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REVIEW

Recent advances in orally administered cell-specific nanotherapeutics for inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD) is a chronic relapsing disease in gastrointestinal tract. Conventional medications lack the efficacy to offer complete remission in IBD therapy, and usually associate with serious side effects. Recent studies indicated that nanoparticle-based nanotherapeutics may offer precise and safe alternative to conventional medications *via* enhanced targeting, sustained drug release, and decreased adverse effects. Here, we reviewed orally cell-specific nanotherapeutics developed in recent years. In addition, the various obstacles for oral drug delivery are also reviewed in this manuscript. Orally administrated cell-specific nanotherapeutics is expected to become a novel therapeutic approach for IBD treatment.

Key words: Oral administration; Nanotherapeutic; Cell-specificity; Inflammatory bowel disease

Core tip: Inflammatory bowel disease includes Crohn's disease and ulcerative colitis. Nanotherapeutics may outperform conventional medications *via* the targeted drug delivery, sustained drug release, and decreased adverse effect. The main purpose of this review is to offer an update of efficacy of the orally administrated cell-specific nanotherapeutics that have been developed recently.

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic relapsing gastrointestinal (GI) disorder with no permanent cure. It mainly includes Crohn's disease (CD) and ulcerative colitis (UC), and affects millions of patients worldwide. After 30 years of living with this disease, 8% of CD and 18%-20% of UC patients develop colitis-associated colon cancer, which is the third most common malignancy and one of the leading causes of cancer mortality[1]. Although the etiology of IBD remains largely unknown, a large amount of researches over the last decades demonstrated that the individual's genetic susceptibility, intestinal microbiota, and immune responses are all involved in the pathogenesis of IBD[2]. Conventionally, IBD is treated by daily administration of high doses of anti-inflammatory or immunosuppressive drugs. Some of these treatments are effective in controlling inflammation. However, their applications have been restricted by problems with long-term efficacy and safety issues. For example, as for corticosteroids, a total daily dose over 20 mg of prednisolone for more than 2 wk is associated with an obvious increased risk of infections[3].

Recently, nanotherapeutics have been recognized as a promising strategy which can potentially revolutionize disease diagnostics and treatments. They offer significant advantages over traditional approaches because of their nanometer scale dimension, targeted drug delivery capacity, controlled drug release, and decreased adverse effects[4,5]. Most importantly, nanotherapeutics have been found to confer similar or even better therapeutic impacts at lower drug concentrations than their conventional counterparts[6]. It was reported that oral administration has been considered as the most convenient approach for colitis therapy-related drug delivery, as it avoids the pain and discomfort associated with injections, minimizes the potential for contamination, and is applicable for a self-medication that can be fully controlled by patients[7]. Accordingly, orally targeted nanotherapeutics have been developed.

The challenges for oral drug delivery are to ensure drug formulations to remain stable in the GI tract, transport adequate amount of active drugs to the specific sites, minimize systemic absorption of the drugs, and lower the risk of adverse side effects[8]. The earliest nanotherapeutics designed for IBD-targeted therapy are based on the physiological features that are particular to colon to trigger drug release[9]. However, physiological conditions can differ among patients and at various stages of IBD, making it very difficult to attain sufficient therapeutic efficiency. Parallel breakthroughs in the understanding of the molecular pathophysiology of IBD and the development of intelligent NPs offer tremendous promise for IBD therapy[10]. In this review, we focus on novel therapeutic approaches using orally targeted nanotherapeutics and their challenges in GI tract.

OBSTACLES FOR ORALLY NANOTHERAPEUTICS

GI tract

After oral administration, NP-based nanotherapeutics pass through the esophagus, the stomach, the small intestine and the colon, successively. The pH in the passage ranges from strongly acidic in the stomach (pH 1.5-1.9), to almost neutral in the small intestine, and then slightly acidic (pH 5-7) in the colon[11]. Therefore, NPs have to be stable over a wide pH range. In addition, they also encounter digestive enzymes in stomach (*e.g.,* pancreatic enzymes), bicarbonate and bile salts in the small intestine, as well as abundant microbial population in colon. All of these contents in the GI tract can destabilize NPs and further reduce the effectiveness of their loaded drugs[12,13]. Besides, the semi-solid contents in colonic lumen prevent NPs from diffusing into the inflamed sites.

