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REVIEW

Current Strategies and Potential Prospects of Nanomedicine-Mediated Therapy in Inflammatory Bowel Disease

Fengqian Chen[1]
Qi Liu[2]
Yang Xiong[3]
Li Xu[4]

[1]Translational Research Program, Department of Anesthesiology and Center for Shock Trauma Anesthesiology Research, University of Maryland School of Medicine, Baltimore, MD, 21201, USA; [2]Department of Dermatology, Johns Hopkins University School of Medicine, Baltimore, MD, 21231, USA; [3]College of Pharmaceutical Science, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, 310053, People's Republic of China; [4]Department of Anorectal Surgery, The First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Traditional Chinese Medicine), Hangzhou, Zhejiang, 310006, People's Republic of China

Correspondence: Li Xu
Email 20053012@zcmu.edu.cn

Abstract: Inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis are highly debilitating. IBDs are associated with the imbalance of inflammatory mediators within the inflamed bowel. Conventional drugs for IBD treatment include anti-inflammatory medications and immune suppressants. However, they suffer from a lack of bioavailability and high dose-induced systemic side effects. Nanoparticle (NP)-derived therapy improves therapeutic efficacy and increases targeting specificity. Recent studies have shown that nanomedicines, based on bowel disease's pathophysiology, are a fast-growing field. NPs can prolong the circulation period and reduce side effects by improving drug encapsulation and targeted delivery. Here, this review summarizes various IBD therapies with a focus on NP-derived applications, whereas their challenges and future perspectives have also been discussed.

Keywords: inflammatory bowel disease, nanoparticles, targeted delivery, nanomedicine applications

Introduction

Inflammatory bowel disease (IBD) is an umbrella term of immune response-mediated chronic remission and relapse bowel diseases. IBD is classified with Crohn's disease (CD) and ulcerative colitis (UC) with different etiologies. CD and UC are diseases of unidentifiable causes. CD presents ulcers and granuloma centered on the small and large intestines where inflammatory occurs in the alimentary canal from the mouth to the anus. UC presents inflammatory response and successive ulcers and abscesses in the colonic mucosa.[1,2] Patients with IBD have a raised potential risk relative to colon cancer. Due to the chronic inflammation development and a great number of immune cell filtration as well as immune cell-mediated organ destruction, IBD has become the third most common disease worldwide.[3]

IBD is a chronic inflammatory syndrome that influences the gastrointestinal (GI) tract and shows clinical variations not only in the developed countries (such as North America and Europe) but also in the developing countries (such as India and China).[4,5] More than 5,000,000 people globally suffered from IBD. Currently, approximately 25 per million people yearly (developed countries) and 5 per one million people yearly (developing countries) lived with.[6] This chronic inflammatory and debilitating disease need lifetime therapy, with enormous financial burden and healthcare system support.[7]

Colitis-associated colorectal cancer and sporadic colorectal cancer are mostly developed due to two significant issues: irregular inflammation and immunosuppression of carcinogenesis.[8] Recent research has shown that chronic inflammation in IBD could trigger the development of colorectal cancer. Oxidative stress from inflammation sites can induce DNA damage, leading to the activation of pro-carcinogenic genes or the silence of tumor suppressor signals. Moreover, microbiota alteration in the gut can lead to chronic inflammation-mediated carcinogenic component productions. These mechanisms are attracting increasing research interests.[9]

Recently, fast-developing diagnosis and treatment in IBD, such as the use of anti-inflammatory agents, have significantly reduced the surgery and hospitalization rates for patients. Therapies such as 5-aminosalicylic acid, corticosteroids, immunomodulators, antibiotics, and biological agents have been widely offered in IBD treatment, significantly reducing colitis-associated colorectal cancer.[10–12] These tools are also defined as effective early preventions. However, immunomodulators may often lead to severe side effects among healthy tissues, such as lymphoma development.[13] Without targeting delivery, IBD treatment drugs may be absorbed into the systemic circulation and exposure to healthy tissues, resulting in increased severe side effects. Drug efficacy and safety have become an emerging question that calls for advanced drug delivery systems that would target-deliver medications into the inflamed sites and avoid absorption from the healthy tissues.[14]

