

News Release

Title

A clue to understand pathogenesis of hereditary spinocerebellar ataxia was obtained

Key Points

- A new electron microscopic method to visualize the intracellular phospholipid distribution at the nanometer scale was developed.
- Distribution of a major phospholipid, phosphatidylserine, was found to be drastically different from what has been believed.
- Distribution of phosphatidylserine changes significantly upon an increase of the intracellular Ca^{2+} concentration.
- This distributional change is attenuated in cells deficient in TMEM16K, mutation of which is known to cause a type of hereditary spinocerebellar ataxia.
- The present findings are expected to help understand pathogenesis of hereditary spinocerebellar ataxia.

Summary

The research team led by Professor Emeritus Toyoshi Fujimoto of Nagoya University Graduate School of Medicine (Dean: Professor Kenji Kadomatsu), currently Research Professor of Juntendo University, developed a new electron microscopic method to analyze intracellular phosphatidylserine (PS) distribution and found that TMEM16K, a causative gene of hereditary spinocerebellar degeneration, is related to PS redistribution in intracellular membranes. This is a collaborative work with the groups of Professor Shigekazu Nagata (Osaka University) and Professor Tomohiko Taguchi (Tohoku University).

PS is a major phospholipid of biological membranes. In the plasma membrane, PS distributes exclusively in the cytoplasmic leaflet. The Professor Nagata's group previously showed that TMEM16F plays a critical role in moving PS to the exoplasmic leaflet of the plasma membrane under some conditions. TMEM16K, a family member of TMEM16F, is present in intracellular membranes and has been presumed to have a similar PS redistributing function, but this idea could not have been tested due to methodological difficulties.

The new method developed in the present study enabled to study PS distribution in intracellular membranes. Using this method, the group found that PS in the endoplasmic reticulum membrane is present abundantly in the cytoplasmic leaflet, but not in the luminal leaflet, and that this PS asymmetry is compromised upon an increase of intracellular Ca^{2+} concentration in a TMEM16K-dependent manner. This result gives a clue to understand pathogenesis of spinocerebellar degeneration caused by TMEM16K mutations.

Research Background

TMEM16K is a causative gene of hereditary spinocerebellar ataxia 10 (SCAR10), but its physiological function has not been known. TMEM16F, which has a structure similar to TMEM16K, is present in the plasma membrane and is known to scramble PS distribution in the plasma membrane (i.e., intermix PS between the two leaflets), thereby playing important roles, such as activation of platelets in blood coagulation. TMEM16K may also have a scrambling activity, but this idea could not have been tested due to difficulties to study phospholipid distribution in intracellular membranes, where TMEM16K exists.

Research Results

The research group developed a new electron microscopic method to analyze intracellular PS distribution by utilizing PS-binding protein, evectin-2 (Fig.1). Using this method, they found that the endoplasmic reticulum (ER) membrane in mouse cells harbors a significant amount of PS in the cytoplasmic leaflet, but not in the luminal leaflet. When the intracellular Ca^{2+} concentration increases, the PS asymmetry in the ER is compromised, whereas PS in the nuclear membrane increases, most prominently in the nucleoplasmic leaflet of the inner nuclear membrane. These Ca^{2+} -induced changes in the PS distribution is attenuated in cells deleted of TMEM16K, and reappears by reintroducing TMEM16K to those cells. The results revealed: 1) the ER membrane has the cytoplasmic leaflet-dominant PS asymmetry, and 2) upon the intracellular Ca^{2+} increase, activated TMEM16K induces drastic changes of PS distribution in the ER and the nuclear membrane (Fig.2).

