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Immune Dysfunction in Cystic Fibrosis

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1. Introduction

Absence of the cystic fibrosis transmembrane regulator (CFTR) function leads to chronic lung disease characterized by inflammation and persistent infections. The mechanisms for the increased susceptibility of the respiratory tract for infections in CF are most likely complex and only partially understood. Most attention has been focused on the effect of the defective expression of CFTR in epithelial cells and submucosal gland cells and the increased susceptibility of the respiratory tract to infections was mostly thought to be related to the abnormal chloride channel function (Welsh MJ, 2011, Ratjen F 2003). However, numerous studies over the past years have shown that the absence of CFTR affects the immune system and that dysfunctional immune responses contribute to pathological processes in the CF lung. In addition, it has become increasingly evident that the chloride channel dysfunction alone cannot completely explain the pathology of CF lung disease and that other pathways known to be regulated by CFTR play a role in the immune dysregulation in the CF lung (Mehta A 2008). This chapter reviews both soluble factors in the CF milieu that modify immune cell function and specific alterations in the cellular components of the innate and adaptive immune system that contribute to the impaired immune defense in CF lung disease.

2. The role of immune responses in CF

Innate host defenses are defective in CF. It is still not entirely clear how defective CFTR results in an impaired host response in the CF lung. Three general components comprise the innate and adaptive immune defenses in the respiratory tract: (1) the mucociliary escalator; (2) a humoral component of surfactant proteins, defensins, and other antimicrobial compounds; and (3) a cellular component that includes epithelial cells, neutrophils, macrophages, monocytes, dendritic cells, and lymphocytes.

2.1 Abnormal humoral responses in CF

The respiratory tract epithelium and the cells of the submucosal glands in the airways constitute a major part of the innate immune defense system of the lung that responds primarily to incoming pathogens with the release of various mediators. They are influenced and/or amplified in their responses by factors such as cytokines derived from neighboring inflammatory and immune cells (Bartlett J 2008). The defective chloride channel function in CF leads to alterations in the physical properties of the airway mucus and the composition of the airway surface liquid that are linked to impairment of innate defense mechanisms. These affect

the shield of antimicrobial factors such as lysozyme, lactoferrin, defensins, and other antimicrobial peptides, as well as disturb the mechanical clearance of inhaled particles and pathogens by the mucociliary escalator. **Table 1** summarizes the known alterations in soluble innate immune factors in the CF lung. One school of thought has pursued the concept that alterations in the chloride secretion and sodium hyperabsorption in the airways lead to the subsequent entrapment of pathogens that then lead to recruitment and activation of neutrophils and macrophages. This has also been supported by the lung phenotype of a mouse model with genetic over-expression of the sodium channel ENaC that mimics CF with thick mucus and inflammation in the absence of infection (Mall MA 2010). Salt-sensitive antimicrobials such as defensins were initially thought to be defective in the human CF lung. However, as the exact concentrations of chloride and sodium in the airway liquid are still not entirely clear, and so the degree of impairment of these innate defense mechanisms in CF is not exactly known.

