Dysregulation of the ADAM17/Notch signaling pathways in endometriosis correlates with disease severity and fibrosis

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Introduction: Endometriosis is a chronic inflammatory disease. Oxidative stress plays an important role in the onset and progression of the disease. Some members of the "A disintegrin and metalloproteases" (ADAM) family, such as ADAM17, are induced by oxidative stress. ADAM17/Notch signaling has been found altered in other inflammatory diseases, but has never been studied in endometriosis.

Methods: One hundred and twenty-one women with histologically proven endometriosis and 81 endometriosis-free controls were included in the study. Endometriosis patients were classified in: superficial endometriosis, ovarian endometrioma and deep infiltrating endometriosis (DIE). Peritoneal fluid (PF) samples were obtained from all participants to detect Advanced Oxidation Protein Products (AOPP) and metalloproteinase activity of ADAM17. Stromal cells from endometrial specimens (n=8) were obtained from endometrium of controls (Cs), and from eutopic (Es) and ectopic (Ps) endometrium of patients with DIE (n=8). ADAM17, Notch and fibrosis were assessed in all endometrial samples.

Results: AOPP and ADAM17 levels were higher in PF of endometriosis patients than controls (median, 1.73 vs. 1.25 nmol/mg; P= 0.001 and median, 0.28 vs. 0.20 pg/mg; P= 0.019 respectively). According to the surgical classification, ADAM17 PF levels resulted increased only in DIE patients compared to controls (P< 0.05). We found a significant correlation between AOPP and ADAM17 levels in PF of endometriosis patients (r = 0.798; P< 0.001). ADAM17 activity was increased in Es and Ps cells with respect to Cs cells (P< 0.001 and P< 0.01 respectively). Furthermore, we found a hyperactivation of Notch signaling in Ps compared to Cs cells (P< 0.05), and fibrosis markers (?-SMA and type-I collagen) were also increased in Ps cells compared to Cs cells (P <0.05 and P <0.001, respectively). The use of a ß-secretase inhibitor (DAPT) to prevent Notch cleavage and intracellular domain release reduced ?-SMA (P= 0.035) and collagen (P= 0.014) in Ps cells, but not in Cs cells.

Conclusion: We demonstrate a relationship between oxidative stress and hyperactivation of ADAM17/Notch signaling in endometriosis. Notch signaling plays a role in fibrotic processes of ectopic lesions in DIE patients.

Mots clefs : ADAM17; Notch; oxidative stress; endometriosis; deep infiltrating endometriosis
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