

Gut Microbiota-Induced Immunoglobulin G Controls Systemic Infection by Symbiotic Bacteria and Pathogens

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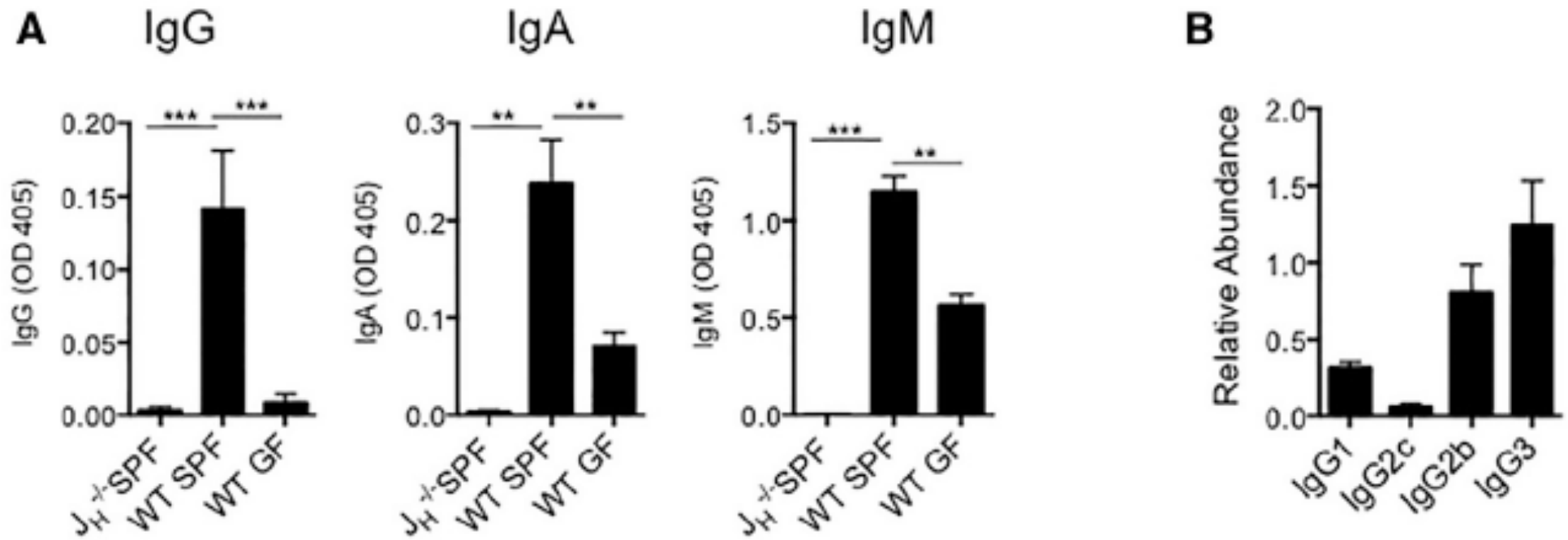
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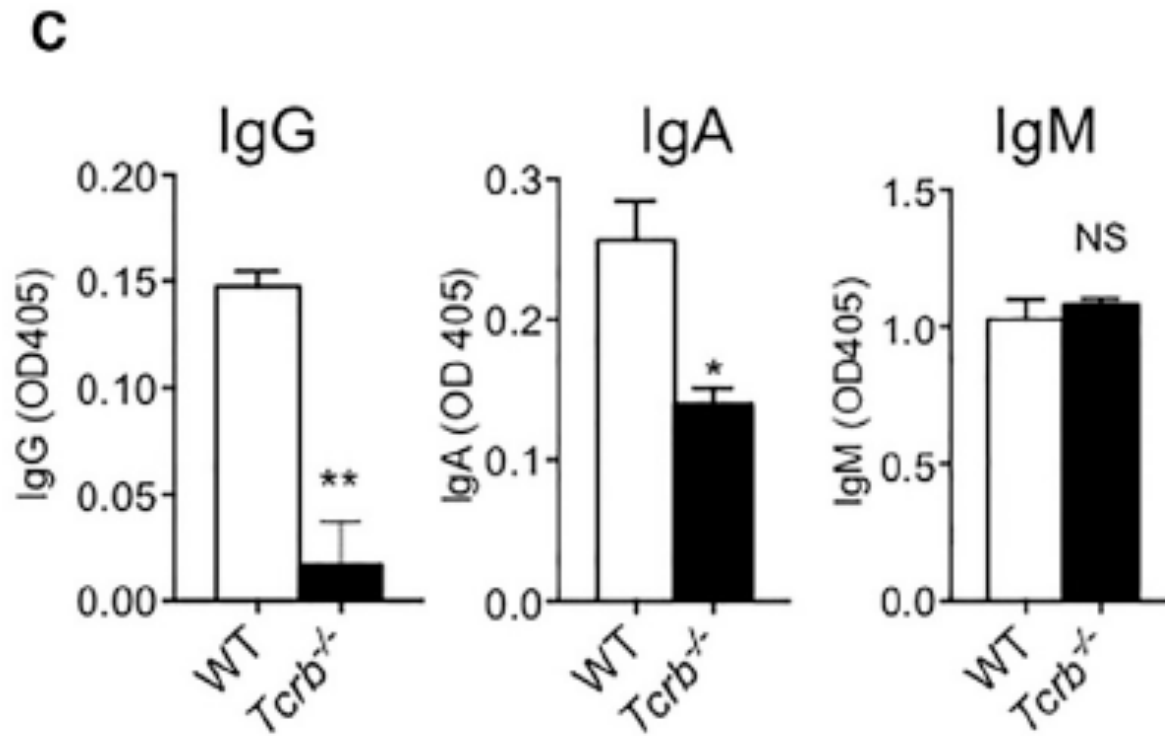
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Dirty plate ELISA

