# News release

**Title**

Lipid droplets in the nucleus have function to fight against stress

**Key points**

- **Nuclear lipid droplets originate from lipoprotein precursor**
- **ER stress induces nuclear lipid droplet formation**
- **Nuclear lipid droplets are a platform for phospholipid synthesis activation**
- **Nuclear lipid droplet formation is a feedback mechanism to fight against ER stress**

**Summary**

The research team led by a graduate student Kamil Soltysik, Dr. Yuki Ohsaki and Prof. Toyoshi Fujimoto (Department of Molecular Cell Biology and Anatomy) of Graduate School of Medicine, Nagoya University (Dean: Prof. Kenji Kadomatsu) found an origin, and for the first time assigned a function of lipid droplets inside the cell nucleus.

Lipid droplets are a structure in the cell where neutral lipids are stored. Lipid droplets are a hallmark of hepatocytes in fatty liver, but possess important functions in the normal cell, such as energy supply and protein degradation. So far lipid droplets have been recognized as a cytoplasmic structure, like mitochondria, but in the liver cell, lipid droplets also exist abundantly in the nucleus. The biogenesis and functions of these nuclear lipid droplets, however, have been left unclear.

The team found that a lipoprotein precursor, or a lipidic particle that formed in the endoplasmic reticulum of hepatocytes, is transferred into the nucleus through the extension of the nuclear membrane, and finally becomes nuclear lipid droplets. They also found that, when cells are under ER stress, nuclear lipid droplets form abundantly and recruit an increased amount of CCTα (the rate-limiting enzyme of the phosphatidylcholine synthesis pathway), thereby accelerating the synthetic rate of phosphatidylcholine, a major lipid constituting biomembranes.

These results indicate that formation of nuclear lipid droplets is a unique way that liver cells mitigate ER stress and maintain their normal function.

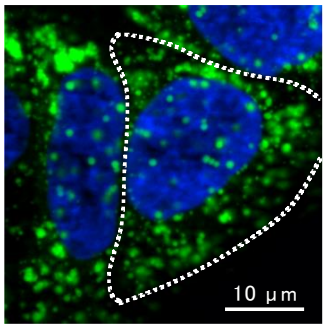
## 1. Research background

Lipid droplets are a cell organelle for neutral lipid storage. Most lipid droplets exist in the cytoplasm, but in some cell types, especially in hepatocytes, lipid droplets are also present in the nucleus (Figure 1). Liver acts as a main source of lipoproteins in the bloodstream. Excess production of lipoproteins leads to atherosclerosis, causing diseases like heart infarction. On the other hand, retention of lipids in the liver causes the other disease – fatty liver.

In hepatocytes, lipoprotein precursors form in the ER lumen, depending on the microsomal triglyceride transfer protein (MTP) function, mature into very low-density lipoproteins (VLDL), and are secreted to the blood. When hepatocytes are under ER stress, in which the ER luminal

space is filled with misfolded proteins, cells expand the ER luminal space by increasing production of phosphatidylcholine, a major phospholipid of the ER membrane.

