

Journal club

Nod-like receptor pyrin domain-containing protein 6 (NLRP6) controls epithelial self-renewal and colorectal carcinogenesis upon injury

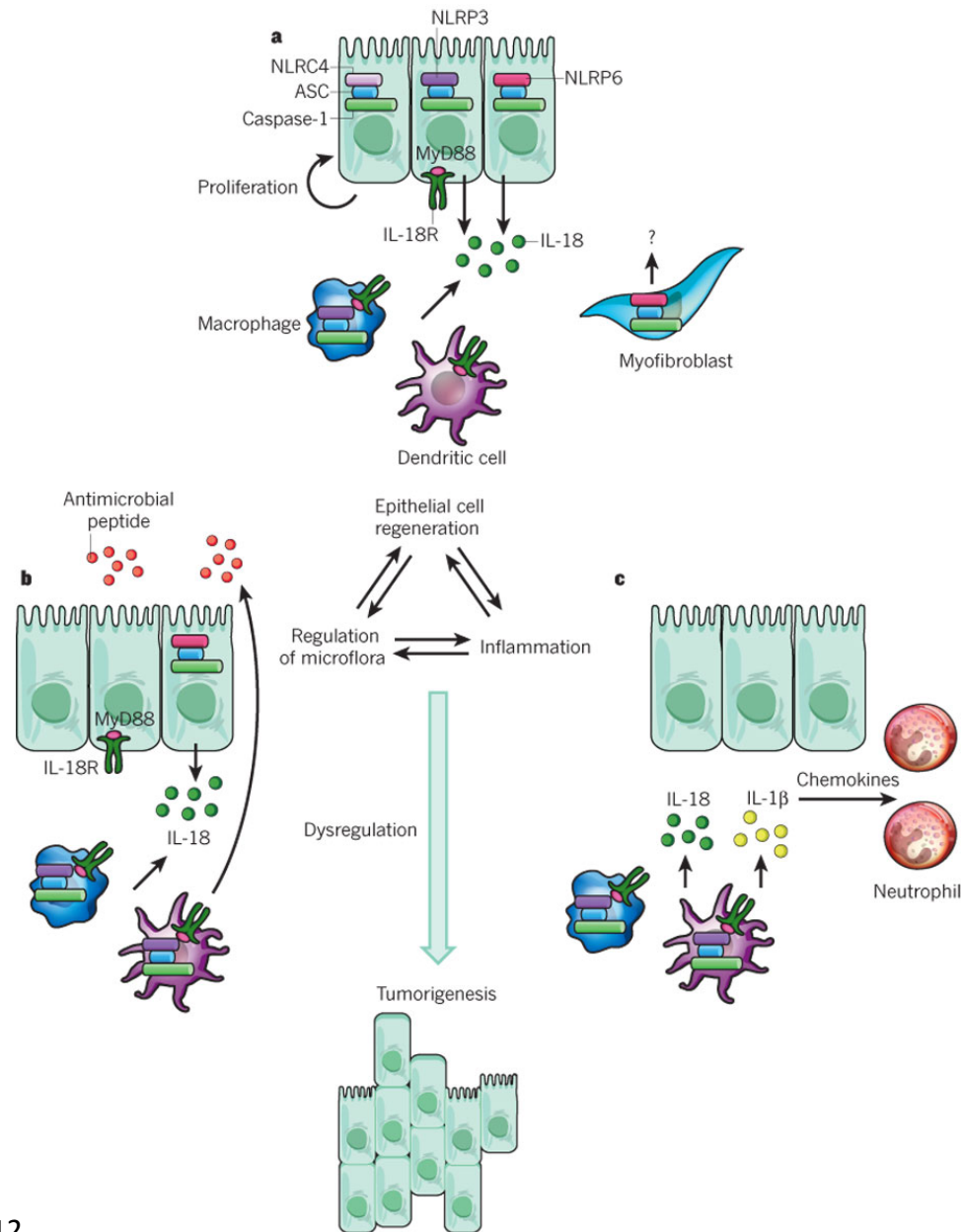
Sylvain Normand^{a,b,c,d}, Anne Delanoye-Crespin^{a,b,c,d}, Aude Bressenot^e, Ludovic Huot^{a,b,c}, Teddy Grandjean^{a,b,c,d}, Laurent Peyrin-Biroulet^e, Yves Lemoine^{a,b,c}, David Hot^{a,b,c}, and Mathias Chamaillard^{a,b,c,d,1}

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Francesca Ronchi

March, 15th 2013

Background



NLRP6 Is Essential for Wound Healing of the Intestinal Mucosa

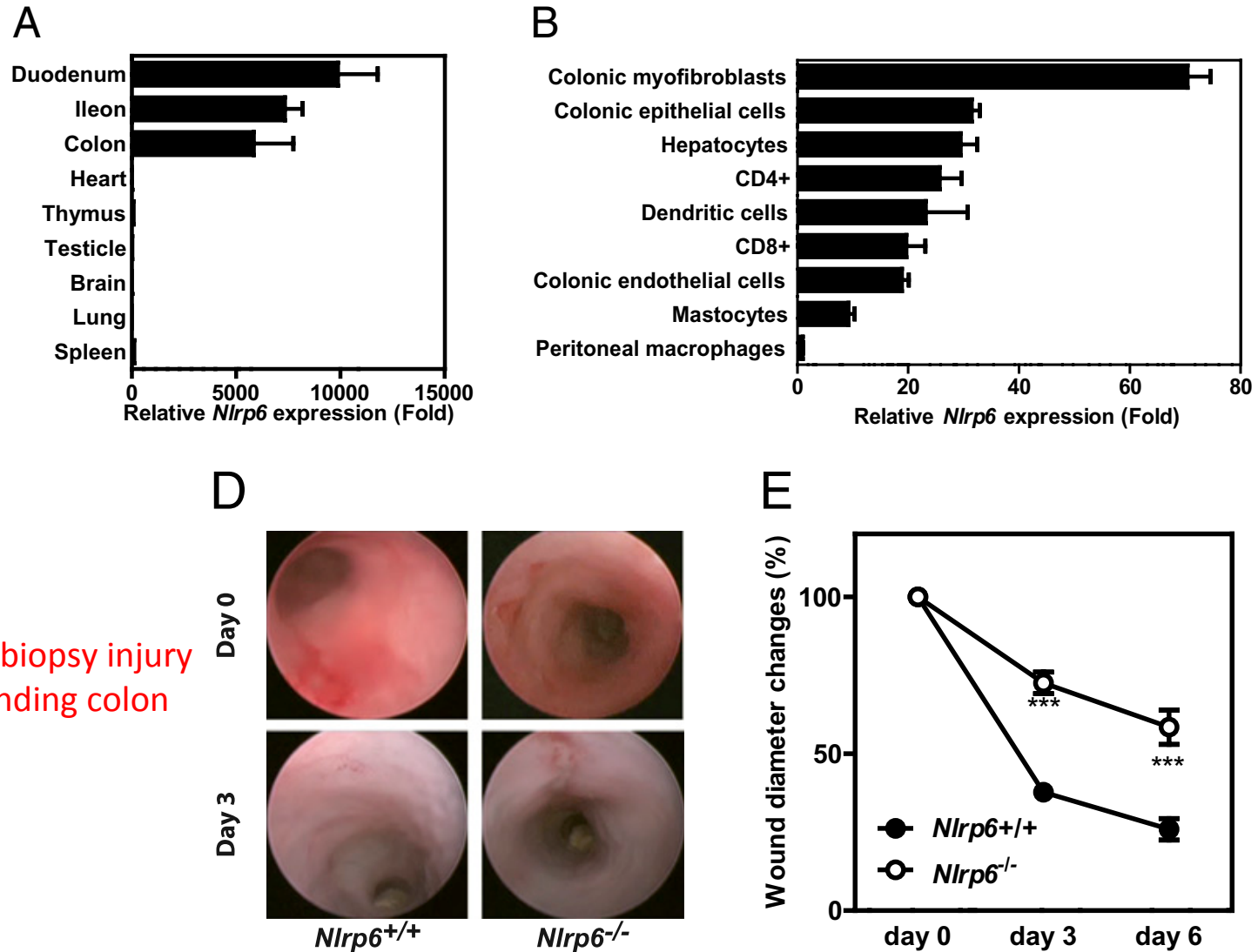


Fig.1

NLRP6 Prevents Relapsing Colitis

experimental model of
relapsing-remitting intestinal wounding:

