

News Release

Title

Presence and Characterization of Two Distinct Nuclear Lipid Droplets in Liver Disease

Key Points

- The frequency of formation of two distinct types of intranuclear lipid droplets (LDs) with different morphologies in hepatocytes has been elucidated *in vivo*.
- The formation of nucleoplasmic LDs (nLDs) in hepatocytes *in vivo* is associated with endoplasmic reticulum stress.
- The formation of cytoplasmic LD invagination with nucleoplasmic reticulum (cLDs in NR) is suppressed in hepatocytes with excessive lipid accumulation.

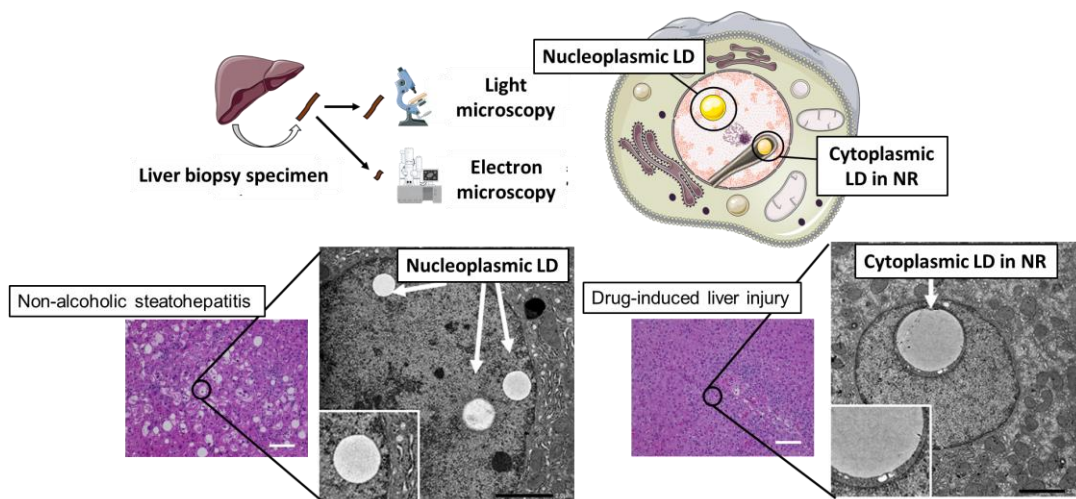
Summary

A research team led by Assistant Professor Norihiro Imai (first author), Professor Hiroki Kawashima from the Department of Gastroenterology and Hepatology at Nagoya University Graduate School of Medicine, Professor Hiroaki Wake from the Department of Anatomy and Molecular Cell Biology at Nagoya University Graduate School of Medicine, and Professor Yuki Ohsaki (co-first author) from the Department of Anatomy (I) at Sapporo Medical University, has identified two distinct types of intranuclear lipid droplets (LDs) observed in hepatocytes, each with different clinical characteristics.

LDs are organelles present not only in adipocytes but also in various cells of the body, and they store excess energy while also serving various physiological functions. Recently, LDs have also been identified in the nucleus of hepatocytes, and their formation mechanism and functions have gained considerable attention.

In this study, the research team analyzed clinical liver biopsy specimens using electron microscopy and identified two types of intranuclear LDs, one with cytoplasm and nuclear membrane invagination and the other without. The formation of "true" nucleoplasmic LDs (nLDs) is associated with endoplasmic reticulum (ER) stress in hepatocytes *in vivo*. The cytoplasmic LD invagination with nucleoplasmic reticulum (cLDs in NR) is correlated with the cholesterol concentration in blood. The study's findings are expected to provide new insights into the pathophysiology of intranuclear LDs.

The research results were published online in the international scientific journal "Scientific Reports" on April 26, 2023.



