Reis-Sobreiro M, Roué G, Moros A, Gajate C, de la Iglesia-Vicente J, Colomer D, and Mollinedo F (2013). Lipid raft-mediated Akt signaling as a therapeutic target in mantle cell lymphoma. *Blood Cancer Journal* 3, e118.

Recent evidence shows that lipid raft membrane domains modulate both cell survival and death. Here, we have found that the phosphatidylinositol-3-kinase (PI3K)/Akt signaling pathway is present in the lipid rafts of mantle cell lymphoma (MCL) cells, and this location seems to be critical for full activation and MCL cell survival. The antitumor lipids (ATLs) edelfosine and perifosine target rafts, and we found that ATLs exerted in vitro and in vivo antitumor activity against MCL cells by displacing Akt as well as key regulatory kinases p-PDK1 (phosphatidylinositol-dependent protein kinase 1), PI3K and mTOR (mammalian TOR) from lipid rafts. This raft reorganization led to Akt dephosphorylation, while proapoptotic Fas/CD95 death receptor was recruited into rafts. Raft integrity was critical for Ser473 Akt phosphorylation. ATL-induced apoptosis appeared to correlate with the basal Akt phosphorylation status in MCL cell lines and primary cultures, and could be potentiated by the PI3K inhibitor wortmannin, or inhibited by the Akt activator pervanadate. Classical Akt inhibitors induced apoptosis in MCL cells. Microenvironmental stimuli, such as CD40 ligation or stromal cell contact, did not prevent ATL-induced apoptosis in MCL cell lines and patient-derived cells. These results highlight the role of raft-mediated PI3K/Akt signaling in MCL cell survival and chemotherapy, thus becoming a new target for MCL treatment.