Journal of Controlled Release 151 (2011) 220–228

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Review

Endosomal escape pathways for delivery of biologicals

Amir K. Varkouhi [a], Marije Scholte [b], Gert Storm [a], Hidde J. Haisma [b,*]

[a] Department of Pharmaceutics, Utrecht Institute for Pharmaceutical Sciences, Faculty of science, University of Utrecht, Sorbonnelaan 16, 3584 CA Utrecht, The Netherlands
[b] Pharmaceutical Gene Modulation, Groningen Research Institute for Pharmacy, A. Deusinglaan 1, 9713 AV Groningen, The Netherlands

ARTICLE INFO

Article history:
Received 6 July 2010
Accepted 19 October 2010
Available online 13 November 2010

Keywords:
Endosomal escape
Cytosolic delivery
Protein
Gene
siRNA

ABSTRACT

Despite continuous improvements in delivery systems, the development of methods for efficient and specific delivery of targeted therapeutic agents still remains an issue in biological treatments such as protein and gene therapy. The endocytic pathway is the major uptake mechanism of cells and any biological agents, such as DNA, siRNA and proteins. These agents become entrapped in endosomes and are degraded by specific enzymes in the lysosome. Thus, a limiting step in achieving an effective biological based therapy is to facilitate the endosomal escape and ensure cytosolic delivery of the therapeutics.

Bacteria and viruses are pathogens which use different mechanisms to penetrate the membranes of their target cells and escape the endosomal pathway. Different mechanisms such as pore formation in the endosomal membrane, pH-buffering effect of protonable groups and fusion into the lipid bilayer of endosomes have been proposed to facilitate the endosomal escape. Several viral and bacterial proteins have been identified that are involved in this process. In addition, chemical agents and photochemical methods to rupture the endosomal membrane have been described. New synthetic biomimetic peptides and polymers with high efficacy in facilitating the endosomal escape, low pathogenicity and toxicity have been developed. Each strategy has different characteristics and challenges for designing the best agents and techniques to facilitate the endosomal escape are ongoing. In this review, several mechanisms and agents which are involved in endosomal escape are introduced.

© 2010 Elsevier B.V. All rights reserved.

Contents

* Corresponding author. Tel.: +31 50 3637866; fax: +31 50 3637953.
E-mail address: H.J.Haisma@rug.nl (H.J. Haisma).

0168-3659/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.jconrel.2010.11.004

1. Introduction

The success in the application of nanomedicines and gene therapy is largely dependent on the development of the vectors that can selectively and efficiently deliver the gene or therapeutic agents to the target cells with minimal toxicity [1,2].

Despite the efforts given in vector technology, development of methods for efficient and protected delivery of therapeutic agents to the target cells still remains a main issue [3,4]. On the other hand, principal considerations to design safe and reliable delivery systems led to the development of physically targeted delivery vehicles [5]. Despite the potent immunogenicity of viral vectors, their developed cell entry mechanism and high transfection efficiency in both dividing and non-dividing cells is desirable [6,7].

Nowadays, non-viral vectors with minimal toxicity and immunogenicity have been developed to mimic the receptor-mediated cell entry mechanism of viruses. Although the early attempts to deliver biologicals, by application of non-viral vectors that follow the receptor-mediated endocytosis have fallen short of the goal of efficient delivery, mainly because of inability to escape the endosomal pathway [8,9].

Several approaches have been tested to facilitate the early release of therapeutic cargos from the endosomal pathway into the cytosol. These approaches were based on identified mechanisms for endosomal escape, like pore formation in the endosomal membrane, the pH-buffering effect and conformational changes in endosomal escape enhancers. These include the use of viral proteins, bacterial proteins and especially synthetic biomimetics as endosomal-releasing agents in nucleic acid and protein delivery systems.

New synthetic biomimetic peptides are used as endosomal escape reagents; however, their usage is limited because of several potential problems and disadvantages such as immunogenicity and low stability. Considering these problems and also inspired by the principle behind these biological strategies, synthetic polymers that contain pH-sensitive chemical functionalities that mimic those of biological delivery systems have been designed and tested as new endosomal-releasing components [10].

However, an optimal agent for endosomal escape should have high efficiency with no toxicity.

The endocytic pathway (Fig. 1) is one of the uptake mechanisms of cells. This pathway is composed of vesicles known as endosomes with an internal pH around 5 that mature in a unidirectional manner from early endosomes to late endosomes before fusing with intracellular organelles called lysosomes which contain certain digestive enzymes [11].

