Gut microbiota utilize immunoglobulin A for mucosal colonization

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Abstract

The immune system responds vigorously to microbial infection, while permitting life-long colonization by the microbiome. Mechanisms that facilitate the establishment and stability of the gut microbiota remain poorly described. We discovered that a sensor/regulatory system in the prominent human commensal *Bacteroides fragilis* modulates its surface architecture to invite binding of immunoglobulin A (IgA). Specific immune recognition facilitated bacterial adherence to cultured intestinal epithelial cells and intimate association with the gut mucosal surface in vivo. The IgA response was required for *B. fragilis*, and other commensal species, to occupy a defined mucosal niche that mediated stable colonization of the gut through exclusion of exogenous competitors. Therefore, in addition to its role in pathogen clearance, we propose that IgA responses can be co-opted by the microbiome to engender robust host-microbial symbiosis.

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Fig. 1 *Bacteroides fragilis* resides as aggregates on the colon epithelium in a CCF-dependent manner.

Transmission Electron Microscopy (TEM) images.

***B. fragilis* shown by green arrows and host epithelial cells are yellow arrows. Yellow lines show the host glycocalyx.**

Wildtype *B. fragilis* forms close associations with the epithelium (panels A, B, F) and is found in crypts (panel C). *ccf*-gene knockout *B. fragilis* shows less association with epithelium (panels D, F, E).

Wildtype *B. fragilis* has a thick, fuzzy-looking capsule around its cells (panels G and I), while the *ccf* knockout does not (panels H and I).

***ccf* is one of the genes that was under selection in Jay and Tami's work. It is up-regulated in the gut and appears to be involved in binding host mucin.**

