

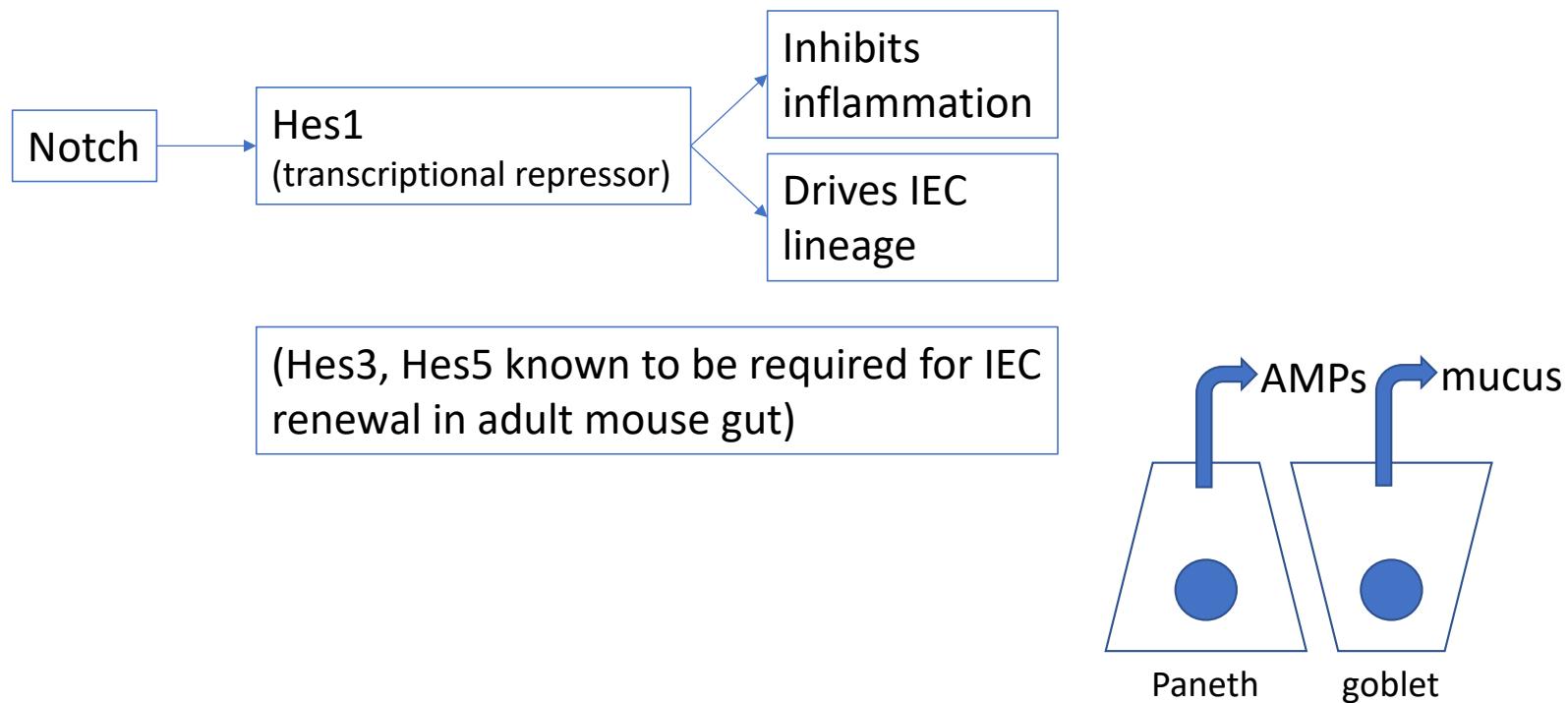
Epithelial Hes1 maintains gut homeostasis by preventing microbial dysbiosis

