Histological disease progression and ALK5i therapeutic efficacy in a chronic DSS-induced mouse model of IBD with intestinal fibrosis

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Background & Aim

Inflammatory bowel disease (IBD) comprises a group of intestinal disorders, including ulcerative colitis and Crohn's disease. Intestinal fibrosis, as result of chronic inflammation, is a common complication in IBD. The high treatment failure rates associated with existing interventions highlight the large unmet need for more effective drugs to improve the management and outcomes of IBD. Consequently, translational animal models of IBD demonstrating chronic, progressive colonic fibrosis are important tools in preclinical drug discovery for IBD. The aim of the present study was to characterize intestinal pathology and therapeutic efficacy of a TGF-β type I receptor inhibitor (ALK5i) in a chronic DSS-induced mouse model of IBD.

Methods

See Fig. 1 for a study outline. 10 weeks old male C57BL/6JRj mice received 3 cycles of 7 days of DSS (2% w/v) in the drinking water (DSS-IBD) or normal water (CTRL) starting at week -9. Animals were terminated at week 1, week 3 or week 6. Study groups terminated at week 6 received twice daily dosing (per oral, PO) with vehicle or ALK5i (SB25334, 30 mg/kg). Terminal endpoints included colon morphometry, quantitative histological markers of inflammation and fibrosis as well as colon transcriptomics in the distal half of the colon

Conclusion

The chronic DSS-IBD mouse model demonstrates:

+ Mild-to moderate weight loss and colonic hypertrophy
+ Marked inflammation at week 1 in the colonic mucosa and submucosa
+ Sustained severe colonic fibrosis

ALK5i treatment in the DSS-IBD mouse model induce:

+ Increased colon weight/length ratio
+ Decreased fractional area levels of collagen 1a1 in colon
+ No changes in gene expression markers of inflammation and fibrosis

The DSS-IBD mouse is a preclinical model with features of progressive IBD, being suitable for testing novel anti-fibrotic drug therapies targeted for IBD patients.

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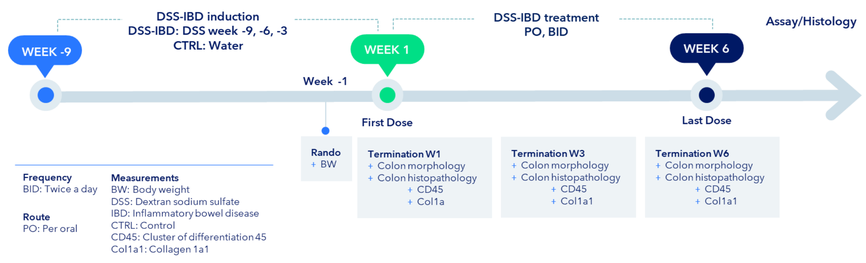
1 Study outline



Group	Group	Number of animals	Treatment	Administration route	Dosing Frequency	Dosing Volume	Dosing concentration
1	CTRL	9	**CTRL**	NA	NA	NA	NA
2	DSS-IBD W1	16	**DSS-IBD**	NA	NA	NA	NA
3	DSS-IBD W3	17	**DSS-IBD**	NA	NA	NA	NA
4	DSS-IBD W6 Vehicle	15	**DSS-IBD**	PO	BID	5 ml/kg	NA
5	DSS-IBD W6 ALK5i	15	**DSS-IBD**	PO	BID	5 ml/kg	30 mg/kg

Figure 1. Study outline and group overview.