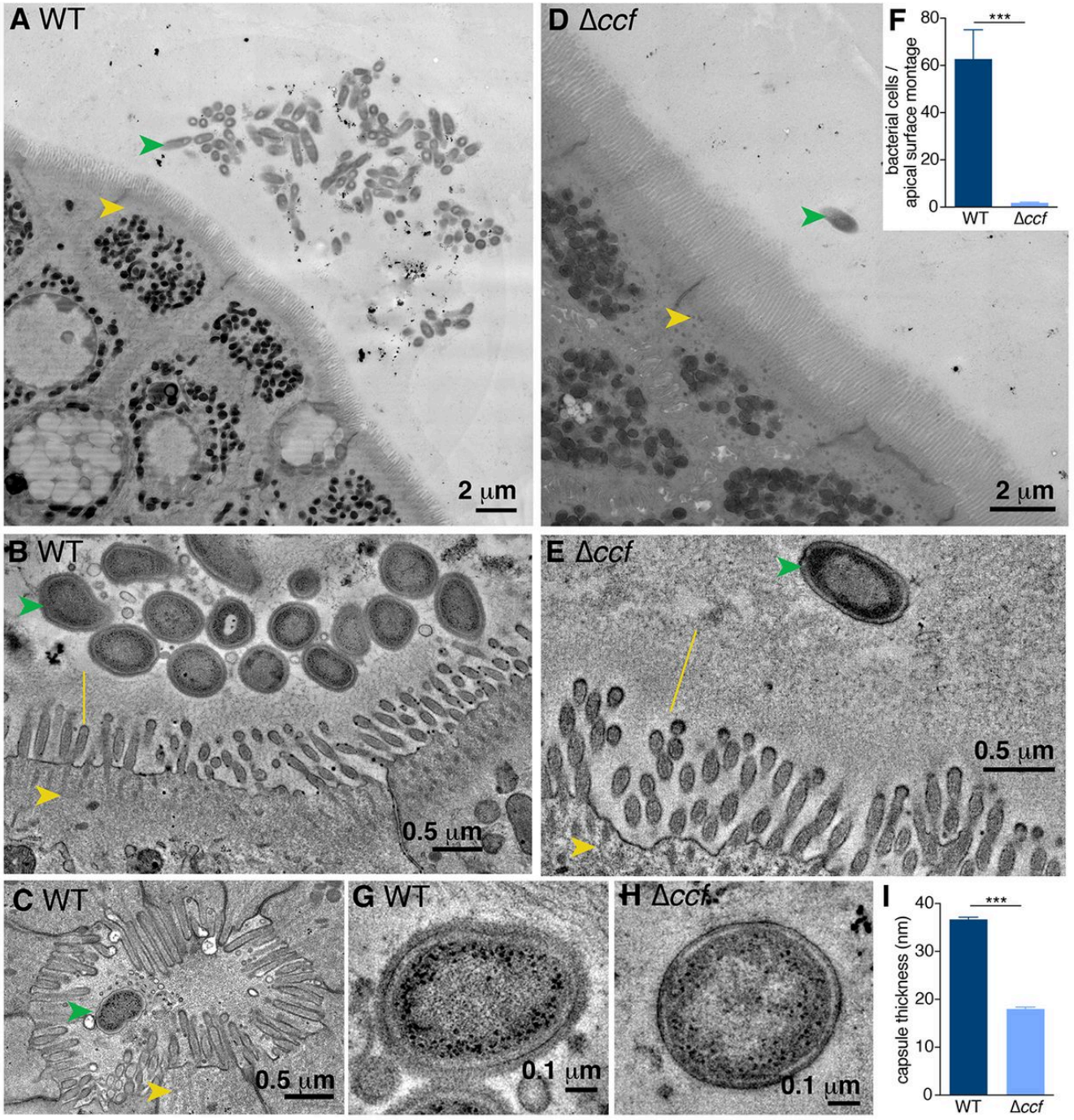
