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Review Article

Stimuli Responsive Nanomedicine for Inflammatory Bowel Disease: Exploiting the Pathological Microenvironment for Targeted Drug Delivery

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ABSTRACT

Introduction IBD is a long-lasting, recurring condition that mainly includes Crohn's disease and ulcerative colitis. It causes ongoing inflammation in the intestines, changes how the immune system works, harms the lining of the gut, and upsets the balance of the gut environment. Even though the way these drugs are given has been improved for treating these diseases, they still aren't very specific to where they're needed, can cause serious side effects, and may lose their effect early on because they don't target the diseased parts of the bowel very precisely. Despite these drawbacks, nanomedicine also helps with stabilizing resistant drugs, targeting the intestines, absorption, and controlled release. Moreover, many pathological changes within IBD relate to abnormal microenvironments (for example, higher levels of ROS, dysfunctional mucus and epithelial barriers, pH changes, abnormal enzymatic activity, disturbance of the redox system and microbial imbalance), providing potential endogenous markers for site-specific delivery of therapeutic agents in the context of stimulus-responsive (e.g. pH, ROS, enzyme, redox, microbiota and multi-responsive) delivery systems. Here, we'll look at the idea of microenvironment-responsive nanomedicine for IBD, covering its design, how it releases drugs, its effects on the disease, and how it can slow progression in the inflamed gut while reducing side effects and overall toxicity, along with discussing important design issues like targeted recognition, nanocarrier stability, biocompatibility, reproducibility, and how to move from preclinical to clinical use. Using natural disease markers to respond specifically fits with new approaches in IBD treatment.

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INTRODUCTION

The underlying mechanism of inflammatory bowel disease (IBD) is an imbalanced immune regulation in the intestinal mucous membrane. According to combined clinical, laboratory, endoscopic, histological and radiological data, IBD can be phenotypically divided into three main forms, which are ulcerative colitis (UC), Crohn's disease (CD) and IBD-U [1].In the current world a distinction has been developed between Ulcerative colitis and Crohn's disease which are the two types of chronic IBD which has immense clinical significance which are differentiated through the clinical manifestation, pathological difference, etiology, genetics in the background and the management techniques adopted for the treatments [2]. Crohn's disease is a transmural inflammatory disease that can affect any part of the GIT, but most common in the terminal ileum. It may also involve the caecum, perianal region, or colon, and is characteristically associated with skip lesions. Severe deep ulcers and fistulas, strictures, granulomas and fibrosis may result from this condition. At the histological level, Crohn's disease demonstrates a transmural inflammatory infiltrate along with granulomas, deep ulceration, and a thickened bowel wall. Ulcerative colitis (UC) is a chronic inflammatory condition isolated to the rectum and colon, which begins in the rectal mucosa and extends proximally in a continuous fashion. Histologically, UC is defined by the presence of mucosal inflammation with acute neutrophilic injury (cryptitis and crypt abscesses). UC involves a self-sustaining cytokine driven inflammatory cascade characterized by cytokines such as the interleukins (IL-6, IL-12, IL-17, IL-23) as well as tumor necrosis factor (TNF) which promotes mucosal immune dysregulation [3]. IBD has a fluctuating course with extrinsic of exacerbations and remissions. The main therapeutic goals are to achieve a full disease remission, induce a persistent long-term remission, and stop the disease progression. Yet, the symptomatology is also characterized by irregular and unpredictable relapses, which have a significant impact on the physical and mental health, and on the social and work ability of patients [4]. The management of IBD is directed towards reducing disease activity, with the goal of achieving and maintaining remission. However, standard treatment used to suppress the disease activity using drugs of groups as 5-aminosalicylates (5-ASA), corticosteroids, immunomodulators and biological drugs brings along side effects and remaining disease activity among the patients. This is why the researchers are trying to develop newer treatment strategies like gene therapy, stem cell transplantation, etc. One way Stem Cells are used for treatment is with mesenchymal stem cells; studies have proven they down-regulate the immune response, modulate the immune system, secrete anti-inflammatory cytokines, and help repair the lining of intestines [5]. Nanomedicines sensitive to external stimuli constitute another example of drug delivery systems. Researchers have designed these systems for potent therapeutic action with little toxicity by demonstrating on-demand payload release triggered by unique physicochemical or external stimuli such as temperature, light, redox potential, pH, enzymes, magnetic fields or other stimuli. Nano-drug delivery systems, such as liposomes, nanoparticles, micelles, dendrimers, and nanocapsules allow for better pharmacokinetics for therapeutics by protecting them from enzymatic degradation and large systemic clearance, supporting personalized and targeted therapy [6]. This review looks at stimuli-responsive nanomedicines designed to exploit pathological changes in the inflamed gut. They aim for disease-specific targeting of inflammatory bowel disease (IBD) itself. Accordingly, this review focuses on stimuli-responsive nanomedicines engineered to exploit pathological alterations in the inflamed gut, enabling disease-specific targeting in inflammatory bowel disease (IBD).

