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EP4 signaling facilitates mucosal repair after DSS-induced colitis by enhancement of lymphangiogenesis

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Lymphatic development in the intestine is related to inflammatory bowel diseases. Prostaglandin E_2 (PGE_2)/EP4 prevents from the development of experimental colitis. We previously reported that EP4 facilitates wound healing and wound-associated lymphangiogenesis. In the present study, we examined whether EP4 is involved in tissue repair from colitis by enhancement of lymphangiongenesis. Experimental colitis was induced in male C57/Bl6 mice by the administration of dextran sulphate sodium (DSS) via drinking water for 5 days followed by free water drinking. Mice were received EP4 selective agonist, EP4 selective antagonist, or vehicle from Day 5 through Day 14. At Day 14, mice post-treated with EP4 antagonist were susceptible to signs of colitis, increased colonic tissue destruction and infiltration of macrophages. The increased lymphatic vessel density (LVD) was increased, but percentage of lymphatic vessel area (LVA%) was reduced. These were associated with decreased levels of lymphatic markers and pro-lymphangiogenic factors including VEGF-C and VEGF-D. By contrast, post-treatment with EP4 agonist improved signs of DSS-colitis, suppressed macrophage infiltration and cytokines. This was associated with further enhancement of lymphatic factors and lymphangiogenesis as evidenced by higher LVD and LVA%, and fluorescence intensity in the mesenteric lymph nodes. These results suggest that EP4 activation is helpful for attenuation of DSS-induced colitis by enhancement of drainage function through enlarged lymphatic vessels.