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Cell-derived biomimetic drug delivery system for inflammatory bowel disease therapy

Wenjing Yang [a,1], Peihong Lin [a,1], Rui Gao [a,1], Zhengyu Fang [a], Zhouru Wang [a], Zhen Ma [a], Jing Shi [a,**], Wenying Yu [a,b,*]

[a] School of Pharmacy, Hangzhou Medical College, Hangzhou, 310013, China
[b] Key Laboratory of Neuropsychiatric Drug Research of Zhejiang Province, Hangzhou Medical College, Hangzhou, 310013, China

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ABSTRACT

Inflammatory bowel disease (IBD) is a chronic recurrent disease with an increasing incidence year by year. At present, no safe and effective treatment for IBD exists. Thus, there is an urgent need to create new therapeutic options that have decreased adverse effects and positive clinical efficacy. A range of nanomaterials have fueled the advancement of nanomedicine in recent years, which is establishing more appealing and prospective treatment approaches for IBD. However, traditional synthetic nanomaterials still have some problems in the IBD drug delivery process, such as weak targeting ability of vectors, difficulty escaping immune surveillance, and poor biosecurity. Natural sources of biological nanomaterials have been identified to solve the above problems. A drug delivery system based on bionic technology is expected to achieve a new breakthrough in the targeted therapy of IBD by nanotechnology due to its organic integration of low immunogenicity and natural targeting of biological materials and the controllability and versatility of synthetic nanocarrier design. We begin this review by outlining the fundamental traits of both inflammatory and healthy intestinal microenvironments. Subsequently, we review the latest application of a cell-derived bionic drug delivery system in IBD therapy. Finally, we discuss the development prospects of this delivery system and challenges to its clinical translation. Biomimetic nanotherapy is believed to offer a new strategy for the treatment of IBD.

1. Introduction

Inflammatory bowel disease (IBD) is a chronic non-specific inflammatory disease that affects the gastrointestinal tract. The cause of its onset is unknown, and it is characterized by recurring attacks. It mainly includes Crohn's disease (CD) and ulcerative colitis (UC) [1]. Currently, more than 10 million people worldwide are affected by IBD, which poses momentous treatment difficulties, negatively affects patients' quality of life, and imposes a significant economic burden on global health care systems [2].

Conventional therapies including 5-aminosalicylic acid, corticosteroids, and azathioprine can alleviate symptoms associated with IBD, but their application is limited due to their non-specific anti-inflammatory properties and potential adverse reactions [3]. Over the past few years, the role of biologics in the treatment of IBD has become increasingly prominent. In particular, tumor necrosis factor-α (TNF-α) inhibitors, interleukin (IL) antagonists, and integrin receptor antagonists have become the treatment of choice for many patients with IBD. These therapies have revolutionized a large number of patients, not only effectively alleviating their condition, but also greatly improving their quality of life. For many patients, the side effects of these biologics are relatively mitigated, making long-term treatment possible [4]. However, despite the remarkable efficacy of biologics, there are still cases of treatment failure or poor efficacy in some patients. In addition, high treatment costs also limit the treatment options for some patients [5]. Therefore, the search for new and more effective treatment strategies to address current clinical challenges remains an important topic in IBD research.

The rise of nanotechnology brings new hope for the development of IBD therapeutic drugs. Compared with ordinary drug-carrying systems, nanocarriers can effectively improve the clinical efficacy of drugs and relieve side effects due to their unique characteristics [6] and have been

** Corresponding author.
* Corresponding author. School of Pharmacy, Hangzhou Medical College, Hangzhou, 310013, China.
E-mail addresses: 420956839@qq.com (J. Shi), zjyuwenying@163.com (W. Yu).
[1] These authors contributed equally to this work.

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applicated widely in the delivery of IBD therapeutic drugs. However, although existing nanotechnology has shown certain advantages in the treatment of IBD, some disadvantages remain. For example, synthetic nanocarriers are easily recognized by the reticulo-endothelial system and accelerate the clearance rate. At the same time, it reduces the accumulation of drugs in the lesion site [7], thus limiting the use of these nanocarriers in IBD treatment. To overcome the limitations of traditional synthetic nanocarriers, researchers drew inspiration from natural source materials and proposed constructing cell-derived biomimetic nanocarriers as potential delivery systems for IBD therapeutic drugs.

Cells are characterized by the ability to sense, integrate and respond to the dynamic environments in the body and can serve as vehicles for therapeutic drugs. At present, existing studies mainly focus on the use of natural cells or cell derivatives as drug carriers, including living cells, cell membranes, extracellular vesicles (EVs), and cell walls [8]. Because of their considerable drug loading capacity, inherent biodegradability, natural ability to overcome biological barriers, superior biocompatibility, and natural tissue targeting, these cell-derived biomimetic vectors show enormous potential for use in drug administration in vivo. When living cells serve as drug carriers, drugs are encapsulated inside the cell or attached to the cell surface and subsequently transported to the lesion site through body fluids. Encapsulation of cells can improve the pharmacokinetic characteristics of drugs and significantly increase the targeting of drugs to the lesion site [9]. However, the toxicity of drugs or nanocapsules may affect cell viability when they are directly encapsulated in living cells, and these drugs are difficult to be released in a spatially or temporally controlled manner. In addition, some cells are suitable for use as drug carriers, but they have limitations such as small number and short life span, thus being unable to meet the large number of cells required for disease treatment. Cell-derived biomimetic vectors (cell membranes, EVs, cell walls, etc.) may avoid the above defects. Compared with synthetic nanoparticles (NPs), cell-derived derivatives have superior biological functions, such as immune escape, targeting to specific cells or tissues, selective binding of harmful molecules or pathogens, and immune regulation [10], as well as good biocompatibility and degradability, which is due to their retention of the characteristics of the source cells. Compared with living cells, biomimetic materials such as EVs have a long storage time, smaller volume, and lower immunogenicity and toxic side effects [11]. Cell-derived drug delivery systems integrate the biomimetic characteristics of biomaterials and the multiple functions of synthetic nanomaterials to become promising nanomedicine platforms for the therapy of IBD.

This review starts from the features of the intestinal microenvironment, explains the advantages and disadvantages of biomimetic nanodelivery systems (BNDS) (Table 1), and focuses on the latest usage of cell-derived BNDS in IBD treatment (Fig. 1). It then discusses the challenges and opportunities of such cell derivatives as drug delivery carriers in the therapy of IBD, thus bringing new inspiration to the development of bionic nanomedicines and providing new prospects for IBD treatment.

2. Features of intestinal microenvironment in IBD

The intestinal microenvironment is mainly composed of intestinal epithelium, mucous layer, intestinal flora, immune cells and cytokines

Table 1
Characteristics of cell-derived biomimetic drug delivery system.

Type	Biomimetic source	Benefits	Limitations	Ref.
Cell membranes	Immune cell membraness	· Immune evasion · Provide host defense · Long systemic circulation · Inflammation targeting	· May induce a harmful immune response · Introduced pro-inflammatory factors · Insufficient cell source	[21, 22]
	Probiotic cell membranes	· Immune evasion · Transcended the body's biological obstacles · Recruited and reaches in targeting areas	· Difficulty in purification · Easily be destroyed	[23, 24]
	Erythrocyte membranes	· Immune evasion · Long circulation	· Insufficient cell source · Long-term storage	[23, 25]
	Platelet membranes	· Evading the immune system · Pathogenic bacterial adhesion protein · Inflammation targeting	· Insufficient cell source · Long-term storage	[26, 27]
	Fusion membranes	· Combine different cell membrane functions	· Quality control of hybrid membrane fusion · Lack of standardized production	[25]
EVs	Immune cells	· Modulated immune cell function · Triggered the phagocytic responses and antigen presentation · Being important regulators of immune cell recruitment	· The extraction procedure is time-consuming · Necessitated several intricate processes for purifying	[28, 29]
	Mesenchymal stem cells (MSCs)	· Immune modulation, homing, differentiation, anti-inflammation and tissue repair · Payload medications to the specific locations of intestinal inflammation · Avoided the potential risk of stem cell transplantation · Generating and releasing a wide variety of bioactive compounds	· Insufficient cell source · Long-term storage	[28, 30]
	Probiotics	· Natural immunostimulatory · Homologous-targeting	· Low cell membrane yield · Immunogenicity	[28, 31]
	Intestinal epithelial cells	· Had higher targeting · Provided abundant biological information · Immune evasion	· Potential security risks · Low yield to scale up production	[5,28, 31]
	Plant cells	· Be easily absorbed by the intestinal tract · Protected biological molecules from degradation in vivo	· Complicated preparation steps · No purification technology	[28, 32]
	Milk	· Keep packaged nucleic acids and other macromolecules intact · Had proven to be stable in harsh environments, including acidic ones · Do not trigger an immune response	· Includes casein, which makes it difficult to isolate EVs · Makes it difficult to distinguish them from other EVs · Contamination may occur	[33, 34]
Cell walls	Yeast cell walls	· Efficiently and precisely regulate the intestinal microbiota · Crossing the liver's first line of defense · Increased medication concentrations in the blood and in the intended tissues to ensure successful treatment · Biodegradable · Effectively phagocytosed	· The separation and purification methods are immature · Clinical evidence on biosafety and bioactivity in human tissue is lacking	[30, 35]

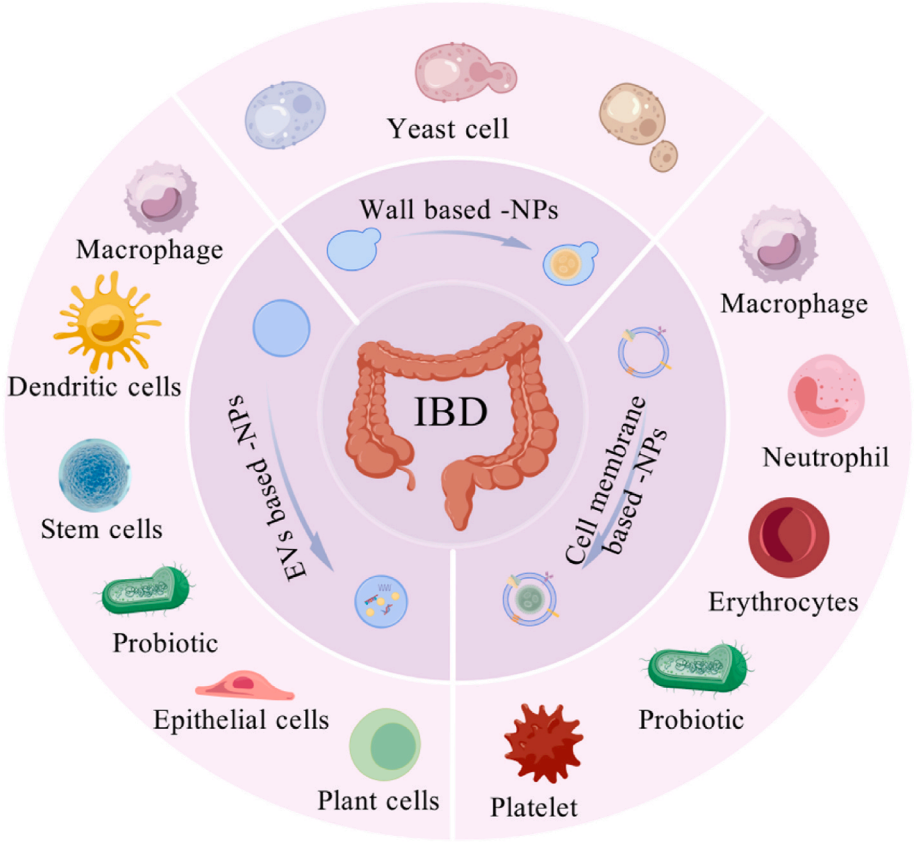

Fig. 1. Schematic diagram of cell-derived BNDS used in IBD treatment. At present, bionic nanocarriers for the treatment of IBD mainly focus on cell membranes from immune cells and probiotic cells, EVs from stem cells, probiotic cells, plant cells, and cell walls from yeast. By Generic Diagramming Platform.

[12]. Unlike the healthy gut, the intestinal microenvironment in IBD is characterized by complex and diverse features (Fig. 2). Firstly, intestinal barrier injury is a characteristic manifestation of human intestinal inflammation, which mainly refers to the impairment of the integrity and function of the epithelial layer [13]. Under normal conditions, a single layer of columnar intestinal epithelial cells (IECs) are closely connected to each other to form a continuous protective layer, which is essential for maintaining the integrity of the intestinal epithelium and inhibiting the migration of bacteria and other luminal contents from the lumen to the underlying tissues [14]. Disruption of this protective layer has been observed in IBD, and this disruption impairs barrier function, leading to enhanced permeability that allows luminal antigens, bacteria, and toxins to enter intestinal tissues. Mucin, a large glycoprotein secreted by specialized epithelial cells in the lining of the gut, called goblet cells, plays a crucial role. They form a protective layer of mucus that covers the epithelial surface and acts as a physical barrier between the luminal contents and the underlying cells. In addition, mucin helps lubricating and hydrating the intestinal surface and prevents direct contact of luminal microbes with IECs [13]. In IBD, however, mucin production is reduced and its composition changes. This disruption would impair the protective function of the mucus layer and facilitate interactions between luminal bacteria and the underlying epithelium. Secondly, the imbalance of intestinal flora is another important factor affecting the occurrence and development of IBD [15]. There is a diverse and complex microbial ecosystem in the human gastrointestinal tract, collectively referred to as the gut microbiota. This microbiota consists of bacteria, viruses, fungi, and other microorganisms that coexist in a symbiotic relationship with the host. The gut microbiome has a variety of important functions, including maintaining intestinal homeostasis, regulating intestinal metabolism, developing the immune system, and defending against pathogen invasion [15]. However, in IBD, the delicate balance between host and microbiota is disrupted, resulting in ecological imbalance, which is manifested as altered composition, diversity, and function of the gut microbiota [16]. It is characterized by reduced microbial diversity and overgrowth of potentially harmful bacteria. In addition to the above pathological features, another key feature of IBD is immune cells dysfunction [17]. Under normal conditions, immune cells are able to recognize and eliminate invading pathogens while maintaining tolerance to their own tissues. However, in IBD patients, dysfunction of immune cells such as dendritic cells, macrophages, and T cells leads to excessive production of proinflammatory cytokines such as TNF-α, IL-6, and IL-1β and abnormal ROS levels [18]. Overexpression of these cytokines in tissues leads to abnormal activation and proliferation of immune cells, which aggravate intestinal inflammation. In addition, neuro-immune regulation is also important for maintaining intestinal homeostasis. A large number of neurons are distributed in the intestinal tract, and these neurons can regulate the immune response by secreting neurotransmitters and neuropeptides [19]. In the healthy intestine, neural signals are mainly regulated through the gut-brain axis to maintain intestinal motility, secretion, blood flow and immune cells activities [20]. However, in the IBD state, changes in neural signaling may lead to increased intestinal inflammation. Therefore, interventions targeting the characteristics of the intestinal microenvironment may be a promising strategy for the prevention and treatment of IBD.

