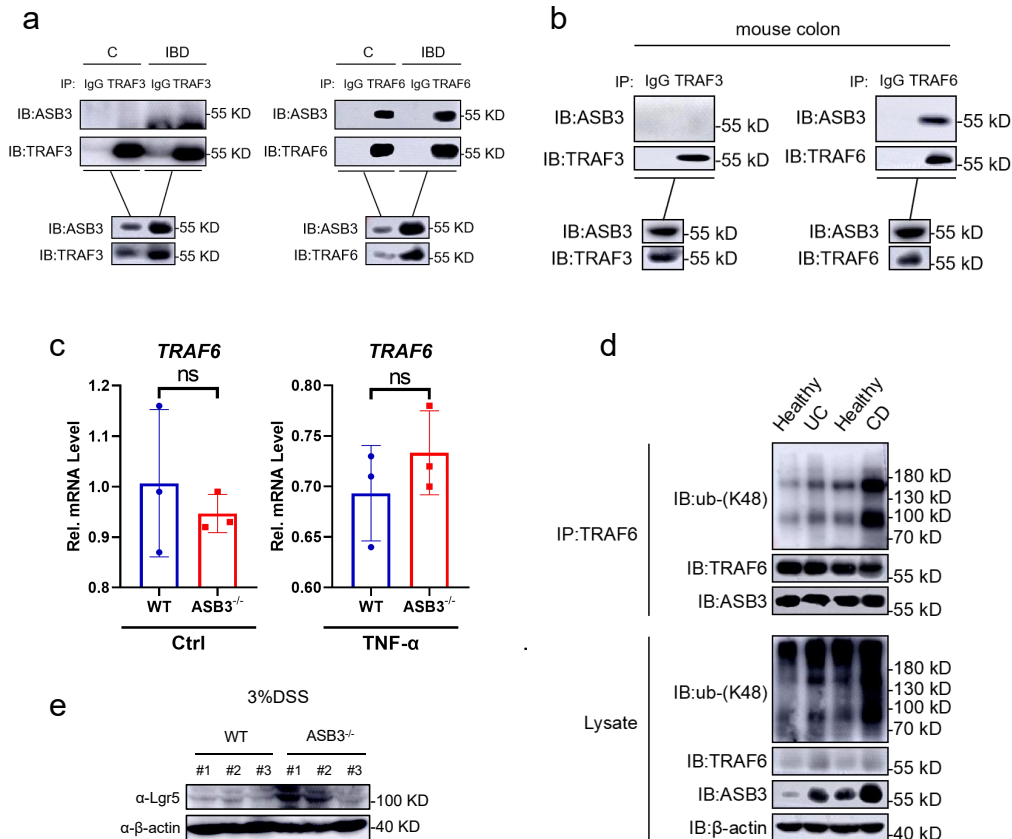
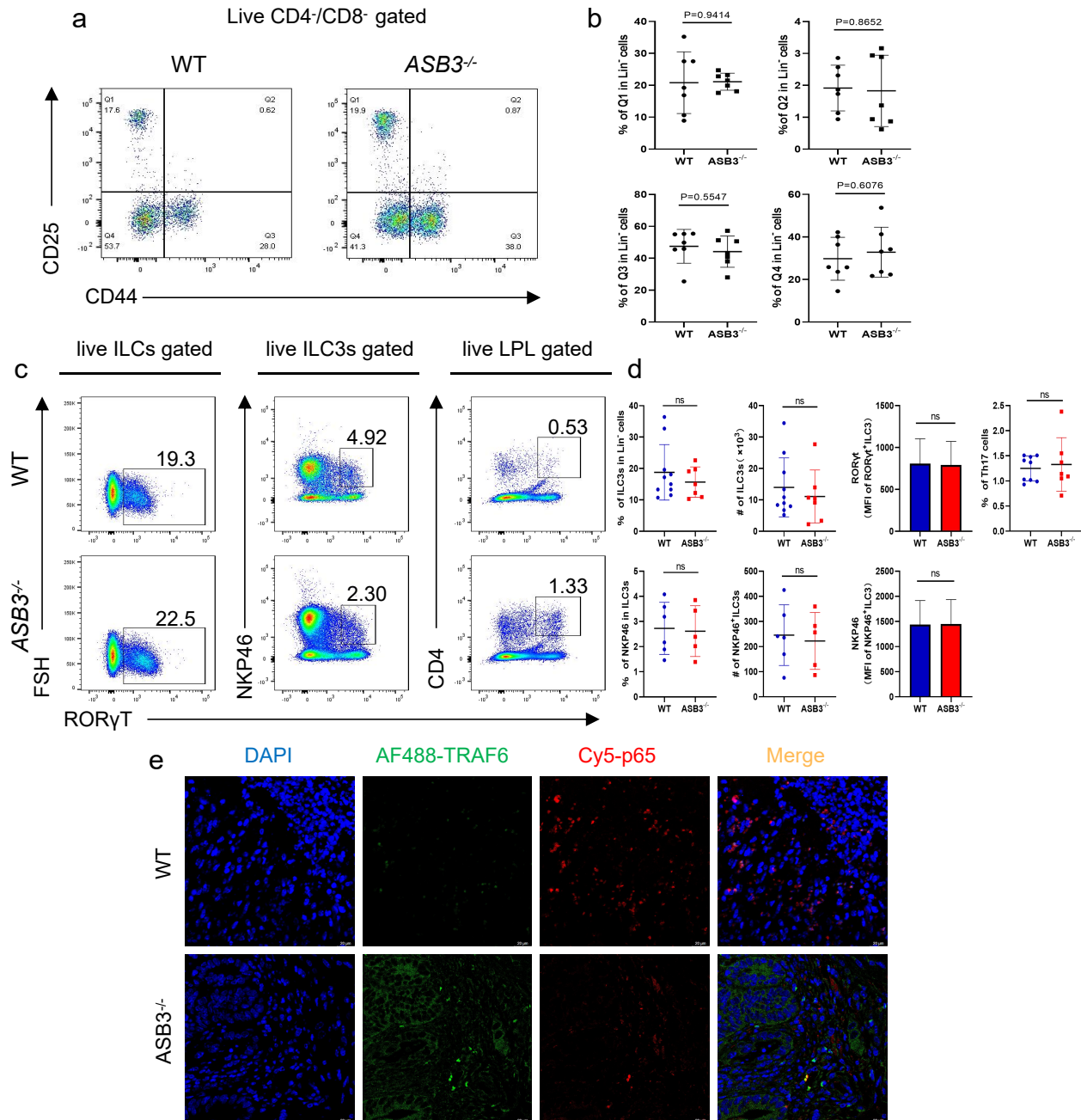