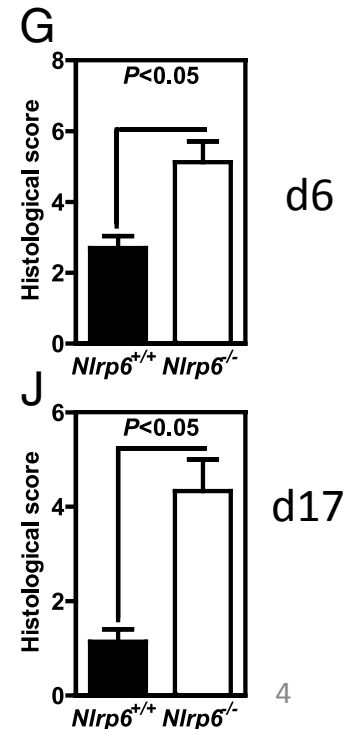
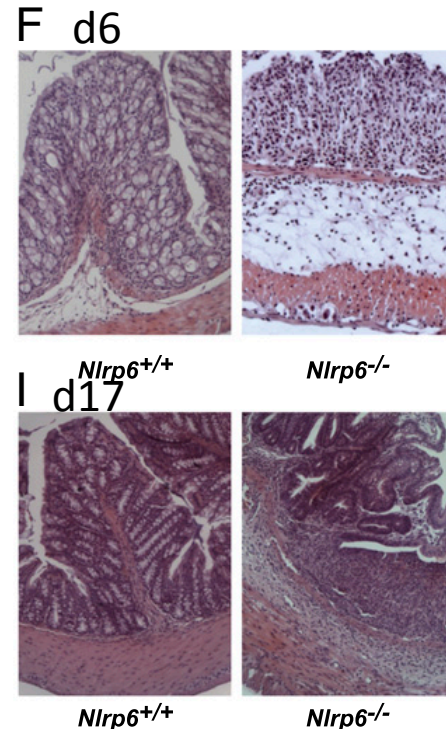
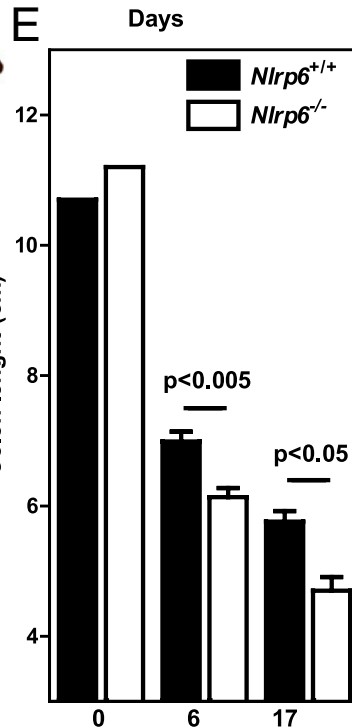
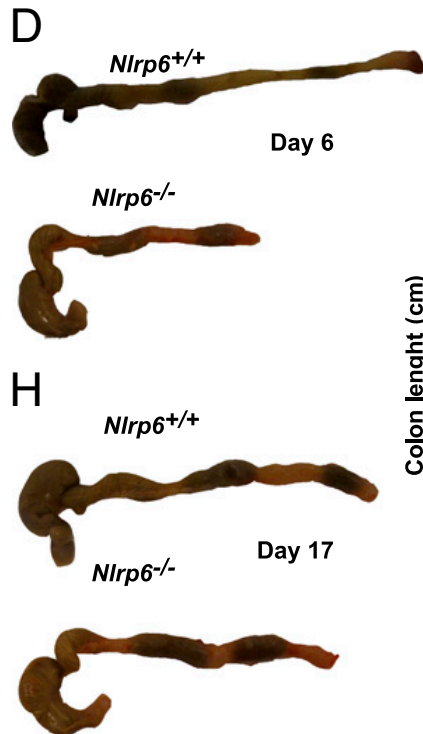
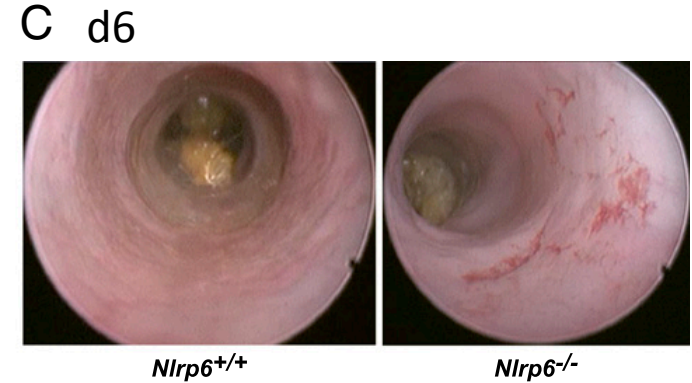
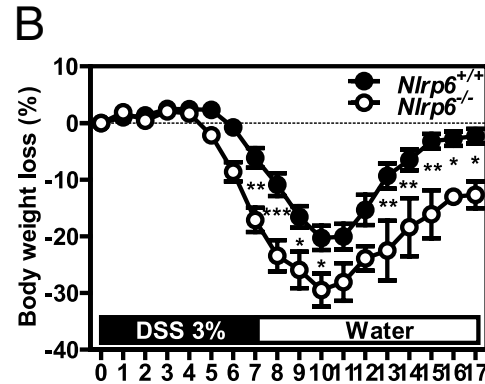
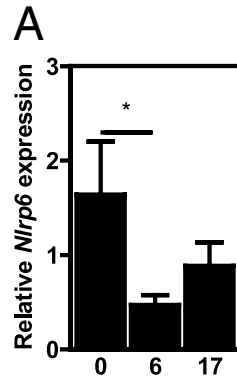
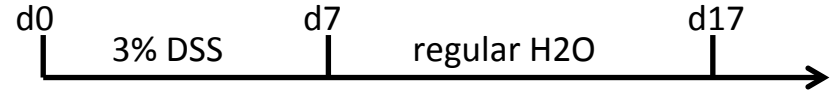
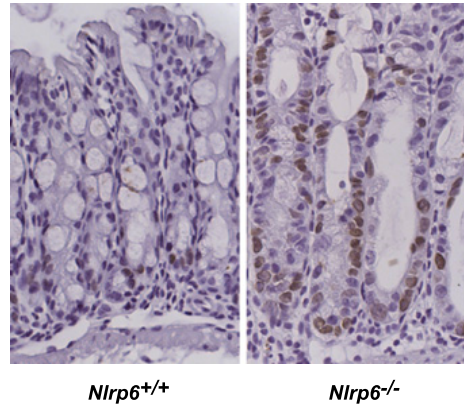


Fig.2

NLRP6 Controls Epithelial Cell Organization and Proliferation upon Injury.

B

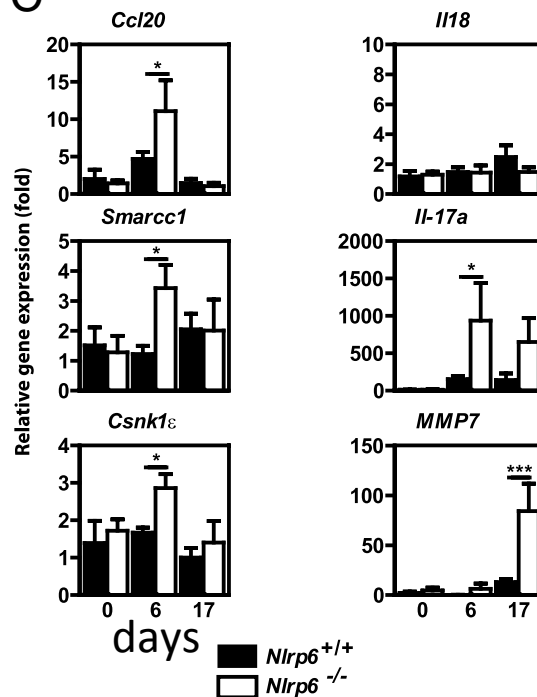
5 BrdU incorporation in the colon of DSS-treated animals after 1-h pulse-chase



C

Member of chromatin remodeling complex

Csnk1ε = tumor-suppressor gene Casein kinase ε that stabilizes β-catenin(involved in cell proliferation)



D

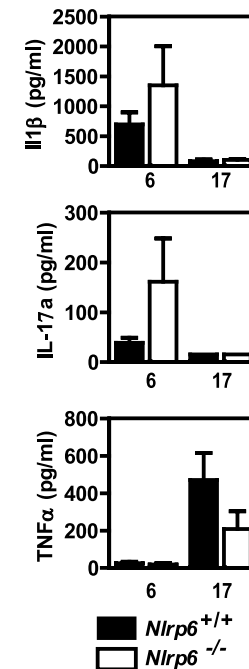


Fig.3

NLRP6 Is a Negative Regulator of Colorectal Tumorigenesis.