3. Application of cell-derived biomimetic drug delivery systems in the treatment of IBD

Currently, the biomimetic nanocarriers for IBD treatment mainly concentrate on the cell membranes derived from immune cells and probiotic cells, EVs derived from mesenchymal stem cells, probiotic cells, and plant cells and cell walls derived from yeast have also shown

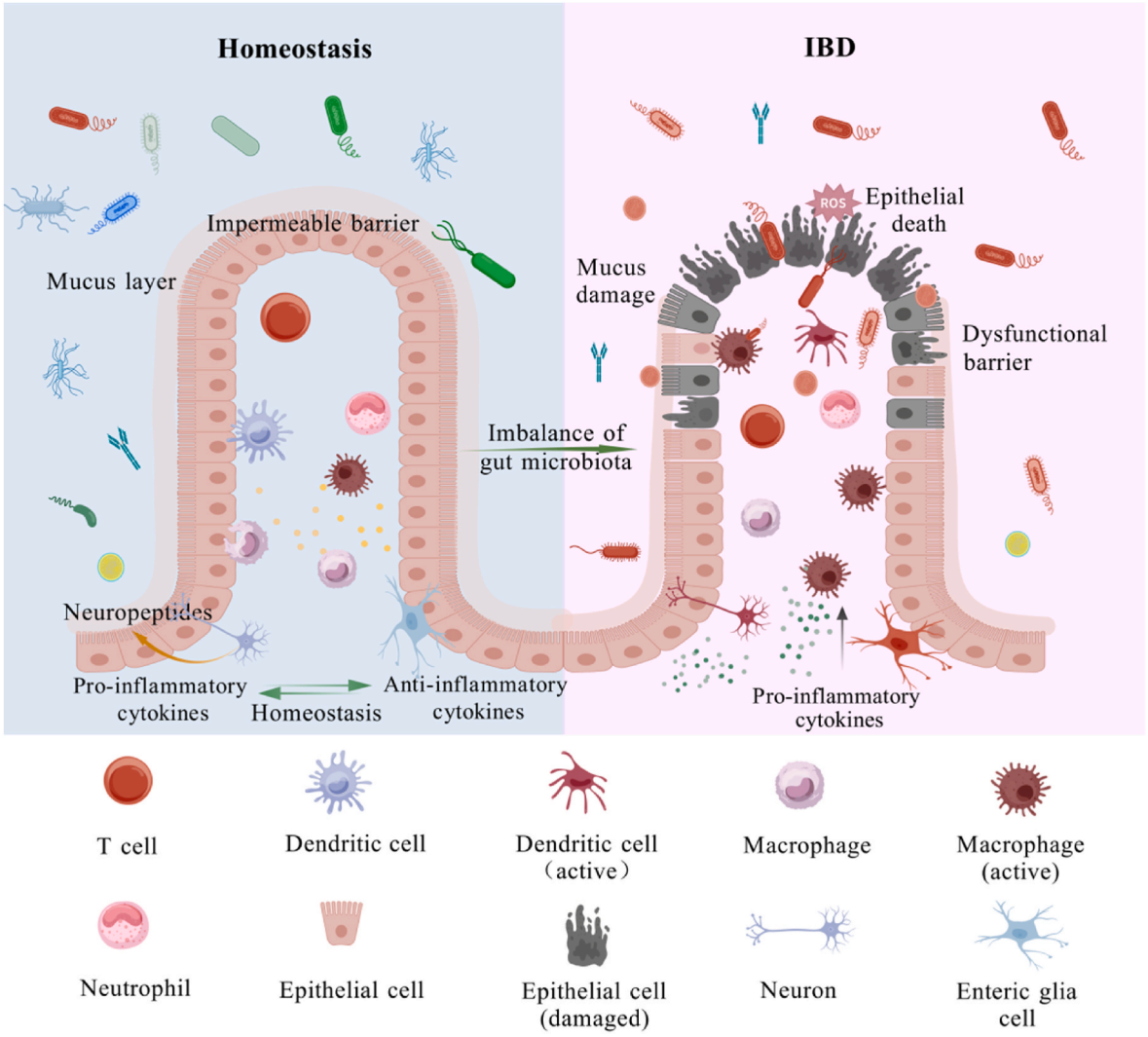

Fig. 2. Characteristics of the intestinal microenvironment in health and IBD. The stable state of a healthy gut depends on the joint cooperation of the intestinal barrier integrity, microbial balance, immune system defense, and neural signal regulation. In the intestinal microenvironment of IBD, it is mainly manifested as intestinal barrier damage, dysbiosis of the microbiota, immune cells dysfunction, and abnormal neural signal regulation. By Generic Diagramming Platform.

significant potential in the therapy of IBD.

3.1. Biomimetic drug delivery systems based on cell membranes

Many circulating cells, such as red blood cells, macrophages and neutrophils, are participated in the occurrence and development of IBD. Not only are these cells implicated in the inflammatory response, but they are also intricately linked to the restoration of intestinal damage [10]. Their membranes and membrane proteins play a momentous role in immune evasion as well as chemotaxis to sites of inflammation. Unlike synthetic NPs, NPs based on cell membranes-coated nanoparticles (CMNs) are mainly composed of biological macromolecules, including sugars, phospholipids and proteins. CMNs exhibit excellent cell affinity because of the abundant membrane proteins on their surface, which can form intercellular combines with other biological macromolecules, and they are ideal carrier materials for drugs to treat intestinal diseases [36]. Table 2 summarizes the application of biomimetic drug delivery systems based on cell membranes in the treatment of IBD in recent years.

3.1.1. Immune cell membranes

Immune cells such as macrophages, neutrophils, lymphocytes and dendritic cells play a crucial role in the body's immune response to foreign substances [10]. During the onset of IBD, immune cells, especially white blood cells, interact specifically with intercellular adhesion molecules (such as selecting, integrin, and immunoglobulin superfamily members) expressed on endothelial cells in the inflammatory region through antigen receptors or chemokine receptors on their surfaces [23]. This process is a key mechanism by which immune cells leak out of the bloodstream and migrate to the site of inflammation. At the same time, immune cells can also respond to the chemical gradient of chemokines (such as CCL2, CXCL8, etc.) released by the inflammatory site, activate intracellular signaling pathways through the signal transduction of chemokine receptors, and promote the directed migration and infiltration of immune cells [48]. This homing mechanism allows immune cells to efficiently reach the site of inflammation and participate in the immune response. Therefore, the use of immune cell membranes to wrap NPs or drugs can form an excellent delivery system that inherits the inherent biological functions of the mother cell membranes [49–51].

MM-coated NPs not only specifically aggregate at the site of inflammation due to its inflammatory homing effect [48,52], but also can absorb lipopolysaccharide (LPS) and inflammatory cytokines to regulate and inhibit local inflammation in the management of sepsis [38,53]. Therefore, MM-coated BNDS may show great potential in targeting and treating a variety of inflammatory diseases, including IBD. However, most BNDS do not typically release payloads in a specific way,

Table 2
Applications of BNDS based on cell membrane in IBD.

Membrane types	Core materials	Cargo	Animal models	Results	Ref.
Macrophage Membrane (MM)	PLGA NPs	RLZ	DSS-induced C57 mice	The drug delivery system utilizes the inflammatory chemotactic and inflammatory cytokines isolation effects of MM for targeted delivery and local inflammation inhibition, the ROS response of β-cyclodextrin matrix for specific load release, and the macrophage polarization effect of RLZ for inflammation regulation, thereby alleviating UC in mice.	[37]
	PLGA NPs	TAS	DSS-induced BALB mice	MM-PLGA-TAS was internalized by RAW264.7 cells exhibiting an inflammatory phenotype in vitro and demonstrated a notable capacity for accumulation in inflamed colitis tissue in vivo. Furthermore, MM-PLGA-TAS markedly mitigated the symptoms associated with UC.	[38]
	PLGA NPs	PD-L1	DSS-induced C57 mice	The immuno-engineered nanodecoys based on PLGA NPs coated with PD-L1-expressing MM afford higher accumulation level in inflamed tissues and stronger scavenging efficiency toward multiple pro-inflammatory cytokines. As such, they provoke potent and cooperative anti-inflammatory and immune-suppressive efficacies to alleviate DSS-induced UC mice.	[39]
	PLGA NPs	–	DSS-induced C57 mice	The capsules protect the NPs from gastric degradation and allow for targeted delivery to the colon. At the inflamed colon, cp-MΦ-NPs act as macrophage decoys that bind and neutralize pro- inflammatory cytokines. In both prophylactic and delayed treatment regimens, the oral delivery of cp-MΦ-NPs significantly alleviates IBD severity.	[40]
	PBAE	CRISPR-Cas9	DSS-induced BALB mice	The systemic administration of CRISPR-Cas9 prodrug nanosystem enables the targeted delivery of dsCas9 plasmid into inflammatory lesions, where the precursory small molecule can be activated by ROS signals to stabilize expressed dsCas9, thereby activating Cas9 function for inflammatory genome editing.	[41]
	PDA NPs	mCRAMP	DSS-induced C57 mice	The MM encapsulated PDA NPs exhibit the obviously enhanced targeting performance in local inflamed tissues. Moreover, they show anti-inflammatory function and positive regulation of intestinal flora, thus providing a new idea for the intervention and treatment of colitis.	[42]
	MOF	C-dots and CD98 CRISPR/Cas9	DSS-induced C57 mice	This biomimetic MOF system has the inflammation targeting property of MM and excellent SOD enzyme activity, which can effectively remove ROS. Both in vitro and in vivo results showed that the biomimetic NPs effectively reduced the expression of pro-inflammatory cytokines and improved the inflammatory symptoms of UC mice model.	[43]
Neutrophil membrane	Liposomes	KGF	DSS-induced ICR mice	After intravenous injection of KGF-Neus, KGF-Neus specifically targets the inflammatory bowel, thereby effectively restoring the morphology and function of the intestine and improving the therapeutic effect of KGF on UC.	[44]
Leukocyte membrane	Liposomes	α4β7	DSS-induced C57 mice	Drug-loaded SLKs have the adhesion molecule LFA-1 on their surface, allows them to specifically target inflammatory vasculature. Treatment of IBD mice with this system can be observed to reduce inflammation with less toxic side effects.	[45]
	Grapefruit-derived nanovectors (GNVs)	Cur	DSS-induced BALB mice	LFA-1 or CXCR1 and CXCR2 on IGNVs significantly enhance their homing to inflammatory tissues, and there is overexpression of chemokines in diseased human tissues. IGNVs with Cur have superior efficacy in inhibiting colitis compared to GNVs with Cur or with Cur alone.	[46]
Probiotic cell membrane	SeM NPs	–	DSS-induced C57 mice	Flagellar associated proteins of probiotics cell membrane have the ability to adhere to mucus, which can prolong the retention time of SeM in colon tissue. This designed nanomedicine restored intestinal redox balance and immune regulation homeostasis in a murine model of acute colitis induced by DSS.	[47]
Platelet membrane	PLGA NPs	PA	DSS-induced BALB mice	PA-encapsulated bionanoparticles (PNPs) were endocytosed by mouse intestinal microvascular endothelial cells in vitro and efficiently enriched in inflamed colon. PNPs significantly alleviated the symptoms of experimental colitis and improved neutrophil infiltration.	[26]
Fusion membrane	Liposomes	AU	DSS-induced C57 mice	Fusion membrane inherited the inflammatory targeting and immune escape capabilities of neutrophil and red blood cell, respectively, and promoted the specific accumulation of AU in the inflammatory gut. Afterwards, AU achieved efficient clearance of ROS, thereby repairing the intestinal barrier, regulating the immune system, and modulating the gut microbiota.	[25]

PLGA: Poly(lactic acid-glycolic acid); RLZ: Rosiglitazone; DSS: Dextran sulfate sodium; MM: Macrophage membrane; TAS: Tasquinimod; ICAM-1: Intercellular adhesion molecule 1; LFA-1: Leukocyte function-associated antigen-1; Cp-MΦ-NPs: Macrophage membrane-coated nanoparticles capsulated inenteric polymer-coated gelatin capsules; PBAE: Poly(β-amino ester); PDA: Polydopamine; MOF: Metal organic framework; KGF: Keratinocyte growth factor; HUVECs:Human umbilical vein endothelial cells; SLKs: Specialized leukosomes; Cur: Curcumin; CXCR: Chemokine receptor; IGNVs: GNVs coated with inflammatory related receptor enriched membranes of activated leukocytes; PA: Patchouli alcohol; AU: AU cluster enzymes.

which can lead to off-target toxicity. In view of the inflammatory tendency of MM and its isolation effect on inflammatory cytokines and chemokines [48,53], the elevated ROS level at the inflammatory site of UC [54], and the potential inflammatory regulatory role of M2 macrophages [55], Sun et al. [37] developed a rosiglitazone (RLZ) -loaded, MM-coated ROS-responsive nanoparticles (RMN NPs) based on ROS-sensitive β-cyclodextrin (Ox-CD) for the targeted treatment of UC by synergistic regulation of inflammation through intravenous administration (Fig. 3). The MM assists NPs in targeting the inflamed colon and absorbing inflammatory mediators to suppress inflammation. In response to significantly elevated ROS levels at the site of inflammation, Ox-CD-based NPs releases the payload RLZ, which subsequently modulates the inflammatory microenvironment. With this synergistic effect, colon inflammation in the mice was significantly alleviated. This novel nanomedical platform, which combines bionic driven targeted delivery and stimulus-response release therapeutic agent payloads, can effectively synergistically treat colitis and may provide implications for treating colitis and other inflammatory diseases by regulating inflammation.

