Y-01

Nicotine ameliorates colonic inflammation via down-regulation of MAdCAM-1 expression on high endothelial venule like vessel.

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Background: Ulcerative colitis (UC) is an intractable colonic disease. Lymphocytes migration to colonic mucosa through endothelial venule like vessel is considered to be involved in pathophysiology of this disease. Anti-adhesion molecule therapy targeting MAdCAM-1 on high endothelial venule like vessel is one of the promising therapy. Smoking has been reported to have a beneficial effect on UC. Nevertheless, pathophysiology of nicotine on activity of UC is still to be elucidated. This time, we investigated the involvement of nicotine in the colonic inflammation using murine colitis model.

Method: In murine study, tissue samples were obtained from colon of C57BL/6J mouse provided with drinking water containing dextran sulfate sodium (DSS). Degree of mRNA expression of TNF- α and MAdCAM-1 was determined by using quantitative RT-PCR. The inhibitory effects of nicotine on activity of colitis and mRNA expression were determined. To induce high endothelial venules in vitro, bEnd3 cell line was treated with TNF- α . Effect of nicotine on MAdCAM-1 expression on high endothelial venule (HEV) like vessel was also measured by using quantitative RT-PCR.

Results: In murine colitis model, administration of nicotine ameliorated DSS colitis. Administration of nicotine also significantly decreased degree of expression of MAdCAM-1 mRNA on HEV-like vessel.

Conclusion: Nicotine ameliorates DSS colitis possibly via down regulation of MAdCAM-1 expression on HEV-like vessel, and accordingly, inhibition of aberrant lymphocyte migration in colonic mucosa.

Y-02

VEGFR1 signaling facilitates diabetic skin wound healing in mice

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Aims: Signaling of vascular endothelial growth factor receptor 1 (VEGFR1) is suggested to involve in angiogenesis and lymphangiogenesis. The objective of the present study was to examine the role of VEGFR1 signaling in angiogenesis/lymphangiogenesis during diabetic skin wound healing.

Methods: VEGFR1-tyrosine kinase knockout mice (KO) or their wild counterparts (WT) were treated with streptozotocin (STZ) or vehicle (Veh). Full-thickness skin wounds were created on the backs of mice.

Results: Compared with non-diabetic mice (Veh/WT), wound healing and angiogenesis were suppressed in diabetic mice (STZ/WT) and non-diabetic KO mice (Veh/KO), with reduced expression of VEGF-A and CD31 in wound granulation tissues. Formation of lymphatic vessels was inhibited with reduced expression of VEGF-C, VEGF-D and VEGFR3. Accumulated VEGFR1-positive macrophages with VEGF-C or VEGF-D-expressing cells in granulation tissues were decreased. This was associated with attenuated expression of mannose receptor (MR) and transforming growth factor-beta (TGF β). Diabetic KO (STZ/KO) showed further delayed wound healing and wound-induced angiogenesis/lymphangiogenesis. Exaggerated reduction in recruitment of VEGFR1-positive macrophages and in expression of MR and TGF β was also demonstrated.

Conclusions: These results indicate that VEGFR1 signaling plays a role in angiogenesis/lymphangiogenesis through recruitment of VEGFR1-positive macrophages during diabetic wound healing.