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Poster Sessions

Ceramide nanoliposomes as a MLKL-dependent, necroptosis-inducing, chemotherapeutic reagent in cancer

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Ceramides are bioactive lipids that mediate cell death in cancer cells and ceramide-based therapy is now being tested in dose-escalating phase 1 clinical trials as a cancer treatment. The most representative ceramide formulation is ceramide nanoliposomes (CNL) that have been preclinically studied. However, the effect of CNL in ovarian cancer still remains an open question. We now investigate the therapeutic efficacy and signaling mechanisms of CNL in ovarian cancer. Treatment of ovarian cancer cells with CNL decreased cell viability in a dose-dependent manner. Importantly, CNL-treated cancer cells died with programmed necrosis (necroptosis), but not apoptosis. Mechanistically, dying SKOV3 ovarian cancer cells exhibit activation of pseudokinase mixed lineage kinase domain-like (MLKL) as evidenced by oligomerization in necroptosis. In addition, inhibition of MLKL, but not upstream RIP kinases, abolished CNL-induced cell death. In a cell-free system, ceramide was revealed to interact recombinant MLKL. Those results suggest CNL exhibited a cytotoxic effect by inducing MLKL-dependent necroptosis. In clinical studies, relapse-free survival was significantly extended in high MLKL mRNA expression group of patients with breast cancer, demonstrating correlation of MLKL expression with good prognosis. Taken together, our studies give insight into pharmacotherapeutic significance of necroptosis-inducing reagents in cancer treatment.