experimental model of colitis-associated CRC

d-5 AOM i.p. d0 2% DSS d5 regular H2O d12 x4

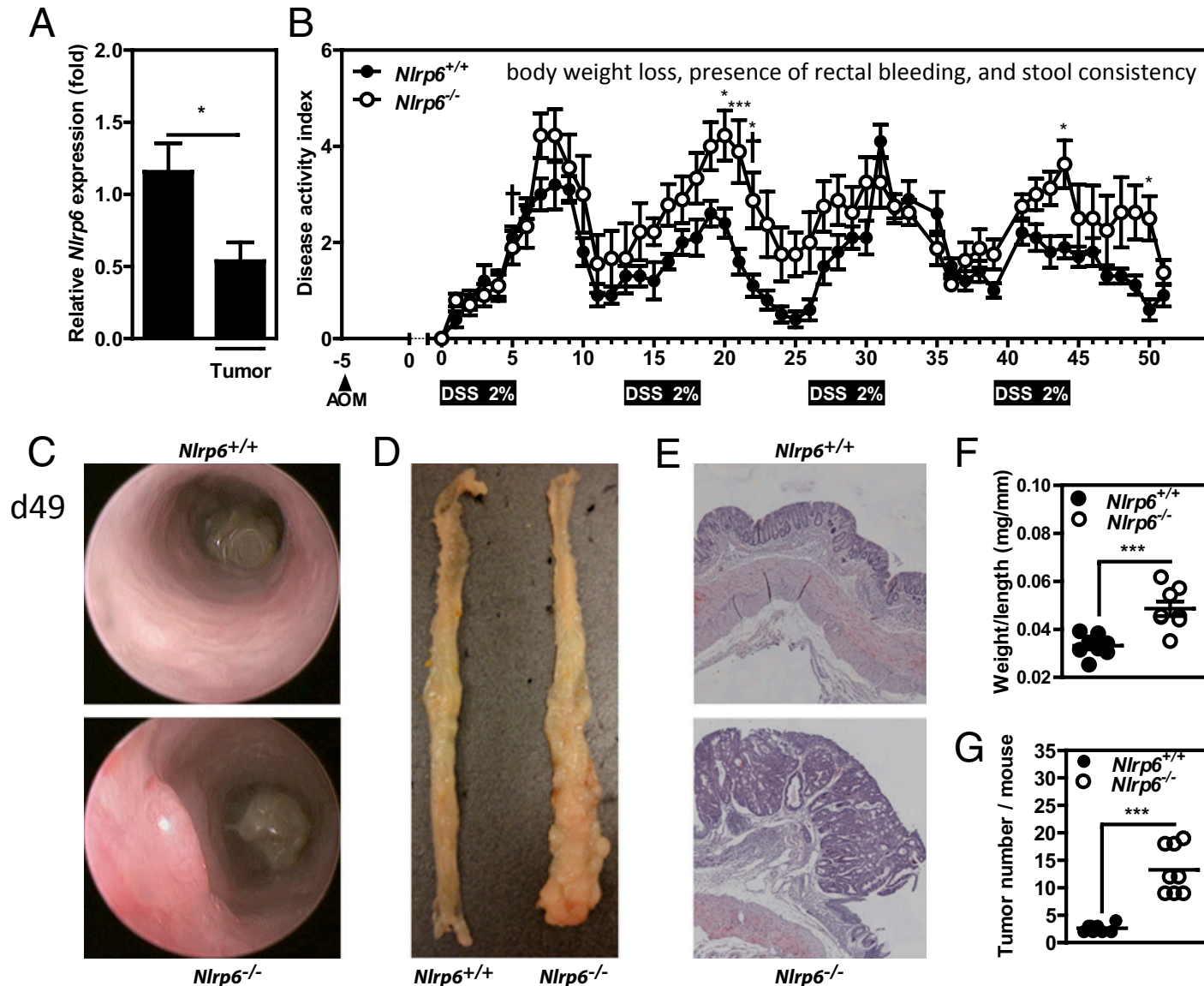
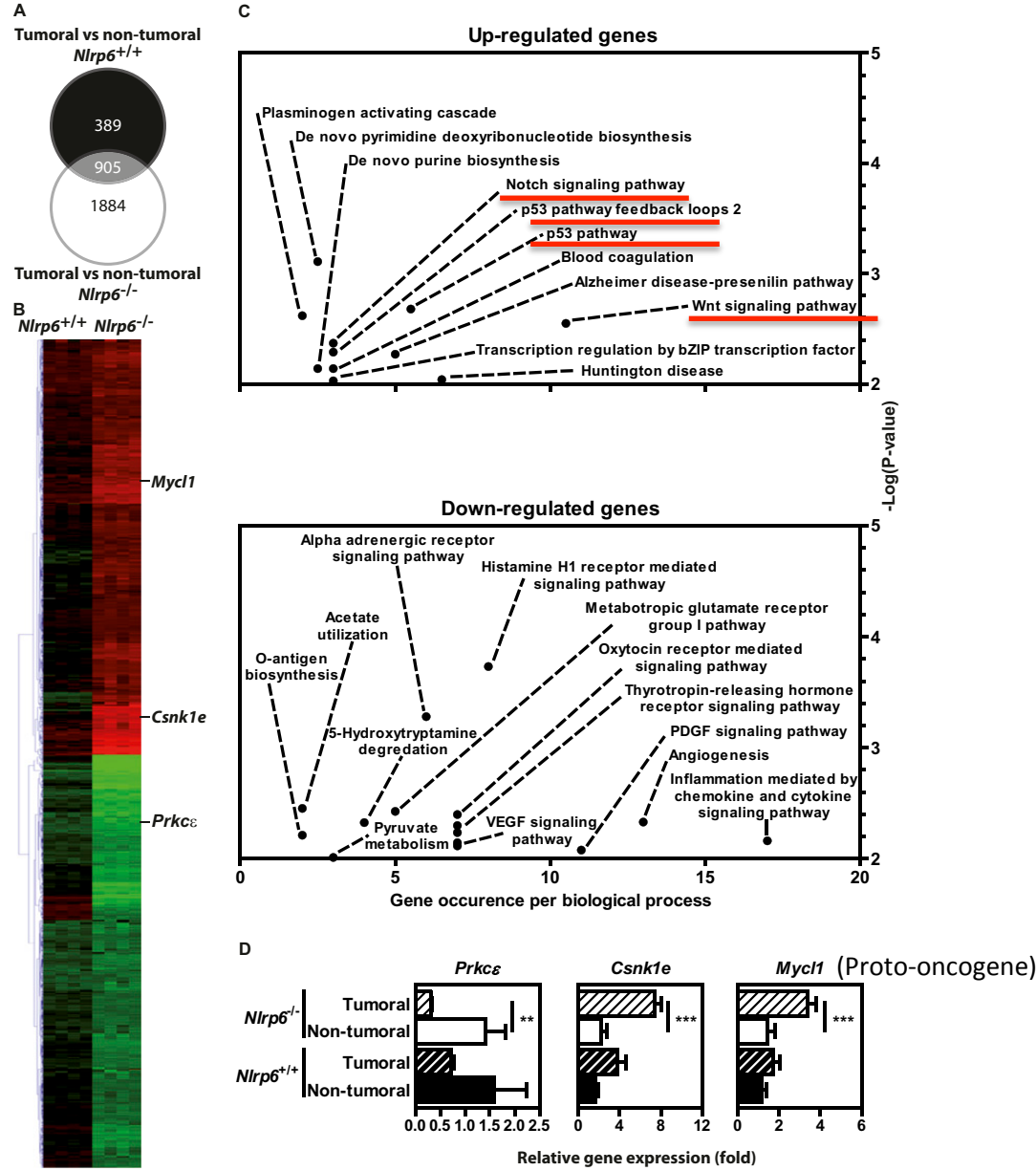


Fig.4

Genetic Ablation of NLRP6 Alters Expression of Paracrine Factors Involved in Colonic Epithelial Proliferation.



(Transcription factor in response to cell stress)

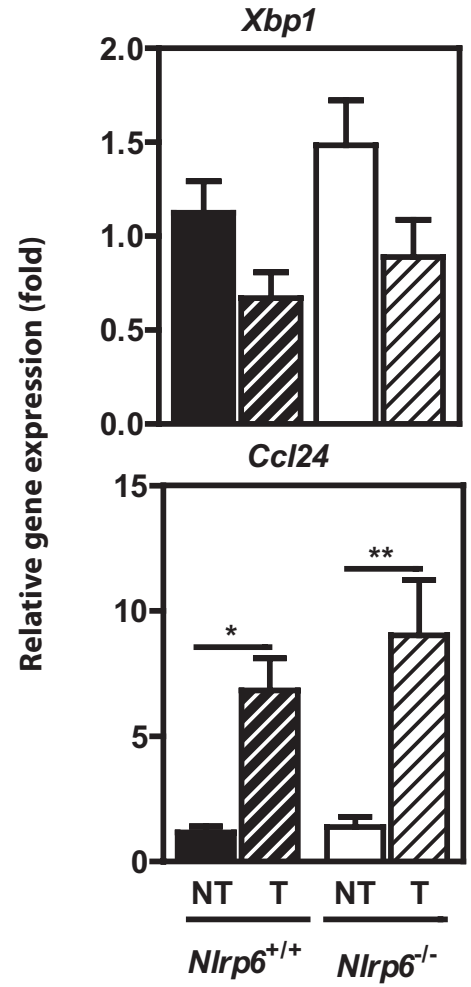


Fig.S3

Fig.S4

Conclusions

- NLRP6 is important in tissue repair.
- Lack of functional NLRP6-coupled inflammasome renders mice prone to develop relapsing colitis.
- The efficiency of the process of wound healing requires functional NLRP6 by regulating several processes involved in proliferation of the adjacent epithelia and in Th17 function.
- Nlrp6-/- mice develop more tumors than control after experimental chronic inflammation in an experimental model of colorectal tumorigenesis.
- NLRP6 may limit epithelial cell depolarization and tissue disintegration upon injury.

