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Targeting cystic fibrosis inflammation in the age of CFTR modulators: focus on macrophages

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CFTR modulators have revolutionised the way that cystic fibrosis is treated and can drastically improve patient quality of life, but questions remain over their long-term effects on the inflammatory processes that underpin cystic fibrosis chronic lung disease https://bit.ly/3lbtUig

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ABSTRACT Cystic fibrosis (CF) is a life-shortening, multi-organ, autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The most prominent clinical manifestation in CF is the development of progressive lung disease characterised by an intense, chronic inflammatory airway response that culminates in respiratory failure and, ultimately, death. In recent years, a new class of therapeutics that have the potential to correct the underlying defect in CF, known as CFTR modulators, have revolutionised the field. Despite the exciting success of these drugs, their impact on airway inflammation, and its long-term consequences, remains undetermined. In addition, studies querying the absolute requirement for infection as a driver of CF inflammation have challenged the traditional consensus on CF pathogenesis, and also emphasise the need to prioritise complementary anti-inflammatory treatments in CF. Macrophages, often overlooked in CF research despite their integral role in other chronic inflammatory pathologies, have increasingly become recognised as key players in the initiation, perpetuation and resolution of CF lung inflammation, perhaps as a direct result of CFTR dysfunction. These findings suggest that macrophages may be an important target for novel anti-inflammatory interventional strategies to effectively treat CF lung function decline. This review will consider evidence for the efficacy of anti-inflammatory drugs in the treatment of CF, the potential role of macrophages, and the significance of targeting these pathways at a time when rectifying the basic defect in CF, through use of novel CFTR modulator therapies, is becoming increasingly viable.