The use of natural MM can help concentrate nanomedicines into

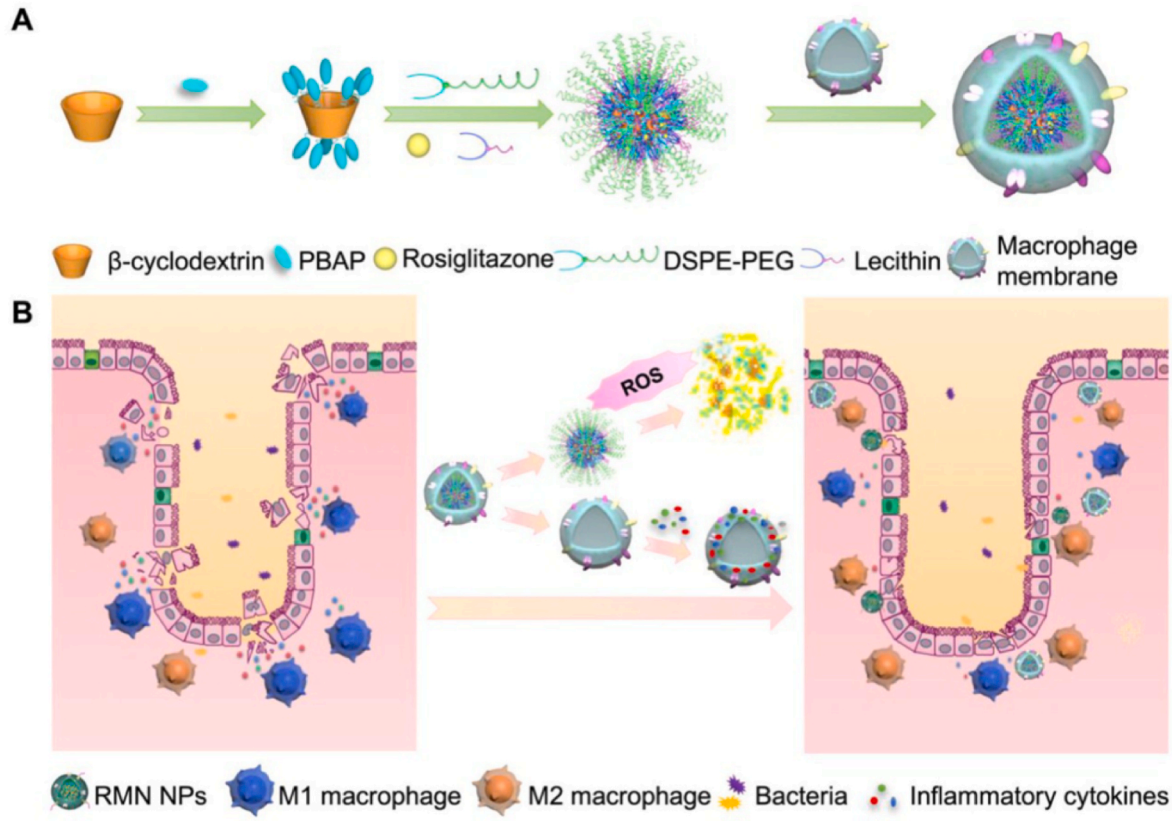

Fig. 3. Schematic of the preparation process of RMN NPs and targeted treatment of UC. (**A**) RMN NPs were obtained by encapsulating RLZ within β-cyclodextrin, followed by wrapping MM; (**B**) RMN NPs can be enriched in the inflamed colon and released drugs at the site where the ROS level increases, thus achieving targeted therapy [37]. Copyright 2019, Ivyspring International Publisher.

inflammatory areas, while modification of cell membranes through genetic engineering technology can further enhance the original functions of cell membranes or give them new properties. Li et al. [38] constructed an oral nano-drug system, using poly(lactic-glycolic acid) (PLGA) to load the S100A9 inhibitor tasquinimod (TAS) to compound PLGA-TAS NPs and overexpress TLR4 on the MM to encapsulate NPs for the preparation of MM-PLGA-TAS. MM-PLGA-TAS enhances the targeting of NPs to inflammatory tissue. MM overexpressing TLR4 can offset inflammatory cytokines such as S100A9. This special characteristic is the key to enhancing the treatment effect of NPs on inflammatory. This system may be a useful way to treating UC.

In addition to macrophages, neutrophils are important immune cells. Neutrophils, which account for about 50%–70% of leukocytes in the blood, are activated in IBD and then perpetually gathered in case of the stimulation of variety adhesion molecules such as P-selectin, E-selectin, VCAM-1, and ICAM-1 into the inflammatory microenvironment [56]. However, beacuse neutrophils are terminally differentiated cells with a half-life period of only 7 h [57], application as a direct drug carrier is finite for neutrophils. NPs covered with neutrophil membranes have analogicalr chemotactic functions and can efficiently deliver medicine to colitics sites.

Keratinocyte growth factor (KGF) is an efficient drug for the therapy of UC [58]. However, its bad stability and non-specific distribution to the irritated intestine are two vital barriers that hinder its sustained effects. Therefore, Zhao et al. [44] first encapsulated KGF with lipids to enhance its stability, then extracted the cell membranes (named NEM) from LPS-activated neutrophils, and inserted it into KGF-Liposomes to construct neutrophil-like liposomes (KGF-Neus) (Fig. 4). KGF-Neus exhibits excellent Dh stability and greatly improves the chemical stability of KGF. Here, HUVECs are used as in vitro models of vascular endothelial cells. KGF-Neus can be specifically internalized by TNF-α induced HUVECs, which may be due to the binding of highly expressed LFA-1 on the surface of KGF-Neus to overexpressed ICAM-1 on the surface of activated HUVECs. Therefore, in DSS-induced UC mice, KGF-Neus can specially localize to the inflamed colon, effectively restoring intestinal morphology and function. These results suggest that activated NEM may be a good carrier for targeted delivery of UC therapeutic drugs.

Wang et al. [46] further confirmed that fully activated CMNs are the preferred carrier for inflammation targeting. They found that wrapping GNVs in leukocyte membranes enriched with activated inflammation-related receptors resulted in enhanced homing ability in inflammatory tissues (Fig. 5). The ability of IGNVs to locate inflammatory areas can be markedly inhibited by blocking LFA-1 or CXCR1 and CXCR2 on IGNVs. The inflammatory consequences of DSS-induced mice models were controlled, providing additional evidence of the therapeutic potential of IGNVs. Furthermore, NPs covered with completely activated leukocyte membranes hindered better targeting potential compared with NPs covered with a single chemokine receptor. This relationship may result from variations in the membrane-associated chemokine and integrin composition of circulating inflammatory cells amongst individuals with IBD. NPs coated with single chemokine receptors may have difficulty optimizing combinations and have low specific targeting. The production cost of recombinant chemokine receptors may be higher, and potential biosafety issues exist. Because fully activated CMNs have good tissue permeability, tissue-specific targeting, and a lengthy in vivo circulation period, they are therefore a more effective delivery technique for drug delivery systems than single ligand-targeted NPs.

3.1.2. Probiotic cell membranes

As a major part of the intestinal microenvironment, intestinal flora can affect intestinal homeostasis. Microbiota-based therapies offer

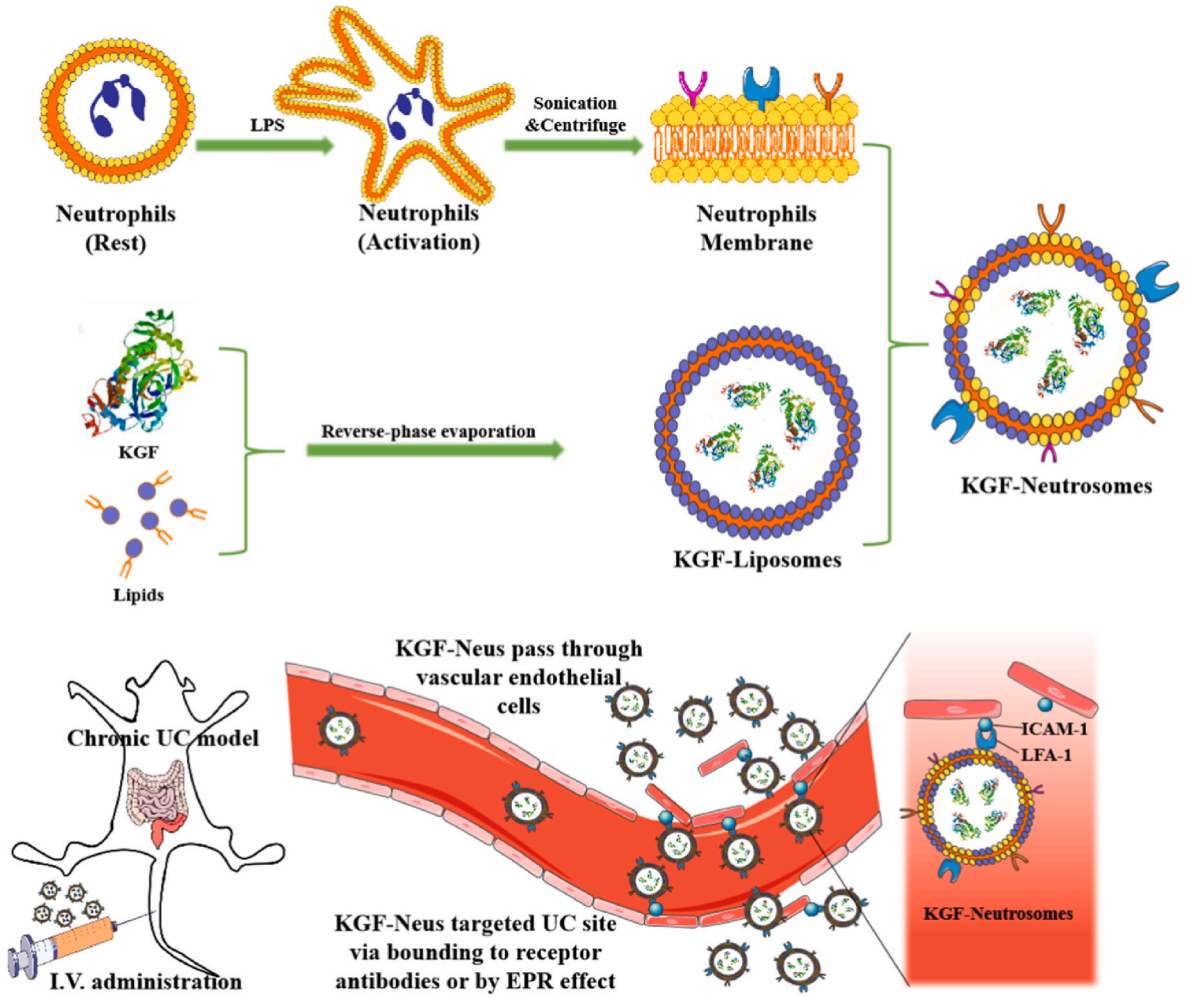

Fig. 4. Schematic of the construction of KGF-Neus and its use in targeted therapy of UC. KGF was first encapsulated in the internal water phase of ordinary liposomes, then NEM was extracted from LPS-activated neutrophils, and then embedded in the bilayer lipid membranes of KGF-Liposomes to construct KGF-Neus. After intravenous administration, KGF-Neus can target UC site through the interaction between LFA-1 highly expressed on activated NEM and ICAM-1 overexpressed in inflammatory HUVECs, as well as EPR effect [44]. Copyright 2019, Elsevier.

innovative strategies for treating IBD. However, the bad clinical results to date and the finite flexibility of bacterial methods need to be addressed. Under the inspiration of the health benefits of helpful probiotics in easing symptoms of intestinal diseases, Xu et al. [47] designed a bio-artificial probiotic consisting of two components: biodegradable diselenide-bridged mesoporous silica NPs (SeM) as the core and *E. coli* Nissle 1917-derived membrane (EM) as the surface (Fig. 6). When administered orally, SeM@EM retained the probiotic function, allowing it to adhere firmly to the mucus layer and attenuate DSS-induced acute colitis. Importantly, SeM@EM can also effectively configure the gut microbiome to restore gut homeostasis. The study's findings demonstrated the efficacy of treating IBD with probiotic membranes, which may open the door for the creation of probiotic mimetic nanomedicines to treat additional inflammatory gastrointestinal tract disorder.

3.1.3. Other cell membranes

In addition to the above common types, other cell membranes, such as platelet membranes, fusion membranes and other biomimetic delivery systems, can be used for the treatment of IBD. For IBD patients to heal, intestinal vascular damage is essential, and vascular endothelial cell targeting is a promising new treatment option. Platelet-mimetic NPs are anticipated to provide targeted treatment for IBD, because of the inherent homing capabilities of platelets to active vascular endothelium. Song et al. [26] constructed biological NPs (PNPs) coated with patchouli alcohol (PA) and observed their effects on the mouse intestinal microvascular endothelial cell (MIMVEC) inflammation models and mice acute colitis models. PNPs were effectively enriched in an inflammatory colon after being endocytosed by MIMVEC in vitro. PNPs increase PA's effectiveness as a calcium antagonist by preventing intracellular Ca^{2+} disturbances to stop endothelial activation. This could stop the recruitment of leukocytes in vivo and treat colitis.

Fusion membranes have gradually become a research hot spot because they combine the functions of different biofilms. Wang et al. [25] designed a biomimetic nanoplatform (AU-LIP-CM) consisting of liposomes (AU-LIP) loaded with Au cluster enzymes (AU) and disguised with a fusion membranes (CM) composed of neutrophil membranes (NCM) and red blood cell membranes (RCM) for the treatment of UC (Fig. 7). NIR-II imaging results showed that AU-LIP-CM was 11.5-fold higher in the inflamed gut than bare AU, and this improved targeting ability may be due to the fact that CM inherited the inflammation targeting ability of neutrophil and the immune evasion of red blood cells, respectively. Moreover, AU-LIP-CM outperformed 5-ASA, a extensively used first-line UC drug, in the cure of UC. This strategy opens up a new way to use the functional peculiarities of natural materials to create artificial substitutes, which may meet the requirements for treating diseases.

