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The so-called alkylphospholipid analogs (APLs) constitute a family of synthetic antitumor compounds that target cell membranes. The ether phospholipid edelfosine has been considered the long-standing prototype of these antitumor agents and promotes apoptosis in tumor cells by a rather selective way, while sparing normal cells. Increasing evidence suggests that edelfosine-induced apoptosis involves a number of subcellular structures in tumor cells, including plasma membrane lipid rafts, endoplasmic reticulum (ER) and mitochondria. Edelfosine has been shown to accumulate in plasma membrane lipid rafts, ER and mitochondria in different tumor cells in a cell type-dependent way. Edelfosine induces apoptosis in several hematopoietic cancer cells by recruiting death receptor and downstream apoptotic signaling molecules into lipid rafts and displacing survival signaling molecules from these membrane domains. However, in vitro and in vivo evidences suggest that edelfosine-induced apoptosis in solid tumor cells is mediated through an ER stress response. Both raft- and ER-mediated proapoptotic responses require a mitochondrial-related step to eventually promote cell death, and overexpression of Bcl-2 or Bcl-xL prevents edelfosine-induced apoptosis. Edelfosine can also interact with mitochondria leading to an increase in mitochondrial membrane permeability and loss of mitochondrial membrane potential. Edelfosine treatment also induced a redistribution of lipid rafts from the plasma membrane to mitochondria, suggesting a raft-mediated link between plasma membrane and mitochondria. The involvement of lipid rafts, ER and mitochondria in the apoptotic response induced by edelfosine may provide new avenues for targeting cancer cells as well as new opportunities for cancer therapy.