Mediator	Abnormality	Reference
Defensins	Impaired activity	Goldman MJ <i>et al.</i> 1997, Bals R <i>et al.</i> 2001
Surfactant proteins	Decreased or inactive	Hartl D, Griese M 2006, Meyer KC <i>et al.</i> 2000, Noah TL <i>et al.</i> 2003
Antioxidants	Reduced glutathione availability in airways	Gao L <i>et al.</i> 1999, Roum JH <i>et al.</i> 1993, Day BJ 2005, Childers M <i>et al.</i> 2007, Hudson VM 2001
Opsonins	Proteolytic degradation	Eichler I <i>et al.</i> 1989
Cytokines		
IFN- γ ¹	Decreased secretion	Moss RB <i>et al.</i> 1996 and 2000
IL-1 ²	Increased secretion	Bonfield TL <i>et al.</i> 1995
IL-4 ³	Increased secretion	Moss RB <i>et al.</i> 1996 and 2000, Mueller C <i>et al.</i> 2010
IL-6 ⁴	Increased secretion	Black HR <i>et al.</i> 1998, Becker MN <i>et al.</i> 2004, Andersson C <i>et al.</i> 2007, Vandivier RW <i>et al.</i> 2009, Bonfield TL <i>et al.</i> 1995, Black HR <i>et al.</i> 1998, Becker MN <i>et al.</i> 2004, Vandivier RW <i>et al.</i> 2009, Bonfield TL <i>et al.</i> 1995, Moss RB <i>et al.</i> 1996 and 2000, Armstrong DS <i>et al.</i> 2005
IL-8 ⁵	Increased secretion	Bonfield TL <i>et al.</i> 1995, Moss RB <i>et al.</i> 1996 and 2000, Armstrong DS <i>et al.</i> 2005
IL-10 ⁶	Altered secretion	Mueller C <i>et al.</i> 2010
IL-13 ⁷	Increased secretion	McAllister F <i>et al.</i> 2005, Tan HL <i>et al.</i> 2011
IL-17 ⁸	Increased secretion	Bonfield TL <i>et al.</i> 1995, Andersson C <i>et al.</i> 2007,
TNF- α ⁹	Increased secretion	Bonfield TL <i>et al.</i> 1995, Andersson C <i>et al.</i> 2007,
Chemokines		
MIP-1 β ¹⁰	Increased secretion	Brennan S <i>et al.</i> 2009
MCP-1 ¹¹	Increased secretion	Brennan S <i>et al.</i> 2009

Notes: ¹ IFN- γ (interferon-gamma); ² IL-1 β (interleukin-1 beta), ³ IL-4 (interleukin-4), ⁴ IL-6 (interleukin-6), ⁵ IL-8 (interleukin-8), ⁶ IL-10 (interleukin-10), ⁷ IL-13 (interleukin-13), ⁸ IL-17 (interleukin-17), ⁹ TNF- α (tumor necrosis factor-alpha), ¹⁰ MIP-1 β (macrophage inflammatory protein-1 beta), ¹¹ MCP-1 (macrophage chemotactic protein-1)

Table 1. Altered humoral mediators in the respiratory tract in CF

2.1.1 Soluble mediators

Numerous humoral factors that affect pulmonary innate immune response have been studied in the CF lung. These include the collectins and surfactant proteins (Hartl D 2006, Noah TL 2003, Meyer KC 2000), defensins (Goldman MJ 1997, Bals 2001), glutathione (Gao TJ 1999, Kogan I 2003, Roum JH 1993, Hudson VM 2001) and antiproteases such as secretory leukoprotease inhibitor (SLPI) and tissue inhibitor of metalloproteinase 1 (TIMP-1) (Gaggar 2007, Cantin AM 1991, Vandivier 2002). Initially, it was thought that defensins in the CF lung were impaired due to the altered salt concentration in the CF airway (Goldmann 1997). Subsequent studies showed the impairment of defensins is not only related to an altered salt concentration, but also to increased inflammation (Bals 2001, Chen CI 2004). The Levels of β -defensin were even found to be similar in bronchial brushings in CF and non CF patients (Dauletbaev N 2002). Surfactant proteins, besides their surface-tension regulating properties, also have immuno-modulatory and anti-inflammatory functions were shown to be degraded (Hartl D 2006, Noah TL 2003) and structurally altered in CF (Meyer KC 2000). Glutathione, a critical component of the antioxidant defense system in the lung, was found to be reduced in the CF lung (Roum JH 1993). Importantly, this seemed to be directly related to the function of CFTR as a channel for the transmembrane transport of glutathione (Gao 1999, Kogan 2003). As glutathione deficiency also leads to activation of nucleic factor kappa B (NF κ B)-mediated inflammation, aerosolized glutathione has been studied as a potential anti-inflammatory therapeutic in CF (Roum 1999).

Antiprotease, which plays an important role in the lung to counter the proteolytic products released by activated neutrophils, did not seem to be altered in the CF lung at baseline (Cartin AM 1991). However, these normal baseline levels were probably insufficient to neutralize the massive invasion of neutrophils and have thus been considered to be relatively deficient in the CF lung.

