c-Jun N-terminal kinase 2 promotes enterocyte survival and goblet cell differentiation in the inflamed intestine

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Background: c-Jun N-terminal kinases (JNKs) contribute to immune signalling but their functional role during intestinal mucosal inflammation has remained ill defined. Using genetic mouse models we characterized the role of JNK1 and JNK2 during homeostasis and acute colitis.

Materials and methods: Epithelial apoptosis, regeneration, differentiation and barrier function were analysed in intestinal epithelium-specific (ΔIEC) or complete JNK1 and bone-marrow chimeric or complete JNK2 deficient mice as well as double knockout animals ($JNK1^{\Delta IEC}JNK2^{-/-}$) during homeostasis and acute dextran sulfate sodium (DSS)-induced colitis. Results were confirmed using human HT-29 cells and wildtype (WT) or JNK2 deficient mouse intestinal organoid cultures.

Results:

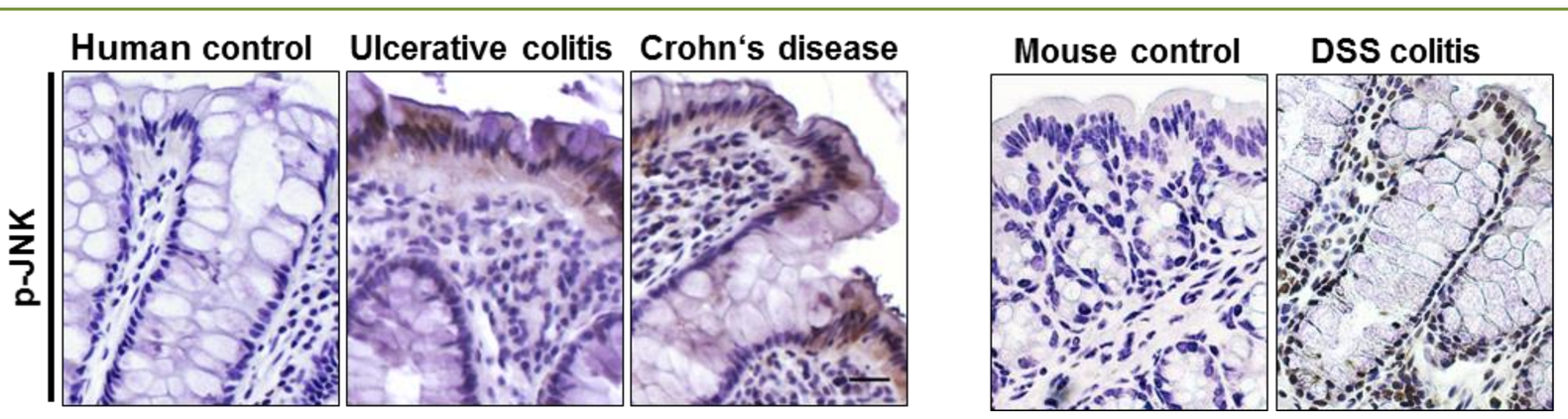


Figure 1. JNK activation in human and mouse colitis.

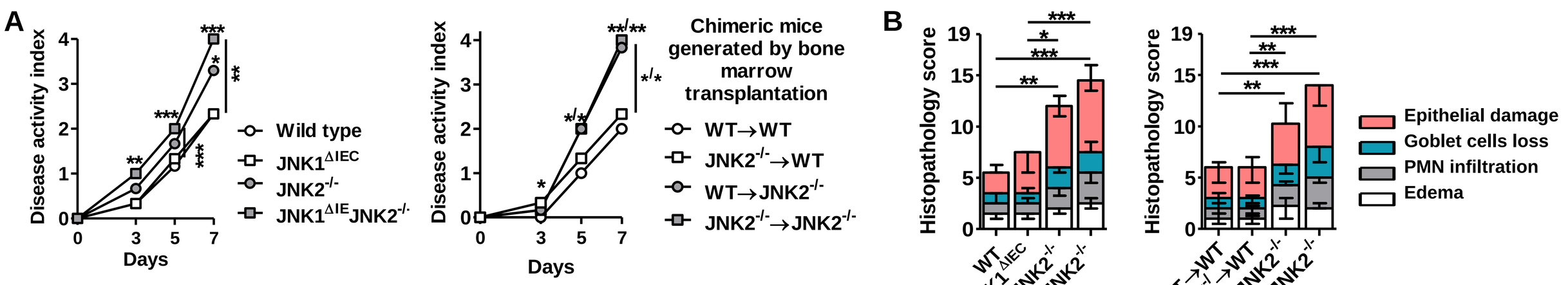


Figure 2. Non-hematopoietic JNK2 confers protection from DSS-induced colonic injury. **(A)** Disease activity score (combined score of weight loss, stool consistency, and bleeding. **(B)** Histopathology score.