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Nucleoplasmic lipid droplet (LD) in hepatocytes and cytoplasmic LD invagination with nucleoplasmic reticulum (NR)

Research Background

Animal cells typically contain intracellular LDs consisting of a phospholipid monolayer membrane and a core of neutral lipids such as triacylglycerols and cholesterol esters. It is thought that these LDs are formed when neutral lipids synthesized in the phospholipid bilayer of the ER grow large and are released into the cytoplasm using the ER membrane phospholipid monolayer as an outer skin. LDs in the cytoplasm contain numerous functional molecules with physiological significance, including energy storage, heat production, and proteolysis. The cell nucleus, separated from the cytoplasm by a phospholipid bilayer, houses the genetic information, DNA, and maintains cellular equilibrium through replication and transcription into mRNA. Recently, LDs have been discovered to be abundant in the nucleus of hepatocytes and hepatocellular carcinoma cells, leading to increased interest in their formation mechanism and function. Previous research by our group has shown that nuclear LDs in hepatocytes play a crucial role in maintaining the physiological functions of the liver under various stress conditions. However, the pathophysiological significance of nuclear LDs in actual liver diseases and whether their expression frequency changes with disease or severity has not been clear. This study aimed to determine the frequency and morphology of intranuclear LDs in hepatocytes in various liver diseases.

Research Results

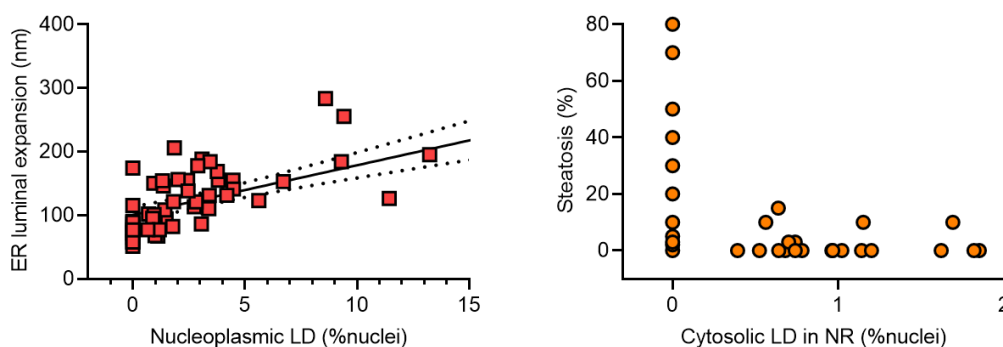
Eighty patients who underwent liver biopsy at Nagoya University Hospital were enrolled in the study. A portion of the liver biopsy specimen was double-fixed for electron microscopy and observed using a transmission electron microscope JEM-1400 Flash. Evaluation of hepatocyte ultrastructure was performed

independently without clinical information. Intranuclear LDs were classified into two types based on the presence or absence of adjacent cytoplasm and nuclear membrane invagination: "true" nucleoplasmic LDs (nLDs) present alone in the nucleoplasm and cytoplasmic LD invagination with nucleoplasmic reticulum (cLDs in NR). The study population comprised 35 male and 45 female patients, with a mean age of 58 years. The pathological diagnosis was non-alcoholic steatohepatitis (NASH) in 12 patients, drug-induced liver injury in 11, malignancy in 22, autoimmune hepatitis (AIH) in 7, and other diagnoses in 28.

Transmission electron microscopy examination revealed that nLDs and cLDs in NR were present in 69% and 32% of liver biopsy specimens, respectively. No correlation was found between the frequency of nLDs and cLDs in NR. Both nLDs and cLDs in NR were more frequent in AIH, but no disease-specific changes in the frequency were observed.

nLDs were also frequently observed in NASH, but there was no correlation between the frequency of nLDs and cytoplasmic lipid accumulation (percentage of fatty liver), indicating that nLDs do not directly reflect cytoplasmic lipid accumulation. The frequency of nLDs was significantly positively correlated with the expansion of the ER lumen, suggesting that cLDs are formed in the nucleus when ER stress is induced (left panel).

In contrast to nLDs, cLD in NR was not observed in cases with more than 20% fatty liver, suggesting that cLD in NR is suppressed in hepatocytes with excessive lipid accumulation (right panel). Furthermore, there was no significant correlation between the frequency of cLDs in NR and the expansion of the ER lumen.



Research Summary and Future Perspective

Future research focused on the two types of LDs in the nucleus of hepatocytes is expected to yield new insights. These findings will help to clarify a novel physiological mechanism centered on intranuclear LDs and provide a stepping stone for elucidating the pathological mechanisms that lead to developing new therapeutic strategies.

Publication

Imai, N., Ohsaki, Y., Cheng, J. et al. Distinct features of two lipid droplets types in cell nuclei from patients with liver diseases. *Sci Rep* 13, 6851 (2023).
<https://doi.org/10.1038/s41598-023-33977-4>

Japanese ver.

https://www.med.nagoya-u.ac.jp/medicalJ/research/pdf/Sci_230511.pdf