CLINICAL IMPLICATIONS OF BASIC RESEARCH

Bugging of the Intestinal Mucosa

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An enormous array of adaptive mechanisms on both sides of the host–microbial interface reflects a complex coevolution. Deciphering the cross-talk at this interface may yield new insights into its relevance to health and disease. For example, Barnich et al.[1] have recently described a host response to bacteria in patients with Crohn's disease.

A vast variety and number of microorganisms normally live within the human intestine.[2] The intestinal microbiome coexists with the intestinal immune system and is required for normal intestinal immune development and homeostasis. Several mechanisms prevent luminal bacteria, or specific subgroups thereof, from damaging the body or entering it in excessive numbers. These include a mucus layer, antimicrobial peptides, IgA, the epithelial-cell barrier, immune cells within the intestine, and competition with other luminal bacteria. Disruption or imbalance of these protective components can result in inappropriate intestinal inflammation, as in Crohn's disease and ulcerative colitis (inflammatory bowel disease).

Investigators have long sought to identify a microorganism that causes inflammatory bowel disease; mycobacterial and yersinia species were past suspects but have not been proved guilty. At present, inflammatory bowel disease is believed to result from excessive intestinal immune activation that is driven by either luminal bacteria as a whole or perhaps particular bacterial subpopulations.[3]

In the host–microbial dialogue, proximity may be an important factor driving host responses. For instance, an increased number of adherent invasive *Escherichia coli* adhere to the ileal mucosa of patients with Crohn's disease. Increased bacterial adherence is not unique to Crohn's disease; various stresses, such as surgery and starvation, modify the characteristics of bacteria in the intestinal lumen, rendering them more adhesive to the intestinal mucosa. It is not clear whether the increased number of adherent invasive *E. coli* seen in patients with Crohn's disease is a primary or secondary event and to what extent it contributes to intestinal inflammation.

Barnich et al. have uncovered a mechanism by which adherent invasive *E. coli* interact with the epithelial cells of persons with Crohn's disease. They discovered that multiple strains of adherent invasive *E. coli* adhere far better to epithelial cells isolated from the ileum of persons with Crohn's disease than they do to cells of the same type isolated from unaffected persons. This suggests that there are specific alterations of the ileal epithelial cells of persons with Crohn's disease that allow adherent invasive *E. coli* to adhere to a greater extent.

The authors discovered that type 1 pili — surface organelles that are critical for maintaining the colonization of epithelial surfaces, especially those of the genitourinary and gastrointestinal tracts — of adherent invasive *E. coli* mediate the ability of the bacterium to adhere to ileal epithelial cells. They then tried to identify the epithelial-cell molecule or molecules responsible for adherence. Mannose was found to diminish adherence, thus implicating a mannose-containing glycoprotein.

Of the various candidate proteins known to enable bacterial adhesion, both carcinoembryonic antigen–related cell-adhesion molecule 6 (CEACAM6) and CEACAM5 are overexpressed in the ileal epithelial cells of patients with Crohn's disease, as compared with those of controls. Barnich et al. showed that this up-regulation occurs in both inflamed and noninflamed regions of the ileum, but not in the colon.

The investigators then found that adherent invasive *E. coli* lost their adherence to enterocytes in patients with Crohn's disease only after the blockade of CEACAM6. Moreover, the presence of adherent invasive *E. coli* causes an increase in the expression of CEACAM6 on the surface of cultured intestinal cells, as does incubation with inter-

feron-γ or tumor necrosis factor α (TNF-α), proinflammatory mediators of which increased levels are typically found in the intestine of patients with Crohn's disease. The same group of investigators had previously shown that adherent invasive *E. coli* can induce the secretion of TNF-α from cultured macrophages.[4] Therefore, adherent invasive *E. coli* may directly and indirectly induce epithelial cells to up-regulate CEACAM6, thereby enabling their own adhesion to these cells (Fig. 1).

An elevated level of CEACAM6 expression may turn out to be a marker of increased levels of inflammatory cytokines in the absence of inflammation on endoscopic or histologic examination, although its degree of specificity will need to be assessed.