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Recent advancements suggest that in addition to its roles in developmental processes, transcription repressor hairy and enhancer of split 1 (Hes1) also acts as a key regulator of inflammatory responses. A healthy gut microbiota ecology is critical for establishment of tissue homeostasis. However, the role of epithelial Hes1 in regulating intestinal microbiota ecology and intestinal homeostasis remains unexplored. Here we show that epithelial Hes1 deficiency leads to intestinal microbial dysbiosis and disturbed homeostasis. Both inducible Hes1 deletion and intestinal epithelial cell (IEC)-intrinsic Hes1 deletion resulted in loss of Bacteroidetes in ileum and increase of *Escherichia coli* and *Akkermansia muciniphila* in colon. Loss of Bacteroidetes closely correlated with decreased expression of commensal-dependent antimicrobial genes, leading to impaired resistance against pathogenic bacterial colonization. Moreover, Hes1 deficiency enhanced susceptibility to Dextran sodium sulphate-induced intestinal inflammation. Of note, transfer of Hes1-deficient-mouse-derived fecal microbiota promoted intestinal inflammation. The increase of *A. muciniphila* in colon was associated with Hes1-deficiency-induced unbalanced mucosal microhabitats. Thus, our results support that IEC-intrinsic Hes1 maintains gut homeostasis by preventing microbial dysbiosis partially through regulating mucosal microhabitats.

IEC-KO and inducible KO

Required background for paper



Significance:

It has been proposed that adult intestine may harbor reservoirs for bacterial cells that can be re-seeded into the intestinal lumen¹⁰ and thus alterations of endogenous genetic factors that influence mucosal reservoirs may have long-lasting effects on shaping microbiota ecology.

