The story about how research on cellular fat clumps led to the discovery of a new abnormality in Niemann-Pick disease type C

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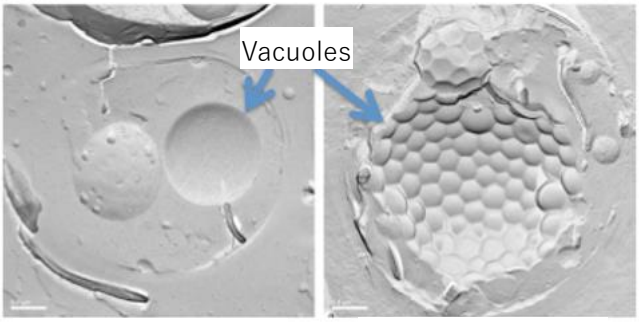
Most cells in the human body contain fatty clumps called lipid droplets. We conducted research aimed at clarifying the mechanism by which lipid droplets are dissolved. As a result, we happened to obtain results related to the intractable hereditary disease called Niemann-Pick disease type C. This was something very unexpected and the pleasure of basic research. Here is a brief history of our study.

Lipid droplets store fat that is not necessary for the moment as esters. For more than a decade, our research has focused on how lipid droplets are made and broken down and what they mean to cells.

In this study, we used yeast to investigate the mechanism of lipid droplet breakdown. Yeast is a useful material for this kind of research because they have a similar structure to human cells and can be genetically manipulated easily. When yeast cells are placed in a nutrient-rich solution, they proliferate by repeating division, but after a few days, the nutrients in the solution are depleted, and they stop dividing and enter a state called the "stationary phase." Yeast in this state can be regarded as a model for human central nervous cells, which do not divide either.

In the stationary phase of yeast, lipid droplets are engulfed by a bag-like structure called a vacuole, which is made of a single membrane, and are broken down by digestive enzymes inside the vacuole. As a result, fatty acids are released from lipid esters contained in the lipid droplets and used as a energy source for the yeast. Sterols (equivalent to cholesterol in human cells) are also released from the lipid droplets, and these sterols are incorporated to the membrane of the vacuole. By electron microscopy, we found that, when the sterol content of the vacuolar membrane increases, the vacuolar membrane begins to show a football-like polygonal shape, and that lipid droplets are surrounded by the polygonal membrane.

Changes in vacuoles as captured by electron microscopy



Yeast in the proliferation phase　　Yeast in the stationary phase

The result up to this point was somewhat expected from previous studies, but what is interesting is as follows. As I mentioned earlier, those sterols were incorporated into the vacuole membrane, but in fact, this does not happen spontaneously. This process requires a protein (NPC

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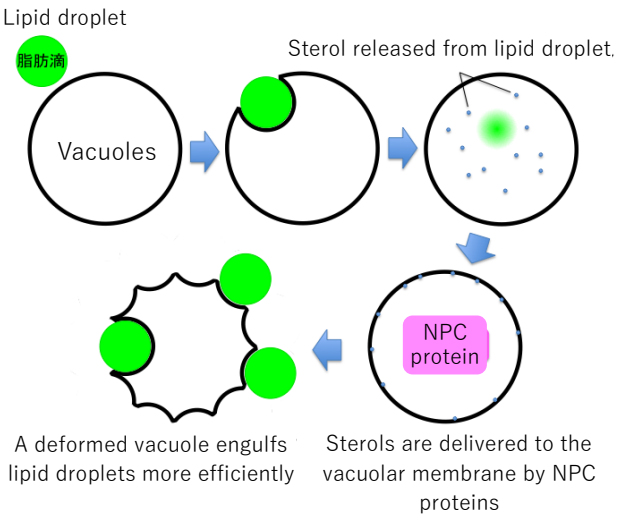

protein) mutated in patients of Niemann-Pick disease type C. If the NPC protein is not functioning correctly, lipid droplet uptake gradually decreases, and yeast will slowly die due to insufficient energy supply. The NPC protein changes the properties of the vacuole membrane by transferring free sterols from the lipid droplets to the vacuole membrane, allowing more fat droplets to be taken up and digested. This enables yeast to survive longer because it can efficiently obtain fatty acids as a source of energy.

Although NPC proteins have been known to be involved in sterol transport, it has been believed that the transported sterols are immediately transported to other parts of the cell. The present results reveal for the first time that sterols transported by NPC proteins are required for the function of the vacuole (equivalent to lysosomes in human cells) membrane itself (i.e., lipid droplet uptake).

The enlarged liver and spleen seen in patients with Niemann-Pick disease type C are thought to be caused by inadequate functioning of the NPC protein, which results in the accumulation of cholesterol in lysosomes. On the other hand, it is less well understood why the abnormalities occur in the CNS of NPC patients. We presume that the reduced uptake of lipid droplets, as shown in this study, may cause CNS abnormalities, although it will need to be studied in human cells.

The results of this research were published in the international journal eLife (Tsuji et al, eLife 6, e25960, 2017; https://elifesciences.org/articles/25960) and in the eLife digest section, which introduces the contents to the general public. The journal is freely accessible without a subscription fee, so please look if you are interested.

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