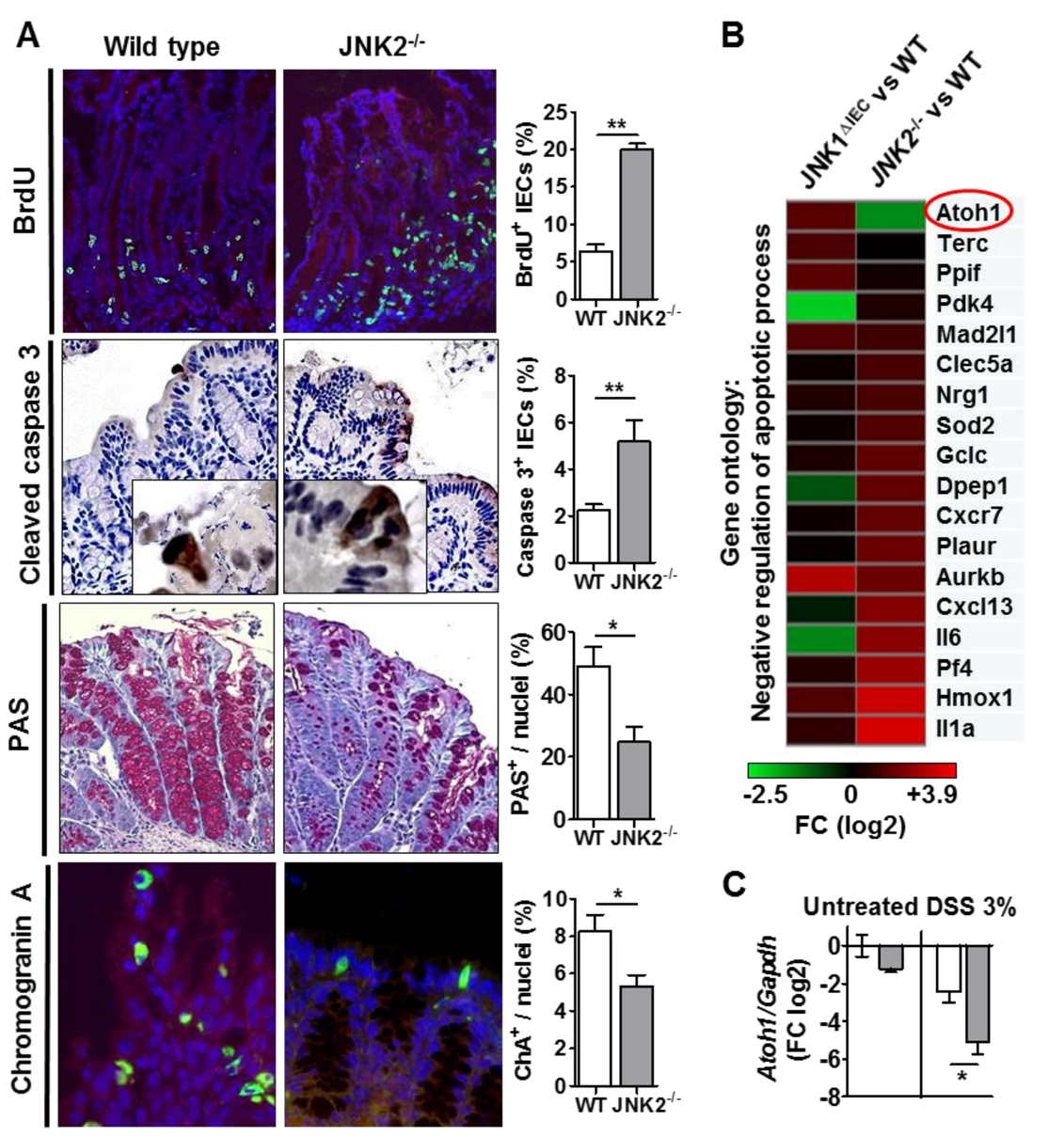


Figure 3. (A) Increased colonic epithelial cell proliferation and apoptosis and reduced goblet and enteroendocrine cell numbers in DSS-exposed $JNK2^{-/-}$ mice. **(B)** Significantly regulated antiapoptotic genes in DSS-treated $JNK1^{\Delta IEC}$ and $JNK2^{-/-}$ compared to WT mice (Affimetrix mRNA gene array). **(C)** RT-PCR confirms downregulation of *Atoh1* in DSS-treated $JNK2^{-/-}$ mice.

