Lipoxin A4 prevents the progression of endometriosis by multiple mechanisms in a murine model of endometriosis

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Endometriosis is one of the leading causes of infertility characterized by ectopic growth of endometrial-like tissue outside uterine cavity. Its pathophysiology is still poorly understood involving inflammatory and angiogenic mediators as well as estrogen-regulated genes. Using an experimental murine model we have investigated the mechanisms leading to the establishment and progression of endometriosis as well as the effect of systemic treatment with Lipoxin A4 (LXA4), a known anti-inflammatory and pro-resolving lipid mediator. LXA4 treatment significantly reduces endometriotic lesions size and downregulates the peritoneal and local pro-inflammatory cytokines IL-1ß and IL-6 as well as the angiogenic factor VEGF. LXA4 attenuates HIF-1α and its target genes including VEGF and COX-2 expression in endometriotic lesions and peritoneal fluid cells thus decreasing the local production of prostaglandins E2 and its transpoter, MRP4. Besides its anti-inflammatory effects, LXA4 differentially regulates the expression of matrix remodeling enzymes including matrix metalloproteinases (MMP)-2 and -9 as well as transforming growth factor (TGF)-β isoforms in peritoneal fluid cells and within the endometriotic lesions. Furthermore, LXA4 treatment attenuates aromatase (CYP19A1) and estrogen receptor α (ER-α) expression which modulate estrogen signaling, resulting into reduced cellular proliferation as evidenced by decreased local expression of cMYC and CCND1 as well as decreased growth of endometriosis lesions. Finally, LXA4 given after the onset of disease was still effective in controlling established endometriotic lesions size by similarly modulating aforementioned mediators. Collectively, our novel findings highlight potential targets for the treatment of endometriosis and suggest a pleiotropic effect of LXA4 treatment on the progression of the disease, by attenuating pro-inflammatory and angiogenic mediators, matrix remodeling enzymes, estrogen signaling and proliferative pathways.

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