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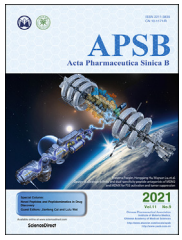

REVIEW

Receptor-mediated targeted drug delivery systems for treatment of inflammatory bowel disease: Opportunities and emerging strategies

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Abstract Inflammatory bowel disease (IBD) is a chronic intestinal disease with painful clinical manifestations and high risks of cancerization. With no curative therapy for IBD at present, the development of effective therapeutics is highly advocated. Drug delivery systems have been extensively studied to transmit therapeutics to inflamed colon sites through the enhanced permeability and retention (EPR) effect caused by the inflammation. However, the drug still could not achieve effective concentration value that merely utilized on EPR effect and display better therapeutic efficacy in the inflamed region because of nontargeted drug release. Substantial researches have shown that some specific receptors and cell adhesion molecules highly expresses on the surface of colonic endothelial and/or immune cells when IBD occurs, ligand-

Abbreviations: ACQ, aggregation-caused quenching; ADR, adverse drug reaction; AIE, aggregation-induced emission; BSA, bovine serum albumin; CAM, cell adhesion molecule; CD, Crohn's disease; CRD, cysteine-rich domain; CS, chondroitin sulfate; CT, computed tomography; CTLD, c-type lectin-like domain; DCs, dendritic cells; DSS, dextran sulfate sodium salt; EGF, epidermal growth factor; EPR, enhanced permeability and retention; FNII, fibronectin type II domain; FR, folate receptor; FRET, fluorescence resonance energy transfer; GIT, gastrointestinal tract; HA, hyaluronic acid; HUVEC, human umbilical vein endothelial cells; IBD, inflammatory bowel disease; ICAM, intercellular adhesion molecule; LMWC, low molecular weight chitosan; LPS, lipopolysaccharide; MAP4K4, mitogen-activated protein kinase kinase kinase kinase 4; MGL, macrophage galactose lectin; MPO, myeloperoxidase; MR, mannose receptor; MRI, magnetic resonance imaging; MPS, mononuclear phagocyte system; PAMAM, poly(amidoamine); PepT1, peptide transporter 1; PEI, polyethylenimine; PSGL-1, P-selectin glycoprotein ligand-1; QDs, quantum dots; RES, reticuloendothelial system; TfR, transferrin receptor; UC, ulcerative colitis; VCAM, vascular cell adhesion molecule.

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Active target;
Targeted therapy

modified drug delivery systems targeting such receptors and cell adhesion molecules can specifically deliver drug into inflamed sites and obtain great curative effects. This review introduces the overexpressed receptors and cell adhesion molecules in inflamed colon sites and retrospects the drug delivery systems functionalized by related ligands. Finally, challenges and future directions in this field are presented to advance the development of the receptor-mediated targeted drug delivery systems for the therapy of IBD.

1. Introduction

Inflammatory bowel disease (IBD), comprised of Crohn's disease (CD) and ulcerative colitis (UC), is characterized by chronic inflammation in the intestine[1]. Patients with IBD may suffer from abdominal pain, rectal bleeding, serious diarrhea, fever, weight loss, anemia and 2-fold higher risk of fatal colorectal cancer relative to healthy populations[2,3]. IBD possesses the highest prevalence with 0.3% in Western counties in 2017, and its incidence is increasing year by year worldwide[4,5]. To date, the exact etiology of IBD still remains unknown, however, it is well-accepted that environmental factors, genetic predeposition, gut microbiota, and immune function dysregulation participate in the occurrence and development of IBD[6]. Conventional medications, including antibiotics, aminosalicylates, corticosteroids, immunomodulators, and monoclonal antibodies, have been applied for achieving and prolonging clinical remission, reducing surgical intervention and improving the quality of life[7]. But prolonged and systemic administration of such therapeutics could lead to heavy economic burden and/or serious adverse drug reaction (ADR), like superinfection, anaphylaxis, myelosuppression, gastrointestinal reaction, and osteoporosis[7].

One of the principal challenges in the therapeutic strategies of IBD is delivering therapeutics specifically to colonic inflammation regions. Conventional colon targeted drug delivery systems are generally designed to release drugs based on the traditional cognition about gastrointestinal pH, transit time, enzyme, and microbiome in the colon. However, the changes of gastrointestinal pH, transit time, enzyme and microbiome are unclear in the development of IBD, which results in aimless drug release, unsatisfactory therapeutic efficacy and enhanced ADR[8]. In recent years, novel nanocarriers, like liposome[9], nanoparticle[10], hydrogel[11], dentrimer[12], have received substantial attention and investigation due to their excellent physicochemical properties. The tissue permeability is increased in the inflamed colon, due to destroyed intestinal tight junction, the loss of cellular integrity and the infiltration of immune cells caused by inflammatory cytokines. Exploiting the leaky intestine, nanocarriers can passively deliver drugs to the inflamed colon sites based on enhanced permeability and retention (EPR) effect[13,14]. In addition, nanocarriers can also improve the solubility and stability of drugs. However, the therapeutics still could not achieve effective concentration in the inflamed region because of nontargeted drug release. Therefore, more strategies are needed to realize the targeted drug delivery in the inflamed colon sites.

When colonic inflammation occurs, some specific receptors and cell adhesion molecules, like mannose receptor, macrophage galactose lectin, transferrin receptor, folate receptor, CD98, CD44, PepT1 and F4/80, are overexpressed on the colonic epithelia and/or immune cells[15,16]. Inspired by the leukocyte-endothelial biochemistry, which mediates the recruitment of leukocytes to the site of inflammation, the ligand−receptor interaction has been widely applied into the design and development of inflammation-related drug delivery systems. Receptor-mediated targeted drug delivery systems exploit ligand-modified drug carriers as "missiles" to deliver drugs to the target area, because specific ligands are linked to the receptors on target cells so it avoids drug release in other parts of the body (Fig. 1). This review briefly introduces the overexpressed receptors and cell adhesion molecules in inflamed colon sites and retrospects the relevant ligand-modified delivery systems that have been applied to improve the therapeutic efficacy of IBD. Then, challenges and future directions in this field are presented to advance the development of the receptor-mediated targeted drug delivery systems for the therapy of IBD.

2. General considerations of IBD targeted therapy

Usually, UC is restricted to diffuse superficial mucosal inflammation in the colon, extending proximally from the rectum. Unlike UC, CD manifests segmental transmural inflammation almost in the entire gastrointestinal tract (GIT), commonly in colon and terminal ileum[17]. Something similar between two diseases is that mucosal integrity and tight junction are destroyed, substantial immune cells infiltrate, certain receptors and cell adhesion molecules overexpress when inflammation occurs[18]. Targeted therapy exploits physiological or pathological characteristics of IBD patients to deliver drug to inflamed colon sites. The consideration for IBD targeted therapy primarily focuses on the *in vivo* fate of drug delivery systems *via* different administration routes and targeting strategies.

Generally, the administration routes of therapeutics for IBD include systemic, oral and rectal delivery. Different administration routes present different requirements on preparation. Systemic administration possesses high bioavailability, but it puts rather strict requirements on drug carriers' preparation. During systemic circulation before targeting to inflamed colon, intravenously administrated drug carriers would encounter many physiological barriers *in vivo*[19]. Drug delivery systems undergo opsonin adsorption and subsequent uptake by mononuclear

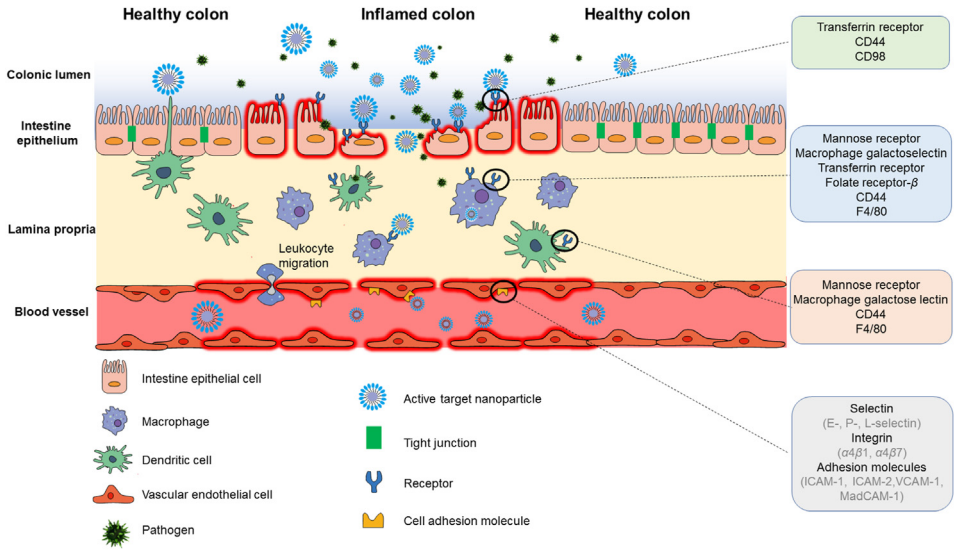

Figure 1 Schematic illustration of receptor-mediated targeted drug delivery for treatment of IBD.

phagocyte and reticuloendothelial system, which leads to non-target accumulation in liver and spleen. Small drug delivery systems (<10 nm) may undergo renal clearance, while large ones around 110 nm are more easily absorbed into inflamed sites compared to those >180 or <50 nm, probably due to EPR limitation, mononuclear phagocyte system (MPS) and reticulo-endothelial system's (RES) attack (>200 nm)[20,21]. Drug delivery systems may undergo other barriers such as cellular endocytosis, endosomal degradation and efflux pumps. Endocytosis mechanisms (*e.g.*, pinocytosis, phagocytosis and receptor-mediated endocytosis) and intracellular fates can be affected by several factors such as shape, size and superficial modification, of which ligands modification could prompt receptor-mediated endocytosis of drug delivery systems. Enzymes and acidic environments in lysosome may degrade drugs loaded in nanoparticles, especially polypeptide and genetic drugs, efflux pumps may transport drug out of cells due to drug resistance[19]. Oral administration is the most acceptable option for IBD patients. The physiological barriers of oral dosage forms are extreme pH gradient (1.0−8.3), substantial digestive enzymes, variable transit time and gut bacterial enzymes[22]. It requires the drug carriers should be stable before they reach the inflamed colon sites. The protective coating with specific functional materials, such as pH resistant or sensitive, enzyme responsive molecules, could address this requirement. Chitosan, alginate and PLGA are commonly used in surface coating due to their stability in upper GIT[23]. Drug delivery systems that enter the systemic circulation *via* intestinal epithelial cells' absorption may encounter the barriers as intravenous delivery systems meet. Unabsorbed drug delivery systems will be excreted with the feces. Rectal administration can achieve high drug concentration topically and reduce the systemic circulation of drugs. From the perspective of anatomy, there is less intestinal liquid and absorption surface area in rectum and rectosigmoid, it requires high drug solubility and low viscosity of drug carrier *via* rectal administration[24]. In conclusion, drug delivery systems are required to bind to inflammatory cells specifically *via* different administration routes. To develop such inflammation specific delivery system, attention could be paid to the pathophysiological changes at inflamed sites during IBD.