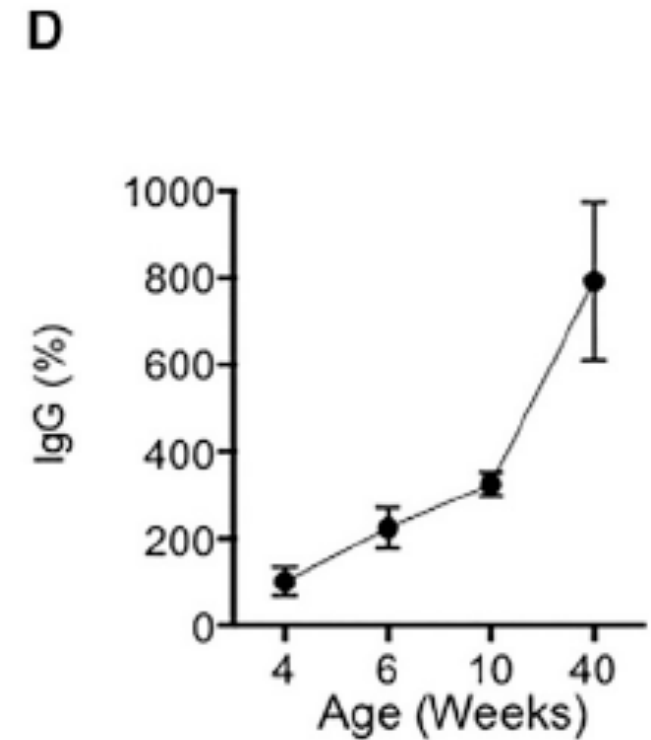
FB: heat-killed faecal bacteria



TCRb^{-/-}

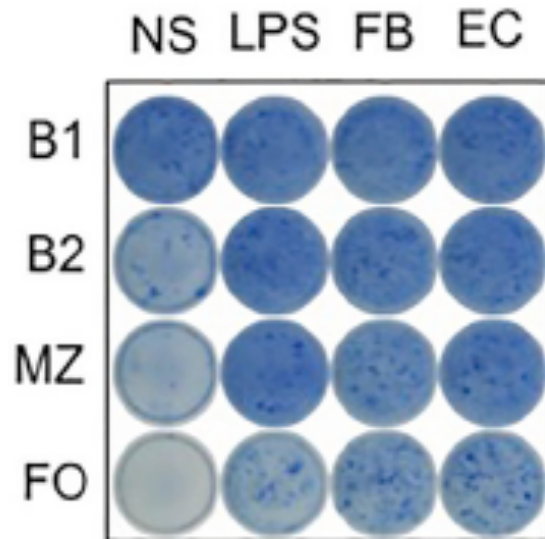


Symbiotic bacteria-specific IgG
is dependent on T cells



The amount of symbiotic
bacteria-specific IgG
Is accumulated by aging

E ELISPOT
72hrs after incubation



Peritoneal B1 and B2
Marginal zone B cells
Follicular B cells

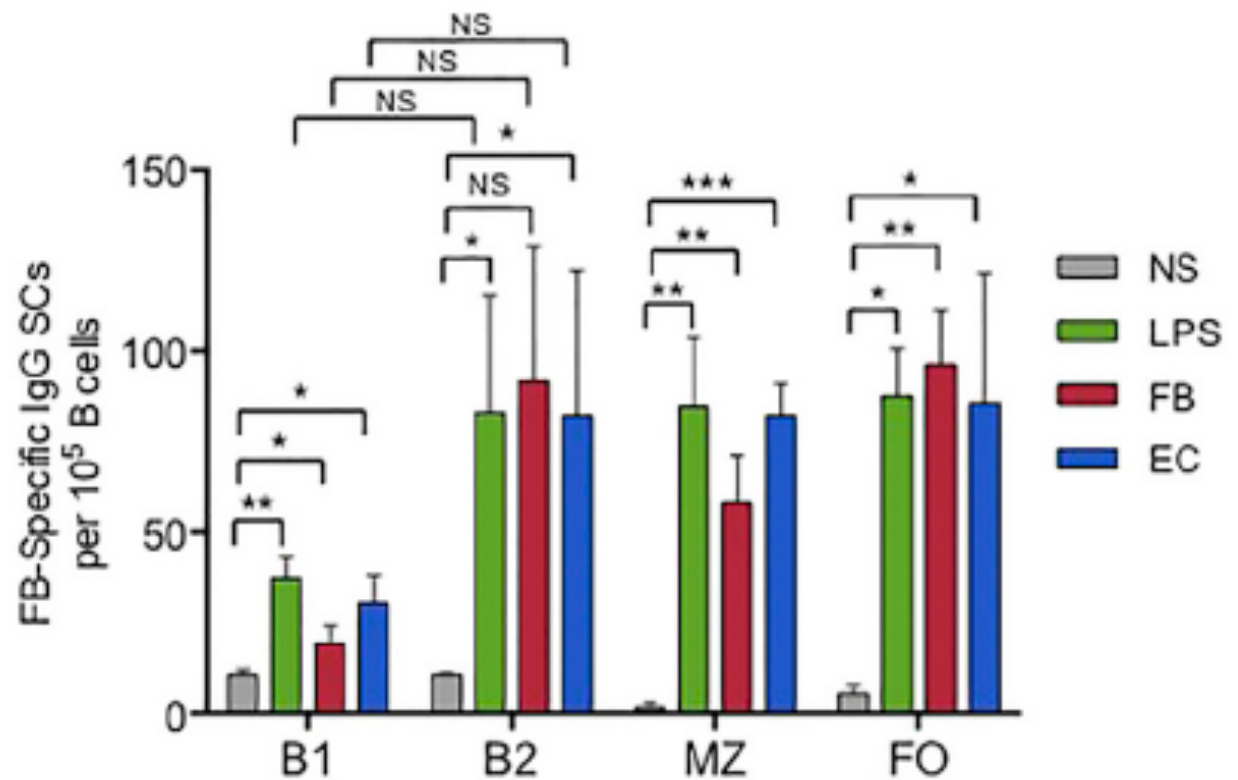
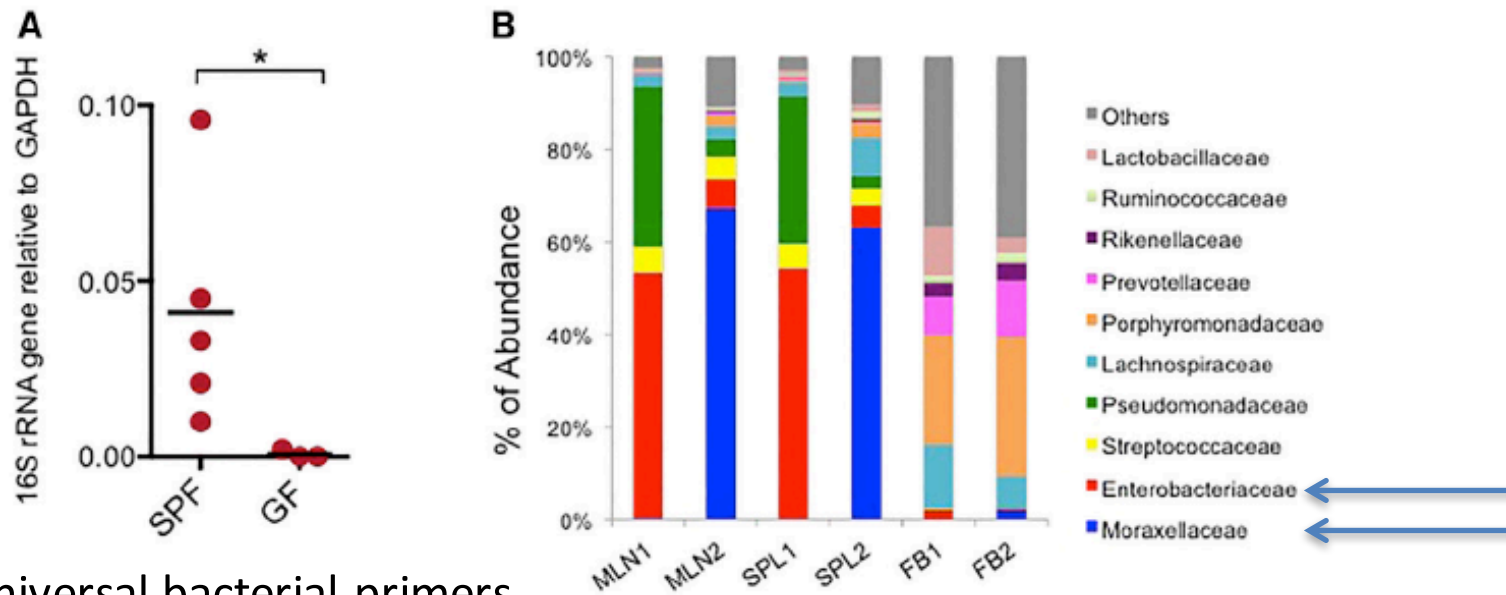


Figure 1. Gut Microbiota Induces Antigen-Specific IgG in the Steady State



16s of universal bacterial primers

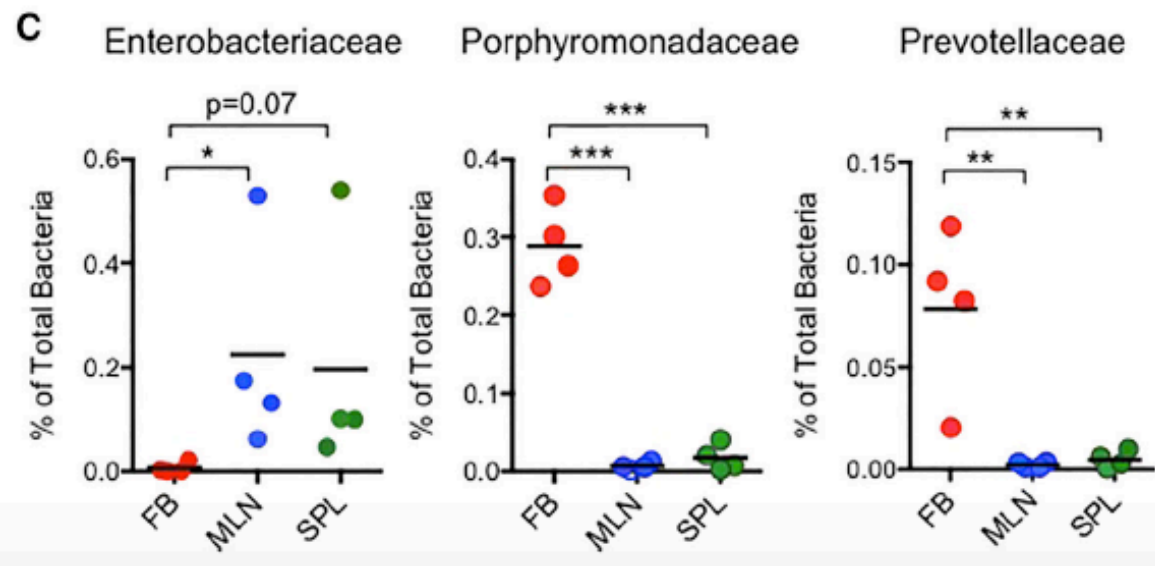
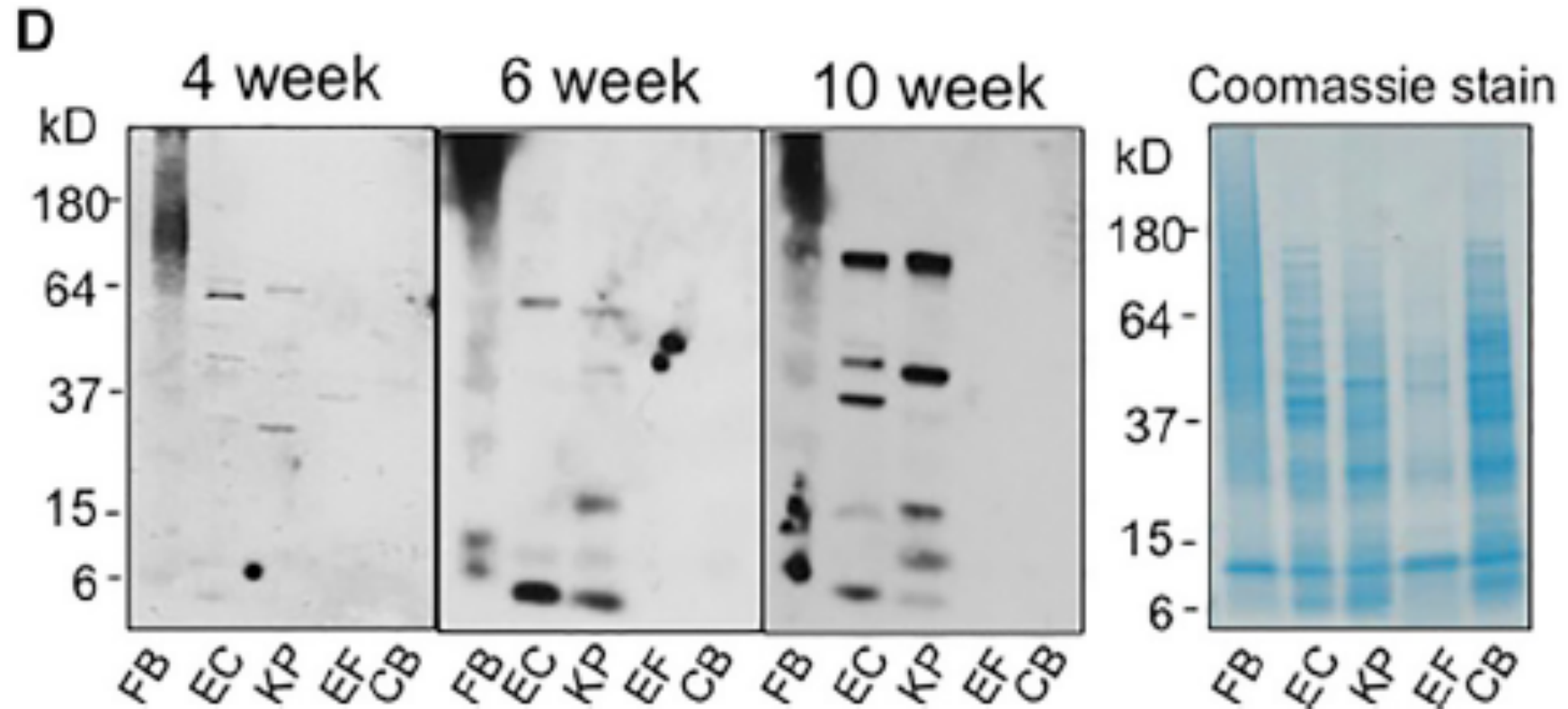


