European Crohn's and Colitis Organisation

Innate mesenchymal MyD88 signals promote spontaneous intestinal tumorigenesis

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Conflict of interest :

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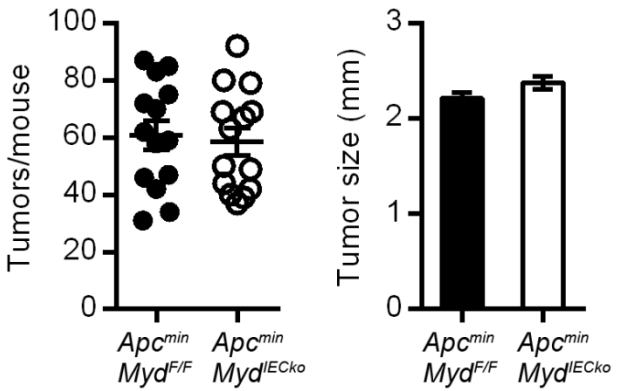
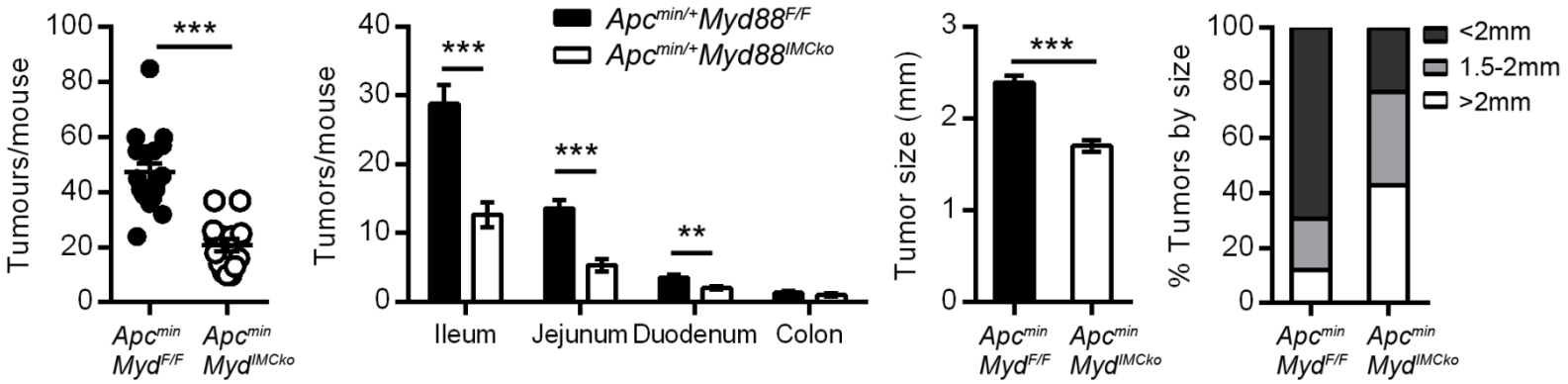
Background

- Antibiotic treatment or germ-free *Apc*$^{min/+}$ mice results in reduced tumor load → important tumor promoting role of the microbiota in intestinal tumorigenesis (Dove et al., 1997; Li et al., 2012; Song et al., 2014).
- Genetic deletion of MyD88 in *Apc*$^{min/+}$ mice results in reduced number and size of tumors and correlates with suppressed proliferation, enhanced apoptosis and a deregulated gene expression profile in tumors (Rakoff-Nahoum and Medzhitov, 2007).
- Bone marrow chimeras have shown that polyp growth in *Apc*$^{min/+}$ mice depends on MyD88 signaling in non-hematopoietic cells (Lee et al., 2010)

Deletion of MyD88 in IECs does not affect tumorigenesis in the APC^{min} mouse model

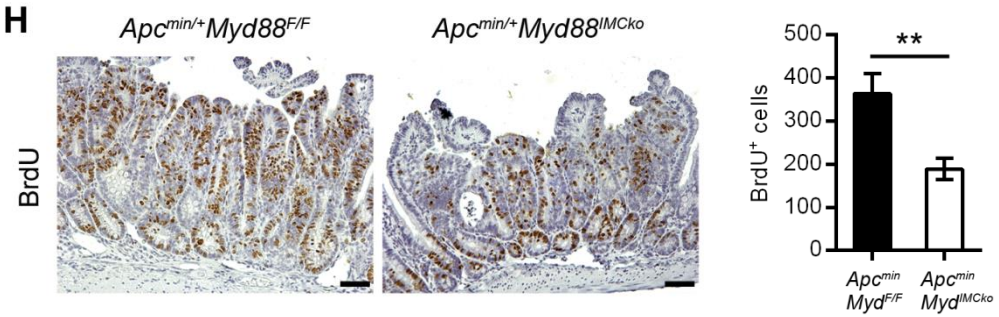


Deletion of MyD88 in IMCs reduces spontaneous tumorigenesis in the APC^{min} mouse model

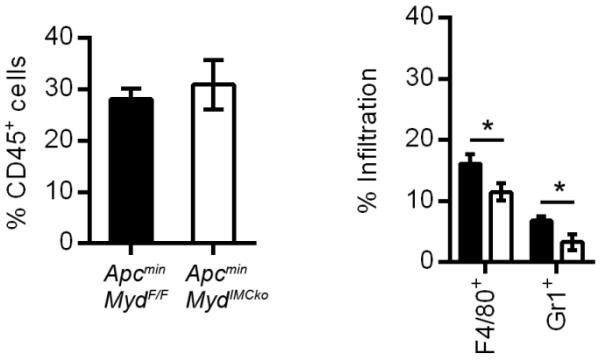


Deletion of MyD88 in IMCs reduces spontaneous tumorigenesis in the APC^{min} mouse model

