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Latest Advances in Gene Therapy in Management of Cystic Fibrosis Lung Disease, Literature Review

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Abstract

Cystic fibrosis is an autosomal recessive disease that affects ion channels on epithelial cells. This leads to thicker and dysfunctional secretions. This can be evident when looking at the major symptoms of CF patients, which include recurrent respiratory tract infections and pancreatic insufficiency. The current management options for CF are either to manage the symptoms or modulate the existing defective genes. Gene therapy aims to correct dysfunctional genes as a way to cure the disease. We aimed to review the literature looking into gene therapy for cystic fibrosis, along with the advancements and current limitations. PubMed database was used for articles selection, papers were obtained and reviewed. There are multiple options for gene therapy in cystic fibrosis. This includes either introducing wild, working genes to the epithelial cells of the respiratory tract, or editing the defective genes. Gene replacement therapy is limited due to the nature of airway administration and the harsh environment of the airway of CF patients. Gene-editing therapy, however, is still under heavy research as it may offer a potential cure for this disease.

Keywords: Cystic fibrosis, Cystic fibrosis management, Recent updates, Gene therapy

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Introduction

Cystic fibrosis (CF) is the most common life-shortening autosomal recessive disease among Northern European descents. At present, more than 100,000 living individuals suffer from this disease (Klimova *et al.*, 2017). This disease affects the lungs and respiratory tract mainly, but also extends into the gastrointestinal tract, pancreas in the form of diabetes mellitus and insufficiency, and reproductive functions (Elborn, 2016; Priyadi *et al.*, 2019; Ahmed *et al.*, 2020). The management of this condition has been challenging ever since its pathophysiology was moderately understood. However, it has received many advances in the latest years, being the most common life-shortening inherited disease (Maule *et al.*, 2020). In this paper, we will have a quick review of CF, along with the latest advances in treatment and possible future management modules.

Materials and Methods

PubMed database was used for articles selection, and the following keys were used in the mesh (cystic fibrosis) AND (gene therapy). In regards to the inclusion criteria, the articles were selected based on the inclusion of one of the following topics; Cystic Fibrosis; CFTR; CRISPR-Cas; genome editing. Exclusion criteria were all other articles that did not have one of these topics as their primary endpoint.

Review

Cystic fibrosis is typically diagnosed if the patient demonstrates clinical disease in one or more organ systems and has a positive sweat chloride test (Brown *et al.*, 2017). Genetic studies have grouped multiple genes that cause or are associated with CF into one category, cystic fibrosis transmembrane conductance regulator (CFTR) genes (Cutting, 2015). These genes are grouped even further into disease-causing and not disease-causing (Cutting,

2015). The major aspect of the pathogenesis, which is still incompletely understood, is that mutations in CFTR genes lead to thicker and disturbed secretions (Cutting, 2015; Brown *et al.*, 2017). This effect becomes clear when we look at CF patients. Thicker pancreatic secretions will lead to pancreatic insufficiency, and disturbed lung secretions will lead to chronic lung infection since fluid clearing mechanisms are not working properly due to the thick secretions. Those two organs, lungs, and pancreas, are the most common symptoms in CF patients (Mall & Hartl, 2014; Cutting, 2015; Ratjen *et al.*, 2015; Brown *et al.*, 2017). The disease affects those of Northern European descent more than other populations (Ratjen *et al.*, 2015; Elborn, 2016; Klimova *et al.*, 2017). However, the disease is also being recognized to affect other populations as well, albeit to a lesser percentage (Stewart & Pepper, 2016; Guo *et al.*, 2018).

CF, as previously mentioned, affects secretions content. Thus, the most common presenting complaints are recurrent upper and lower respiratory tract infections, pancreatic insufficiency, infertility in male patients, and multiple musculoskeletal disorders due to multiple factors such as malabsorption, physical inactivity, and glucocorticoid therapy (Cutting, 2015; Brown *et al.*, 2017). The diagnosis requires two criteria, clinical and laboratory diagnosis. The clinical criteria require either a classical symptom consistent with CF in at least one organ system, a positive newborn screening test, or having a sibling with CF. The laboratory criteria require a demonstration of a defective CFTR gene or its function, this includes elevated sweat chloride test ≥60mmol/L or the presence of two disease-causing mutations in the CFTR gene on both parental alleles (Farrell *et al.*, 2017). In areas where the disease is prevalent, screening programs have been established to detect individuals that carry the disease much earlier in their life, this is to offer treatment and therapies much earlier. In the US, all newborns are subjected to the screening test for CF. However, it is important to know that newborn screening is not a diagnostic test, rather a method to detect who should receive diagnostic testing and who does not (Fox *et al.*, 2020). The management of CF lung disease had two goals, improve chest functions and reduce infections (Brown *et al.*, 2017). Chest function improvement has been done with chest physiotherapy, airway clearance agents such as DNase, and exercise (Ratjen *et al.*, 2015; Brown *et al.*, 2017; Ding & Zhong, 2020). Preventing chest infections has been done with vaccinations and other infection control measures (Ratjen *et al.*, 2015; Elborn, 2016; Brown *et al.*, 2017). CFTR modulators have been used and proven to improve lung functions and quality of life in multiple randomized controlled trials (Heijerman *et al.*, 2019; Middleton *et al.*, 2019).