NLRP6 negatively regulates innate immunity and host defence against bacterial pathogens

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16 AUGUST 2012 | VOL 488 | NATURE | 389

Nlrp6^{-/-} mice are resistant to *Listeria* infection.

i.p. 10⁶ CFU *L. monocytogenes*

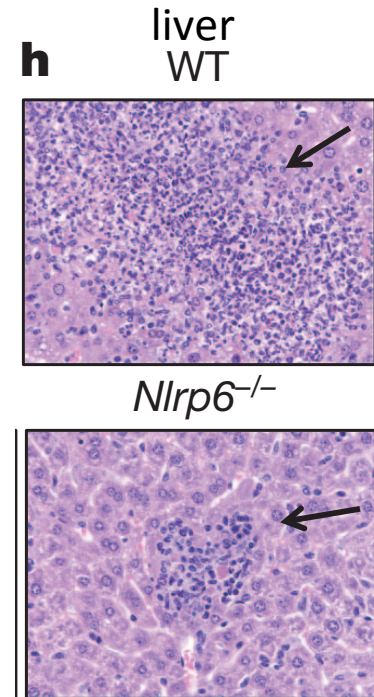
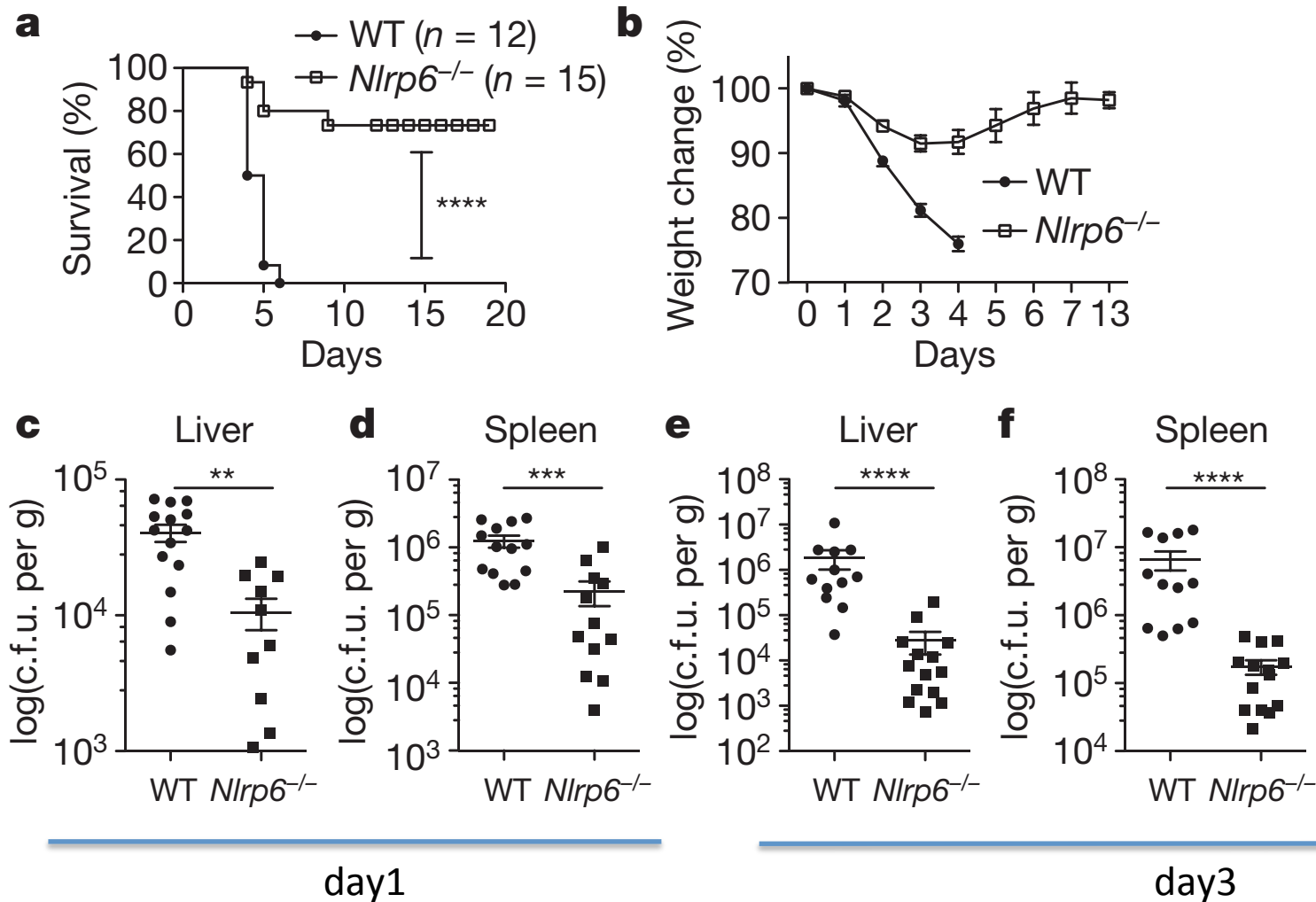
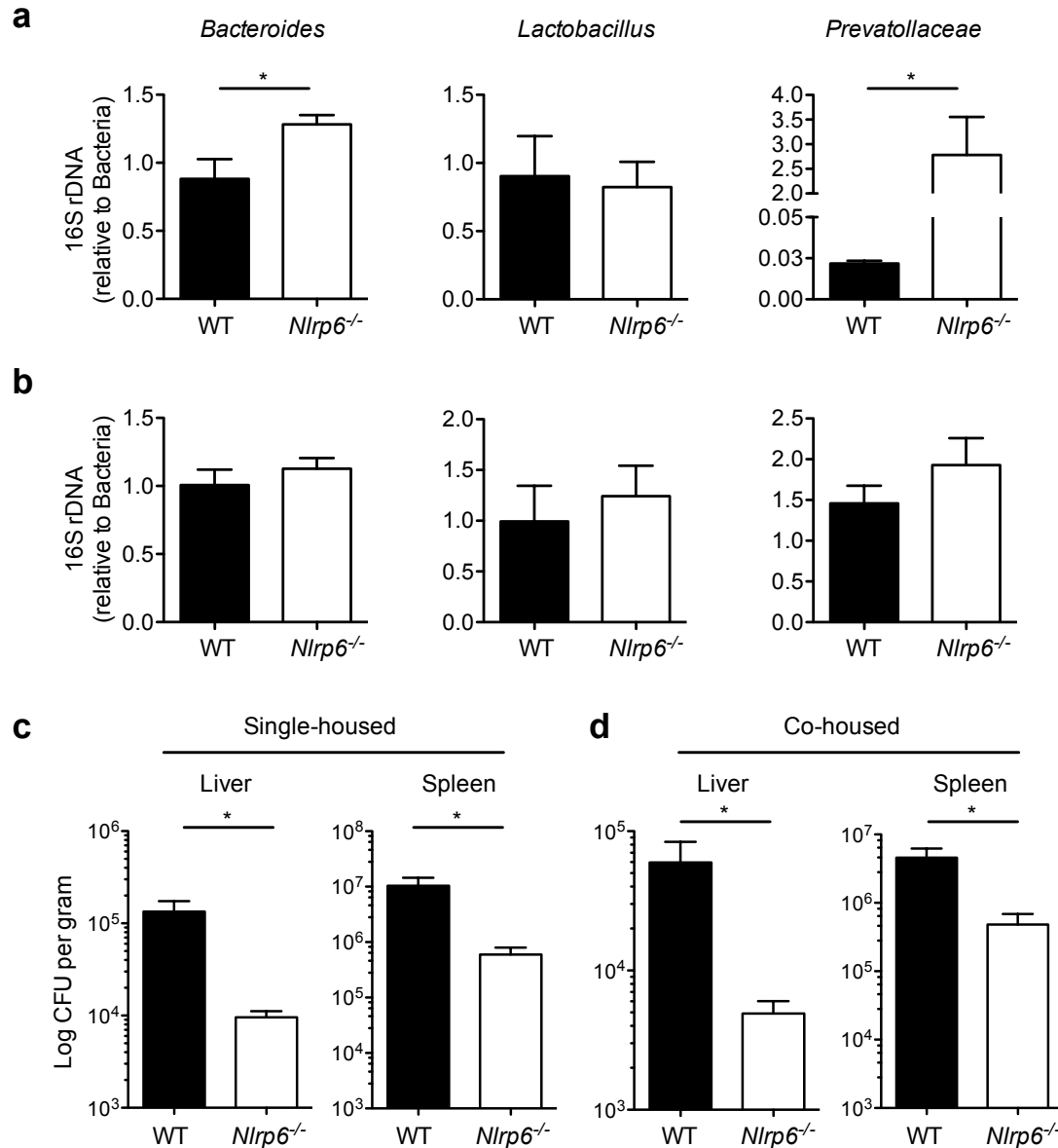


Fig.1

Nlrp6^{-/-} mice are resistant to *Listeria* infection independently of its microflora composition



Nlrp6^{-/-} mice are resistant also to *Salmonella* infection.