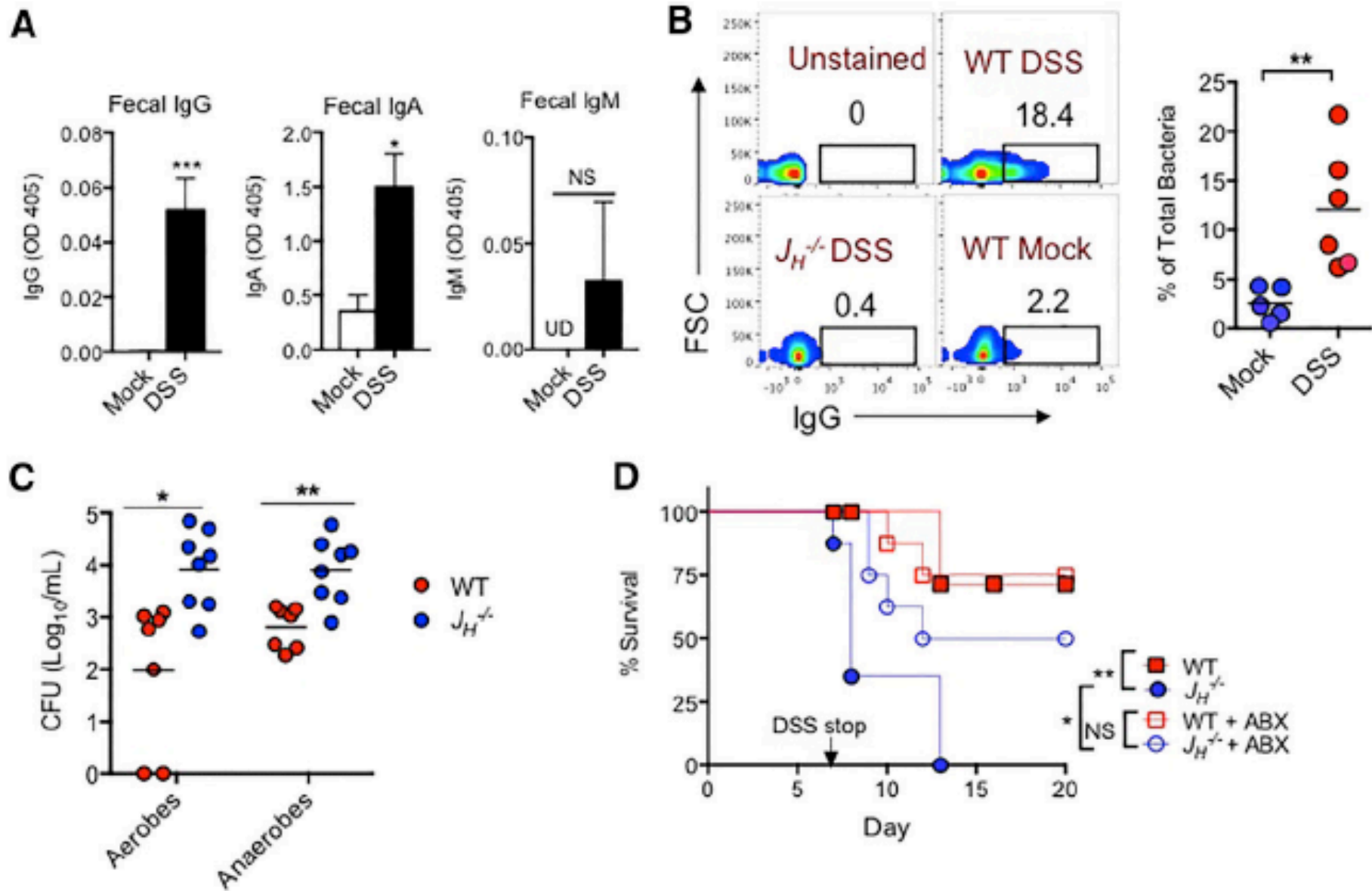
Figure 2: A selective group of gram-negative symbiotic bacteria might be able to breach the Intestinal epithelial barrier and disseminate systemically to induce IgG response.

IgG in SPF serum can recognize antigens in particular bacterial species



fecal bacteria (FB), *Escherichia coli* (EC), *Klebsiella pneumoniae* (KP), *Enterococcus faecalis* (EF), and *Clostridium bifermentans* (CB)

Fecal



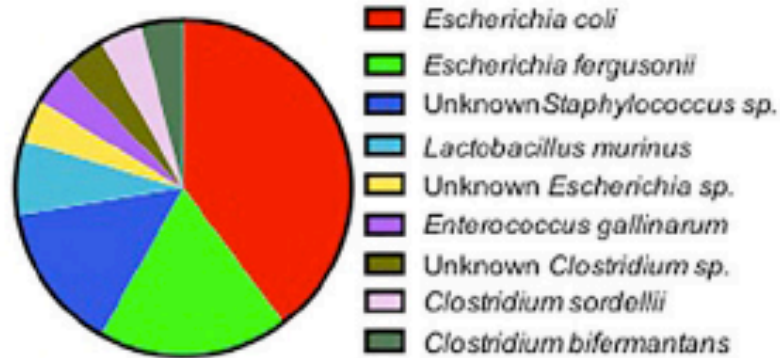
Protect host from bacterial translocation

ECML4-an isolated E. coli from JH-/-

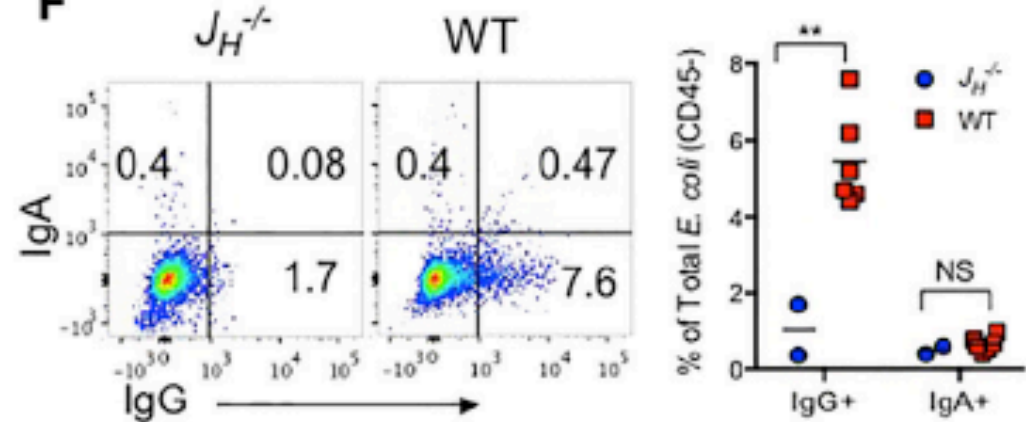
i.p. and wait for 6hrs to see the preexisting Ig binding

JH-/- spleen

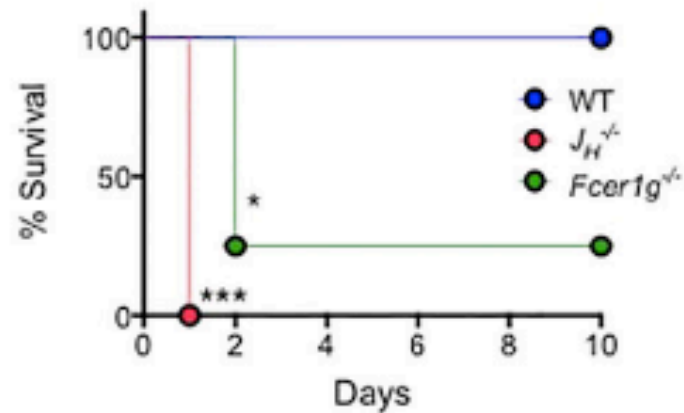
E



F

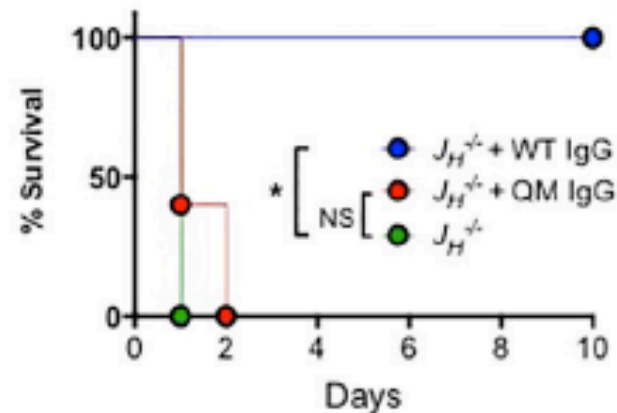


G



FcγR-deficient mice (*Fcer1g*^{-/-})

H



(QM) mice with very contracted B cell repertoire

Figure 3. Gut Microbiota-Induced IgG Confers Protection against DSS-Induced Bacteremia.

