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Cholesterol- and sphingolipid-rich membrane domains, termed lipid rafts, have been recently involved in the triggering of death receptor-mediated apoptosis. The alkyl-lysophospholipid analogue edelfosine was the first antitumor drug reported to induce apoptosis in cancer cells through co-clustering of lipid rafts and Fas/CD95 death receptor. Recruitment and aggregation of Fas/CD95 in lipid raft clusters was independent of its cognate ligand FasL/CD95L, and could be pharmacologically modulated. The adaptor molecule Fas-associated death domain protein (FADD) and procaspase-8 were also recruited into lipid rafts following edelfosine treatment, forming the death-inducing signaling complex (DISC), and hence these membrane microdomains can act as scaffolds for Fas/CD95 death signaling. Edelfosine accumulated in lipid rafts of cancer cells, altering raft protein and lipid composition. Subsequently, an increasing number of antitumor drugs have been found to induce apoptosis through recruitment of Fas/CD95 into membrane rafts, and some of these compounds accumulated in raft membrane domains. Additional downstream apoptotic signaling molecules have also been reported to be recruited into rafts following treatment of cancer cells with antitumor agents, thus facilitating protein-protein interactions and conveying apoptotic signals. On these grounds, lipid rafts have become an appealing and promising target for therapeutic intervention in cancer chemotherapy. Co-clustering of lipid rafts and Fas/CD95 signaling provides a new insight in the regulation of death receptor-mediated apoptosis, opening a new avenue in cancer therapy. In this regard, an increasing number of patents are dealing with the above insights in order to improve cancer treatment.