Inorganic selenium sensitizes prostate cancer cells to TRAIL-induced apoptosis through superoxide/p53/Bax-mediated activation of mitochondrial pathway.

Abstract:
Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) has been shown to induce apoptosis in prostate cancer cells through DR4 and DR5 death receptors, but not in normal prostate cells, which do not express these receptors. Therefore, TRAIL has excellent potential to be a selective prostate cancer therapeutic agent with minimal toxic side effects. However, prostate cancer cells, as many other cancer types, develop resistance to TRAIL, and the underlying molecular mechanisms require further investigation. We hypothesize that selenium may sensitize TRAIL-resistant cells to undergo caspase-mediated apoptosis and increase therapeutic efficacy. Here, we report that TRAIL signaling in LNCaP prostate cancer cells stalled at downstream of caspase-8 and BID cleavage, as indicated by the lack of Bax translocation into mitochondria, and no subsequent activation of the caspase-9 cascade. Selenite induced a rapid generation of superoxide and p53 Ser(15) phosphorylation and increased Bax abundance and translocation into the mitochondria. Selenite and TRAIL combined treatment led to synergistic increases of Bax abundance and translocation into the mitochondria, loss of mitochondrial membrane potential, cytochrome c release, and cleavage activation of caspase-9 and caspase-3. Inactivating p53 with a dominant-negative mutant abolished
apoptosis without affecting superoxide generation, whereas a superoxide dismutase mimetic agent blocked p53 activation, Bax translocation to mitochondria, cytochrome c release, and apoptosis induced by selenite/TRAIl. In support of Bax as a crucial target for cross-talk between selenite and TRAIL pathways, introduction of Bax into p53 mutant DU145 cells enabled selenite to sensitize these cells for TRAIL-induced apoptosis. Taken together, the results indicate that selenite induces a rapid superoxide burst and p53 activation, leading to Bax up-regulation and translocation into mitochondria, which restores the cross-talk with stalled TRAIL signaling for a synergistic caspase-9/3 cascade-mediated apoptosis execution.

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