2 Body weight and colon morphology

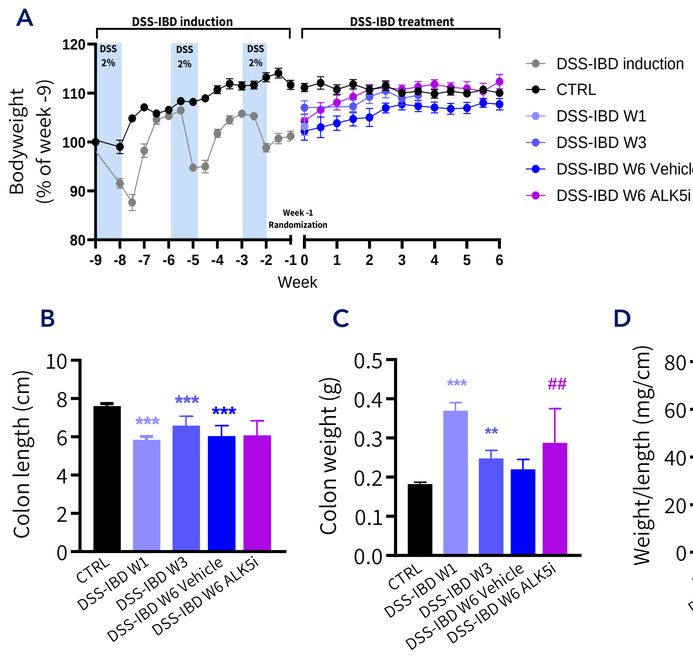


Figure 2. Body weight and colon morphology in DSS-IBD mice. (A) Body weight (% of week -9); **(B)** Colon length (cm); **(C)** Colon weight (g); **(D)** Colon weight/length ratio (mg/cm). **: P < 0.01, ***: P < 0.001 compared to CTRL, #: P < 0.05, ##: P <0.01 compared to DSS-IBD W6 vehicle

3 Colon inflammation

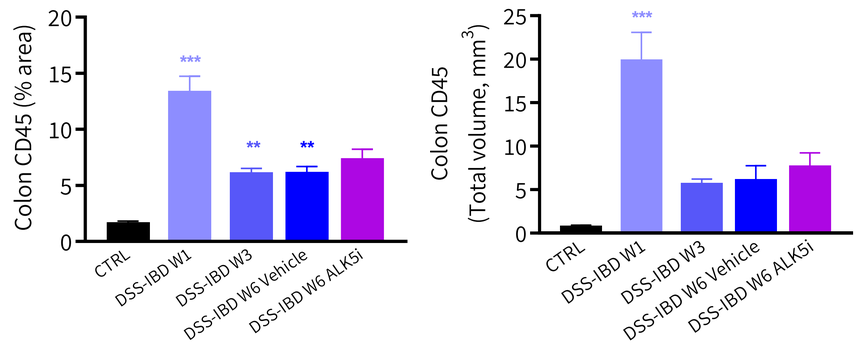


Figure 3. Quantitative histological markers of colon inflammation in DSS-IBD mice. Quantitative IHC image analysis for CD45. **A)** Fractional (%) area of CD45. **B)** Total volume (mm^3) of CD45. **: P < 0.01, ***: P < 0.001 compared to CTRL.

4 Colon fibrosis

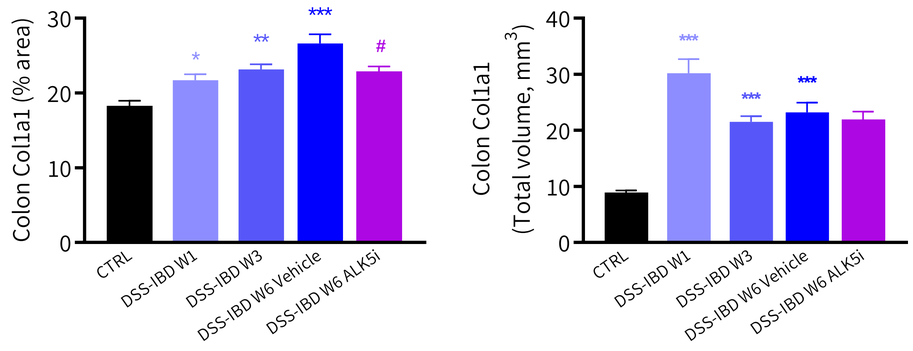


Figure 4. Quantitative histological markers of colon fibrosis in DSS-IBD mice. Quantitative IHC image analysis for Col1a1. **A)** Fractional (%) area of Col1a1. **B)** Total volume (mm^3) of Col1a1. *: P < 0.05, **: P < 0.01, ***: P < 0.001 compared to CTRL.. #: P < 0.05 compared to DSS-IBD W6 vehicle.