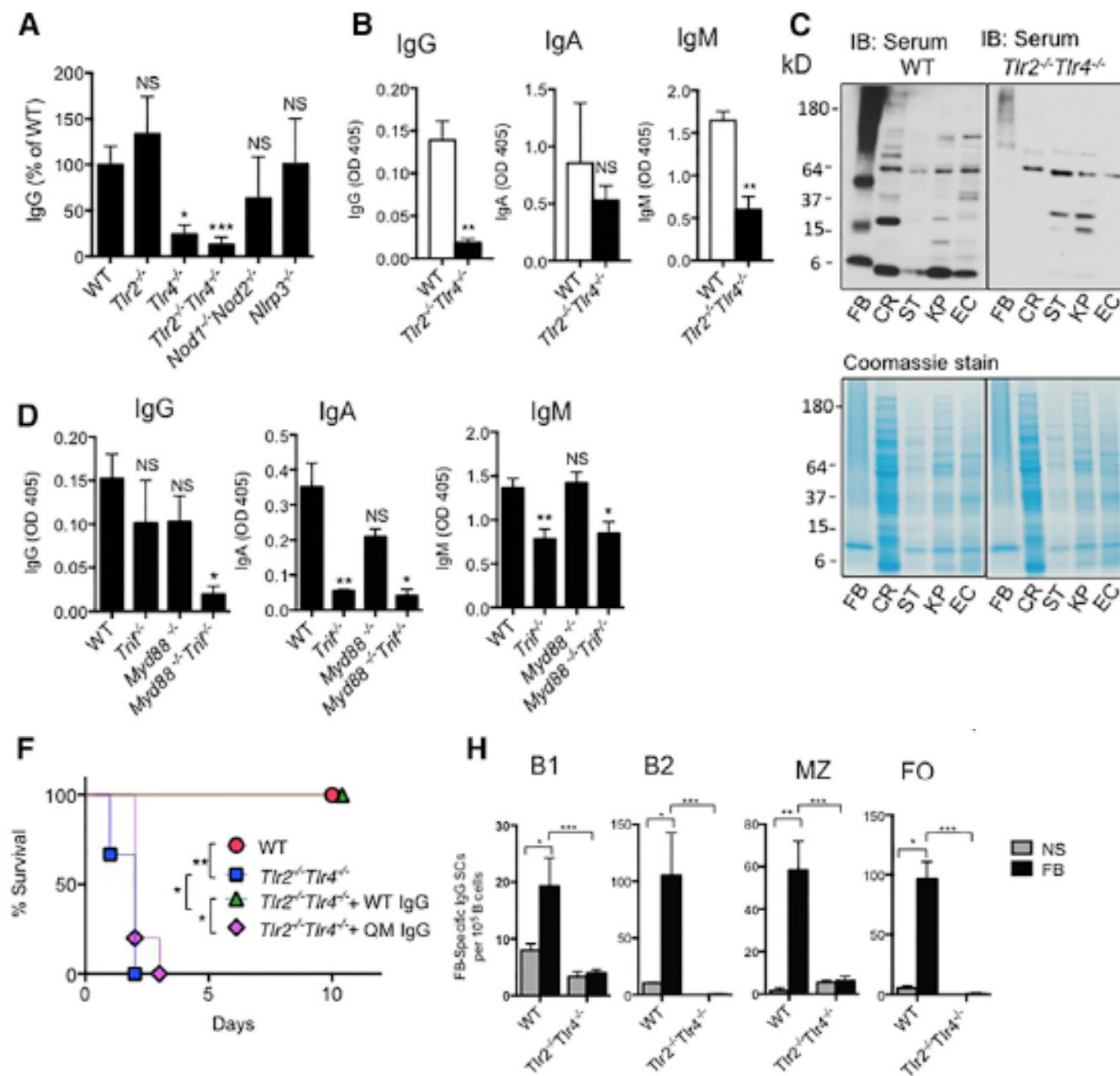
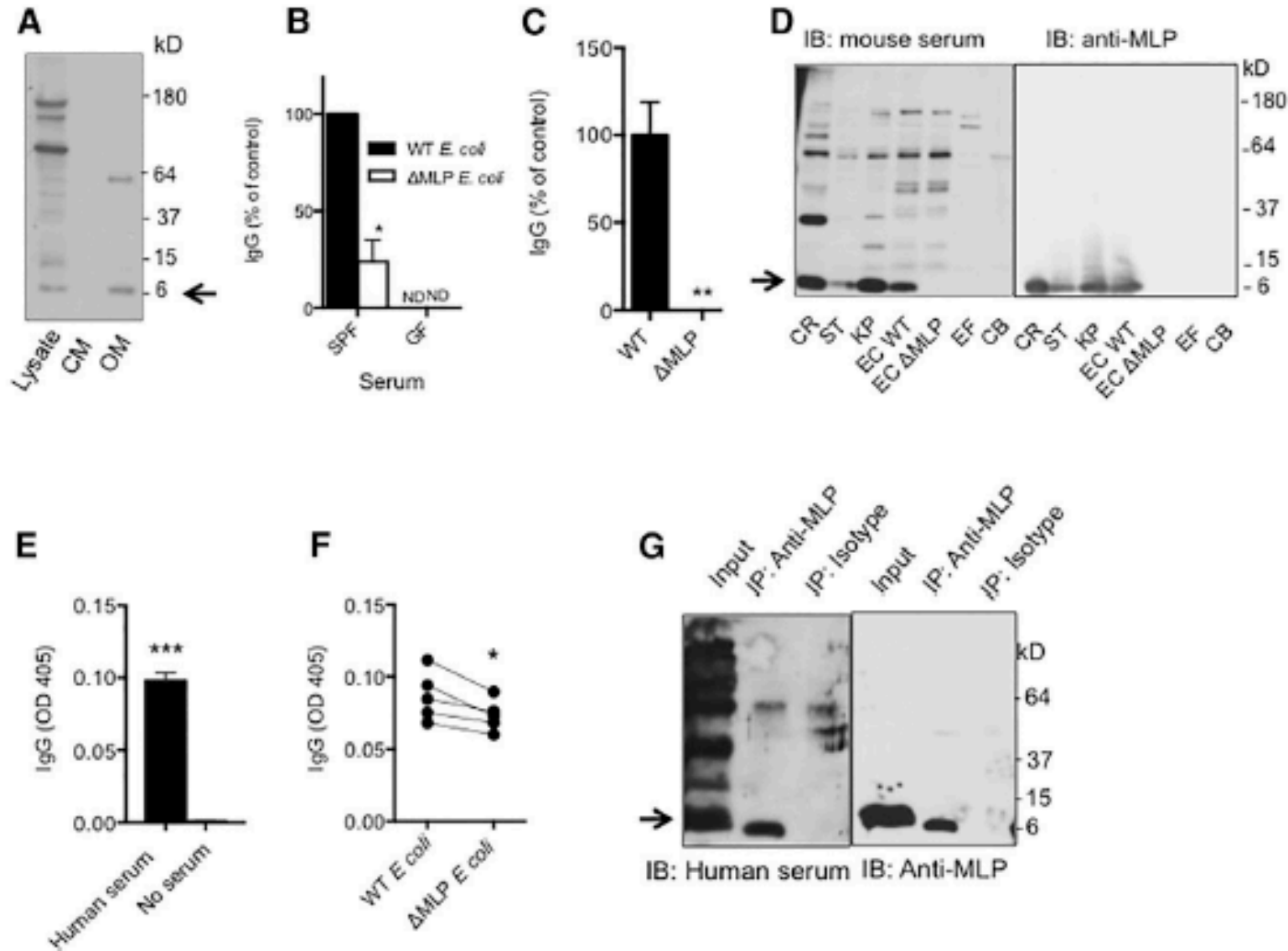


Figure 4. TLR4 Signaling Is Required for Induction of Microbiota-Specific IgG.

Culture
supernatant



Murein lipoprotein: a highly conserved outer membrane protein of 7 kD expressed abundantly in gram-negative enterobacteria

In vitro neutrophil killing assay

5×10^7 CFU *E. coli* i.p.

