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## Elesclomol and chemotherapy agents synergistically induce apoptosis in breast cancer cells.

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Elesclomol represents a new strategy of anticancer therapy - selectively increasing oxidative stress in cancer cells leading to the induction of mitochondrial apoptosis. The combination of elesclomol plus paclitaxel was shown to prolong progression-free survival as compared with paclitaxel alone in a phase II clinical trial in patients with metastatic melanoma. The agent is now in a phase III clinical trial for metastatic melanoma. Currently, the mechanism underlying this potential synergy between elesclomol and chemotherapy agents in cancer cells is not fully understood. Here we report that elesclomol alone had modest activity in inhibiting breast cancer cell growth and had no effect on the growth of normal breast epithelial cells. However, combined treatment with elesclomol and either doxorubicin or paclitaxel synergistically induced apoptosis and suppressed breast cancer cell growth. Sensitive breast cancer lines included triple negative breast carcinoma cells. While both JNK and p38 MAPK were activated by elesclomol, only JNK was involved in the apoptosis induction by elesclomol. IAPs, a family of pro-survival proteins, were markedly down-regulated, whereas pro-apoptosis proteins like cleaved caspase-3 and cell cycle regulators p21CIP1 and p27KIP1 were strongly induced by elesclomol. Surprisingly, the Akt/Hsp70 survival signaling was also strongly induced as a cell feedback mechanism. Blockade of Akt activation enhanced elesclomol-induced apoptosis in breast cancer cells. These results implicate Akt signaling as a mechanism of potential acquired resistance to elesclomol. In summary, our data indicate that elesclomol can increase the efficacy of chemotherapy agents in breast cancer cells, which may warrant clinical trials of combined treatment of elesclomol and chemotherapy drugs in breast cancer patients.