5 Histopathological markers

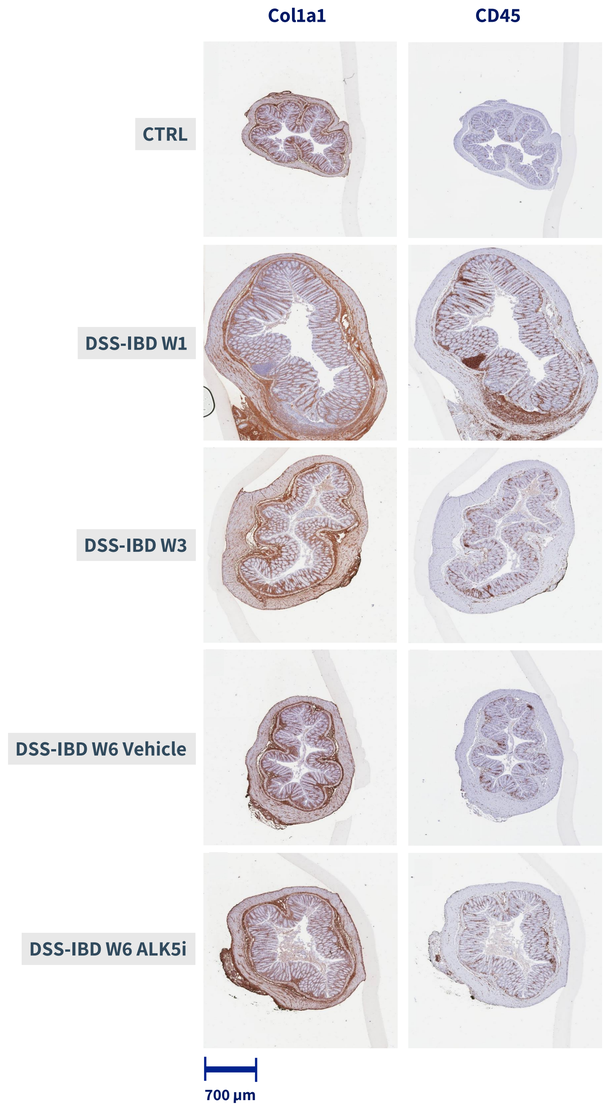


Figure 5. Representative photomicrographs demonstrating histological markers of inflammation and fibrosis in DSS-IBD mice. Colon sections stained for markers of fibrosis (Col1a1) and inflammation (CD45). Objective 4x, scale bar = 700 µm.

6 Colon transcriptome signatures

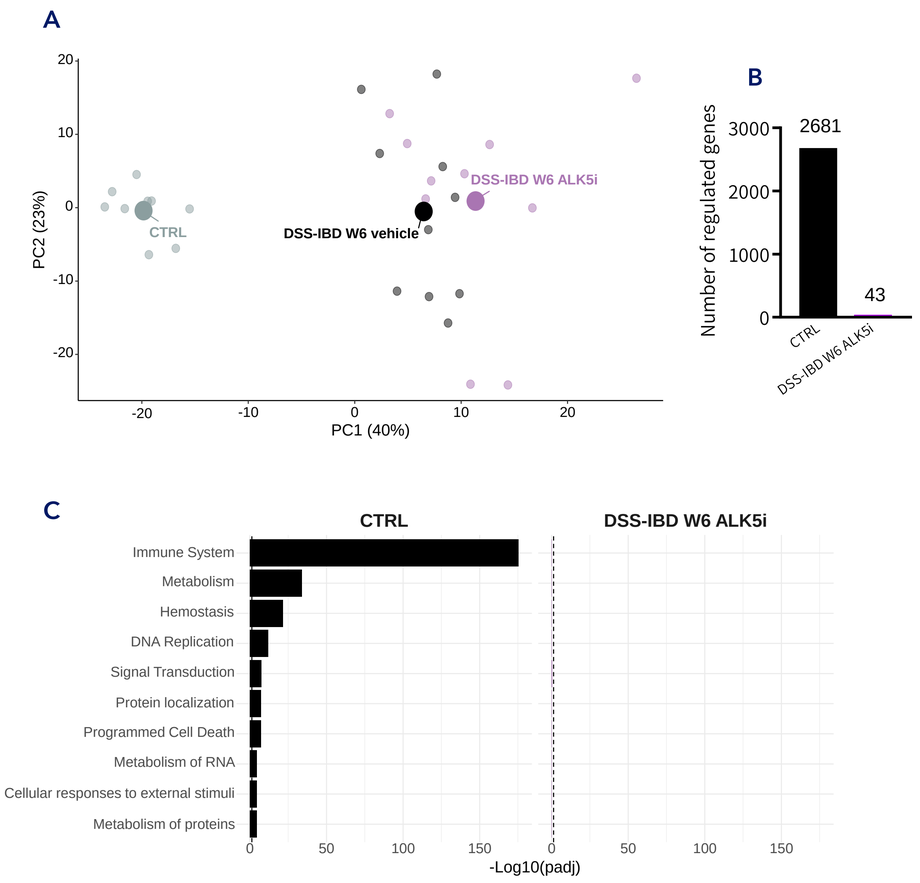


Figure 6. Colon RNA sequencing analysis DSS-IBD mice. **A)** Principal component analysis of the 500 most variable genes. **B)** Total number of differentially expressed genes mice compared to DSS-IBD W6 vehicle. **C)** Top-10 regulated Reactome Pathways (according to statistical significance, p<0.05 indicated as vertical dotted line in plot) compared to DSS-IBD W6 vehicle.