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#4406 Synergistic effect of Bcl-xL small interfering RNA and genistein in human neuroblastoma SH-SY5Y and SK-N-DZ cells for induction of apoptosis and inhibition of angiogenesis and tumor growth in nude mice. Joseph George, Stephen Tomlinson, Naren L. Banik, Swapan K. Ray. Medical University of South Carolina, Charleston, SC.

Genistein is a phytoestrogenic isoflavone with anti-cancer properties. The anti-apoptotic molecule Bcl-xL is upregulated in many cancers including neuroblastoma to provide protection from apoptosis. The aim of our present study was to downregulate Bcl-xL using cognate siRNA during genistein treatment in two highly invasive neuroblastoma cell lines SH-SY5Y and SK-N-DZ, and to examine apoptosis, and inhibition of angiogenesis, and tumor growth in nude mice. The cells in cultures were treated with 100 nM Bcl-xL siRNA or 100 μM genistein or both agents together for 48 h. Morphological analysis and TUNEL assay demonstrated apoptosis in about 60% of cells after combination treatment with Bcl-xL siRNA and genistein. Apoptosis was associated with increase in Bax:Bcl-2 ratio, mitochondrial release of cytochrome c, and activation of caspase-9 and caspase-3 through the intrinsic pathway. Genistein also triggered the extrinsic pathway leading to apoptosis through upregulation of FasL and TNF-α associated death domains and activation of caspase-8. Furthermore, treatment with Bcl-xL siRNA and genistein resulted in significant increases of tBid, cleaved lamin, caspase-3-activated DNase (CAD) and cleaved poly (ADP-ribose) polymerase (PARP) indicating occurrence of apoptotic cell death through activation of both extrinsic and intrinsic pathways. In vivo angiogenesis in nude mice demonstrated formation of neo-vasculature with untreated neuroblastoma cells and complete inhibition after treatment with Bcl-xL siRNA and genistein. Administration of Bcl-xL siRNA and genistein also showed a remarkable decrease of subcutaneous tumor growth in immunocompromised mice. Thus, our study demonstrated that combination treatment with Bcl-xL siRNA and genistein worked synergistically to induce apoptosis and inhibit angiogenesis, and decreases tumor growth and therefore could serve as potential therapeutic tool for controlling the growth of human neuroblastomas. This work was supported by the R01 NS-57811 grant from the NINDS.

Citation Format

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