Lipid droplets play crucial roles beyond fat storage

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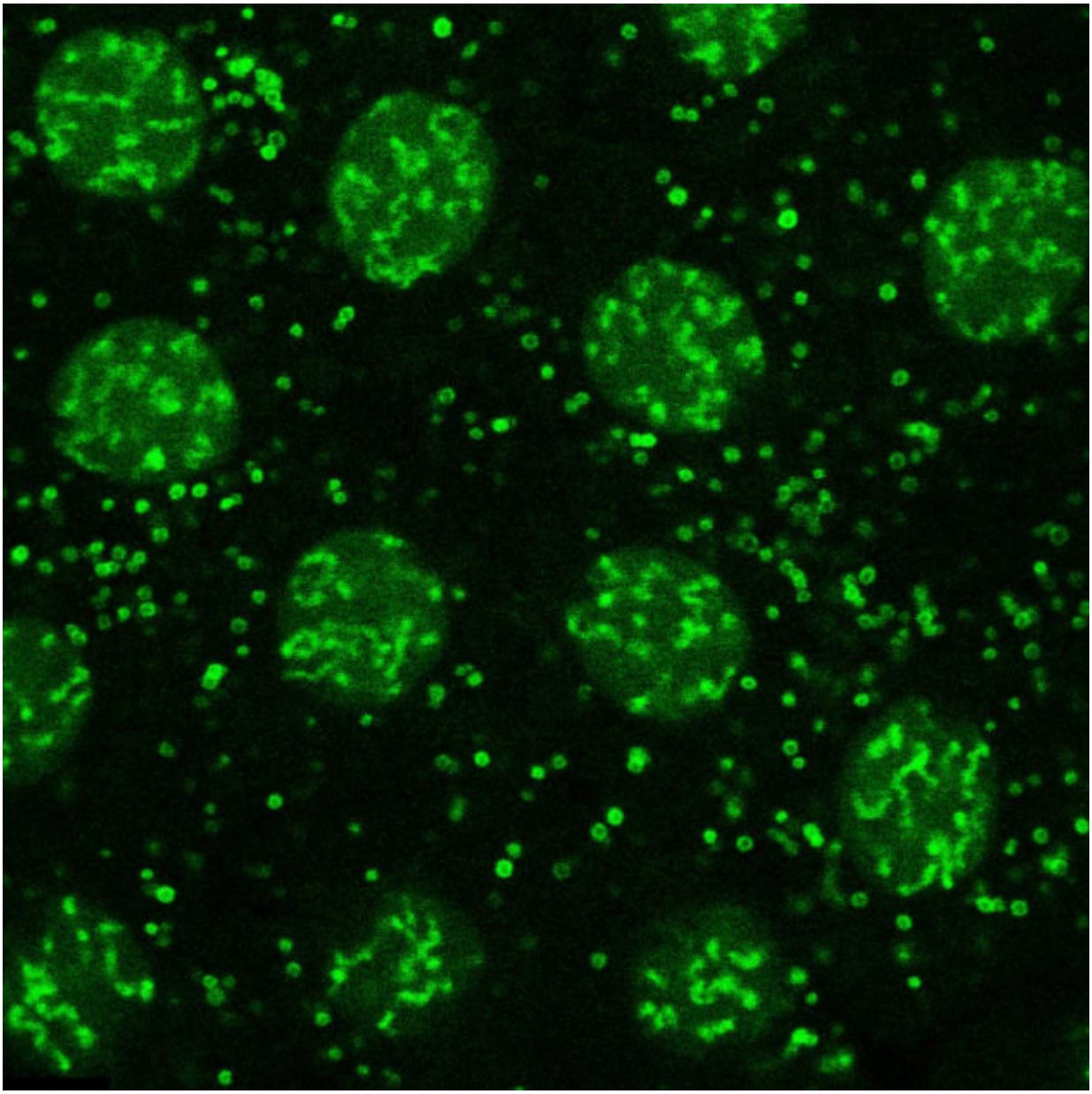

The researchers used advanced fluorescence microscopy to view lipid droplets in fruit fly embryos. Here, H2Av (fluoresced in green) is present in the cell's nuclei (the large blobs) and on lipid droplets (the smaller rings). The lipid droplets regulate how fast H2Av enters a cell's nucleus by storing the H2Av until the nucleus needs it. Credit: University of Rochester image / Zhihuan Li

Lipid droplets: they were long thought of merely as the formless blobs of fat out of which spare tires and muffin tops were made. But these days, they're "a really hot area of research," says Michael Welte, professor and chair of biology at the University of Rochester.