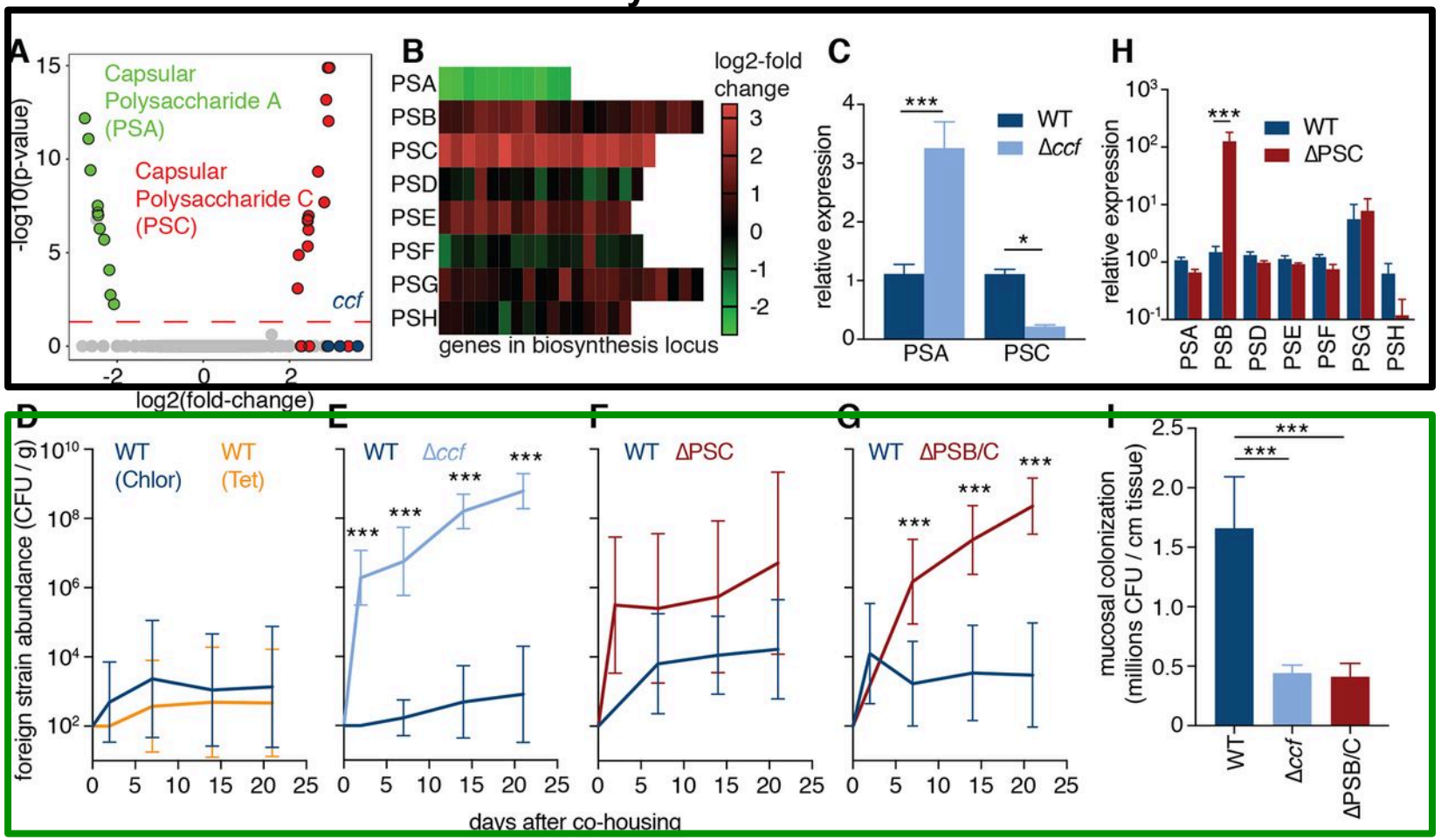