Conventional pharmaceutical strategies utilize gastrointestinal pH gradients, transit time and gut bacterial enzyme to target inflamed colon, as shown in Table 1[25−27]. pH-Dependent drug delivery systems exploit the highest pH values (7.2−8.3) of terminal ileum and colon to passively target colon. The common way is to coat the drug with biocompatible polymer which dissolves under alkaline environment, such as Eudragit[28]. The transit time of small intestine is 2−4 h[29]. Based on this, time-dependent delivery system is designed to control the drug release sites by coating immediate-release drug core with sustained-release materials, like ethylcellulose[30]. Substantial bacterial enzymes exist in terminal ileum and colon, like azoreductases, polysaccharidases, nitroreductase[31,32]. Such enzymes are used to design enzyme-degradation drug delivery system. Some azoreductase-mediated prodrugs have been approved for IBD treatment, such as sulphasalazine, olsalazine and balsalazine[25]. However, the pH, transit time and gut bacterial enzyme are closely related to the individual differences and pathological changes of IBD patients[33]. It is difficult for conventional passive drug delivery systems to deliver drugs into inflamed sites accurately and exhibit consistent therapeutic effects, even a dual targeting strategy combining pH- and time-dependent or enzyme-degradation, because they didn't combine the pathophysiological changes in GIT of IBD. The pathophysiological changes, like overexpressed receptors and cell adhesion molecules, should be taken into consideration when designing the delivery strategies.

3. Receptors and cell adhesion molecules for active targeting

When colonic inflammation occurs, some specific receptors and cell adhesion molecules, like mannose receptor, macrophage galactose lectin, transferrin receptor, folate receptor, CD98, CD44, PepT1, F4/80, are overexpressed on the colonic epithelial cells and/or immune cells, as summarized in Table 2. Drug delivery systems superficially modified with related ligands can specifically bind to receptors on inflamed cells, deliver drug into target area and achieve great curative effect. Based on the ligand−receptor interaction, receptor-mediated active targeted drug delivery systems could be a promising therapeutic strategy for IBD, as listed in Table 3[34−57].

Table 1 Representative approved delivery systems for the treatment of IBD.

Mechanism of targeting	Drug	Brand name	Company	Administration route	Formulation	Indication
pH-Responsive	Aminosalicylate	Asacol HD	Allergan (USA)	Oral	Tablet coated with Eudragit S	Moderate UC
	Aminosalicylate	Salofalk	Dr. Falk Pharma GmbH (Germany)	Oral	Tablet coated with Eudragit L	Mild to moderate UC
	Budesonide	Entocor	Tillots Pharma (Japan)	Oral	Capsule coated with Eudragit S	Induction and maintenance of remission of mild-to-moderate CD
	Beclomethasone	Clipper	Chiesi Pharma (Italy)	Oral	Tablet coated with Eudragit L 100/55	Mild-to-moderate
Time-dependent	Aminosalicylate	Pentasa	Kyorin (Japan)	Oral	Microgranule coated with ethylcellulose	Mild-to-moderate UC
pH-Responsive and time-dependent	Aminosalicylate	Lialda	Shire (USA)	Oral	A multi matrix core comprised of amphiphilic and lipophilic excipients outer coated with Eudragit S	Mild-to-moderate UC
	Budesonide	Uceris	Salix (USA)	Oral	A multi matrix core comprised of amphiphilic and lipophilic excipients outer coated with Eudragit S	Active or mild-to-moderate UC
Enzyme-degradation	Olsalazine	Dipentum	Alaven (USA)	Oral	Olsalazine is synthesized by two molecules of aminosalicylate *via* azo bond	Induction and maintenance of remission of mild-to-severe UC
	Sulfasalazine	Azulfidine	Pfizer (USA)	Oral	Sulfasalazine is synthesized by aminosalicylate and sulfapyridine *via* azo bond	Introduction of remission of UC
	Balsalazide	Colazide	Salix (USA)	Oral	Balsalazide is synthesized by aminosalicylate and 4-aminobenzoyl-β-alanine *via* azo bond	UC & CD
Enzyme-degradation and pH-responsive	Aminosalicylate	CODESTM	Yamanouchi Pharmaceuticals (Japan)	Oral	A tablet core coated with lactulose and acid-soluble materials	IBD
Anti-$\alpha4\beta7$ integrin	Anti-$\alpha4\beta7$ integrin mAb	Entyvio (Vedolizumab)	Takeda (Japan)	i.v. infusion	Each single-dose vial contains vedolizumab (300 mg), L-histidine (23 mg), L-arginine hydrochloride (131.7 mg), polysorbate 80 (3 mg), L-histidine monohydrochloride (21.4 mg), and sucrose (500 mg)	Moderate-to-severe CD & UC
Anti-$\alpha4$ integrin	Anti-$\alpha4$ integrin mAb	Tysabri (Natalizumab)	Elan (Ireland)/ Biogen Idec (USA)	i.v. infusion	Each single-dose vial contains: natalizumab (300 mg), sodium chloride (123 mg), phosphate (17 mg), monohydrate (17 mg), monobasic (17 mg), sodium phosphate (7.24 mg), heptahydrate (7.24 mg), dibasic (7.24 mg), polysorbate 80 (3 mg)	Induction and maintenance of remission of moderate -to-severe CD
Anti-TNF-α	Anti-TNF-α mAb	Remicade (Infliximab)	Johnson & Johnson (USA)/ Merck & Co. (USA)	i.v. infusion	Each single-dose vial contains: infliximab (100 mg), dibasic sodium phosphate (6.1 mg), dihydrate (6.1 mg), monobasic sodium phosphate (2.2 mg), monohydrate (2.2 mg), polysorbate 80 (0.5 mg), and sucrose (500 mg). No preservatives are present	Induction and maintenance of remission of moderate -to-severe CD & UC
Anti-IL-12 and IL-23	Anti-IL-12 and IL-23 mAb	Stelara (Ustekinumab)	Johnson & Johnson (USA)	i.v. infusion	Each single-dose vial contains: ustekinumab (130 mg), edetate disodium (0.52 mg), histidine (20 mg), histidine monohydrochloride monohydrate (27 mg), methionine (10.4 mg), polysorbate 80 (10.4 mg), Sucrose (2210 mg)	Moderate-to-severe UC

CD, Crohn's disease; IBD, inflammatory bowel disease; i.v., intravenous; UC, ulcerative colitis.

Table 2 IBD-related cell types and highly expressive receptors or cell adhesion molecules.

Cell type	Receptor and cell adhesion molecule
Intestine epithelial cell	Transferrin receptor, CD44, CD98
Macrophage	Mannose receptor, macrophage galactose lectin, transferrin receptor, folate receptor-β, CD44, F4/80
Dendritic cell	Mannose receptor, macrophage galactose lectin, CD44, F4/80
Vascular endothelial cell	Selectin (E-, P-, L-selectin), integrin ($\alpha4\beta1$, $\alpha4\beta7$), adhesion molecule (ICAM-1, ICAM-2, VCAM-1, MadCAM-1)

CAM, cell adhesion molecules; ICAM, intercellular adhesion molecule; VCAM, vascular cell adhesion molecule.

3.1. *Mannose receptor*

Mannose receptor (MR), also named as cluster of differentiation 206 (CD206), is an effective endocytic carbohydrate-binding receptor[58,59]. MR is overexpressed on the surface of macrophages and dendritic cells (DCs) under inflammation conditions[36,60]. It's a transmembrane receptor contains C-type lectin-like domains (CTLD), fibronectin type II domains (FNII), R-type cysteine-rich domains (CRD)[61,62]. Each domain has different affinity to few special carbohydrates, in which CRD highly binds to 3′(or 4′)-sulfated galactose or N-acetyl-D-galactosamine[63,64], FNII highly binds to collagens I–IV[65], and CTLD highly binds to mannose, fucose and *N*-acetyl-D-glucosamine[59,66]. Macrophages are responsible for pathogen phagocytosis, antigen processing and presentation, and mediator secretion. DCs receive and integrate signals from surroundings; they both significantly accelerate the pathological progress of IBD and proliferate in quantities during IBD[67,68]. Targeting MR on macrophages and DCs is gradually becoming a promising drug delivery strategy for IBD. Mannose is the most common ligand of MR. Mannose-modified delivery systems exhibit superior inflamed colon targeting *via ex vivo* and oral routes.

Coco et al.[34] fabricated three types of nanoparticles, Eudragit S100 coated ovalbumin NPs, *N*,*N*,*N*-trimethylchitosan chloride coated ovalbumin NPs, mannose modified ovalbumin NPs, respectively, to compare their ability to reach the inflamed colon sites. Only mannosylated ovalbumin NPs could cross the Caco-2 intestinal barrier through endocytosis, and then significantly accumulated in inflamed colon *ex vivo*. Another mannose conjugated polycation (PPM) is synthesized through *N*,*N*′-cystamine bisacrylamide (CBA) and branched polyethylenimine (bPEI). TPP-crosslinked PPM kept the sustained release of *siTNF-α* in a reductive cellular environment. Importantly, TPP-PPM/*siTNF-α* was efficiently uptaken by Raw264.7 cells, dramatically silenced *TNF-α* expression in Raw264.7 cells and colitis colon tissues *ex vivo* compared to polycation without mannose conjugation[35].

Ex vivo researches above proved the superior targeting properties of mannose modification. However, nanoparticles may be destroyed by gastrointestinal pH gradient (1.0−8.3) *via* oral administration (discussed in Section 2). Inert or pH-responsive materials could be used as protective outer layers. Chitosan is acid and alkali resistant and widely used in colon target delivery systems. Mannosylated trimethylchitosan (MTC) could keep the structure intact before reaching the colon, specifically bind to macrophages in inflamed intestine, primarily distribute in the intestine and show a long-term of 48 h intestinal retention without any significant cytotoxicity[37]. *Mir-146b* loaded in MTC remarkedly prompted the anti-inflammatory IL-10 secretion and intestinal epithelia proliferation *via* STAT3 signaling pathway, and downregulated pro-inflammatory *iNOS*, *TNF-α* and *IL-1β* gene through TLR4 signaling pathway in colitis tissues. Budesonide is a novel glucocorticoid that significantly and nonspecifically inhibits inflammation *via* nongenomic corticosteroid effects[69]. Since budesonide has hepatic first pass effect, oral route is suggested for administration[70]. Mannosylated nanoparticles with Eudragit coating could deliver budesonide to inflamed colon sites *via* oral route, exhibited noncytotoxic properties and significantly inhibited the increase of colon/body weight ratio, clinical activity index, histopathological score, TNF-α and IL-1β level in oxazolone-induced colitis tissue compared to drug suspension and non-mannosylated group[36].

