ZEB1 in Normal Myometrium, Leiomyomas and Leiomyosarcomas

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ZEB1, a transcription factor containing a homeodomain box plus two clusters of Kruppel-like zinc fingers, has been implicated in epithelial to mesenchymal transitions during development and tumor formation. While ZEB1 is known to be upregulated by estrogen in the chick oviduct, its expression and function in mammalian steroid hormone target tissues was unknown.

Objective: To study the expression and regulation of ZEB1 by female sex steroids in the normal and diseased uterus.

Methods: Mice lacking ZEB1 (EF1 in mice) die at birth; however, ZEB1/ EF1^{LacZ} heterozygote mice live to adulthood and reproduce. We used these mice to study the spatiotemporal regulation of ZEB1/ EF1 in the uterus by x-gal staining at different time points (virgin, pregnant, lactatation and involution, corresponding to different hormonal states). Short term estrogen (E) and progesterone (P) treatments were also performed on ovariectomized wild-type mice. In addition, real time RT-PCR for ZEB1 was conducted on primary human myometrial cells treated *in vitro* with E and P. We have also examined ZEB1 expression by immunohistochemistry in normal human myometrium, leiomyomas, and leiomyosarcomas.

Results/Conclusions: In the mouse uterus, we find that ZEB1 is strongly expressed in the myometrium and is upregulated by E and P. In human surgical resection specimens, nuclear ZEB1 expression was detected in normal myometrium, leiomyomas, and leiomyosarcomas and the intensity of ZEB1 staining appeared to correlate with the degree of nuclear atypia in leiomyosarcomas. ZEB1 expression was also noted in benign endometrial stromal cells but not normal glandular endometrium. These observations support the hypothesis that sex steroid hormonal modulation of ZEB1 expression could be involved in the pathogenesis of uterine smooth muscle tumors.