Check for updates

Received: 11 June 2021 | Revised: 17 July 2021 | Accepted: 06 August 2021

DOI: 10.1111/pai.13619

SUPPLEMENT ARTICLE

WILEY

Type 2 inflammation in cystic fibrosis: New insights

Sara Manti[1] | Giuseppe Fabio Parisi[1] | Maria Papale[1] | Gian Luigi Marseglia[2] | Amelia Licari[2] | Salvatore Leonardi[1]

[1]Pediatric Respiratory Unit, Department of Clinical and Experimental Medicine, San Marco Hospital, University of Catania, Catania, Italy

[2]Pediatric Clinic, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy

Correspondence
Sara Manti, Pediatric Respiratory Unit, Department of Clinical and Experimental Medicine, San Marco Hospital, University of Catania, Via Santa Sofia 78, 95123, Catania, Italy.
Email: saramanti@hotmail.it

Editor: Elena Chiappini

Abstract

Recently, type 2 inflammation has been recognized as one of the most critical factors participating in the pathogenesis of cystic fibrosis (CF). On the one hand, type 2 inflammation restores tissue homeostasis and contributes to the resolution of inflammation following an injury. On the other hand, type 2 response-activated immune cells may become dysregulated or chronically activated, causing tissue fibrosis. Among the type 2 cytokine-driven inflammatory pathways, the transforming growth factor β (TGFβ), interleukin (IL)-17, IL-33, and IL-13 have been identified as essential mediators in patients suffering from CF. Given their critical role, we firmly believe that an adequate comprehension of the type 2-mediated pathways can identify attractive targets to decrease pharmacologically the inflammation and fibrosis occurring in the pulmonary tissue of patients suffering from CF.

KEYWORDS
adult, children, cystic fibrosis, tissue fibrosis, type 2 inflammation

Recently, airway inflammation has been recognized as one of the most critical factors participating in the pathogenesis of cystic fibrosis (CF), an autosomal recessive disorder caused by mutations in a single gene, expressed on the long arm of chromosome 7, which encodes a transmembrane conductance regulator (CFTR).[1] Absent, defective, or mislocalized CFTR leads to impaired transport of salt and water across epithelial barriers and, consequently, to dehydration and plugging of mucous secretions in the gland ducts with multisystemic involvement. Recent studies suggest that the release of reactive oxygen species and pro-inflammatory cytokines due to chronic pulmonary and/or bacterial infections result in a sustained inflammation occurring and maintaining even in the absence of infection.[1] Particularly, literature data support the evidence that airway inflammation in CF patients is also marked by type 2 immune response.[1]

Firstly, described as a simple counter-regulatory mechanism controlling type 1 immunity, type 2 immune response is now primarily recognized as critical protagonist exhibiting both host-protective or pathogenic properties.[1] Whether, on the one hand, type 2 inflammation restores tissue homeostasis and contributes to the resolution of inflammation following an injury; on the other hand, type 2 response-activated immune cells may become dysregulated or chronically activated, causing tissue fibrosis.[2]

Type 2 immune response describes inflammatory pathways mediated by a subpopulation of CD4+ T cells, called Th2 cells, able to release pro-inflammatory interleukins (ILs) such as IL-4, IL-5, IL-9, and IL-13 which, in turn, drive a cascade of events resulting in the recruitment of mast cells, basophils, Th2 cells, eosinophils, type 2 innate lymphoid cells (ILC2s), and B cells releasing IgE.[3,4] At the airway epithelium, these events are sustained and amplified by the local production of critical mediators, such as IL-33, IL-25, or thymic stromal lymphopoietin, which, by regulating the maturation of CD4+ T cells into Th2 cells, induce a further release of type 2 interleukins (e.g., IL-4, IL-5, and IL-13). These events result in inflammatory changes and airway remodeling featured by hyperplasia and hypertrophy of the smooth muscle cells; hyperplasia and metaplasia of

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 The Authors. *Pediatric Allergy and Immunology* published by European Academy of Allergy and Clinical Immunology and John Wiley & Sons Ltd.