i.p. 10⁶ CFU *S. typhimurium*

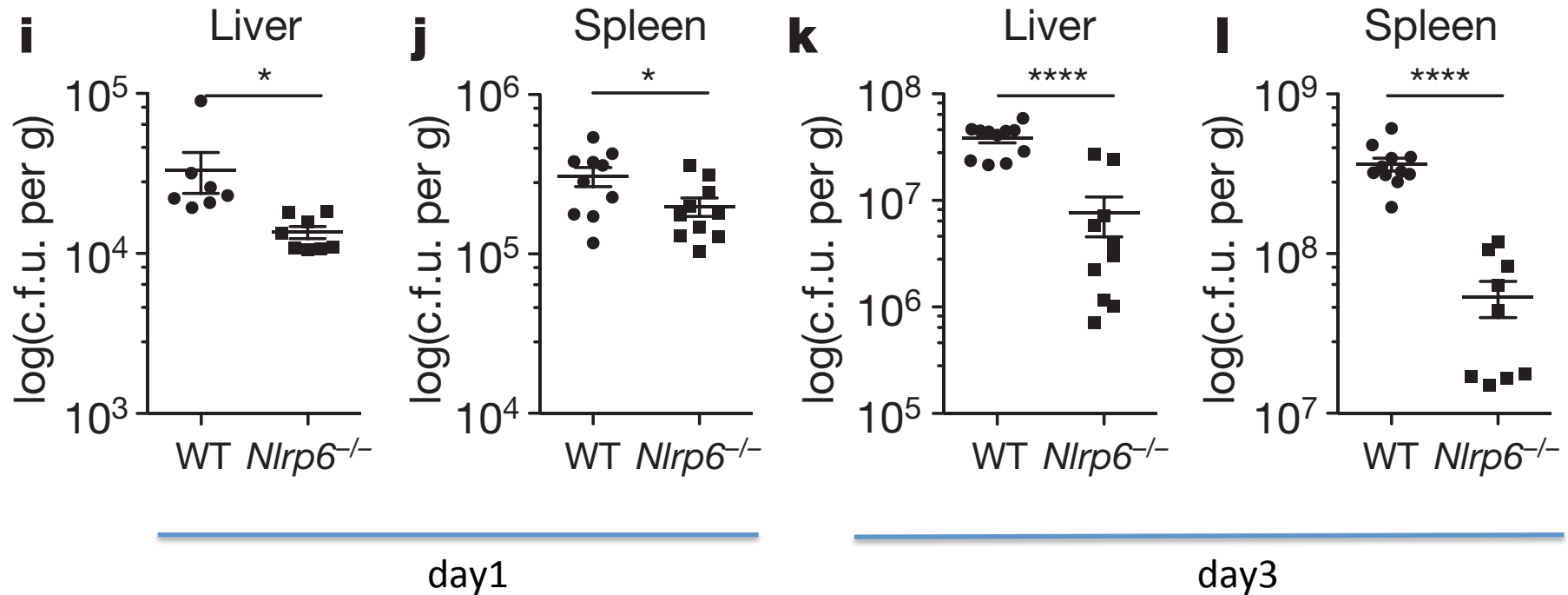
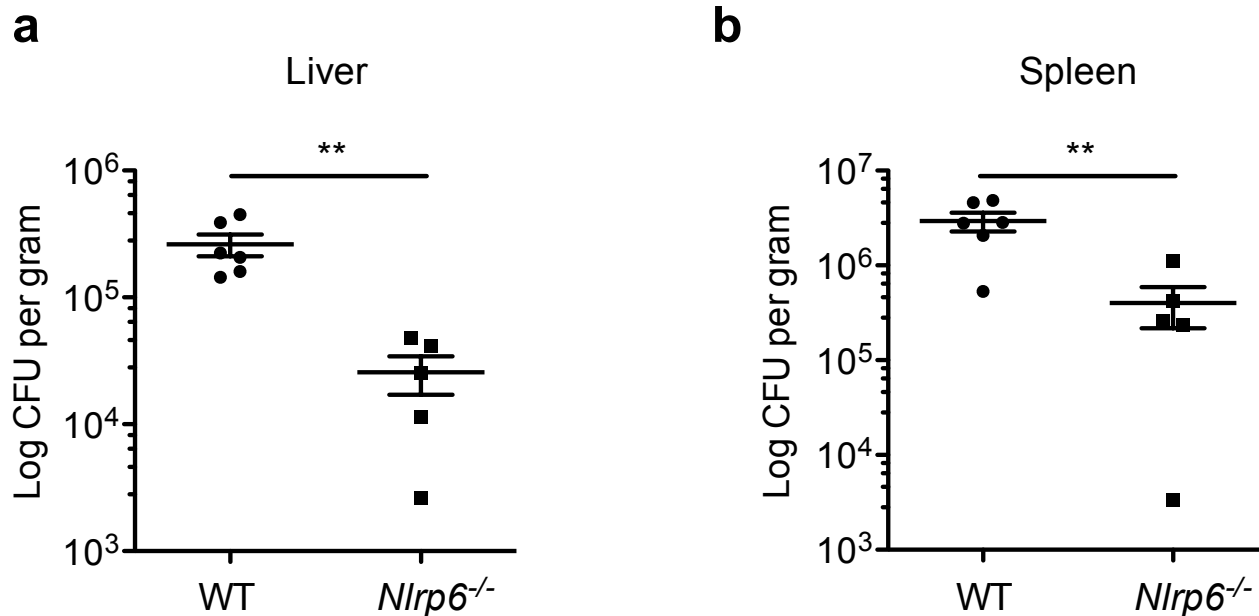


Fig.1

Nlrp6^{-/-} mice are resistant also to *E.coli* infection.

i.p. 5×10^7 CFU *E. coli*

day2

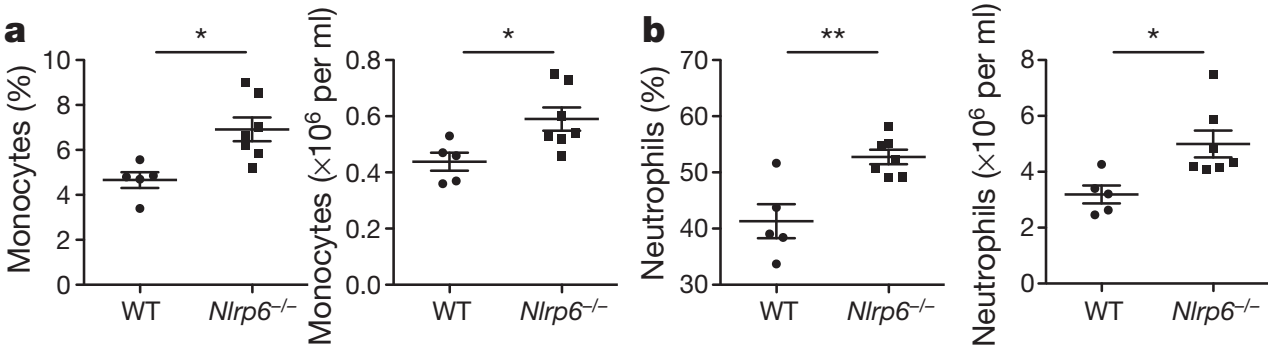


NLRP6 may promote systemic dissemination and growth of Gram- and Gram+ bacteria and of intra- and extra-cellular bacteria in infected host

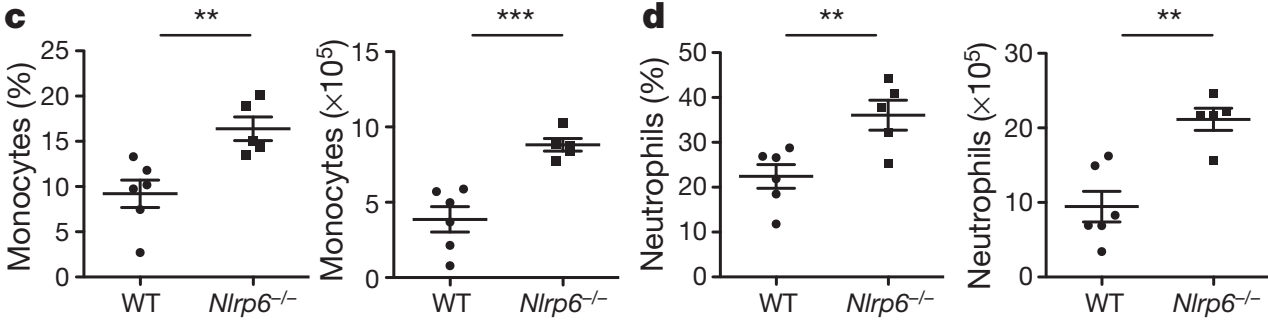
Enhanced monocyte and neutrophil recruitment in infected NLRP6^{-/-} mice

Listeria infection

Peripheral blood



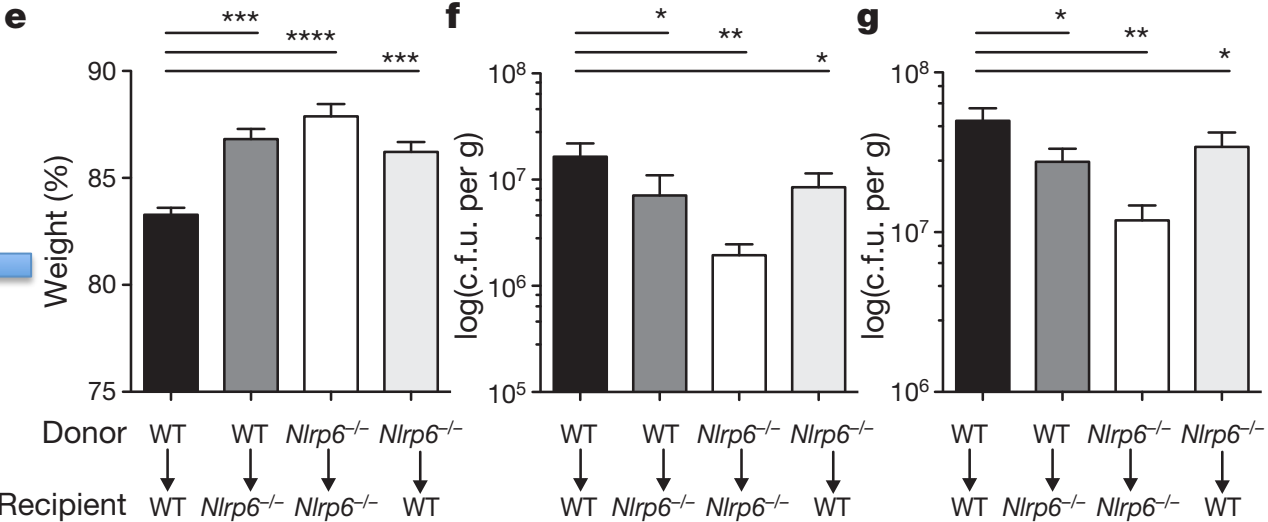
Peritoneal cavity
6 hrs p.i.



