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Research Article

Multistage-Responsive Nanocomplexes Attenuate Ulcerative Colitis by Improving the Accumulation and Distribution of Oral Nucleic Acid Drugs in the Colon

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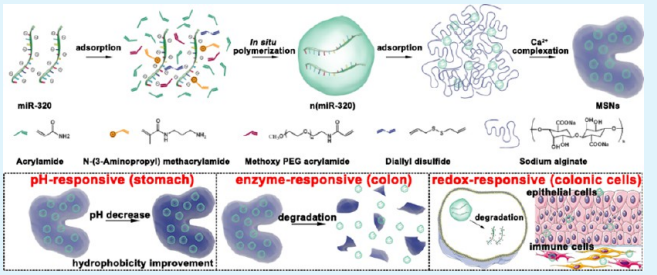
ABSTRACT: Oral gene therapy has emerged as a potential optimal treatment for ulcerative colitis (UC). Nucleic acid drugs possessing versatility can not only inhibit inflammation but realize colon mucosal healing, fulfilling the clinical objective of UC therapy. However, the effective accumulation and distribution of oral nucleic acid drugs in the colon remain a considerable challenge. Furthermore, current delivery systems pay more attention to the accumulation of nucleic acid drugs in the colon, while the distribution of nucleic acid drugs in the colon, which plays a key role in the UC treatment, never catches the attention of researchers. Here, we used miR-320 as a model nucleic acid drug to develop a kind of multistage-responsive nanocomplexes (MSNs) based on polymeric nanocapsules and alginate. MSNs possess the pH responsiveness in the stomach, the enzyme responsiveness in the colonic lumen, and the redox responsiveness in the cytoplasm. In vivo imaging results showed that MSNs reach the colon within 2 h and effectively release miR-320 nanocapsules in the colonic lumen. The nanocapsules can further deliver miR-320 to the submucosal layer and even the muscular layer. Moreover, MSNs decreased the activity of myeloperoxidase and proinflammatory cytokines and exhibited anti-inflammatory activity by inhibiting the phosphorylation of IκBα and AKT, reducing colonic inflammation and enhancing mucosal repair. Therefore, MSNs can successfully alleviate UC by improving the accumulation and distribution of oral nucleic acid drugs in the colon, promoting the clinical translational application of nucleic acid drugs in the treatment of UC.



KEYWORDS: *nucleic acid drug, oral delivery, multistage-responsive nanocomplexes, ulcerative colitis, distribution*

1. INTRODUCTION

Ulcerative colitis (UC) is a kind of chronic inflammatory bowel disease characterized by nonspecific inflammation of the colon and impaired mucosal repair, and its incidence has risen rapidly in recent years.[1] The combination of both dysfunctions can result in life-threatening complications, such as colorectal cancer.[2] Conventional strategies for UC treatment are mainly restricted to control inflammation using anti-inflammatory drugs and immunosuppressive agents,[3] showing low therapeutic effects.[4] To date, the clinical objective of high-efficiency UC therapy is to not only inhibit inflammation but also realize colon mucosal healing.

Combination therapy taking advantage of multiple drugs that can respectively act on the corresponding target cells can be a better strategy for UC. As an example, Xiao et al. adopt RNA interference to downregulate tumor necrosis factor-alpha (TNF-α) in macrophages for the inhibition of inflammation and simultaneously use interleukin-22 (IL-22) to stimulate colon epithelial cells for the mucosal healing, showing much better efficacy in treating UC compared with the single drug-based treatment.[5] Once drugs act on nontarget cells, however, they may cause serious side effects. For example, it has been proved that sulfasalazine can efficiently inhibit inflammation by regulating intestinal immune cells, but it would damage colon epithelial cells, potentially aggravating UC and causing patients diarrhea and abdominal pain.[6] Therefore, there is an urgent need to exploit novel therapeutic strategies to address the limitations of current treatments.

Gene therapy based on nucleic acid drugs, to date, has been an alternative preclinical treatment strategy for UC.[7] Compared with clinical UC therapy medicines, nucleic acid drugs can provide multitargeted regulation, which makes them versatile.[8] For example, miR-146 not only inhibits M1

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