The cellular endocytosis efficiency is not always proportional to the densities of ligands[71]. 21% densities mannose coverage of *siTNF-α*-loaded trimethylchitosan cysteine nanoparticle (21-TMC) exhibited the maximum cellular uptake and gene silencing capability *in vitro* compared with 4% (4-TMC) and 13% (13-TMC) densities. Surprisingly, the highest level of 4-TMC was found *in vivo* after oral administration. The siRNA loading dose of 4-TMC was 2−3 orders of magnitude less than the published *siTNF-α* vectors to inflamed colon, it still significantly reduced the TNF-α level *in vivo* compared with 13-TMC and 21-TMC (Fig. 2)[38]. Consequently, to achieve high performance and low toxicity, the ligand density screening is a crucial procedure in the development of drug delivery systems.

Unlike protein ligands, mannose is a small molecule compound with low immunogenicity and low cost, and thus derivatives of mannose are widely exploited for surface modification. MR is overexpressed on macrophages and DCs, it is noteworthy that MR is highly expressed on anti-inflammatory M2 macrophage, rarely expressed on pro-inflammatory M1 macrophage. Considering this, mannosylated anti-inflammatory drug-loaded delivery systems are more likely to target M2 macrophage, not M1 macrophage, and then therapeutic effects of mannosylated drug delivery system is controversial. Although substantial studies demonstrated that mannosylated drug delivery systems could target inflamed or cancerous sites and exert significant therapeutic effects, rare studies revealed the interaction between mannosylated delivery systems and cells, as well as the progress of macrophage phenotype transformation. Besides, since MR is also highly expressed in the liver, oral or rectal routes are suggested for mannosylated drug delivery systems to avoid hepatic endocytosis[72].

3.2. *Macrophage galactose lectin*

Macrophage galactose lectin (MGL), also named as cluster of differentiation 301 (CD301), is highly expressed on the surface of activated macrophages and dendritic cells[73]. Unlike MR, MGL is a transmembrane type II C-type lectin composed of N-terminal cytoplasmic domains, transmembrane domains, extracellular stalk domains, and C-type CRD that only specifically binds to galactose and *N*-acetylgalactosamine[74,75]. Based on efficient carbohydrate−protein interaction, compounds with galactose residue have been widely used in drug delivery system decoration to improve the targeting ability. In the current researches, there are two routes for galactosylated nanoparticles to target CD301 in inflamed colon: oral and rectal routes.

Table 3 Representative drug delivery systems targeting receptors for the treatment of IBD.

Receptor	Ligand	Carrier	Loading cargo	Delivery route	Characterization	Experimental model	Principal finding	Ref.
Mannose receptor	Mannose	Nanoparticle: PLGA−PEG	Ovalbumin	*Ex vivo*	S: 212.0 ± 8.0 Z: −7.0 ± 2.0	Proinflammatory cytokines treated Caco-2 cell, DSS-induced female C57BL/6 mice colitis	Mannose modification enhanced the endocytosis by Caco-2 cells and accumulation in inflamed colon	34
	Mannose	Nanoparticle: TPP/poly (CBA-bPEI)-PEG	*siTNF-α*	*Ex vivo*	S:275.00 Z: –	Raw264.7 macrophage, DSS-induced male FVB mice colitis	Introduction of mannose demonstrated a significant increase in intracellular uptake, gene silencing *in vitro* and *ex vivo*	35
	Mannose	Nanoparticle: lipid phase: Compritol 888 ATO/ Labrafac WL 1349/ stearylamine/Span 80 aqueous phase: Poloxamer 188/ Polysorbate 80	Budesonide	Oral	S: 301.7 ± 2.88 Z: +7.51 ± 0.71	Oxazolone-induced Wistar rat colitis	Surface conjugation of mannose led to superior effects in reduction of MPO, inflammatory cytokines (TNF-α, IL-1β) *in vivo*	36
	Mannose	Nanoparticle: trimethyl chitosan	*Mir-146b*	Oral	S: 213.6 ± 16.6 Z: +28.3 ± 6.3	Bone marrow-derived macrophage, DSS-induced C57BL/6 mice colitis	Mannosylated nanoparticles could be efficiently recognized and endocytosized by activated intestine macrophages	37
	Mannose	Nanoparticle: trimethyl chitosan	*siTNF-α*	Oral	S: 143.3 ± 1.1 Z: +18.7 ± 0.6	Raw264.7 macrophage, DSS-induced C57BL/6 mice colitis	Different densities of mannose on nanoparticle displayed different effects on the intracellular uptake and therapeutic efficacy *in vitro* and *in vivo*	38
Macrophage galactose lectin	Lactobionic acid	Nanoparticle: chitosan-PLGA	*siTNF-α*	Oral	S: 245.60 ± 0.33 Z: +13.03 ± 0.65	Raw264.7 macrophage, DSS-induced male C57BL/6 mice colitis	Galactosylation remarkedly improved the targeted delivery into macrophage and *TNF-α* silencing effect *in vitro* and *in vivo*	39
	Lactobionic acid	Nanoparticle: trimethyl chitosan-cysteine	*siMap4k4*	Oral	S: 147.2 ± 7.8 Z: +26.2 ± 2.0	LPS-stimulated Raw264.7 macrophage, DSS-induced C57/BL6 mice colitis	The endocytosis kinetics and gene silencing effect of galactosylated nanoparticle outperformed those nanoparticles without galactosylation	40
	Lactobionic acid	Nanoparticle: PLGA/PVA/ chitosan	*siTNF-α* & IL-22	Oral	S: 261.3 ± 5.6 Z: −6.3 ± 1.4	Raw264.7 macrophage, DSS-induced male FVB mice colitis	Co-delivery of *siTNF-α* and recombinant human IL-22 could significantly inhibit the infiltration of mucosal neutrophils, promoted the colon epithelia regeneration and mucosal integrity	41

(*continued on next page*)

Table 3 (*continued*)

Receptor	Ligand	Carrier	Loading cargo	Delivery route	Characterization	Experimental model	Principal finding	Ref.
	Lactobionic acid	Nanoparticle: LMWC	*TNF-α* antisense oligonucleotide	Oral	S: – Z: –	TNBS-induced mice colitis, *CD45RB^{hi}* transferred mice colitis	Activated macrophages in the colon lamina propria of colitis mice efficiently absorbed galactosylated TNF-α antisense oligonucleotide nanoparticles	42
	Lactobionic acid	Nanoparticle: LMWC	*Mir-16*	Rectal	S: – Z: –	TNBS-induced BALB/c mice colitis	Galactosylated nanoparticle significantly accumulated in inflamed colon and delivers *Mir-16* into colonic macrophages rather than T cells and colonic epithelial cells	43
CD44	HA	Nanoparticle: BSA-KPV/ PLGA/PVA-chitosan	KPV	Oral	S: 272.3 Z: −5.3	LPS-stimulated Raw264.7 macrophage, DSS-induced FVB mice colitis	Colon-26 cells and Raw264.7 macrophages selectively absorbed HA modified nanoparticles	44
	HA	Nanoparticle: spermidine/ PLGA/chitosan	Curcumin& *siCD98*	Oral	S: 246.2 ± 7.8 Z: −13.7 ± 4.1	LPS-stimulated Raw264.7 macrophage, DSS-induced FVB mice colitis	Surface grafting with HA enhanced the nanoparticles binding to colitis tissues and to be endocytosed by colonic macrophages	45
	HA	Copolymer: HA-bilirubin	Bilirubin	Oral	S:171 ± 30 Z: −39.1 ± 0.7	M0/M1/M2 J774A.1 macrophage, DSS-induced C57BL/6 mice colitis	HA-bilirubin copolymer could accumulate in inflamed colon epithelia and be internalized into M1 macrophages	46
	CS	Nanoparticle: silk fibroin	Curcumin	Oral or I.V. injection	S: 180.8 Z: −30	LPS-stimulated Raw264.7 macrophage, DSS-induced mice colitis	CS functionalization facilitated nanoparticle to be internalized into macrophage *via* CD44-mediated endocytosis	47
	HA	Hydrogel: methylcellulose/ HA	BSA	Rectal	S: – Z: –	Caco-2 monolayer	HA/ Methylcellulose hydrogel could rapidly permeate across Caco-2 monolayer	48
Folate receptor	Folate	Nanoparticle: PLGA/PLA−PEG	6-shogaol	Oral	S: 249.60 ± 1.30 Z: −24.17 ± 0.41	Raw264.7 macrophage, DSS-induced FVB/NJ mice colitis	Efficacy of 6-shogaol increased significantly after loading into folate modified nanoparticle, compared to drug suspension	49

	Folate	Dendrimer: PAMAM-PEG/ acetic anhydride	–	Tail vein injection	S: – Z: –	Raw264.7 macrophage, DSS-induced C57BL6 mice colitis	Folate conjugation facilitated dendrimers binding to macrophages and accumulating in inflamed colon sites after tail vein injection	50
	Folate	Liposome: DSPC/ cholesterol/PEG_{3400}-DSPE	Betamethasone	Tail vein injection	S:100 ± 10 Z: –	Raw264.7 and peritoneal macrophage, DSS-induced C57/BL6 mice colitis	Folate grafting directed the liposomes to significantly accumulate in the inflamed colon and bind to peritoneal macrophages	51
CD98	CD98 Fab'	Nanoparticle: PLA/bPEI/ PVA/Mal-PEG	Quantum dots	*Ex vivo*	S: 458 Z: +19	Colon-26 cell and Raw264.7 macrophage, DSS-induced FVB mice colitis	CD98 Fab' dramatically promoted the nanoparticle transporting into the CD98 glycoprotein overexpressed cells and inflamed colon.	52
	Single-chain CD98 Ab	Nanoparticle: PEI/UAC-PEG-scCD98	*siCD98*	Oral	S: 210 Z: +15	Raw264.7 macrophage, colon-26 cells, DSS-induced C57/BL6 mice colitis, $CD4^+$ $CD45RB^{high}$ T cell transferred $RAG^{-/-}$ mice colitis	Antibody conjugation endowed the nanoparticle with excellent biometrics capacity to bind CD98 glycoprotein on activated macrophage and polarized colon epithelia	53
Transferrin receptor	TfR antibody	Liposome: HSPC/HSPG/ DSPE-PEG-NHS	–	*Ex vivo*	S:105.60 ± 7.00 Z: −14.10 ± 3.30	Proinflammatory cytokines co-incubated Caco-2 cell, DNBS-induced rat colitis	Surface modification with TfR antibody resulted in more endocytosis by Caco-2 cells and accumulation in inflamed colon sites *ex vivo*	54
	Seven peptides	Nanoparticle: PEG-*b*-PCL	Coumarin 6	*In vitro*	S: 35.94 ± 2.76 Z: −3.10 ± 0.84	Caco-2 cell	Specific 7 peptides conjugation exhibited faster absorption rate in live cells	55
Peptide transporter 1	KPV	Nanoparticle: PLGA/ montmorillonite/chitosan	Cyclosporine A	Oral	S:185.7 ± 3.0 Z:30	DSS-induced mice colitis	Surface modification with KPV promote nanoparticle to accumulate in inflamed colon.	56
F4/80	F4/80 Ab Fab'	Nanoparticle: PLA−PEG	*siTNF-α*	Oral	S: 609 ± 37 Z: –	LPS-stimulated Raw264.7 macrophage, DSS-induced mice colitis	F4/80 Ab Fab' introduction increased the phagocytosis of nanoparticles by intestinal macrophages in mice	57

–, not applicable; BSA, bovine serum albumin; CS, chondroitin sulfate; DSS, dextran dulfate sodium salt; HA, hyaluronic acid; I.V., intravenous; LMWC, low molecular weight chitosan; LPS, lipopolysaccharide; MPO, myeloperoxidase; KPV, lysine-proline-valine tripeptide; S, size (nm); Z, zeta potential (mV).