2.1.2 Defective CFTR leads to release of inflammatory cytokines

One of the dominant features of CF lung disease is the exaggerated inflammatory response. Numerous studies have linked the CFTR defect to activation of inflammatory cytokines, in particular interleukin-8 (IL-8). IL-8 is closely related to the CF inflammation as it is one of the major chemoattractants for neutrophils. Neutrophils dominate the inflammatory milieu in the CF lung. The importance of the vast number of neutrophils has been underscored by the successful use of recombinant DNase to break down DNA released from neutrophils as one of the few effective therapeutics to ameliorate CF lung disease (Suri R 2002). Although it is still debated if inflammation precedes infection in the lungs of infants and young children with CF, it is undisputed that CFTR is linked to the NF κ B pathway, a crucial transcription activator for inflammatory and immune responses. These intrinsic activations of NF κ B and cytokines, such as IL-8 and tumor necrosis factor alpha (TNF- α), have been observed both in naïve lung macrophages from CFTR knockout mice (CF mice) and in un-stimulated human macrophages with decreased CFTR expression (Bruscia EM 2008, Xu Y 2010). It seems that the intrinsic activation of NF κ B-mediated inflammatory cytokine release is independent of the chloride channel function of the CFTR protein. Neutrophil elastase and other products of neutrophils, that are abundant in the CF lung, also induce IL-8 expression in epithelial cells (McElvaney NG 1992). Besides an increase in inflammatory cytokines, the CFTR defect has

also been associated with a decrease in the anti-inflammatory cytokine interleukin-10 (IL-10). Increased susceptibility to CF pathogens such as *Pseudomonas aeruginosa* (*P. aeruginosa*) has been demonstrated in IL-10 deficient mice (Soltys J 2002).

2.2 Abnormal cellular immune response in CF

Cells of the innate and adaptive immune system have been studied in CF. The main findings are outlined in **Table 2**. As the role of epithelial cells in CF will be discussed in other chapters, the following details the functions and abnormalities seen in the neutrophils, macrophages, monocytes, dendritic cells, and lymphocytes that are likely playing a part in the pathogenesis of CF lung disease.

2.2.1 Neutrophils

Neutrophils are the dominating cell type in the inflammatory milieu of the CF airways. The content of their granules and products, in particular DNA and neutrophil elastase, contribute significantly to the CF lung damage. The increase in the serum and lung cytokine levels, especially of IL-8, preactivates neutrophils and lowers their threshold for granule release (Swain SD 2002). A number of abnormalities have been observed in CF neutrophils, including defective phagocytosis and oxidative burst (Alexis NE 2006), increased degranulation (myeloperoxidase) (Koller DY 1995), augmented proteolytic activity with elevated elastase and matrix metalloprotein release (Brockbank S 2005, Ratjen F 2002, Sagel SD 2005), increased apoptosis and chemotaxis (Brennan S 2001, Watt AP 2005), decreased acidification of phagolysosomes and reduced antimicrobial activity (Painter RG 2006), defective protein kinase C (Graff I 1991), and dysregulated cytokine secretion (Corvol H 2003). Blood neutrophils from CF patients were impaired in chlorination of ingested bacteria due to defective hypochlorous acid (HOCl) production within phagolysosomes, whereas extracellular HOCl production was normal (Painter RG 2006). Profound functional and signaling changes have been shown in viable inflammatory neutrophils collected from airways of CF patients compared to their blood counterparts (Tirouvanziam R 2007). On CF airway neutrophils, the surface expression of phagocytosis receptors CD16 and CD14 was lost, whereas other lineage markers such as CD80 and MHCII appeared, indicating potential functional reprogramming (Tirouvanziam R 2007).

The study by Hartl D *et al.* has provided another pathophysiologic mechanism showing unopposed proteolytic cleavage of chemokine receptor CXCR1 on CF neutrophils and subsequent failure of their bacterial-killing capacity (Hartl D 2007). One of the most important features of the neutrophils in CF is their delayed apoptosis, which could be even measured in CF heterozygous individuals (Moriceau S 2010).