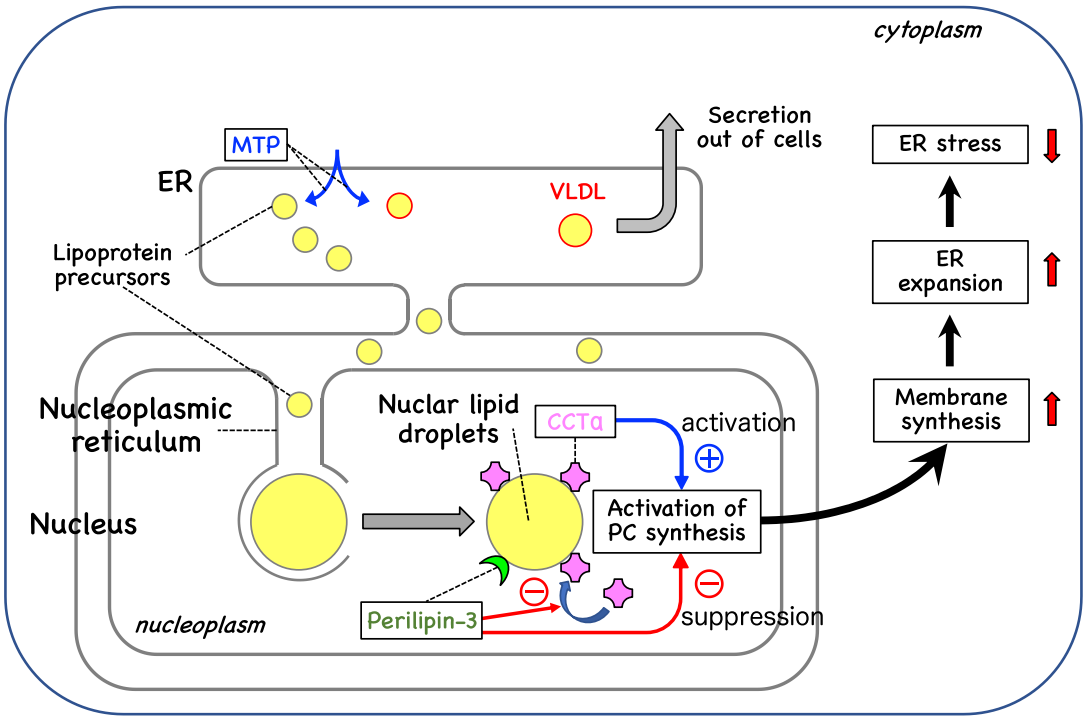
**Figure 1.** Lipid droplets are formed in the nucleus of hepatic cells




Lipid droplets are abundantly observed in the nucleus as well as in the cytoplasm when cells are treated with oleic acids.

Lipid droplets (green)
Nucleus (blue)
Cell edge (white dashed line)

**Figure 2.** Nuclear lipid droplets are derived from lipoprotein precursors, and function to activate PC synthesis and mitgate ER stress




**2. Research Results**

The research team hypothesized that the function and origin of nuclear lipid droplets are linked to liver-specific properties. They actually found that formation of nuclear lipid droplets is strictly dependent on the enzyme activity of MTP. Interestingly, lipoprotein precursors synthesized excessively in the ER accumulated in the lumen of the nucleoplasmic reticulum, an invagination of the inner nuclear membrane toward the nuclear interior. Using multiple

microscopic techniques, they have shown that the membrane of the nucleoplasmic reticulum forms small defects, which allow lipoprotein precursors to escape into the nucleus. The result shows that nuclear lipid droplets are derived from lipoprotein precursors and explains why nuclear lipid droplets are abundant in hepatocytes.

They also found that nuclear lipid droplets increase when cells are under an ER stress and recruit the rate-limiting enzyme of phosphatidylcholine synthesis – CCTα. They further found that a classical lipid droplets protein, perilipin-3, competes with CCTα in binding to nuclear lipid droplets, and thus, functions as a "switching molecule". For example, an increase of perilipin-3 decreases recruitment of CCTα to nuclear lipid droplets and suppresses cellular PC production. These results indicate that nuclear lipid droplets in hepatocytes constitute a feedback mechanism to regulate phospholipid synthesis in response to ER stress (Figure 2).

**3. Research Summary and Future Perspective**

Liver has multiple functions, such as lipoprotein secretion, protein and lipid synthesis, drug metabolism, etc., and is thought to be in continuous danger of being exposed to ER stress. Normal hepatocytes have a mechanism to maintain their normal function even under ER stress, but its dysfunction may lead to illness including fatty liver. Understanding how to regulate formation of nuclear lipid droplets and activation of CCTα by using the switching molecule is expected to lead to new therapeutic methods for such diseases.

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**Publication**

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**Japanese ver.**

https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/Nature_C_20190129.pdf