Proposed sphingolipid sensor affects vacuolar morphology and function

Jan Malinsky

Institute of Experimental Medicine, Czech Academy of Sciences, Prague, Czech Republic

Integral membrane protein Nce102 accumulating in the plasma membrane microdomains of MCC (Membrane Compartment of Can1 [1, 2]) has been proposed to function as a sensor of the actual sphingolipid content within the plasma membrane [3].

In agreement with this proposal, we observed upregulation of Nce102 expression under conditions of sphingolipid depletion, and a gradual internalization of the protein during stationary phase, when the amount of sphingolipids in the plasma membrane increases. In contrast to other plasma membrane proteins, accumulation of Nce102 within the vacuolar membrane was observed following the protein internalization, suggesting functional relevance of this Nce102 localization. And indeed, we describe vacuole-related phenotypes induced by the absence of Nce102 in the vacuolar membrane. We document a significant delay in vacuolar morphogenesis and vacuolar membrane domain-related lipophagy in Nce102-deficient cells. As a possible reason for this delay we suggest a compromised stability of V-ATPase in these cells.

We conclude that being localized to the sterol-enriched microdomains both in the plasma membrane and in the vacuolar membrane, Nce102 regulates sterol metabolism through modulation of the vacuolar pH.

[1] Malinska K., Malinsky J., Opekarova M., Tanner W. (2003) Visualization of protein compartmentation within the plasma membrane of living yeast cells. *Molecular Biology of the Cell* 14:4427-36

[2] Grossmann G., Malinsky J., Stahlschmidt W., Loibl M., Weig-Meckl I., Frommer W.B., Opekarova M., Tanner W. (2008) Plasma Membrane Microdomains Regulate Turnover of Transport Proteins in Yeast. *Journal of Cell Biology* 183(6):1075-88

[3] Frohlich F., Moreira K., Aguilar P.S., Hubner N.C., Mann M., Walter P., Walther T.C. (2009) A genome-wide screen for genes affecting eisosomes reveals Nce102 function in sphingolipid signaling. *Journal of Cell Biology* 185:1227-42