Mucus

The mucus on the surface of colon epithelial layer is highly viscoelastic and adhesive, and forms a thick layer (830 ± 110 μm)[14]. It is mainly composed of mucins and lipids, and acts to trap and remove bacteria, viruses, and foreign matters[15]. In healthy colon, there is a continuous mucus which has two layers of sub-structures: the outer is a loosely adherent layer for bacterial adhesion; while the inner is a tightly adherent layer, normally sterile. In colon tissue with IBD, there is a marked increase in bacteria associated with colonic adherent mucus layer[2,16].

Maisel *et al*[17] developed an unmodified NPs that were mucoadhesive (mucoadhesive particles, MAP), and a PEG-coated NPs which were non-mucoadhesive (mucus-penetrating particles, MPP). In comparison to MAP, MPP tended to penetrate in the GI tract, including colitis tissue. In addition, Ijssennagger *et al*[18] demonstrated that hydrogen sulfide, mainly produced by sulfate-reducing bacteria, reduced disulfide bonds presented in the mucus network, thereby breaking the mucus barrier. Reduction of disulfide bonds in the gut lumen might represent an exciting method for the penetration of NPs to mucosa.

Epithelial enhanced permeability and retention effect

Inflamed colon is associated with disruption of the intestinal epithelial layer and accumulation of immune cells, leading to the loss of barrier function and

increased epithelial permeability[19]. NPs are likely to penetrate into the gaps among epithelial cells, thus increasing the local drug concentration and exerting therapeutic effects there. This phenomenon is called "epithelial enhanced permeability and retention" effect[20,21]. This effect is size-dependent, showing a maximum efficacy in the nano range. Furthermore, in comparison to free drugs in solution or suspension, drug-loaded NPs were shown to accumulate to a greater extent in inflamed tissues and prolong therapeutic effects[20]. Additionally, anti-inflammatory chemical drugs loaded into NPs also showed enhanced cellular uptake by cells in colitis tissues, due to protection of the drugs from efflux systems and mucosal metabolism[22].

Cellular uptake

NPs generally undergo cellular internalization by paracellular transport or endocytosis into epithelial cells in the GI tract. In the context of cellular uptake by inflamed colon, endocytosis might be the main NP cellular uptake approach. Endocytosis can be triggered by the interaction between the surface moieties of NPs and the specific receptors, which are highly over-expressed on the surface of IBD therapy-related key cells in colitis tissue. Critically, the internalization and transportation of NPs may be enhanced by the specific targeting to these receptors[23].

Endosomal escape

NPs are entrapped in endosomes after internalization into cells. Subsequently, proton pump, an integral membrane protein, moves protons across the endosome membrane, inducing the pH continuously decrease from 7.2-7.4 to 4.5-5.0[24]. To avoid their degradation in endosome, many therapeutics (*e.g.,* protein, plasmid DNA and siRNA) have to escape from the endosome into the cytosol, where they can associate their targets[25].

To induce efficient endosomal escape, a common strategy is to introduce chemical groups with proton-sponge effect to NPs. Our group previously synthesized a mannosylated bioreducible cationic polymer (PPM) and further spontaneously assembled NPs with siRNA assisted by sodium triphosphate (TPP). In these TPP-PPM/siRNA NPs, the abundant primary and tertiary amine groups in PPM can promote endosomal escape efficiently[26].

Nuclear localization

After escaping from the endosome, drugs often have to enter certain organelles in order to exert their functions there. Nuclear entry is a prerequisite for some drugs, such as inhibitors of transcription or the cell cycle[27]. For instance, plasmid DNA must be transported into the nucleus. Otherwise, transcription cannot occur[28].

Wang *et al*[29] synthesized a series of *N*-terminal stearylated nuclear localization signals, and their further studies showed that such vectors could effectively deliver plasmid DNA into nuclei. The maximum transfection efficiency of these vectors was 80% of that of jetPEI™.

NANOTHERAPEUTICS FOR IBD

Conventional NPs

Polyester NPs: Polylactic-co-glycolic acid (PLGA) and polylactic acid (PLA), FDA-approved biodegradable polyesters, have the capacity to encapsulate hydrophilic or hydrophobic drugs to form NPs. Thus, they have been commonly used as drug carrier materials[5,30,31].