mucus cells; and vascular remodeling with increasing fibrosis.[5] It well appears how an uncoordinated and uncontrolled tissue repair predisposes to lung dysfunction, pulmonary fibrosis, and subsequent infections, a triad featuring several pulmonary diseases, including CF.[6] Particularly, among the type 2 cytokine-driven inflammatory pathways, the transforming growth factor β (TGFβ), IL-17, IL-33, and IL-13 have been identified to be important mediators in patients suffering from CF.[2,6] The three mammalian isoforms of TGFβ, TGFβ1, TGFβ2, and TGFβ3 are expressed in the healthy lung where they play as essential regulators of lung development, inflammation, injury, and repair; however, when they are overexpressed, such as in patients suffering from CF, they drive myofibroblast differentiation from fibroblasts to the alveolar type II cells and primarily perpetuate the epithelial injury. Accordingly, two TGFβ1 polymorphisms (SNPs) (C-509T and T29C SNPs) are linked to more severe CF lung disease and, in parallel, increased TGFβ1 levels, both in serum and bronchoalveolar lavage (BAL), have been associated with pulmonary exacerbations, the severity of lung disease, increased neutrophilic inflammation, and infection with *Pseudomonas aeruginosa in* CF patients.[2,6,7]IL-17, a pro-inflammatory cytokine implicated in the neutrophil recruitment in the airway wall submucosa, is elevated both in young and old CF patients, correlates with severity of lung function, and predisposes to bacterial infections.[8] Whether the infection persists or progresses, IL-17 promotes the release of other cytokines (IL-6, IL-21, and IL-1β), polarizes the Th0 cells toward a Th17 phenotype, and inhibits the development of Th1 polarization. Moreover, the persistent IL-17-mediated neutrophilia cannot effectively clear bacterial antigens. Thus, further neutrophil recruitment occurs, and chronic infection is promoted.8 Similarly, in a murine model, the blockade of IL-17 protected the mice from both eosinophilic and neutrophilic inflammation with a significant decrease in mucus production and airway hyperreactivity.[8]IL-33 is a member of the IL-1 family and is passively secreted by cellular necrosis. It has been isolated from both the nuclei of basal airway epithelial cells, fibroblasts, and endothelial cells. Following its binding to the ST2 receptor, IL-33 acts together with other alarmins to induce an inefficient suppression of pro-inflammatory response and contribute to Th2 responses.[1,2,9] Specifically, IL-33 leads to an increased synthesis of IL-5 and IL-13, promotes chemotaxis and survival of neutrophils, lastly, stimulates mast cells and eosinophils to produce chemokines and radicals free and superoxide, contributing to the tissue injury featuring CF patients.

IL-13 is a pro-inflammatory cytokine primarily produced by ILCs2 and, secondly, by eosinophils, basophils, macrophages M2-subset, and natural killer cells. By sharing with IL-4 the receptor a-subunit (IL-4Ra), IL-13 is involved in the isotype switch to IgE synthesis crucial in allergic diseases.[1,2] Moreover, cytokine profiles in pulmonary fibrosis suggest a critical role for IL-13 as it induces the activation and proliferation of fibroblasts, increases the smooth muscle cell contraction, promotes the extracellular collagen deposition and periostin release, and favors mucus synthesis. IL-13–induced pulmonary fibrosis was reported both as TGF-ß- or JNK-dependent and mediated by platelet-derived growth factor (PDGF) gene expression in lung fibroblast. Furthermore, IL-13 secretes factors stimulating the production and recruitment of more neutrophils to the site of infection or inflammation. However, although present in the pulmonary tissue, they are unable to effectively control infection as they exhibit a dysfunctional phenotype due to the expression on their surface of defective CFTR.[1,2]

Key messages

Airway inflammation is recognized as one of the most critical factors participating in the pathogenesis of pulmonary disease in cystic fibrosis (CF).

Literature data support the evidence that airway inflammation in CF patients is also marked by type 2 immune response.

Adequate comprehension of type 2 inflammation-mediated pathways might provide the identification of attractive targets in treating patients affected by CF.

