Neutralization of TGF-β1 signaling reduces myometrial infiltration and alleviates generalized hyperalgesia in mice with induced adenomyosis

Abstract ID : 2448
Submitted by : Xishi Liu the 2017-01-26 06:27:00
Category : SEUD CONGRESS
Typology : Communication orale / Oral communication
Status : Validated
Authorisation to disclose : Yes/Oui

INTRODUCTION□Adenomyosis is a fairly common gynecologic disorder with a poorly understood pathogenesis, as endometriosis. Similar to endometriosis, our current knowledge of the mechanisms underlying adenomyosis-caused pain is still woefully inadequate. Consequently, treatment of adenomyosis has been a challenge, with hysterectomy being the treatment of choice for severe symptomatic adenomyosis. Clearly, medical treatment of adenomyosis represents an unmet medical need that so far has not been fulfilled. We have previously reported that induction of adenomyosis in mice results in uterine hyperactivity and progressive hyperalgesia, and that in both endometriosis and adenomyosis platelet-derived TGF-β1 induces the activation of the TGF-β1/Smad3 signaling pathway, resulting in progressive epithelial-mesenchymal transition (EMT), fibroblast-to-myofibroblast transdifferentiation (FMT), smooth muscle metaplasia (SMM), and, ultimately, fibrosis. Since TGF-β1 is a potent inducer of EMT, FMT, and fibrosis, we hypothesized that the neutralization of the TGF-β1 signaling should have therapeutic value in treating adenomyosis. This study was undertaken to test this hypothesis in a mouse model of adenomyosis.
METHODS□Adenomyosis was induced in 17 female ICR mice by neonatal feeding of tamoxifen as reported previously. At the 5th week, the mice were randomly divided into two groups, one receiving daily intragastric administration of GW788388 (a TGF-β receptor kinase inhibitor) at 3 mg/kg, and the other, the untreated group (n=9) received the same volume of vehicle buffer only in similar fashion. After 4 weeks of treatment, all mice were sacrificed and their uterine horns were harvested. Before treatment and prior to sacrifice, bodyweight and hotplate latency were measured. The harvested uterine horns were used for immunohistochemistry analysis of CD41 (a marker for platelets), E-cadherin, vimentin, α-smooth muscle actin (α-SMA), and collagen I, i.e. markers for platelet aggregation, EMT, FMT, and fibrosis. The extent of fibrosis was evaluated by Masson trichrome staining.
RESULTS□We found that mice treated with GW788388 had significantly reduced myometrial infiltration of endometrial tissues in conjunction with improved hyperalgesia. In addition, TGF-β1 neutralization significantly reduced the expression of vimentin (in epithelial component), α-SMA, and collagen I but elevated the expression of E-cadherin in ectopic endometrium. It also significantly reduced the extent of fibrosis in adenomyotic lesions. However, TGF-β1 neutralization did not have any effect on the extent of platelet aggregation in lesions.

CONCLUSIONS□These data demonstrate that TGF-β1 neutralization can effectively hamper the progression of EMT, FMT, SMM and fibrogenesis in the development of adenomyosis in mouse, resulting in retardation of myometrial infiltration and the improvement of hyperalgesia. As such, TGF-β1 appears to be an important therapeutic target in treating adenomyosis.

Keywords : Adenomyosis; hyperalgesia; mouse; myometrial infiltration; TGF-? blockade
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