PATHOLOGICAL MICROENVIRONMENT OF INFLAMMATORY BOWEL DISEASE

Nanomedicine in IBD is one of the highest ranked orphan indications, since this is one of the most hostile gastrointestinal microenvironments for nanocarriers targeting due to impaired epithelial barrier, along with mucosal inflammation and dysbiosis which can alter the transport, retention and therapeutic effect of the nanocarriers. For these disease states, the intestinal environment is characterized by too many reactive oxygen species (ROS), mucus barrier disruption, luminal pH changes, too much H2S and irregular enzyme activities, cargo instability and limited access to

inflammatory regions. Such features have motivated the design of nanocarriers that either directly restore biochemical aberrations such as ROS scavenging and H2S clearance, or that respond to disease-associated biochemical cues such as ROS, luminal pH, luminal enzymes and mucus abnormalities. Meanwhile, modulation of the immunological microenvironment through nanomedicine platforms that regulate inflammatory signaling, target the mucosal surface, protect cargoes from early degradation and improve their retention time has been achieved [7]. The Inflammatory Bowel Disease (IBD) is the relapsing-remitting chronic disease characterized as a multifaceted origin pathology. Despite numerous studies conducted on this disease, the pathogenesis has not yet been completely clarified. There is a growing body of evidence recognizing the key players playing a role in such a complex process, namely a dysregulated immune response, barrier dysfunction, oxidative stress, intestinal microbiome alterations, genetic factors and environmental influences, although, there are still some gaps in the path to further comprehend the disease. Of all these elements, the Disease Accelerators are a leading factor involved in IBD the pathogenesis-one of them is oxidative stress. It occurs when the ROS, mustered during normal cell respiration, exceed the capacity of the cell's antioxidant defense and result to mucosal injury. Self-amplifying between ROS and antioxidants can impact on the risk of IBD significantly and not increasing the risk of this disease by neutralizing ROS and eliminating [8]. Standard colon-specific approaches for inflammatory bowel disease–such as pH-, time-, pressure- or microbiota-triggered delivery systems– have often not resulted in demonstrable benefit in the clinic due to the variable physiology of the GI tract between patients, as well as the complex, multifaceted nature of IBD. Rational design of inflammation-targeted drug delivery systems (DDS) for inflammatory bowel disease (IBD) must respect the inflamed intestinal microenvironment. Its distinct pathophysiological features drive every decision. inflammation-targeted drug delivery systems (DDS) for inflammatory bowel disease (IBD) must account for the distinct pathophysiological features of the inflamed intestinal microenvironment [9]. Many studies have shown altered activity of enzymes in the degradation of ECM in the inflamed tissues of IBD patients. For example, elevated amounts of central enzymes in the hyaluronan pathway, for example TSG-6, are associated with major hyaluronan waste and upregulated leukocyte entry into tissue. This rationale could be exploited to design carriers that are specifically degraded by hyaluronidase, which is upregulated in inflamed tissue. At the same time, the expression of esterase in activated macrophages in the inflamed tissue could be targeted as well; for example, macrophage carboxylesterase Ces1d is lipid signaling-regulated and modulates the macrophage inflammatory phenotype, as evidenced by tumor microenvironment studies, providing a plausible base for the design of inflammation-responsive delivery systems. Further, there is no evidence for cellulase and -amylase targeting, but these enzymes have been shown to have a higher enzymatic activity in the healthy colon compared to the upper GI tract, which could be used for colon-specific targeting [10]. The prevalence of gut microbiota dysbiosis is positively related to oxidative stress. ROS will influence bacteria population and activity selectively, and bacterial metabolism stimulated by dysbiosis, will further intensify oxidative harm and mucosal inflammation. This positive feedback loop is widely accepted to be the leading factor for the development of IBD, MS, CKD and different kinds of cancer [11]. Intestinal epithelial cell dysfunction. Dysfunction of the intestinal epithelium is a common feature in IBD, and has been shown in a number of animal models. Cell dysfunction at a number of different levels of the gut epithelial innate immune response can be identified, including abnormal PRR expression, defective AMPs secretion, defective mucus barrier, defective autophagy, and defective epithelial permeability. This overall decrease in epithelial protection facilitates bacterial adherence and invasion and causes ongoing inflammatory injury to the mucosa in IBD. In this adverse combination, it seems, more bacteria are in direct contact with the epithelium and the mucosal immune processes, which could start the cascade of immune processes leading to the chronic intestinal inflammatory process, particularly in the relevant regions of distal ileum and colon. Some evidence indicates that the process of inflammation and the pathogenesis is probably associated with the flora [12].

