Gene Therapy of Uterine Fibroids: Adenovirus-Mediated Expression of Dominant Negative Estrogen Receptor Inhibits ERE-Reporter Transactivation in Rat and Human Leiomyoma Cells

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Introduction: Uterine leiomyomas (fibroids) are the most common tumors in premenopausal women. Currently there is no medicinal treatment for this condition and surgery is the main stay. This constitutes a clinical dilemma especially in young fibroid patients who desire to preserve their fertility. We have recently (Am J Obstetrics and Gynecology, 2004,191:00-00) demonstrated the ability of a mutated dominant-negative estrogen receptor gene delivered via an adenoviral vector (Ad-DN-ER) to induce apoptosis in leiomyoma cells as well as ablate pre-existing fibroids in vivo.

Objective: To assess the mechanism of Ad-DN-ER-induced apoptosis in leiomyoma cells.

Methods: As experimental models we used primary cultures of human leiomyoma cells (LM155) derived from fibroid tumors removed at hysterectomy as well as rat leiomyoma cells (ELT3). We also used a telomerase-immortalized human myometrial cell line (HM9). Adenovirus carrying two copies of the estrogen responsive element upstream of luciferase reporter (Ad-ERE-Luc) was used at 10-100 pfu/cell.To investigate the effect of Ad-DN-ER on ERE-reporter transactivation, cells were infected with the therapeutic viral vector for 48 hours. Luciferase expression was measured using standard methods.

Results: In ELT3 rat leiomyoma cells, treatment with Ad-DN-ER at 10, 50, 100, and 200 pfu/cell induced a reduction of ERE-luciferase activity by 30%, 92%, 96% and 97% respectively ($P<0.0001$). A similar trend was observed in HM9 as well as LM155 cell lines. We are currently testing the effect of Ad-DN-ER treatment on expression of genes involved in apoptosis, angiogenesis, and cell cycling in human leiomyoma cells.

Conclusion: In this work, we demonstrate the ability of dominant negative ER to decrease ERE gene transactivation. This suggests that Ad-DN-ER therapeutic efficacy is at least in part due to perturbing estrogen receptor signaling that is essential for leiomyoma tumor progression.