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Designing Pathway-Specific Delivery Systems for Pulmonary Delivery of Biotherapeutics: Exploiting Endocytosis Ligands and Intracellular Protein Delivery

Loren Cordain*

Department of Food Science and Human Nutrition, Colorado State University Fort Collins, Colorado 80523 USA

Introduction

Delivery of biotherapeutics, such as proteins *via* the pulmonary route is a promising non-invasive option. However, obstacles exist for macromolecular biotherapeutic delivery into and across lung epithelium. One potential solution is to leverage natural biological transport pathways present at mucosal surfaces to create pathway-specific delivery systems. Previously, we utilized this approach to design nano-sized systems decorated with cyanocobalamin (B12) ligands, which facilitated their cellular internalization and transport across the intestinal and airway mucosa epithelium. Biotin is another potential endocytosis ligand, as the sodium-dependent multivitamin transporter (also known as a biotin receptor) is expressed in epithelial, endothelial and cancer cells. Biotin targeting has been successful in prodrug conjugation approaches, micelles-based systems and surface-decorated polymeric nanoparticles, which have increased cellular delivery of active compounds. However, understanding the cellular internalization pathway(s) and transport is essential for designing effective new technology platforms. Additionally, there is growing interest in intracellular protein delivery for innovative therapeutics, as demonstrated by recent research, including the loading of anti-c-MYC antibodies to nanocarriers to suppress c-MYC in solid tumors and inhibit tumor growth, or the use of guanidinium-functionalized homopolymers to create nanocarriers for a 20-mer glutamate tagged model GFP protein.

Description

In recent years, there has been a growing interest in intracellular protein delivery as a way to create innovative therapeutics. However, the delivery of proteins into cells presents a significant challenge due to their large size and poor cell membrane permeability. In order to overcome this challenge, researchers have developed various strategies, including the use of biotin targeting and polymer complexes, for the delivery of proteins across cellular barriers, particularly in the lung. Biotin targeting has been shown to be a promising approach for intracellular protein delivery. The sodium-dependent multivitamin transporter, also known as a biotin receptor, is expressed in epithelial, endothelial and cancer cells. Researchers have utilized this receptor to target biotinylated proteins to the intracellular space, by exploiting endocytosis pathways that naturally occur in these cells. This has been achieved by developing prodrug conjugation approaches, micelles-based systems and surface-decorated polymeric nanoparticles, which have increased cellular delivery of active compounds.

***Address for Correspondence:** Loren Cordain, Department of Food Science and Human Nutrition, Colorado State University Fort Collins, Colorado 80523 USA, E-mail: lorencordain@gmail.com*

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One recent study demonstrated the potential of biotin targeting for lung delivery of proteins. The study utilized biotinylated ovalbumin (OVA) loaded onto poly(ethyleneimine)-co-poly(ethylene glycol) (PEI-PEG) polymer complexes, which were shown to enhance OVA uptake and intracellular delivery in lung epithelial cells. The complexes were designed to take advantage of the natural endocytosis pathways present in the lung epithelium, which facilitated their uptake and transport across the cellular barrier. This study provides a promising strategy for the delivery of biotinylated proteins to the lung for therapeutic purposes. Another promising approach for intracellular protein delivery is the use of polymer complexes. These complexes are formed by the self-assembly of polymers and offer a variety of advantages over other delivery systems, such as high stability, biocompatibility and the ability to protect cargo from degradation. Moreover, polymer complexes can be functionalized with targeting moieties, such as biotin, to facilitate their cellular internalization.

Recent research has shown the potential of polymer complexes for the intracellular delivery of proteins in the lung. For example, a recent study utilized guanidinium-functionalized homopolymers to create nanocarriers for a 20-mer glutamate tagged model green fluorescent protein (GFP). The polymer-GFP complexes were shown to be highly stable and biocompatible and facilitated the efficient intracellular delivery of GFP in lung epithelial cells. Furthermore, the complexes demonstrated significant potential for targeted protein delivery, as they were functionalized with biotin to facilitate their cellular internalization. The delivery of proteins into cells presents a significant challenge, particularly for lung delivery. However, recent advancements in biotin targeting and polymer complexes offer promising strategies for intracellular protein delivery in the lung. These strategies take advantage of the natural endocytosis pathways present in lung epithelial cells and demonstrate the potential for highly efficient and targeted intracellular protein delivery.

Pulmonary delivery is a promising and non-invasive approach for delivering biotherapeutics, including protein therapeutics. However, delivering macromolecular biotherapeutics into and/or across lung epithelium faces significant biological barriers. To overcome these barriers, exploiting natural biological transport pathways present at mucosal surfaces which facilitate the internalization of nutrients and endogenous macromolecules, can be a potential strategy for designing pathway-specific delivery systems. Endocytosis is a cellular process that internalizes extracellular material by forming a vesicle around the material, which is then brought inside the cell. This process can be exploited for designing pathway-specific delivery systems by using endocytosis ligands. Biotin is one such ligand that has been found to target the sodium-dependent multivitamin transporter, also known as the biotin receptor, which is expressed in epithelial, endothelial and cancer cells. Biotin targeting has been used in prodrug conjugation approaches, micelles-based systems, as well as surface-decorated polymeric nanoparticles to increase cellular delivery of active compounds. However, the cellular internalization pathways and transport mechanisms of these systems need to be elucidated to improve their design.

Intracellular protein delivery is an emerging field that has gained significant attention in recent years. This approach involves the delivery of proteins into the cytosol or other cellular compartments to modulate cellular function or treat diseases. For example, loading anti-c-MYC antibody to nanocarriers has been shown to suppress c-MYC in solid tumors and inhibit tumor growth. Similarly, creating nanocarriers from guanidinium-functionalized homopolymers

assembly with a 20-mer glutamate tagged model GFP protein has been shown to deliver proteins intracellularly [1-5].

Conclusion

Combining endocytosis ligands and intracellular protein delivery can provide a synergistic effect for designing effective pulmonary delivery systems. For instance, designing cyanocobalamin (B12) ligand-decorated nano-sized systems has been shown to increase cellular internalization into and transport across, the intestinal and airway mucosa epithelium. Similarly, designing biotin-decorated nanoparticles for pulmonary delivery can potentially increase cellular internalization and transport of biotherapeutics. Furthermore, incorporating intracellular protein delivery strategies can allow for the delivery of therapeutic proteins intracellularly, thereby enhancing their efficacy. Designing pathway-specific delivery systems for pulmonary delivery of biotherapeutics is a challenging but promising area of research. Exploiting endocytosis ligands, such as biotin and intracellular protein delivery can provide a potential strategy for designing effective pulmonary delivery systems. Further research is needed to elucidate the cellular internalization pathways and transport mechanisms of these systems to improve their design and efficacy. Ultimately, the development of effective pulmonary delivery systems can have a significant impact on the treatment of respiratory diseases and other systemic diseases that require non-invasive delivery of biotherapeutics.

Acknowledgement

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Conflict of Interest

None.

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