Mahajan *et al*[32] loaded mesalamine into PLGA NPs, and they further administered them once a day to rats with colitis through oral administration or intracolonic administration. It was found that these NPs exerted much higher efficiency in mitigating colitis, in comparison to the free drug in suspension. In addition, the researchers also demonstrated that the mesalamine-loaded PLGA NPs showed selective adherence and enhanced drug accumulation into colitis tissues.

Silicon NPs: Silicon NPs have been widely used as drug vectors since they possess a range of beneficial features for drug delivery, including well-controlled size and size distribution, easily surface functionalization, and negative cytotoxicity, as well as large surface area and pore volume that facilitate drugs to be encapsulated[33].

Moulari *et al*[34] prepared 5-aminosalicylic acid-loaded silica NPs (around 140 nm), which showed 6-fold better adherence to inflamed colon than tissues from the healthy control mice after oral administration. In trinitrobenzene sulfonic acid (TNBS)-induced colitis mouse model, the NPs tended to accumulate in inflamed sites, and exerted excellent therapeutic efficacy in terms of clinical activity score and myeloperoxidase activity at lower drug doses than those applied in conventional delivery.

COMPLEX NPS

pH-sensitive NPs: pH-sensitive NPs take advantage of the pH differences in different regions of the GI tract[35]. The pH in the terminal ileum and colon is generally higher than that in any other regions of the GI tract. One of the simplest ways to modify dosage forms for pH-dependent drug delivery is to coat them with pH-sensitive biocompatible polymers.

Ali *et al*[36] showed that budesonide-loaded PLGA NPs that were further coated with Eudragit S100 (Figure 1A upper) significantly alleviated inflammation in the dextran sulfate sodium (DSS)-, TNBS- and oxazolone-induced mouse colitis models. A pH-sensitive NPs can

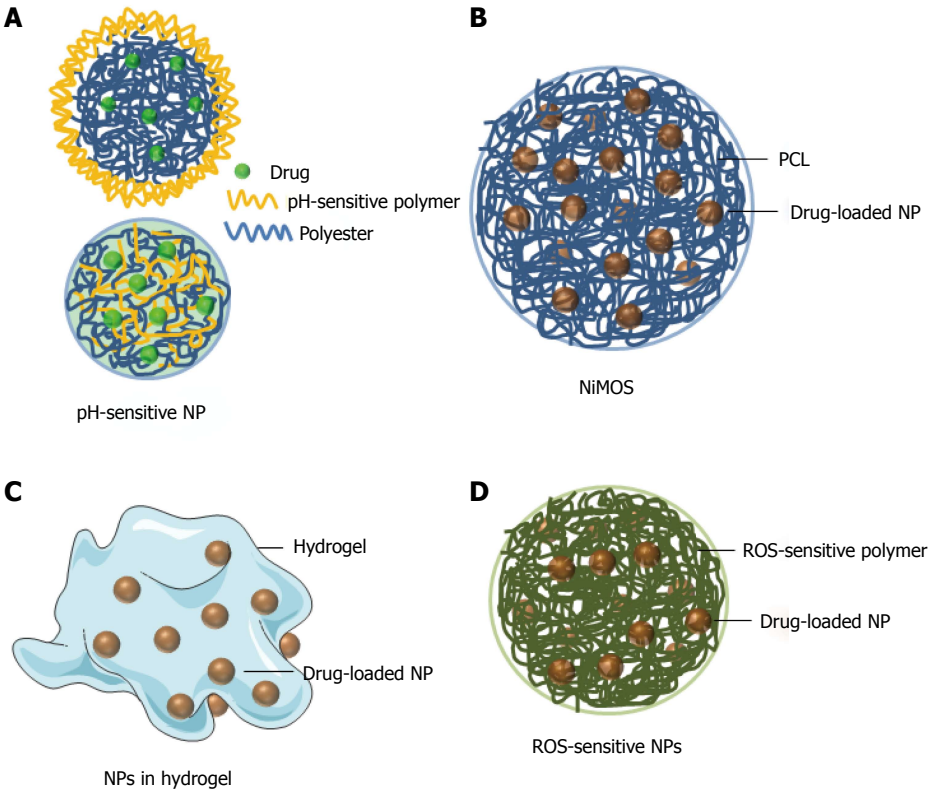

Figure 1 Various types of complex NPs for oral drug delivery. A: pH-sensitive NP; B: NiMOS; C: NPs in hydrogel; D: ROS-sensitive NP.