Toll-like receptors (TLRs) play crucial roles in the innate host defense against *P. aeruginosa*. Neutrophils express all human TLRs except for TLR3. TLR2 and TLR5 present the main TLRs for the recognition of *P. aeruginosa*. TLR2 and TLR4 are involved in the cytokine response to *P. aeruginosa* infection. Intact flagellin/TLR5 signaling is a prerequisite for an efficient clearance of acute *P. aeruginosa* infection. The expression levels of TLRs in CF neutrophils have been investigated (Koll B 2008, Petit-Bertron AF 2008). Circulating and airway neutrophils from CF patients displayed a distinct pattern of surface markers as compared to the cells from healthy controls (Petit-Bertron AF 2008). CF blood neutrophils

Cell type	Function	Reference
Epithelial cells	Bacterial killing	Moskwa P <i>et al.</i> 2007
	Transport of GSH ¹	Velsor LW <i>et al.</i> 2001
	Redox balance	Xu Y <i>et al.</i> 2006
	Cytokine production	Tabary O <i>et al.</i> 2000
Neutrophils	Phagocytosis	Morris MR <i>et al.</i> 2005, Alexis NE <i>et al.</i> 2006
	Degranulation	Gaggar A <i>et al.</i> 2007, Koller DY <i>et al.</i> 1995, Brockbank S <i>et al.</i> 2005, Ratjen F <i>et al.</i> 2002, Sagel SD <i>et al.</i> 2005
	Apoptosis	Vandivier RW <i>et al.</i> 2002, Watt AP <i>et al.</i> 2005
	Chemotaxis	Brennan S <i>et al.</i> 2001
	Chlorination of phagolysosomes	Painter RG <i>et al.</i> 2006
	Anti-microbial activity	Painter RG <i>et al.</i> 2006, Moraes TJ <i>et al.</i> 2006
	Cytokine production	Corvol H <i>et al.</i> 2003, Tirouvanziam R <i>et al.</i> 2007
	CXCR1 ² cleavage	Hartl D <i>et al.</i> 2007
	TLR ^{3-2, 4, 5} expression	Petit Bertron AF <i>et al.</i> 2008
	Macrophages	Clearance of apoptotic cells
Cytokine production		
Phagocytosis		Knight RA <i>et al.</i> 1997, Di A <i>et al.</i> 2006
Acidification of lysosomes		Di A <i>et al.</i> 2006, Haggie PM, Verkman AS 2007 and 2009
Antigen presentation PPAR ⁴ /LXR ⁵ regulation		Knight RA <i>et al.</i> 1997 Andersson C <i>et al.</i> 2007
Dendritic cells	CD1d-restricted natural killer T cells activation	Rzemieniak SE <i>et al.</i> 2010
	Differentiation and maturation	Xu Y <i>et al.</i> 2009
	Activation, antigen presentation, and cytokine secretion	Roghianian A <i>et al.</i> 2006, Xu Y <i>et al.</i> 2009
Monocytes	Phagocytosis	del Fresno C <i>et al.</i> 2009
	Antigen presentation	Sorio C <i>et al.</i> 2011
	MHCII expression	del Fresno C <i>et al.</i> 2008
	TREM-1 ⁶ expression	del Fresno C <i>et al.</i> 2008
	Cytokine production	del Fresno C <i>et al.</i> 2008
	Toll-2, 4 expression	Sturge N C <i>et al.</i> 2010
Lymphocytes	Chloride channel function	McDonald TV <i>et al.</i> 1992, Dong YJ <i>et al.</i> 1995, Moss RB <i>et al.</i> 1996 Knutsen AP <i>et al.</i> 1989 and 1990, Lahat N <i>et al.</i> 1989, Moss RB <i>et al.</i> 1996 and 2000, Hubeau C <i>et al.</i> 2004, Hartl D <i>et al.</i> 2005
	Cytokine production	Muller C <i>et al.</i> 2010, Tan HL <i>et al.</i> 2011

Notes: ¹ GSH (glutathione); ² CXCR (C-X-C chemokine receptor), ³ TLR (toll like receptor), ⁴ PPAR (peroxisomal proliferator activated receptors), ⁵ LXR (liver X receptors), ⁶ TREM-1 (triggering receptor expressed on myeloid cells-1)

