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Cystic fibrosis molecular targets and the therapeutic potential of monoclonal antibodies

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INTRODUCTION

The lungs and digestive tracts are both impacted by the autosomal, progressive genetic illness known as cystic fibrosis (CF). It is one of the most prevalent fatal autosomal recessive genetic illnesses among Caucasians, affecting an estimated 48,000 people in Europe and 30,000 people in the US. The Gulf region and Saudi Arabia both have high rates of the illness (CF). Its incidence in the Middle East is estimated to be 1 in 2000–5800 live births, with a prevalence of 1 in every 30,000–50,000 live births. Extrapolating from known cases to the general population, it has been estimated that 1 in 4243 Saudi Arabian children and adolescents will have the disease. The gene for the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) produces a protein. This protein functions as a channel across the cell membrane to control the production of digestive enzymes, perspiration, saliva, tears, and mucus [1].

DESCRIPTION

The development of thick and sticky mucus that clogs the ducts of organs where the CFTR protein is produced is caused by a mutation in the CFTR gene, which interferes with the flow of ions into and out of cells. Patients with CF consequently experience chronic lung infections and respiratory problems. Additionally, because the CFTR protein is expressed at numerous locations throughout the body, its expression is impaired, which leads to a variety of clinical symptoms. The lungs are the most often impacted organs by CFTR mutation, despite the fact that the CFTR protein affects many different body parts. Indeed, in the United States of America, lung disease is the main factor contributing to CF-related morbidity and mortality. The underlying causes of the thick, sticky mucus that is typical of CF patients include chronic lung inflammation, recurring infections, and issues with the cystic fibrosis transmembrane conductance regulator protein. It is believed that cystic fibrosis contributes to mucociliary dysfunction and airway dryness, both of which can lead to tonic epithelial sodium channel (ENaC) activity. Electrogenic sodium absorption that is amiloride-sensitive is driven by this action. Reducing ENaC, which reduces sodium absorption, can reverse the drying up of the airway surface fluids [2].

The CFTR protein typically forms a channel to transport chloride through the membranes of cells that line various surfaces in the body, including the surface of the lung. Chloride is a component of salt. But CF patients

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are unable to generate this channel. Chloride becomes trapped inside cells and is unable to draw in the fluids required to hydrate the cell surface when the protein is not working properly or when it is absent from the cell surface. Furthermore, in the absence of a functional CFTR, the epithelial Na+ channel is also dysregulated. Mucus obstruction, neutrophilic infiltration, and chronic bacterial infection are caused by mucus dehydration brought on by CFTR deficiency and increased ENaC activity. The outcome is a dehydration of the cell surface. Lack of the necessary fluids causes mucus to lose its moisture and thicken. The airways may suffer long-term consequences from this. One of the main innate immune defence systems in the respiratory tract, mucociliary clearance, is hampered by defective ion transport caused by the CFTR gene. The development of innovative treatments that are logically crafted to provide a precise, long-lasting suppression of ENaC activity in the airways while concurrently limiting off-target fluid transport effects, systemic exposure, and negative consequences has been the focus of recent study. There are several approaches, such as oligonucleotide-based therapies, next-generation small molecules direct inhibitors, synthetic peptide analogues, and indirect channel-activating protease inhibitors. It is quite exciting that the development of ENaC-directed therapeutics for cystic fibrosis is being advanced by these novel drugs. Endogenous heterotrimeric ENaC channels are inhibited by the addition of mutant ENaC mRNA (mutENaC). It was successful to transfect CF-based airway cells with lipid nanoparticles carrying the mutENaC mutation both in vitro and in vivo. Macroscopic ENaC currents significantly decreased, amiloride-sensitive ENaC currents in CF airway cells increased, and the liquid height of the airway surface increased [3].

In treating CF, a palliative strategy is used. In essence, it aims to improve the patient's quality of life while also slowing the progression of the illness. The use of long-term pharmacological therapy is necessary for management techniques that aim to reduce inflammation, mucus clearance, and pancreatic enzymes. The need for antibiotics is crucial since they suppress infection. There is also a requirement for intensive physical therapy, ongoing lung function monitoring, and dietary care. The aim of CF treatment heavily depends on where it developed. According to the sensitivity patterns of bacteria to the commonly prescribed antibiotics like azithromycin, tobramycin, aztreonam, ciprofloxacin, levofloxacin, cephalexin, amoxicillin, and doxycycline, infections are often controlled by the development of CF in the lungs. Utilizing nonsteroidal anti-inflammatory drugs (NSAID), steroids, and cromolyn to decrease inflammation is also crucial. Lower airway mucus build-up is a defining feature of the CF pathogenesis. In CF, pus made of viscous materials like polymerized DNA acquired from dead neutrophils serves as the main component of mucus rather than mucin, which is released by mucus-producing cells. To ensure the patient's health and freedom of breathing, mucus clearance from the airway is a crucial treatment strategy. Inhaled N-acetylcysteine and -agonists with humidified oxygen are two examples of mucolytic medications that are helpful in CF. A medication for inhalation called dornase alfa reduces pulmonary exacerbations brought on by CF and so enhances lung function. According to reports, CF patients' lung function was enhanced by hypertonic saline (3-6%). Oral rehydration, osmotic laxatives, hyperosmolar contrast enemas, electrolyte intestinal lavage solution, and other treatments may be used to treat CF that develops in the gastrointestinal tract (GIT), Depending on the severity of the aetiology, a diatrizoate sodium and meglumine enema may be used. For 6 to 12 months, regular oral osmotic-laxative polyethylene glycol 3350 treatment is utilised to stop the recurrence of CF [4].

As part of pancreatic enzyme replacement therapy, a mixture of pancreatic enzyme proteases, lipases, and amylases is recommended. Dehydration is a serious pathogenic condition in cystic fibrosis (CF), but it can be prevented by giving patients the right nutrition, including high-calorie, high-fat diets, extra amounts of the fat-soluble vitamins A, D, E, and K (ADEK), as well as fluoride and zinc. The majority of the treatment targets for the present and the future are directed at CFTR protein structural and functional abnormalities. CFTR moderators like ivacaftor, lumacaftor, and orkambi are now recommended. According to earlier studies, mAbs could be useful for diagnosing cystic fibrosis (CF), treating particular CFTR mutations, and developing antibodies against Pseudomonas aeruginosa (P. aeruginosa), the most prevalent infection detected in the lungs of CF patients. Patients with CF require CFTR correction, modification, and strict symptomatic treatment aimed at lowering inflammation and infection while making sure their bronchial tubes are properly hydrated and fed. For this goal, numerous medicinal compounds have been created. They are still in the clinical trial stages, though. Information on potential molecular targets, biomolecules, and medications for the therapy of CF is included in the current review [5].

CONCLUSION

A significant barrier to the treatment of the disease is the non-target specific approach in the reduction of the degenerative effects of CF. the mAbs produced by a single B cell clone in response to a particular antigen. Because of their better specificity, more efficient biodistribution, excellent tolerability, and longer half-life than other medicines, therapeutic proteins are used in these applications. A major improvement in human healthcare will be the creation of novel mAbs for CF. However, it is essential to comprehend the pathology of the illness in order to produce creative particular mAbs for the treatment of CF. The use of mAbs in the treatment of CF is still being researched. Due to the underlying genetic issues, numerous research have been done over a long period of time on the potential use of mAbs in the detection of molecular abnormalities in CF patients.

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