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Drug delivery strategies in the therapy of inflammatory bowel disease ☆,☆☆

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ABSTRACT

Inflammatory bowel disease (IBD) is a frequently occurring disease in young people, which is characterized by a chronic inflammation of the gastrointestinal tract. The therapy of IBD is dominated by the administration of anti-inflammatory and immunosuppressive drugs, which suppress the intestinal inflammatory burden and improve the disease-related symptoms. Established treatment strategies are characterized by a limited therapeutical efficacy and the occurrence of adverse drug reactions. Thus, the development of novel disease-targeted drug delivery strategies is intended for a more effective therapy and demonstrates the potential to address unmet medical needs.

This review gives an overview about the established as well as future-oriented drug targeting strategies, including intestine targeting by conventional drug delivery systems (DDS), disease targeted drug delivery by synthetic DDS and disease targeted drug delivery by biological DDS. Furthermore, this review analyses the targeting mechanisms of the respective DDS and discusses the possible field of utilization in IBD.

Contents

1. Introduction . . . 0
1.1. A brief insight in inflammatory bowel disease . . . 0
1.2. Paul Ehrlich's concept of drug targeting . . . 0
1.3. The therapeutic benefit of targeted drug delivery strategy in IBD . . . 0
1.4. Targeted drug delivery strategy in IBD — what are the basic requirements for success? . . . 0
2. Conventional drug delivery strategies . . . 0
2.1. Parenteral route of administration . . . 0
2.2. Rectal route of administration . . . 0
2.3. Peroral route of administration . . . 0
2.3.1. Coated drug delivery systems . . . 0
2.3.2. Time dependent drug release systems . . . 0
2.3.3. Prodrug design . . . 0
2.3.4. Embedding in polysaccharide matrices . . . 0
2.3.5. Osmotic-controlled drug delivery systems . . . 0
2.3.6. Pressure-controlled drug delivery systems . . . 0
2.4. Self micro-emulsifying drug delivery systems (SMEDDS) . . . 0
3. Disease targeted drug delivery by synthetic drug delivery systems . . . 0
3.1. Healthy and diseased intestinal barrier and their role in drug targeting strategies . . . 0
3.2. Polymeric drug carriers . . . 0
3.2.1. Micro- and nanoparticles . . . 0
3.2.2. Muco-adhesion . . . 0
3.2.3. Bio-adhesion . . . 0

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3.2.4. Muco-penetration . . . 0
3.2.5. Uptake by M cells . . . 0
3.2.6. Endothelial targeting via synthetic drug delivery systems . . . 0
3.3. Liposomal drug carriers . . . 0
3.3.1. Endothelial targeting via liposomal drug delivery systems . . . 0
3.4. Small interference RNA therapy by polymeric and liposomal drug carriers . . . 0
4. Disease targeted drug delivery by biological drug delivery systems . . . 0
4.1. Bacteria-based drug delivery systems . . . 0
4.1.1. Recombinant bacteria . . . 0
4.1.2. Bacteria-attached-nanoparticles . . . 0
4.1.3. Bacterial ghosts . . . 0
4.2. Eukaryotic-based drug delivery system . . . 0
4.2.1. Red blood cells . . . 0
4.2.2. Macrophages . . . 0
4.2.3. Lymphocytes . . . 0
4.3. Synthetic eukaryotic cells . . . 0
5. Comparison of different drug delivery strategies . . . 0
6. New challenges in regulatory and scientific aspects . . . 0
7. Conclusion . . . 0
Conflict of interest . . . 0
References . . . 0

1. Introduction

1.1. A brief insight in inflammatory bowel disease

Crohn's disease (CD) and ulcerative colitis (UC) collectively referred to as inflammatory bowel disease (IBD), are characterized as a chronic inflammatory disease of the gastrointestinal tract with unknown aetiology (see Fig. 1). IBD is very common in the Western industrialized countries and it is estimated that 1.4 million people in the United States as well as 2.2 million people in Europe are affected by IBD [1]. The prevalence of 50–250/100.000 per year is similar in CD and UC [2,3]. The onset of IBD is verifiably associated with a complex and elusive interaction between genetic and environmental factors, such as oral contraceptive use, breastfeeding, infections, microbial agents, smoking, appendectomy, sanitation and stress [4]. Genetic alterations in intestinal barrier function, innate and acquired immunity, autophagy, apoptosis and signal transduction modulate the onset, severity and course of IBD [5].