STIMULI RESPONSIVE NANOMEDICINE FOR INFLAMMATORY BOWEL DISEASE

Traditional approaches to IBD management over the last 40 years have been based on anti-inflammatory and immunosuppressive drugs. There is now increasing awareness that colon specific drug targeting can improve treatment outcomes by increasing local drug exposure while limiting systemic exposure. Traditional drug delivery systems for IBDs face many problems to reach the colon, such as physiological barriers and disease activity. PH-sensitive delivery vehicles emerged as another encouraging therapeutic targeting strategy for UC, which can be further refined by taking advantage of physiological pH differences between different sites along the gastrointestinal (GI) tract to achieve site-specific release of therapeutics in the inflamed colon. 48 UC pH-responsive smart carriers provide a solution for colonic targeting of drugs that can lead to improved therapeutic outcomes, less systemic absorption and less premature elimination of drug from diseased sites. They incorporate pH-sensitive polymers to ensure the protection and targeted release of drugs on reaching the distal GIT [13]. Eudragit-coated gelatin microparticles are readily prepared from low-cost, non-toxic materials. Particle preparation is a highly reproducible, adaptable process that also allows direct encapsulation of hydrophilic therapeutic agents within the aqueous core, including biologic protein-based drugs. The microparticles' high resistance to acid degradation, coupled with rapid dissolution in neutral media, highlights their suitability for targeted delivery of biologic drugs to the inflamed colon via the oral route. Such a platform has the potential to enhance the efficacy and tolerability of currently available biologic therapies, while reducing adverse events and simplifying treatment. It also could facilitate the delivery of several promising new biologic therapies, such as IL-10, to the gut mucosa [14]. Existing therapies are often hampered by poor efficacy and serious side effects, and there is an urgent need for better options. A novel ROS-responsive nanocarrier (TPN) for synergistic colitis therapy by ROS scavenging and immune regulation. TPN was synthesized by encapsulating cerium oxide nanozymes (Ceria NPs) and thalidomide (Tha) into an amphiphilic ROS-responsive polymer (PP) with a double layer structure. TPN significantly scavenged ROS and released Tha under ROS stimulation. TPN significantly suppressed ROS-induced apoptosis and oxidative stress in vitro. In DSS-induced mouse colitis model, TPN accumulated in colon and relieved body weight loss, colon length shortening, disease activity index and histological damage. TPN activated immune response, suppressed oxidative stress, and modulated gut microbiota towards a healthy composition [15]. Enzyme-, ROS-, and microbiota-responsive nanocarriers are promising strategies for targeted IBD therapy. Enzyme-responsive nanocarriers use colonic bacterial enzymes to degrade material such as chitosan, dextran, pectin, guar gum, and alginate, thus to elicit a location-specific drug release in the colon. ROS-responsive nanocarriers target the gut inflammation sites that harbour heightened oxidative stress through the controlled release of the drug, thus alleviating systemic adverse events. Microbiota-based delivery systems use the gut's existing microbes to give prebiotics, probiotics, postbiotics, or drugs, aiming to restore balance in the gut and prevent dysbiosis [16]. The nanoparticles loaded with anti-miR-301a and designed to be pH-responsive with the aim of achieving colon-specific delivery in order to allow targeted treatment of inflammatory bowel disease were reported. The prepared nanoparticles by this method showed good stability, pH-responsiveness, colon targeting and uptake capacity by macrophages. Pharmacodynamic results found by experimentally validation indicated that O. The antimiR@HCeP nanoparticles substantially lowered the disease activity index, diminished macroscopic colon damage, and alleviated histopathological injury in the DSS induced IBD mice. In addition, the nanocarrier showed good biocompatibility, indicating that it may be an effective and safe drug delivery platform. As a result, this nanotherapeutic carrier could lead to a promising IBD therapy drug candidate [17].