Nanomedicines have been widely utilized in the pharmaceutical field for loading hydrophobic drugs, showing a significantly reduced dosage use and increased treatment efficiency, leading to promisingly minimized systemic side effects.[15,16] Current conventional therapeutic agents, such as powders and tablet formulations (orally administrated) as well as solution and emulsion formulations (intravenously injected), are widely used for improving drug bioavailability.[17] Nanocarriers may facilitate such conventional delivery systems in a way that could overcome existing biological barriers, thus delivering drugs to designed specific sites.[18,19] In the following content, we will focus largely on such new strategies that the nanocarrier system could bring in for IBD treatments.[20,21]

Disease Pathogenesis

In a closer look, IBD is a consequence of the dysregulated immunology among the chronic damaged of inflamed gut against antigens activation.[22] In specific, bacterial load and alpha diversity significantly decreased in the microbiome environment, with a change of pH ranging from 2.3 to 8.3 within ~24 h transit time frame.[23,24] Compared to healthy bowel, IBD induces multiple unwanted symptoms such as fever, abdominal pain, bowel obstruction, chronic diarrhea, rectal bleeding, and weight loss, eventually causing colorectal cancer. The development and pathogenesis of IBD are multifactorial, representing a complex reciprocation between different elements such as environmental factors, microbial dysbiosis, and genetic variations.[25,26]

When IBD occurs, innate immunity is the first line to initiate a primary defense by neutrophil accumulation and antigen activation, and then mononuclear phagocyte infiltration.[27] In a normal homeostatic stage, macrophages and dendritic cells could effectively recruit TNF-β and IL-10-secreting T regulatory cells to sites to prevent imbalanced inflammation. The activated antigen presentation cell, such as dendritic cells, could provide antigens to activate naive T cells into effector cells. But this is not the case during IBD.[28,29]

Physical barriers and chemical barriers both changed in the inflamed tissue, resulting in epithelial barrier integrity loss and immune cell (such as Th1, Th2, and Th17) recruitment. Functional reprioritizing of leukocytes and leukocyte-mediated "genetic storm" have been widely studied in IBD.[30] Such studies showed that immune activation during IBD arouses protective effects, balancing the excessive amount of pro-inflammatory and anti-inflammatory factors. These factors are dynamically mediated by the production of targeted chemotaxis, cytokines, and the generation of reactive oxygen species (ROS), phagocytosis, nitric oxide, and matrix metalloproteases.[31] The systemic inflammatory responses expanded into numerous immune system-activating aspects, as well as considerably suppressive aspects. Although naturally developed to clear molecular dangers, these extensively generated pro-inflammatory cytokines (such as IFN-γ, IL-17, IL-4, and IL-13) may often facilitate IBD pathogenesis.[32]

Current Therapeutics

Traditional therapeutic approaches often function on mediating the systemic immune responses via regulating mucosal and aggravated inflammatory progression. These therapeutics are based on immune-modulatory medicines (such as aminosalicylic acid, corticosteroids, immunomodulators (6-Mercaptopurine and Azathioprine), antibiotics,

and biological agents (Infliximab)), as well as strategies against pro-inflammatory factors (chemokines, integrins, and cytokines).[33–37]

For instance, corticosteroid dampens the initiation of the inflammatory response by hampering pro-inflammation cytokine production, inhibiting immune cell recruitment, and suppressing cellular translation of nuclear factor-κB (NF-κB). As a result, it improves vascular permeability, vasodilation, neutrophil infiltration, fibroblast activation, vascular proliferation, and collagen deposition.[38,39] Immunosuppressive medicines, such as tacrolimus,[39] mercaptopurine,[40] methotrexate,[41] azathioprine,[42] and cyclosporine,[43] could effectively inhibit lymphocytes activation and proliferation. Amino salicylate, for example, suppresses macrophage chemotaxis, mitogen-activated protein (MAP) kinase, and NF-κB signaling pathways. It also increases the peroxisome proliferator activator receptor gamma (PPARγ).[44]

