ISP-31-2 Increased secretion of monocyte chemoattractant protein-1 (MCP-1) in endometriotic stroma cells is mediated by cell-extracellular matrix adhesion and focal adhesion kinase (FAK)

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[Objective] Integrins have been demonstrated to regulate cell survival, proliferation and invasion via FAK in many types of cells including endometriosis. MCP-1 is one of the highly upregulated chemokines in endometriotic tissues. In the current study, we investigated that FAK and adhesion-mediated MCP-1 secretion from endometrial and endometriotic stromal cells. [Methods] We purified and cultured stromal cells from surgically removed specimens of endometrium and endometriotic cysts. All human samples were obtained with informed consent. We assayed the concentrations of MCP-1 in the culture media of endometrial stroma cells with or without endometriosis (eESC and ESC, respectively) and endometriotic cyst-derived stromal cells (CSC). [Results] The concentration of MCP-1 was more than 10-fold in CSC culture media compared to ESC and eESC. MCP-1 secretion was increased by attachment to collagen and fibronectin, although significance was only found in the fibronectin. FAK inhibitor and Jnk inhibitor inhibited secretion of MCP-1 from CSC, while MEK inhibitor did not show any inhibition. [Conclusion] Increased secretion of MCP-1 from endometriotic stromal cells was mediated via FAK which was stimulated by integrin-extracellular matrix adhesion. These results suggest that inflammatory response and cell adhesion is interrelated and implicated in the development endometriosis.

ISP-31-3 SR-16234, a selective estrogen receptor modulator, represses development of endometriosis-like lesions in rat model

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[Objective] Selective estrogen receptor modulators (SERM) have tissue-selective actions. SR-16234 (SRI licensed to Nobelpharma for endometriosis) is a newly developed SERM, which has an estrogen receptor (ER) αpure antagonist and ERβpartial agonist activity. We investigate the efficacy of SR16234 for the treatment of endometriosis by using the rat model. [Methods] A rat endometriosis model was established by transplanting autologous endometrial tissue (7 weeks, CD rat : n=36). All rats were ovariectomized and had subcutaneous estradiol (E2) injections. The lumen of one uterine horn was opened longitudinally and divided into two pieces. Two everted segments were sutured to the parietal peritoneum. After 4 weeks of oral SR-16234 (0.1-1 mg/kg/day) treatment, the endometriosis-like lesions were evaluated. Gene expression in the lesions was analyzed by real time RT-PCR. [Results] SR16234 decreased the weight of endometriosis-like lesions. Maximal dose (1mg/kg) of this drug completely inhibited the formation of lesions. By E2 treatment, IL (interleukin)-6 and MCP (monocyte chemotactic protein)-1, PEDF (pigment epithelium-derived factor) mRNA expression in the lesions was upregulated. Among them, SR16234 repressed E2-induced IL-6 mRNA expression and showed tendency to increase PEDF expression. [Conclusion] SR16234 had a regressive effect on the development of rat endometriosis-like lesions.

ISP-31-4 Upregulation of versican in apparently normal peritoneum in women with endometriosis is not be secondary event but may be the cause

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[Objective] In development of peritoneal endometriosis, we hypothesized that upregulation of versican, a major proteoglycan component of ECM, in the normal peritoneum plays an essential role. Because, our microarray analysis showed versican mRNA expression in apparently normal peritoneum is significantly higher in women with endometriosis than those without. In vitro studies showed that versican V1 enhances the attachment of primary endometrial stromal cells (ESCs) to normal peritoneal mesothelial cells (HMrSV5), and increased the invasiveness of ESCs. In present study, we examined the possible regulators in the microenvironment of women with endometriosis. [Methods] Under approval of the Ethical Committee of Kyoto University, peritoneal fluid of endometriotic women (PF, n=3) was obtained at laparoscopy. HMrSV5 cells were incubated for 24 hours in the presence or absence of PF or various cytokines. mRNA levels of versican and various cytokines in HMrSV5 cells were assessed by RT-PCR. [Results] Treatment with PF upregulated the expression of IL-6 and IL-8, but did not alter the expression of versican V1 in HMrSV5 cells. Among the factors examined, only activated TGFb1 significantly increased versican V1. [Conclusion] Upregulation of versican in the apparently normal peritoneum of women with endometriosis may not be the result of stimulation by the endometriotic peritoneal fluid.