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Experiments suggest research avenues for treating excess fat storage and obesity

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A team of scientists at the Gladstone Institutes and Yale University have begun to unravel the complex process by which cells take in and store microscopic fat molecules, suggesting new directions for further research into solutions for obesity and its related conditions, such as heart disease, type 2 diabetes and fatty liver disease.

In a paper being published today in Cell Metabolism, Gladstone Senior Investigator Robert Farese, Jr., MD, and Yale University Associate Professor Tobias Walther, PhD, detail the critical role an enzyme called CCT plays in separating and storing fat molecules safely in each cell. When CCT malfunctions and the process fails, the molecules fuse together into ever-larger and toxic globules that can build up throughout the body and in the liver.

"Identifying CCT's crucial role in the proper storage of fat molecules is a big step towards understanding how the growth of large fat globules in the cell can lead to fatty liver disease," said Dr. Farese, who studies fat storage, metabolism and cell-energy dysfunction in his laboratory at Gladstone, a leading and independent biomedical-research organization. "Sequencing the human genome provided the parts list—now we are beginning to figure out how these parts work together to build structures such as fat droplets."

"Heart disease is the number one cause of death in the United States, while diabetes affects more than 25 million Americans," added Yale's Dr. Walther. "Discovering pieces of the molecular machinery of how fat

molecules accumulate in the body is a significant step towards exploring new avenues for treating these conditions."

The Gladstone and Yale team set out to understand how the body's dense and combustible fat droplets, made up of long chains of hydrocarbons, are constructed. Their experiments found that CCT acts as a key regulator during fat storage, effectively directing the assembly of other molecules to store fats safely and effectively for later use as fuel.

Thanks to CCT, they found, fat molecules get coated with a layer of phosphatidylcholine, a lipid known as PC, as they enter the cell. The PC layer keeps the coated molecules—also known as lipid droplets—small, inactive and clustered in groups. The droplets remain inactive until stores are low, at which point they are released to provide energy for the body. But when the scientists turned off the CCT enzyme in experiments involving fruit flies and mice, the PC layer didn't form correctly. Instead, the fat droplets formed with gaps through which they began clustering together. This clustering, in turn, led to the accumulation of abnormally large fat droplets—which ultimately are at the root of diseases such as obesity.

"Now that we know how lipid droplets are constructed under normal circumstances, we can potentially look for new treatments for when lipid-droplet formation goes awry," said Dr. Farese, who is also a professor of medicine, biochemistry and biophysics at the University of California, San Francisco (UCSF), with which Gladstone is affiliated. "In the future, drug targets could modify the capacity of lipid droplets so they would more safely encapsulate potentially toxic fat molecules."

Plus, these insights into efficient creation and storage of compact, combustible fat may have an impact beyond medicine—such as for the biofuels industry, which creates industrial fuel from biological sources such as algae and corn.

"The field of biofuels is keenly interested in the molecular processes involved in the storage of fat—or oil," Dr. Farese added. "The better we understand the building blocks, the better the chances of improving biofuel yields."

Provided by Gladstone Institutes