Innate Immunity in Cystic Fibrosis: Novel Pieces of the Puzzle

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Cystic fibrosis (CF) is the most common inherited fatal disease in Caucasians and is caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene [1]. Despite CF being a multisystemic disease, CF patients mainly die from their respiratory manifestations and complications, characterized by chronic airway infections and nonresolving inflammation. Peculiar and probably unique among human disease conditions is the early and persistent interaction between airway epithelial cells (impaired mucociliary clearance), recruited innate immune cells (mainly neutrophils) and microbial components (mainly bacteria and fungi) within the CF airway compartment. This intimate host-microbe relationship is: (1) mutual and highly complex in its nature, since it evolves/intensifies over time, (2) co-regulatory (immune cells kill microbes and vice versa) and (3) affected by several CF medications (particularly antibiotics, antifungals, steroids and DNase). The era of the microbiome, recently extended to the pulmonary microbiome in CF and other lung diseases [2–4], has added another layer of complexity.

Despite fascinating new omics technologies some simple old questions remain surprisingly poorly answered. (1) Is the innate inflammatory response in the CF airway

protective or harmful? (2) Which innate immune cells that accumulate in CF lungs are protective and which ones cause more harm than protection by releasing proteases and oxidants? (3) Which receptors or downstream pathways could be harnessed to therapeutically interfere with innate immunity in CF lung disease?

In an attempt to address these questions, we have composed a review series on innate immunity in CF lung disease, comprising dedicated reviews from 3 key international opinion leader groups in the field. First, Ralhan et al. [5] provide a comprehensive overview covering and discussing several key players in the innate immune response in the context of the CF lung, i.e. airway epithelial cells, CF characteristic pathogens (focus: bacteria and fungi) and microbial pattern recognition receptors (e.g. Toll-like receptors) as well as a summary of the major innate immune cells that migrate into the inflamed CF microenvironment. Second, Vencken and Greene [6] focus on 2 distinct key players regulating host-pathogen interactions in infective CF lung disease, i.e. Toll-like receptors and microRNAs. Both systems fine-tune and orchestrate the outcome of pathogen sensing and its consequences for mounting immune responses, particularly at the airway epithelial level. Third, Bruscia and Bonfield [7]

dig deeper into the complex topic of macrophage plasticity (M1 vs. M2 and beyond) and functionality in CF lung disease, a promising though controversial field of research.

The areas that are not covered by our review series, but are of interest for the CF community and discussed in previous publications are: (1) novel anti-inflammatory therapeutic approaches in CF lung disease, such as roscovitine [8, 9], antiproteases [10] and others [11], (2) the quantitatively dominant, though functionally controversial role of neutrophils in CF airways, including disturbed apoptosis, neutrophil extracellular trap (NET) formation and other deviations/alterations [12–17], (3) impairments of the chemokine system in CF [12, 18, 19] and (4) the microbiome [3, 20, 21].

Summarizing the studies in the field of innate immunity in CF lung disease reveals the emergence of new players, i.e. microRNAs, novel pathogen-sensing pathways, specialized immune cell subsets, e.g. innate lymphoid cells and myeloid-derived suppressor cells, and the microbiome. All of these, in combination, add several layers of complexity to the puzzle of innate immunity and inflammation in CF lung disease. Comparative studies using *in vitro* and *in vivo* (focus: mouse, ferret and pig) approaches as well as biomarker readouts from clinical trials will help to consolidate our mechanistic understanding of the networks in innate immunity, with the final aim to assess their diagnostic and therapeutic applicability in CF lung disease.

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