THERAPEUTIC APPLICATIONS

Nanomedicine constitutes an application of nanotechnology in biology and medicine that it has been proposed to revolutionize the detection and management of many diseases, among them IBD, by profiting from special properties of the structural, physical and chemical features of these nanomaterials. First of all,

nanoimaging could be used to help diagnosis of IBD at an early stage and is likely to contribute to the follow-up of the disease's activity. It is reported that NPs with different sizes and coatings preferentially increased at the sites of colitis. The inflammation was visualized and a diagnosis of colitis may be better and timelier. Additionally, the application of nanomaterials for IBD therapy is a new and promising field, whose primary advantages are improved drug delivery, greater stability, and targeted therapy. Nanomaterials can improve important drug properties such as solubility, stability, and plasma half-life, thus enhancing the drug's therapeutic performance [18]. Inflammatory bowel disease (IBD; includes Crohn's disease and ulcerative colitis) is a chronic, relapsing-remitting disease. It is the product of a complex interplay of various genetic, microbial, environmental and immune factors. Current drug treatment for IBD remains unsatisfactory due to inefficient drug delivery to sites of intestinal lesions and systematic side effects. Traditional techniques involve pH-, time- and microbiota-dependent systems for drug release in colon, while a better colon targeting can be obtained via nanodelivery systems by entraining variables such as size, surface charge, PEGylation, ROS responsiveness as well as active targeting of the receptor to be expressed in abnormal tissue. Stimuli-responsive hydrogels could achieve more sustainable drug release at the lesion site by pH, temperature or ROS stimulus [19]. Nanomaterials have rapidly developed in recent years. The purpose of research on nanomaterials is to develop and develop new property and function of materials in the range of 1-1000nm, that is, nanoparticles (NPs). NPs are minuscule, have a high surface-to-volume ratio, and are quite different from traditional materials in form. As a new biological active carrier, NPs could increase the local concentration of drugs at the lesion to maximize the therapeutic effect of drugs, which has played an important role in the field of treatment of intestinal diseases. Nanoparticle delivery systems have revolutionized the delivery of anti-inflammatory drugs for inflammatory bowel disease (IBD). Targeted nanocarriers, including polymeric, lipid-based, liposomal, silica, nanogel, and core-shell carriers, which promote site-specific delivery of drug at the site of colonic inflammation with minimal systemic absorption, adverse effects, number of doses required, and non-specific diffusion, of the distal to proximal gut by exploiting physiological disparities, of the colonic versus proximal gut through passive, active, and hybrid targeting [20]. The gastrointestinal (GI) tract is responsible for ROS homeostasis, defending against pathogens, and absorbing nutrients, and any disruption in these processes will lead to inflammatory cytokine secretion and an oxidative stress response. As there are high levels of ROS at the lesion sites of IBD, ROS-responsive NPs have been reported for the diagnosis and treatment of IBD.

In addition, owing to the relatively high colonic pH (pH 6.4-7.0), compared to those of the stomach (pH 1.5-3.5) and the intestine (pH 5.5-6.8), pH-responsive nanoparticles have been used to treat IBD. Nevertheless, it has been suggested that the pH at the sites of IBD lesions might decrease, which could reduce the effectiveness of pH-responsive drug delivery systems and prevent controlled drug release [21]. A nanoparticle that responds to oxidation and uses the pro-resolving annexin A1-mimetic peptide Ac2-26 is made to make inflammatory bowel disease (IBD) treatment safer and more effective. Too much ROS in inflamed tissue makes the nanoparticles break apart and release the peptide, which could help protect the peptide longer from the enzyme-filled environment in the gut. Meanwhile, the systemic application of this nano-therapeutic to the inflamed colons of mice with IBD achieved ROS-induced release and accumulation of Ac226 at inflammatory sites [22].Therapeutic effect of colon-homing NPs that can directly release specific siRNAs to target cells The research harnessed the benefits of NPs, such as the easy passage through biological barriers, resistance to phagocytosis, rapid kinetics of mixing, high loading concentrations, no or little toxicity, and inertness to degradation. We specifically administered an orally given encapsulated Fab'-bearing TNF-siRNA-loaded NPs targeting intestinal-MPs and assessed its therapeutic effect in a mouse model of colitis [23]. Delivering drugs directly to the inflamed parts of the colon helps manage UC more effectively by getting more medication to where it's needed, improving results, and eventually allowing for lower doses and less risk of side effects. Nanoparticles (NPs) are amongst few molecular systems which gained so much attention in accumulating drug at the inflamed colonic sites.