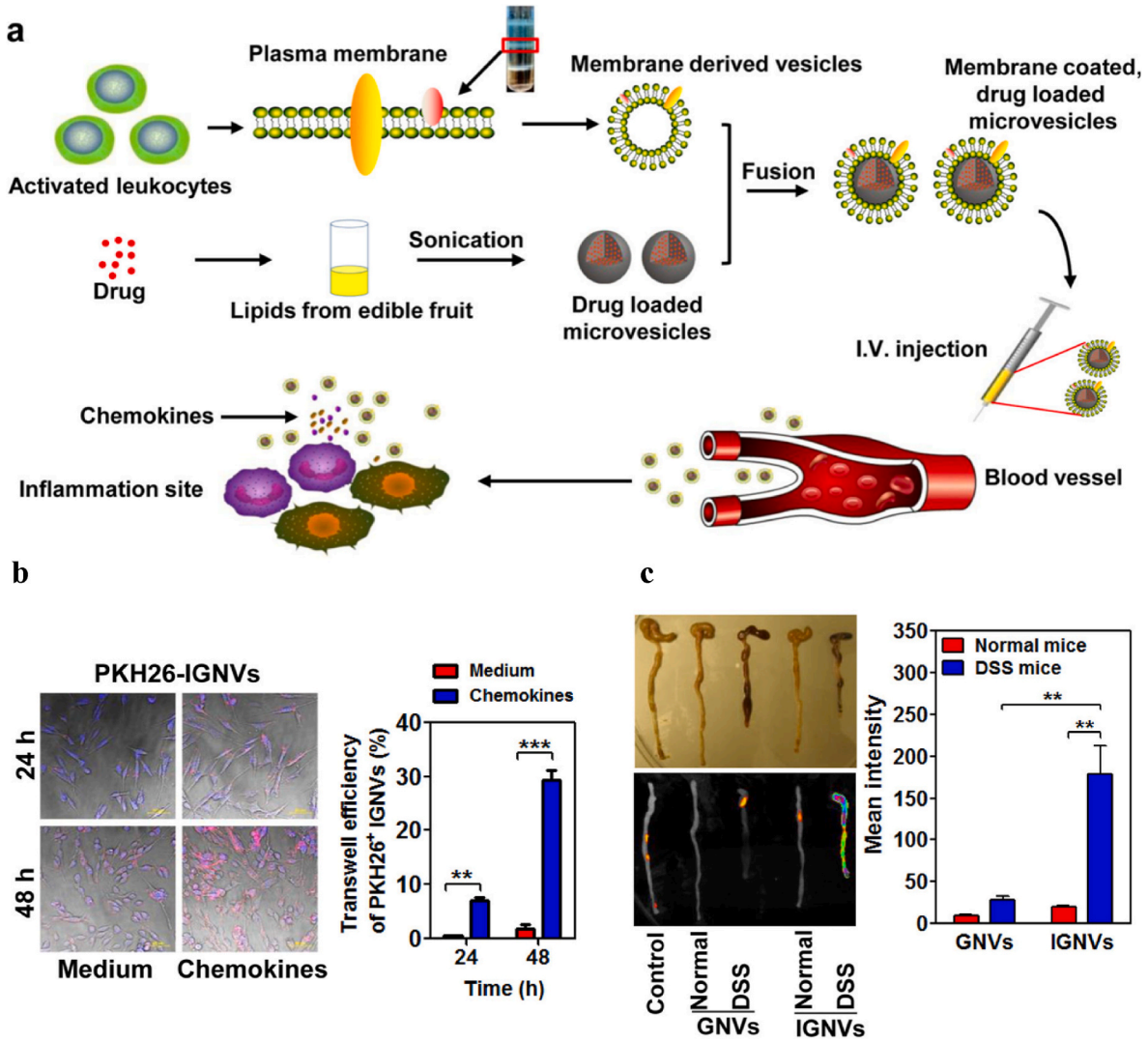

Fig. 5. Preparation of IGNVs and targeted therapy for IBD. (**a**) Schematics of the preparation process of the IGNVs and drug loaded-GNV microvesicles for targeted delivery of therapeutic agents to inflammatory sites. (**b**) Transwell assay for detecting chemotaxis of IGNVs. Transmigration of the PKH26 labeled IGNVs were imaged after 24 h and 48 h in culture using a confocal microscope. (**c**) Distribution of DiR dye labeled IGNVs in DSS induced colitis mice [46]. Copyright 2015, American Association for Cancer Research Inc.

3.2. Bionic drug delivery system based on EVs

EVs are natural nanocarriers that carry bioactive molecules such as sugars, lipids, nucleic acids and proteins, which contribute to communicating of information between tissues and cells and intestinal homeostasis. Thus, EVs take a pivotal part in cellular exchanges and engaged in numerous significant physiological and pathological processes, including immune system modulation and tissue regeneration [59]. EVs also participate in the intestinal microenvironment in host-microbiota interactions. In the microbiota-dysregulated IBD intestinal microenvironment, EVs act as modulators that target immune responses and microbial reconstitution. Considering the EVs play a part in intercellular communication throughout the pathophysiology of IBD, EVs may serve as therapeutic agents or intestinal disease vectors. Table 3 summarizes the applications of EVs-based bionic drug delivery systems in IBD therapy in recent years.

3.2.1. Immune cells-derived EVs

Immune cells include innate immune cells (including dendritic cells, granulocytes, and macrophages) and adaptive immune cells (including T cells and B cells) [79]. It is becoming increasingly clear that immune cells secrete EVs, which then participate in the transmission of information [80]. The pathogenesis of IBD is mediated by macrophages that maintain intestinal homeostasis. Macrophages can be divided into M1 or M2 depending on the microenvironment in which they are located. An important part of the inflammation process is the production of pro-inflammatory cytokines by M1-type macrophages. For example, EVs miR-21a-5p based on M1 macrophages inhibits E-cadherin expression, which in turn ILC2 was activated and destroyed the intestinal mucosal epithelium in UC mice [81]. In contrast, M2-type macrophages increase the production of anti-inflammatory cytokines and are also involved in the resolution of inflammation and tissue repair [61,82]. M2-derived EVs carry a variety of anti-inflammatory cytokines and have an effect on repairing tissue damage and treating inflammation.

Researches have indicated that EVs produced from M2 macrophages (M2-EVs) may prevent pro-inflammatory cytokines expression and mitigate DSS-induced IBD [61]. Deng et al. [60] demonstrated that M2-type macrophages increased the proliferation of colonic epithelial cells in an EVs-dependent way (Fig. 8). MiR-590-3p, which was highly concentrated in M2-EVs, may be transported from macrophages to epithelial cells, where it would encourage wound healing and epithelial cell proliferation. Mechanistically, miR-590-3p binds to the coding

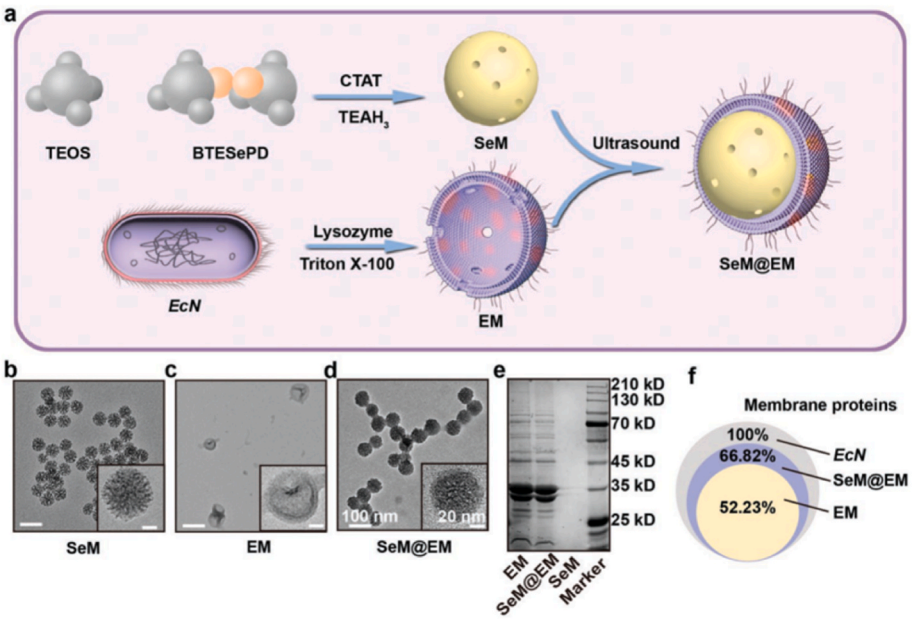

Fig. 6. Schematic representation of the synthesis and representation of SeM@EM. (**a**) Schematic illustration of the synthesis of SeM@EM. (**b-d**) TEM images of bare SeM (**b**), EM (**c**) and SeM@EM (**d**). (**e**) SDS-PAGE analysis of total membrane proteins isolated from EM, SeM@EM, and SeM. (**f**) Fraction of the total membrane proteins of EcN preserved in EM and SeM@EM [47]. Copyright 2023, Wiley-VCH GmbH.

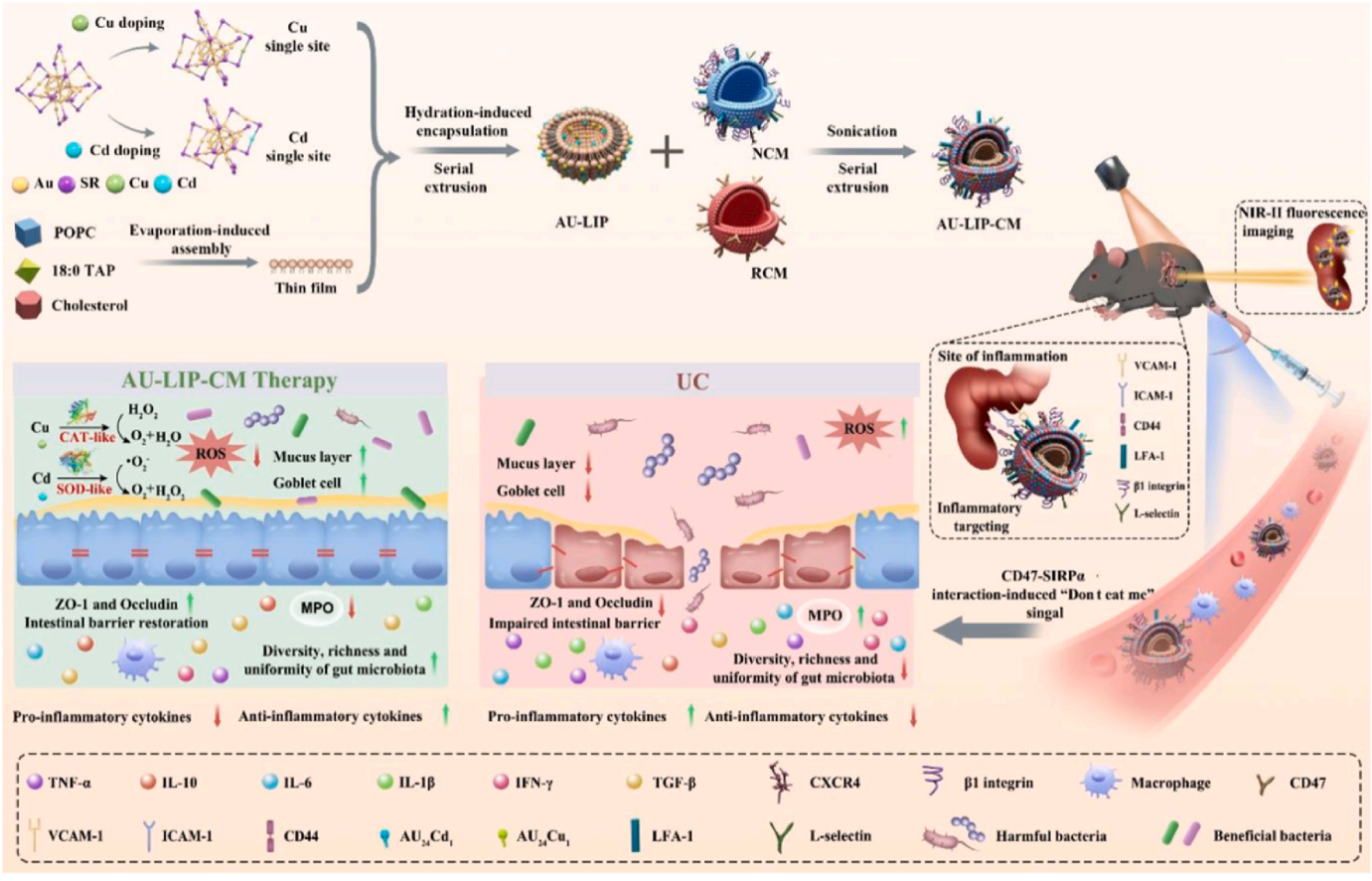

Fig. 7. Schematic diagram of the construction of AU-LIP-CM and its application in DSS induced treatment of UC mice. Firstly, AU-LIP was prepared by thin film hydration method, and then disguised with a fusion membrane composed of NCM and RCM to obtain AU-LIP-CM. The fusion membrane promotes the specific accumulation of AU in the inflamed intestine. Afterwards, AU achieved effective clearance of ROS, thereby repairing the intestinal barrier, regulating the immune system, and modulating the gut microbiota [25]. Copyright 2023, Wiley-VCH GmbH.

Table 3
Applications of BNDS based on EVs in IBD.