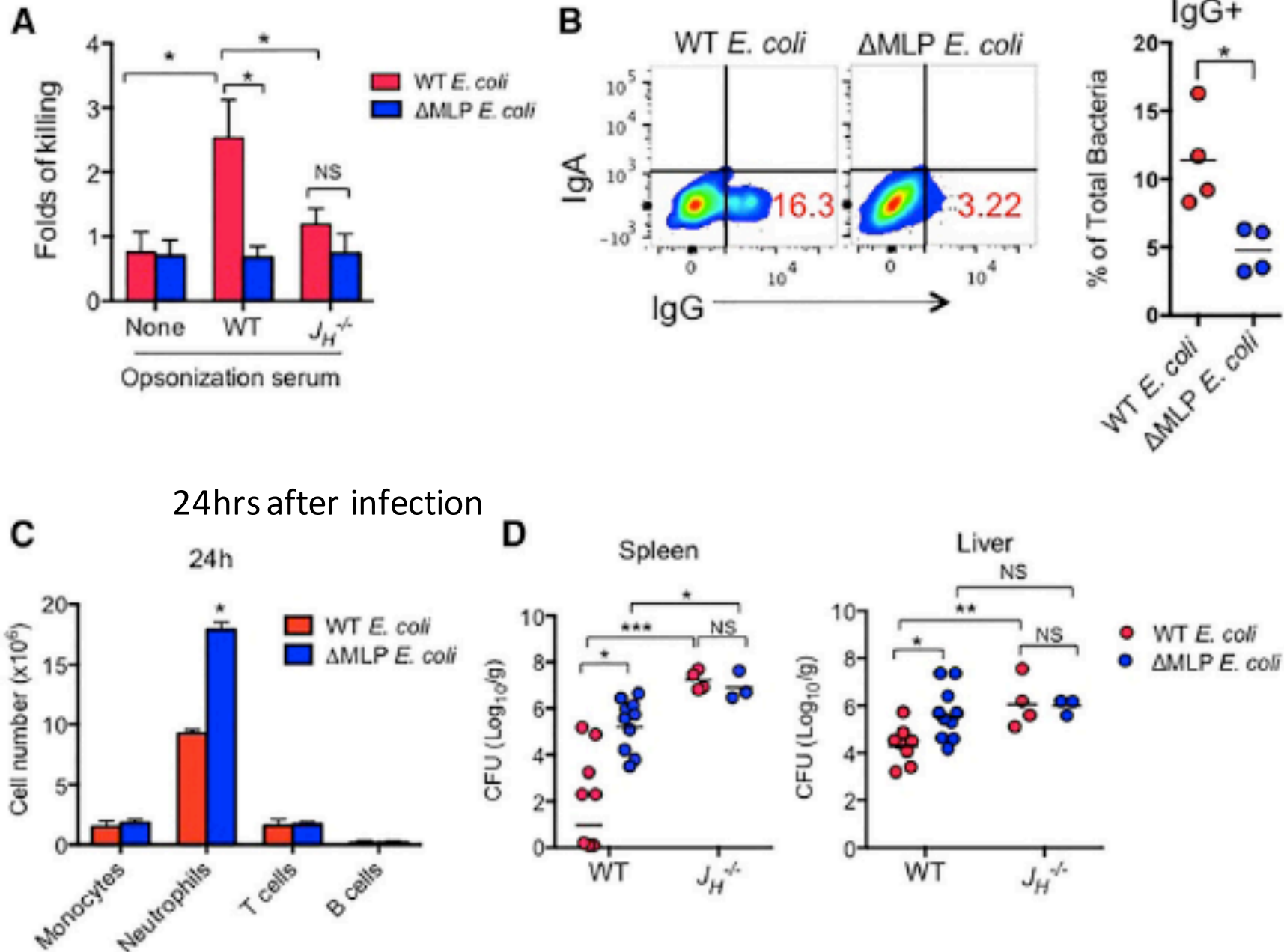
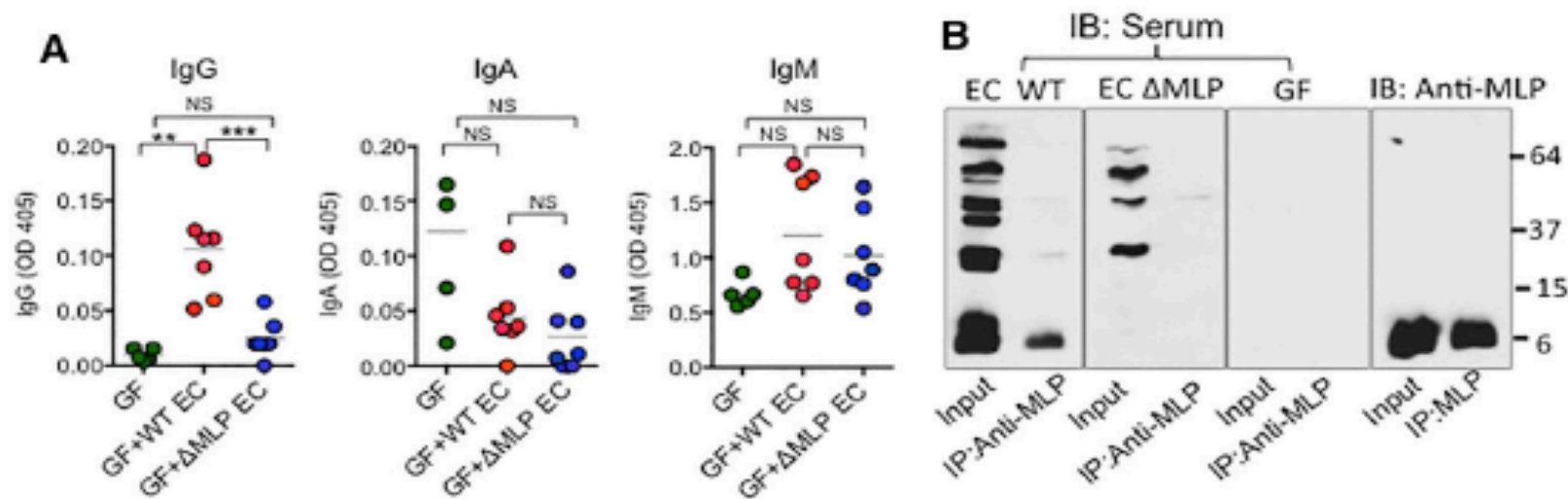
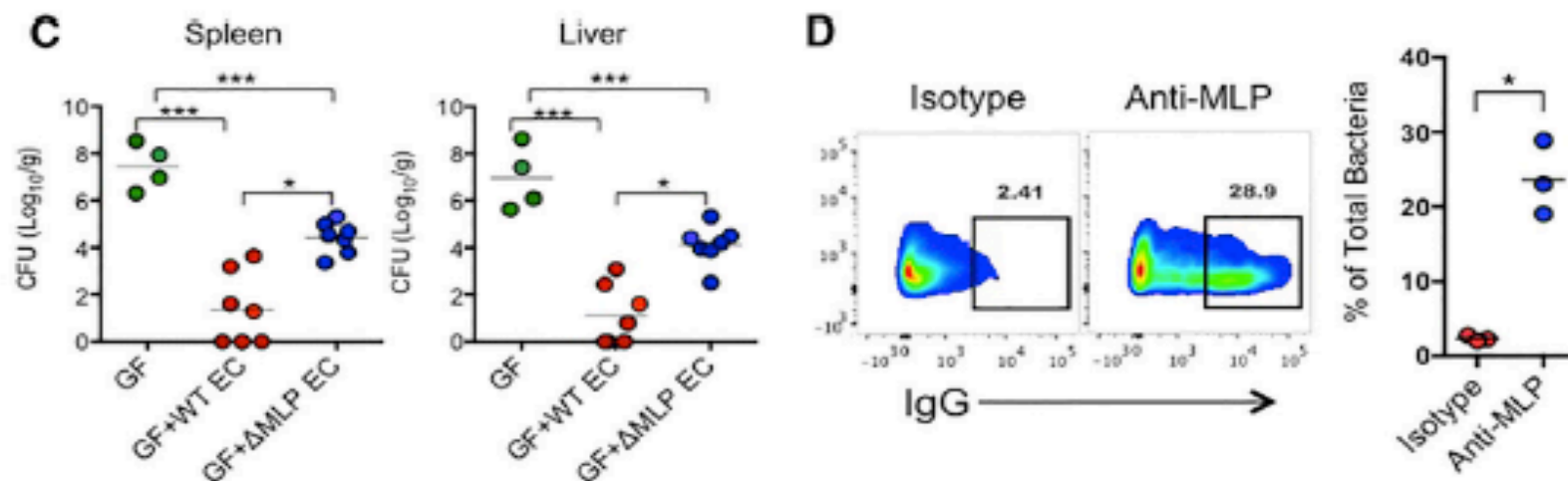


Figure 6. Anti-MLP IgG Promotes Killing of *E. coli* In Vitro and In Vivo



i.p. with *E. coli* WT/ΔMLP 2 weeks after i.v. salmonella



i.p. for 24 hr before i.p. with ST

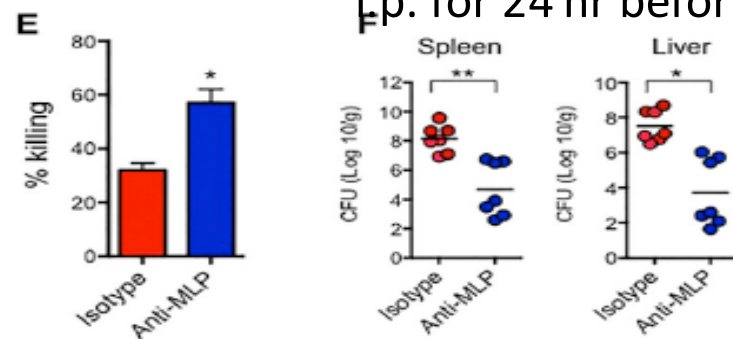


Figure 7. IgG against Murein Lipoprotein Confers Protection against Salmonella Infection

Discussion

- ◆ Selective gut symbiotic gram-negative bacteria were able to disseminate systemically to induce immunoglobulin G (IgG) response in homeostatic status.
- ◆ TLR4 on B cells in the generation of microbiota-specific IgG is indispensable.
- ◆ MLP, a highly conserved gram-negative outer membrane protein as a primary antigen for systemic IgG response.

High-fat diet enhances stemness and tumorigenicity of intestinal progenitors

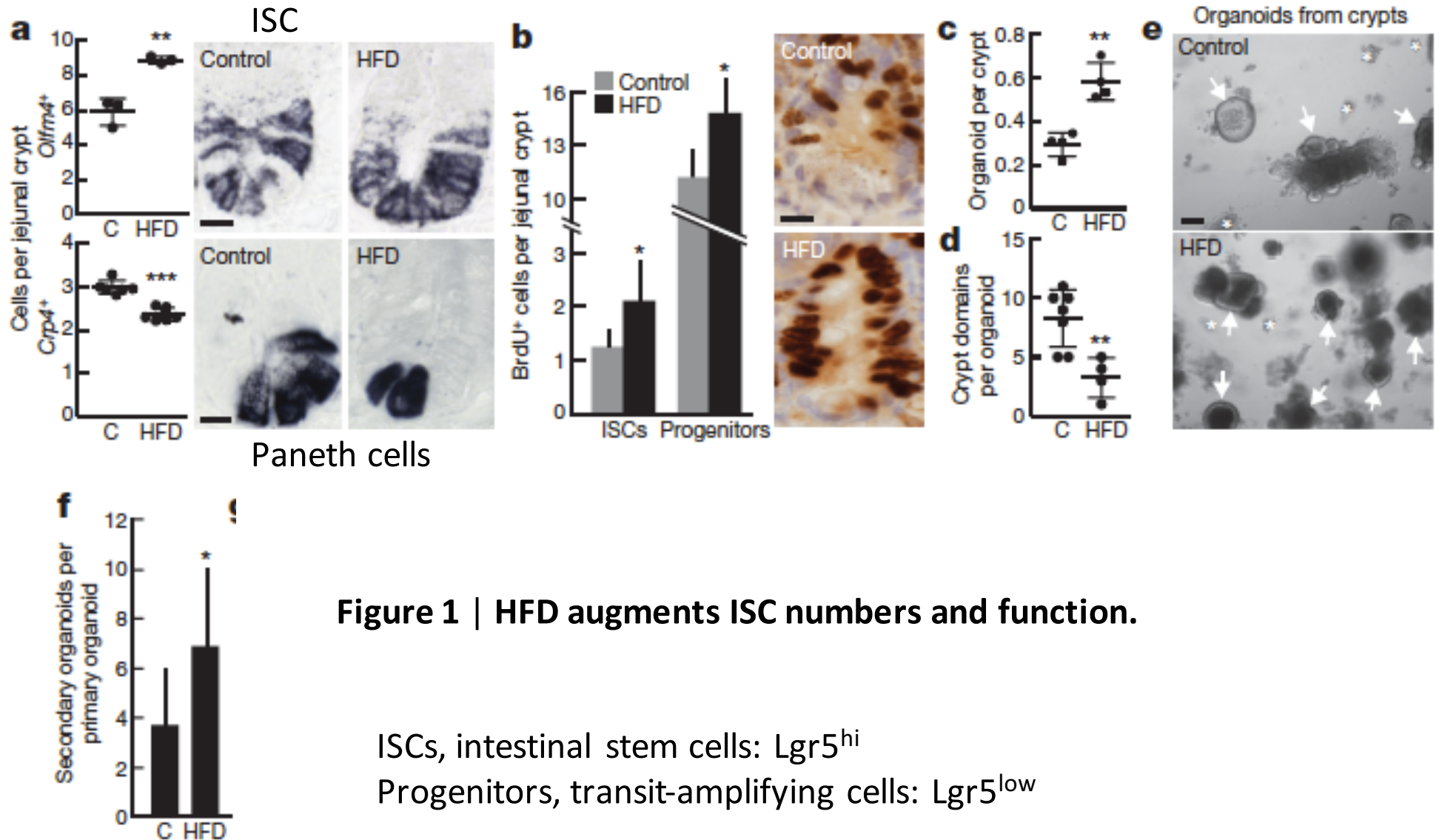
Semir Beyaz^{1,2*}, Miyeko D. Mana^{1*}, Jatin Roper^{1,3*}, Dmitriy Kedrin^{1,4}, Assieh Saadatpour⁵, Sue-Jean Hong⁶, Khristian E. Bauer-Rowe¹, Michael E. Xifaras¹, Adam Akkad¹, Erika Arias¹, Luca Pinello⁵, Yarden Katz⁷, Shweta Shinagare¹, Monther Abu-Remaileh^{1,6}, Maria M. Mihaylova^{1,6}, Dudley W. Lamming⁸, Rizkullah Dogum¹, Guoji Guo², George W. Bell⁶, Martin Selig⁴, G. Petur Nielsen⁴, Nitin Gupta⁹, Cristina R. Ferrone⁴, Vikram Deshpande⁴, Guo-Cheng Yuan⁵, Stuart H. Orkin², David M. Sabatini^{1,6,7} & Ömer H. Yilmaz^{1,4,7}