Weight

Liver

Spleen



Both hematopoietic and non hematopoietic cells contribute to NLRP6-mediated inhibition of bacterial clearance

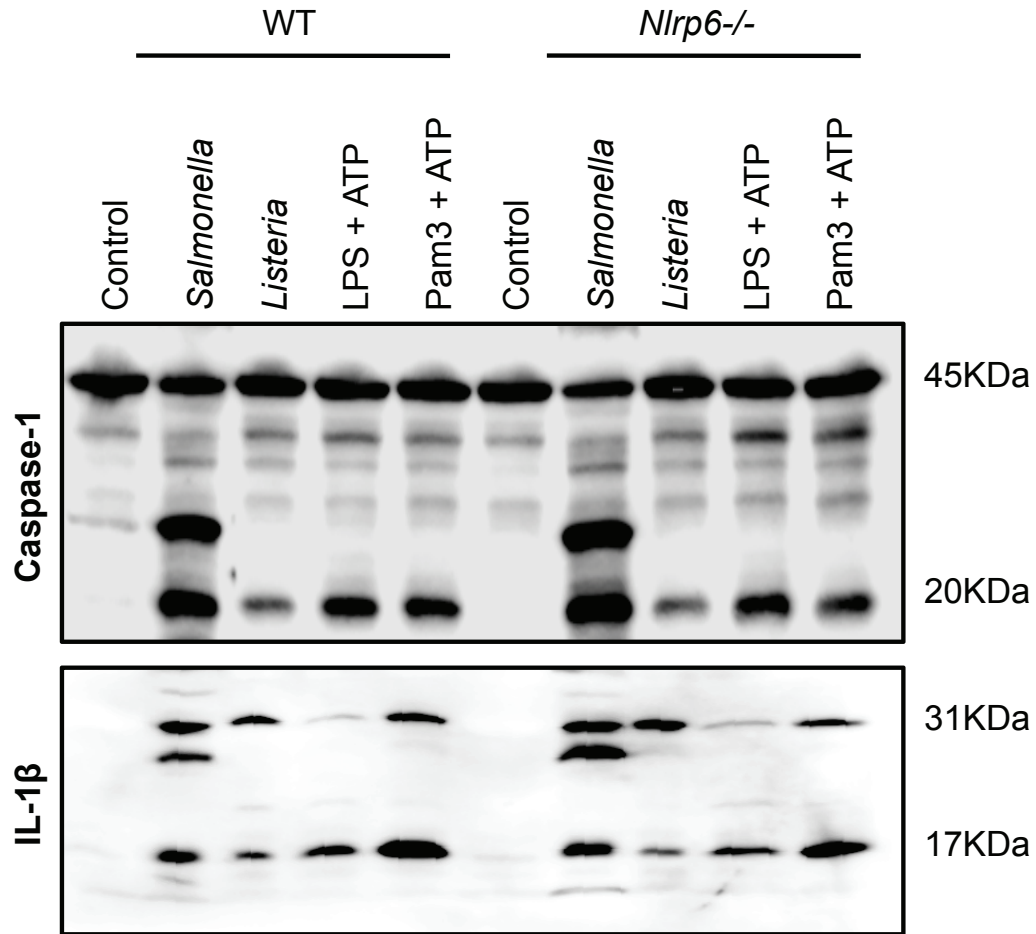


Fig.2

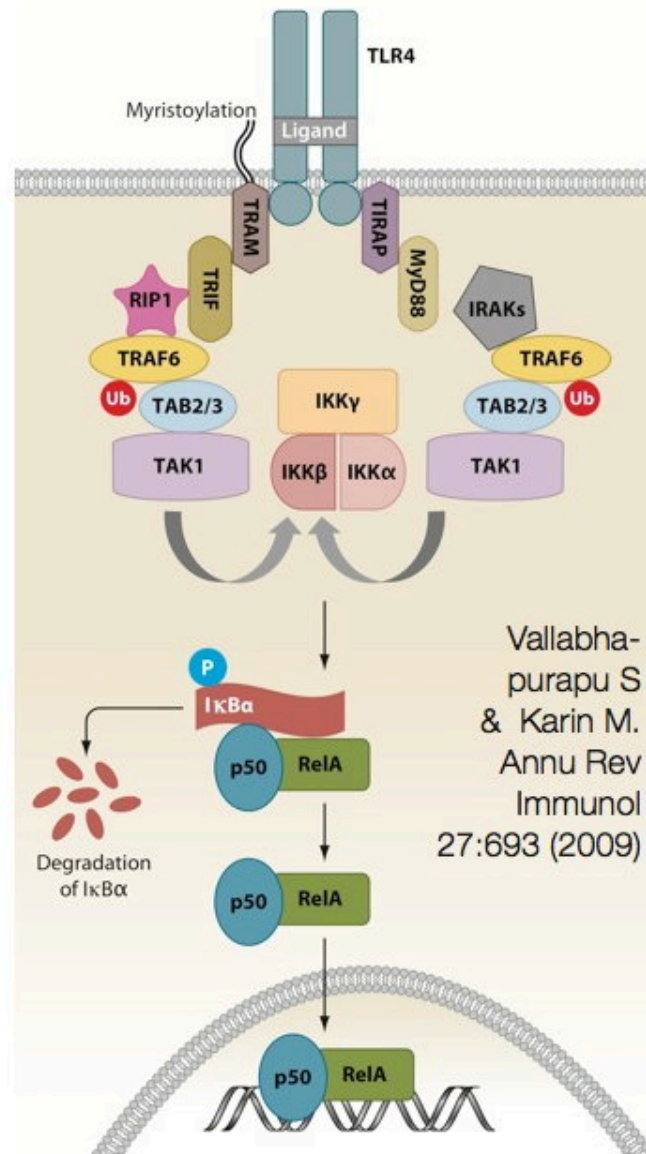
NLRP6 is dispensable for inflammasome activation

Macrophages

a



Activation of the NF- κ B pathway by TLRs



NLRP6 negatively regulates NF- κ B and ERK signalling downstream of TLRs.