EVs sources	Target	Cargo	Animal models	Treatment effects	Ref.
Macrophages	Colonic epithelial cells	MiR-590-3p	DSS-induced C57 mice	EVs produced from macrophages inhibited the damage that DSS caused to mucosa and encouraged epithelial healing through the β-catenin/LATS1/YAP signaling axis	[60]
	Tregs	–	DSS-induced BALB mice	EVs derived from M2b macrophages suppressed the key cytokines associated with colitis (IL-1β, IL-6, and IL-17A), and alleviated the seriousness of DSS-induced colitis in models	[61]
Dendritic Cells	Tregs	IL-10	TNBS-induced Wistar rats	EVs generated from DCs treated with IL-10 inhibited acute colitis induced by TNBS, increased the level of IL-10 mRNA in colon tissues, and increased regulatory T cells in the colonic lamina propria	[62]
	Tregs	TGF-β1	DSS-induced C57 mice	Through the induction of regulatory T cells, EVs originated from DCs treated with the TGF-β1 gene reduced the development of Th17-mediated murine IBD induced by DSS	[63]
MSCs	Macrophages and IECs	–	DSS-induced C57 mice	Internalized by intestinal epithelial cells and macrophages, EVs produced by MSCs had anti-inflammatory and tissue-repairing properties that reduced UC	[11]
	Macrophages	–	DSS-induced BALB mice	Through the JAK1/STAT1/STAT6 signaling pathway, EVs generated from bone marrow MSCs promoted M2 macrophage polarization, which decreased DSS-induced UC	[64]
	Macrophages	–	DSS-induced KM mice	DSS-induced colitis in mice is lessened by EVs made from human umbilical cord MSCs because they reduced inflammation and prevented macrophages from expressing IL-7	[65]
	Intestinal stem cell	–	DSS-induced C57 mice	EVs originated from human adipose MSCs facilitated intestinal barrier integrity maintenance, decreased inflammatory reactions, decreased intestinal cell death, and enhanced functional recovery	[66]
	Macrophages	–	DSS-induced CIA mice	EVs produced from MSCs preserved the integrity of the intestinal barrier, upregulated the amount of anti-inflammatory cytokines, and reduced the invasion of macrophages in colon tissue	[67]
Probiotics	Endoplasmic reticulum	–	DSS-induced C57 mice	EVs produced from Lactobacillus paracasei increased the endoplasmic reticulum stress pathway, which reduced the intestinal inflammation reaction	[68]
	IECs	–	DSS-induced C57 mice	EVs produced from Akkermansia improved mucus integrity, decreased intestinal permeability, and elevated MUC2 production to avoid colitis symptoms and colonic tissue damage	[69]
	Macrophages	FX	DSS-induced BALB mice	FX-loaded probiotics EVs improved the colonic inflammatory response and reshaped the gut microbiota communities	[70]
	Goblet cells	–	TNBS-induced BALB mice	Lactobacillus-derived EVs from kefir grains can reduce TNF-induced intestinal cell inflammation by blocking the generation of inflammatory cytokines through the NF-kB signaling pathway	[71]
	IECs	–	DSS-induced C57 mice	By lessening mucosal destruction of colon tissue, lowering inflammatory response, encouraging mucosal barrier repair, restoring gut microbiota diversity, and restoring gut microbiota balance in mice, Bacteroides acidifaciens-derived EVs can relieve DSS-induced colitis	[72]
	Macrophages	–	DSS-induced C57 mice	EVs produced from *C. butyricum* enhanced gut microbiota homeostasis in UC, preserved the gut barrier, and reduced colitis symptoms overall	[73]
	Colon epithelial cells	–	DSS-induced C57 mice	By suppressing the activation of the TLR4-NF-κB-NLRP3 axis, *Lactobacillus rhamnosus GG* generated EVs have the potential to mitigate intestinal inflammation, avoid colonic tissue damage, and shorten the colon	[74]
	Colon epithelial cells	Manganese dioxide nano-zymes	DSS-induced C57 mice	EVs based on probiotics have the ability to stick to inflamed colonic epithelium, remove excessive ROS from the gut, and change the microbiota and pro-inflammatory milieu	[75]
IECs	IECs	EpCAM	DSS-induced C57 mice	IBD severity was reduced by IECs' EpCAM-dependent EVs, which produced regulatory T cells and immunosuppressive DCs	[76]
Plant cells	IECs	Han-miR3630-5p	DSS-induced C57 mice	EVs originated from garlic have the ability to shield the colon from harm caused by DSS by controlling the gut microbiota and blocking the TLR4/MyD88/NF-κB signaling cascade	[32]
	Bacteria in the intestine	MicroRNAs	DSS-induced C57 mice	EVs generated from ginger modified the intestinal microbiota and improved mice colitis through IL-22-dependent processes	[77]
	IECs	–	DSS-induced BALB mice	By reducing pro-inflammatory cytokines, ginseng-derived EVs reduced inflammation in the injured colon and assisted in restoring equilibrium to the intestinal barrier's microbiota	[78]
Milk	Macrophages	TNF-α siRNA	DSS-induced BALB mice	TNF-α mRNA can be degraded by milk-derived EVs, which can stably enter colitis regions through the GI tract	[33]
	–	miRNA	DSS-induced C57 mice	EVs based on milk enhanced intestinal barrier function, reduced local intestinal inflammation, and inhibited the production of pro-inflammatory cytokines	[34]

DCs: Dendritic cells; TNBS: Trinitrobenzene sulfonic acid; FX: Fucoxanthin; EpCAM: Epithelial cell adhesion molecule; GI: Gastrointestinal.

sequence of Lats1 to limit its expression. This, in turn, stimulates the transcriptional process mediated by YAP/β-catenin, which enhances the ability of epithelial cells to heal wounds. Additionally, pro-inflammatory cytokine production was reduced by miR-590-3p. Moreover, the inhibition of miR-590-3p in M2-EVs led to more serious impaired colonic repair and mucosal damage in DSS-induces UC mice than in M2-EVs-treated mice. This finding suggests that miR-590-3p in M2-EVs may act as a preventive treatment means for UC.

Further subtypes of M2 macrophages were identified as M2a, M2b, M2c, and M2d. The first three subtypes participate in anti-inflammation, tissue reconstruction, Th2 activation, and immune regulation. Yang et al. [61] analyzed the role of EVs based on M2a, M2b, and M2c macrophage phenotypes in DSS-induced colitis. M2b macrophage EVs greatly eased the severity of DSS-induced UC models. After cure with M2b macrophage-derived EVs, the amount of regulatory T cells and the level of IL-4 in the spleen of colitis mice increased, while the key colitis-related cytokines (IL-17A, IL-1β, and IL-6) were observably inhibited, indicating that M2b macrophage-derived EVs possessed a protective effect on DSS-induced UC. These findings offer new methods for the therapy of UC.

In recent years, the classification of macrophages is no longer limited to the classical M1 and M2 subtypes, but has expanded to include tumor-associated macrophages, CD169+ macrophages, TCR + macrophages and other types [83]. The expansion and deepening of this classification contributes to a better understanding of the role of macrophages in immune response and disease processes, and provides more possibilities for future research on bionic agents and the treatment of IBD.

DCs are professional antigen-presenting cells, and DC derived-EVs

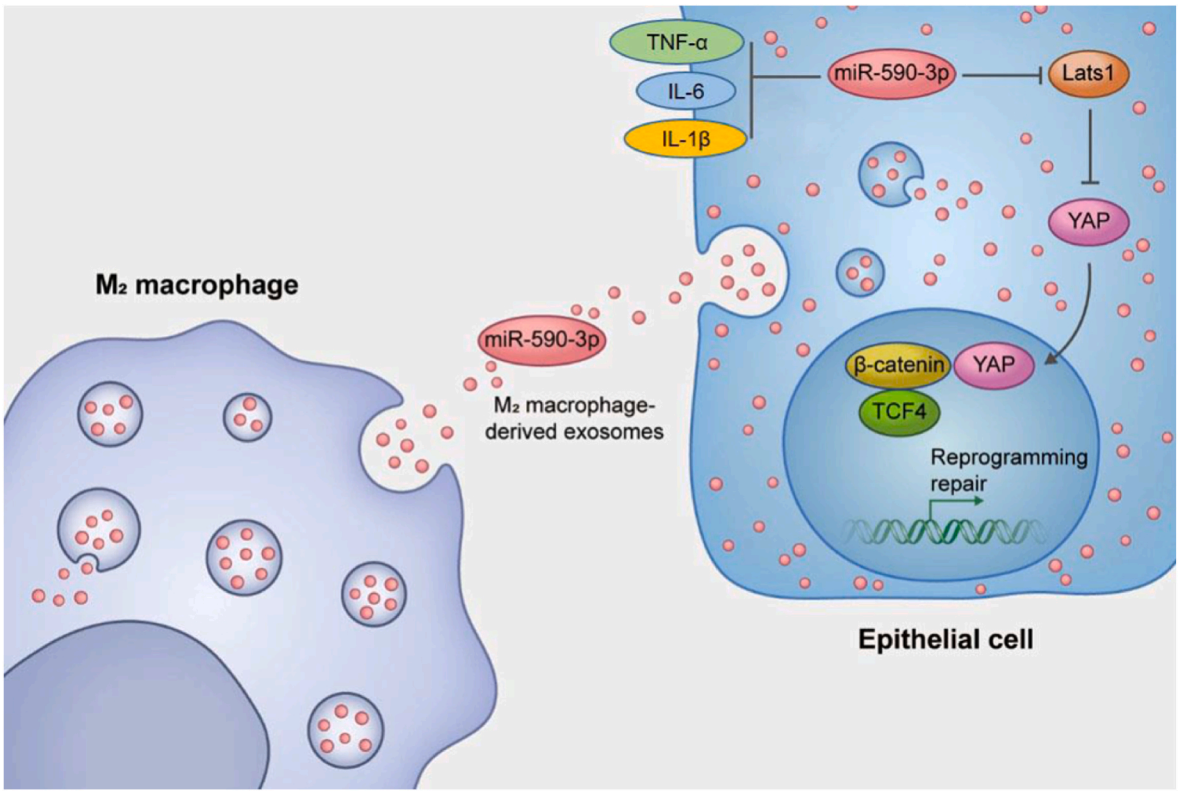

Fig. 8. Schematic diagram of M2 macrophages promoting colon epithelial cell proliferation in an EVs dependent manner. MiR-590-3p, which was significantly enriched in M2-EVs, could be transferred from macrophages into epithelial cells. Mechanistically, miR-590-3p suppressed the expression of Lats1 by binding to its coding sequence and subsequently activated the YAP/β-catenin-modulated transcription process to improve epithelial cell wound-healing ability. MiR-590-3p also inhibited the induction of pro-inflammatory cytokines [60]. Copyright 2021, Oxford University Press.

can adjust immune function via various types of antigen peptides [84]. In addition, DCs can produce a variety of immunomodulatory EVs subtypes after treatment with anti-inflammatory cytokines such as TGF-β1, IL-10 and IL-4 [63,84]. The frequency and severity of collagen-induced arthritis in mice can be decreased by IL-10-treated bone marrow-derived DCs derived-EVs [62]. Given the significance of IL-10 in the proper formation of mucosal immunity, Yang et al. [62] investigated whether DCs-derived EVs treated with IL-10 (IL-10-EVs) could inhibit TNBS-induced UC. The results confirmed that IL-10-EVs therapy greatly alleviate all macroscopic, clinical, and histopathological parameters of TNBS-induced models. The curative effect of IL-10-EVs is related to the down-regulation of TNF-α, IL-2 and IFN-γ mRNA expression in inflamed tissue. Furthermore, IL-10-EVs treatment markedly increased IL-10 mRNA level in colon tissue and expression of regulatory T cells in the lamina propria of the colon. This finding suggests that IL-10-EVs therapy have the ability to inhibit TNBS-induced acute colitis, providing a innovative method for IBD.

TGF-β1 is a multifunctional cytokines that plays an important role in intestinal immune regulation [85]. However, there are several issues with direct oral or injectable administration of TGF-β1. Firstly, it is unstable in the body and prone to degradation [86]; secondly, TGF-β1 has a wide range of biological effects, but direct administration lacks targeting, making it difficult to precisely act on the lesion site, which may affect the efficacy and increase the risk of systemic side effects [87]. To address the above issues, Cai et al. [63] investigated whether TGF-β1 gene-modified EVs (TGF-β1-EVs) from bone marrow-derived DCs have immunosuppressive functions and play a protective role in the succession of IBD. The results revealed that TGF-β1-EVs greatly prevented DSS-induced weight loss and reduced the intestinal bleeding and disease activity index (DAI). Moreover, DSS-induced mice treated with TGF-β1-EVs had much less damage of colonic tissue, exhibiting more intact glandular structures and confined leukocyte infiltration in the submucosa and mucosa. In contrast, TGF-β1 treatment alone did not show a protective effect against IBD and showed only a slight protective effect even at an injection dose of up to 4500 pg. The better protective effects of TGF-β1-EVs than TGF-β1 alone may be due to two factors. First, TGF-β1 in the form of EVs shows a stronger stability than TGF-β1 cytokines do, and second, EVs may be recruited to sites of inflammation and enrich TGF-β1. Therefore, these properties make TGF-β1-EVs one of the popular candidates for clinical intervention in autoimmune diseases.

3.2.2. *MSCs-derived EVs*

MSCs are multifunctional stem cells with all the common characteristics of stem cells, such as self-renewal and multidirectional differentiation ability, clonal expansion ability under specific stimuli in vitro, and the ability to differentiate into chondrocytes, osteoblasts and adipocytes. It has long been known that MSCs-derived EVs (MSC-EVs) can be used as a cell-free therapy for IBD because of their anti-inflammatory, tissue-repair, and immunomodulatory properties, among others [11].