The dysfunction of the intestinal immune system may lead to microbial dysbiosis in the gut microbial community, resulting in IBD. A variety of therapeutics is applied for immune dysregulation. For initial therapy and remission, antibiotics (such as ciprofloxacin and rifaximin) and probiotics (such as Bifidobacterium and Lactobacillus) are applied.[45] One of the vital biological treatments in IBD is monoclonal antibodies (mABs).[46] The mABs against pro-inflammation cytokines such as TNF-α and IFN-γ would target crosstalk among IL-23, IL-6, IL-17, IL-13, and TGF-β. The mABs against adhesion molecules like ICAM-1 could inhibit the recruitment of effector T cells.[47,48] Inhibitors against chemokine receptors, homing-linked receptors (such as α4β7 integrin), and sphingosine-1-phosphate receptors have also shown promising effects on IBD treatment.[49,50] Notably, in the clinic, current large-scale applications for IBD treatment include infliximab (anti-TNF-α mAbs),[51] vedolizumab (α4β7 integrin inhibitor),[52,53] ustekinumab (IL12/IL-23 inhibitor),[52,54] and tofacitinib (JAK inhibitor).[55]

Immune cells are also largely investigated in IBD treatment. Cell-based therapies often include the suppression of immune response associated with antigen-presenting cells (macrophages and dendritic cells) and effector T cells, and also the depression of pro-inflammatory cytokines produced by leukocytes.[28,56] Recently, mesenchymal stem cells and hematopoietic stem cells are regarded as potential treatments for IBD.[57–61] These cells have shown cell renewing property and may differentiate into multiple cell types with immune-suppressive and anti-inflammatory effects, as well as long-term gene expression tendency.

Although comparably effective, conventional treatments for IBD are limited in many aspects, such as minimal drug-bioavailability and systemic drug exposure-induced side effects.[62,63] Nowadays, a fast-growing field of IBD treatment is focusing on developing new therapeutic strategies with various drug delivery systems. These systems may help us gain insights into disease progression and prognosis.[63,64]

Nano-mediated Therapies

In 2001, the targeted accumulation of small nanoparticles (NPs) size around 100 nm in the inflamed murine colon rather than a healthy murine colon was first demonstrated.[65,66] Because of this passive accumulation property, NPs have become a promising drug delivery system for IBD treatment. Defective mucus layer and loss of barrier integrity of the inflammatory intestinal mucosa enable NPs to leak into the inflamed tissue passively. In specific, the defective epithelial barrier of inflamed intestinal tissue would increase gut barriers' permeability, which promotes NPs' infiltration. Moreover, inflamed mucosa increases mucus secretion, which facilities NPs' adhesion and diffusion through the layer of intestinal mucus. In the meantime, immune cells such as neutrophils and macrophages also infiltrate into the layer of inflamed mucosal and submucosal, promoting cellular uptake of NPs to the inflammation sites.[15,67,68]

Accumulated research has shown the safety and effectiveness of nanomedicines as a promising approach for IBD treatment. With the help of rational drug delivery systems, conventional treatment drugs can be packed into the inflammatory tissues to treat IBD. Not only delivering natural compounds and conventional agents, but these delivery systems can also facilitate remission of IBD by enhancing treatment efficacy and reducing systemic exposure in the healthy tissues.[69–71] On the one hand, these delivery systems had passively or actively target themselves to the inflammation sites. On the other hand, they increase drug bioavailability and concentrations. Owing to epithelial enhanced permeability and retention effect (EPR), small size NPs were selectively uptake into the inflamed tissues' intracellular matrix.[72–74] Increased permeability of the intestinal epithelial barrier due to IBD also facilitates the transcellular transport of NPs. Once uptake, endocytosis induces NPs to transcytosis at the apical membrane of cells. NPs are then released at the

basolateral pole and interact with leukocytes at the submucosal layer.[75–79]

By increasingly understanding pathophysiological and pathogenesis in the inflammatory GI tract, we herein review the current nanocarriers attributed to inflammatory-targeted drug delivery.