also be produced by mixing a pH-sensitive polymer and a non-pH-sensitive polymer in the NP fabrication process (Figure 1A lower). Beloqui *et al*[37] found that curcumin-loaded Eudragit S100/PLGA NPs showed obvious pH sensitivity profiles and efficiently decrease the expression/secretion of TNF-α in lipopolysaccharide-activated macrophages. Critically, oral administration of these pH-sensitive NPs significantly reduce neutrophil infiltration and TNF-α secretion in DSS-induced colitis mice. Additionally, histological studies revealed that the treatment mice exhibited almost the same colonic structure morphology as that observed in the healthy control group.

NP-in-microparticle: Recently, Amiji's group developed a colon-targeted drug formulation named the NP-in-microparticle (MP) oral drug delivery system (NiMOS), as demonstrated in Figure 1B[38]. A multi-compartmental NiMOS drug delivery system consists of gelatin nanoparticles encapsulated within polyε-caprolactone (PCL) MPs[39]. The MP matrix inhibits protein/enzyme degradation, and thus avoids the harsh environment of the GI tract capable of destroying the embedded NPs. When NiMOS reaches the colon, lipases degrade the PCL coating and the encapsulated NPs will be released to colon, which would become available for the uptake by colonic cells[40-43].

Kriegel *et al*[43] prepared TNF-α siRNA (siTNF)-loaded gelatin NPs, and further encapsulated them in PCL matrix to yield NiMOSs. The animal experiment results based on a DSS-induced colitis mouse model demonstrated that the above NiMOSs remarkably suppressed the expression levels of TNF-α and other pro-inflammatory cytokines (*e.g.*, IL-1β, IFN-γ, and monocyte chemotactic protein-1), and increased the body weight and colon length, in comparison to DSS-treated control mice. These results indicated that siTNF-loaded NiMOS could be a valuable therapeutic option for IBD patients.

NPs in hydrogel: Hydrogels are highly absorbent polymeric networks, and they can contain over 90% water. Chitosan and alginate are biocompatible and biodegradable polysaccharides, and used to prepare oral hydrogel by Merlin's group[44]. This chitosan/alginate hydrogel was sensitive to the colonic pH and could also be degraded by colonic enzymes. Thus it would collapse when they arrived at colon.

Laroui *et al*[45] embedded Lysine-proline-valine (KPV)-containing PLA NPs in this hydrogel (Figure 1C). Under its protection, NPs were able to pass through the stomach and upper small intestine, and were released in the inflamed colon. Using this improved NPs in hydrogel system, a 12000-fold lower dose was sufficient to ameliorate mucosal inflammation in mice subjected to acute DSS-induced colitis, in comparison to free KPV in solution.

Reactive oxygen species-sensitive NPs: IBD is accompanied by abnormally high reactive oxygen species (ROS) level in the GI tract, especially in the

Table 1 Ligands for orally targeted drug delivery in inflammatory bowel disease

Ligand	Delivery system	Effect	Ref.
Lectin	PLGA	Exhibited a much higher binding and selectivity to inflamed tissue compared to plain NPs	[54]
TfR antibodies	Liposomes	Exhibited mucopenetration and a 4-fold increase in uptake by inflamed colon tissues	[58]
CD98 antibodies	PEG–urocanic acid-chitosan	Approximately 24% of colonic macrophages were found to have taken up the targeted NPs within 12 h of administration	[66]
Mannose	Branched polyethylenimine	29.5% of the NPs were internalized by colon macrophages	[26]
Galactose	Trimethyl chitosan-cysteine	Cellular uptake in activated macrophages was significantly higher for Galactose trimethyl chitosan-cysteine/TPP NPs compared to trimethyl chitosan-cysteine/TPP NPs	[75]
F4/80 Ab Fab'	Poly(lactic acid)-poly(ethylene glycol) block copolymer	Improved DSS-induced colitis in vivo, and higher therapeutic efficacy was obtained using Fab'-bearing NPs compared to non-conjugated NPs	[77]
Amphiphilic hyaluronic acid	Decylamine	Budesonide loaded HANPs demonstrated higher anti-inflammatory effect on IL-8 and TNF-α secretion in inflamed cell model compared to the same dose of free drug	[78]

