α-TEA-induced death receptor dependent apoptosis involves activation of acid sphingomyelinase and elevated ceramide-enriched cell surface membranes. J. Li, W. Yu, R. Tiwary, S.-K. Park, A. Xiong, B. G Sanders, and K. Kline, *Cancer Cell Int.*, **10**:40 (2010).

Background: Alpha-tocopherol ether-linked acetic acid (α-TEA), an analog of vitamin E (RRR-alpha-tocopherol), is a potent and selective apoptosis-inducing agent for human cancer cells in vivo and in vitro. α-TEA induces apoptosis via activation of extrinsic death receptors Fas (CD95) and DR5, JNK/p73/Noxa pathways, and suppression of antiapoptotic mediators Akt, ERK, c-FLIP and survivin in breast, ovarian and prostate cancer cells.

Results: In this study, we demonstrate that α-TEA induces the accumulation of cell surface membrane ceramide, leading to co-localization with Fas, DR5, and FADD, followed by activation of caspases-8 and -9 and apoptosis in human MDA-MB-231 breast cancer cells. α-TEA treatment leads to increased acid sphingomyelinase (ASMase) activity by 30 min, peaking at 4 hrs, which is correlated with ASMase translocation from cytosol to the cell surface membrane. Functional knockdown of ASMase with either the chemical inhibitor, desipramine, or siRNA markedly reduces α-TEA-induced cell surface membrane accumulation of ceramide and its co-localization with Fas, DR5, and FADD, cleavage of caspases-8 and -9 and apoptosis, suggesting an early and critical role for ASMase in α-TEAinduced apoptosis. Consistent with cell culture data, immunohistochemical analyses of tumor tissues taken from α-TEA treated nude mice bearing MDA-MB-231 xenografts show increased levels of cell surface membrane ceramide in comparison to tumor tissues from control animals.

Conclusion: Taken together, these studies demonstrate that ASMase activation and membrane ceramide accumulation are early events contributing to α-TEA-induced apoptosis in vitro and perhaps in vivo.