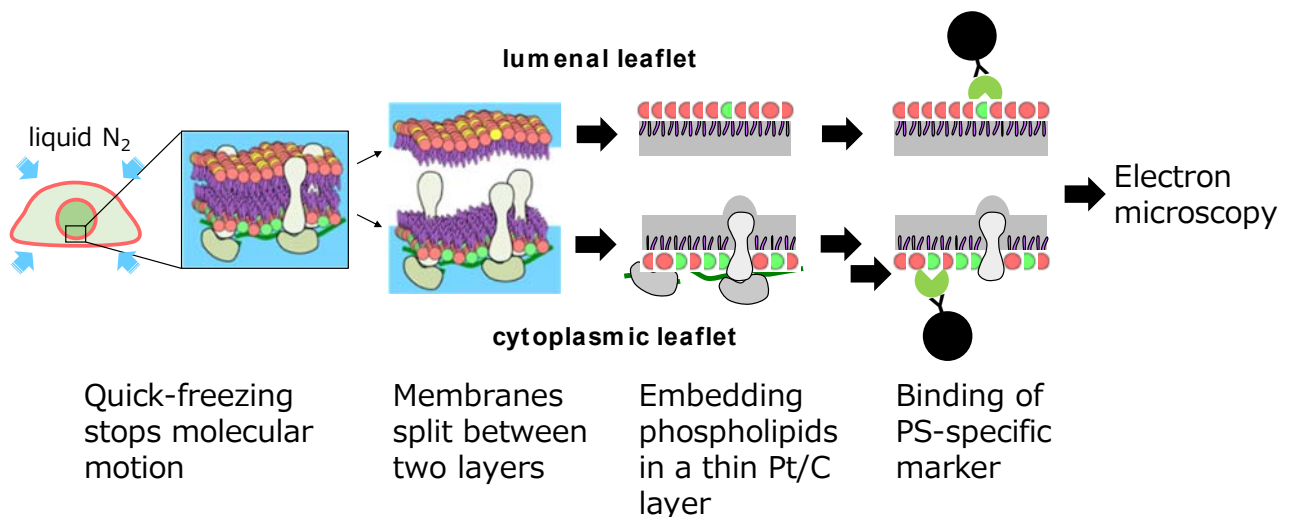


Fig.1: Outline of our method

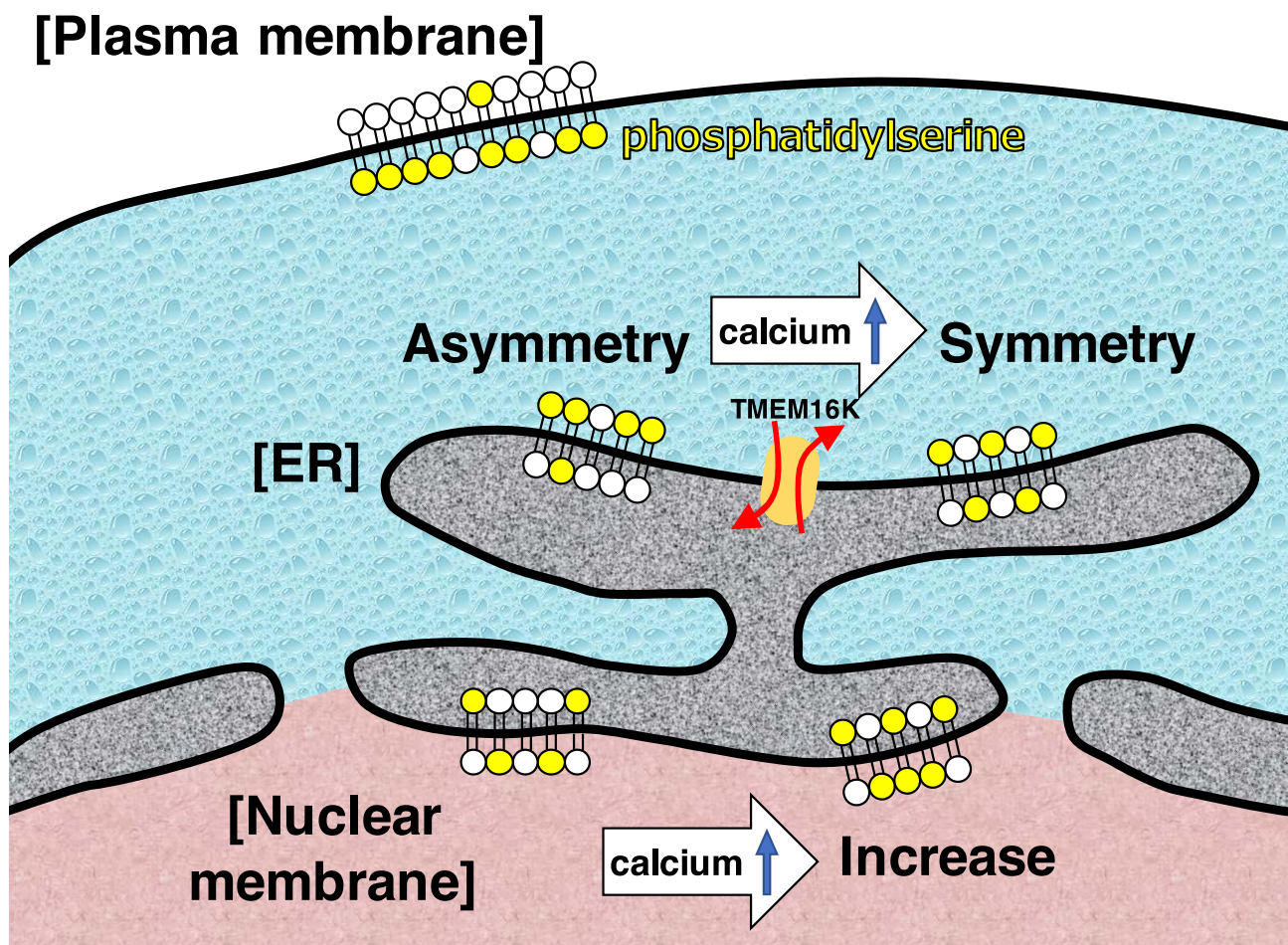


Fig.2: Summary

Research Summary and Future Perspective

The present study showed the intracellular PS distribution in detail, and indicated that TMEM16K causes significant distributional change of PS in intracellular membranes. It is tempting to speculate that a deficiency in phospholipid scrambling due to TMEM16K mutation may affect ER and nuclear membrane functions, thus causing dysfunction of neuronal cells. Research in this direction is expected to elucidate pathogenesis of SCAR10.

Publication

Takuma Tsuji, Jinglei Cheng, Tsuyako Tatematsu, Aoi Ebata, Hiroki Kamikawa, Akikazu Fujita, Sayuri Gyobu, Katsumori Segawa, Hiroyuki Arai, Tomohiko Taguchi, Shigekazu Nagata and Toyoshi Fujimoto; Predominant localization of phosphatidylserine at the cytoplasmic leaflet of the ER, and its TMEM16K-dependent redistribution, Proceedings of the National Academy of Sciences of the United States of America (PNAS), in press.

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