TfR: Transferrin receptor; PLGA: Polylactic-co-glycolic acid.

inflamed areas[46]. The excessive ROS can degrade the extracellular matrix and injure tissues[47]. Based on this fact, ROS-sensitive NPs (Figure 1D) are supposed to specifically release loaded drugs to inflamed colon or scavenge ROS.

Wilson *et al*[48] synthesized poly(1,4-phenyleneacetone dimethylenethioketal) (PPADT), which is a novel ROS-sensitive polymer. PPADT were further used to encapsulate siTNF/DOTAP complexes to generate thioketal NPs (TKNs). In a DSS-induced colitis mouse model, the mRNA expression levels of TNF-α and several other pro-inflammatory cytokines (IL-1, IL-6 and IFNγ) were significantly decreased and DSS-induced acute colitis was efficiently ameliorated after 5 days of oral administration of TKNs (0.23 mg siRNA/kg body weight)[49].

It was also reported that antioxidant compounds and free radical scavengers improved colitis[50,51]. Vong *et al*[52] synthesized a novel antioxidative nitroxide radical-containing NP (RNP^O) with a diameter of 40 nm. The further mice experiments indicated that the extent of inflammatory reactions and the severity of colitis have been relieved after oral administration of RNP^O.

LIGAND-MEDIATED TARGETED DRUG DELIVERY

To further reduce side effects and increase the drug concentration at inflamed sites, researchers have sought to induce active targeting[53]. The interactions between targeting ligands on the NPs surface and specific receptors over-expressed at inflamed sites are expected to improve the bioadhesion and the internalization of NPs to specific cells. Various ligand-mediated targeted drug delivery systems are compared in Table 1, and their targeted drug delivery process is shown in Figure 2.

Lectin

Lectin is a type of naturally occurring protein that is highly specific for carbohydrate residues. It has been widely used as a ligand facilitating colon-specific drug delivery.

Moulari *et al*[54] prepared two types of lectin-functionalized NPs that were peanut (PNA)-functionalized NPs and wheat germ (WGA)-functionalized NPs. *Ex vivo* quantitative adhesion analyses showed that lectin-functionalized NP exhibited a much higher binding and selectivity to inflamed tissue compared to plain NP. In terms of therapeutic efficacy, all glucocorticoid containing formulations revealed an enhanced therapeutic effect with lectin functionalization, especially by the PNA-NP compared to plain NP.

Transferrin receptor antibody

Healthy colon tissue has low expression level of transferrin receptor (TfR), whereas inflamed colon overexpresses TfR. Its elevated expression was detected in both basolateral and apical membranes of enterocytes from the colon biopsies of IBD patients and rats with colitis[55]. In addition, TfR levels are also found to be elevated in activated immune cells (*e.g.,* lymphocytes and macrophages)[56,57]. Thus, it is reasonable to speculate that TfR could be used as a targeting receptor for colitis-targeted drug delivery.

Harel *et al*[58] investigated the *ex vivo* adhesion capacity of anti-TfR antibody-functionalized immunoliposome to inflamed mucosal tissue[59]. The results indicated that this liposome exhibited mucopenetration and a 4-fold increase in uptake by colitis tissues from TNBS-induced colitis mice, compared to healthy colon tissues.