Hes1 deficiency leads to microbiota differences

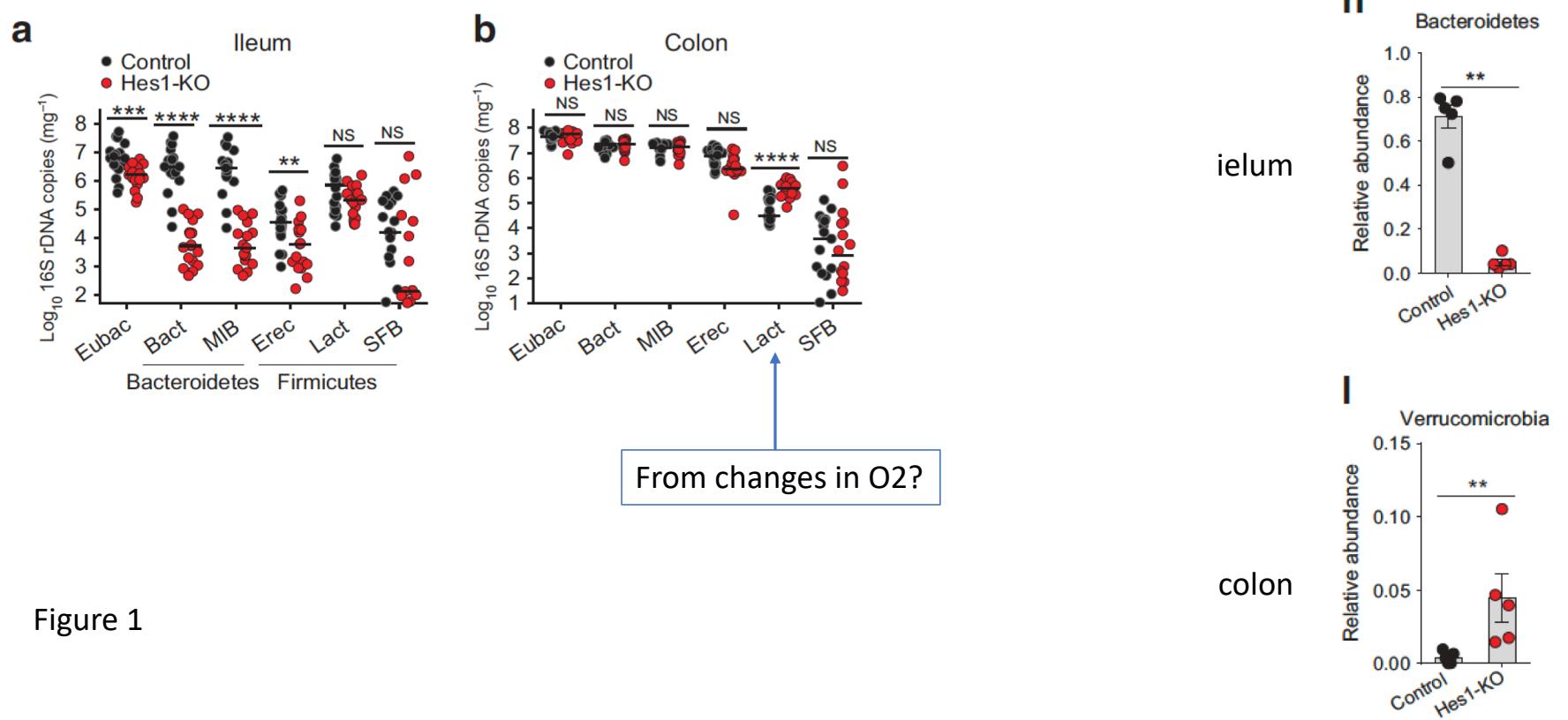


Figure 1

Clear distinction between Hes1+ and Hes1-

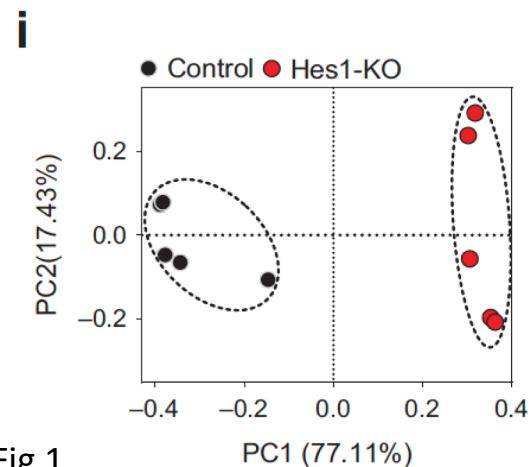
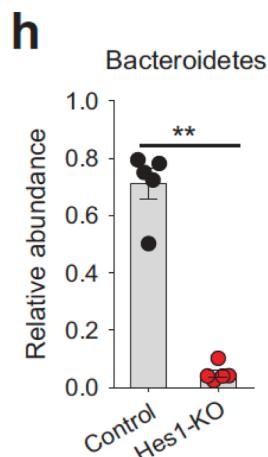
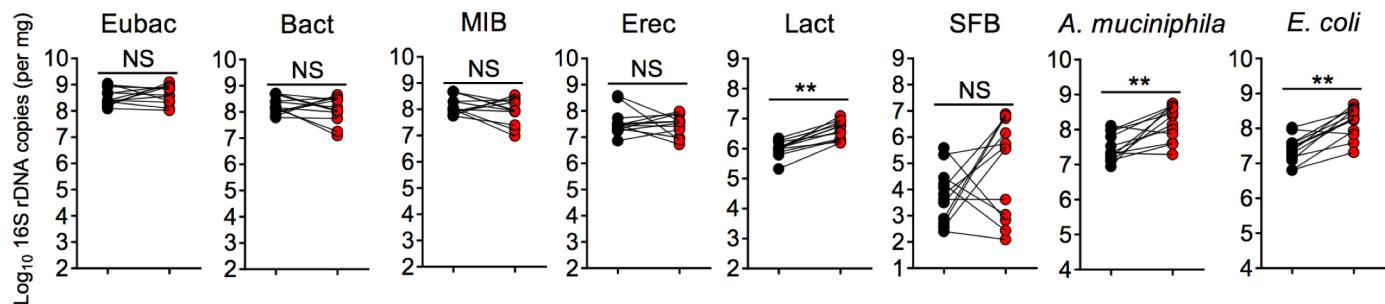