Nanocarrier Systems

Biodegradable Nanomedicines

Drug delivery systems aiming to protect the hydrophobic agents often work by avoiding premature degradation and enhancing the sustained release of drugs at the targeted site.[80] A controlled-release system, in such cases, provides an ideal strategy to maintain the frequency and concentration of drug release.[73,81–83]

For instance, high-water content hydrogel, a copolymer with a cross-linked network, has high biocompatibility with its physical similarity to biological tissues.[84] Hydrogels are proven effective in loading hydrophilic drugs and protecting them from being desaturated or aggregated.[85] It has been shown that a hydrogel drug delivery system with alginate and chitosan in encapsulating anti-inflammatory tripeptide Lys–Pro–Val (KPV) to be significantly effective. Upon delivering to the inflamed colon, the hydrogel was efficiently released for treating colitis disorder in this dextran sulfate sodium-induced colitis model.[86]

Lipid NPs packaged with budesonide, when orally administrated, have shown a significant anti-inflammatory effect in colitis in vivo compared to free drug usage. After 12 hours of administration, a significantly higher concentration of NPs was detected in the inflamed colon. Alongside, these lipid NPs also improved histological scores, reduced myeloperoxidase activity, and suppressed pro-inflammatory cytokines in the inflamed colon.[87] On the other hand, hyaluronic acid-conjugated self-assembled NPs, when loaded with budesonide, have also shown a significant suppression of TNF and IL-8 among inflamed cells in vitro.[88] In these studies, NPs are proven as biocompatible vehicles with minimal toxicity. As hyaluronic acid showing an anti-inflammatory effect, blank NPs also elicited significant IL-8 reduction.[88]

In rodent colitis models, dexamethasone-loaded solid lipid nanoparticles, when orally administrated, could significantly suppress pro-inflammatory cytokines IL-8 and TNF compared to the free drug.[89] Orally administered the Immunosuppressant tacrolimus-loaded PLGA NPs when orally administrated have also shown significantly higher drug accumulation in the inflamed tissue and greater colitis resolution than standard formulations in comparison.[90]

When incorporated into NPs, anti-sense oligonucleotides could achieve high stability by NPs' protection away from DNases' degradation. In a rodent colitis model, orally administrated NF-κB anti-sense oligonucleotides showed efficacy.[91] In the clinic, anti-sense oligonucleotide treatments such as Alicaforsen and Mongersen are also involved.[92,93] These treatments are believed to be beneficiaries of the NP-mediated drug delivery system.[78,94–96] Moreover, recombinant protein prohibitors-loaded PLGA-NPs, when orally administrated, have shown significant antioxidant effect and suppression of colitis disease severity.[97]

TNF is one of the vital targets for IBD treatment which plays an essential role in disease immunity.[98] It originates from innate immune cells, feedbacks between innate and adaptive immune systems, and dominates IBD pathogenesis. In the mice model, intraperitoneal administration of engineered NPs loaded with polyethyleneimine/TNF-α siRNA had significantly suppressed TNF-α expression compared to siRNA itself.[99,100]

Natural Product-based Nano-systems

Natural polysaccharides, such as pectin, alginate, and chitosan, have been developed as oral hydrophobic drug delivery systems for targeting inflamed colon. These systems are non-toxic, easily manufactured, and FDA approved. These applications from the polysaccharide family protect against premature drug release and selectively release IBD drugs into the small intestine, colon, and also stomach.[101,102]

For instance, an engineered polysaccharide system significantly suppressed colitis by inhibiting IL-22 expression.[103] *Eucheuma cottonii* and *Acmella oleracea*-extracted polysaccharides have been shown to regulate inflammation and inhibit colonic damage in dextran sulfate sodium (DSS)-induced colitis.[103,104] Non-starch polysaccharides were used for IBD treatment in vitro and in vivo, exhibiting significant improvement of immune stimulation, gut-microbiota modulation, anti-inflammation, and reoccurrence rates.[105] Amylose cornstarch packaged with Mesalamine has shown an accurate release of drug in the inflamed colon with a high withstandment of enzymatic and acidic conditions in the GI tract.[106]

Poly (epsilon-caprolactone) (PCL) microspheres, consisting of NPs-in-microparticles, were designed to load plasmids and nucleic acids in oral deliveries. These

microspheres have been shown to target released at the inflamed intestine and tolerance against enzymatic degradation in the upper GI tract.[107,108] Moreover, quercetin-loaded chitosan-based NPs have been reported in an acetic acid-induced colitis rabbit model, demonstrating effectiveness compared to free drug.[109,110]

Edible plant-derived non-toxic NPs have also been studied for IBD treatment.[111] Grapefruit-derived NPs have the capacity of biodegradable, biocompatible, and stable in various pH conditions. Methotrexate-loaded grapefruit-derived NPs upgraded anti-inflammatory response in dextran sulfate sodium-induced IBD by reducing IL-1β and TNF-α in macrophages of intestine tissue.[112] Ginger-derived NPs have been developed to increase intestinal epithelial cell proliferation by upregulating anti-inflammatory cytokines and reducing pro-inflammatory cytokines (IL-6, TNF-α, and IL-1β).[113]

