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Activation of conserved MST-FOXO pathway by α-tocopheryl succinate in cancer cells: New possibility for cancer treatment

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α-Tocopheryl succinate (α-TOS) is a cancer cell-selective inducer of apoptosis in cancer cells, which involves accumulation of reactive oxygen species (ROS) followed by apoptotic cell death. We have recently observed that α-TOS causes upregulation of the BH-3 only protein Noxa in cancer cells and that this upregulation is p53 independent. Individual transcription factors and signaling pthways responsible for this phenomena remain unknown.

Employing cis-RED database we found a conserved FoxO-binding site in the Noxa promoter and confirmed the affinity of FoxO to this sequence by fluorescence anisotropy. We observed also accumulation of the FoxO proteins in the nucleus and association of this proteins with Noxa promoter using the ChIP assay in cancer cells exposed to α-TOS. We identified Mst1 as pro-apototic kinase strongly activated by α-TOS in cancer cells. Activation of Mst1 resulted in FoxO translocation to the nucleus, inhibition of the pro-survival Akt signaling and activation of apoptotic mediators (e.g. caspase activation and apoptotic chromatin condensation).

We have demonstrated α-TOS as a new anti-cancer agent, which induces apoptosis through the MST-FOXO pathway. This pathway is conserved from *Drosophila* to humans and its activation in cancer cells by α-TOS leads to increased Noxa expression. Since Noxa is a pro-apoptotic protein with therapeutic potential in the selective elimination of cancer cell, activation of this pathway epitomize a new paradigm for cancer treatment.