The clinical picture of CD and UC is associated with a variety of intestinal complaints, such as bloody diarrhoea, fever, weight loss, abdominal pain, or vomiting. Extra-intestinal manifestations of CD and UC are relatively common and affect mostly joints, skin, eyes and bile ducts [6–8]. Presently, a permanent cure for IBD is not established, so a lifetime administration of drugs for the maintenance of the health-related quality of life is often necessary.

The treatment of UC and CD is dependent on the severity of IBD, on the disease subtype, on pre-existing illnesses and on the patient's tolerance of drugs. The most common classes of drugs are anti-inflammatory and immunosuppressive agents. The treatment pyramid of UC and CD include 5-aminosalicylates (5-ASA, mainly in UC) and corticosteroids as the mainstays for therapy. 5-ASA drugs, like mesalazine or olsalazine, are mainly used for the treatment of mild attacks and for the maintenance of remission in UC. Corticosteroids, like prednisolone are more effective drugs in the treatment of moderate to severe IBD [9]. Immunosuppressive agents, like azathioprine, 6-mercaptopurine, methotrexate, calcineurin inhibitors and most important anti-TNF-α-antibodies have an important role in the treatment of severe disease stages [10]. Refractory and fulminate disease stages may require surgery as an acceptable option to improve the medical conditions of these IBD patients [11].

A major challenge in the therapy of IBD is the prevention and the reduction of drug-related side effects. Most drugs in the treatment of IBD have a large list from mild to severe adverse drug reactions, including mortality. Corticosteroids show short- and long-term side effects including hypertension, hyperglycaemia, osteoporosis, glaucoma, depression and many others [12]. The treatment with immunosuppressive agents is unmistakably associated with an increased susceptibility to infections and malignoma [13,14]. In consequence, the treatment of IBD requires a balance between high therapeutic efficacy and the risk of adverse drug reactions, because short- and long-term adverse drug reactions may deteriorate the health-related quality of life and thus may counteract a successful therapy of the condition [15,16].

1.2. Paul Ehrlich's concept of drug targeting

Paul Ehrlich (1854–1915) was a German physician, scientist and Nobel laureate in physiology or medicine (1908) and the first one who designed the concept of a drug targeting of active agents to pathogens and cancer cells to maximize the therapeutic efficacy with a simultaneous prevention/reduction of side effects [17].

More than a hundred years later, this concept is as topical as never before. Many efforts in the research of cancerous tumours and autoimmune diseases were performed to design such drug targeting systems. New insights in the pathophysiology of IBD make it possible to develop new and innovative drug carrier systems, including disease targeted drug delivery by synthetic or biological drug delivery systems. Many efforts and attempts have been made to ensure a more effective disease-oriented therapy in IBD compared to the established treatment options. The aspiring and rising natural sciences enable the development of innovative drug carriers, which can accumulate efficiently into inflamed intestinal areas via luminal or endothelial pathways. Sufficient drug carriers demonstrate advanced potential for a targeted drug as well as gene therapy in IBD specific to the site of inflammation.

1.3. The therapeutic benefit of targeted drug delivery strategy in IBD

The therapy of IBD via targeted drug delivery in the first instance is addressed to patients with a mild to moderate disease activity. The strategy of targeted drug delivery is primarily suitable for an effective medical treatment of luminal IBD manifestation, like isolated ileocecal disease in CD or distal colitis in UC. Whereas a discontinuous and extensive localization of inflammation, like from mouth to rectum in CD patients, is treatable via targeted drug delivery systems (see Fig. 2). An effective treatment strategy via targeted drug delivery systems is more promising compared to the present and established drug delivery strategies. Such novel targeted drug delivery systems offer a range of

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