Phytochemicals can target various pathogenesis and inflammation routes in IBD. A natural biopolymer-based nanocarrier is designed to carry an active compound 6-shogaol to the inflamed colon.[101,114] *Ulva lactuca* polysaccharide-selenium NPs represent a promising therapeutic approach in anti-inflammatory for acute colitis.[115] Broccoli-extracted NPs demonstrated suppression of colitis by stimulating adenosine monophosphate-activated protein kinase.[116] In another study of the colitis model, krill oil liposomes loaded with budesonide could also inhibit TNF-α and have shown great potential in oral drug delivery.[117]

Cells and Exosomes

Bioengineered red blood cells as nanoparticle carriers is a new strategy for IBD treatment, showing high biocompatibility capacities and a significantly longer circulation time within blood.[118,119] In a clinical trial among pediatric steroid-dependent CD patients, autologous red blood cells were used to load dexamethasone-21-phosphate, showing a significant therapeutic effect with 44% remission in patients.[120] In the next six years' continued study, 50% of patients showed sustained therapy efficacy and safety.[121,122]

Exosomes are extracellular vesicles (EVs) that are released by mammalian cells. Due to their nano-sizes, these EVs are considered natural NPs. EVs can transport signals such as proteins and RNAs from host cells to the recipient cells.[123] EVs have been used for various innovative drug delivery strategies so far. For instance, intestinal exosomes have been proven as a new strategy for IBD therapy.[124,125] Intestinal epithelial cell-derived EVs contain a large amount of transforming growth factor-beta 1 (TGF-β1) with immunosuppressive activity.[126] In dextran sulfate sodium-induced colitis, these EVs worked on immunosuppressive dendritic cells and regulatory T cells to protect against colitis progression. In an in vivo model, EVs secreted by granulocytic myeloid-derived suppressor cells were demonstrated to reduce dextran sulfate sodium-induced colitis, showing an attenuated Th1 cell population and an enhanced T regulator cell population in mesenteric lymph.[127]

Reduced levels of interferon (IFN)-γ and TNF-α were found in mice models of IBD. A study exhibited that IL-10 incubated bone marrow-derived DCs would secret EVs to reduce colitis from trinitrobenzene sulfonic acid induction. In specific, EVs from IL-10 treated cells were associated with IL-10 mRNA upregulation, IL-2, IFN-γ, and TNF-α mRNAs downregulation, and T regulator cell upregulation in colonic tissue. These studies implied the importance of EVs as potent natural nanoparticles for transporting biological contents in IBD treatment.[128]

The repairs of injured cells/tissues in the intestine can also benefit IBD treatment. Mesenchymal stem/stromal cell-derived EVs have shown therapeutic efficacy on tissue injury repair in colitis.[129,130] EVs secreted by mesenchymal stem/stromal cells in bone marrow, adipose tissue, and the umbilical cord could provide a promising approach for regenerative therapy. These EVs have the ability to migrate into damaged tissues, promote tissue repair, and modulate immune responses.[20,129,131] Therefore, EVs may serve as potential nanocarriers for efficient, targeted drug delivery in IBD treatment.

Targeted Drug Delivery System

Targeted Nano-systems

Depending on the inflammation level (luminal or systemic) and severity (mild, moderate, or severe) of IBD, nano-delivery systems can be administrated either orally or intravenously.[122] Luminal and mild inflammation can be nano-targeted orally, whereas severe systemic inflammation often requires targeted intravenous delivery. In IBD, various nano-systems have adapted different targeting strategies to enhance inflammation site-delivery. These strategies include but not limited to passive targeting NPs; mannose receptor targeting NPs; inflammatory receptor targeting NPs; charge-mediated targeting NPs; and micro-environment-responsive targeting NPs (eg, redox, ROS, and pH-triggered release).[62,132]

