News Release

Title

A novel function of Niemann-Pick type C proteins

- To promote incorporation and degradation of lipid droplets in the yeast lysosome through the specialized sterol-rich membrane domain –

Key Points

○Niemann-Pick type C (NPC) is a storage disease caused by mutational change of NPC proteins, which transport cholesterol in the lysosome.

○By using a sophisticated electron microscopic method, a specialized sterol-rich membrane domain, called raft, was observed in the yeast lysosomal membrane.

○Lipid droplets are engulfed by expanding raft domain and degraded in the lysosome.

○NPC proteins play a crucial role in this lipid droplet degradation process, called microautophagy, by transporting sterol to the lysosomal membrane.

Summary

The research team led by Dr. Takuma Tsuji and Prof. Toyoshi Fujimoto (Department of Molecular Cell Biology and Anatomy) of Graduate School of Medicine, Nagoya University (Dean: Kenji Kadomatsu, M.D., Ph.D) found a novel functionality of Niemann-Pick disease type C proteins. Niemann-Pick type C (NPC) is a storage disease caused by mutational dysfunction of NPC proteins, which transport cholesterol from the lumen to the membrane in the lysosome. The mechanism causing problems in NPC patients, including neurodegeneration, however, is not fully understood. The team hypothesized that NPC dysfunction should affect lysosomal membrane properties in addition to general sterol metabolism, and so they studied the role of the yeast NPC orthologs, Ncr1p and Npc2p, in the vacuole (i.e., lysosome).

By using a sophisticated electron microscopic method called freeze-fracture, they found that a specialized sterol-rich membrane area, called raft, formed in the vacuolar membrane and that lipid droplets are engulfed by expanding raft domain, which leads to degradation of lipid droplets in the vacuole. Importantly, they found that NPC proteins are crucial in this process, by supplying the vacuolar membrane sterol, an indispensable raft component.

The NPC proteins with mutations show defects in intracellular trafficking of sterols derived from lipoproteins and this abnormality is thought to cause NPC disease. In this study, the research team showed that the dysfunction of NPC proteins affects the lysosomal membrane property and suppressed degradation of lipid droplets in the lysosome. Their results should help understand the pathogenic mechanism of NPC disease.

Research Background

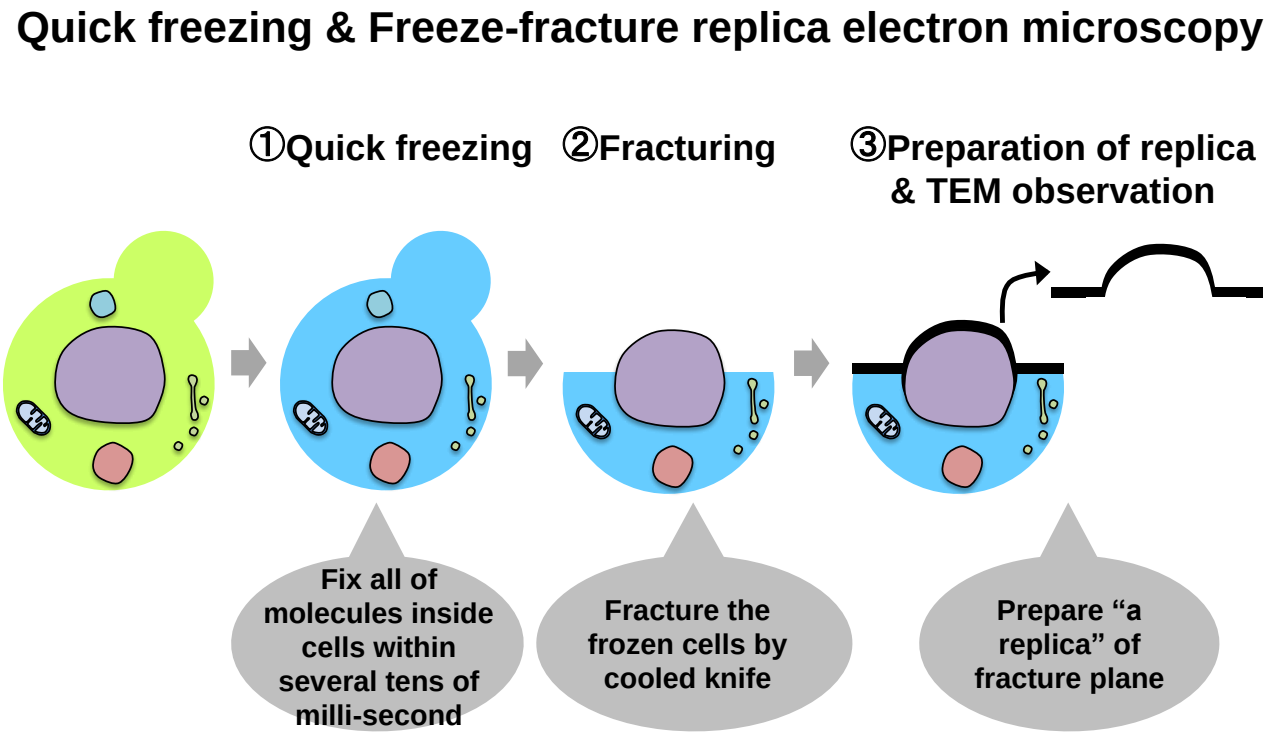
Niemann-Pick type C (NPC) is a storage disease caused by mutational dysfunction of NPC