Fig 1

● Day 0 ● Day 11

Fig S2b, same mouse, feces before and after depletion



Hes1 loss leads to decreased AMPs

Figure 2

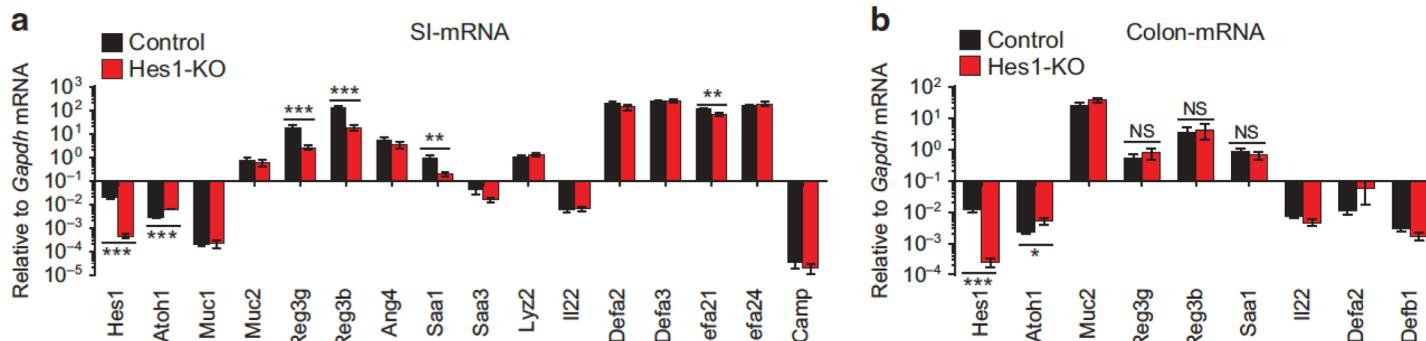
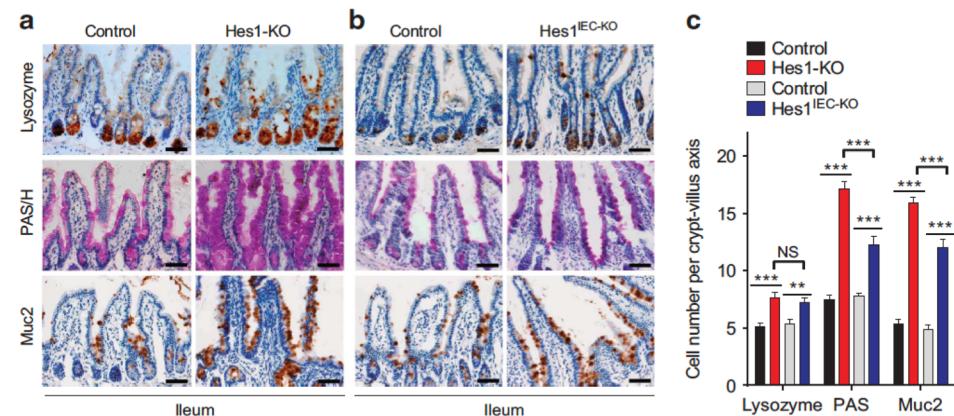
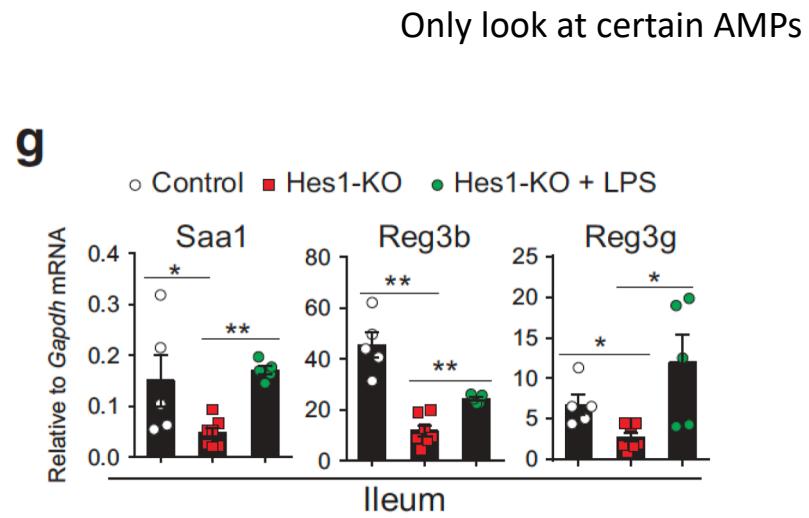
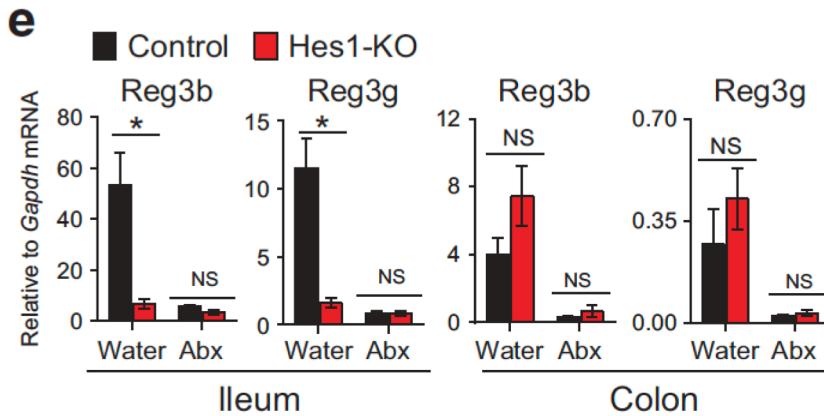


