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#4662 Survivin knockdown enhanced efficacy of N-(4-hydroxyphenyl) retinamide for apoptosis in human glioblastoma U138MG and U251MG cells and inhibited invasion, angiogenesis, and tumor growth. Joseph George[1], Naren L. Banik[2], Swapan K. Ray[1]. [1]University of South Carolina School of Medicine, Columbia, SC; [2]Medical University of South Carolina, Charleston, SC.

Upregulation of the anti-apoptotic molecule survivin inhibits apoptosis and promotes tumor growth. Survivin is selectively upregulated in various cancers including glioblastoma, which is the most malignant brain tumor characterized by high angiogenesis, invasion, and cell proliferation. Treatment of cancer cells with N-(4-hydroxyphenyl) retinamide (4-HPR) induces apoptosis due to destabilization of mitochondrial membrane and activation of caspase mediated apoptotic pathways. In the present investigation, we examined whether survivin knockdown using cognate siRNA could enhance efficacy of 4-HPR for apoptosis in human glioblastoma U138MG and U251MG cells and inhibit cell invasion, angiogenesis, and tumor growth in athymic nude mice. Using a plasmid vector expressing cognate siRNA, we down regulated expression of survivin in both U138MG and U251MG cells and simultaneously treated them with 1 μM HPR for 48 h. Following the treatment of cells, we performed MTT assay, double immunofluorescent staining, TUNEL staining, FACS analysis, and matrigel invasion assay. We also carried out Western blotting for examining the molecules involved in caspase mediated apoptotic pathways. Double immunofluorescent stainings showed marked decrease in survivin expression and conspicuous increase in active caspase-3 after transfection of cells with survivin siRNA and treatment with 4-HPR. Both TUNEL staining and FACS analysis demonstrated apoptosis in more than 80% of cells after treatment with combination of both agents. MTT assay and invasion studies demonstrated marked decreases in tumor cell proliferation and invasion, respectively. Thereafter, we performed in vivo angiogenesis and tumor regression studies in athymic nude mice. Angiogenesis studies under the dorsal skin of athymic nude mice depicted remarkable inhibition of neovascularization after treatment with combination of survivin siRNA and 4-HPR. In vivo imaging studies on intracerebral and subcutaneous tumorigenesis and also longitudinal studies on solid tumor development showed marked decreases in tumorigenesis and solid tumor development after treatment with combination of survivin siRNA and 4-HPR. Therefore, simultaneous survivin knockdown using cognate siRNA and 4-HPR treatment could be a novel therapeutic strategy for controlling growth of human glioblastomas. This investigation was supported in part by the R01 grants (CA-91460 and NS-57811) from the National Institutes of Health (Bethesda, MD).

Citation Format

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