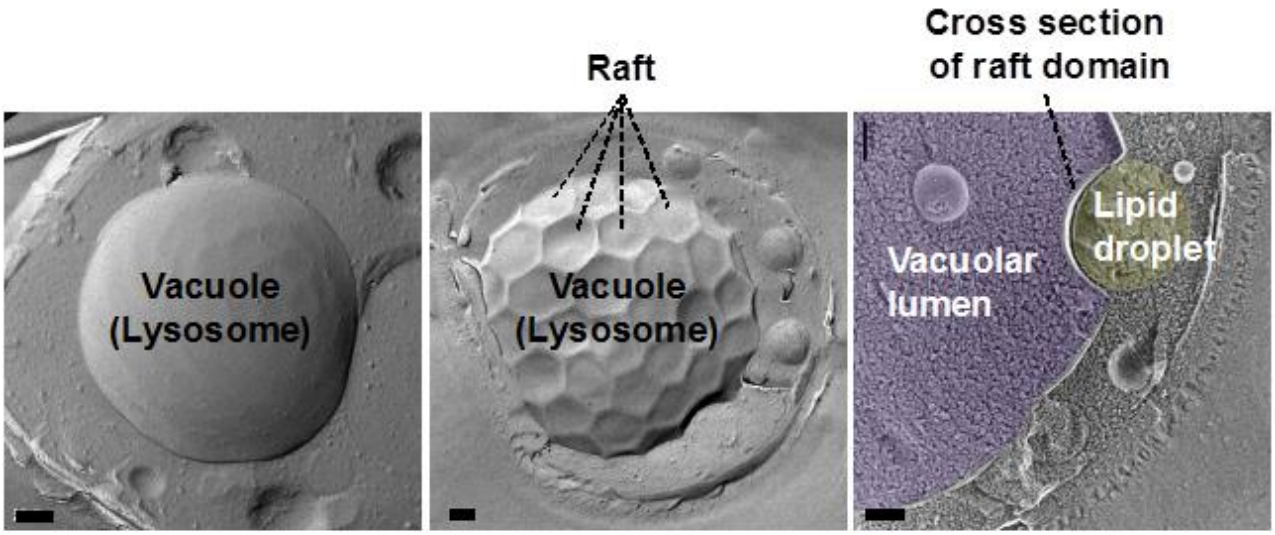
proteins, which transport cholesterol from the lumen to the membrane in the lysosome. Cells take up cholesterol from the blood and NPC proteins transport cholesterol to the lysosomal membrane. Thereafter cholesterol is transported to other parts of cells and utilized in many important activities. The dysfunction of NPC proteins is known to cause abnormal accumulation of cholesterol in the lysosome, but the mechanism that such NPC dysfunction causes various problems in human NPC patients, including neurodegeneration, is not fully understood.