Table 2. Cellular immune dysfunction in CF

expressed elevated levels of CD64, an activation marker, and lower levels of TLR2 compared to blood neutrophils from healthy controls (Petit-Bertron AF 2008). In contrast, CF airway neutrophils expressed an elevated level of TLR4 and spontaneously released IL-8 that was neither enhanced by microbial activators nor inhibited by recombinant human IL-10, indicating intrinsic resistance to anti-inflammatory signals delivered by IL-10 (Petit-Bertron AF 2008). A similar study by Koller B *et al.* investigated the expression levels of TLR2, TLR4, TLR5, and TLR9 on airway neutrophils compared to circulating neutrophils in CF patients infected with *P. aeruginosa*. TLR5 was the only TLR that was significantly higher expressed in CF airway neutrophils compared to the controls (Koller B 2008).

2.2.2 Macrophages

Alveolar macrophages (AM) are important as a first line host defense in the lung. Besides the phagocytosis of inhaled pathogens and apoptotic cells and the release of inflammatory mediators they play an important role in orchestrating innate immune defenses (Takabayshi 2006). One of the important regulatory functions of AM may be to dampen immune responses (Lambrecht 2006), so that dysfunction of AM in CF could be related to increased inflammation. The antigen-presenting capacity of AM is low, compared to other macrophages and a majority of their function is related to phagocytosis. Dysfunctional CFTR in macrophages has been linked to impaired clearance of apoptotic cells, pro-inflammatory cytokines production, deficient antigen presentation, abnormal TLR4 trafficking, decreased bactericidal activity, and defective phagocytosis (Bonfield TL 1995, Bruscia EM 2009 and 2011, del Porto P 2011, Di A 2006, Knight RA 1997, Vandivier RW 2002a and 2002b, Xu Y 2010). Lipopolysaccharide (LPS) stimulated peritoneal macrophages from CF mice showed increased TNF- α and IL-6 secretion as well as NF κ B p65 activity. It also demonstrated attenuated induction of peroxisomal proliferator activated receptors (PPAR) and liver X receptors (LXR), those are two mediators known as the inhibitory regulators of pro-inflammatory cytokines (Andersson C 2007). Bruscia *et al.* showed that macrophages directly contributed to the exaggerated inflammatory response following LPS administration in CF mice with increased secretion of cytokines including IL-6 and keratinocyte chemoattractant (Bruscia EM 2009). The same group also demonstrated that abnormal trafficking and degradation of TLR4 might underlie the elevated inflammatory response in CF (Bruscia EM 2011). Macrophages isolated from lavage samples from CF patients were not able to stimulate allogeneic lymphocytes and to present antigen, while peripheral blood monocytes from the same patients were functional in both assays (Knight RA 1997). Macrophages derived from peripheral blood from CF patients did not differ in phagocytic activity when infected with *P. aeruginosa*, whereas the percentage of surviving bacteria was significantly higher inside CF cells compared to the controls (del Porto P 2011). As AM in human CF lungs are highly activated by the inflammatory milieu, our group assessed the direct influence of CFTR on the function of AM by knockdown CFTR expression in normal human AM with siRNA silencing. A pro-inflammatory phenotype and increased apoptosis were seen in human AM with defective CFTR, possibly due to increased expression of the lipid raft protein Caveolin-1 (Xu Y 2010). The CFTR defect has been linked to augmented apoptosis with an abnormal cellular ceramide composition which is thought to be dependant on alteration in the lipid rafts in CF cells (Becker KA 2010). Altered pH of lysosome in CF macrophages has been suggested to induce defective acidification and bactericidal activity (Di A 2006). These findings have been disputed by others as the pH in the CF lysosomes was not altered using pH sensitive fluorescent probes (Haggie PM 2007 and 2009).

Macrophages may be part of an abnormal priming process in CF during fetal development. This has been suggested by the analysis of fetal lungs for early features of immune dysregulation, which showed that the number of macrophages in the lung was higher in CF fetal lungs compared to non-CF lungs during the later stages of lung development (Hubeau 2001). Findings in the lungs of young infants with CF also point to the presence of increased macrophages as the macrophage recruiting CC chemokines elevated (Brennan S 2008; Starner 2003).

