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Cell signaling does not apparently occur randomly over the cell surface, but it seems to be integrated very often into cholesterol-rich membrane domains, termed lipid rafts. Membrane lipid rafts are highly ordered membrane domains that are enriched in cholesterol, sphingolipids and gangliosides, and behave as major modulators of membrane geometry, lateral movement of molecules, traffic and signal transduction. Because the lipid and protein composition of membrane rafts differs from that of the surrounding membrane, they provide an additional level of compartmentalization, serving as sorting platforms and hubs for signal transduction proteins. A wide number of signal transduction processes related to cell adhesion, migration, as well as to cell survival and proliferation, which play major roles in cancer development and progression, are dependent on lipid rafts. Despite lipid rafts harbor mainly critical survival signaling pathways, including insulin-like growth factor I (IGF-I)/phosphatidylinositol 3-kinase (PI3K)/Akt signaling, recent evidence suggests that these membrane domains can also house death receptor-mediated apoptotic signaling. Recruitment of this death receptor signaling pathway in membrane rafts can be pharmacologically modulated, thus opening up the possibility to regulate cell demise with a therapeutic use. The synthetic ether phospholipid edelfosine shows a high affinity for cholesterol and accumulates in lipid rafts in a number of malignant hematological cells, leading to an efficient in vitro and in vivo antitumor activity by inducing translocation of death receptors and downstream signaling molecules to these membrane domains. Additional antitumor drugs have also been shown to act, at least in part, by recruiting death receptors in lipid rafts. The partition of death receptors together with downstream apoptotic signaling molecules in membrane rafts has led us to postulate the concept of a special liquid-ordered membrane platform coined as "cluster of apoptotic signaling molecule-enriched rafts" (CASMER), referring to raft platforms enriched in apoptotic molecules. CASMERs act as scaffolds for apoptosis signaling compartmentalization, facilitating and stabilizing protein-protein interactions by local assembly of cross-interacting molecules, which leads to apoptosis amplification and a decrease in apoptotic signal threshold. Edelfosine also displaced survival PI3K/Akt signaling from lipid rafts, leading to Akt inhibition, in mantle cell lymphoma cells. Thus, membrane rafts could act as scaffold structures where segregation of pro- from anti-apoptotic molecules could take place. In this review, we summarize our view of how reorganization of the protein composition of lipid raft membrane domains regulates cell death and therefore it might be envisaged as a novel target in the treatment of cancer.