2-YIA-57 YIA

VEGFR1 signaling plays a critical role in endometriosis through increasing lymphangiogenesis

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Lymphangiogenesis is associated with the growth of endometriosis. In this study, we examined the role of vascular endothelial growth factor (VEGF) receptor 1 (VEGFR1) signaling in lymphangiogenesis and tissue growth in an endometriosis model. Using wild-type (WT) and VEGFR1 tyrosine kinase (TK) deficient mice, endometrial fragments were implanted into the peritoneal wall of mice. Endometrial tissue growth and lymphangiogenesis as indicated by lymphatic vessel density were determined. Endometrial fragments from wild-type (WT) mice transplanted into in host WT mice (WT→WT) grew with increased lymphangiogenesis accompanied by increases in pro-lymphangiogenic factors, VEGF-C and VEGF-D. The implant size and lymphangiogenesis were reduced in the $TK^{-/-}$→$TK^{-/-}$. Immunofluorescence demonstrated that both VEGF-C and VEGF-D were expressed in both $CD11b^{+}$ and $S100A4^{+}$ cells. When cultured bone marrow-derived macrophages and fibroblasts were stimulated with placental growth factor (PlGF), a specific agonist for VEGFR1, the mRNA levels of VEGF-C and VEGF-D were increased in a VEGFR1 dependent manner. A VEGFR3 kinase inhibitor significantly suppressed the size of implants, lymphangiogenesis, pro-lymphangiogenic factors, and accumulation of $CD11b^{+}$ and $S100A4^{+}$ cells. These results suggest that VEGFR1 signaling in macrophages and fibroblasts promote the growth and lymphangiogenesis in endometrial tissue. Therefore, VEGFR1 blockade is a potential treatment for endometriosis.