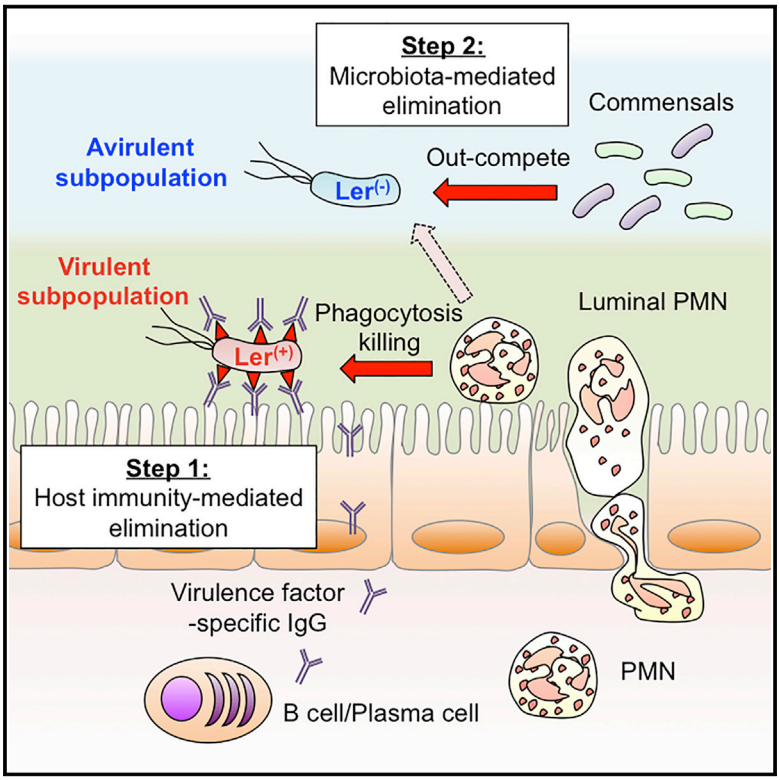
Article

Cell Host & Microbe

Humoral Immunity in the Gut Selectively Targets Phenotypically Virulent Attaching-and-Effacing Bacteria for Intraluminal Elimination

Graphical Abstract



Highlights

- Enteric pathogens reside as phenotypically virulent and avirulent subpopulations
- Enteric pathogen infection induces virulence-factor-specific IgG
- Virulent pathogens, but not commensals or avirulent pathogens, are recognized by IgG
- IgG-bound virulent bacteria are eliminated intraluminally by migrated neutrophils

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In Brief

Kamada et al. demonstrate that humoral immunity elicits selective elimination of phenotypically virulent bacteria in the gut. Immunoglobulin recognizes virulent bacteria, which leads to their selective elimination by neutrophils in the intestinal lumen. Phenotypically avirulent bacteria that are not targeted by host immunity are outcompeted by the commensal microbiota.

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Humoral Immunity in the Gut Selectively Targets Phenotypically Virulent Attaching-and-Effacing Bacteria for Intraluminal Elimination

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SUMMARY

Virulence factors expressed by enteric bacteria are pivotal for pathogen colonization and induction of intestinal disease, but the mechanisms by which host immunity regulates pathogen virulence are largely unknown. Here we show that specific antibody responses are required for downregulation of virulence gene expression in *Citrobacter rodentium*, an enteric pathogen that models human infections with attaching-and-effacing bacteria. In the absence of antibodies against the pathogen, phenotypically virulent *C. rodentium*, accumulated and infected the epithelium and subsequently invaded the lamina propia, causing host lethality. IgG induced after infection recognized virulence factors and bound virulent bacteria within the intestinal lumen, leading to their engulfment by neutrophils, while phenotypically avirulent pathogens remained in the intestinal lumen and were eventually outcompeted by the microbiota. Thus, the interplay of the innate and adaptive immune system selectively targets virulent *C. rodentium* in the intestinal lumen to promote pathogen eradication and host survival.

INTRODUCTION

Host innate and adaptive immune responses against invading pathogenic microorganisms are critical for pathogen eradication and host survival. To establish infection and successful replication, pathogens have evolved many strategies to acquire nutrients, circumvent host defenses, and exploit the host cellular machinery (Roy and Mocarski, 2007). A key strategy is the expression of specific virulence factors that enable pathogens to colonize their host and replicate within its tissues by subverting host signaling pathways (Okumura and Nizet, 2014; Roy and Mocarski, 2007). While the virulence factors involved in pathogen colonization and invasion have been heavily studied, the immune mechanisms that regulate the expression of bacterial virulence during infection are largely unknown. Furthermore, it remains unknown whether the host immune system can recognize virulence factors to promote pathogen clearance. Enterohemorrhagic *Escherichia coli* (EHEC) and enteropathogenic *E. coli* (EPEC) are major causes of diarrheal disease and lethal infections worldwide (Kaper et al., 2004; Mundy et al., 2005). These Gram-negative bacteria are food- and water-borne non-invasive pathogens that attach to and colonize the intestinal tract by inducing characteristic attaching-and-effacing (A/E) lesions on the intestinal epithelium, leading to transient enteritis or colitis in humans (Kaper et al., 2004; Mundy et al., 2005). The genomes of EHEC, EPEC and the related natural mouse pathogen *Citrobacter rodentium* harbor the locus for enterocyte effacement (LEE) pathogenicity island, which is critical for these pathogens to colonize hosts and cause pathology (Deng et al., 2001; Deng et al., 2004). The LEE virulence genes include those encoding several effector proteins, a type III secretion system (T3SS), proteins that mediate intimate epithelial attachment such as intimin and its translocated receptor as well as Ler, a global regulator that is required for expression of most, if not all, LEE genes (Deng et al., 2004). Notably, patients infected with EPEC develop IgG antibodies reactive to LEE virulence factors (Jenkins et al., 2000; Li et al., 2000; Martinez et al., 1999). However, the physiological relevance of such antibodies including their role in pathogen eradication is unclear.

C. rodentium is widely used to model human infections with EPEC and EHEC (Collins et al., 2014). In the early phase of the infection, *C. rodentium* expresses LEE virulence genes (Deng et al., 2001, 2004) that allow it to localize and replicate near the epithelium where competing commensals are largely absent (Kamada et al., 2012). By day 12 post-infection (p.i.), the expression of LEE virulence is downregulated, and as a result, non-LEE expressing pathogens relocate to the lumen where they are outcompeted by resident microbes (Kamada et al., 2012). Infection of germ-free (GF) mice with *C. rodentium* is also associated with downregulation of LEE virulence at the late stages of infection,