2.2.3 Monocytes

Peripheral blood monocytes, the precursors of AM, represent a pool of cells available to migrate to the lungs in response to bacterial infection. Abnormal functions of monocytes in peripheral blood from CF patients have been shown despite of absence of systemic infection in CF (del Fresno C 2008 and 2009, Sturges NC 2010, Zaman MM 2004). Augmented IL-8 secretions at baseline and in response to LPS were seen in monocytes of adult subjects heterozygous for $\Delta F508$ mutation, with no increased expression of LPS receptors including CD14 and TLR4 but possible association with alterations in mitogen activated phosphate kinase (MAPK) signaling (Zaman MM 2004). Blood peripheral monocytes isolated from CF patients were found to be locked in an endotoxin tolerance state in comparison to those exacted from healthy volunteers, not due to a deficient TLR activation but likely resulted from down-regulation of Triggering Receptor Expressed on Myeloid cells-1 (TREM-1) (del Fresno C 2008). Further investigation demonstrated potent phagocytic activity with impaired antigen presentation in LPS-tolerant monocytes from CF patients, possible by reason of decreased expression of MHCII and co-stimulatory molecules CD80, CD83, and CD86 (del Fresno C 2008). Contradictory to Zaman's finding, Sturge *et al.* have shown enhanced expression of TLR4 but similar TLR2 levels in monocytes from young CF patients with median age of 3.3 compared to healthy controls (Sturges NC 2010). The conflicting results may be due to difference in the age of subjects, and longitudinal studies are required to determine TLR4 expression as CF lung disease progresses.

2.2.4 Dendritic cells

Dendritic cells (DC), the most potent antigen presenting cells, are critical at the interface of innate and adaptive immune response. It is not known if DC function is affected in CF in humans. Only one study assessed blood-derived DC from CF patients in their capacity to activate CD1d-restricted natural killer T cells (NKT cells). The finding was that CF and non CF DC could comparably stimulate NKT cells with no apparent impact from defective CFTR chloride channel function (Rzemieniak SE 2010). Normal murine bone marrow derived DC (BMDC) were cultured in sputum from CF patients. These DC showed down-regulated expression of co-stimulatory molecules CD40, CD80, and CD86 (but not MHCII), inhibited LPS-induced activation, and defective antigen-presenting ability, partially owing to the inflammatory mediator neutrophil elastase (Roghianian A 2006). In our study, BMDC from CF mice expressed CFTR but were delayed in the early phase of differentiation. The expression levels of a number of genes related to lipid metabolism including caveolin-1, 3 β -hydroxysterol- $\Delta 7$ reductase (Dhcr7), and stearoyl-CoA desaturase 2 (Scd2) were altered (Xu Y 2009). The roles of pulmonary DC, crucial in orchestrating innate and adaptive immune responses, have been investigated in lungs from CF mice in our laboratory (Xu Y 2009).

Phenotypic and functional abnormalities in CF lung DC were found including decreased numbers, altered maturation and activation profiles, and an impaired T cell-stimulation capacity. In response to respiratory syncytial virus infection, recruitment to the lung and T cell stimulatory potential of lung DC of CF mice were impaired in comparison to controls (Xu Y 2009). The dysfunctional CFTR might play a direct role in impaired lung DC. Indirect influence from the environment, where DC reside, on the phenotype and function of lung DC could not be excluded, although inflammation in lungs of CF mice at baseline is considerably mild compared to lungs of CF patients. Further investigation is undertaken to elucidate the mechanism of mal-functional DC in CF lungs.

2.2.5 Lymphocytes

Like the other immune cells, lymphocytes express CFTR and CF lymphocytes have a defective cAMP-regulated chloride channel function (Dong YJ 1995, McDonald TV 1992). B-lymphocytes from CF patients produced similar amounts of IgG compared to non-CF cells, but showed resistance to dexamethasone. This was proposed as a potential factor for the susceptibility to bacterial bronchopulmonary infections (Emilie D 1990). Selective cytokine dysregulation has been shown in CF CD4⁺ T cells after maximal activation with anti-CD3 or phorbol myristate acetate. It included decreased IFN- γ secretion and reduced IL-10 production, whereas the levels of IL-2, IL-4, and IL-5 remained similar to controls (Moss RB 1996 and 2000). IL-2 has been known to stimulate the growth, differentiation and survival of antigen-selected cytotoxic T cells. IL-4 is a cytokine that induces differentiation of naïve helper T cells (Th0 cells) to Th2 cells. The functions of IL-5 are to stimulate B cell growth and increase immunoglobulin secretion.

