Halofuginone Inhibits Proliferation and Collagen Production by Leiomyoma Smooth Muscle Cells

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One of the hallmarks of uterine leiomyomas is the excessive collagen that is laid down by the smooth muscle cells (SMCs) of these tumors. We are interested in the potential use of anti-fibrotic drugs as therapeutic agents for treatment of leiomyomas. Halofuginone is a drug that has been reported to inhibit collagen production and proliferation by renal mesangial cells and vascular SMCs.

Objectives: To determine 1) whether halofuginone inhibits proliferation of leiomyoma SMCs through effects on DNA synthesis and/or apoptosis; 2) if halofuginone inhibits collagen type I and type III synthesis; and 3) whether these inhibitory effects are due to inhibition of TGFβ production.

Methods: Myometrial and leiomyoma SMCs from 5 patients were used to assess the effects of halofuginone on serum-stimulated DNA synthesis. Effects on apoptosis were measured using a caspase 3/7 assay. Cells from patients were treated with 0, 25, 100 or 200 ng/ml halofuginone for 24 hrs. The effects of halofuginone on levels of collagen type I, collagen type III, TGF-β1, and TGF-β3 mRNAs after 24 hrs treatment were determined in myometrial and leiomyoma SMCs by northern blot analysis.

Results: Halofuginone inhibited DNA synthesis in a dose dependent way in both myometrial and leiomyoma SMCs. Caspase 3/7 levels were not increased over the untreated control for any of the concentrations tested. Halofuginone did not inhibit mRNA levels of collagen type I, collagen type III, or the TGFβs in myometrial SMCs. In contrast, halofuginone caused a dose dependent suppression of both collagen type I and type III mRNA levels in leiomyoma SMCs. In addition, halofuginone inhibited both TGF-β1 and TGF-β3 mRNA levels in leiomyoma SMCs.

Conclusion: These results suggest that halofuginone may be a useful therapeutic agent for treatment of leiomyomas.