Although intravenous injection of MSC-EVs can improve UC to some extent, oral administration of EVs is the preferred method for treating gastrointestinal diseases such as UC. However, EVs contain proteins and nucleic acids that are easily degraded by the gastrointestinal environment, making oral administration difficult to implement. Therefore, Deng et al. [11] constructed an efficient self-assembled system of LbL-EVs (Fig. 9) using layer-by-layer (LbL) self-assembly technology for oral delivery of EVs targeting the site of inflammatory to improve UC therapy. The outer layers of the MSC-EVs were composed of biocompatible and biodegradable N-(2-hydroxy) propyl-3-trimethyl ammonium chitosan chloride (HTCC) and oxidized konjac glucomannan (OKGM) polysaccharides. These materials were selected to facilitate targeted delivery to the colon and to safeguard the EVs from degradation. In comparison to intravenous administration, the oral delivery of LbL-EVs demonstrated a significant capacity to mitigate UC while

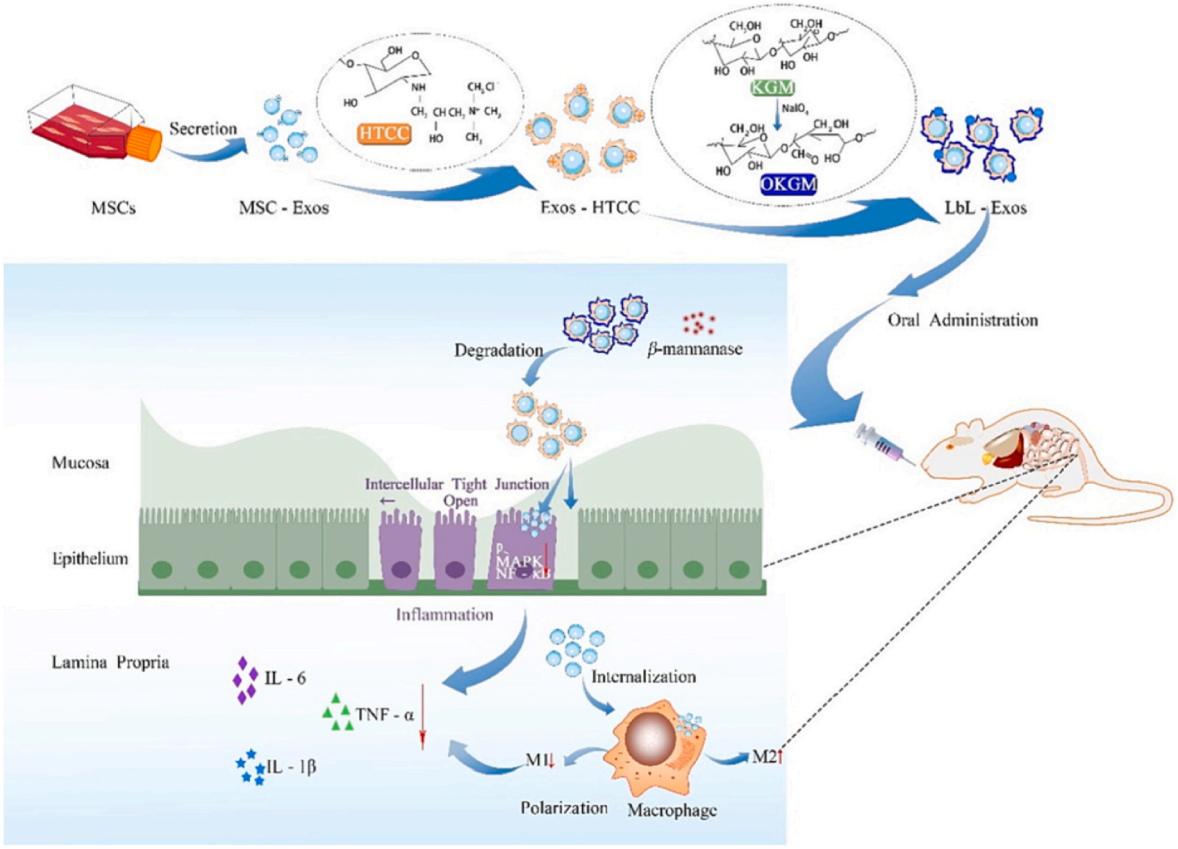

Fig. 9. Schematic representation of preparation of LbL EVs (namely LbL-Exos) and colon targeted therapy. The LbL self-assembly technique was performed to encapsulate MSC-EVs using HTCC and OKGM. After oral administration, OKGM can be degraded by β-mannanase in the colon, and LbL-EVs were internalized by macrophages and alter macrophage phenotype, thereby inhibiting the expression of pro-inflammatory cytokines and repairing the intestinal barrier [11]. Copyright 2023, Elsevier.

utilizing only half the quantity of EVs. Mechanistic investigations revealed that LbL-EVs were internalized by macrophages and intestinal epithelial cells, facilitating anti-inflammatory responses and promoting tissue repair, thereby contributing to the alleviation of UC. Therefore, LbL-EVs may develop into a novel UC therapy approach in the future.

MSCs are a type of pluripotent progenitor cell that can be extracted from bone marrow, dental pulp, amniotic fluid, umbilical cord tissue, and adipose tissue [88,89]. On the basis of the reparative role of EVs based on human bone marrow-MSCs (hBM-MSCs) in tissue injury, Cao et al. [64] investigated their role and possible mechanisms in the treatment of UC. In vitro, EVs facilitate LPS-induced macrophage proliferation and inhibited the inflammatory reaction, as evidenced by the down-regulation of pro-inflammatory cytokines and the up-regulation of anti-inflammatory cytokines. EVs administration release UC symptoms by decreasing weight loss, DAI, severity of colonic mucosal injury, and increasing colon length, as indicated by in vivo models. Mechanistically, EVs encouraged M2-type macrophage polarization, which is indicated by an uptick in the M2 marker CD163. Thus, the utilization of hBM-MSCs-derived EVs may offer a unique method for controlling UC by regulating inflammatory characteristics and macrophage phenotype.

Other EVs derived from other tissues play an important role in IBD treatment. EVs based on human umbilical cord MSCs are able to enhance the expression of the anti-inflammation cytokine IL-10; inhibit the levels of the pro-inflammatory cytokines TNF-α, IL-1β, and IL-6; and attenuate DSS-induced colitis [65]. In DSS-induced colitis, EVs produced from human adipose MSCs keep the integrity of the intestinal obstacle, encourage the growth of IECs, and fend off intestinal inflammatory damage [66]. MiR-146 is a well-known anti-inflammatory miRNA that is overexpressed in MSCs. It controls the level of IL-1 receptor-associated kinase 1 and TNF receptor-associated factor 6 and regulates NF-κB p65 phosphorylation. These actions prevent macrophages from releasing inflammatory agents and lessen colonic inflammation [67]. Therefore, MSCs-derived EVs have great potential for IBD treatment.

3.2.3. *Probiotic derived-EVs*

Probiotics are a class of live microorganisms that colonize the body and change the flora in specific areas of the host to benefit the host. They can maintain intestinal health and increase nutrient absorption by modulating the immune function of the host's mucous membranes and systems or by adjusting the balance of the flora in the intestinal tract. Probiotics are key components of the gut and have been shown to be significantly reduced in abundance in the pathogenesis of IBD. EVs derived from probiotics are attractive carriers for active ingredients due to their favorable immunogenicity and ability to penetrate physiological barriers that cannot be penetrated by synthetic carriers.

Lactobacillus paracasei is a major probiotic known for its anti-inflammatory qualities. Therefore, Choi et al. [68] revealed the effects of *Lactobacillus paracasei*-derived EVs (LpEVs) on LPS-induced inflammation in HT29 cells and DSS-induced UC mice. During in vitro experiments, pro-inflammatory cytokines expression was down-regulated while anti-inflammatory cytokine expression was up-regulated by LpEVs. At the same time, LpEVs reduced the activation proteins of inflammation, which attenuated the inflammation of HT29 cells induced by LPS. During in vivo mice models, by decreasing DAI, preserving colon length, and reducing weight loss, oral delivery of LpEVs prevented DSS-induced colitis. These findings imply that in inflammation-mediated pathophysiology, LpEVs play a major part in preserving colorectal homeostasis.

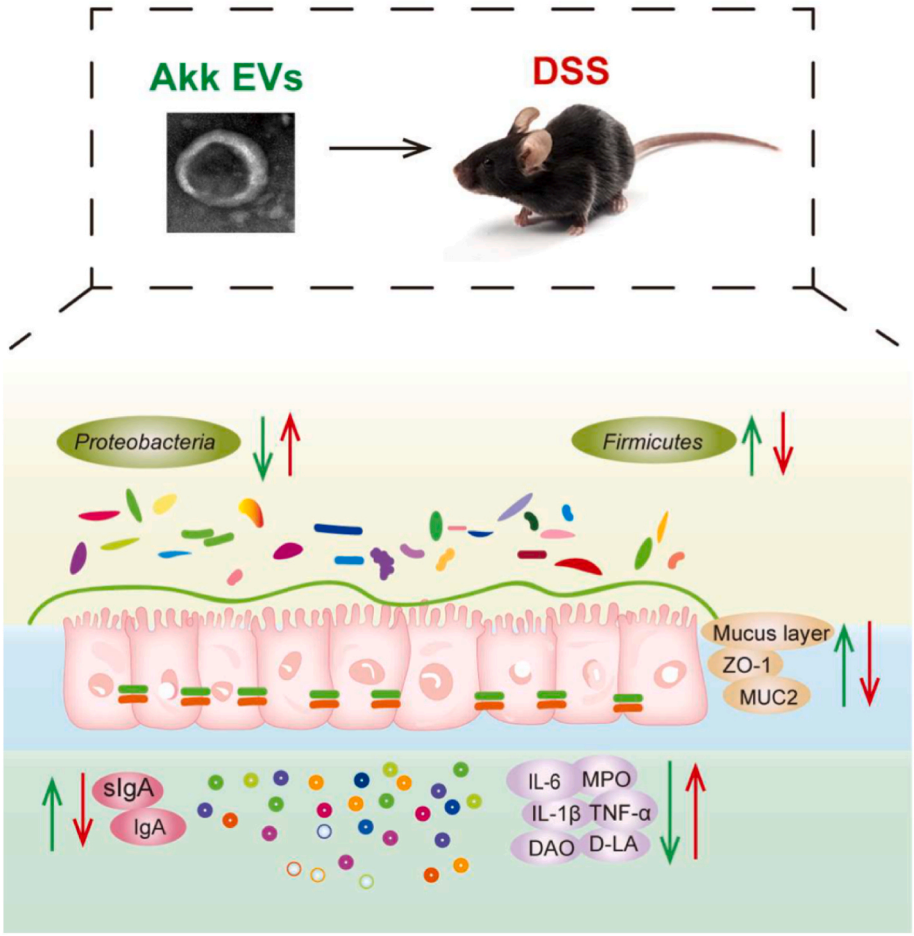

Fig. 10. Schematic representation of Akk EVs adjusting the intestinal barrier. Akk EVs can protect the intestinal barrier and inhibit the exudation of diamine oxidase (DAO) and d-lactic acid (D-LA) by increasing mucin content and promoting ZO-1 expression. In addition, Akk EVs can enhance the secretion of IgA and sIgA, while inhibiting the secretion of TNF-α, IL-6, IL-1β, and MPO. These effects are achieved by regulating the intestinal immune response and the structure of the intestinal microbiota [69]. Copyright 2023, MDPI.

Akkermansia muciniphila-derived EVs (Akk EVs) are nanovesicles that maintain a variety of biologically active macromolecules (Fig. 10) with the hope to regulate the intestinal barrier. Zheng et al. [69] estimated the anti-inflammatory activity of Akk EVs and their ability to regulate the intestinal barrier through in vivo and in vitro UC models. RAW264.7 cells have the ability to absorb Akk EVs, which notably decreased the levels of NO, IL-1β and TNF-α. In vivo tests further confirmed that Akk EVs can efficiently prevent inflammatory symptoms and reduce intestinal tissue damage. Meanwhile, by upregulating MUC2, strengthening mucus integrity, and reducing permeability in the gut, Akk EVs may improve the efficiency of the intestinal barrier. In addition, Akk EVs enhanced the scale of beneficial bacteria *Firmicutes* and down-regulated the proportion of harmful bacteria *Aspergillus phylum*. These results imply that Akk EVs have the ability to control intestinal flora, shield the intestinal barrier, and modify the immunological response.

3.2.4. *EVs from other sources*

Apart from these common cell-derived EVs, other sources of EVs, such as IECs-derived EVs, plant cells-derived EVs, and milk-derived EVs, play a key role in the prevention and treatment of IBD.

IECs-derived EVs interact with host immune cells and intestinal microbiota to assist remain microenvironmental homeostasis in the colon [90–92]. Jiang et al. [76] found that EVs based on IECs with TGF-β1-dependent immunosuppressive activity under physiological conditions. Transferring these EVs into DSS-induced IBD models reduced the severity of IBD through inducing regulatory T cells and immunosuppressive DCs to reduce the severity of IBD. IBD is encouraged to develop when endogenous EVs generation is reduced. In an ERK-dependent way, IECs generate EVs with elevated TGF-β1 levels during the progression of IBD. These EVs typically aggregate in the gut in relation to the chemical known as epithelial cell adhesion molecule (Ep CAM). Knockdown of Ep CAM in vivo increased the seriousness of IBD in mice, and EVs produced by Ep CAM-reduced IECs had attenuated protective effects against IBD in mice. EVs derived from IECs are suggested to take part in the maintenance of intestinal immune homeostasis.