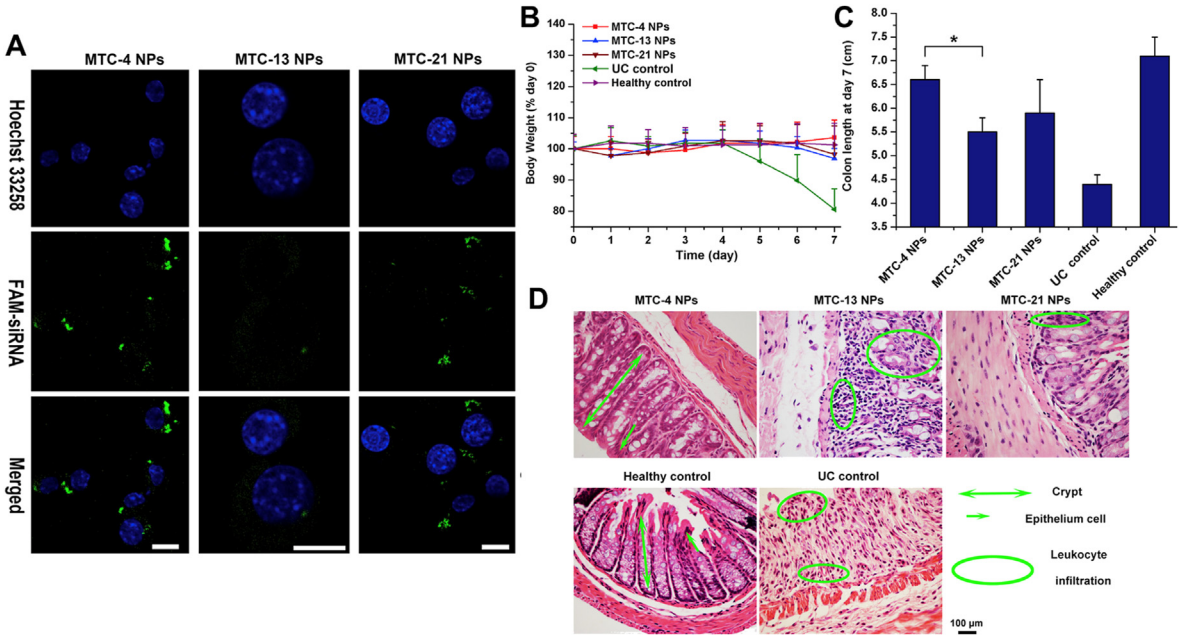

Figure 2 MR-mediated targeted therapy for IBD. (A) The endocytosis of FAM-siRNA loaded MTC NPs by Raw264.7 macrophages after 4 h incubation. Green represents the labeling of FAM, blue represents the fluorescence of Hoechst 33258. Scale bar represents 10 μm. (B) Changes of mice body weight over time. Data are presented as mean ± standard deviation (SD, $n = 6$). (C) Changes of mice colon length over time. Data are presented as mean ± SD ($n = 6$). *$P < 0.05$. (D) H&E staining of mice colon sections. Scale bar represents 100 μm. Reprinted with permission from Ref. 38. Copyright © 2015, Elsevier.

Chitosan derivatives and PLGA are the most common used matrices for oral dosage forms of IBD due to their stability in upper GIT. TNF-α is a critical inflammatory cascade reaction cytokine that highly participates in the deterioration of IBD, anti-TNF-α is an effective strategy for IBD therapy[76]. *TNF-α* antisense oligonucleotide loaded in galactosylated low molecular weight chitosan (LMWC) nanoparticles could be efficiently uptaken by activated macrophages in inflamed colon, markedly decrease colonic *TNF-α* mRNA level and some other inflammatory cytokines, and significantly ameliorate the acute or chronic clinical symptom of TNBS-induced or *CD45RB*^{hi}-transfered colitis, respectively[42]. Galactosylated *siTNF-α*-loaded PLGA nanoparticle (GPN) could promote the recognition and uptake of nanoparticles by Raw264.7 cells compared with galactose-negative control, significantly inhibiting the *TNF-α* mRNA transcription and translation *in vitro*. The GPN could resist the acid and alkali in GIT, keep the *siTNF-α* intact before reaching the inflamed colon, ameliorate the serous clinical symptoms of colitis, and display superior efficacy in colonic *TNF-α* gene silencing than galactose-negative group[39]. Mitogen-activated protein kinase kinase kinase 4 (MAP4K4) can activate the expression of *TNF-α* and *IL-1β* simultaneously without passing through JNK1/2, ERK1/2, P38 and NF-κB pathways, which indicates that it's a potential therapeutic target for IBD[77]. Galactosylated trimethylchitosan−cysteine (GTC/TPP) nanoparticles could keep *siMap4k4* intact in serum and intestinal fluids, allowed more *siMap4k4* to accumulate in inflamed colon tissue rather than being absorbed into systemic circulation, significantly decreased TNF-α level and relieved clinical symptom of colitis[40]. IL-22 could promote the recovery of IBD by accelerating colonic epithelia proliferations and enhancing mucosal barrier[78]. However, the colonic IL-22 level decreases accordingly after anti-TNF-α antibody treatment, like Infliximab[41]. Encapsulating *siTNF-α* and recombinant IL-22 into galactosylated chitosan/PLGA NPs could precisely target macrophages in inflamed colon, chitosan/PLGA kept RNA structure integrity during delivery process. Co-delivery of *siTNF-α* and IL-22 significantly inhibited the TNF-α level and infiltration of mucosal neutrophils, promote the colon epithelia regeneration (Fig. 3).

Galactosylated drug carriers still could target CD301 *via* the rectal route. Mir-16, a small noncoding RNA, can lead to breakage of *TNF-α* mRNA and *IL-12p40* mRNA after specifically binding to their respective 3′-untranslated AU-rich regions[43,79]. Since Mir-16 can regulate multiple genes, systemic absorption of Mir-16 may cause cellular dysfunction and impede its therapeutic efficacy. Galactosylated LMWC (Gal-C) could deliver Mir-16 to activated colonic macrophage rather than colon epithelia and T cells in TNBS-induced colitis mice through rectal administration, significantly ameliorate the weight loss, colon shortening and increased myeloperoxidase (MPO) level, and exhibit long-term therapeutic effect which still remarkedly inhibited the expression and production of TNF-α and IL-12p40 in colon tissues up to 3 days.

Lactobionic acid, consisted of galactose residue and carboxyl group, was commonly used for functional modification to target CD301. However, the asialoglycoprotein receptor, which highly expressed on hepatocytes, could also efficiently recognize and internalize galactose and *N*-acetylgalactosamine[80]. Galactosylated drug delivery system administrated by injection would be absorbed by the liver. To achieve desirable therapeutic effects, oral administration is suggested for such delivery systems when treated to patients with IBD.

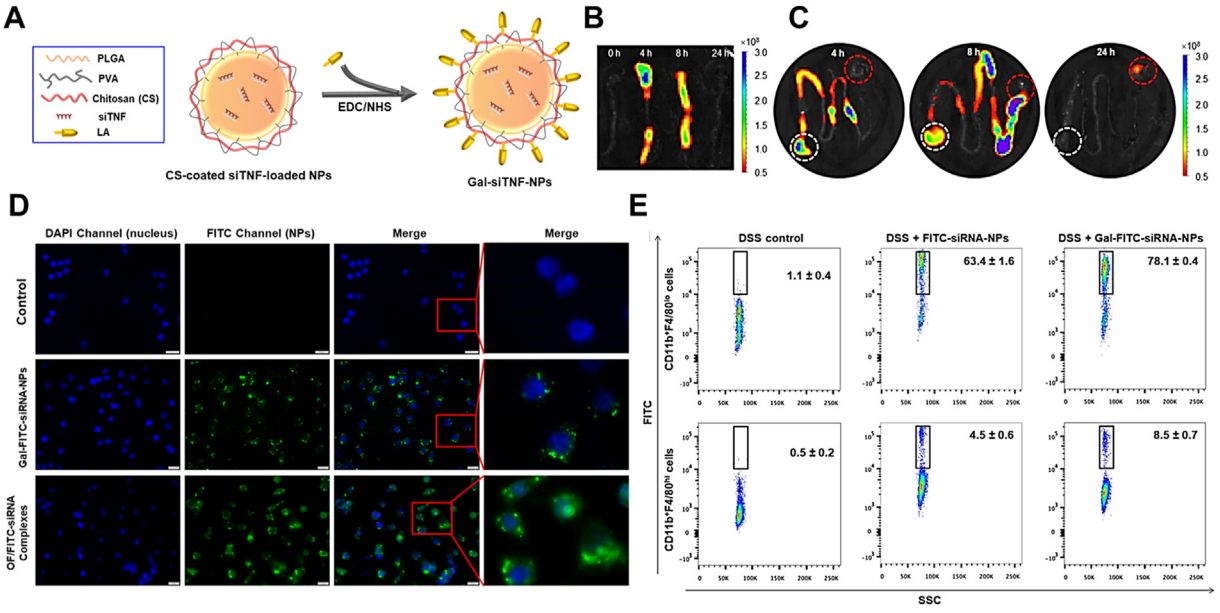

Figure 3 MGL-mediated targeted therapy for IBD. (A) Schematic illustrations of fabrication of Gal-siTNF-NPs. The colonic accumulation of Gal-FITC-siRNA-NPs in mice colon sites (B) and other sections of GIT (C) at 4, 8 and 24 h after oral administration. White circle and red circle represent stomach and cecum, respectively. (D) Cellular uptake of Gal-FITC-siRNA-NPs (green) by macrophages. Scale bar represents 10 μm. (E) FCS analysis of colonic macrophages in mice after 12 h of FITC-siRNA-NPs or Gal-FITC-siRNA-NPs administration. Data are presented as mean ± SD ($n = 3$). Reprinted with permission from Ref. 41. Copyright © 2018, Elsevier.