These results showed that Cur-HA-PLGA-NPs could be a useful way to deliver medicine for treating UC. The smooth, round Cur-HA-PLGA-NPs had almost the same physicochemical properties as the Cur-PLGA-NPs without HA. HA-PLGA-NPs demonstrated targeted accumulation in the inflamed colitis tissue while showing negligible accumulation in healthy colon tissue. Furthermore, HA functionalization facilitated targeted drug delivery to intestinal macrophages and led to a significant increase in the cellular uptake of HA-PLGA-NPs. Notably, in vivo studies indicated that rectally administered Cur-HA-PLGA-NPs was more effective in the treatment of UC than Cur-PLGA-NPs [24].

CHALLENGES AND FUTURE PERSPECTIVES

Challenges - Current IBD research challenges Summary of current Challenges The future IBD focuses on identifying the current gaps in research, with targeted key actions that can address these gaps, namely how to make them lead to great Bowel-Interception, Remission, and Restoration in IBD. IBD is a chronic extremely complex disease with variable clinical symptoms; people tend to present with different clinical symptoms, and response variably to the same therapeutic. It needs long term regular, lifelong monitoring to optimize clinical outcomes and prevent disease from complications [25]. Bowel inflammation – IBD improves outcomes of disease by aiming for objective targets like mucosal healing instead of vague symptom control to achieve better long-term outcomes, like reducing risk of CD-related surgical or hospitalization rates, or achieving sustained clinical remission. Standardization and validation of inflammation: adherence to monitoring and validation of clinical practice remains unsatisfactory, costs of hospital participation for invasive, costly, repeated endoscopy, difficulty in establishing standard definition, validated criteria for mucosal healing, poor patient adherence to repeated routine monitoring in everyday practice, biopsies, clinical uncertainty for treatment adjustment and maintaining treatment in asymptomatic patients versus marketing of current number of medication options[26]. Caring for IBD over time—like regular doctor visits, checkups, treatments, and managing it on your own—can end up costing a lot of money. Overall, the cost is continuously rising as mentioned above, again largely due to the surveillance costs of endoscopy and other modalities. Endoscopy is really important for diagnosing and managing IBD, as it helps make the diagnosis more accurate and can also find dysplastic lesions in patients who don't have symptoms but still have ongoing inflammation from IBD. New ways to manage IBD awareness and investigations depend on understanding patients' concerns and treatment options, especially by creating treatments tailored to each person's genes, immune system, and environment; this helps reduce failed treatments by improving how well they work, their safety, and how much of the drug gets into the body. New drugs for IBD include ones that change how the immune system works, block immune checkpoints, or target certain cytokine pathways. Diagnosing IBD depends on a mix of practical thinking, a standard approach, and making sure information is available to everyone; learning about IBD shows it goes from being something you can change to a lifelong condition with good outcomes, but these results need support from research funding and plans that focus on patients' well-being [27].

CONCLUSION

In the same way, the most recent step in improving IBD treatment involves severe disease associated with long-term chronic inflammation, oxidative stress, impaired epithelial barrier and pH fluctuations, increased enzymatic activities, and microbial dysbiosis. Although there are existing treatments that are able to provide patients with effective control on disease activities, there are undesired nonspecific distribution, side effects, increased drug loss, and poor retention at disease sites that reduce the therapeutic efficacy. So, using targeted or controlled-release drug delivery is a promising way to, hopefully, get better treatment results. Responsive nanomedicine can use the unusual conditions in the gut to release drugs right where they're needed. Creating nanocarriers that respond to pH, ROS, enzymes, and microbes could help target the intestines, protect drugs from being released too soon, allow controlled release, lower exposure to the rest of the body, and support treating both oxidative stress, inflammation, and gut imbalance at the same time. On the other hand, there are still plenty of challenges to

bringing this kind of nanomedicine into real-world use, like differences between patients, the stability and safety of the nanocarriers, and how easy they are to reproduce and make on a larger scale. Future studies should focus on making stimuli more selective, building systems that are both multifunctional and tailored to each patient's disease, and making sure these systems are safe and effective. Therefore, taking advantage of the pathological signals yielded from disease processes would be a practicable route to develop intelligent nanomedicine for IBD.

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