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Commentary

Supramolecular Nanogels for Localized Immunomodulation in Inflammatory Bowel Disease

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DESCRIPTION

Inflammatory Bowel Disease (IBD) presents significant therapeutic challenges due to the complex interplay of immune dysregulation, microbiome alterations, and epithelial barrier dysfunction. Current systemic treatments often result in substantial off-target effects while achieving suboptimal drug concentrations at intestinal inflammation sites. We have developed orally administered supramolecular nanogels specifically designed for localized immunomodulation in IBD, combining pH-responsive delivery with selective targeting of activated immune cells within inflamed intestinal tissues. These nanogels, approximately 150 nm in diameter in their collapsed state, were engineered to expand selectively in the inflamed intestinal environment, enabling enhanced retention and cell-specific therapeutic delivery.

The nanogels were synthesized through host-guest chemistry utilizing cyclodextrin-based hydrogels with adamantane-modified polyethylene glycol crosslinks, creating a dynamic network structure with tunable degradation properties. This supramolecular architecture enables protection of incorporated therapeutic agents during gastric transit while facilitating controlled expansion in response to the elevated pH and enzymatic environment of the small and large intestine. The hydrogel backbone was functionalized with mannose moieties to facilitate specific binding to overexpressed mannose receptors on activated macrophages, a central mediator of intestinal inflammation in IBD. The therapeutic payload consisted of a combination of siRNA targeting TNF-α production and a small molecule inhibitor of NF-κB, creating a dual-action approach addressing both cytokine production and inflammatory signaling pathways.

In vitro characterization using simulated gastrointestinal fluids demonstrated stability in gastric conditions followed by controlled expansion to approximately 3-fold their original volume in simulated intestinal fluid, with further responsive behavior to enzymes overexpressed in inflamed tissues. This dynamic behavior facilitates multimodal retention mechanisms, including physical entrapment within the mucus layer and specific cellular targeting. Flow cytometry and confocal microscopy confirmed preferential uptake by activated macrophages, with approximately 6-fold higher internalization compared to non-activated controls. Functional assessment demonstrated approximately 78% reduction in Tumor Necrosis Factor Alpha (TNF-α) production by activated macrophages following nanogel treatment, with corresponding decreases in downstream inflammatory mediators and restoration of epithelial barrier integrity in co-culture models.

In vivo evaluation utilized the Dextran Sodium Sulfate (DSS) mouse model of colitis, which recapitulates key features of human ulcerative colitis. Oral administration of fluorescently labeled nanogels demonstrated selective accumulation in inflamed colonic tissues, with minimal distribution to non-inflamed regions or systemic circulation as confirmed by whole-body fluorescence imaging and tissue analysis. Therapeutic efficacy studies showed significant improvements in clinical parameters, including reduced weight loss, improved stool consistency, and decreased bleeding scores compared to untreated controls. Histopathological examination revealed marked reduction in inflammatory infiltrates, preservation of crypt architecture, and reduced tissue damage scores across multiple intestinal segments.

Molecular analysis of colonic tissue demonstrated significant reductions in proinflammatory cytokine levels, with TNF-α, IL-1β, and IL-6 levels approaching those of healthy controls. Immunohistochemical characterization revealed normalization of macrophage phenotypes, with increased proportions of anti-inflammatory M2-like cells and reduced numbers of proinflammatory M1-like populations. Intestinal permeability studies using FITC-dextran demonstrated restoration of barrier function, correlating with increased expression of tight junction proteins as confirmed by Western blot analysis. Importantly, no significant alterations in systemic immune parameters were observed, with serum cytokine levels and peripheral blood immune cell populations remaining within normal ranges throughout the treatment period.

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Safety assessment through comprehensive histopathological examination of major organs revealed no evidence of toxicity following 4 weeks of daily administration. The gut microbiome, often negatively impacted by conventional IBD treatments, showed no significant perturbations in diversity or composition as assessed by 16S rRNA sequencing. These orally administered supramolecular nanogels represent a promising approach for localized immunomodulation in IBD, potentially addressing key limitations of current therapies through enhanced targeting specificity and reduced systemic exposure.