Immunomodulation in Cystic Fibrosis: Why and How?

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Cystic fibrosis lung disease is characterized by unconventional mechanisms of inflammation, implicating a chronic immune response dominated by innate immune cells. Historically, therapeutic development has focused on the mutated cystic fibrosis transmembrane conductance regulator (CFTR), leading to the discovery of small molecules aiming at modulating and potentiating the presence and activity of CFTR at the plasma membrane. However, treatment burden sustained by CF patients, side effects of current medications, and recent advances in other therapeutic areas have highlighted the need to develop novel disease targeting of the inflammatory component driving CF lung damage. Furthermore, current issues with standard treatment emphasize the need for directed lung therapies that could minimize systemic side effects. Here, we summarize current treatment used to target immune cells in the lungs, and highlight potential benefits and caveats of novel therapeutic strategies.

The study of cystic fibrosis (CF) lung disease has generated a wealth of knowledge on epithelial cell dysfunction and potential options for targeted therapeutics. While these findings have provided key information needed for the development of modulator therapies directed at the cystic fibrosis transmembrane conductance regulator (CFTR), growing interest in the role of immune cells in CF, especially in the lungs, is advancing our understanding of previously unknown disease mechanisms. CFTR mutations have been associated with impaired pathogen clearance by myeloid cells, altered B-cell activation, and cytokine secretion by T-cells.

However, the exact role that CFTR plays in modulating key immune cell functions remains unclear, as recent studies have challenged early findings that CFTR deficiency impairs pathogen clearance by myeloid cells . As such, the adaptability of immune cells, particularly neutrophils, to diseased microenvironments may be of greater importance than loss of CFTR regarding their role in CF. In addition, there is a great variety of CFTR mutations, with over 2000 identified mutations spread across seven classes. Each of these classes represents different mechanisms causing CFTR deficiency or dysfunction, and thus many opportunities for precision medicine. However, no therapy to date has been able to address the onset of chronic inflammation in the CF lung. New therapies directly addressing cellular mechanisms of inflammation, especially regarding neutrophils, are urgently needed. Neutrophils are the most abundant leukocyte subset in the human body in terms of new cells produced per day (approximately 10^9 per kg) and an essential component of innate immunity for their role as highly efficient phagocytes and regulators of immune responses. In CF patients, neutrophils are massively recruited to the airways and are major drivers of lung inflammation. Among resident immune cells, tissue-resident macrophages are important for maintaining lung homeostasis, and another focal point of immune imbalance in CF airways.

Immunological dysfunction or reprogramming of innate cells is gaining significant attention as a contributing factor to the inability to control infections, either due to intrinsic or acquired defects. These infections include common CF pathogens such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*, but also emerging and possibly more dangerous pathogens such as *Mycobacterium abscessus*. Although innate immune cells have captured much of the growing interest in the immunology of CF, important discoveries have been made in adaptive immune cells, as well. T cells are heavily suppressed by neutrophil activity in CF lungs. While this suppression may avoid autoimmune responses to self-antigens present in this chronically inflamed environment, it also be problematic by excluding regulatory subsets of T cells. Fewer studies have been conducted on the role of B cells in CF, but there is preliminary evidence for CFTR deficiency contributing to heightened B cell activation and development of lymphoid follicles. These observations form a foundation from which to investigate in more depth the interplay between immune subsets in the CF lung, and identify key mechanisms of immunomodulation for therapeutic targeting.

There is a plethora of candidate protein or nucleic acid-based therapies being developed that show promising results for either personalized medicine-based or one-size-fits-all approaches to curing CF disease. Although some have moved forward to the clinical testing phase most of these candidate therapies have not been tested in patients yet. A critical bottleneck in drug development is that existing CF animal models do not include all of the relevant barriers to entry nor fully recapitulate the peculiar immunological landscape in the lung of CF patients. Improved in vitro and animal models are therefore needed to further optimize not only candidate treatments, but also delivery methods to target specific airway cells. Particular attention should be directed to the mechanisms underlying the architecture of lung tissue, as chronic inflammation triggers tissue remodeling and repair mechanisms. To this end, the investigation of small molecules targeting both inflammation and tissue remodeling is of interest. However, while novel therapies have reduced toxicity, using drugs affecting a large variety of cell types may lead to increased side effects, particularly in CF, where patients are subjected to an already heavy therapeutic regimen. It will also be critical to assess use of these new therapies in combination with CFTR modulators, which have become the “new normal” in CF clinical management.

Keywords

Cystic fibrosis;Inflammation;Immunotherapy;Lung disease;Proteases