into the exact crystallographic orientation of quantum dots within the superlattice. The researchers identified two distinct orientations that, after chemical treatment to initiate epitaxial fusion, led to the formation of two distinct topologies. More importantly, the detailed analysis of the structures before and after epitaxial fusion enabled the identification of the specific lattice deformation and quantum dot orientation involved in the transformation.

This mechanistic insight is an important advance in our understanding of how collective, multiscale topotaxy and epitaxy leads to the formation of mesoscale 'crystals of crystals'. Whereas the proposed mechanism involves lattice deformation and quantum dot rotation, the detailed mechanistic description of the sequence of transformations remains an outstanding question. Understanding, and ultimately controlling, the complex interplay of thermodynamic and kinetic aspects of this transformation should enable the formation of even higher fidelity epitaxially connected superstructures. Beyond the specific model of polyhedral PbSe quantum dots demonstrated in this work it will be interesting to see how this mechanistic understanding can guide future efforts to create epitaxially connected quantum dot solids with other structures or compositions. From a processing perspective, important challenges related to the formation of macroscopic cracks due to volume reduction accompanying the transformation remain to be resolved. Multicomponent (such as binary or ternary) superlattices present a very intriguing future direction in this sense since advanced processing knowhow could enable the formation of superstructures in which one or both sublattices are epitaxially connected. The extent of connectivity between constituent dots in the superlattice thus presents a valuable degree of freedom in the fabrication and study of artificial materials with programmable optical and electronic structure. ❐

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INFLAMMATORY BOWEL DISEASE

Materials modulate immunity and gut microbiome

In a murine model of acute colitis, hyaluronic acid–bilirubin-based nanomaterials have been shown to modulate immune response and the gut microbiome, as well as restore the epithelial barrier.

Ankur Singh

Perturbations in beneficial host–microbe interactions cause an aberrant immune response to enteric microbiota and are implicated in metabolic disorders and inflammatory bowel diseases (IBDs), such as ulcerative colitis and Crohn's disease[1]. Inflammation in IBDs occurs in proximity to the epithelium and mucosa, meaning that colonocytes and the diffusely abnormal epithelium are implicated in the pathogenesis. A critical translational challenge is to deliver therapeutics that can treat IBDs. Writing in *Nature Materials*, James Moon and colleagues demonstrate that engineered nanomaterials can perturb the intestinal bacteria and dysregulated innate immunity to treat IBD in mice[2]. The researchers developed a nanoscale hyaluronic acid–bilirubin nanomedicine (HABN) conjugate that enables aqueous formulation of water-insoluble bilirubin using a nano-aggregation process. The HABNs accumulate in the inflamed colonic epithelium, restore the gut barriers, alter the gut commensal microbiota likely to be due to an increase in anti-microbial peptides, and regulate innate immune response to manifest a therapeutic response in a mouse model of colitis (Fig. 1).

The development of advanced sequencing techniques and computational tools has revolutionized the study of the gut microbiome[3,4]. However, therapeutic manipulation of gut-associated diseases remains challenging. A ten-year assessment indicates that ~30–50% of patients with IBD do not respond to current anti-inflammatory treatments[5], necessitating the need for new therapies. A potential therapeutic biomolecule for IBD is bilirubin, a natural antioxidant and an immunosuppressant. Unconjugated bilirubin has protective effects in experimental colitis[6]; however, bilirubin is hydrophobic, which makes delivery difficult and excessive dosing can result in serious toxic events limiting its clinical development. Previously, Lee et al.[7] developed polyethylene glycol (PEG)-conjugated bilirubin nanoparticles and intravenous injection resulted in preferential accumulation in the colon of a colitis mouse model, inhibiting the progression of acute inflammation. However, Moon and colleagues demonstrate that oral administration of HABN in the colitis mice normalized the expression of tight junction-associated proteins that play pivotal roles in gut homeostasis and altered microbiome. HABNs accumulated in the damaged