Fig. 2 Specific capsular polysaccharides, regulated by ccf, are necessary for single-strain stability.

***ccf* expression alters expression of capsular polysaccharide genes. In particular, PSA is downregulated and PSC is upregulated.**



Slightly confusing plots. Each line represents how many *invading* strain cells are present over time (label indicates the *original colonizing* strain). Panel D shows how wildtype strains cannot invade another wildtype strain once it has established in the mouse. Panels E-G show how initial colonization with *ccf* or capsular polysaccharide gene knockout strains can be invaded by the wildtype (i.e. they are unable to exclude the wildtype, probably due to low niche-saturation; see panel I)

Fig. 3 B. fragilis induces a specific IgA response, dependent on ccf regulation of surface capsular polysaccharides, which enhances epithelial adherence.

Knocking out the *ccf* gene influences host gene expression. Half of the genes that differed in expression levels encoded immunoglobulin variable chains.

Wildtype B. fragilis is bound more by IgA than either knockout *in vivo*.

IgA induced by *ccf* knockout *in vivo* has lower efficiency binding the wildtype *in vitro* (G).

IgA-bound bacteria adhere more to epithelial tissue (H).

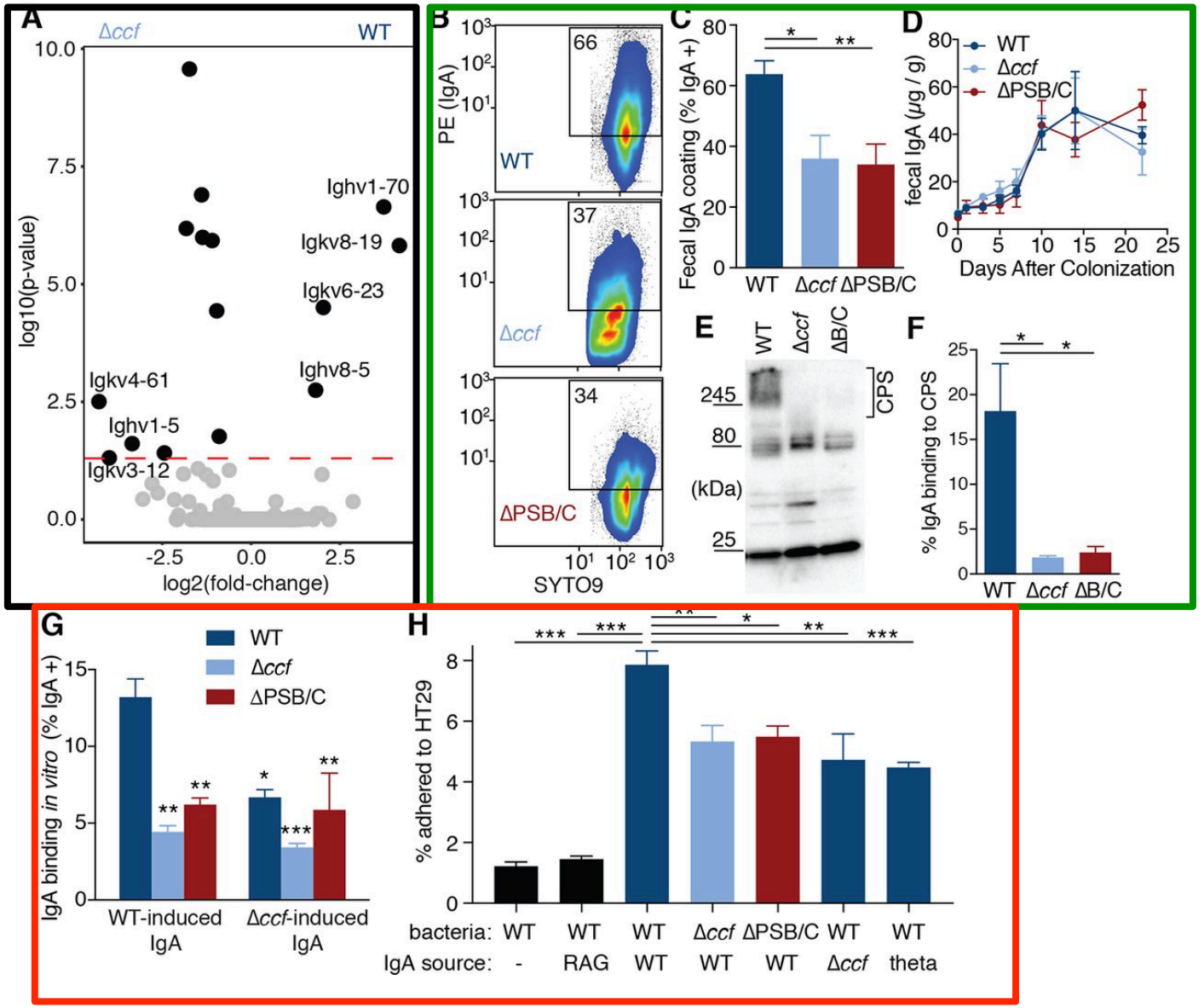


Fig. 4 IgA production in vivo is necessary for single-strain stability, mucosal colonization, and epithelial aggregation.

in vivo **IgA levels were depleted by applying an anti-CD20 antibody to deplete B cells (A).**

B. fragilis **was treated with IgA from Rag1-/- mice (i.e. no adaptive immunity), IgA from control mice not treated with CD20 antibody, and mice treated with CD20 antibody. CD20 antibody treatment resulted in IgA that does not promote binding to the epithelium (B).**

In the presence of CD20 antibody, and in IgA knockout mice, ***B. fragilis*** **strains can be invaded by a foreign strain (i.e. low niche saturation) (C-D). Fewer** ***B. fragilis*** **cells are found near the epithelium in IgA knockout mice (E-G).**

In the presence (but not in the absence) of IgA, there were significant differences in microbial community structure between the colonic lumen and mucus (H).

Loss of IgA resulted in reduced ***B. fragilis*** **and Rikanellaceae abundances, but also led to an increase in Blautia and segmented filamentous bacteria (I). All of these bacterial taxa were highly IgA-coated in wildtype SPF mice. Thus, IgA can serve to both enrich and deplete bacterial populations near the colonic epithelium.**