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Pancreatic cancer remains as one of the most deadly cancers, and responds poorly to current therapies. The prognosis is extremely poor, with a 5-year survival of less than 5%. Therefore, search for new effective therapeutic drugs is of pivotal need and urgency to improve treatment of this incurable malignancy. Synthetic alkyl-lysophospholipid analogs (ALPs) constitute a heterogeneous group of unnatural lipids that promote apoptosis in a wide variety of tumor cells. In this study, we found that the anticancer drug edelfosine was the most potent ALP in killing human pancreatic cancer cells, targeting endoplasmic reticulum (ER). Edelfosine was taken up in significant amounts by pancreatic cancer cells and induced caspase- and mitochondrial-mediated apoptosis. Pancreatic cancer cells show a prominent ER and edelfosine accumulated in this subcellular structure, inducing a potent ER stress response, with caspase-4, BAP31 and c-Jun NH_2-terminal kinase (JNK) activation, CHOP/GADD153 upregulation and phosphorylation of eukaryotic translation initiation factor 2 α-subunit that eventually led to cell death. Oral administration of edelfosine in xenograft mouse models of pancreatic cancer induced a significant regression in tumor growth and an increase in apoptotic index, as assessed by TUNEL assay and caspase-3 activation in the tumor sections. The ER stress-associated marker CHOP/GADD153 was visualized in the pancreatic tumor isolated from edelfosine-treated mice, indicating a strong in vivo ER stress response. These results suggest that edelfosine exerts its pro-apoptotic action in pancreatic cancer cells, both in vitro and in vivo, through its accumulation in the ER, which leads to ER stress and apoptosis. Thus, we propose that the ER could be a key target in pancreatic cancer, and edelfosine may constitute a prototype for the development of a new class of antitumor drugs targeting the ER.