High IL-13 levels were detected both in the blood and BAL fluid of patients with idiopathic pulmonary fibrosis, and they correlated with disease severity.[1,2]

By targeting a wide array of pro-inflammatory cytokines and different immune cell types, including epithelial and endothelial cells, macrophages, and fibroblasts, the type 2 inflammation can orchestrate a dysregulated tissue repair.[1,2,10] After initial damage of airways epithelium and in response to recurring alveolar injuries, the subsequent aberrant repair, and inflammatory response lead to a repeated and self-sustaining tissue damage resulting in lung fibrosis. Adequate comprehension of the above-elucidated pathways might provide the identification of attractive targets to decrease pharmacologically the inflammation and fibrosis occurring in the pulmonary tissue of patients suffering from CF.

ACKNOWLEDGEMENTS

Open Access funding provided by Universita degli Studi di Catania within the CRUI-CARE Agreement. [Correction added on 11-May-2022, after first online publication: CRUI-CARE funding statement has been added.]

CONFLICT OF INTERESTS

Authors declared they have no conflict of interests.

AUTHOR CONTRIBUTIONS

Sara Manti: Conceptualization (equal); writing-review and editing (equal). **Giuseppe Fabio Parisi**: Conceptualization (equal); writing-review and editing (equal). **Maria Papale**: Conceptualization (equal); writing-review and editing (equal). **Gian Luigi Marseglia**: Supervision (lead); writing-review and editing (equal). **Amelia Licari**: Conceptualization (equal); writing-original draft (equal). **Salvatore Leonardi**: Conceptualization (equal); supervision (lead); writing-review and editing (equal).

13993038, 2022, S27, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/pai.13619 by Fondazione Ircss Policlinico San Matteo, Wiley Online Library on [20/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

ORCID

Sara Manti https://orcid.org/0000-0002-7664-3083
Giuseppe Fabio Parisi https://orcid.org/0000-0003-4291-0195
Gian Luigi Marseglia https://orcid.org/0000-0003-3662-0159
Amelia Licari https://orcid.org/0000-0002-1773-6482

REFERENCES

1. Roesch EA, Nichols DP, Chmiel JF. Inflammation in cystic fibrosis: an update. *Pediatr Pulmonol*. 2018;53:S30-S50.
2. Gieseck R, Wilson M, Wynn T. Type 2 immunity in tissue repair and fibrosis. *Nat Rev Immunol*. 2018;18:62-76.
3. Nakayama T, Hirahara K, Onodera A, et al. Th2 cells in health and disease. *Annu Rev Immunol*. 2017;35:53-84.
4. Licari A, Manti S, Castagnoli R, et al. Measuring inflammation in paediatric severe asthma: biomarkers in clinical practice. *Breathe (Sheff)*. 2020;16:190301.
5. Kotton DN, Morrisey EE. Lung regeneration: mechanisms, applications and emerging stem cell populations. *Nat Med*. 2014;20:822-832.
6. Harris WT, Kelly DR, Zhou Y, et al. Myofibroblast differentiation and enhanced TGF-B signaling in cystic fibrosis lung disease. *PLoS ONE*. 2013;8:e70196.
7. Manti S, Parisi GF, Papale M, et al. Allergic bronchopulmonary aspergillosis in children. *Pediatr Allergy Immunol*. 2020;31(Suppl 26): 20-22.
8. Dubin PJ, Kolls JK. IL-17 in cystic fibrosis: more than just Th17 cells. *Am J Respir Crit Care Med*. 2011;184:155-157.
9. Tiringer K, Treis A, Kanolzer S, et al. Differential expression of IL-33 and HMGB1 in the lungs of stable cystic fibrosis patients. *Eur Respir J*. 2014;44:802-805.
10. Licari A, Manti S, Castagnoli R, et al. Targeted therapy for severe asthma in children and adolescents: current and future perspectives. *Paediatr Drugs*. 2019;21:215-237.

How to cite this article: Manti S, Parisi GF, Papale M, Marseglia GL, Licari A, Leonardi S. Type 2 inflammation in cystic fibrosis: New insights. *Pediatr Allergy Immunol*. 2022;33(Suppl. 27):15–17. https://doi.org/10.1111/pai.13619

13993038, 2022, S27, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/pai.13619 by Fondazione Ircss Policlinico San Matteo, Wiley Online Library on [20/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License