3.3. CD44

CD44 is a multifunctional transmembrane receptor responsible for cell adhesion, cellular uptake or degradation of hyaluronic acid (HA), immune activation[81]. CD44 almost presents on all cells, whereas highly presents on cancer cells and inflammatory cells. Colon epithelia and macrophages in colitis tissues possess abundant CD44 on their surface, which makes CD44 as an effective drug delivery target in the treatment of IBD[82]. The ligand of CD44, like HA, laminin, collagen and chondroitin sulfate, has been widely used in superficial modification[83]. CD44 ligand-modified nanoparticles can target the inflamed colon *via* different routes, including oral, systemic and rectal routes.

Partial nanoparticles administered by oral routes take chitosan and/or PLGA as protective matrices. Lysine-proline-valine tripeptide (KPV), the dissociation products of α-melanocyte-stimulating hormone, manifests stronger anti-inflammatory effect inside the cells by blocking inflammatory pathway[84,85]. Free KPV could significantly inhibit colonic TNF-α level, MPO activity and the severity of dextran dulfate sodium salt (DSS)-induced or TNBS-induced colitis *via* oral administration, but 12,000-fold lower concentration than free KPV could achieve identical therapeutic efficacy after loading into HA modified PLGA/chitosan nanoparticles (Fig. 4)[44,86]. As described in CD98 chapter, topical interfering the CD98 expression could attenuate colitis. Curcumin can attenuate colitis *via* blocking multiple signaling pathways, like NF-κB and Toll-like receptor signaling pathways[87]. Combination therapy of curcumin and siCD98 displayed stronger efficacy in downregulation of CD98 and TNF-α level compared to curcumin or *siCD98* treatment alone[45]. HA does not only act as ligand of CD44, it could also be applied as formulation matrix. HA with different molecular weights vary in pro- or anti-inflammation regulatory effects[88]. Compared to 10 or 700 kDa, 100 kDa HA-bilirubin copolymer could self-assemble into spherical nanoparticle with desirable diameter, possesses notable efficacy in inhibiting pro-inflammatory cytokines, increasing anti-inflammatory cytokines, and regulating gut microbiota and its efficacy outperformed HA, bilirubin and HA & bilirubin[46]. Maybe due to the specific covalent binding, chemical structure HA-bilirubin structure is not destroyed by gastrointestinal acid-base and enzyme, copolymer still possesses anti-inflammatory effects when reaching inflamed colon *via* oral routes.

Whether by oral or systemic routes, chondroitin sulfate-functionalized silk fibroin nanoparticles (CS-SFs) dramatically guided curcumin to accumulate in the colitis tissues compared to carboxymethyl cellulose or plain functionalization. Due to the long circulatory, maximum curcumin concentrated at inflamed colon *via* systemic route exhibited the best therapeutic efficacy through downregulating TNF-α, IL-6 and IL-12 level, upregulating IL-10 level and improving gut microbiota composition[47].

A novel thermoresponsive hydrogel administrated by rectal route is formed by the cross-linking of HA and methylcellulose at a ratio of 0.225% or 3.5%. The resultant hydrogel is liquid-like with good flowability at 20 °C, but it seems freezing at 37 °C. The model drug, bovine serum albumin (BSA), can be released from the gel rapidly in the presence of sodium dodecyl sulfate and permeated across Caco-2 monolayer, which suggested that the HA-methylcellulose hydrogel could be a potential rectal drug carrier for IBD[48].

wSince CD44 can present on all cells, delivery system targeting CD44 may not be able to deliver the drug specifically to the inflamed colon, which could result in aimless drug release and systemic ADR. There are some other ligands of CD44, including osteopontin, matrix metalloproteases, collagens and antidody[89], which have not been used in targeted modification of drug delivery systems for IBD yet, at least to our best knowledge. It would be very interesting to investigate them in practice.

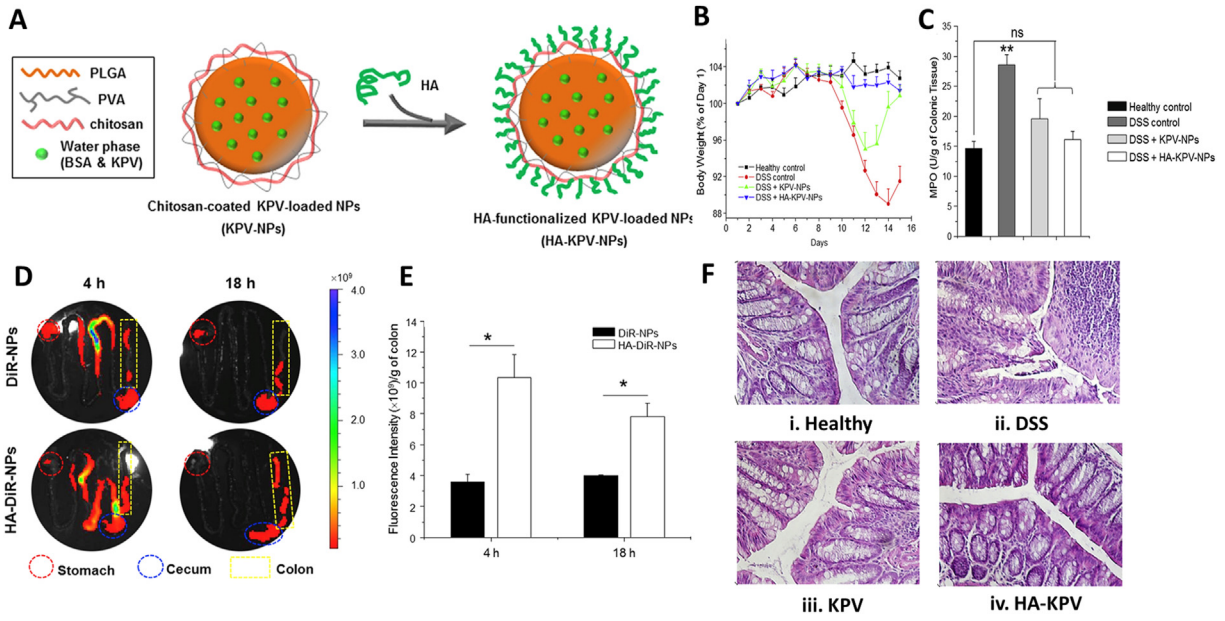

Figure 4 CD44-mediated targeted therapy for IBD. (A) Schematic illustrations of preparation of HA-KPV-NPs. (B) Changes of mice body weight over time. Data are presented as mean ± SD ($n = 5$). (C) Colonic MPO level in different mice groups. Data are presented as mean ± SD ($n = 5$). $^{**}P < 0.01$. ns, not significant. (D) The accumulation of KPV-NPs and HA-KPV-NPs in GIT at 4 or 8 h after oral administration, red circle and blue circle represent stomach and cecum, respectively. (E) Colonic quantification of the fluorescence intensity. Data are presented as mean ± SD ($n = 5$). $^{*}P < 0.05$. (F) H&E staining of mice colon sections. The scale bar represents 100 μm. Reprinted with permission from Ref. 44. Copyright © 2015, Elsevier.

3.4. *Folate receptor*

Folate receptor (FR), the collective name of four isoforms (FR-α, -β, -γ, and -δ), could highly bind to folate and efficiently transport them into cytoplasm through receptor-mediated endocytosis[90]. Since folate is essential for one-carbon metabolism, protein metabolism and DNA synthesis, FR (except for FR-γ) is usually overexpressed on the surface of rapid proliferating cells[91], of which FR-α mainly exists on apical sides of epithelia, like lung and kidney[92], FR-γ only exists on hematologic normal tissue or malignancies, like spleen and bone marrow[93], FR-δ is merely found on regulatory T cells and oocytes[94], FR-β exists on activated macrophages at an extremely high level but cannot be detected on resting/quiescent macrophages or any other normal cells[51]. Studies elucidated that substantial FR-β-positive macrophages infiltrated into human inflamed colon during IBD[95]. Due to the accurate expression pattern, targeting FR-β provides a novel way for targeted therapy of IBD. Folate-functionalized nanoparticles could target FR-β on macrophages in inflamed colon *via* systemic and oral routes.

Chitosan/alginate (3:7) hydrogel is commonly used in the encapsulating of drug delivery systems administrated by oral routes. Zhang et al.[49] fabricated folate modified PLGA/PLA−PEG nanoparticles (PPNs). Folate modification could improve the biocompatibility of PPNs, the viability of Raw264.7 cells isn't altered during 48 h incubation with FA-PPNs up to 1 mg/mL and no toxicological or pathological changes were found in blood biochemistry and major organs during the 7 days' treatment with FA-PPNs. 6-Shogaol, a component in ginger, possesses significant antioxidant and anti-inflammatory effects[96]. 6-Shogaol/FA-PPNs encapsulating into chitosan/alginate (3:7) hydrogel exhibited superior effect by significantly decreasing the level of lipocalin-2, inhibiting the expression of *TNF-α, IL-6*, *IL-1β* and *iNOS*, facilitating the healing gene expression of *Nrf-2* and *HO-1* compared to 6-shogaol suspension[49].

Folate functionalized drug carriers still exhibit great targeting properties when administrated *via* the systemic route. The fluorescence intensity of folate functionalized poly(amidoamine) (PAMAM) dendrimers in macrophage was significantly higher than that of non-functionalized group, but when co-incubation with free folate, all dendrimers displayed the same negative results. *In vivo* imaging experiments demonstrated that folate-dendrimer preferred to accumulate in inflamed colon rather than healthy colon after tail vein injection[50] (Fig. 5). This excellent FR targeted accumulation capacity was consistent with Scott Poh's findings[51], that only 0.1% folate could statistically direct DSPC/cholesterol/DSPE (56:40:4) liposome to concentrate in inflamed colon and adhere for 4-times longer than healthy colon after intravenous administration. Betamethasone is a kind of glucocorticoid (the anti-inflammatory mechanism of glucocorticoid is introduced in Section 3.1). Betamethasone loaded in folate-conjugated liposome possessed a superior effect in decreasing colon thickness compared to blank-conjugated liposome[51].

