How the body makes triglycerides

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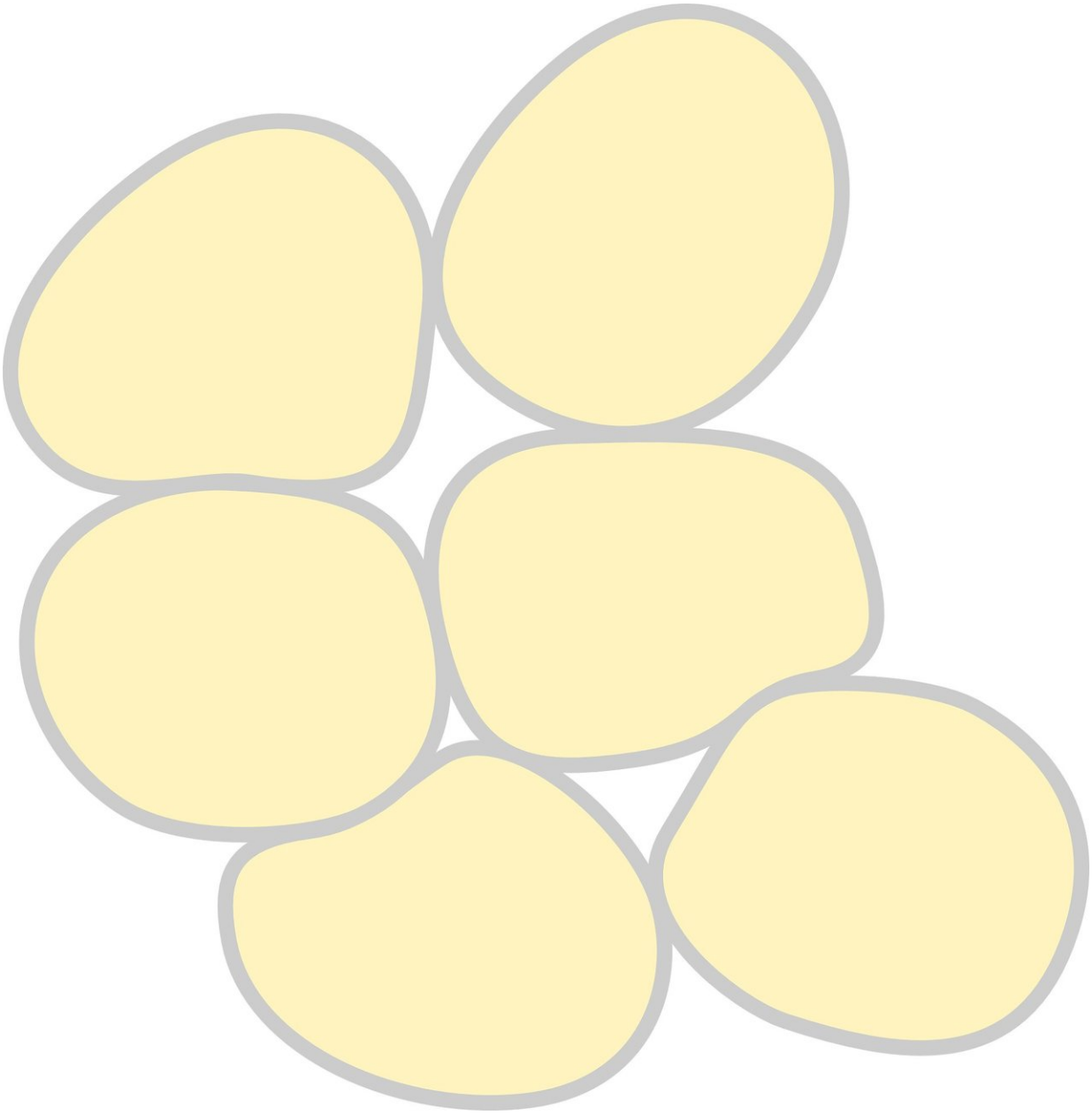

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Doctors regularly warn their patients that having high levels of triglycerides, a major dietary fat, can increase the risk of heart disease, diabetes, obesity and fatty liver disease. There is considerable interest in finding novel ways to effectively regulate triglycerides in the blood to help manage these potentially life-threatening common conditions.

Now, researchers at Baylor College of Medicine, Princeton University and Texas A&M University are closer to achieving this goal after discovering the 3-D structure and mode of action of diacylglycerol O-acyltransferase-1 (DGAT1), the enzyme that synthesizes triglycerides and also is required for human dietary fat absorption and storage. DGAT1 is a known target to treat obesity and other metabolic diseases, so having a detailed understanding of what DGAT1 looks like and how it works opens opportunities for designing novel strategies for managing these conditions. The findings are published in the journal *Nature*.

"DGAT1 is a particularly interesting enzyme because it synthesizes triglycerides, which are the main component of hard fat, the type of fat usually found in the belly or midsection in our body. Triglycerides also are part of the particles that transport cholesterol—high-density lipoproteins (HDL, or 'good cholesterol'), and low-density and very-low-density lipoproteins (LDL and VLDL, or 'bad cholesterols')," said co-corresponding author Dr. Ming Zhou, Ruth McLean Bowman Bowers Professor in Biochemistry in the Department of Biochemistry and Molecular Biology at Baylor. "Learning to regulate this enzyme can help regulate fat synthesis and potentially manage related conditions."

Lie Wang, a graduate student in the Zhou lab, took the lead on this project. He applied cryo-electron microscopy, a technique that enables scientists to see how biomolecules move and interact as they perform their functions, to visualize the 3-D structure of DGAT1.

"This project was challenging because DGAT1 is embedded in biological membranes where it carries its function," Wang said. "We also developed an enzymatic assay, or test, to monitor the activity of DGAT1 in real time. Thanks to the integration of high-quality structure and precise functional studies we were able to unveil the structure of this important enzyme and gain novel insights into the mechanism of action."

DGAT1 is located in the membrane of the endoplasmic reticulum, a cellular structure engaged in the synthesis of proteins and lipids.

"It was exciting to discover that DGAT1 forms a large chamber inside the membrane, which was unexpected," Wang said. "This 'reaction chamber' isolates a space within the membrane where the enzymatic synthesis of triglycerides takes place."

"The reactants meet inside the chamber and that is where the reaction occurs. Then, the triglycerides bud-off the membrane in lipid droplets that carry them to where they are needed in the cell," Zhou said. "Neither this 3-D structure of DGAT1 nor its mechanism of action were known before in such detail."

This study not only reveals the structure and mode of action of a human enzyme that is essential for proper human metabolism, but it also enables researchers to explore the effects of molecules that interact with DGAT1 and potentially regulate its activity.

More information: Structure and mechanism of human diacylglycerol O-acyltransferase-1, *Nature* (2020). DOI: 10.1038/s41586-020-2280-2 , www.nature.com/articles/s41586-020-2280-2

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