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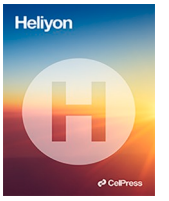

Review article

Role of innate immunity and systemic inflammation in cystic fibrosis disease progression

Anand Kumar Purushothaman, Everette Jacob Remington Nelson *

Gene Therapy Laboratory, Department of Integrative Biology, School of Bio Sciences and Technology, Vellore Institute of Technology, Vellore, India

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ABSTRACT

Pathophysiological manifestations of cystic fibrosis (CF) result from a functional defect in the cystic fibrosis transmembrane conductance regulator (CFTR) paving way for mucus obstruction and pathogen colonization. The role of CFTR in modulating immune cell function and vascular integrity, irrespective of mucus thickening, in determining the host cell response to pathogens/allergens and causing systemic inflammation is least appreciated. Since CFTR plays a key role in the conductance of anions like Cl^-, loss of CFTR function could affect various basic cellular processes, such as cellular homeostasis, lysosome acidification, and redox balance. CFTR aids in endotoxin tolerance by regulating Toll-like receptor-mediated signaling resulting in uncontrolled activation of innate immune cells. Although leukocytes of CF patients are hyperactivated, they exhibit compromised phagosome activity thus favouring the orchestration of sepsis from defective pathogen clearance. This review will emphasize the importance of innate immunity and systemic inflammatory response in the development of CF and other CFTR-associated pathologies.

1. Introduction

Cystic fibrosis (CF) is a chronic disease which severely damages the respiratory and digestive tracts, and is the most common genetically inherited disease among Caucasians (1:2500). It is caused by a defect in the cystic fibrosis transmembrane conductance regulator (CFTR) that mainly functions as a Cl^- channel on many epithelial cells. Although lungs, gut, pancreas, kidneys, and liver are primarily impacted from dysfunctional CFTR, other parts of the body including bone marrow, central nervous system, reproductive system, immune system, and cardiovascular system are also affected owing to endothelial cell activation with subsequent loss of its systemic barrier function throughout the body [1–3]. Currently, over 100,000 people suffer from this disease worldwide with wide-ranging disparity in disease severity among affected populations depending on the type of CFTR mutation, and factors like age, pollution, lifestyle, and diet [1]. Although the extent of pathophysiological outcome of CF is determined by the degree of infection and pathogen load throughout the body, death ensues merely due to lung-related complications such as lung fibrosis, and in extreme cases sepsis-associated pneumonia and acute respiratory distress syndrome [1,2]. CFTR is also expressed on the endothelium where it mediates vascular homeostasis by maintaining the epithelial barrier and *trans*-endothelial salt gradient, and modulating the aquaporins. Dysfunctional CFTR may contribute to loss of epithelial integrity, microbial defence, and vascular dysfunction, thereby mediating a systemic inflammatory response [4,5]. The consequence of CFTR-associated mucus obstruction leading to pathogen colonization is well-known, whereas the role of systemic inflammatory response due to pathogen-associated molecular patterns

* Corresponding author.
E-mail address: everette.nelson@gmail.com (E.J.R. Nelson).

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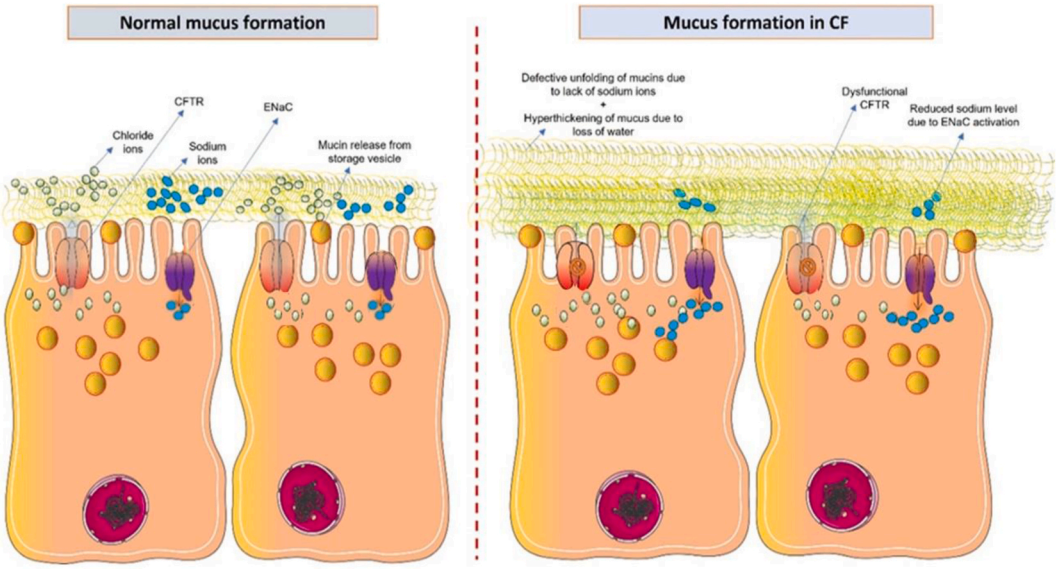