Background

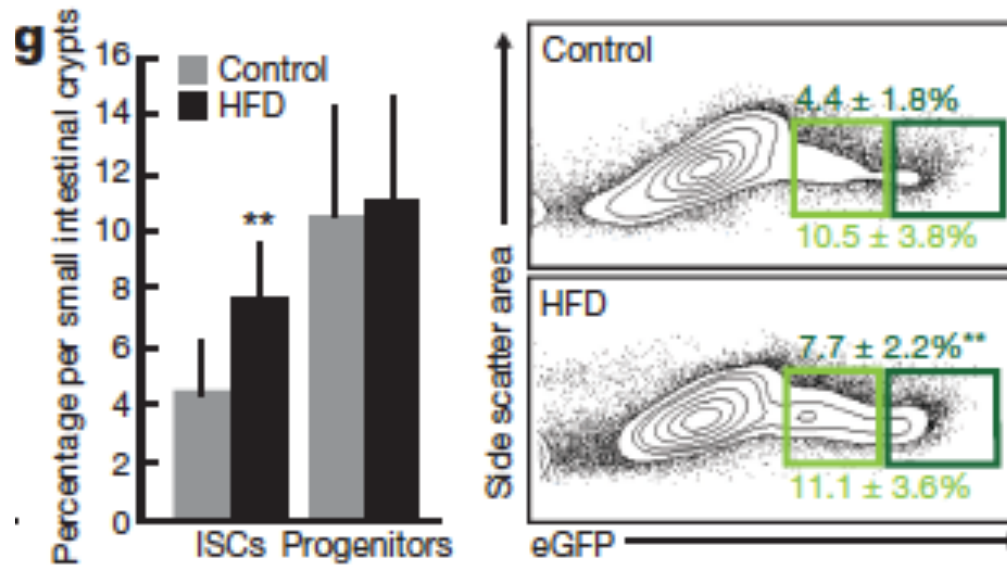
- The *Lgr5*⁺ ISCs reside at the base of intestinal crypts adjacent to Paneth cells, which are a central component of the ISC niche and regulate stem cell biology in response to calorie-restricted diets.
- In the mouse intestine, *Lgr5*⁺ ISCs serve as the cell-of-origin for the precancerous adenomatous lesions caused by loss of the *Apc* tumour suppressor gene.

Question: how long-term HFD-induced obesity influences intestinal stem and progenitor cell function and the cellular origins of intestinal dysplasia.

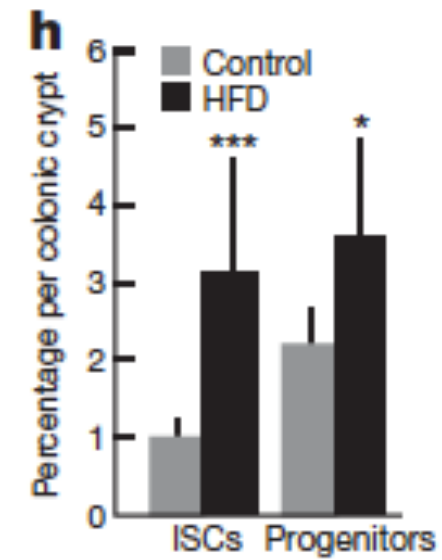
Mice were fed with HFD (60%) or standard chow for 9-14 months



Small intestine

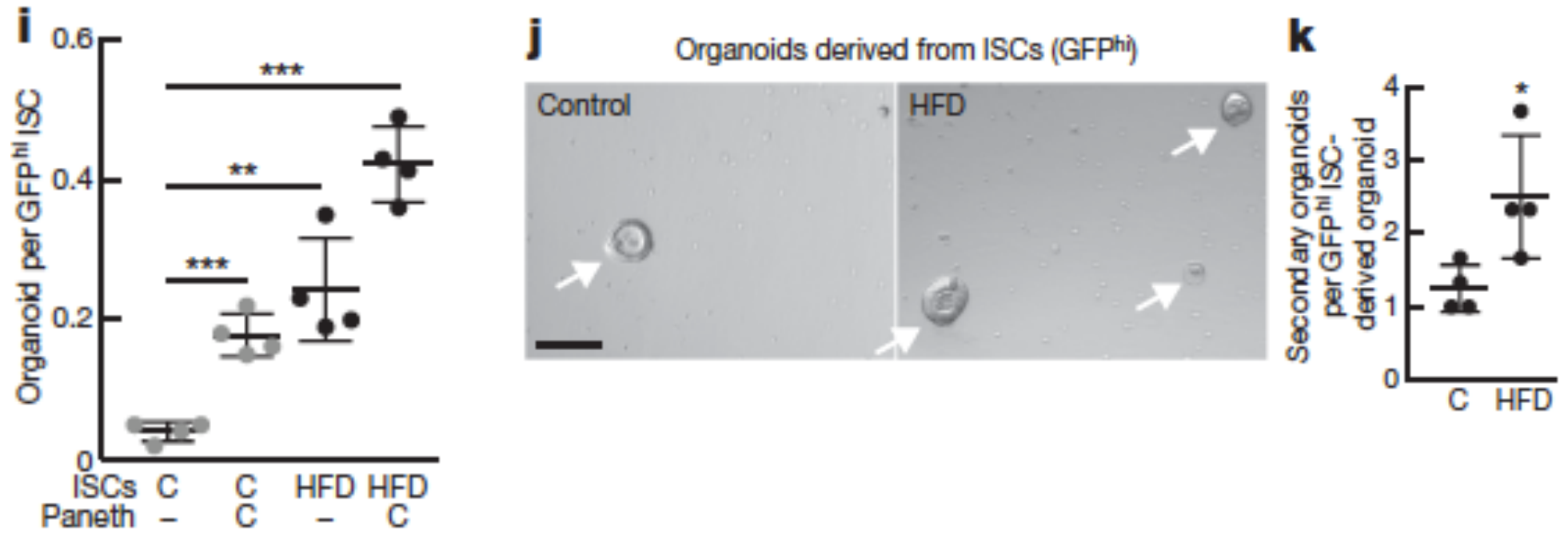


Colon

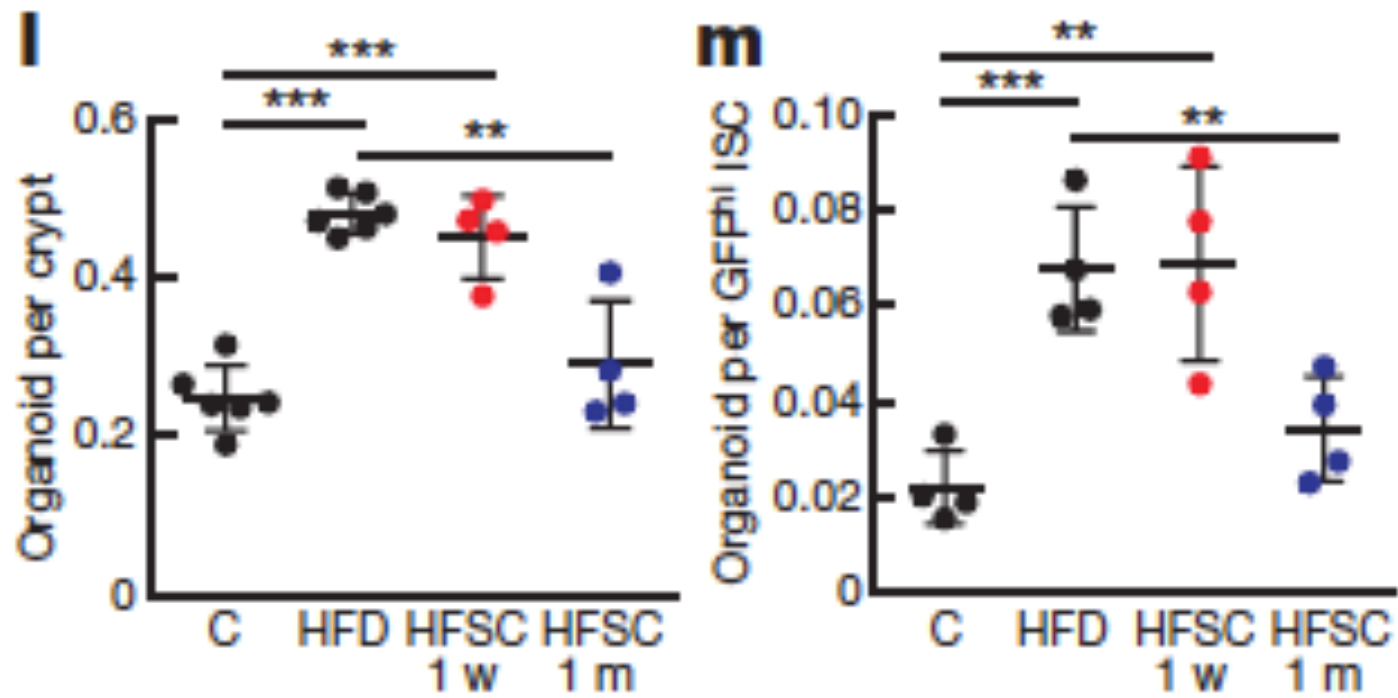


HFD derived crypts contain more ISCs and progenitors

Co-culture with paneth cells
1:1 seeds in matrigel



HFD alters ISC niche dependence.