Figure 5
Increased Paneth cells
Authors do not address



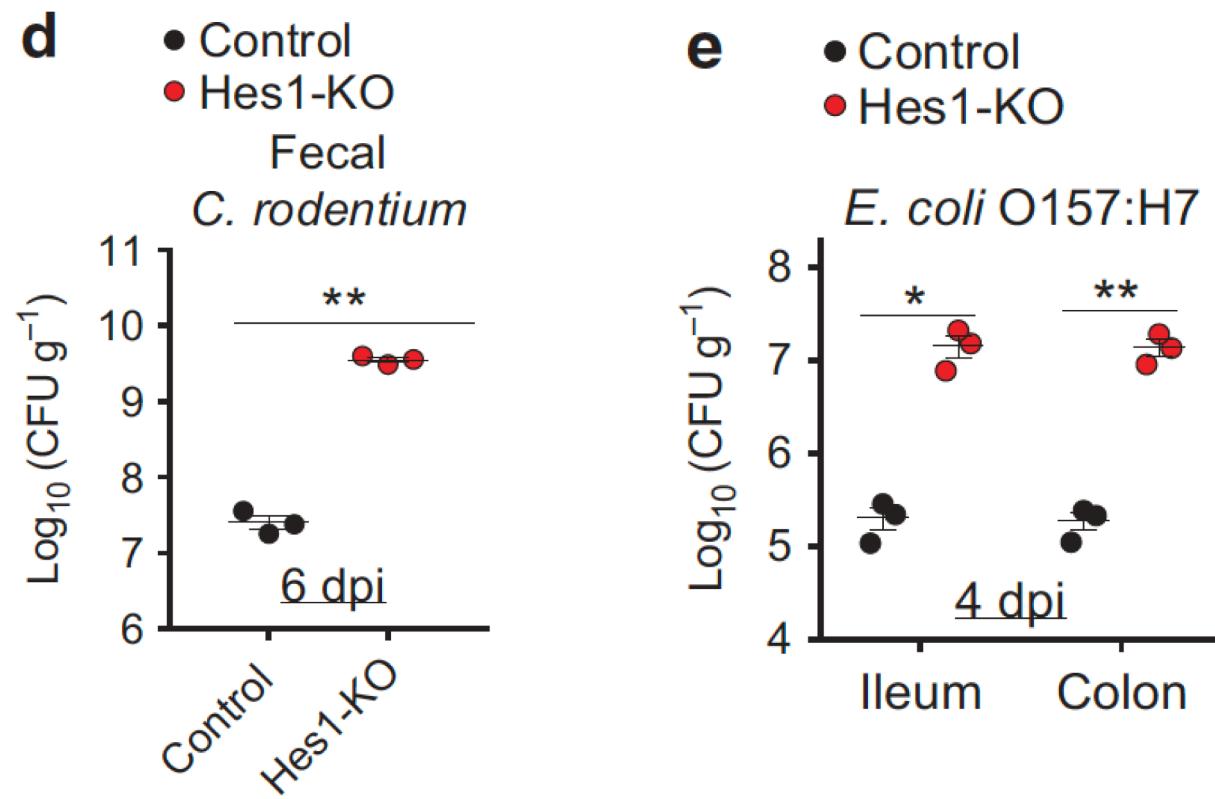
AMP expression is commensal-dependent

Figure 2



