

Mollinedo, F, Fernández, M, Hornillos, V, Delgado, J, Amat-Guerri, F, Acuña, AU, Nieto-Miguel, T, Villa-Pulgarín, JA, González-García, C, Ceña, V, and Gajate, C (2011). Involvement of lipid rafts in the localization and dysfunction effect of the antitumor ether phospholipid edelfosine in mitochondria. *Cell Death & Disease* 2:e158.

Lipid rafts and mitochondria are promising targets in cancer therapy. The synthetic antitumor alkyllysophospholipid analog edelfosine (1-*O*-octadecyl-2-*O*-methyl-*rac*-glycero-3-phosphocholine) has been reported to target lipid rafts. Here, we have found that edelfosine induced loss of mitochondrial membrane potential and apoptosis in human cervical carcinoma HeLa cells, both responses being abrogated by Bcl-x_L overexpression. We synthesized a number of new fluorescent edelfosine analogs, which preserved the proapoptotic activity of the parent drug, and colocalized with mitochondria in HeLa cells. Edelfosine induced swelling in isolated mitochondria, indicating an increase in mitochondrial membrane permeability. This mitochondrial swelling was independent of reactive oxygen species generation. A structurally related inactive analog was unable to promote mitochondrial swelling, highlighting the importance of edelfosine molecular structure in its effect on mitochondria. Raft disruption inhibited mitochondrial localization of the drug in cells and edelfosine-induced swelling in isolated mitochondria. Edelfosine promoted a redistribution of lipid rafts from the plasma membrane to mitochondria, suggesting a raft-mediated link between plasma membrane and mitochondria. Our data suggest that direct interaction of edelfosine with mitochondria eventually leads to mitochondrial dysfunction and apoptosis. These observations unveil a new framework in cancer chemotherapy that involves a link between lipid rafts and mitochondria in the mechanism of action of an antitumor drug, thus opening new avenues for cancer treatment.