Lymphocytes from CF patients or CF mice showed a profile skewed towards T_H2 (Hartl D 2005, Mueller C 2010). In CF patients with *P. aeruginosa* infection, the prevalence of a pulmonary T_H2 immune response has been shown with higher levels of CCR4⁺CD4⁺ (T_H2) cells, increased levels of IL-4, IL-13, and lower levels of IFN- γ compared with non-infected patients with CF and healthy controls (Hartl D 2005). Comparably, CF mice mounted an exaggerated IgE response upon *Aspergillus fumigatus* infection in the lung with increased levels of IL-4 and IL-13, mimicking both the T_H2 biased immune responses seen in CF patients (Mueller C 2010). Similar findings are also reported in studies with peripheral blood derived monocytes or whole blood cultures from CF patients infected with *P. aeruginosa* (Brazova J 2005, Moser C 2000). A dysregulated T_H1/2 response might contribute to the impaired clearance of pathogens in CF.

Recently, more attention has been focused on the role of T_H17 cells and interleukin-17 (IL-17) in the CF lung disease (McAllister F 2005, Tan HL 2011). IL-17 receptor signaling is critical for pulmonary neutrophil recruitment and host defense against Gram-negative bacteria through the coordinated release of granulocyte-colony stimulating factor (G-CSF) and CXC chemokine elaboration (Steinman L 2007, Bettelli 2007). Significantly elevated levels of IL-17A, IL-17F and IL-17R were found in the sputum of patients with CF who were colonized with *P. aeruginosa* at the time of pulmonary exacerbation. These levels were declined with therapy directed against *P. aeruginosa* (McAllister F 2005). T_H17 lymphocytes and other T_H17⁺ cells, including neutrophils, $\gamma\delta$ T cells, and natural killer T cells, have been shown to be present in the airway sub-mucosa in CF patients even in a young, newly diagnosed group. Highest levels of IL-17 were found in bronchoalveolar lavage from established CF

compared to the controls, with a significant correlation between IL-17 and neutrophil counts as well as IL-4 (Tan HL 2011). IL-17 pathway could serve as a new therapeutic candidate for CF, while the exact pathogenic mechanisms of IL-17 in CF still remain to be elucidated.

3. Conclusion

Augmented inflammation, increased susceptibility of the respiratory tract for infections and lack of efficient clearance of the pathogens are features of a defective immune function. Abnormal CFTR chloride channel function (and potentially associated sodium hyperabsorption) in epithelial and mucous gland cells in the lung can only partially explain the pathophysiology of CF lung disease. Members of the innate and adaptive immune system are clearly affected by the milieu created by the altered salt and water composition. There is also evidence that CFTR dysfunction directly affects immune responses, probably beyond the stimulation of inflammatory cytokines. CFTR is expressed and is functional in a variety of immune cells. CFTR-related abnormalities have been shown in neutrophils, macrophages, monocytes, dendritic cells, and lymphocytes independent of exposure to the CF milieu of the respiratory tract as demonstrated in **Fig 1**. Thus, direct CFTR-mediated dysfunction of these cells may play a role in the enigmatic CF lung disease.

