PLATELET-SPECIFIC DELETION OF CYCLOOXYGENASE-1 AMELIORATES DEXTRAN SULFATE SODIUM-INDUCED COLITIS IN MICE

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Introduction: Inflammatory bowel disease (IBD) is associated with an increased risk for thromboembolism, platelet activation and abnormalities in platelet number and size. Platelet function is altered in IBD and platelets can accumulate outside of the colonic vasculature. Platelets may contribute to the development of inflammatory diseases, through their ability to orchestrate the activation of vascular, immune and inflammatory cells by the release of a wide array of biological molecules, including thromboxane(TX)A_2 which enhances lymphocyte and macrophage functions and stimulates the biosynthesis of extracellular matrix proteins. Platelet TXA_2 is generated by the activity of cyclooxygenase (COX)-1 which is the main target of the antithrombotic actions of low-dose aspirin. In this study, we generated a mouse with a specific deletion of COX-1 in megakaryocytes/platelets (COX-1 cKO) to clarify the role of platelet activation in the development of inflammation and fibrosis in dextran sodium sulfate (DSS)-induced colitis.

Methods: Colitis was induced in wild-type (WT) and COX-1 cKO female mice through the administration of 2% DSS in drinking water for 5 days(acute phase) followed by tap water for 16 days (chronic phase) and the disease activity index (DAI), calculated as the sum of blood in stool (EMO Score) and stool consistency(STOOL Score), was assessed. In WT and COX-1-cKO mice, 24-hour urine collections were performed and the systemic production of prostaglandin(PG)E_2, PGD_2, prostacyclin (PGI_2) and TXA_2 was determined by quantifying the urinary levels of their major enzymatic metabolites: 7-hydroxy-5,11-diketotetranorprostane-1,16-dioic acid (PGE-M), 11,15-dioxo-9alpha-hydroxy-2,3,4,5-tetranorprostan-1,20-dioic acid (tetranor PGD-M), 2,3-dinor 6-keto-$PGF_{1\alpha}$(PGI-M), and 2,3-dinor TXB_2(TX-M), respectively, by liquid chromatography/tandem mass spectrometry(LC/MS/MS). Colonic specimens were evaluated for histological features of epithelial barrier damage, inflammation, and fibrosis.

Results: Specific deletion of COX-1 in platelets, which recapitulated the pharmacodynamics of low-dose aspirin, i.e., suppression of platelet TXA_2 production associated with substantial sparing of the systemic production of PGI_2, resulted in milder symptoms of colitis, in the acute phase, and almost complete recovery from the disease after DSS withdrawal. The area under the curve[(AUC), curve of scores vs time], from day 0 to 21 of DAI resulted lower in COX-1 cKO mice than in WT mice [30.70 ± 5.24 vs 51.05 ± 5.33 (mean ± SD, $p<0.01$), respectively]. The capacity of the colon to generate TXA_2 was not significantly altered in the acute and the recovery phase of DSS-induced colitis. However, enhanced systemic biosynthesis of TXA_2, as assessed by measuring the urinary levels of TX-M(a non-invasive marker of in vivo platelet activation), was detected reaching a significant difference vs baseline in the chronic stage of the disease. These findings suggest the occurrence of systemic activation of platelets in colitis. Reduced systemic TXA_2 biosynthesis in COX-1 cKO mice was associated with lower colonic collagen deposition and myofibroblast number in the chronic phase of colitis. Interestingly, colonic TXB_2 was not substantially affected by DSS challenge and platelet COX-1 deletion, thus suggesting that the enhanced systemic biosynthesis of TXB_2 detected in colitis was from extracolonic origin mainly from platelets.

Discussion and conclusions: Our results highlight the role of platelet-derived TXA_2 in the development of colitis and fibrosis induced by gut epithelial damage, thus opening the avenue to novel therapeutic strategies in IBD. The findings of the present study provide the rationale to investigate the potential efficacy and safety of low-dose aspirin in limiting the inflammation and tissue damage associated with IBD. Low-dose aspirin, through downstream effects of platelet inhibition, might also reduce the enhanced risk of colon cancer in IBD patients.