That's in part because lipid droplets have been found to play critical roles in the life cycles of certain proteins involved in gene expression. Now, a study by Welte and his colleagues, published in the journal *eLife*, describes how lipid droplets regulate these proteins. The research has implications for understanding what helps embryos survive and could cause us to reconsider how we look at lipid-related diseases like obesity.

Beyond fat storage

You may not know it, but whenever you eat cheese, ice cream, or yogurt, you are also ingesting microscopic lipid droplets.

"The mammary gland cells that make milk make lots of lipid droplets and then secrete those," says Welte. "Any dairy product or animal product that we consume is full of lipid droplets."

Lipid droplets perform functions in various parts of the human body: in the liver, they store vitamin A; in the retina of the eye, they help store the pigment that cells use to recognize light. They are even in the sebaceous glands, which make the oily material that covers our hair and

skin.

But lipid droplets aren't just fat deposits. According to Welte, recent research found that lipid droplets have three main functions beyond their roles in fat storage:

1. Maturation: Some proteins, when they are first made, need lipid droplets to achieve their mature form.
2. Breakdown: Lipid droplets keep certain proteins out of the way when the proteins are either damaged or obsolete but are not yet destroyed.
3. Storage: Lipid droplets act as storage units for various proteins, so the proteins are sequestered until they are needed elsewhere in the cell.

'Pacemakers' for histones

Welte's current research uses fruit fly embryos to study how lipid droplets influence a particular set of proteins called histones. Histones are present in many organisms, from yeast to fruit flies to humans, and are responsible for wrapping long strands of DNA so the DNA will fit into a cell's nucleus. Fruit flies embryos are ideal to study because they duplicate their DNA about every 10 minutes, and, as a result, need large quantities of histones.

Histones are essential to life for most organisms "because they control everything in the nucleus and package DNA to regulate gene expression," Welte says. "If we have the wrong amount of histones—either too many or too few—there will be widespread defects."

If there are too few histones, genes might be expressed that shouldn't be. Too many histones can cause cells to have trouble dividing their

chromosomes.

Welte discovered that lipid droplets play an important role in regulating a particular histone called H2Av. A mother fly produces huge amounts of histones, which are then transferred to her eggs so an embryo's DNA can be packaged as the embryo develops and makes more cells. Acting like pacemakers, the lipid droplets regulate how fast H2Av enters a cell's nucleus by storing the H2Av until the nucleus needs it.

The researchers used sophisticated microscopy to observe exactly how lipid droplets keep out H2Av. Welte and his colleagues discovered, to their surprise, that the storage function is not static—histones don't stay on the droplets all the time. Instead, the H2Av molecules are constantly shuffled back and forth between lipid droplets. The exchange allows the fruit fly embryo to always have free H2Av available to transport into the cell nucleus, but at the same time keeps the concentration of free H2Av low so that it is transported to the nucleus at a slower pace—a pace more in sync with the speed of DNA synthesis.

The researchers also showed that the regulating function is turned off in the fruit fly embryo once the embryo reaches a particular stage, indicating that cells can control when to employ the protein-handling function of lipid droplets.

Embryo survival and lipid-related diseases

Identifying these functions of lipid droplets gives researchers more insight into how embryos develop and survive: without lipid droplets regulating H2Av, embryos can become compromised.

What we now know about the various functions of lipid droplets also means that researchers need to consider these factors when examining the effects of obesity. Lipid droplets are dysfunctional in disease states

like obesity (too many lipid droplets) or lipodystrophies (too few lipid droplets), Welte says. "The cause of these diseases—too much or too little fat—has to do with how much lipid you have. Our work suggests that when looking at these disease states, people also need to look at what happens to the proteins, because these lipids droplets have this second function beyond handling fat."

More information: Matthew Richard Johnson et al. Developmentally regulated H2Av buffering via dynamic sequestration to lipid droplets in Drosophila embryos, *eLife* (2018). DOI: 10.7554/eLife.36021

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