BMDMs

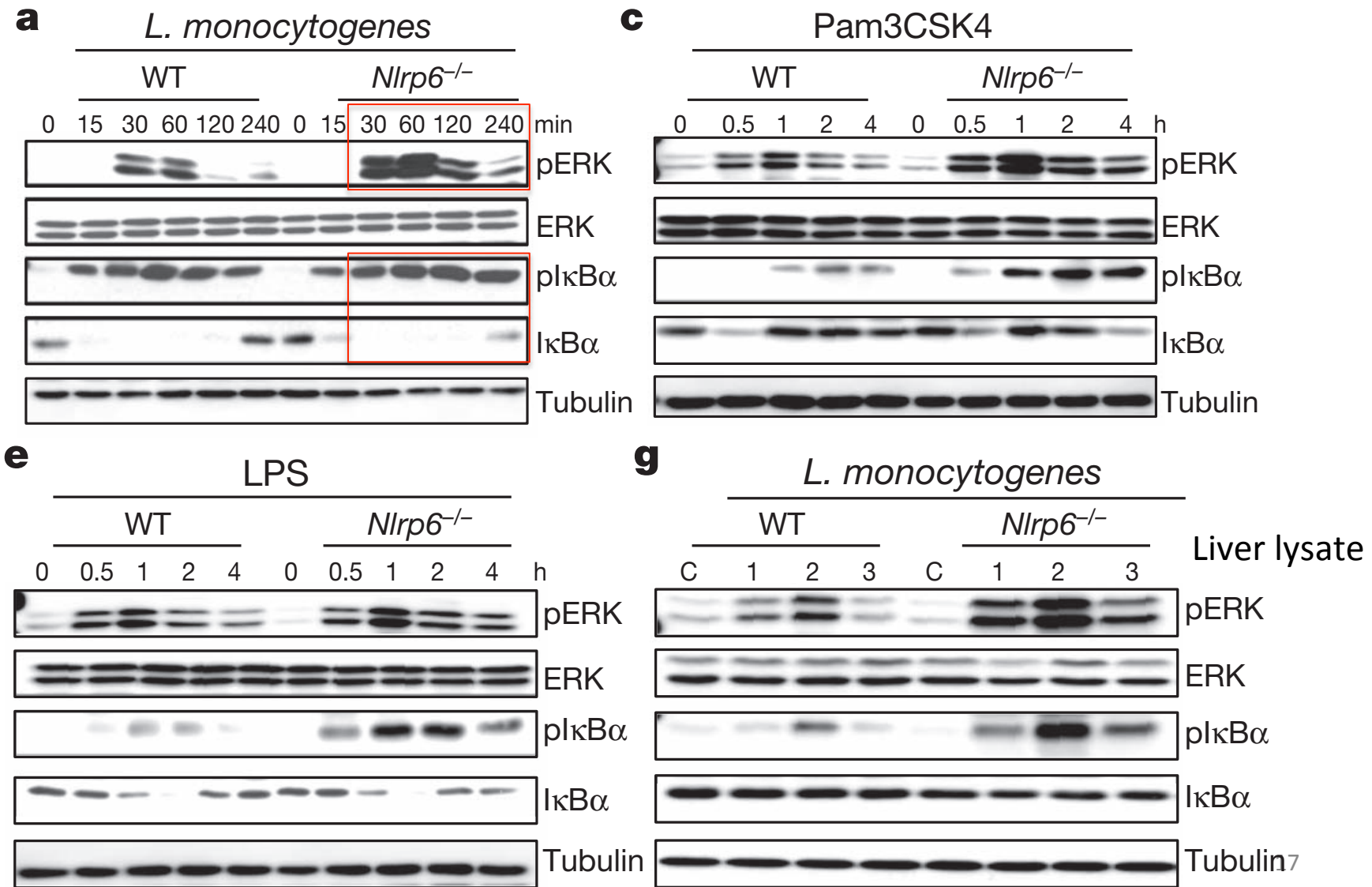
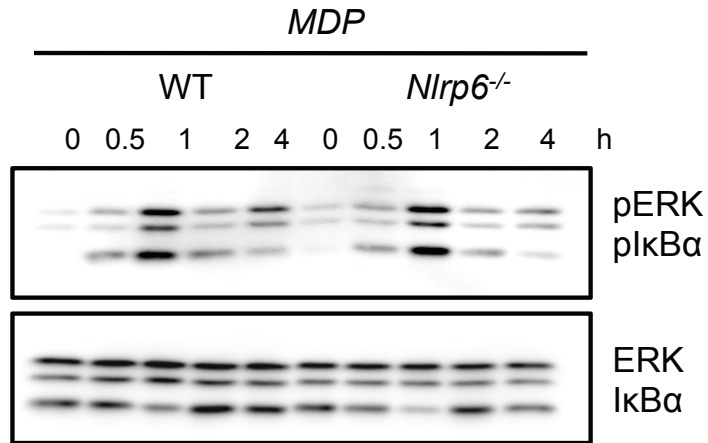


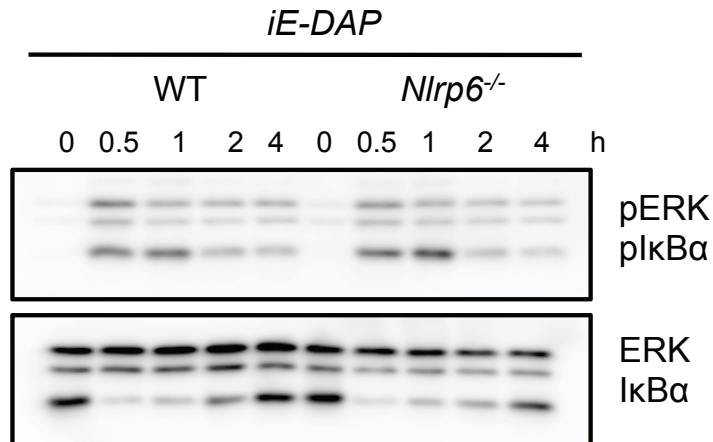
Fig.3

NLRP6 does not negatively regulates NF- κ B and ERK signalling downstream of NOD1 and NOD2.

b

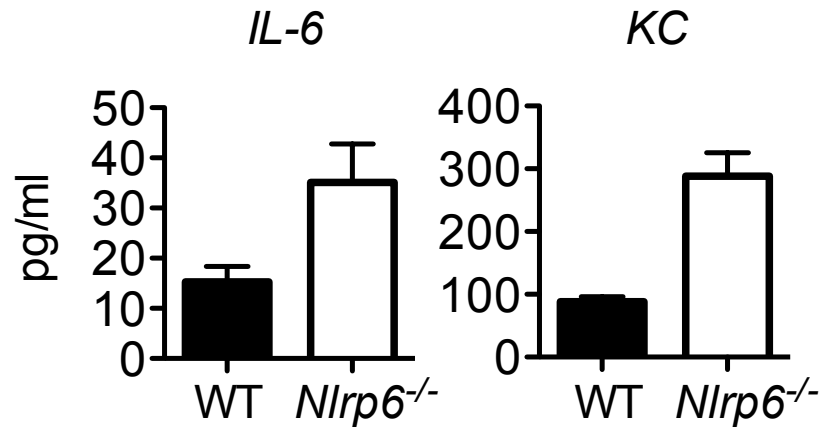


c

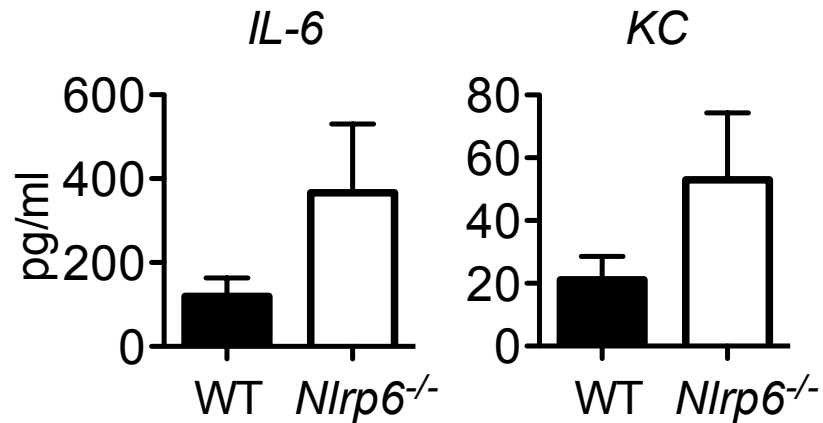


NLRP6^{-/-} show higher levels of IL-6 and KC after *Listeria* infection

e Serum



f Peritoneal lavage

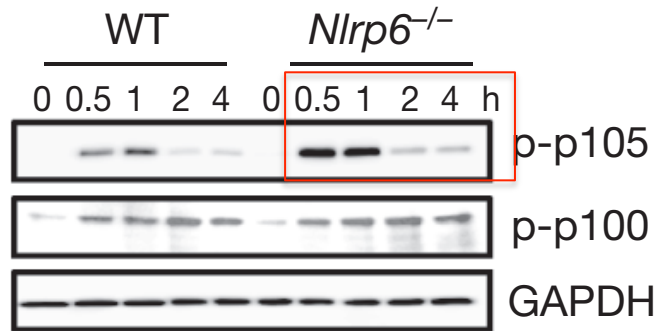


NLRP6 negatively regulates canonical NF- κ B activation pathway.