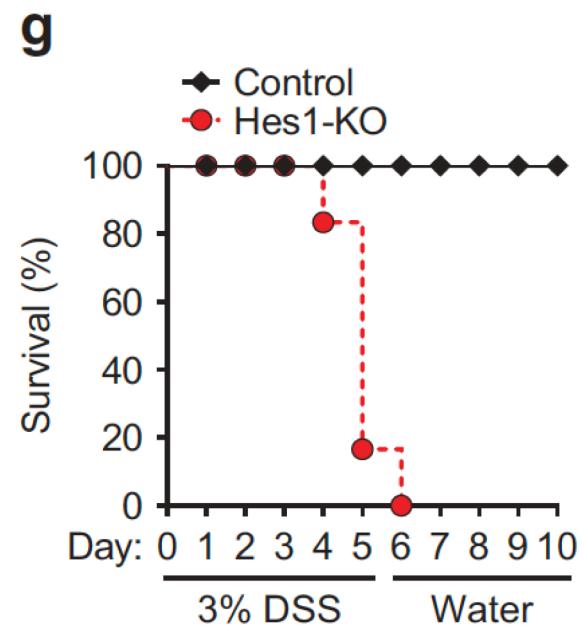
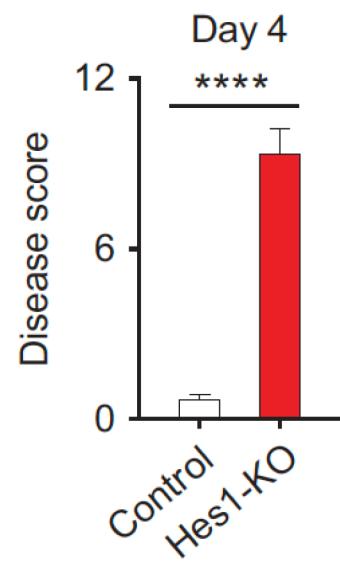
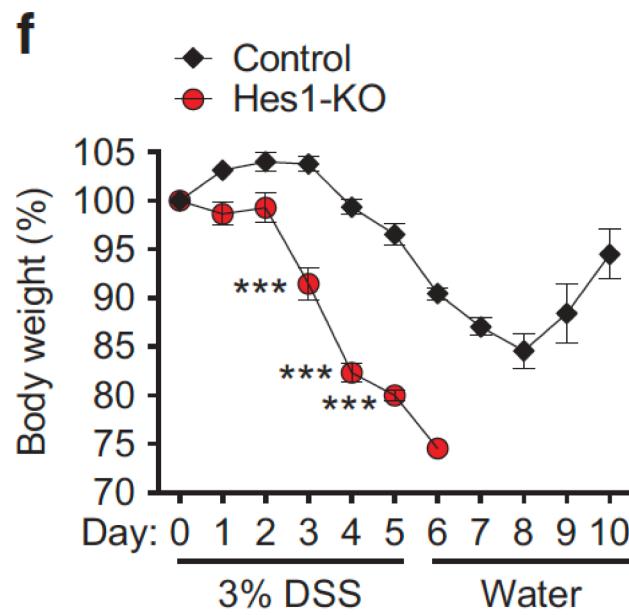
Hes1 required for colonization resistance

