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Improving the efficacy of inhaled drugs in cystic fibrosis: Challenges and emerging drug delivery strategies ☆

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ABSTRACT

Cystic fibrosis (CF) is the most common autosomal recessive disease in Caucasians associated with early death. Although the faulty gene is expressed in epithelia throughout the body, lung disease is still responsible for most of the morbidity and mortality of CF patients. As a local delivery route, pulmonary administration represents an ideal way to treat respiratory infections, excessive inflammation and other manifestations typical of CF lung disease. Nonetheless, important determinants of the clinical outcomes of inhaled drugs are the concentration/permanence at the lungs as well as the ability of the drug to overcome local extracellular and cellular barriers. This review focuses on emerging delivery strategies used for local treatment of CF pulmonary disease. After a brief description of the disease and formulation rules dictated by CF lung barriers, it describes current and future trends in inhaled drugs for CF. The most promising advanced formulations are discussed, highlighting the advantages along with the major challenges for researchers working in this field.

Contents

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1. Introduction

Cystic fibrosis (CF) is the most common life-shortening genetic disorder of Caucasians caused by mutations in the CF transmembrane conductance regulator (CFTR) [1]. CFTR is expressed in epithelia throughout the body, and affects secretory functions in a number of organs, including the lungs, liver, gut and sweat glands. In the lungs, defective CFTR reduces the epithelium sodium channel (ENaC) function leading to an altered fluid and electrolyte composition of airway secretions [1–3]. This condition predisposes CF patients to recurrent/persistent bacterial infections and neutrophil-dominated endobronchial chronic inflammation, which are still considered the primary cause of bronchiectasis, respiratory failure and consequent death in patients affected by CF.

For long time the pillar of CF treatment has been symptomatic therapy aimed at attenuating disease progression and delaying the onset of irreversible lung damage through the use of different drugs (*i.e.*, antibiotics, anti-inflammatory drugs, bronchodilators, mucolytics and osmotic agents) with complicated daily regimens [4,5]. Nevertheless, novel pharmacological agents, such as nucleic acid-based therapeutics (*e.g.*, oligonucleotides, siRNA, gene), are being developed to selectively target the underlying causes of the CF lung pathology and to widen the available arsenal of drugs aiming to counteract the effects of CFTR on the airways rather than the resulting symptoms [6,7]. Despite dramatic improvements in patient survival, good health outcomes are often accompanied by several adverse effects, low patient adherence to the therapy and poor quality of life [8,9].

Although dated back of some years [10], the opportunity to selectively target a drug to the lungs remains a fascinating option to strongly limit ubiquitous distribution of systemically, and often chronically, administered drugs used to treat CF pulmonary disease [5,11,12]. In fact, local drug delivery may allow maximum pharmacological targeting, and thus therapeutic efficacy, while maintaining low drug levels at non-target sites. As a consequence, increasing research efforts have been devoted to the development of new inhalation devices and advanced drug delivery formulations intended for local treatment of CF pulmonary disease [13–16].

Conventional jet nebulizer devices are often preferred in the clinical practice, although some negative aspects include liquid formulation, time needed for drug administration, subsequent cleaning of the equipment and, sometimes, device portability [17]. Nonetheless, new nebulizer systems strongly reduce treatment time and also deposition is greater than that achieved with conventional nebulizers [16]. On the other hand, breath-actuated dry powder inhalers (DPIs) are portable and considered the choice to limit drug loss and to control delivered dose, thus increasing drug lung availability [14,18]. However, DPIs demand for dry powders with peculiar technological features, affecting drug deposition in the established region of the lungs [19]. Furthermore, the ability of patients to use DPIs, as well as efficacy of CF treatments, may vary by age [8].

Whatever the device employed, optimal inhalable formulations should be able not only to deliver the intact drug in CF lung, but also to shield its interactions with the lung environment and, when desired (*e.g.*, nucleic acid therapeutics), to enhance uptake by lung epithelial cells [20,21]. This aspect is especially critical in CF, where submucosal glands and distal airways are obstructed by thick tenacious secretions, resulting in a failure of normal mucociliary clearance and defective airway defense mechanism against bacteria [22,23]. CF mucus may strongly limit the amount of drug reaching the target, such as lung epithelial cells, macrophages or bacterial cells [13,24]. The way to the target is even more complicated for inhaled antimicrobial agents due to the biofilm-like mode of growth adopted by *Pseudomonas aeruginosa*, which chronically infects CF lung [12]. In fact, the slow penetration and possible entrapment within the biofilm can strongly reduce drug availability in proximity of bacteria colonies [25,26].

Advanced delivery strategies based on nano- and micro-particulate systems are currently being investigated for pulmonary delivery to improve drug transport to its target [15,27–30]. Amid them, lipid-based vesicles, such as liposomes, are the most extensively investigated carriers for delivery of antimicrobial agents in CF lung, and some products are now facing the market (*e.g.*, Arikace®, Lipoquin®) [30]. On the other hand, a fundamental advantage of polymer systems relies on their ability to exert a temporal control over the released dose [27,29,31]. This is crucial to reduce the number of administrations and to increase patient adherence to the complex therapeutic regimens for chronic lung diseases. Furthermore, it has been recently demonstrated that the potential of polymer particles to penetrate airway mucus can be tuned through special engineering of particle size and surface properties [32–34].

This review focuses on emerging delivery strategies used for local treatment of CF pulmonary disease. After a brief description of CF lung disease and formulation rules dictated by CF lung barriers, it describes current and future trends in inhaled drugs for CF. The most promising advanced formulations are discussed, highlighting the advantages along with the major challenges for researchers working in this field.

2. General considerations on CF lung disease

CF is a complex multisystem disease caused by the defect in a single gene [2]. The faulty gene was identified in 1989, and encodes an epithelial ion channel known as the CFTR, which regulates chloride ion and water movements [1]. Since CFTR is expressed throughout the body, CF disease affects multiple systems (*i.e.*, lungs, pancreas, gastrointestinal systems). Nevertheless, pulmonary disease is still the most important cause of CF morbidity and mortality.

In the lungs, CFTR is detectable on the apical membrane of ciliated cells within the gland ducts and in the superficial epithelium of healthy individuals. The most widely accepted explanation for the clinical effects of CFTR deficiency in the lung is known as “the low volume hypothesis” (Fig. 1) [1–3]. Since CFTR normally down-regulates ENaC in the lungs, the loss of CFTR function leads to ENaC over-activation. This results in depletion of airway surface liquid, which is essential to support ciliary stability and functioning, ciliary collapse and consequent decreased mucociliary transport. Retained secretions encourage bacterial adherence, chronic neutrophilic infection, and a vicious cycle of persistent/recurrent lung infection, chronic inflammation and tissue destruction. The hallmark of the condition is progressive and irreversible bronchiectasis and respiratory failure.

The dominant pathogen in CF airways is *P. aeruginosa*, although other microorganisms (*e.g.*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Burkholderia cepacia*) may play an important role in the pathogenesis of lung function decline [5]. While *H. influenzae* and *S. aureus* colonize the lungs early in life, sometimes causing recurrent infection, *P. aeruginosa* chronically infects 80% of CF patients by late adolescence [2,35]. *P. aeruginosa* possesses a large genetic diversity and a number of features that contribute to its ability to persist in the environment, and to its pathogenicity. In the environment, it exists as a single motile bacteria, the so-called “non-mucoid form” of the organism. As colonization progresses, the cell density and the collective growth pattern of *P. aeruginosa* change, thus improving its capacity for survival.

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