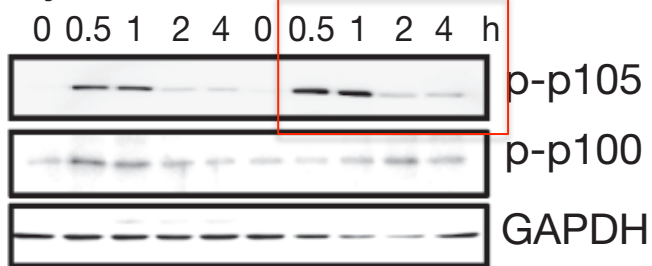
BMDMs infected with *Listeria*

a

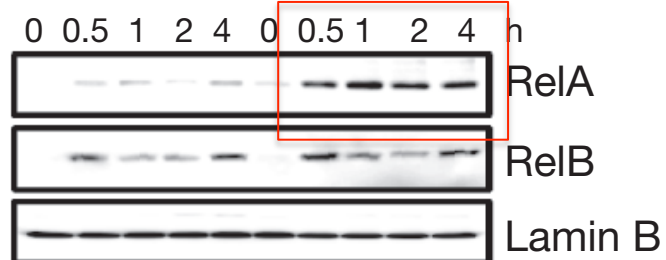
Total lysate



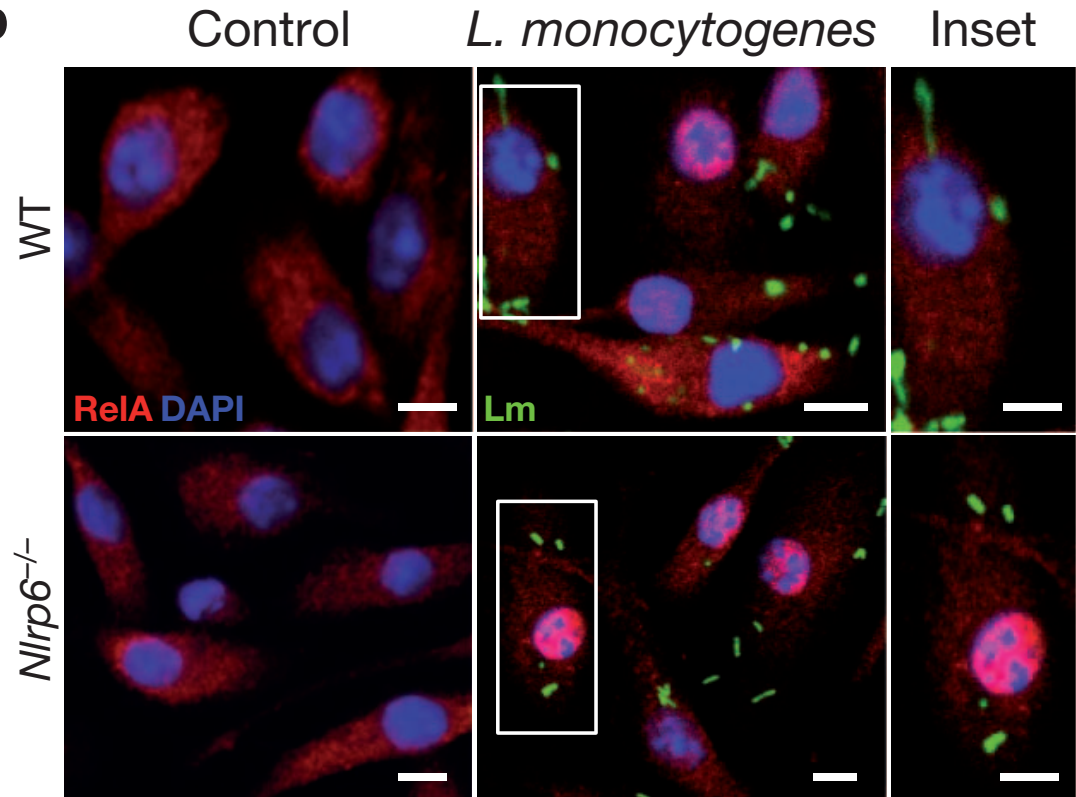
Cytosolic fraction



Nuclear fraction



b



c

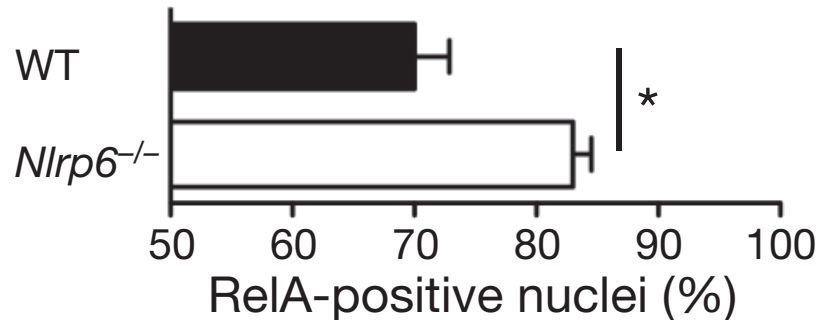


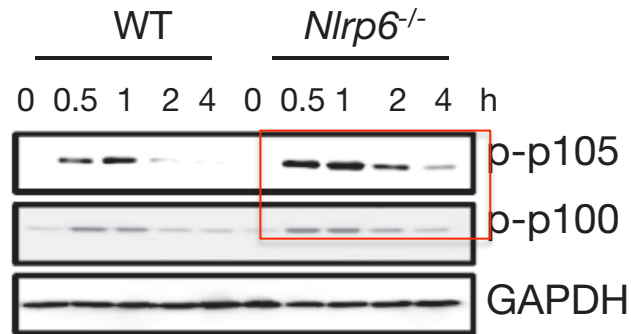
Fig.4

NLRP6 negatively regulates canonical NF- κ B activation pathway.

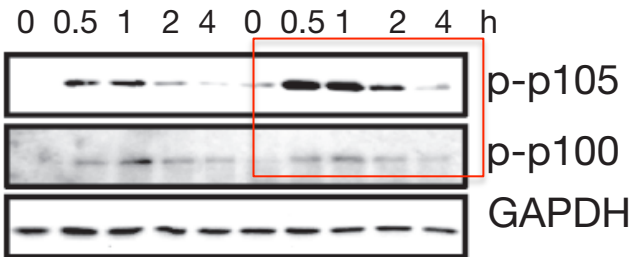
Pam3-stimulated macrophages

d

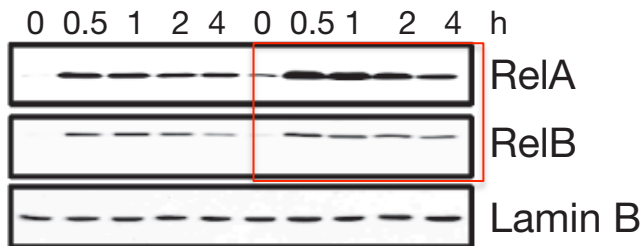
Total lysate



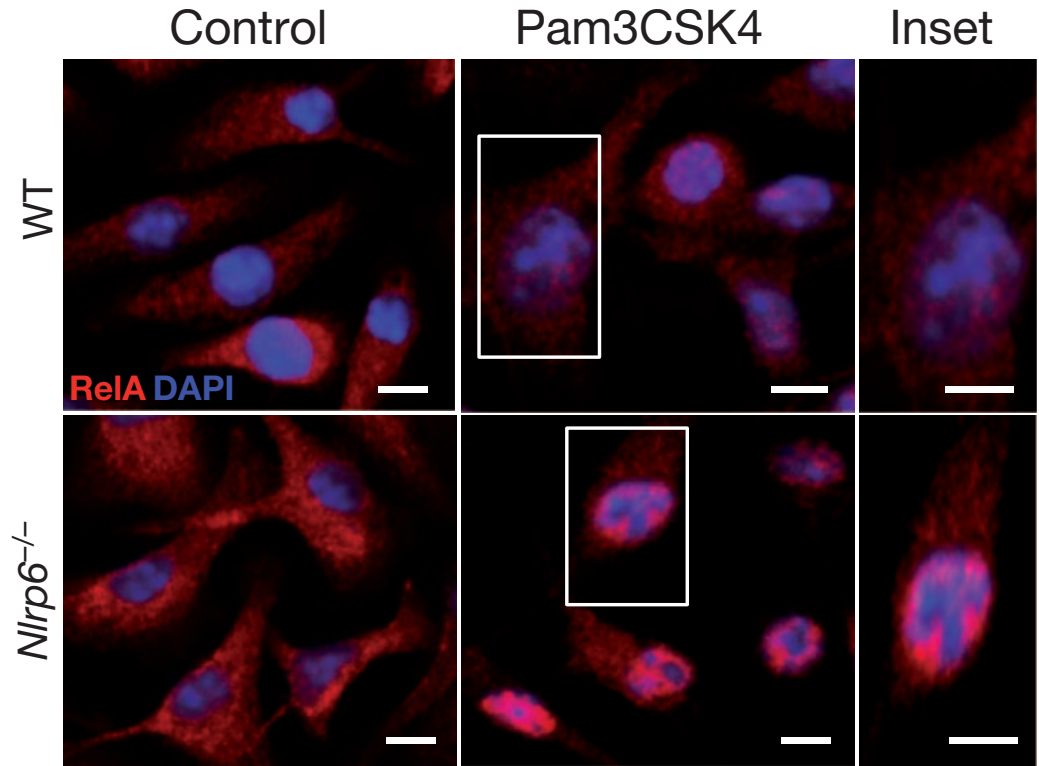
Cytosolic fraction



Nuclear fraction



e



f

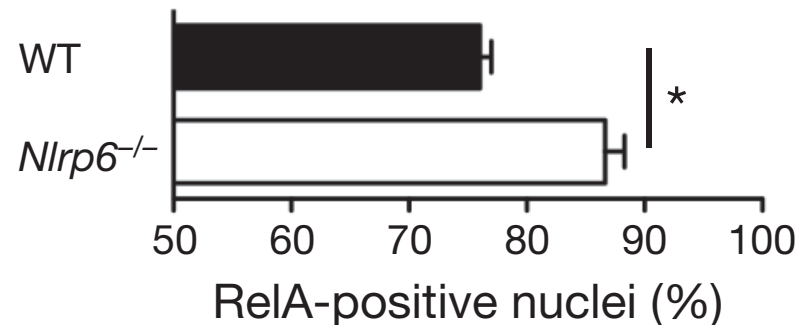


Fig.4

Conclusion

- NLRP6 suppresses TLR-induced MAPK and canonical NFκB signalling to dampen the production of pro-inflammatory cytokines and chemokines during bacterial infection.
- NLRP6 activation leads to increased susceptibility to intracellular and extracellular as well as Gram- and Gram+ bacterial pathogens.
- Hematopoietic and non-hematopoietic compartments contribute to the increased resistance of Nlrp6^{-/-} mice to infection.
- Some NLRs, such as NLRP6, may respond to bacterial infection by initiating pro-inflammatory signalling that contributes to bacterial clearance.