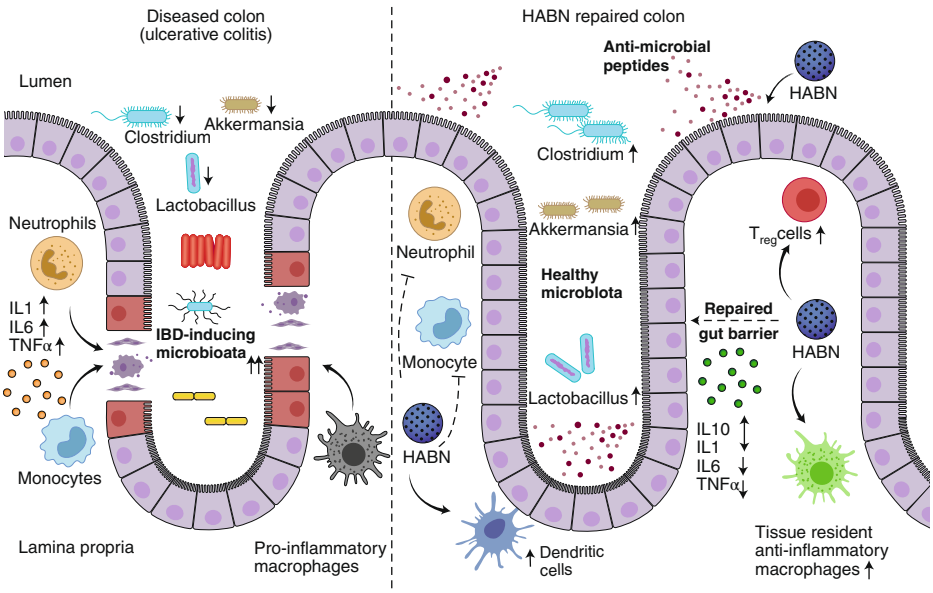

Fig. 1 | Nano-aggregated HABN restores gut homeostasis, microbiome and innate immune responses in IBD. Left: abnormalities in ulcerative colitis include an epithelial-barrier defect, increase in neutrophils and monocyte or pro-inflammatory macrophages, cytokines (IL1, IL6, TNFα and so on), as well as microbiota that further helps in disease progression. Epithelial-barrier dysfunction results in increased permeability and damage to the colon. In addition, abnormalities of regulatory T (T_{reg}) cells may contribute to immune-mediated events in the pathogenesis of ulcerative colitis. Right: HABN restores gut–epithelial barrier, increases tissue-resident macrophages, dendritic cells and T_{reg} cells, and restricts neutrophils and monocytes. HABN tips the balance of anti-inflammatory factors and anti-microbial peptides to modify diversity and relative abundance of the gut microbiome.

colonic epithelium and pro-inflammatory macrophages. HABN treatment was non-toxic and remarkably alleviated colitis in early and delayed therapeutic intervention in vivo. In contrast, PEG-conjugated bilirubin had a minimal therapeutic impact.

A notable advancement in the current study is that HABN nanoparticles perturbed the intestinal microbiome and modulated the immune response (Fig. 1). How oral or systemic administration of nanomedicines can modulate gut microbiome is poorly understood. In a recent study, Mosquera et al.[8] discovered that chronic, systemic inflammation arising from a change in the gut microbiome sensing in engineered mice or antibiotic-treated mice diminishes the immune response induced by polymeric nanovaccines. The poor immune response was linked to changes in microbiota post-vaccination and can be overcome by a new immunomodulatory nanomaterial that stimulates immune cells[8]. Moon and colleagues now show that oral delivery of HABN nanomedicine increased the diversity and relative abundance of microbial species, which are implicated in IBD patients and associated with mucus production, expression of tight junction proteins and induction of regulatory T cells. These exciting results are further supported by antibiotic-mediated depletion of commensal gut microbes. However, at the same time, it raises a question of what other factors account for HABN's efficacy.

Another hallmark of IBD is dysregulation of secreted cytokines[9–11], such as an increase in pro-inflammatory IL-6 and loss of anti-inflammatory IL-10. Indeed, Mosquera et al.[8] attributed failure of polymeric nanovaccines in a mouse model of gut-mediated metabolic syndrome to increased IL-6 levels. In the current study, the authors conducted in vivo tests to assess the ability of HABN to induce a potent immunomodulatory impact in the lamina propria, through antimicrobial peptides, causing a decrease in several pro-inflammatory cytokines with concomitant increases in anti-inflammatory macrophages, regulatory T cells and cytokines. Given that the authors were successfully able to deliver a highly hydrophobic drug and modulate both microbiome and immune cells, the insights from these studies are noteworthy because they enable testing of the impact of many insoluble small-molecule inhibitors. Simultaneously, they open the potential to co-deliver complex microbial therapeutics.

The considerable variation in the microbiota between individuals and variation in drug metabolism imposes a significant challenge to the next phase of research in this area. Deciphering the dynamic ecosystem of a patient's microbiota and learning how to embrace its complexity could improve our chances in our battle with bacterial pathogens and related disorders. Accordingly, achieving individually tailored nanomedicines to adjust specific microbial species and immune cells is probably where this nanomedicine field is heading. ❐

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