Various receptors are overexpressed in the endothelium of the inflammatory bowel. Therefore, ligand-mediated NPs may target these receptors and increase the accumulation of drugs in the inflamed sites.[133,134] For instance, hyaluronic acid could precisely target to CD44 receptor. Overexpressed CD44 on the surface of inflamed macrophages and epithelial cells can be specifically bond to hyaluronic acid among colitis tissues.[135,136] On a UC mice model, hyaluronic acid-incorporated copolymeric NPs were encapsulated with tripeptide for colitis delivery.[137]

Inflammatory sites also exhibit an overexpressed level of folate receptors. Folate receptor-targeted NPs have been demonstrated to bind to activated macrophages and accumulate in the inflamed intestine in mice colitis via active-mediated targeting.[114,138,139] Moreover, macrophages express abundant mannose receptors in the membranes. An ex vivo study has shown that mannosylated-target PLGA-PEG NPs had more accumulation of model drug ovalbumin in inflamed murine colonic tissues than non-targeted PLAG-PEG NPs.[15]

Mesalazine-loaded pectin-silica-based NPs were designed to be controlled-release in the colon. These NPs exhibited a minimized release in the upper GI tract but increased release of mesalazine in the simulated colonic fluid due to enhanced sensitivity of pectin towards the pectinase.[140] On the other hand, TNF siRNA loaded macrophage-targeted copolymer NPs effectively targeted macrophages and increased therapeutic effect than non-targeted NPs in IBD treatment. In rodent colitis models, the combination of TNF and cyclin D1 siRNA-loaded multi-compartmental NPs-in-microsphere oral system showed lipase-triggered drug release in the intestine. It exhibited significant gene silencing, suppression of myeloperoxidase activity, and also IL-1 and IFN reduction.[141]

CD98 plays a vital role in the homeostasis of the intestinal immune responses. It is overexpressed in epithelial cells and macrophages in the colon of IBD.[142] In the mice model, upregulated CD98 leads to colitis-associated tumorigenesis. In the dextran sodium sulfate-induced mice model, CD98 siRNA-coated polyethyleneimine (PEI)/polylactic acid NPs were orally administered to treat colonic inflammation.[143] The results showed a significant suppression of CD98 protein in the macrophages and epithelial cells of the intestine. In another rodent colitis model, this NPs-mediated drug delivery system has also been used for the local delivery of IL-10 expressing plasmid. Their results showed significant suppression of inflammation, and highly improved clinical activity score.[143,144] Thus, ligand-incorporated NPs are demonstrated effective in various applications.

The Trigger-release Nano-systems

Resveratrol is a hydrophobic therapeutic agent from a natural herb for the treatment of IBD. A study has shown that a pH-trigger-released poly(N, N-dimethylamino ethyl methacrylate) NP system was established. In this system, chitosan was integrated into a hydrophilic vector, showing high biocompatibility and low toxicity. The loaded resveratrol was sustain-released for drug efficacy.[145]

Eudragit-coated budesonide-loaded PLGA NPs were pH-dependent in ameliorating murine colitis model and demonstrated significantly increased efficacy compared to non-coated NPs. Eudragit loaded PLGA-modified copolymeric blend. Eudragit®L and Eudragit®S are anionic copolymers containing methacrylic acid and methyl methacrylate and are approved non-biodegradable by FDA. These non-absorbable, non-toxic, and pH-dependent polymers are often utilized for IBD treatment.[146] Moreover, dual sensitive (pH/time, pH/enzyme, etc.) release NPs have also been developed to improve IBD therapy. For instance, carboxymethyl inulin responds to both redox and pH. Carboxymethyl inulin-engineered NPs showed a high accumulation in the inflamed tissue than that of free drug in colitis mice.[147]

The concentration level of endogenous ROS indicates oxygen metabolism. Increased ROS was found in the inflammatory intestinal mucosa. In IBD patients, mucosal ROS concentration is 10–100 times higher in the inflamed intestine than health controls.[148,149] Nitroxide radicals in NPs have been shown to selectively and effectively inhibitions ROS. In a colitis model, the disease activity index was significantly lower after seven days of orally administering engineered NPs.[150] In another study, NPs were designed to trigger release molecules' free radical scavenger tempol to increase ROS concentrations in inflamed intestinal sites. Their design exhibited high therapeutic efficacy in both acute and chronic colitis mice.[151]