Thus, particles entering the cells via the endocytic pathway become entrapped in endosomes and eventually end up in the lysosome, where active enzymatic degradation processes take place. This results in a limited delivery of therapeutic agents to the intracellular targets. Therefore, many compounds with a promising potential in vitro, cannot be applied in vivo because of bioavailability problems. So far, several attempts have been made to deliver various macromolecular components directly into the cytosol, escaping the endocytic pathway to protect them from degradation [12–14].

While many viruses have evolved quite efficient systems for endosomal release [15,16], the situation is different for non-viral vectors, where in many cases the lack of endosomal escape is a major obstacle for efficient biological delivery, implying that more efficient methods for endosomal release would lead to improvements in designing synthetic transfection systems. In contrast to synthetic vectors, viral vectors are known to be efficient both for in vitro and in vivo applications [17,18]. However, in the case of the adeno-associated viruses, intracellular barriers such as the endosomal membrane have been described [19,20] which highlights the potential beneficial effects of the enhanced endosomal escape for viruses [21–24]. The importance of preventing the degradation of therapeutics in the endosomes/lysosomes has been exemplified by the use of lysosomotrophic agents such as chloroquine which prevents the activity of lysosomal enzymes [25,26]. In this review, several mechanisms which have been proposed for endosomal escape as well as the agents which are known to have the endosomal release properties are introduced.

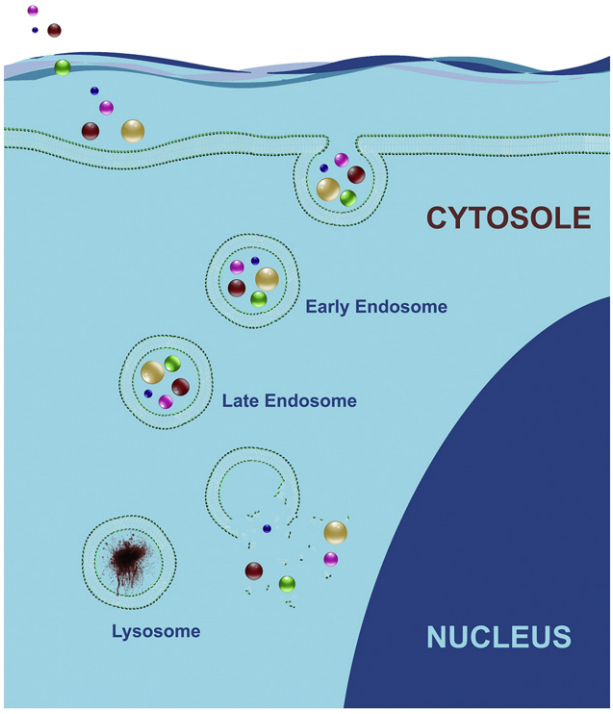

Fig. 1. An artistic representation depicting the internalization of therapeutics into the cell through endocytosis and subsequent endosomal escape. Early endosomes consist of the vesicles containing the therapeutics coming from the cell surface. Late endosomes which are thought to mediate a final set of sorting events prior to interaction with lysosomes, receive the internalized materials from early endosomes. Lysosomes as the last parts of the endocytic pathway contain the hydrolytic enzymes which digest the contents of the late endosomes. Therefore, the endosomal release of the therapeutics is necessary before lysosome mediated digestion of the therapeutics.

2. The mechanisms of endosomal escape

Understanding the mechanisms of viral and bacterial escape from endosomes is important for improving cellular delivery of therapeutic agents. The mechanisms of these processes have been intensely studied. Enveloped and non-enveloped viruses have evolved mechanisms for membrane penetration, which are essential for endosomal escape. In enveloped viruses, the fusion of the viral envelope with the lipid bilayer may occur and non-enveloped viruses either lyse the vesicular membrane or generate a pore through it to allow escape of the viral genome into the cytosol [27,28].

In the case of bacteria, pore formation is one of the basic methods for endosomal escape which is mediated by bacterial exotoxins [29]. The acidic pH of endosomes triggers the endosomal escape by affecting the peptides and leading to interactions between the peptides and the lipid bilayer of the endosomes. In some cases these peptides form a random coil structure at pH 7 and as the pH decreases, some domains of amino acids are protonated leading to the transition into an amphipathic α-helical conformation. Consequently, the peptides can interact with phospholipid membranes to form pores or induce membrane fusion and/or lysis [30].

In the following paragraphs a number of mechanisms proposed for endosomal escape are described.

Download English Version:

https://daneshyari.com/en/article/1425234

Download Persian Version:

https://daneshyari.com/article/1425234

Daneshyari.com