Abnormal activation of RhoA/ROCK-I Signaling in junctional zone smooth muscle cells of patients with adenomyosis

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Introduction: The exact pathogenesis of adenomyosis (ADS) remains unclear. It has been suggested that aberrant junctional zone (JZ) peristalsis plays an integral part in the pathogenesis of ADS. And hyperperistalsis induced by the local production of estrogen would constitute a mechanical trauma resulting in an increased desquamation of fragments of the basal endometrium. The RhoA/ROCK signaling pathway is involved in smooth muscle contraction. We examined the potential role of this pathway in JZ contraction in women with and without ADS.

Materials /Patients and methods? 43 patients were recruited during February to November of 2014. 23 women who underwent hysterectomy for ADS were enrolled as the case group. The control group consisted of 20 patients with cervical intraepithelial neoplasia (CIN) III. We investigated the expression of RhoA and Rho-kinase in cultured JZ smooth muscle cells (JZSMCs) by western blotting and Real-Time PCR. We also examined the effect of estrogen on the expression of Rho-kinase signaling molecules and estrogen-mediated functional contractile responses in JZSMCs from patients with ADS.

Results: We demonstrated that in the normal JZ, RhoA and ROCK-I messenger RNA and protein expression was significantly higher in the proliferative phase of the menstrual cycle than in the secretory phase. RhoA, ROCK-I expression in the JZ from women with ADS were significantly higher than in the control and showed no significant differences across the menstrual cycle. Treatment of JZSMCs with estrogen at 0, 1, 10, or 100 nM/L for 24 h resulted in increased expression of RhoA, ROCK-I, and myosin light-chain (MLC) phosphorylation in a dose-dependent manner. In parallel to its effects on MLC phosphorylation (p-MLC), estrogen mediated dose-dependent contraction responses in JZSMCs. Estrogen-mediated contraction in the ADS group was significantly higher than in the controls and also showed no significant differences across the menstrual cycle. These effects were suppressed in the presence of ICI182, 780 or Y27632, supporting an estrogen receptor (ER)-dependent and RhoA activation-dependent mechanism.

Conclusion: Our results indicate that the level of RhoA and ROCK-I increases in patients with ADS and the cyclic change is lost. Estrogen may affect uterine JZ contraction of ADS by enhancing RhoA/ ROCK-I signaling.

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