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Gladstone scientists reveal the genetics of fat storage in cells

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New research by the Gladstone Institutes of Cardiovascular Disease (GICD) and the University of California, San Francisco (UCSF), has revealed the genetic determinants of fat storage in cells, which may lead to a new understanding of and potential treatments for obesity, diabetes, and heart disease. While scientists have long understood that lipid droplets contribute to fat build up in cells, the genes involved in droplet biology have been a focus of extensive research.

In a study published in Nature, scientists in the laboratories of Drs. Robert V. Farese, Jr., of Gladstone and UCSF, and Peter Walter, of UCSF, devised a genetic screen to identify genes responsible for fat storage in cell of fruit flies, and potentially other species.

“For some time, we have been studying the enzymes that make fats,” said Dr. Farese, senior investigator. “But clearly, we need to know a lot more about the most basic processes that regulate cellular fat storage to be able to make progress on some very serious human diseases.”

To identify novel genes involved in fat storage, GICD scientist Dr. Yi Guo, and Dr. Tobias Walter, formerly of Dr. Walter’s laboratory and now of the Max Planck Institute of Biochemistry in Germany, initiated a major discovery project, in which they used RNAi screens to individually inactivate all the genes in cells from fruit flies. Basic cellular processes in humans are highly conserved in cells from fruit flies, so the results should mostly be applicable to human biology. Drs. Guo and Walther completed the initial survey and have now begun to study in

detail the genes that have the most striking effects on fat storage in cells.

Surprisingly, they found that ~1.5% of all genes function in lipid-droplet formation and regulation. These genes proved to be determinants of the size and number of lipid droplets in cells. Several of these genes were investigated in detail and shown to profoundly affect droplet morphology and lipid utilization. When the individual genes were deleted, the resulting cells could be separated into five distinct phenotypic classes, based on the number and appearance of the lipid droplets.

The most interesting genes will be advanced into functional studies in flies and mice. These new studies promise two major outcomes: significant advances in understanding the processes that regulate fat metabolism in cells and novel therapeutic targets for treating diseases, such as obesity and diabetes. Additionally, the findings have implications for engineering plants and microorganisms to maximize seed oil production and biofuels, respectively.

“With this screen completed, the work turns now to many fascinating questions,” said Dr. Guo. “How are lipid droplets formed" What regulates their size, numbers, and cellular locations" Do they help to traffic lipids within the cell" How does this cell biology relate to physiology and disease" These are early days in this area of biology, and the field is wide open.”

Source: Gladstone Institutes