Gajate, C., and Mollinedo, F. (2015). Lipid raft-mediated Fas/CD95 signaling in leukemic cells and normal leukocytes and implications in cancer and autoimmune diseases. *Journal of Leukocyte Biology* 98, 739-759.

Membrane lipid rafts are highly ordered membrane domains enriched in cholesterol, sphingolipids and gangliosides that have the property to segregate and concentrate proteins. Lipid and protein composition of lipid rafts differs from that of the surrounding membrane, thus providing sorting platforms and hubs for signal transduction molecules, including CD95 death receptor-mediated signaling. CD95 can be recruited to rafts in a reversible way through S-palmitoylation following activation of cells with its physiological cognate ligand as well as with a wide variety of inducers, including several antitumor drugs through ligand-independent intracellular mechanisms. CD95 translocation to rafts can be modulated pharmacologically, thus becoming a target for the treatment of apoptosis-defective diseases, such as cancer. CD95-mediated signaling largely depends on protein-protein interactions, and the recruitment and concentration of CD95 and distinct downstream apoptotic molecules in membrane raft domains, forming raft-based supramolecular entities that act as hubs for apoptotic signaling molecules, favors the generation and amplification of apoptotic signals. Efficient CD95-mediated apoptosis involves CD95 and raft internalization, as well as the involvement of different subcellular organelles. In this review, we briefly summarize and discuss the involvement of lipid rafts in the regulation of CD95-mediated apoptosis that may provide a new avenue for cancer therapy.