Gene Therapy

The recent advancement of genetic engineering in living cells lead to an increase in the research into gene therapy for cystic fibrosis. This is evident by the increasing literature on this subject. Gene therapy is a wide topic and has shown promise in treating genetic disorders, such as blindness due to a defect in the *RPE65* gene (Russell *et al.*, 2017). There are multiple features for gene therapy when compared with current treatment options for CF, one of which is that gene therapy targets the disease at its origin, unlike current therapies that either treat the symptoms or work with defective CFTR gene products. Another point is that gene therapy is not mutation-class specific, meaning they don't require a specific mutation to be administered, rather they can be virtually given to all patients with CF (Griesenbach *et al.*, 2015). The options for gene therapy for CF can be grouped into two categories, gene replacement therapy, and genome editing (Quon & Rowe, 2016).

Gene replacement therapy aims to, as the name suggests, replace defective genes in lung tissue with normal functioning genes (Quon & Rowe, 2016). This can be achieved with the use of viral vectors or other carrier systems. However, the focus has been shifted towards non-viral vectors because of the reduced risk of immunogenicity as has been shown with viral vectors (Quon & Rowe, 2016; Guggino & Cebotaru, 2017; Yan *et al.*, 2019). While this method is potentially curative of the disease, it still suffers from major limitations. The major limitation for viral vectors is the development of an immune response to the viral particles, thereby reducing their efficacy (Guggino & Cebotaru, 2017). For other delivery systems, they have to overcome the harsh environment of the airways in cystic fibrosis, since the secretions are thick and clearing mechanisms are not working efficiently (Maule *et al.*, 2020). Moreover, due to the limitations of today's technology, the delivery of new CFTR genes requires periodic, repeated administrations of the gene due to the shedding of the epithelial layer in the airway (Steffin *et al.*, 2019). The integration of retroviral vectors may lead to eliminating repeated administration if they can fuse with the DNA of epithelial cells. However, the use of retroviral vectors has been reduced due to concerns raised by insertional mutagenesis reported in gene therapy trials (Maule *et al.*, 2020).

Genome editing is the second option for treating CF. This technique focuses on editing the defective CFTR genes, rather than introducing new, working genes to the cells (Quon & Rowe, 2016). The techniques involve either DNA editing or RNA editing (Quon & Rowe, 2016). DNA editing is achieved by the invention of the targeted molecular scissors. These scissors break the double-stranded DNA at the site of the defective CFTR gene, replace the defective genes, and then insert a working gene in its place (Arjmand *et al.*, 2019; Miah *et al.*, 2019; Yan *et al.*, 2019). This method has gained popularity since the invention of the CRISPR (clustered regularly interspaced short palindromic repeats) technology. CRISPR-Cas9, the programmable nuclease for CF, uses an RNA guide with a region complementary to the target DNA, thus allowing the nuclease to work only on the intended gene (Steffin *et al.*, 2019; Maule *et al.*, 2020). This is a powerful tool for the treatment of CF and has been shown to work efficiently in vitro (Schwank *et al.*, 2013). Additionally, CRISPR technology can be used for point mutations, since almost 60% of known genetic diseases are caused by a base mutation (Rees & Liu, 2018). However, base editing is now efficient in the treatment of CF since the disease is not caused by point mutations most of the time (Geurts *et al.*, 2020). RNA editing is potentially more applicable since it is easier to access and the edits are more efficient (Quon & Rowe, 2016; Steffin *et al.*, 2019; Maule *et al.*, 2020). However, the major limitation to RNA editing techniques is the lifelong

administration of the corrected RNA particles, unlike DNA editing (Quon & Rowe, 2016; Steffin *et al.*, 2019; Maule *et al.*, 2020).

Conclusion

Cystic fibrosis is an autosomal recessive disease that affects multiple organ systems. The defect in the CFTR gene leads to thickened and dysfunctional secretions. The main goals in the management of CF lung disease are to improve lung functions and reduce chronic infections. With current-day management options, the life expectancy for CF patients does not pass the 50 years mark. Gene therapy is a potentially curative therapy for CF and other genetic conditions. This can be achieved either by introducing a working gene to the epithelial cells or by editing the existing DNA or RNA. While they offer a potential cure, they suffer from multiple issues regarding administration and longevity. Researchers are still studying and optimizing these therapies in the hope of curing this debilitating disorder.

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