Research Results

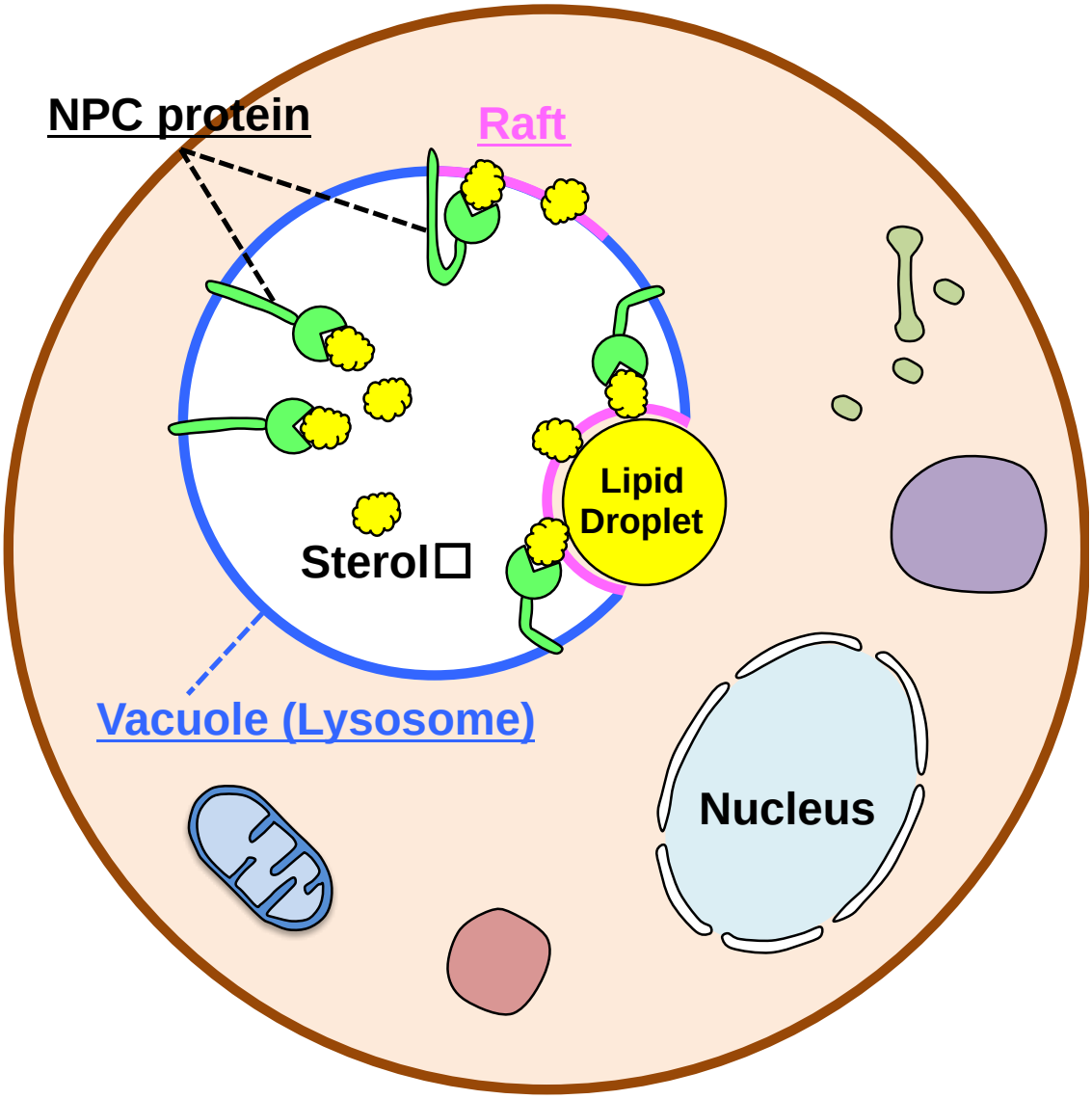
The research team hypothesized that NPC dysfunction should affect lysosomal membrane properties besides abrogating general sterol metabolism, and so they studied the role of the yeast NPC orthologs, Ncr1p and Npc2p, in the vacuole (i.e., lysosome).

By using a sophisticated electron microscopic method called freeze-fracture, they found that a specialized sterol-rich membrane area, called raft, formed in the vacuolar membrane and that lipid droplets are engulfed by expansion of this raft domain and eventually degraded in the vacuole. This way of degradation is known as microautophagy, a subtype of autophagy. Importantly, they found that transport of sterol by NPC proteins is crucial in inducing expansion of the raft domain and that dysfunction of NPC proteins suppressed degradation of lipid droplets.





Left: Vacuole without raft
Middle: Vacuole with raft
Right: Lipid droplet surrounded with raft domain was engulfed into vacuole
Bar = 200 nm



Research Summary and Future Perspective

The NPC proteins harboring mutations show defects in intracellular trafficking of sterols derived from lipoproteins and this abnormality is thought to cause NPC disease. In this study, the research team showed that degradation of lipid droplets in the lysosome was abrogated by dysfunction of NPC proteins. This result revealed a new functionality of NPC proteins and should help understand the pathogenic mechanism of NPC disease.

Publication

Takuma Tsuji, Megumi Fujimoto, Tsuyako Tatematsu, Jinglei Cheng, Minami Orii, Sho Takatori and Toyoshi Fujimoto, Niemann-Pick type C proteins promote microautophagy by expanding raft-like membrane domains in the yeast vacuole, *eLife* 2017;6:e25960
DOI: http://dx.doi.org/10.7554/eLife.25960

Japanese ver.

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