Czyz O, Bitew T, Cuesta-Marbán A, McMaster CR, Mollinedo F, and Zaremberg V (2013). Alteration of plasma membrane organization by an anticancer lysophosphatidylcholine analogue induces intracellular acidification and internalization of plasma membrane transporters in yeast. *Journal of Biological Chemistry* 288, 8419-8432.

The lysophosphatidylcholine analogue edelfosine is a potent antitumor lipid that targets cellular membranes. The underlying mechanisms leading to cell death remain controversial, although two cellular membranes have emerged as primary targets of edelfosine, the plasma membrane (PM) and the endoplasmic reticulum. In an effort to identify conditions that enhance or prevent the cytotoxic effect of edelfosine, we have conducted genome-wide surveys of edelfosine sensitivity and resistance in Saccharomyces cerevisiae presented in this work and the accompanying paper (Cuesta-Marbán, Á., Botet, J., Czyz, O., Cacharro, L. M., Gajate, C., Hornillos, V., Delgado, J., Zhang, H., Amat-Guerri, F., Acuña, A. U., McMaster, C. R., Revuelta, J. L., Zaremberg, V., and Mollinedo, F. (January 23, 2013) J. Biol. Chem. 288,), respectively. Our results point to maintenance of pH homeostasis as a major player in modulating susceptibility to edelfosine with the PM proton pump Pma1p playing a main role. We demonstrate that edelfosine alters PM organization and induces intracellular acidification. Significantly, we show that edelfosine selectively reduces lateral segregation of PM proteins like Pma1p and nutrient H(+)-symporters inducing their ubiquitination and internalization. The biology associated to the mode of action of edelfosine we have unveiled includes selective modification of lipid raft integrity altering pH homeostasis, which in turn regulates cell growth.