Figure 3



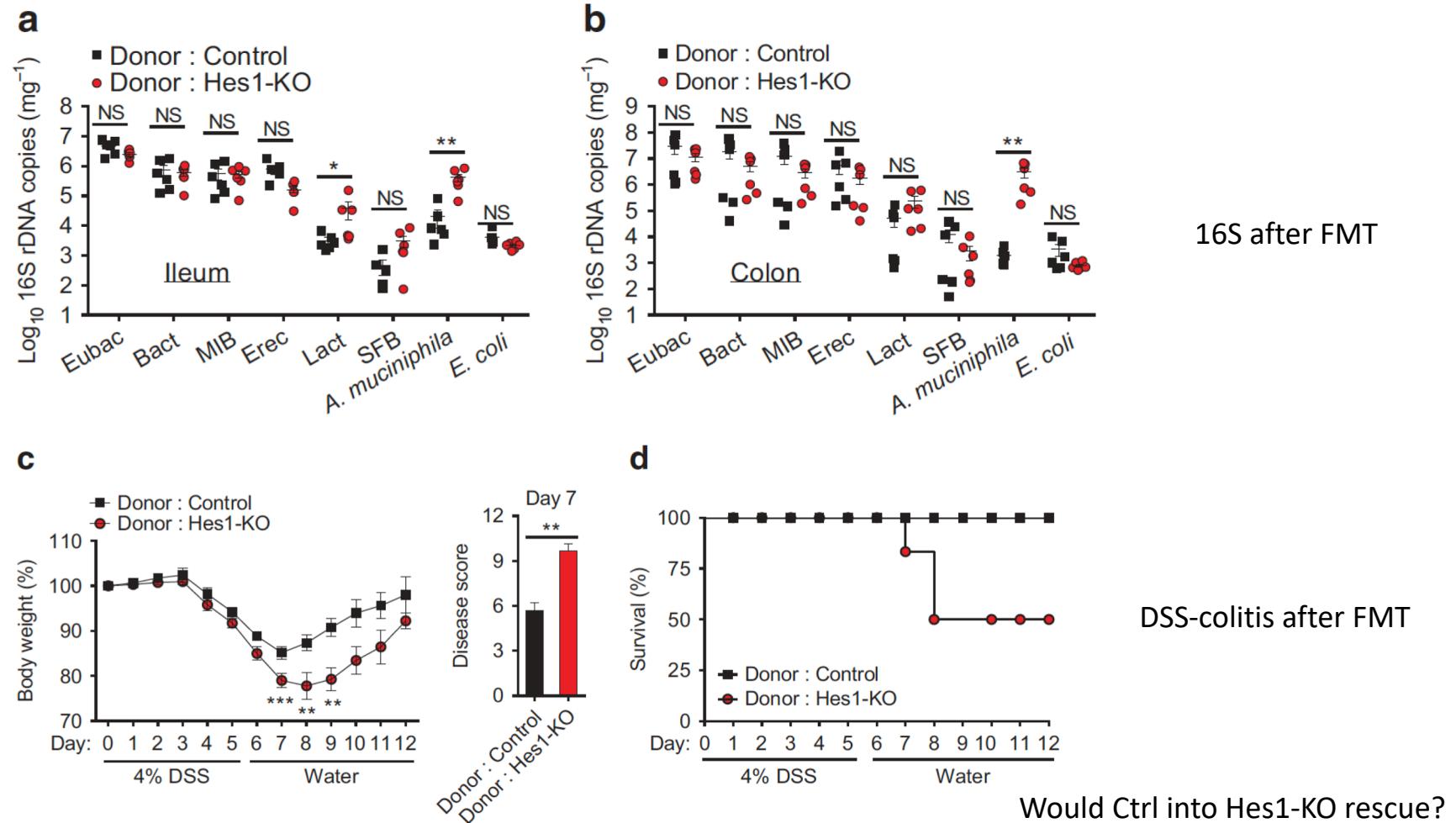
Hes1 loss sensitizes to DSS-colitis

Figure 3



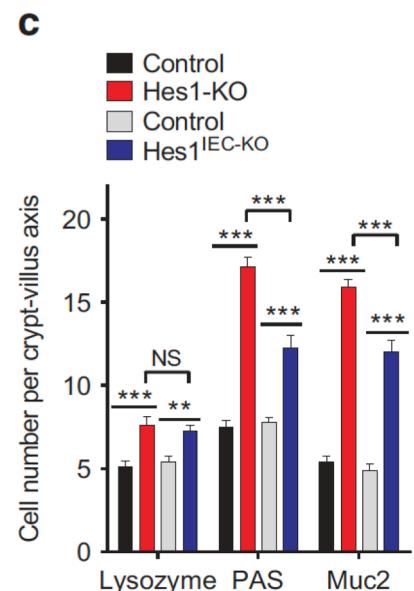
Inflammation is also commensal dependent