The effects of a HFD on ISC stemness are reversible.

Primary organoids formation has no clear difference

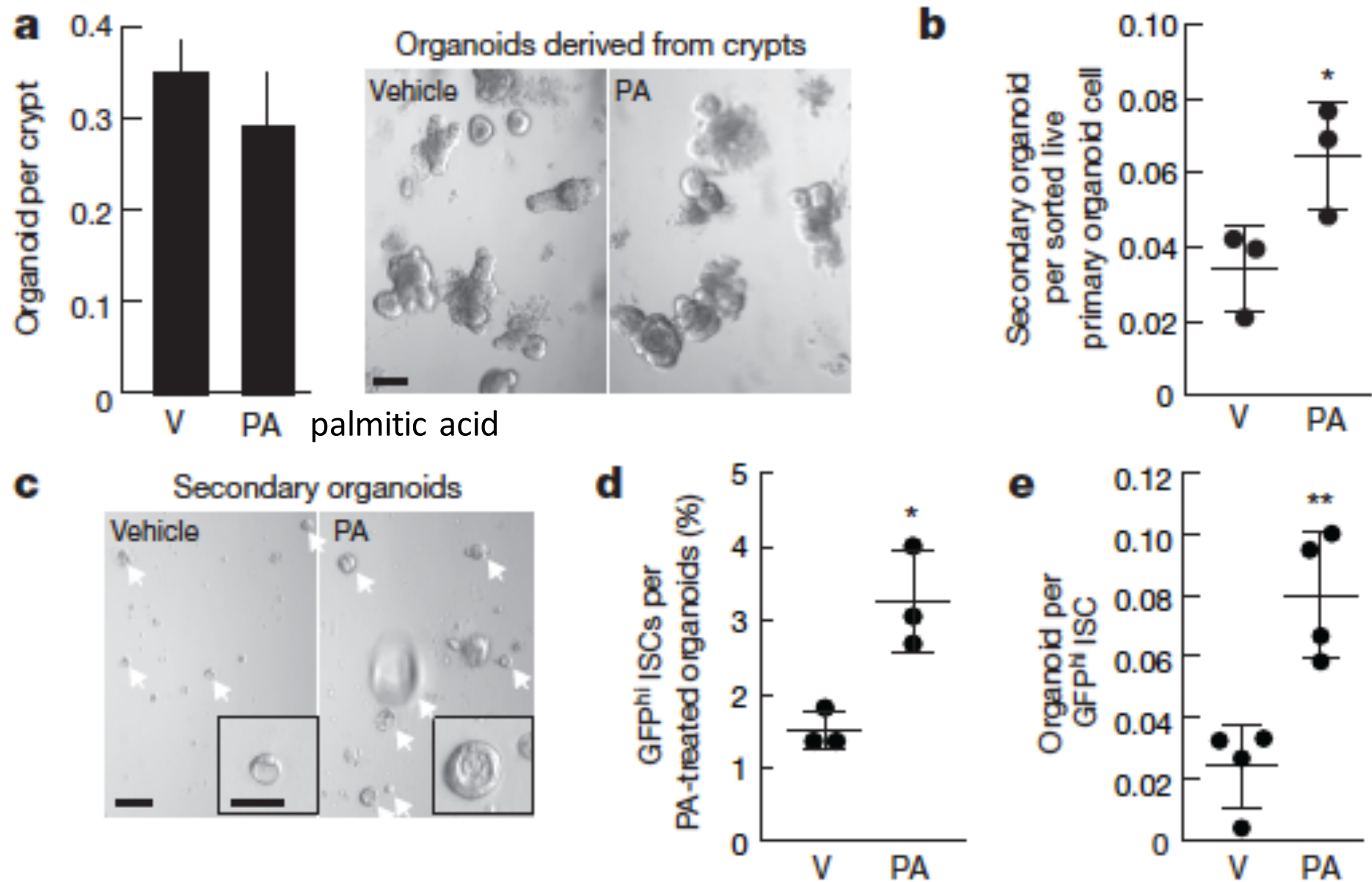


Figure 2 | *Ex vivo* exposure of intestinal organoids to palmitic acid recapitulates aspects of a HFD.

RNAseq reveals a enrichment of PPAR regulated genes in HFD derived ISC and progenitors
 PPAR- δ RNA level is predominate in ISCs.

PPAR- δ agonist GW501516
 Performed by i.p. every day

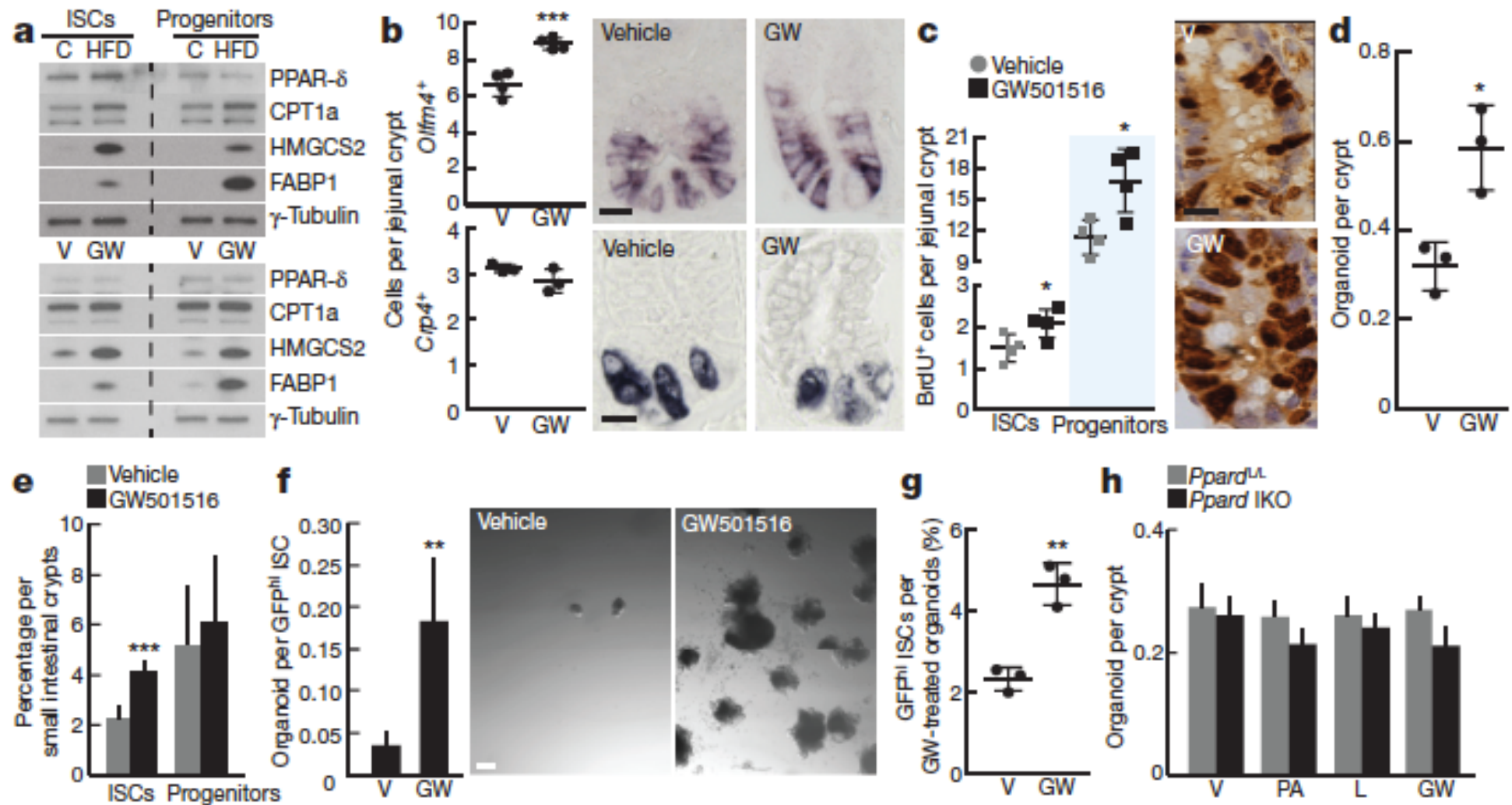


Figure 3 | Activated PPAR- δ in ISCs mediates the effects of a HFD.