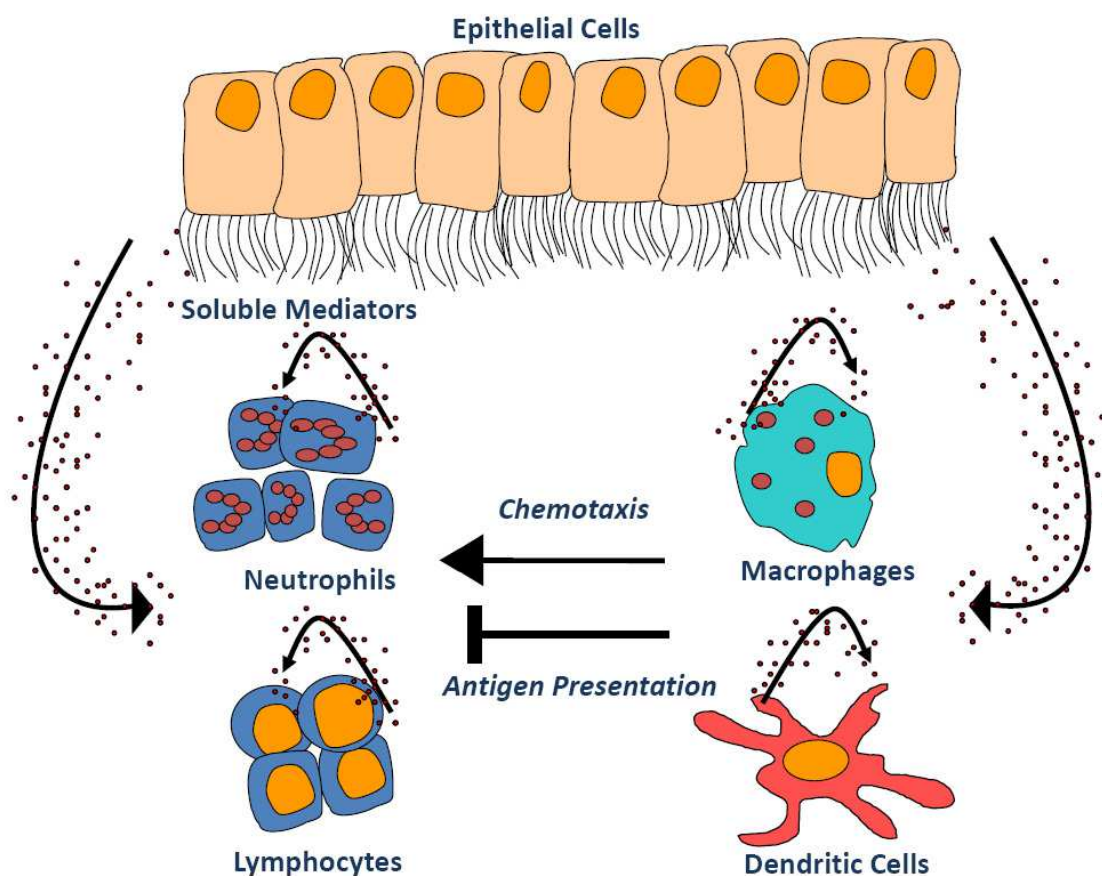


Fig. 1. Model of abnormal humoral and cellular immune responses in the CF lung. Altered humoral responses are comprised of soluble mediators including cytokines, chemokines, antioxidants, and antiproteases. Neutrophils, macrophages, dendritic cells, and lymphocytes are either affected by the altered soluble mediators from the CFTR-deficient epithelial and immune cells or by their own defective CFTR function.

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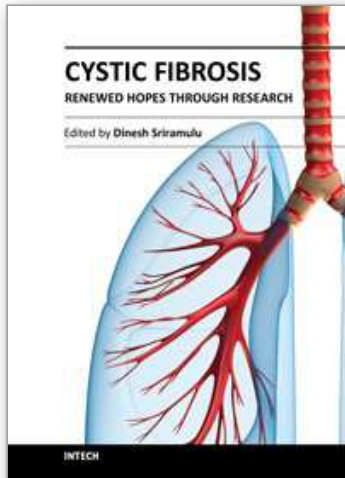
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Living healthy is all one wants, but the genetics behind creation of every human is different. As a curse or human agony, some are born with congenital defects in their menu of the genome. Just one has to live with that! The complexity of cystic fibrosis condition, which is rather a slow-killer, affects various organ systems of the human body complicating further with secondary infections. That's what makes the disease so puzzling for which scientists around the world are trying to understand better and to find a cure. Though they narrowed down to a single target gene, the tentacles of the disease reach many unknown corners of the human body. Decades of scientific research in the field of chronic illnesses like this one surely increased the level of life expectancy. This book is the compilation of interesting chapters contributed by eminent interdisciplinary scientists around the world trying to make the life of cystic fibrosis patients better.

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