- Reduced proliferation

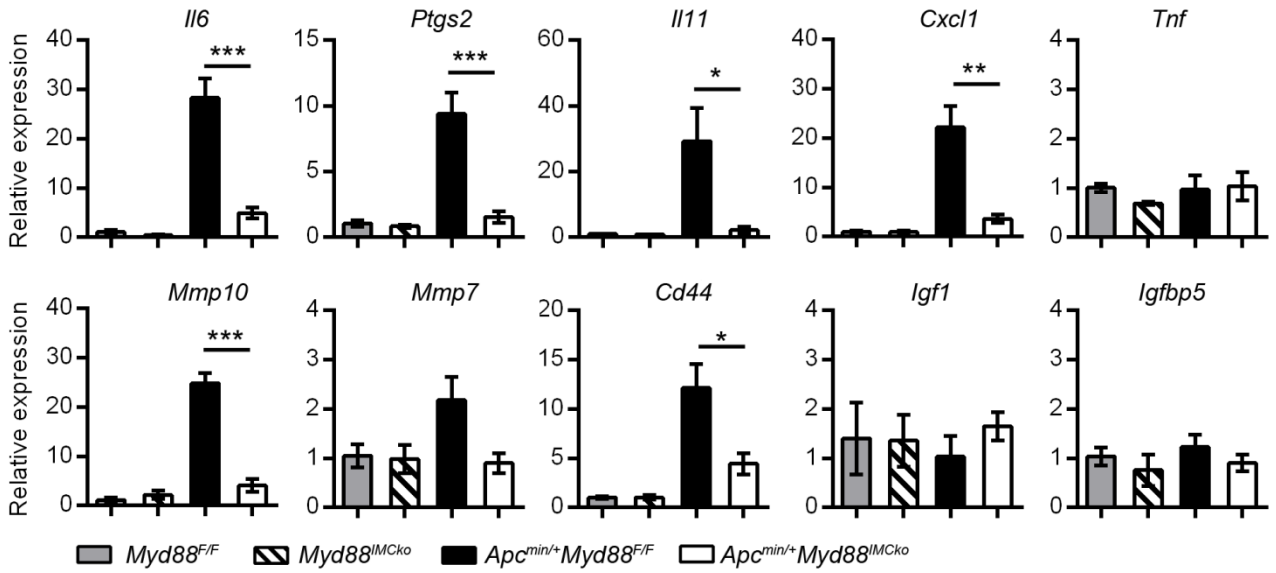


- Altered inflammatory cell infiltration



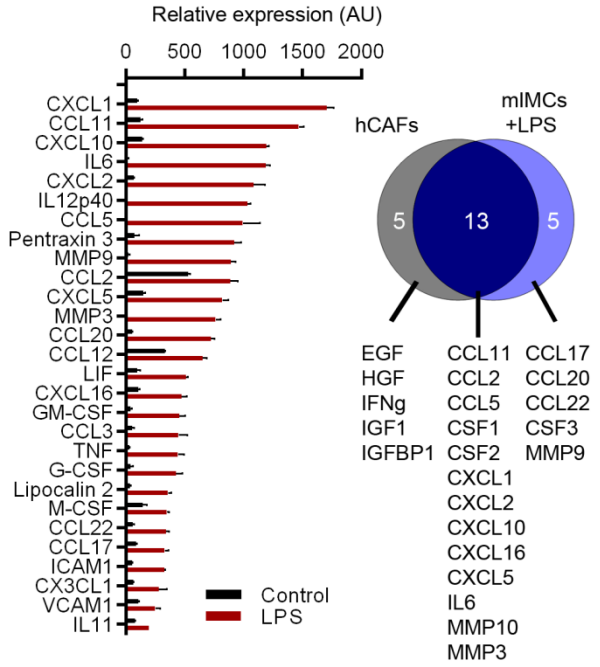
Deletion of MyD88 in IMCs reduces spontaneous tumorigenesis in the APC^{min} mouse model

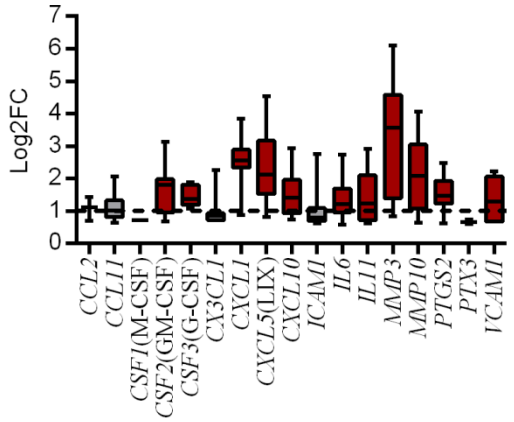
- Altered gene expression



Upstream innate sensing by fibroblasts leads to activation of inflammatory and ECM-regulating signature genes, also found in human CAFs

- LPS-induced secretome similar to human CAFs
- LPS-induced IMC signature in human colon cancer





Conclusions

Our results provide the first direct in vivo evidence that IMCs and cancer-associated fibroblasts are activated in response to innate stimuli and respond to orchestrate immunity and carcinogenesis in the intestine