Orally administered nucleic acid for IBD therapy is usually hindered by poor cell membranes trans passing. NPs, when logically designed, may enhance RNA payload delivery. For instance, the pro-inflammatory cytokine TNF plays an important role in the progression and development of IBD. A recent study found that orally administrated, TNF siRNA-loaded Thioketal NPs may degrade in an environment of high ROS concentration in the inflamed

sites and may successfully suppress colonic TNF protein expression in colitis in vivo.[150,152]

The Charge-mediated Targeting

In IBD, the charged surface of inflammatory tissues can be specifically targeted by NPs of opposite charge via electrostatic interactions. The mucosal composition of the inflamed colonic mucins comprises negatively charged carbohydrate fractions, unlike the healthy regions. Thus, cationic NPs as nanocarriers can increase mucous interaction and prolong drug residency.[153–155] In ex vivo studies, researchers have demonstrated significantly increased targeting efficiency of positively charged chitosan NPs to the human inflammatory intestinal mucosa.[156]

On the other hand, cationic proteins such as transferrin and eosinophil cationic proteins are abundant in inflamed areas. Thus, negatively charged NPs give preferential adhesion to these cationic proteins. In a colitis model of rats, negatively charged liposomes exhibited a higher accumulation in the inflammatory regions than cationic or neutral charged liposomes.[157] These results showed that NPs positively or negatively charged can interact with components in the GI tract and offer specificity in drug deliveries.[87] However, unwanted electrostatic interactions remain issues among these systems. Charged NPs may interact with the oppositely charged GI tract components like soluble mucins and bile acids. Thus, the efficacy remains investigated. The combination of ligand-mediated and charge-mediated NPs may facilitate the specificity.[158–160]

Conclusion and Future Perspectives

Current drugs for IBD, such as 5-aminosalicylic acid derivatives, corticosteroids, anti-TNF mediators, immunosuppressive agents, and other biologic components, suffer from immunosuppression and long-term systemic exposure. The utilization of nanocarriers could provide an efficient and safe approach for IBD therapy. To date, various nanocarriers have been studied, including self-assembled polymeric NPs, natural product-based NPs, exosomes, etc.

Compared with the conventional method, nanocarriers may prolong the retention period at inflamed sites and minimize administration frequency. Moreover, with the help of specific ligands-conjugated NPs, therapeutical agents can be delivered and accumulated to the inflamed GI tract, showing both high drug concentration at the disease sites and minimal systemic exposure to healthy tissues. Here we summarized recent research using nano-delivery strategies for IBD treatment. These delivery systems have been studied in multiple types of research and clinical trials with satisfactory results.

In summary, inflammatory region-specific targeting nanocarriers are likely to present a promising result in IBD treatment. The orally administrated formulation is the most desirable route so far, giving a suitable alternate for parenteral administrations. The versatility design of nanocarriers for proteins and nucleic acids also opens up opportunities for more advanced drug delivery designs, such as charge-mediated targeting, micro-environment triggered release targeting, and ligand-mediated targeting. These advanced drug delivery systems have shown the potential to improve current IBD treatment with enhanced therapeutic efficacy and improved patients' life qualities.

Although general concerns have been brought up on the level of nanocarriers' adverse effects, no factual data or conclusion has occurred so far. Nanotoxicology studies in animal models and the human GI tract are a must. NP sciences expand to various sizes, materials, and surface interactions. Thus, their applications in IBD therapy should be further explored with an increasing understanding of the human GI tract. Immune cells and immune functions altered dramatically during inflammatory diseases' pathogenesis. Major immune regulators such as macrophages polarized to a pro-inflammatory state, facilitating system dysfunction. Thus, the switch of immune cells' phenotypes with the help of NPs can be further investigated. With most nanocarrier designs applied in UC inflammation, therapies toward CD should be emphasized in the future.

The trend of applying multifunctional, multi-targeting NP in diagnosis and therapy is rising, but for successful clinical translation achieving long-term safety and minimizing pre-metabolism within system circulation are still the key. NP structural stability needs further optimization and validation. For NP scale-up and reliable manufacturing, delivery systems are often simplified from bench to bedside. Such simplification should base on achieving reduced drug load as well as prolonged remissions. Designing efficacious formulations and dosage forms for human administration needs to be further explored. Personalized patient IBD therapy tailored by targeted nanomedicine will be realized.

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Disclosure

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