebrafish to better understand the cellular mechanisms of cholesterol processing and have discovered a surprising link between dietary fat and cholesterol absorption.

"One reason these questions remain unknown is because of the difficulty of studying such a complex biological system as the intestine," which in addition to multiple cell types also includes a diverse array of enzymes, mucus, and symbiotic bacteria, he said in a June 20 presentation at the ongoing 2012 International Zebrafish Development and Genetics Conference in Madison, Wisconsin.

As a postdoctoral fellow in Dr. Steven Farber's lab at the Carnegie Institution for Science, in Baltimore, Maryland, Dr. Walters turned to young zebrafish, which provide a biologically complete and scientifically accessible system for studying the workings of the gut.

"Because the larval zebrafish are optically clear, we can visualize fat transport and processing by looking right through their body wall into the intestine where the action is," Dr. Walters said.

He developed a way to feed zebrafish a diet high in lipids (e.g., fat and cholesterol) or high in protein and low in lipids. He accomplished this by turning to the chicken egg, whipping fish water with the yolk for a high-lipid diet and the egg white as a high-protein diet. Before feeding these diets, fluorescently tagged cholesterol or fatty acid was added, enabling the microscopic viewing of how lipids are absorbed and processed by the intestinal cells.

Dr. Walters found that cholesterol was only absorbed when the fish ate a high-fat diet, not a low-fat diet. The fats and cholesterol were packaged into separate and clearly visible compartments within the cells. "You can tell which larvae had eggs for breakfast," he said.

The researchers also found that some long-chain fatty acids, particularly a common one called oleic acid, were especially effective for promoting cholesterol uptake. They provided evidence that oleic acid acts to drive a cholesterol transport protein from within the intestinal cell to the cell surface, where it can interact with cholesterol passing through the gut and pull it into the cell. More details of the new work will be published next week.

Their findings suggest a tightly regulated system in which cholesterol is only taken up by the intestine in the presence of fats. One reason such regulation is important, Dr. Walters said, is that unprocessed cholesterol can be toxic to cells and requires fatty acid-mediated modification to render it safe in a process called esterification.

"In nature, cholesterol and fatty acids go hand in hand. It makes sense that you could use dietary fatty acids as a cue for the transport protein to translocate to the cell surface and that dietary cholesterol may be available for absorption," he said. "The protein isn't displayed on the cell surface unless its preferred substrate for making cholesterol less toxic is also there."

Dr. Walters and his colleagues are now exploring the system's potential for studying and testing compounds that can block the absorption of dietary cholesterol, including one drug already on the market.

"Diet is a huge modulator of human disease," says Dr. Walters. "Our work demonstrates the power of the zebrafish larval system to provide fresh insights into the process of intestinal cholesterol absorption. It gives us a way to look at these processes for the first time in the context of a whole organism."

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