CD98 antibody

CD98 is a heterodimeric neutral amino acid transporter, which consists of a heavy chain (CD98hc or SLC3A2)

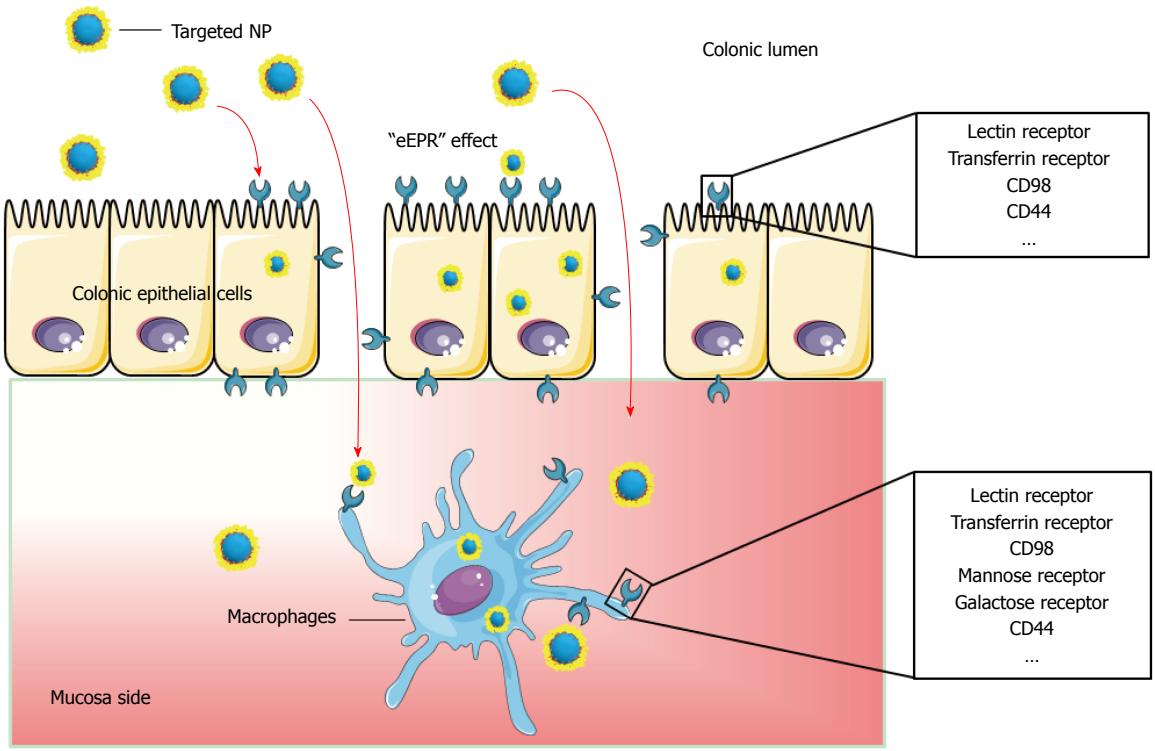

Figure 2 Schematic illustration of cell-specific drug delivery by nanotherapeutics after oral administration.

and one of several versions of the L-type amino acid transporter 1[60]. In colonic tissues from mice with active colitis, the expression level of CD98 is highly up-regulated at the surface of intestinal B cells, $CD4^+$ T cells, and $CD8^+$ T cell[61-63]. Additionally, CD98 is over-expressed in intestinal macrophages[64] and colonic epithelial cells from mice with colitis[61,65].

Recently, Xiao *et al*[66] fabricated an orally delivered hydrogel that releases CD98 antibody-functionalized NPs with the diameter of around 200 nm. In mice with acute or chronic colitis, orally administrated CD98 antibody-functionalized NPs significantly reduced the CD98 expression level in colitis tissue. Further studies revealed that about 24% of colonic macrophages internalize the targeted NPs within 12 h after oral administration, and the severity of colitis was significantly alleviated compared to the DSS control group.

Mannose

The mannose receptor is a 175-kDa transmembrane protein, and it is exclusively expressed on the surfaces of macrophages[67]. MRs have high-affinity binding to infectious agents with terminal mannose groups[61]. Moreover, this receptor can also bind to mannose-functionalized NPs, inducing the subsequent rapid internalization[68]. Numerous reports demonstrated that the functionalization of mannose on NP surface provides selective macrophage targeting and promotes cell internalization efficiency[69,70].

Xiao *et al*[26] synthesized a mannosylated bioreducible cationic polymer (PPM). It could spontaneously complex with siRNA to form NPs assisted by TPP. The resultant TPP-PPM/siTNF NPs exhibited obvious macrophage-targeting property. Further *ex vivo* experiment indicated that these NPs markedly inhibited TNF-α secretion in DSS-induced colitis tissues. Importantly, flow cytometry results showed that TPP-PPM/siTNF NPs were efficiently taken up by macrophages (29.5%), whereas there was no significant uptake by the epithelial cells.