The majority of plant-derived exosome-like NPs (PDENs) are obtained from plants that are edible, including grapefruit, garlic, ginger, and broccoli. It is well established that edible PEDNs preserve intestinal immunological homeostasis and reduce intestinal inflammation. Among its various biological properties are antibacterial and anti-inflammatory properties [93]. Garlic is a good contender for the prevention of IBD since it helps eradicate digestive problems like colitis, diarrhea, and dysentery when taken daily. Zhu et al. [32] explored the effect of garlic-derived exosome-like nanovesicles (GENs) on DSS-induced colitis in mice (Fig. 11). GENs contain 61 proteins, 26 lipids, and 127 known microRNAs. Han-miR3630-5p in GENs could bind to the 3' untranslated region of TLR4, thereby suppressing TLR4 expression. Moreover, GENs greatly up-regulate the expression of barrier-associated proteins in LPS-induced Caco-2 cells and suppress the overproduction of pro-inflammatory cytokines. The in vivo results further confirmed that pretreatment with 100 $mg \cdot kg^{-1}$ of GENs was effective in ameliorating

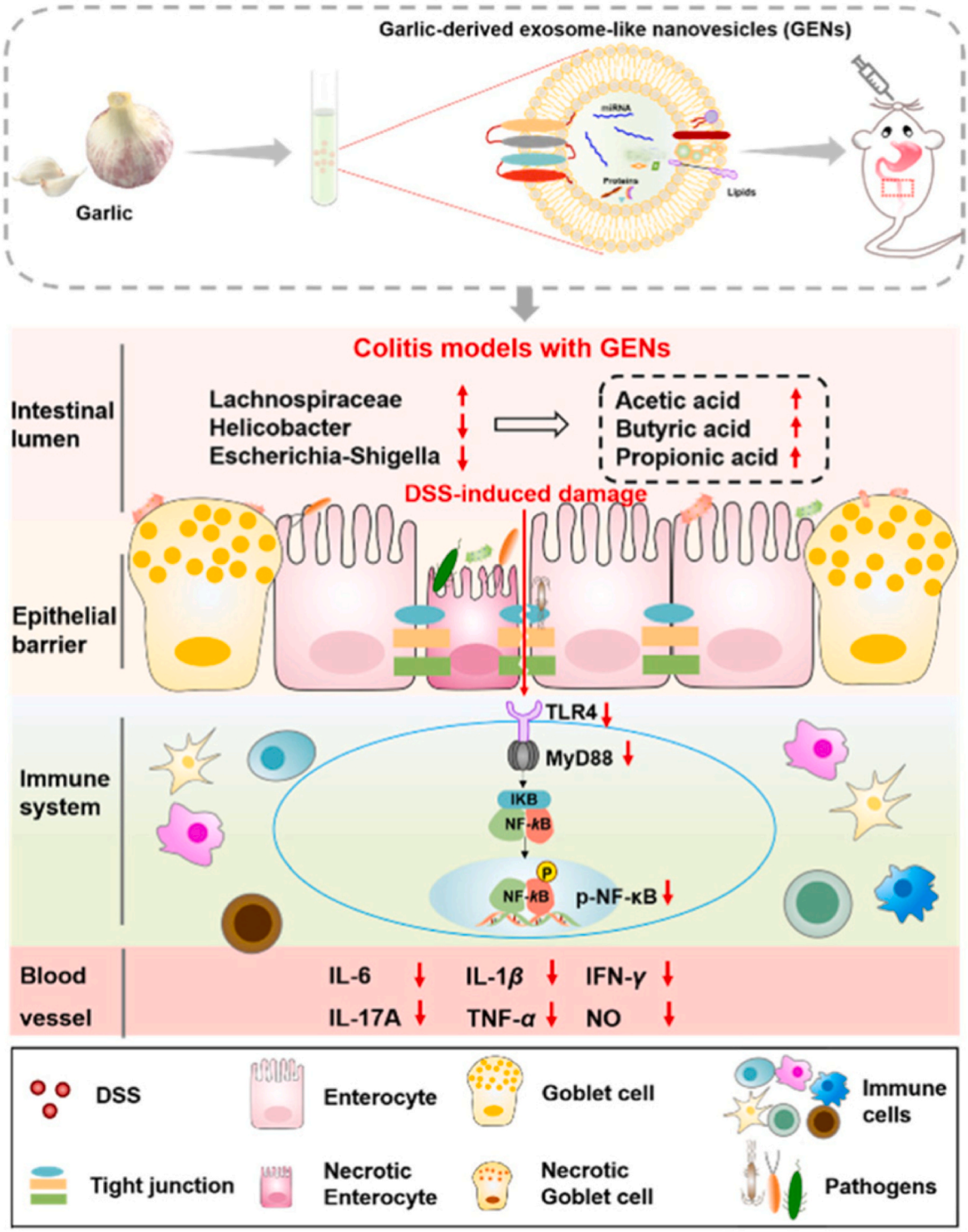

Fig. 11. Schematic diagram of GENs ameliorating DSS-induced colitis in mice via inhibiting TLR4/MyD88/NF-κB pathway and regulating intestinal flora [32]. Copyright 2023, Royal Society of Chemistry.

inflammatory bowel behavior, pathological damage of intestinal histology, and tight junction protein dysfunction. In addition, by increasing the relative abundance of *Lachnospiraceae* and lowering the relative richness of *Helicobacter*, GEN pretreatment changed the gut microbiota features of colitis mice. These results elucidate the potential application of GENs in IBD prevention and offer novel perspectives for the progression of garlic-derived products for IBD prevention.

Milk-derived EVs (MEVs) are an important component of milk and are released by mammary epithelial cells in all mammals, including cows and humans [94]. By regulating intercellular signaling, inflammatory reactions, and immunological responses, MEVs are essential to the formation of the gastrointestinal tract and can help prevent a number of disorders, including IBD [34,95,96]. On the basis of this condition, Han et al. [33] exploited a new oral siRNA delivery system for the therapy of IBD. This delivery system encapsulates TNF-α siRNA through MEVs, thus protecting nucleic acid against the rigorous

environment of the GI tract and safely reaching the site of colonic inflammation. MEVs have remarkable structural stability compared to EVs from HEK293T cells, which enables them excellent siRNA carriers. In vitro studies revealed that MEVs carried with TNF-α siRNA (MEVs/-siR) efficiently inhibited the level of TNF-α-associated inflammatory factors. Furthermore, considering that MEVs consist of special lipids with high bioavailability, oral administration of MEVs/siR effectively reached the colonic tissues, thereby decreasing the level of TNF-α and successfully alleviating the symptoms of colitis in DSS-induced IBD models. Therefore, MEVs have good prospects for clinical application as oral gene delivery vectors.

3.3. Bionic drug delivery system based on cell wall

Fungi are a class of eukaryotic cell-based microorganisms that are widely found in nature, including microorganisms such as yeasts and molds, as well as the well-known mushrooms. Yeast cells have received enhancing concentration as an oral delivery system for bioactive substances due to their great potential for encapsulating hydrophilic and hydrophobic compounds and protecting them from biodegradability, controlled release, biocompatibility, external environmental stresses. An intact yeast cell wall consists of β-glucan, mannoprotein, and a little amount of chitin, and is permeable to both hydrophobic and hydrophilic compounds. Therefore, intact yeast cells require no modification and can be directly used as carrier materials [97]. In oral drug delivery systems, yeast cell wall microparticles (YPs) can act as gastroprotectants to prevent the gastric environment from damaging the drug delivery system, while intestinal flora metabolites in the colon, such as β-glucanase, can facilitate the slow release of drugs from the drug delivery system. In recent years, YPs obtained from baker's yeast and brewer's yeast have emerged as a potential oral drug carrier [98]. Table 4 summarizes the applications of bionic drug delivery systems based on YPs in IBD.

YPs exhibit three advantages for UC cover other oral drug carriers. First, because of their strong peptidoglycan coating, they can function as a barrier in the stomach environment [103–105]. Second, they can be broken down into carbon dioxide and short-chain fatty acids with the help of the many intestinal microorganisms that surround the colon, which releases the loaded medication [106]. Third, YPs can be made into multifunctional YPs by loading several types of NPs into their porous microsphere structure [107]. Thus, YPs are a promising carrier for the management of UC as a result.

Utilizing the potential advantages of YPs, Chen et al. [99] designed a inflammatory-targeted NPs-YP drug delivery system for the therapy of UC (Fig. 12). YPs encapsulate hyaluronic acid (HA) and polyethyleneimine-modified rhodopsin-loaded ovalbumin NPs (HA/PEI-RH NPs) to form HA/PEI-RH NYPs. The YPs enable HA/PEI-RH NPs to move steadily by the gastric environment and are decomposed by β-glucanase, thereby facilitating drug release from the HA/PEI-RH NYPs in the colon. Cellular uptake assessment indicated that HA/PEI-RH NPs could specifically target macrophages via HA ligands to enhance uptake. In vivo assays further confirmed that HA/PEI-RH NYPs efficiently aggregated in the site of inflammation in the mice and alleviated colonic inflammation. Thus, HA/PEI-RH NYPs have the virtues of good β-glucan-sensitive release ability, macrophage-targeting ability, gastric stability, and anti-UC effect. The multifunctional NPs wrapped in YPs are a prospective oral drug delivery system for UC treatment.

UC therapeutic agents face the dilemma of not being able to synchronize the modulation of the intestinal microbiota, aside from the lack of targeting. To address this dilemma, Li et al. [100] constructed a novel drug delivery system based on a metal polyphenol network (MPN) through metal coordination between EGCG and Fe^{3+}. Cur is a polyphenolic compound with significant anti-inflammatory activity, was encapsulated in MPN to produce Cur-MPN. Subsequently, Cur-MPN was encapsulated into YM to obtain CM@YM (Fig. 13). The results indicate that YM can protect Cur-MPN from adverse gastrointestinal environments and enhance the targeting and retention ability of inflamed colon. When administered orally, CM@YM can alleviate DSS-induced colitis by clearing ROS, reducing pro-inflammatory cytokines, and regulating macrophage polarization towards M1, thereby restoring barrier function and maintaining intestinal homeostasis. It is worth noting that CM@YM can also regulate the gut microbiome to a favorable state by improving bacterial diversity, transforming the composition structure into an anti-inflammatory phenotype, and increasing the content of short chain fatty acids (SCFAs). This natural product targeted oral delivery system provides a new approach for treating IBD by anti-inflammatory, antioxidant, and regulating gut microbiota.

4. Challenges and prospects

With further exploration of the complex pathogenesis and pathological microenvironment of IBD, we have found that the development of biomimetic systems that simulate the biological environment to achieve precision drug delivery and local immune regulation may be one of the key strategies to promote the clinical treatment of IBD. The potential advantages of this biomimetic delivery system are reflected in the following aspects: (1) Traditional chemical drug therapies may lack targeting, resulting in side effects. This bionic system can simulate the natural homing mechanism of cells and accurately deliver drugs to IBD lesions [23]; (2) Biomimetic systems based on cell membranes, EVs or

Table 4
Applications of BNDS based on YPs in IBD.

Cell wall types	Core materials	Target	Targeting mechanisms	Cargo	Animal models	Treatment effects	Ref.
Yeast cell wall	HA/PEI NPs	Macrophages	Targeted the macrophages excessively expressed CD44 receptors and improved their capacity to target inflammatory areas after being released from YPs	RH	DSS-induced BALB mice	Demonstrated the ability to target macrophages, release β-glucanase in a sensitivity-sensitive manner, high stomach stability, and anti-UC actions	[99]
	MPN	Macrophages	β-glucan makes up the majority of YM, and macrophages can identify it via a variety of pattern recognition receptors	Cur and EGCG	DSS-induced C57 mice	Deduced pro-inflammatory cytokines, scavenged reactive oxygen species, and controlled macrophage polarization to M1 to relieve DSS-induced colitis	[100]
	Lf NPs	Macrophage and intestinal epithelial cells	Lactoferrin, a food-source nanocarrier, can assist EMO in targeting intestinal epithelial cells, and YPs naturally have the capacity to target macrophages	EMO	DSS-induced C57 mice	The dual-targeting approach may strengthen EMO's twin benefits of reducing inflammation and promoting mucosal repair, respectively	[101]
	Man NPs	Macrophage	Utilizing the distinct configuration of β-CD, the D-Man ligand is included to enable macrophage targeting	Cur	DSS-induced BALB mice	Treating ulcerative colitis by scavenging ROS, reprogramming macrophages, and reducing inflammation	[102]

HA: Hyaluronic acid; PEI: Polyethylenimine; RH: Rhein; MPN: Metal polyphenol network; YM: Yeast microcapsules; Cur: Curcumin; EGCG: Epigallocatechin Gallate; Lf: Lactoferrin; EMO: Emodin; Man:D-mannose.

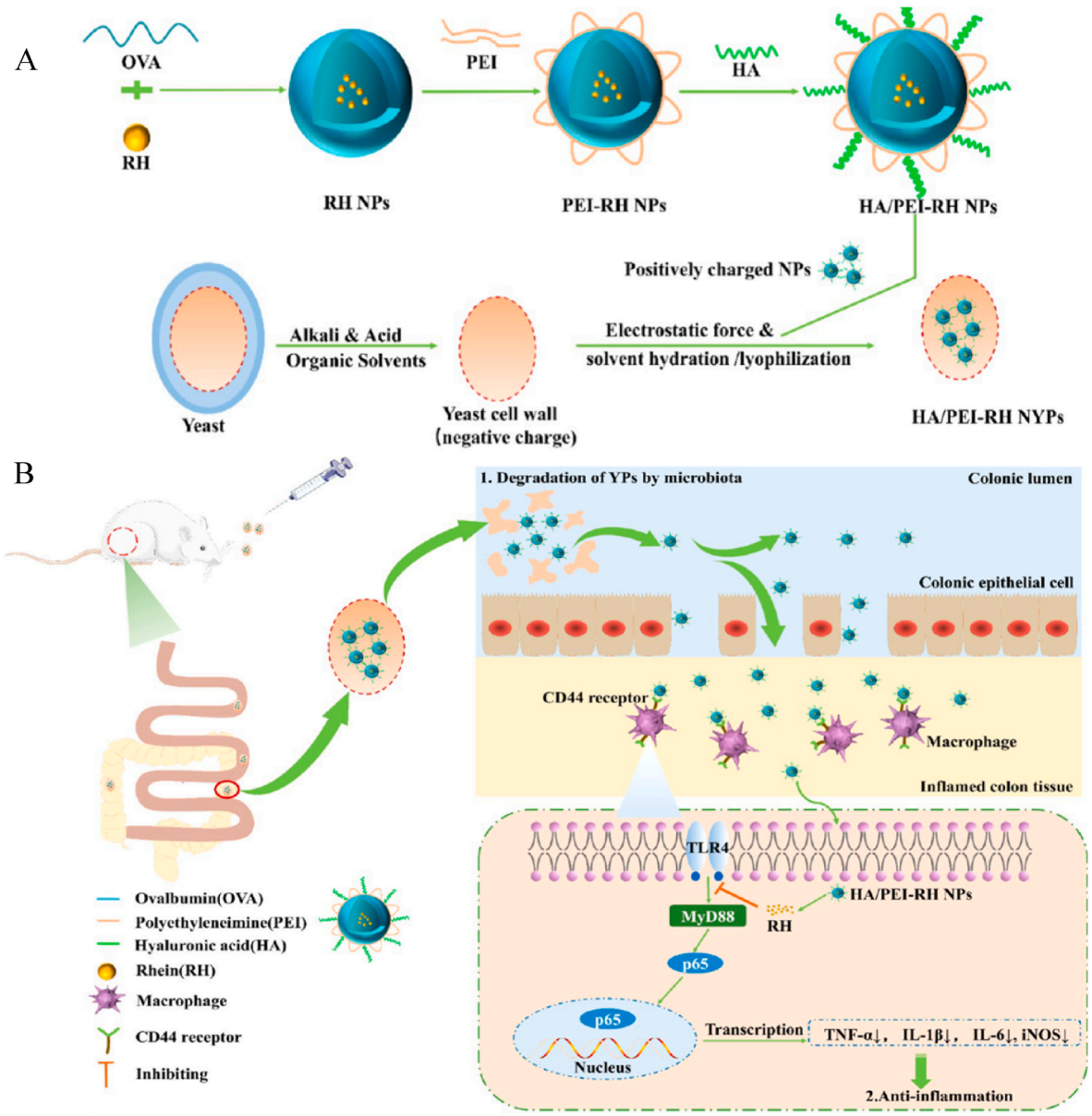

Fig. 12. Schematic diagram of HA/PEI-RH NYPs for UC treatment. (**A**) The manufacturing process of HA/PEI-RH NYPs. (**B**) HA/PEI-RH NYPs can safely pass through the gastric environment after oral administration and release drugs after degradation by the gut microbiota. HA/PEI-RH NYPs can target macrophages and effectively enhance anti-inflammatory ability through the TLR4/MyD88/NF-κB signaling pathway, thereby exerting anti-UC ability [99]. Copyright 2021, American Chemical Society.