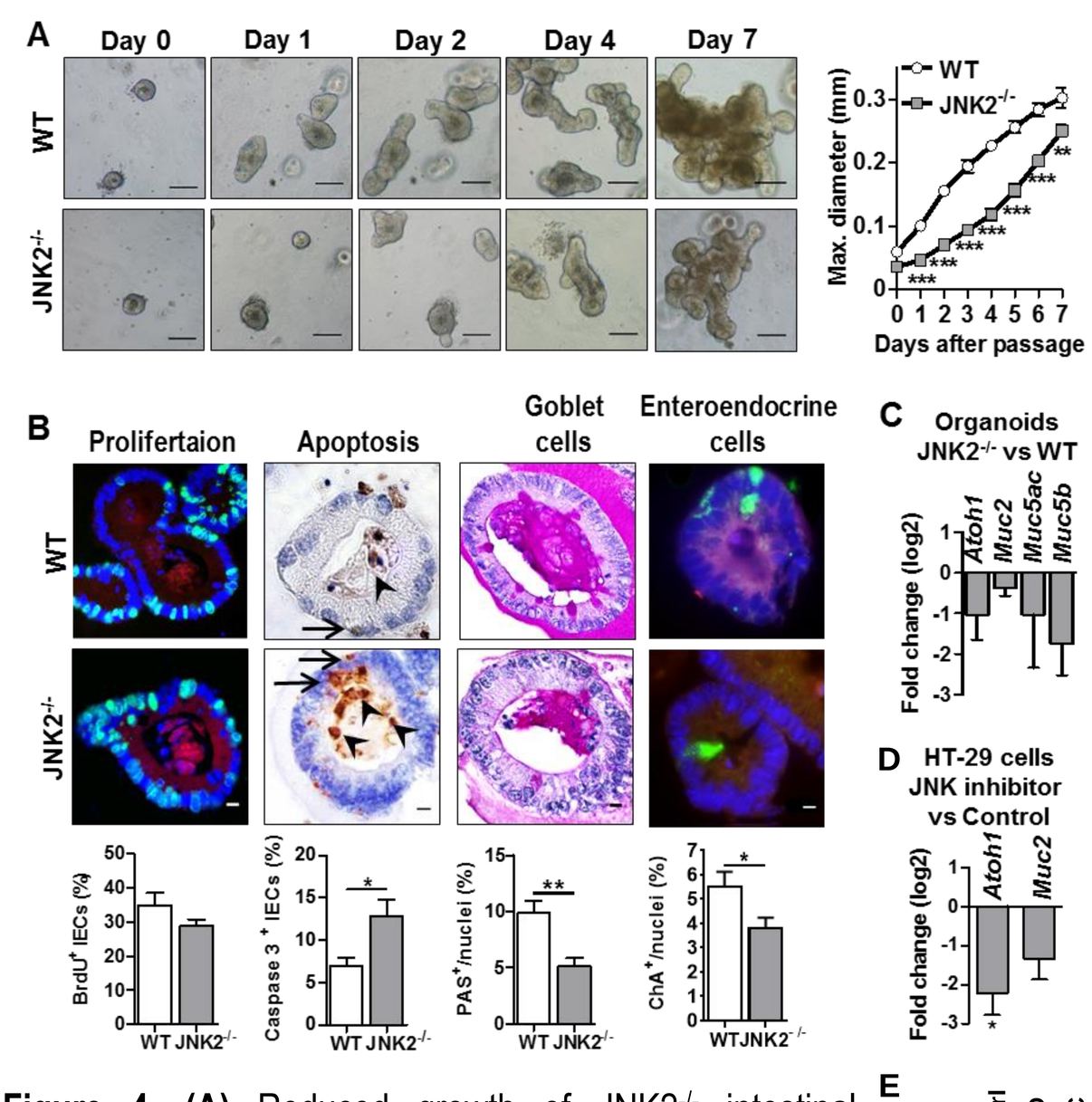
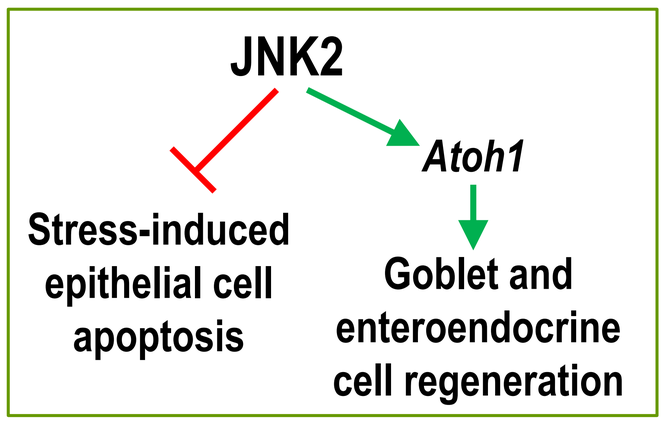


Figure 4. (A) Reduced growth of $JNK2^{-/-}$ intestinal organoids is associated with **(B)** increased apoptosis, impaired goblet and enteroendocrine cell differentiation and **(C)** decreased *Athoh1* and mucin mRNA expression. **(D)** *Atoh1* and *Muc2* expression in JNK Inhibitor treated colon epithelial cells. **(E)** Colonic *Atoh1* expression in IBD patients. Crohn's disease (CD); Ulcerative colitis (UC).

Conclusions: We show that non-hematopoetic JNK2 but not JNK1 expression confers protection from DSS-induced intestinal inflammation reducing epithelial barrier dysfunction and enterocyte apoptosis. JNK2 additionally enhanced Atonal homolog 1 (*Atoh1*) expression, a transcription factor supporting goblet and enteroendocrine cell differentiation. Our results identify a protective role of epithelial JNK2 signalling to maintain mucosal barrier function, epithelial cell integrity and mucus layer production in the event of inflammatory tissue damage.



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SEVENTH FRAMEWORK PROGRAMME

SysmedIBD