Figure 4

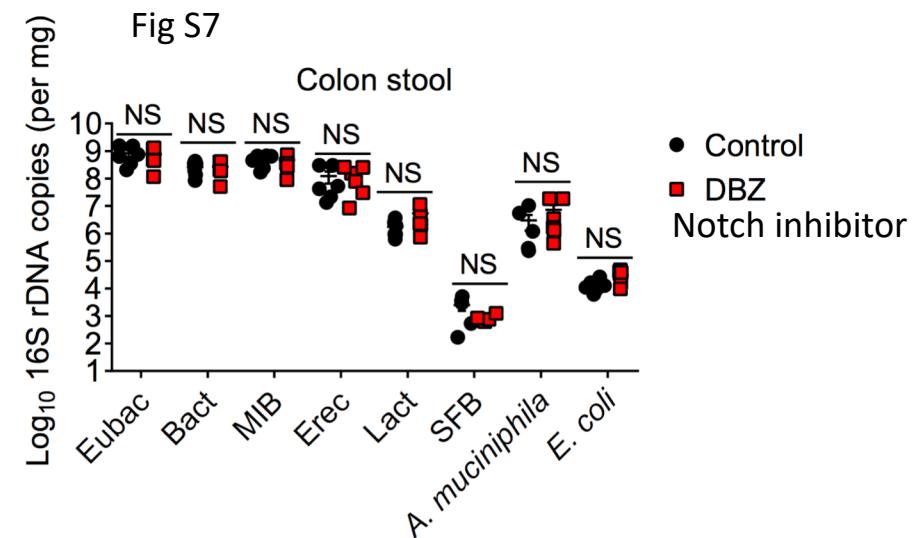


Hes1 alters mucus

Figure 5



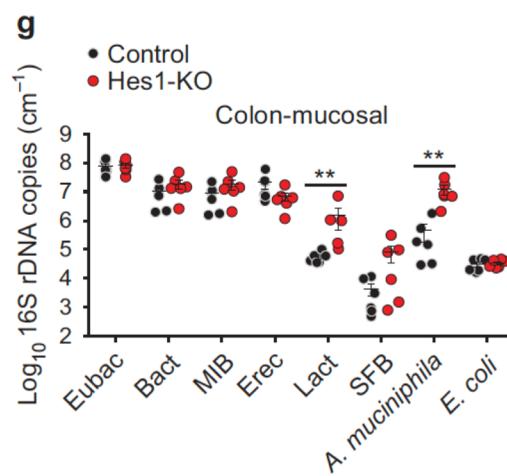
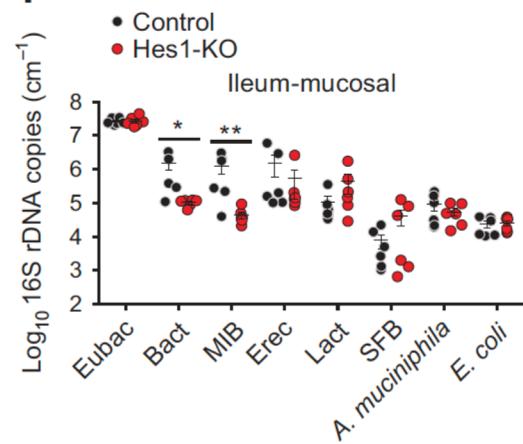
“mucus hyperplasia”



Which is not simply due to lost Notch signaling (yes hyperplasia, no dysbiosis)

Hes1 altered mucus alters microbiota

Figure 5 f



Unclear how they ruled out the possibility that Akkermansia → mucus