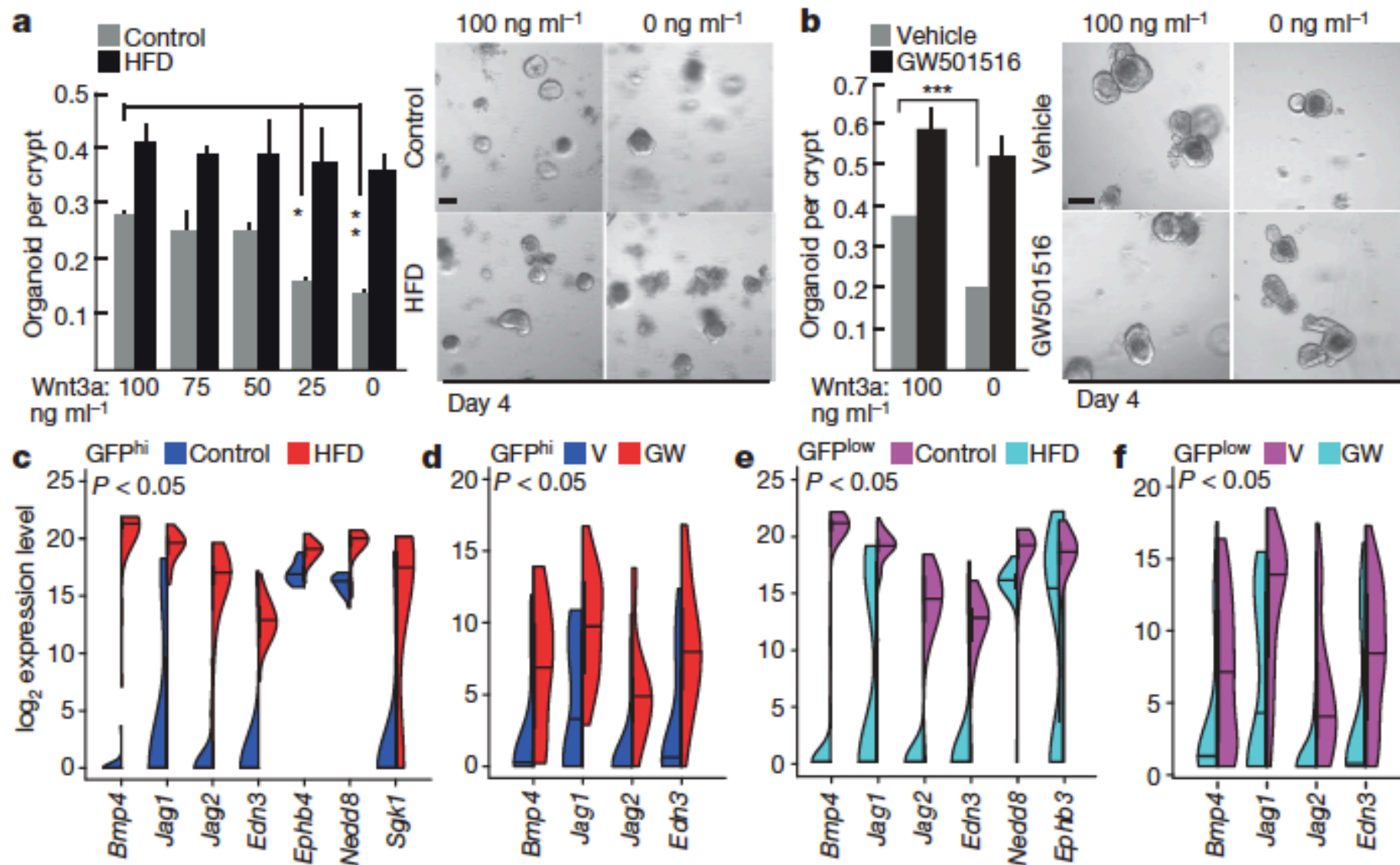
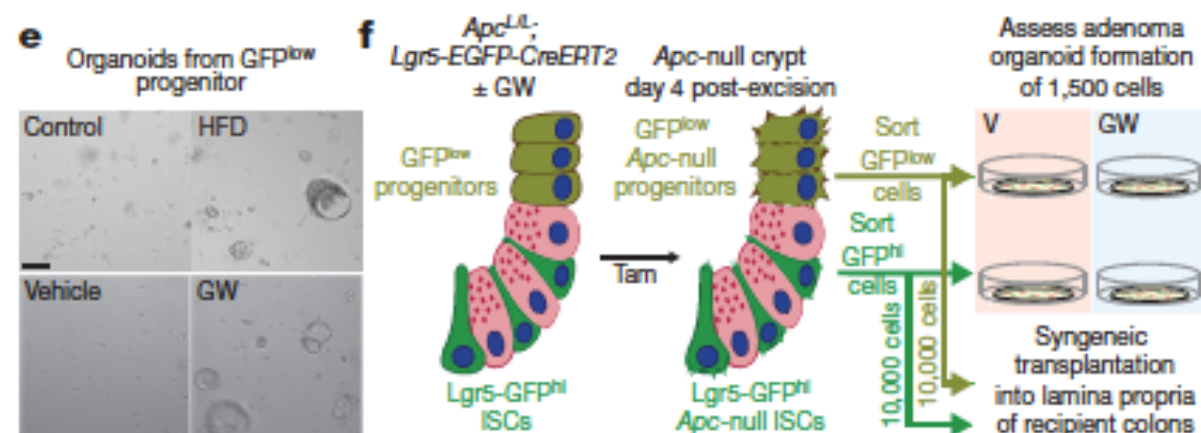
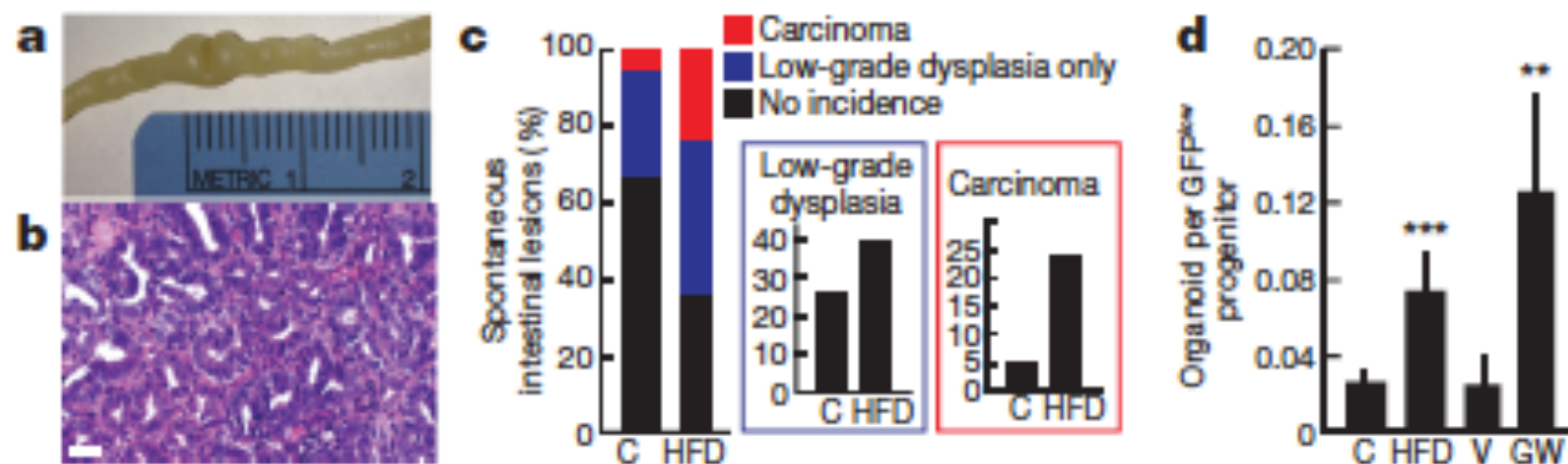
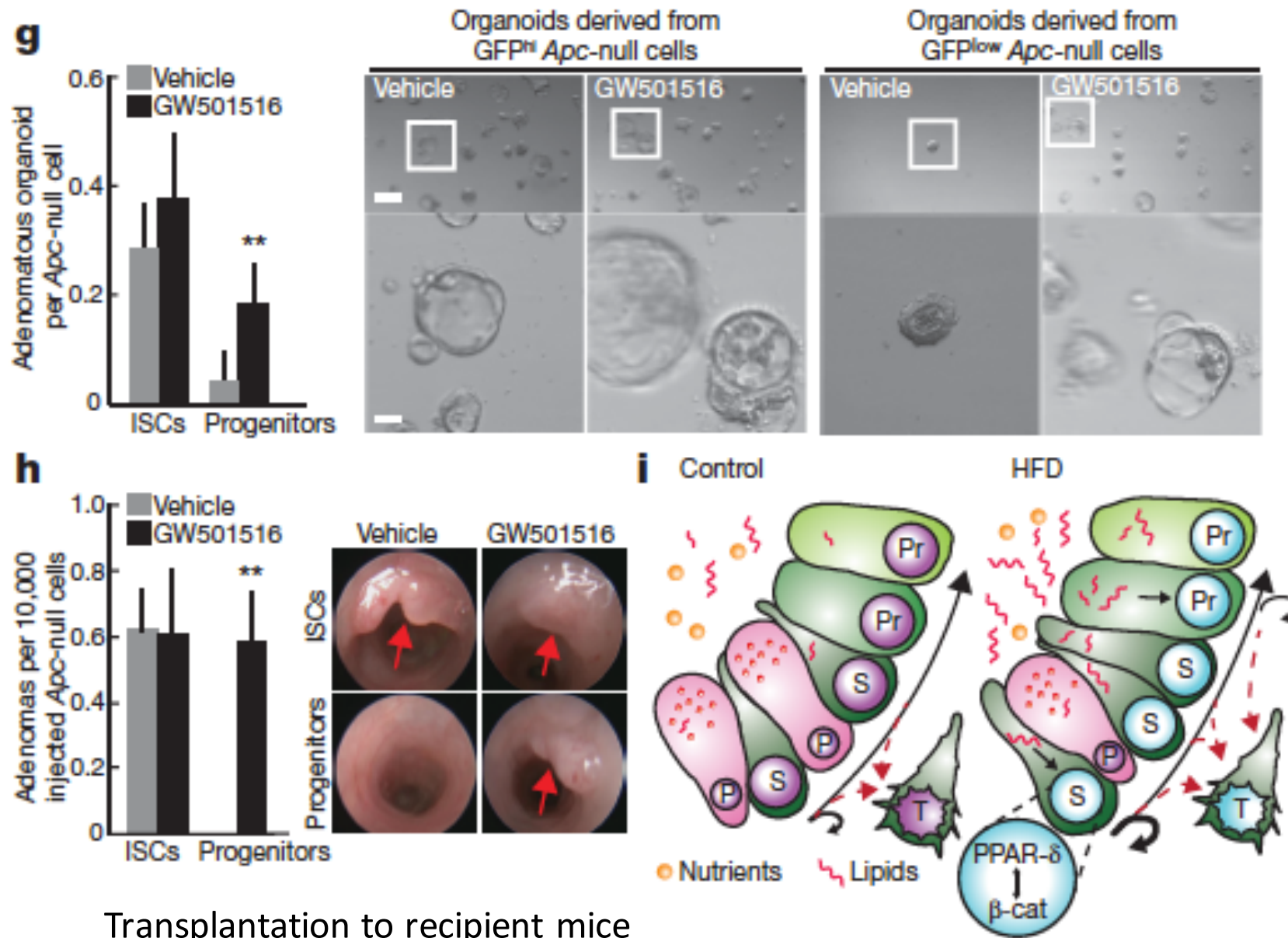


Figure 4 | HFD-induced PPAR- δ signalling induces expression of a subset of β -catenin target genes.





Transplantation to recipient mice

Figure 5 | PPAR- δ activation confers organoid and tumour-initiating capacity to non-stem-cells.