Another study presented the similar result by Huang *et al*[71]. They fabricated a drug formulation by cationic konjac glucomannan (cKGM), phytagel and an antisense oligonucleotide (ASO) against TNF-α. The unique swelling properties of cKGM induced the spontaneous release of cKGM/ASO NPs from the phytagel matrix to colon lumen. Subsequently, mannose groups can be recognized by MRs that are abundant on the surface of macrophages. The treatment of this oral drug formulation significantly decreased TNF-α expression level and alleviated the symptoms of colitis in DSS-treated mice.

Galactose

It was reported that galactose receptor is highly overexpressed on the surface of activated macrophages[72,73]. Recently, Zhang *et al*[74] fabricated galactosylated trimethyl chitosan-cysteine (GTC) NPs loaded with siRNAs against mitogen-activated protein kinase kinase kinase kinase 4 (MAP4K4), which is a key enzyme of TNF-α production. *In vitro* results showed that the cellular uptake efficiency of GTC/TPP NPs was significantly higher than that of trimethyl chitosan-cysteine/TPP NPs, owing to galactose receptor-mediated endocytosis. Further *in vivo* experiments

demonstrated that oral administration of siMAP4K4-loaded GTC/TPP NPs obviously improved DSS-induced colitis, as characterized by body weight, histology, and myeloperoxidase activity.

F4/80 antibody

F4/80 is one of the vital macrophage-specific markers, and its antibody has been widely applied to separate macrophages[75,76]. Laroui *et al*[77] synthesized poly(lactic acid)-poly(ethylene glycol) block copolymer (PLA-PEG), and then conjugated with a macrophage-specific ligand (F4/80 Ab Fab') *via* maleimide/thiol group-mediated covalent bonding. They further used this polymer to encapsulate TNF-α siRNA (siTNF) to obtain F4/80 Fab'-functionalized siTNF-loaded NPs. Oral administration of siTNF-loaded NPs markedly improved DSS-induced colitis, and exhibited much higher therapeutic efficacy for F4/80 Fab'-functionalized NPs, in comparison to non-functionalized NPs. Further flow cytometry experiments indicated that functionalization of F4/80 Fab' significantly improved their macrophage targeting ability and the endocytosis of these NPs.

Hyaluronic acid

Hyaluronic acid (HA) is a natural anionic polysaccharide, composed of alternating D-glucuronic acid and *N*-acetyl-D-glucosamine units. It has a high affinity for the CD44 receptor, which is overexpressed on the surface of epithelial cells and activated inflammatory cells in colitis tissue[78]. Recently, Vafaei *et al*[78] synthesized HA-decylamine (DA) by chemical conjugation of DA to the backbone of HA. This amphiphilic HA-DA polymer could then form self-assembled HANPs. FITC-labeled HANPs revealed greater cellular uptake in inflamed Caco-2 BBE cell compared to untreated Caco-2 BBE cell and CD44-negative cell line (NIH3T3). Cytotoxicity test reveals that budesonide (BDS)-loaded HANPs displayed almost no toxicity, indicating HANPs were biocompatible nano-carriers. Importantly, BDS-loaded HANPs exhibited much higher anti-inflammatory effect in inflamed cell model compared to the same dose of free drug.

Overall, these studies demonstrate that active targeting is a very promising approach to enhance the accumulation and uptake of drugs by inflamed tissues.

CONCLUSION

Nanotherapeutic has been widely used as a novel approach for IBD treatment, and is much more effective than traditional drug formulation. Surface functionalization of these nanotherapeutics with targeting moieties (*e.g.,* antibody, monosaccharide, or polysaccharide) can further promote drug accumulation in the IBD therapy-related cells through receptor-mediated endocytosis and decrease the potential adverse effects. As summarized in this review, we provide some novel nano-formulations specific to the organs, tissues, cells, or organelles. We must clearly understand the barriers impeding the specific delivery of drugs to inflamed colonic tissues or IBD therapy-related key cells. Specifically, there is a need for further investigation of the pathophysiology of IBD (especially in the molecular level) and the development of intelligent NPs.

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