Tissue or organism may express different FR isoforms simultaneously, simple folate cannot distinguish the difference, and thus folate conjugated carrier may not completely deliver drugs into inflamed sites. N^5,N^{10}-dimethyl tetrahydrofolate, a synthetic folate derivative, could evade other FR's recognition and only bind to FR-α[97]. But as for FR-β, we haven't retrieved any correlative reports. There is an extremely urgent need for FR-β special ligand because of so many prevalent macrophage-related inflammatory diseases, like UC, CD, rheumatoid arthritis, atherosclerosis, psoriasis, and diabetes[51]. A meta-analysis revealed that IBD patients are intimately related to serious serum folate deficiency[98], which

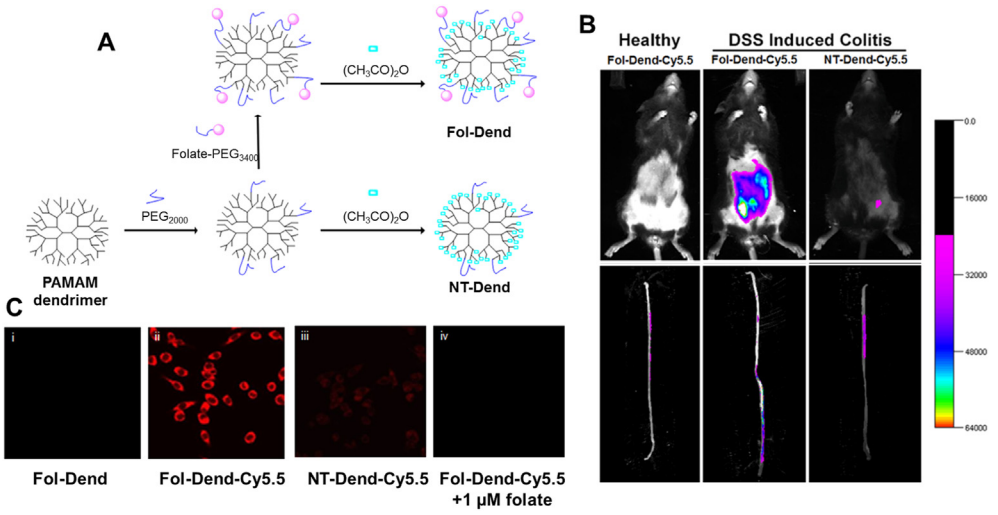

Figure 5 FR-mediated targeted therapy for IBD. (A) Schematic illustration of fabrication of folat-modified PAMAM dendrimers. (B) Fluorescence image of Cy5.5-labled dendrimer *in vivo* or *ex vivo* 12 h after 1 mg/kg Fol-Dend or NT-Dend administration through tail vein injection ($n = 4$). Colitis mice were induced by drinking 3% DSS water for 6 d $\lambda_{ex} = 625$ nm, $\lambda_{em} = 700$ nm. (C) The endocytosis of dendrimers by Raw264.7 macrophages after 2 h incubation at 37 °C. $\lambda_{ex}=670$ nm, $\lambda_{em} = 700$ nm. Reprinted with permission from Ref. 50. Copyright © 2017, American Chemical Society.

promote the deterioration progress of colitis to colitis-related cancer[99], appropriate folate supplement may be an auxiliary method for the treatment of IBD[98]. Considering this, maybe folate-conjugated drug delivery system will display special advantages.

3.5. *CD98*

CD98 is a transmembrane glycoprotein heterodimer linked by disulfide bond between CD98 heavy chain (hc) and CD98 light subunit[52,53]. CD98, responsible for protein transport[100], can express on the surface of all normal cells except platelets at a balanced level, but substantial CD98 glycoprotein is found on colon epithelia in apical side when the integrity of intestinal epithelial barrier is broken and pathogenic microorganisms invade[101]. Meanwhile, overexpressed CD98 glycoprotein was detected in colonic tissues from mice and patients with colitis, which highly promoted the intestinal inflammation initiation, development, and cancerization of colitis[102–104]. Hence, CD98 provides a novel approach for IBD targeted therapy.

Nanoparticles modified by CD98 ligands can bind to CD98 on epithelia of inflamed colon *via ex vivo* and oral route. Quantum dots (QDs) is a promising imaging agent but with cytotoxicity, encapsulating with biocompatible polymers could decrease the cytotoxicity of QDs[105]. To target the CD98 and track the intracellular progress, Xiao et al.[52] digested the CD98 antibody with pepsin to obtain Fab' fragment, and then grafted it onto the surface of QDs-loaded polymer. As expected, the Raw264.7 and Colon-26 cells rapidly endocytosed CD98 Fab'-QDs NPs into cytoplasm in a concentration-dependent manner, but the uptake efficiency decreased 65.0% and 87.4%, respectively, after blocking down the CD98 expression. The CD98 Fab' accelerated QDs' NPs penetrating the inflamed colon *ex vivo*.

To investigate the potential of CD98 *in vivo*, single-chain CD98 antibody-conjugated *siCD98*-loaded nanoparticles (ssCD98 NPs) were administrated *via* oral route (Fig. 6)[53]. Nanoparticles were encapsulated in chitosan/alginate hydrogel to ensure the integrity of nanoparticles during upper GIT. Severe clinical manifestation of acute colitis had been significantly ameliorated after ssCD98 NPs treatment, including weight loss, enhanced MPO activity, upreguated CD98, TNF-α, IL-6 and IL-12 level, and aberrant histology. The same excellent therapeutic effect was observed in chronic $RAG^{-/-}$ mice colitis induced by $CD4^{+}CD45RB^{high}$ T cells. Even though it showed excellent efficacy *in vivo*, flow cytometry revealed that only 24.1% of colon macrophage and 9.6% colonic epithelia isolated from inflamed colon tissue internalized the ssCD98 NPs during 12 h post-administration, which is consistent with the research result that medicine could manifest effective effect *in vivo* with cellular absorptivity ranging from 5% to 20%[106].

CD98 highly promotes the intestinal inflammation initiation, development, and cancerization of colitis[94]. Blocking the CD98 expression of experimental colitis mice has achieved good therapeutic effects. It indicates that CD98 is also a good target for the treatment of IBD[45,107]. Meanwhile, CD98 glycoprotein is a translocation protein that could be a target for drug delivery into cytoplasm. However, CD98 can express on the surface of all normal cells except platelets. Therefore, necessary measures should be employed to avoid the binding of nanoparticles with other cells when designing delivery systems targeting CD98.

3.6. *Transferrin receptor*

Transferrin receptor (TfR), a transmembrane glycoprotein, could efficiently uptake transferrin through receptor-mediated endocytosis to maintain intracellular iron homeostasis[108]. TfR almost presents on all normal cell types at low level, but highly exists on rapidly proliferating cells like activated macrophages, lymphocytes and some cancer cells[109]. Transferrin derivatives and some special ligands have been extensively used in the targeted modification of drug delivery systems. Modified nanoparticles have exhibited great therapeutic effects on cancer therapy and other inflammatory diseases[110,111]. The drug delivery systems targeting TfR have been gradually applied to the researches of IBD.

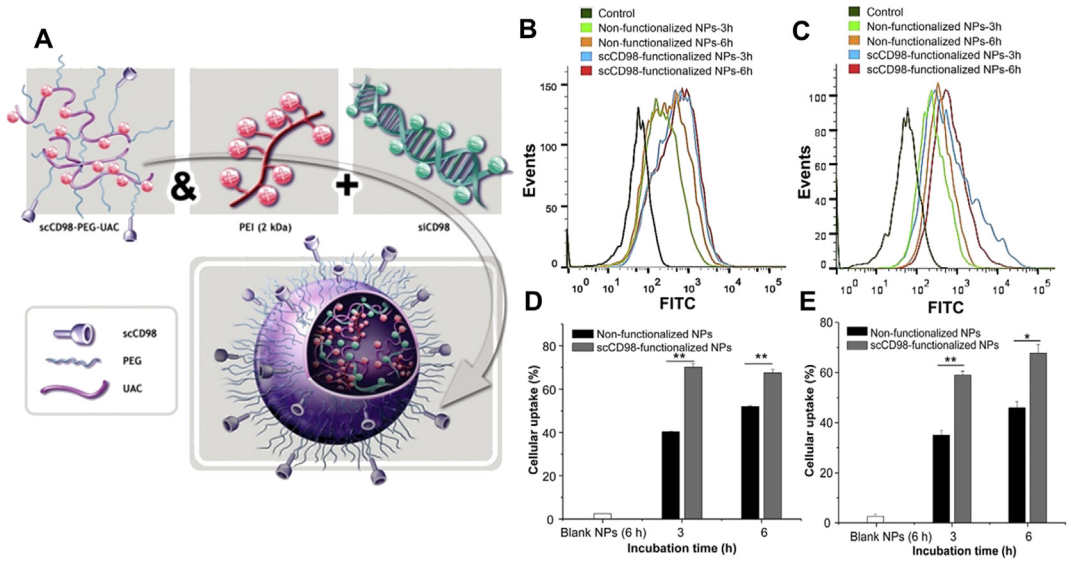

Figure 6 CD98-mediated targeted therapy for IBD. (A) Schematic illustration of self-assembly procedure of scCD98′-*siCD98* loaded nanoparticles. FCS analysis about cellular uptake of FITC-siRNA loaded NPs by Colon-26 cells (B) and Raw264.7 macrophages (C) at 3 or 6 h. And related percentage analysis of FITC positive Colon-26 cells (D) and Raw264.7 macrophages (E), data are expressed as mean ± SEM (standard error of mean, $n = 3$); $^{*}P < 0.05$, $^{**}P < 0.01$. Reprinted with permission from Ref. 53. Copyright © 2014, Elsevier.

Specific polypeptides and antibodies are used as ligands for functional modification of drug delivery systems. Septapeptide (His-Ala-Ile-Tyr-Pro-Arg-His) conjugation could facilitate Caco-2 cells to recognize and endocytose coumarin-6-loaded PEG-*b*-PCL copolymer, further transporting more copolymer across cell monolayer[55]. Pro-inflammatory cytokines co-incubated Caco-2 cells also possess a high TfR level and internalized more TfR antibody modified immunoliposomes than liposomes without antibody[54]. Unlike healthy colonic tissue, enterocytes of murine or human inflamed colon overexpress TfR both in apical and basolateral domains[54,112]. The everted gut-sac experiments showed that more than 4.5-fold of TfR antibody modified liposome prefer accumulating in DNBS-induced colitis colon sites rather than healthy colon *ex vivo*.

Nevertheless, current strategies targeting TfR are limited in *in vitro* and *ex vivo* models. It is noteworthy that the pharmacological efficacy of these delivery systems in IBD animal models has not been reported. When administered orally or intravenously, necessary measures must be taken to avoid the possible degradation of ligands by acid, base, hydrolase, phagocytosis by reticuloendothelial system, especially for antibody and polypeptides. Since the excellent serum stability, transferrin conjugation could shield drug from renal filtration and concentrate at the inflamed colon sites through receptor−ligand interaction and EPR effect. Studies pointed out rice-derived recombinant transferrin could be a substitute of human serum transferrin, which indicates that transferrin would be a promising and economic ligand for IBD targeted therapy[113].

3.7. *Peptide transporter 1*

Peptide transporter 1 (PepT1) is a small intestinal receptor responsible for the absorption of oligopeptides and peptidomimetic drugs from the diet[114]. Normally, PepT1 does not exist in colon tissues but is highly expressed on inflammatory colonic epithelial cells and macrophages when IBD occurs[115,116]. Lysine-proline-valine tripeptide (KPV) possesses a high affinity to PepT1, and it has been used in superficial modification to target PepT1[85]. A novel KPV-conjugated fluorescent probe for ulcerative colitis real-time monitoring has been reported previously[117]. KPV−PepT1 interaction is also used in the design of drug delivery system for IBD.

