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New role for protein in fat cells may improve understanding of obesity and diabetes

Bethesda, Md. -- Scientists have shown for the first time that a protein involved in the transfer of fat in the blood may also influence how fat cells store fat. Richard E. Morton and Lahoucine Izem, research scientists at the Cleveland Clinic Foundation, have shown that the protein, called cholesteryl ester transfer protein (CETP), is involved in the cellular storage and regulation of cholesterol and other fats and, as a result, probably has unexpected contributions to obesity and diabetes.

"CETP is known to shuttle different types of fat between lipoproteins – combinations of fat and protein that transport fats in the blood," Morton says. "In this study, we show that CETP also shuttles fats inside fat cells between two separate areas and that fat cells with reduced levels of CETP are unable to process fats normally."

The new study, to be published in the July 27 issue of the Journal of Biological Chemistry, was selected as a "Paper of the Week" by the journal's editors, meaning that it belongs to the top one percent of papers reviewed in significance and overall importance.

Research performed during the past decade has shown that CETP affects how a type of fat called cholesteryl ester is moved from the blood plasma into cells. Since fat cells make abundant CETP, Morton and Izem decided to examine what CETP does inside a fat cell and what would happen to fat cells that are deficient in CETP.

The scientists noticed that fat cells lacking CETP could not make and store cholesterol, cholesteryl ester, and another fat called triglyceride like normal fat cells do. In CETP-deficient cells, cholesteryl ester and triglyceride accumulated in a cellular compartment called the endoplasmic reticulum (ER), while an abnormally low amount of these fats was seen in "lipid droplets" – local accumulations of fat in fat cells.

Morton and Izem suggest that, in normal cells, CETP transfers cholesteryl ester and triglyceride from the ER, where they are made, to the lipid droplets, where they are stored. In cells lacking CETP, only

a fraction of both fats is carried from the ER to the lipid droplets. Also, since cholesterol is produced by breaking down cholesteryl ester in lipid droplets, lower levels of cholesteryl ester lead to smaller amounts of cholesterol in the droplets.

"CETP-deficient cells have unbalanced amounts of cholesterol and fats," Morton says. "They have too much cholesteryl ester and triglycerides in the ER and not enough of them in the lipid droplets. Also, these cells sense that they have too much cholesterol, although they actually have low amounts of cholesterol. Overall, the cells don't correctly control the amount of fats they make and store anymore."

A consequence of the abnormal distribution of fats between cell compartments is that cholesteryl ester and triglycerides cannot be used easily. In normal cells, when these two fats accumulate in the droplets, they can be removed from the droplets and then used by the cell after the fats are broken down by enzymes called hydrolases. But since hydrolases are in the droplets and not in the ER, cells low in CETP cannot break down the fats they store as effectively, Morton and Izem say.

The scientists conclude that CETP is probably essential for lipid metabolism and storage in fat cells and that fat tissue is not only an energy storage tissue but also a major endocrine organ.

"CETP deficiency disrupts storage of important fats in fat cells, which can lead to insulin resistance – a major contributor to diabetes – and the abnormal release of cytokines, proteins that stimulate the immune system," Morton says. "This unexpected contribution of CETP provides a new understanding of how our body stores and regulates fats and of conditions such as obesity and diabetes."

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ARTICLE: "Possible Role for Intracellular Cholesteryl Ester Transfer Protein in Adipocyte Lipid Metabolism and Storage," by Lahoucine Izem and Richard E. Morton

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