Niemann-Pick C2 protein regulates sterol transport between plasma membrane and late endosomes in human fibroblasts.

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Streszczenie

Niemann-Pick disease type C2 is a lipid storage disorder in which mutations in the NPC2 protein cause accumulation of lipoprotein-derived cholesterol in late endosomes and lysosomes (LE/LYSs). Whether cholesterol delivered by other means to NPC2 deficient cells also accumulates in LE/LYSs is currently unknown. We show that the close cholesterol analog dehydroergosterol (DHE), when delivered to the plasma membrane (PM) accumulates in LE/LYSs of human fibroblasts lacking functional NPC2. We measured two different time scales of sterol diffusion; while DHE rich LE/LYSs moved by slow anomalous diffusion in disease cells ($D \sim 4.6 \cdot 10^{-4} \mu m^2/sec$; $\alpha \sim 0.76$), a small pool of sterol could exchange rapidly with $D \sim 3 \mu m^2/s$ between LE/LYSs, as shown by fluorescence recovery after photobleaching (FRAP). By quantitative lipid mass spectrometry we found that esterification of ^{13}C-labeled cholesterol but not of DHE is reduced 10-fold in disease fibroblasts compared to control cells. Internalized NPC2 rescued the sterol storage phenotype and strongly expanded the dynamic sterol pool seen in FRAP experiments. Together, our study shows that cholesterol esterification and trafficking of sterols between the PM and LE/LYSs depends on a functional NPC2 protein. NPC2 likely acts inside LE/LYSs from where it increases non-vesicular sterol exchange with other organelles.

Słowa kluczowe

cholesterol, Vesicle tracking, Fluorescence recovery after photobleaching, Diffusion, Niemann-Pick disease type C2, Lysosome, Non-vesicular, Lipid mass spectrometry, Kinetics

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