cell walls offer better control and repeatability than using cells directly as therapeutics. It can simulate the behavior of cells, but can try to avoid issues such as immune rejection that may be triggered in cell therapy [30]; (3) Compared with microbiota based therapies (such as fecal microbiota transplantation and probiotics), biomimetic drugs that mimic probiotics can not only effectively target and regulate the intestinal microenvironment of IBD mice, but also avoid the risks of live bacterial administration, including the production of toxic substances, unpredictable proliferation in the body, and possible phenotypic variations once implanted [108]; (4) Compared with drug delivery systems designed using synthetic biology strategies, bionic systems derived from natural cells usually have better biocompatibility and lower production costs, while the former may require additional surface modifications to improve compatibility with organisms and have higher synthesis and production costs [29]; (5) Compared with nerve signal intervention in the treatment of IBD, this bionic drug delivery system does not directly act on the nervous system, avoiding possible neurological side effects or damage [109].

Although research on bionic delivery systems has made significant headway, there are still several obstacles in the way of practical translation. First, the cause of IBD is not entirely known, which contribute to the disease's incurable nature. IBD is a highly complex gastrointestinal illness in addition to an inflammatory one. Thus, a challenge is to conduct a thorough investigation of the mechanisms underlying IBD. Such a study will offer insight into the mechanisms by which medications exert their pharmacological effects in addition to potential treatment targets. A growing body of research is concentrating on the gut microbiota in an effort to identify novel targets for host-microbe interactions and create effective treatment strategies to improve IBD.

Secondly, cell-derived BNDS are not yet well suited for large-scale production because ensuring the integrity of the bionic material and the availability of the active ingredient during production is challenging due to the difficulty in controlling the quality and purity of the cells and biomolecules. Moreover, the preparation process of these delivery

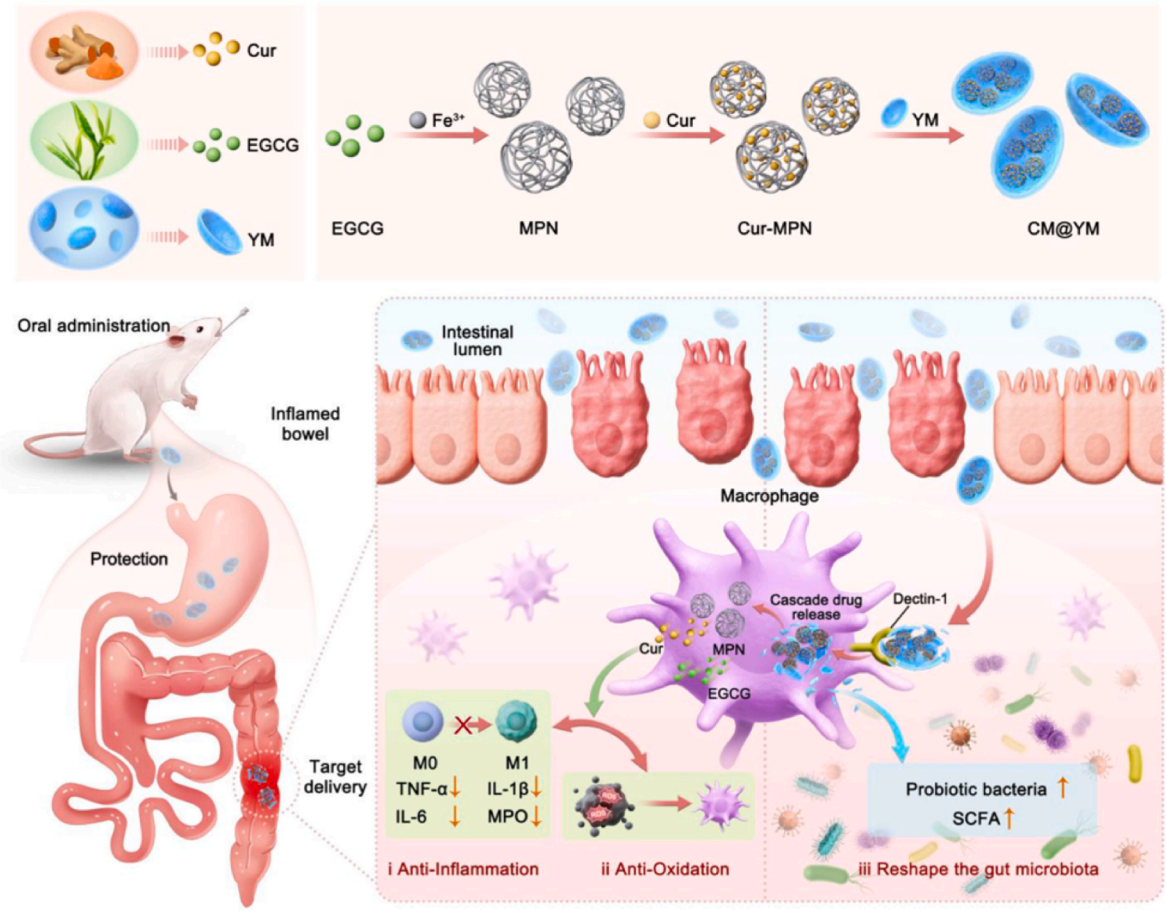

Fig. 13. Schematic representation of the preparation and potential therapeutic mechanisms of CM@YM. Cur was self-assembled into MPN formed by EGCG and Fe^{3+} coordination, and then encapsulated into YM to obtain CM@YM. When administered orally, CM@YM could efficiently deliver the drug to the colon site, and be specifically recognized by macrophages in the intestine. Furthermore, CM@YM could reduce the production of pro-inflammatory cytokines, inhibit M1 macrophage differentiation, and promote epithelial barrier repair. CM@YM also restored the abundance and diversity of gut microbiota [100]. Copyright 2024, KeAi Chinese Roots Global Impact.

systems is relatively complex and requires highly specialized technology and equipment. Therefore, with the help of multidisciplinary expertise, reasonably designing and constructing BNDS with specific functions is expected to achieve large-scale production and targeted on-demand release of drugs.

In addition, the safety of bionic nanocarriers is still subject to some uncertainty. For example, excessive use of immune cell membrane-coated NPs may trigger or exacerbate inflammatory responses through interactions with the immune system, potentially leading to the release of pathological mediators [51]. MSC-EVs have anti-inflammatory and immunosuppressive effects, and therapies based on such EVs may directly or indirectly promote tumorigenesis or accelerate the progression of existing tumors [110]. When performing drug loading operations on EVs, there is a risk of altering the orientation of membrane proteins, which may lead to recognition by the immune system and trigger adverse reactions [111]. Therefore, future research could explore membrane fusion techniques between liposomes and EVs to enhance drug loading capacity and reduce the amount of EVs used, or attempt comprehensive artificial synthesis of EVs. At the same time, surface modification methods that have minimal impact on the content and composition of EVs should be chosen to reduce potential cytotoxicity issues.

Another challenge in IBD-related research is the lack of accurate animal models of IBD. Currently, most in vivo studies in the field of IBD therapy are limited to chemically induced IBD models (e.g., DSS or TNBS). In fact, alternative genetically engineered or immune-induced IBD models are also available. Moreover, most IBD investigators using animal models rarely address long-term dosing outcomes or provide insights into IBD relapse. Therefore, the exploration of more diverse and accurate animal models of IBD can comprehensively upgrade and transform the nanomaterial-based drug delivery platform for clinical application, which is of great significance in the advanced nanotherapy strategy of IBD. Additionally, gastrointestinal tissues or cells from IBD patients can be transplanted into immunodeficient animals with reference to the PDX model in cancer research, and specialized IBD-related animal models can be established for drug discovery in IBD therapy.

Despite the above challenges, this medication strategy still exciting and rapidly developing, with great hope for IBD treatment. Over the last few years, the application and development of cell-derived biomimetic nanotechnologies based on EVs have been granted an increasing number of relevant patents (Table 5). Clinical trials on EVs are actively underway to determine the therapeutic effects (Table 6). MSCs are known for their self-renewal ability, multi-differentiation potential, and natural targeting ability, which leads to a better tendency for their secreted EVs to act at the site of inflammation. Therefore, EVs derived from MSCs show unique advantages in clinical trials.

5. Conclusion

In this review, we summarize the application of cell-derived bionic-based drug delivery systems in the treatment of IBD, which show superior promise because of their unique properties. Although this

Table 5
Patents of biomimetic nanotechnology in IBD.

Patent number	Patent title	Assignee	Filing year
US20180078581A1	Exosomes sourced from granulocytic myeloid-derived suppressor cells and application thereof	Jiangsu University, China	2018
CN115806615A	Antibody and MSC-derived exosomes preparation methods and their combined use in the treatment of diseases	Shenzhen Betis Biotechnology Co., Ltd., China	2023
EP3218521A1	Method and device for diagnosing organ injury	Resonac Corp., JP; Hitachi Chemical Co. America Ltd., US; Regents of the University of California, USA	2016
CN116063493A	Pharmaceutical composition comprising antibodies and mesenchymal stem cell exosomes and preparation method thereof	Guizhou Cel Biological Technology Co., Ltd., China	2023
CN115404205A	A novel exosome, preparation method and application thereof	Zhejiang Sheng Chuang precision Medical Technology Co., Ltd.; Zhejiang Puhui Medical Technology Co., Ltd., China	2022
CN112063575A	A method for extraction of dandelion exosomes and its application	Wuhan Cureen Technology Co., Ltd., China	2020
KR1020190098052A	A composition containing EVs originate from adipose stem cells as an active ingredient for the improvement of ulcerative colitis	Exoco Bio Co., Ltd., Korea	2019
US10632161B1	Method for improving or treating a bowel disease	PROSTEMICS CO., Ltd., JP	2020
WO2023140602A1	Composition that includes EVs made from Bifidobacterium or roseburia species for the prevention, treatment, or amelioration of inflammatory disorders	Korea Institute of Science & Technology, Korea	2023
US20220202866A1	Milk based on EVs for using in treating IBD	Hadasit Medical Research Services & Development Ltd., USA	2022
WO2022098124A1	Novel lactobacillus sp. strain and use of EVs derived from same strain	Sphere Power, Inc., JP	2022
CN116271007A	A drug used to treat IBD	Zhejiang University, China	2023
KR1020220061555A	Application of extracellular Vesicles derived from a new strain of lactobacillus genus and the above strain	Sphere Power, Inc., Korea	2022
CN114748522A	The invention discloses a frankincense extract containing frankincense exosome, a preparation method and application thereof	Institute of Basic Theory of Traditional Chinese Medicine, China Academy of Chinese Medical Sciences, China	2022
WO2021222806A1	Compositions and methods for preventing, detecting, and treating IBD	Icahn School of Medicine at Mount Sinai., USA; Icahn School of Medicine at Mount Sinai., CA	2021
WO2023134122A1	The production and use of a cell membrane-coated nanodecoy that can eliminate proinflammatory factors and prevent T cell activation	Soochow University, China	2023

Table 6
Current clinical trials of EVs in IBD.

EVs sources	Target diseases	Cargo	Phase	Current Clinical Trials.gov identifiers
Bone marrow MSC–derived EVs	UC	–	Phase I	NCT05176366
Bone marrow MSC–derived EVs	CD	–	Phase I	NCT05130983
Bone marrow MSC–derived EVs	UC	–	Phase I	NCT05176366
Bone marrow MSC–derived EVs	Perianal fistula	–	Phase I/II	NCT05836883
Human placenta MSC-derived EVs	Perianal fistula in patients with CD	–	Phase I/II	NCT05499156
Plant cells-derived EVs	Irritable bowel disease	Cur	–	NCT04879810
Human placenta MSC-derived EVs	Perianal fistula	–	Phase I/II	NCT05402784

delivery strategy is still in a relatively early stage of development and many challenges need to be overcome before clinical application, its meaningful therapeutic potential makes it worthy of further investigation as a promising therapeutic option. In addition, with the rapid development of nanotechnology, attention and focus on bio-nanotherapies for IBD will increase, which will facilitate further clinical translation of bionanomedicine in the near future. We believe that in future studies, cell-based bionic nanodelivery systems will have the potential to revolutionize the treatment of IBD and improve the management of other gastrointestinal diseases.

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CRediT authorship contribution statement

Wenjing Yang: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Peihong Lin:** Writing – review & editing, Methodology, Formal analysis. **Rui Gao:** Writing –

review & editing, Visualization, Data curation. **Zhengyu Fang:** Visualization, Investigation. **Zhouru Wang:** Data curation. **Zhen Ma:** Investigation. **Jing Shi:** Writing – review & editing, Supervision. **Wenying Yu:** Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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