RAMP1 signaling facilitates angiogenesis and lymphangiogenesis in the endometriotic lesions in mice

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Newly formation of blood and lymphatic vessels is involved in the development of endometriosis. We have demonstrated that calcitonin gene-related peptide (CGRP) promotes wound healing and wound-associated formation of blood and lymphatic vessels via receptor activity-modifying protein 1 (RAMP1), a subunit of the CGRP receptor. In the present study, using wild-type (WT) mice and RAMP1 deficient (RAMP1^{-/-}) mice, we examined whether RAMP1 plays a role in the growth of endometriosis by angiogenic responses. Ectopic endometriosis model was created by transplantation of endometrial tissue fragments from donor mice into the peritoneal wall of host mice. The sizes and density of blood and lymphatic vessels in the RAMP1^{-/-} implants from host RAMP1^{-/-} mice (RAMP1^{-/-}→RAMP1^{-/-}) were reduced as compared with the WT→WT. The mRNA levels of markers for blood and lymphatic vessels as well as growth factors for angiogenesis and lymphangiogenesis in the RAMP1^{-/-}→RAMP1^{-/-} were lower than those in the WT→WT. Immunofluorescence demonstrated that RAMP1 was expressed in CD11b⁺ and S100A4⁺ cells, and these cells also co-localized with VEGF-A, VEGF-C, and VEGF-D. Cultured macrophages and fibroblasts increased the mRNA levels of VEGF-A, VEGF-C, and VEGF-D in a RAMP1 dependent manner. These results suggest that RAMP1 signaling in macrophages and fibroblasts is critical for the growth of endometriosis by promoting angiogenesis and lymphangiogenesis.