KPV-conjugated PLGA nanoparticles (KPNs) exhibited great PepT1 targeting properties *via* oral route. Due to the excellent stability in upper GIT, montmorillonite/chitosan nanocomposites were employed to coat KPNs as a protective layer. KPV conjugation promoted the accumulation of nanoparticles in inflamed colon and prolonged the retention time of nanoparticle up to 24 h. As a immunosuppressant, cyclosporine A (CyA) can specifically inhibit the activation of T cell and expression of pro-inflammatory cytokine[118]. Loading CyA into KPNs increased the concentration of CyA in inflamed colon by 23-fold. CyA KPNs significantly reduced DSS-induced mice mortality, colon atrophy, weight loss, oxidative stress, and elevated TNF-α and IL-1β level compared with free CyA (Fig. 7)[56].

A report revealed that 5-aminosalicylate could inhibit the transportation of PepT1, hence it had better not deliver 5-aminosalicylate and its derivatives with PepT1 ligand-modified drug delivery system[119].

3.8. *F4/80*

F4/80, also named as EMR1 and ADGRE1, is a transmembrane glycoprotein composed of 7 transmembrane motifs and some epidermal growth factor-like domains (EGFs) outside the cells[120]. F4/80 only exists on eosinophils in human and monocytes, macrophages, myeloid dendritic cells, eosinophils in mouse[121], it is highly expressed when IBD occurs[122]. F4/80 is an essential marker of macrophage, and its antibody has been used for surface modification.

Laroui et al.[57] covalently linked the F4/80 Ab Fab' to PLA−PEG-maleimide polymer through amino−thiol reaction.

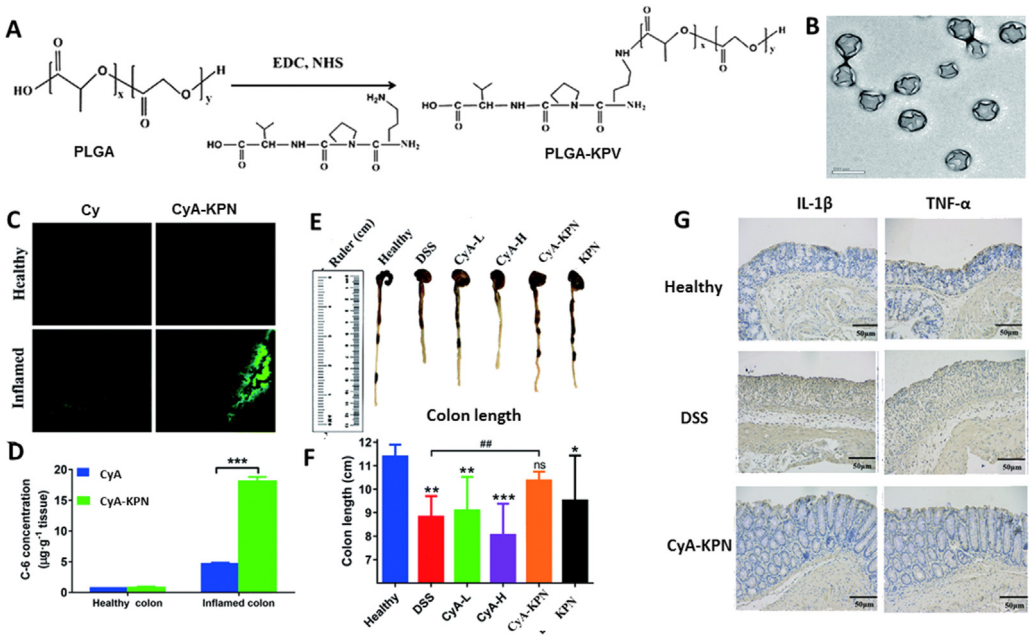

Figure 7 PepT1-mediated targeted therapy for IBD. (A) Schematic illustration of KPNs synthesis. (B) Morphology of KPNs characterized by TEM. (C) The distribution of KPNs in colon. (D) Quantitative analysis of KPNs distribution in colon, data are expressed as mean ± SD ($n = 3$); $^{***}P < 0.001$. The Visual expression (E) and quantitative analysis (F) of colon length from different groups, data are expressed as mean ± SD ($n = 4–9$); $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{\#\#}P < 0.01$. ns, not significant. (G) The immunohistochemistry analysis of TNF-α and IL-1β. The scale bar represents 50 μm. Reprinted with permission from Ref. 56. Copyright © 2019, the Royal Society of Chemistry.

The resultant copolymers didn't aggregate and could self-assemble into uniform spherical nanoparticles (F4/80 Fab' NPs) with good colloidal stability. Besides, *siTNF-α*-loaded F4/80 Fab' NPs could be efficiently endocytosed by Raw264.7 cells and significantly dampen the sharply elevated TNF-α level induced by LPS *in vitro* (Fig. 8). *siTNF-α*-loaded F4/80 Fab' NPs encapsulated in chitosan/alginate (3:7) hydrogel exerted superior curative effect than F4/80 Fab'-deficient NPs in weight loss, MPO activity, TNF-α overproduction, IK$\beta\alpha$ accumulation and aberrant histopathology of DSS-induced colitis mice after oral administration.

Since F4/80 is only expressed on eosinophils which plays a key role in IBD deterioration in human[123], it indicates that F4/80 would be a potential delivery target. However, the ligand of F4/80 is merely monoclonal antibody so far, which brings huge costs on preparation. Design and screening of novel cheaper ligands based on computer-aided drug design technology would help a lot. Even though the surface modification of F4/80 antibody has achieved effective efficacy in mice, it still needs to be carefully studied when it's applied to human with IBD.

3.9. *Cell adhesion molecules*

When gut inflammation occurs, mucosal microvasculature endothelia overexpress cell adhesion molecules (CAMs) in the luminal sides to recruit leukocytes from blood, and subsequently trigger a more severe inflammatory cascade[124]. Some CAMs, comprised of selectin (E-, P-, and L-selectin), integrin ($\alpha4\beta1$ and $\alpha4\beta7$), adhesion molecules (ICAM-1, ICAM-2, VCAM-1 and MadCAM-1), participate in the leukocytes recruitment process[125]. Such CAMs are expressed on most cells normally, but they are expressed on inflamed colonic epithelia or tissues at a high level during IBD. Substantial researches *in vitro* and *in vivo* demonstrated that CAMs are promising targets for drug delivery of IBD, as listed in Table 4[126–130].

Usually, the ligands of CAMs are antibodies and some specific peptides[131,132]. Nanoparticles modified by related ligands could effectively target CAMs *in vitro*. ICAM-1^{+} Caco-2 cells could rapidly recognize ICAM-1 Ab coated polystyrene beads and internalize it into cytoplasm compared to mice IgG coating. The significant internalization could be dramatically reversed by the inhibitor of CAM-endocytic pathways, amiloride and EIPA[126]. Sialyl Lewis^{x} (sLe^{x}), a sialylated and fucosylated carbohydrate, is the ligand of P-selectin. Laminar flow assay revealed that sLe^{x} conjugated PLGA microsphere could bind to P-selectin through leukocytes–endothelial interaction, and the binding intensity was positively correlated with the density of sLe^{x}[127]. Sakhalkar et al.[128] explored the adhesion property of PEG–PLA NPs which were grafted with different endothelial CAMs ligands (PSGL-1, ICAM-1 mAb, VCAM-1 mAb, and E-selectin mAb) to inflamed endothelia *in vitro*, and ligands modified nanoparticles displayed significant targeting properties.

When administrated to mice *via* oral route, ICAM-1 Ab modified nanoparticles without any protective outer layer encountered destructive enzyme-dependent degradation, negligible nanoparticles with integral structure arrived at colon sites[129]. Cyclin D1 (CyD1) is the vital cell cycle regulating molecule that participated in the pathogenesis of IBD[130]. Peer et al.[130] encapsulated *siCyd1* into integrin $\beta7$ Ab functionalized liposomes ($\beta7$-LPs), and then administrated $\beta7$-LPs to mice *via* systemic route. 10% $\beta7$-LPs accumulated in inflamed colon, 3.5-fold higher than that of healthy group. The mRNA of CyD1 level and cell proliferation decreased remarkedly in mononuclear leukocytes of inflamed colon. Moreover, severe weight loss, tissue damage, abnormally high IL-10 and IL-12 level were significantly inhibited

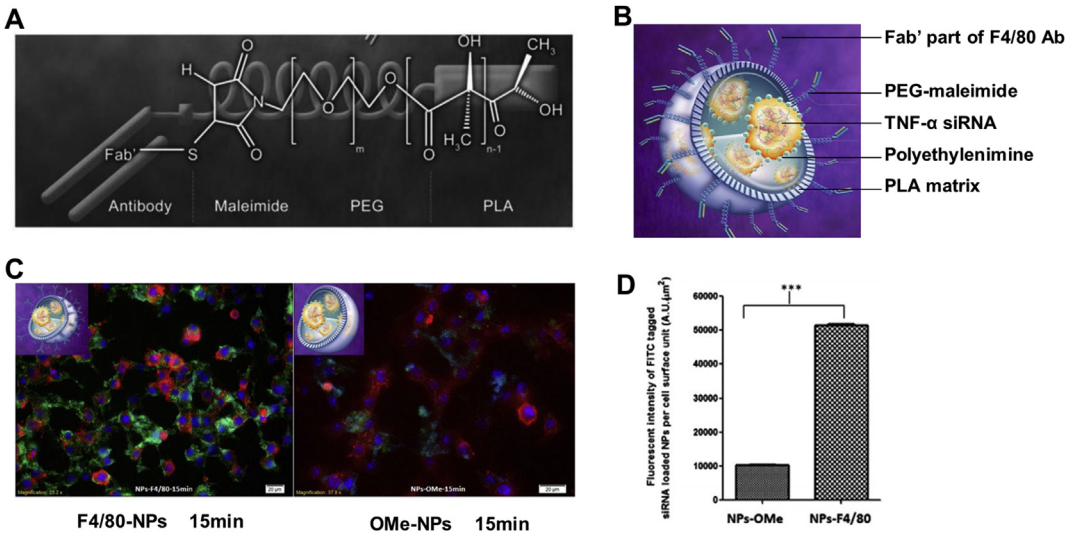

Figure 8 F4/80-mediated targeted therapy for IBD. (A) Semi-developed formula of basic unit of nanoparticles. (B) Tridimensional schematic of F4/80 Fab' TNF-α siRNA/PEI-loaded nanoparticles. (C) Cellular uptake fluorescent microscopy of 500 μg/mL F4/80 Fab'- FITC-tagged NPs (green) and OMe F4/80 Fab'- FITC-tagged (green) NPs by MPs after 15 min incubation. Red represents cell cytosol, purple represents cell nucleus. The scale bar represents 20 μm. (D) Quantification of the fluorescent intensity. Reprinted with permission from Ref. 57. Copyright © 2014, Elsevier.

by *siCyd1*-loaded β7-LPs. As for IgG-LPs, it was almost undetectable in the colon and no any therapeutic effect.