So far, attempts to treat inflammatory bowel

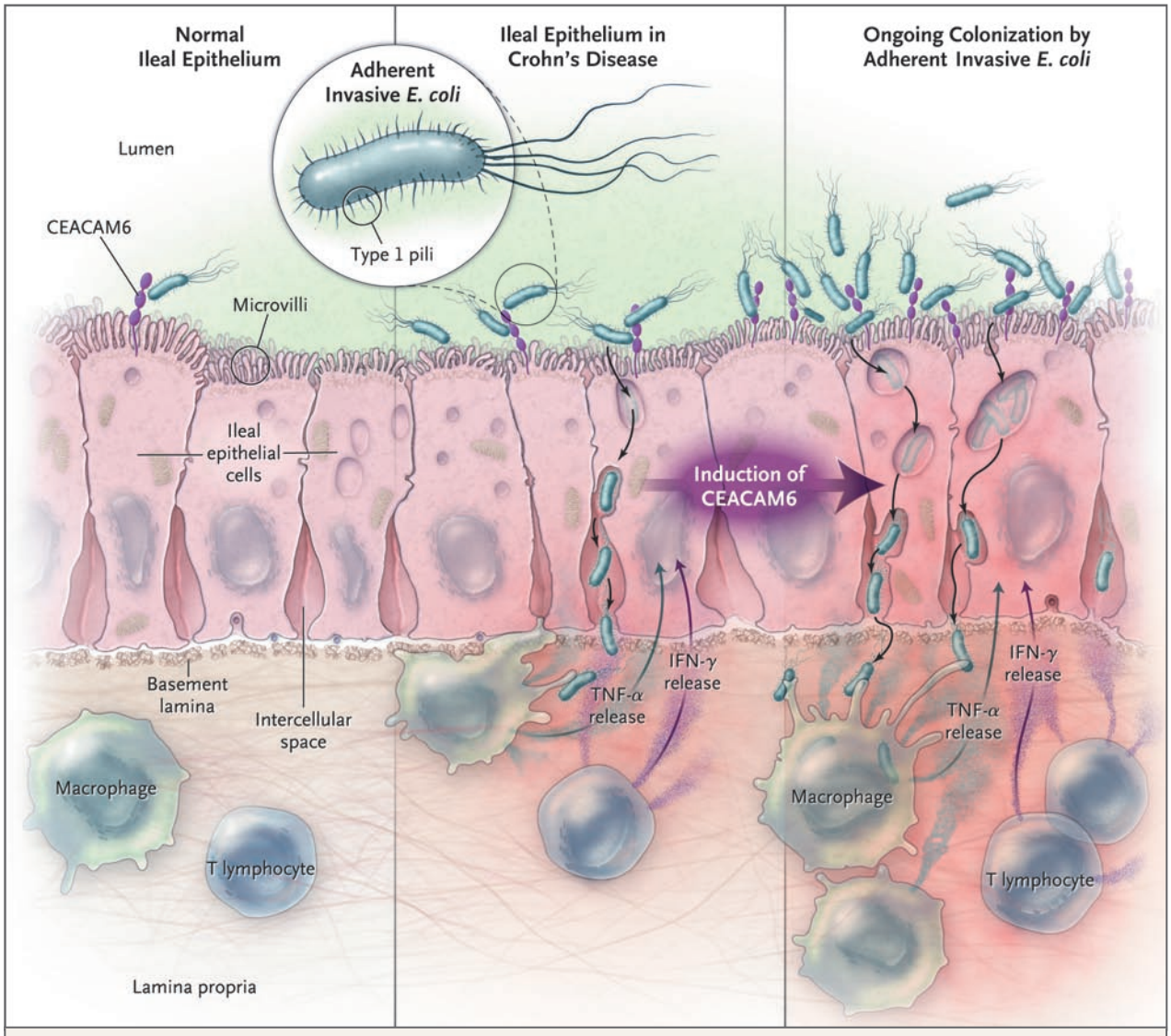

Figure 1. Crohn's Disease and Carcinoembryonic Antigen–Related Cell-Adhesion Molecule 6 (CEACAM6).

A potential model comparing the normal ileum and the ileum in Crohn's disease is shown. A study by Barnich et al.[1] showed that the presence of the proinflammatory cytokines interferon-γ (IFN-γ) and tumor necrosis factor α (TNF-α), as well as exposure to adherent invasive *Escherichia coli*, results in increased expression of CEACAM6 in the ileal epithelium of patients with Crohn's disease. Increased CEACAM6 expression then mediates the adhesion of adherent invasive *E. coli* to the ileal epithelium; mechanisms of subsequent bacterial entry are not fully defined. Interactions among adherent invasive *E. coli*, CEACAM6, and inflammatory mediators such as TNF-α and IFN-γ in the inflammatory amplification loop are incompletely defined.

disease by modulating the intestinal microbiome (for example, with the use of probiotics and antibiotics)[5] have met with mixed results, probably reflecting the enormous complexity of the interactions within the microbiome and the host. By increasing the adhesion of adherent invasive *E. coli*, CEACAM6 may contribute to an amplification loop of increased colonization and inflammation. If adherent invasive *E. coli* are critical to the initiation or maintenance of inflammation in Crohn's disease, blocking of the interaction between the type 1 pili of adherent invasive *E. coli* and epithelial CEACAM6 (e.g., with the use of monosaccharides, oligosaccharides, or anti-CEACAM6 antibodies) might serve as a specific means of disrupting the inflammatory amplification loop.

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