**Supplementary Fig. 1** (a) The transcription levels of ASB3 in colon adenocarcinoma (TCGA). (b, c) Colon length of WT and ASB3<sup>-/-</sup> mice treated without DSS. (d) Representative images of pathological H&E stained colon sections collected. Scale bar, 100  $\mu$ m. (e, f) The protein expression of p-I $\kappa$ B $\alpha$ , I $\kappa$ B $\alpha$ , and  $\beta$ -actin was detected by Western blotting.



**Supplementary Fig. 2** (a) Total colonic tissue proteins from healthy and IBD samples. (b) Total colonic tissue proteins from DSS-treated mice. The samples were used in Co-IP assays with the indicated antibodies. (c) The mRNA expression levels of TRAF6 in organoids were determined by qPCR assay. (d) Total colonic tissue proteins from healthy and IBD samples. The samples were used in ubiquitination assays with the indicated antibodies. (e) Western blotting was used to analyze Lgr5 protein expression in colons harvested from WT and ASB3<sup>-/-</sup> mice.



**Supplementary Fig. 3** (a, b) Frequencies of CD44<sup>-</sup>CD25<sup>+</sup>, CD44<sup>+</sup>CD25<sup>+</sup>, CD44<sup>+</sup>CD25<sup>-</sup> and CD44<sup>-</sup>CD25<sup>-</sup> T-cells in thymuses from WT and ASB3<sup>-/-</sup> mice. (c, d) Frequencies, absolute number and MFI of RORγT<sup>+</sup> ILC3s, NKp46<sup>+</sup> ILC3s and Th17 cells in cLPLs from WT and ASB3<sup>-/-</sup> mice. (e) Colon tissues were analysed on day 8 from WT and ASB3<sup>-/-</sup> mice and imaged by confocal microscopy after immunofluorescent staining for TRAF6 (green), NF-κB p65 (red) and DAPI (blue). Scale bar, 20 μm.