Since the ligands of CAMs are antibodies and some specific peptides, additional protective coating must be taken into account when such ligands were applied to IBD targeted therapy[131,132]. CAMs usually express on vasculature endothelial cells in the apical side when inflammation occurs. Therefore, systemic administration is a desirable route for CAMs ligand-modified nanoparticles to target inflamed sites.

4. Discussion and perspectives

Receptor-mediated targeted drug delivery strategy through ligand−receptor interaction does achieve excellent curative effects in the treatment of IBD. Since the pathogenesis of IBD is still unclear, the recommended prevention measures for IBD are healthy lifestyles and balanced nutrition supplement[5]. IBD has a long disease cycle, high relapse and cancerization rate. To prevent disease relapse and colitis-induced cancerization, long-term maintenance chemotherapy is needed. Common chemoprevention strategy is administration of nonsteroidal anti-inflammatory drugs, ursodeoxycholic acid, statins and folic acid[133]. Long-term non-targeting chemotherapy could lead to serious ADR, and receptor-mediated targeted drug delivery system can reduce the drug dosage and systemic ADR, improving the topic drug concentration and efficacy. Actually, there are lots of known receptors or cell adhesion molecules highly upregulated in colon tissues of IBD patients, like lipocalin-2 receptor[134], human H^+-coupled oligopeptide transporter[85], fractalkine[125], and G protein-coupled bile acid receptor[135]. They are still not applied in the targeted delivery studies, and their specific ligands remain unknown. In addition, there are lots of unknown molecules involved in the pathological process of IBD, so more advanced techniques, like molecular docking, proteomics, transcriptomics and high throughput screening, should be introduced to design, screen and confirm more IBD-related specific receptors, ligands or biomarkers, for instance, N^5,N^{10}-dimethyl tetrahydrofolate, a synthetic folate derivative, could evade other FR subnets' recognition and only bind to FR-α[97]. It will be extremely meaningful to understand the pathogenesis of IBD and develop more effective targeted drug delivery systems for IBD diagnosis and therapy.

Interestingly, some peptides and biologically derived exosomes preferentially interact with inflammatory cells and have been investigated in colitis model. TKPR is a serum-stable peptide that could specifically interacts with macrophages, polymersomes superficially functionalized by TKPR could significantly accumulate at inflamed colon sites and showed superior therapeutic effects[136]. Maybe due to the presence of CAMs on surface, TGF-β1 gene-edited bone marrow-derived dendritic cells-derived exosomes could be recruited to the inflamed colon sites, activate $CD4^+Foxp3^+$ T-regs in mesentery lymph nodes lymphocytes, and significantly ameliorate the colitis symptoms even only containing 150 pg TGF-β1. However, 4500 pg TGF-β1 cytokines injection worked slightly[137]. Exosomes derived from mesenchymal stem cells[138], and M2b macrophages[139] could specifically home to inflamed colon tissues, and significantly inhibit the severity of colitis. Exosomes isolated from edible ginger possessed excellent stability in stomach and intestine simulated solution, and preferentially accumulated in inflamed colon[140]. Meanwhile, *siCD98*-loaded ginger-derived exosomes effectively targeted inflamed colon and inhibited the expression of CD98[107]. Grapefruit derived exosomes (GDEs) also possessed high affinity to intestinal macrophages, methotrexate loading into GDEs presented lower toxicity and higher therapeutic effects[141]. In addition, some biomimetic nanoparticles exploited proteolipid from human leukocytes[142], and neutrophil[143] could also specifically target the inflamed vasculatures *in vivo*. Biomimetic strategy is widely used in diagnosis and targeted therapy due to its great biocompatibility, prolonged systemic circulation and desirable targeting ability[14]. It provides an additional option for the development of active targeted drug delivery system for IBD.

Table 4 Representative drug delivery systems targeting cell adhesion molecules for the treatment of IBD.

Cell adhesion molecules	Ligand	Carrier	Loading cargo	Delivery route	Characterization	Experimental model	Principal finding	Ref.
ICAM-1	ICAM-1 Ab	Nanoparticle: polystyrene bead	α-Galactosidase	*In vitro*	S: 258.5 ± 11.3 Z: −12.9 ± 0.4	TNF-α-activated Caco-2 cell	62.4 ± 6.2-fold higher ICAM-1 Ab coated NPs bound to Caco-2 cell compared to mice IgG coating	126
P-Selectin	Sialyl Lewis^x	Nanoparticle: PLGA	Diclofenac sodium salt	*In vitro*	S: 4,630 Z: –	Slides coated with P-selectin	The binding capacity of PLGA microsphere to selectin increased with sLe^x density	127
ICAM-1 VCAM-1 E-selectin	ICAM-1 VCAM-1 E-selectin Ab	Nanoparticle: PLA−PEG	–	*In vitro*	S: – Z: –	TNF-α or IL-1β-treated HUVEC	Ligand conjugation promoted nanoparticle to adhere to inflamed epithelia in a density-dependent manner	128
P-Selectin	P-selectin glycoprotein ligand-1	Nanoparticle: PLA−PEG	–	i.v. injection	S: – Z: –	Trauma-induced mice endothelium inflammation	PSGL-1 conjugation led to 10-fold higher adhesion to inflamed endothelium	128
E-Selectin	E-Selectin Ab	Nanoparticle: PLA−PEG	–	i.v. injection	S: – Z: –	TNF-α-induced mice endothelium inflammation	E-selectin mAb conjugation led to 6-fold more adhesion to inflamed endothelium	128
ICAM-1	ICAM-1 Ab	Nanoparticle: polystyrene bead	–	Oral	S: 269.8 ± 6.3 Z: −7.1 ± 0.2	Normal C57BL/6 mice	ICAM-1 Ab coating significantly prolonged the nanoparticles retention in GIT compared to mice IgG	129
Integrin β7	Integrin β7 Ab	Liposome: PC:DPPE:Chol (3:1:1)	*SiCyclin D1*	i.v. injection	S: 114 ± 7 Z: +13.5 ± 1.2	DSS-induced C57BL/6 mice colitis	Integrin β_7 liposomes specifically and efficiently bound to leukocyte and internalized into cytoplasm immediately	130

–, not applicable; CAM, cell adhesion molecules; GIT, gastrointestinal tract; ICAM, intercellular adhesion molecule; I.V., intravenous; S, size (nm); VCAM, vascular cell adhesion molecule; Z, zeta potential (mV).

Receptor-mediated targeted delivery systems had been applied in IBD diagnosis and imaging studies. Current diagnostic approaches, such as colonoscopy, tissue biopsy, computed tomography (CT) and magnetic resonance imaging (MRI), are invasive, low sensitivity, false positive or non-targeted imaging[144,145]. A PepT1-targeted fluorescent probe could accurately bind to inflamed colon sites and distinguish between chronic and acute colitis, it provided guidance for IBD chemotherapy[117]. Ligand-conjugated contrast agents overcome the problem of non-targeted imaging, and it had been used for *in vivo* targeted diagnosis and obtained superior imaging effects, like folic acid modified Gd[146], folic acid-cysteamine modified Au[147], transferrin conjugated Fe_3O_4[148]. Furthermore, cathepsins B and matrix metalloproteinase are universal inflammatory biomarkers that have been applied in IBD diagnosis researches[149]. But if IBD-specific biomarkers are found and applied in IBD diagnosis combined with receptor-mediated targeted technology, it will revolutionize the diagnosis of IBD.

Substantial receptor-mediated targeted delivery systems had been published recent years, only few of them had entered clinical trials, such as MCC-465[150], SGT-53[151], BIND-014[152]. There are many challenges in the clinical transformation of nanomedicine, including the researches of *in vivo* fate, the design of nanomedicine, the evaluation of biological properties and industrial production. Few researches were conducted on the *in vivo* fate of drug delivery system for the treatment of IBD, but it's essential for the pharmacokinetics exploration and clinical transformation of nanomedicine. Detecting the signal of isotope or fluorescent probe labeled delivery system is a common method to study *in vivo* fate. However, isotope and fluorescence probes still produce signals after dissociating from the delivery system, which can interfere with the experimental results. Environmental-responsive fluorescent dyes can avoid this problem by distinguishing the signals of free probe from probe-labeled delivery system. It can be classified into three categories, namely fluorescence resonance energy transfer (FRET), aggregation-induced emission (AIE) and aggregation-caused quenching (ACQ)[153,154]. Because of high sensitivity, small interference and strong universality, ACQ dyes have been used in tracing nanoparticles *in vivo via* different administration routes[155,156]. So ACQ dyes are suggested for IBD researches. Optimal design is helpful to overcome physiological barriers (as mentioned in Section 2.1), imprecise targeting and aim-less drug release of nanomedicines *in vivo*[27,157,158]. Surface functionalization can address such problems, for instance, PEG modification could inhibit reticuloendothelial attack and prolong systemic circulation[159], chitosan-coating could restrain acidic or alkaline degradation in upper GIT[160], and ligands conjugation could evade the intervention of immune systems and prompt cellular endocytosis[161]. The shape, size and surface potential could also affect endocytosis and targeting of nanoparticles. For instance, neutrophils are more likely to uptake negatively-charged, cube-shaped, >100 nm sized nanoparticles[162]. Different delivery systems present different requirements for the design, and thus it needs to be carefully optimized during the preclinical study. Biological evaluation comprises cytological evaluation *in vitro* and zoological evaluation *in vivo*. Cytological evaluation could preliminarily demonstrate the biocompatibility and the interaction between nanomedicine and cells, but cell culture plate can't fully simulate the complicated GIT environment, physiological barrier and inflamed colon tissues. Zoological evaluation could reveal biocompatibility, pharmacokinetics, biodistribution and targeting properties of nanomedicine *in vivo*. However, the passive targeting properties through EPR effect is weaker in human, and widely used colitis model induced by DSS and TNBS can't fully reflect pathological changes in IBD patients[163]. And some receptors' expression pattern in mice is different from that in human, like F4/80. The lack of animal experimental models that can accurately reflect human diseases is one of the obstacles that leads to the discrepancy between the results of preclinical studies and clinical trials[164]. Novel animal models could be introduced into IBD preclinical researches, like humanized mouse model[165], genetic engineering mouse model[166], or large mammal (dog, pig and monkey) models. Industrial production is another challenge to clinical transformation. Complex preparation process and harsh preparation conditions will increase the difficulty of industrialization. The simplification of formulation design and preparation process is more conducive to large-scale production. Although the clinical transformation progress is slow, receptor-mediated active targeted strategy still possesses great promise in revolutionizing the diagnosis and treatment of IBD.

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Author contributions

Peng Liu and Caifang Gao performed the literature search and wrote the manuscript. Hongguo Chen, Chi Teng Vong, Xu Wu and Xudong Tang reviewed the manuscript. Shengpeng Wang and Yitao Wang designed the study and revised the manuscript. All of the authors have read and approved the final manuscript.

Conflict of interests

The authors have no conflicts of interest to declare.

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