

Cystic fibrosis: current treatment and future direction

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ABSTRACT

Cystic fibrosis is an autosomal recessive genetic disorder, characterized by mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, leading to abnormality in the chloride channels of the mucus and sweat producing glands. Multiple organs systems are affected in this disorder, like respiratory systems and gastrointestinal tract, severely impacting the patient's quality of life, eventually leading on to several complications and death. Since the uncovering of the underlying genetic defect in cystic fibrosis (CF), our knowledge of the disease process has increased substantially, but we still lack a holistic approach to its management, which comprises of multiple facades, requiring both pharmacological and non-pharmacological or rehabilitative approaches. So far, the therapeutic options were limited to targeting the consequences and complications of the disease, such as respiratory infection, mucus retention, pancreatic insufficiency, etc., but now several promising therapies may be able to address the underlying pathology rather than its long-term effects. This review summarizes the current and upcoming pharmacological options for CF, such as those targeting the CFTR gene defect directly, including gene editing, CFTR correctors and potentiators; drugs targeting the epithelial sodium channels (ENaC inhibitors); repositioning of some existing drugs and evaluating their role in CF; and understanding the disease better by transcriptomic approaches and the role of gut microbiota in the disease process and severity.

Keywords: Cystic fibrosis, CFTR, Chloride ion channels, Sodium epithelial channels

INTRODUCTION

Cystic fibrosis (CF) is a progressive, autosomal recessive disorder characterised by severe damage to the various mucus, sweat and digestive juices secreting organs, such as lungs, sweat glands and pancreas, and currently affects more than 30,000 individuals in the United States. With an incidence of 1 in 3400 live births, about 900-1000 new cases of CF are diagnosed each year in US. Although CF is common in people of all races and ethnicity, it is most commonly diagnosed in Caucasians, with one in every 29 individuals a carrier of the CF gene mutation.¹⁻³

The gene defect in CF is in the cystic fibrosis transmembrane conductance regulator (CFTR), which functions as a chloride ion trafficker in the plasma

membrane of the epithelial cells of pancreas, liver, intestines, epididymis, sweat glands and lungs. Adequate chloride transport across ion channels helps maintain the movement of water in tissues, necessary for production of thin, free flowing mucus. Normal CFTR protein is exported from the endoplasmic reticulum (ER) to the Golgi apparatus for further processing, following which it gets transported to the cell membrane of acinar and other epithelial cells, where it regulates sodium and chloride ion transportation, thereby modulating the composition and amount of exocrine glands' secretion. It encodes an adenosine triphosphate gated chloride channel, which has different roles in different organ systems. CFTR aids in chloride secretion in the lungs and gastrointestinal tract, whereas it promotes the reabsorption of chloride in sweat glands. Failure or disruption of this mechanism causes

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