Fig. 1. Altered mucin unfolding and mucus formation from secretory cells in CF. In normal conditions, CFTR-mediated regulation of Cl^- conductance and ENaC suppression facilitates even distribution of Na^+ and water molecules across the lumen, forming the basis for proper mucin unfolding and spreading. In CF, ENaC is activated leading to inadequate levels of Na^+ in the extracellular space resulting in altered mucin unfolding, wherein the absence of water molecules from ENaC activation and aquaporin suppression stifle the hydration of heavily glycosylated mucins to result in improper spreading and hypercondensation. Also, loss of mucociliary action results in the accumulation and thickening of mucus.

(PAMPs) and excessive leukocyte activation in defining the course of CF is still least understood, which necessitated this review.

2. CFTR function and normal physiology

Channels that conduct chloride ions across the plasma membrane and organelles belong to multiple families, including voltage-gated chloride channels (ClCs), chloride intracellular ion channel (CLIC), and cAMP-activated chloride channel (such as CFTR and TMEM16A). CFTR serves as the major conduit of Cl^- and remains the only ABC family member that functions as an ion channel across the plasma membrane of many cell types, especially epithelial cells. In addition to Cl^-, CFTR also conducts other small anions, like HCO_3^-, PO_4^- as well as reactive oxygen species (singlet oxygen) [5]. It is responsible for the maintenance of intracellular and lysosomal pH, endomembrane reorganization, cell volume, intracellular calcium and redox status, extracellular environment by regulating aquaporins, ceramide metabolism, Toll-like receptor 4 (TLR4) signaling, tight junctions, and ion channels like epithelial sodium channel (ENaC) and transient receptor potential vanilloid type 4 channel (TRPV4) [6,4,7–9]. Quantitative loss of CFTR activity underlies CF pathogenesis due to reduced conductance and thereby significant build-up of intracellular Cl^- and HCO_3^- levels. This higher than usual levels promote increased absorption of Na^+ and water from the luminal surface causing depletion of the airway surface liquid. Overall, this affects the nature of mucous lining the epithelium which has now thickened instigating defective mucociliary clearance leading to ductal obstruction and onset of infections (airways and gut) enough to trigger CF-related pathological changes [10–14]. Although over 2000 candidate CFTR mutations are known to cause CF in humans, about 70% of patients harbour a frameshift mutation at codon 508 in exon 10 of the CFTR gene resulting in the absence of phenylalanine at this position of the mature CFTR protein leading to its defective Golgi processing and subsequently reduced trafficking to the apical membrane [1,11]. Since CFTR expression and function is vital for physiological homeostasis in epithelial cells, immune cells, and neurons throughout the body, it is no surprise that CF is a multi-system disorder [2]. In this review, we have made an attempt to address the neglected immunological links and bring to light some recent findings to fill the knowledge gap on CF pathophysiology.

2.1. The role of mucus

Mucus is the earliest developed immune response during the course of evolution of multicellular organisms. In humans, mucus is the first line of defence which forms an integral part of innate immunity [15,16]. Usually, four types of heavily glycosylated mucins (with glycans making up to 90% of protein mass) are predominantly secreted from specialized epithelial cells called the goblet cells (and also mucous cells in submucosal glands) [17,18]. In the presence of HCO_3^- and water, calcium bound to mucin is released thus facilitating the formation of disulphide bonds between the cysteine residues of mucins to form polymers. Concomitant with polymerization, water gets trapped within the polymer due to hydrophilic glycans resulting in spreading of mucus wherein the size of mucins gets enlarged by more than 1000 times [15,16,18]. These form a mucus layer (aka, mucosal barrier) over the epithelial lining of tissues to act as a barrier for foreign bodies (microbes and toxins) and moisturize the epithelial surface to maintain its integrity. This

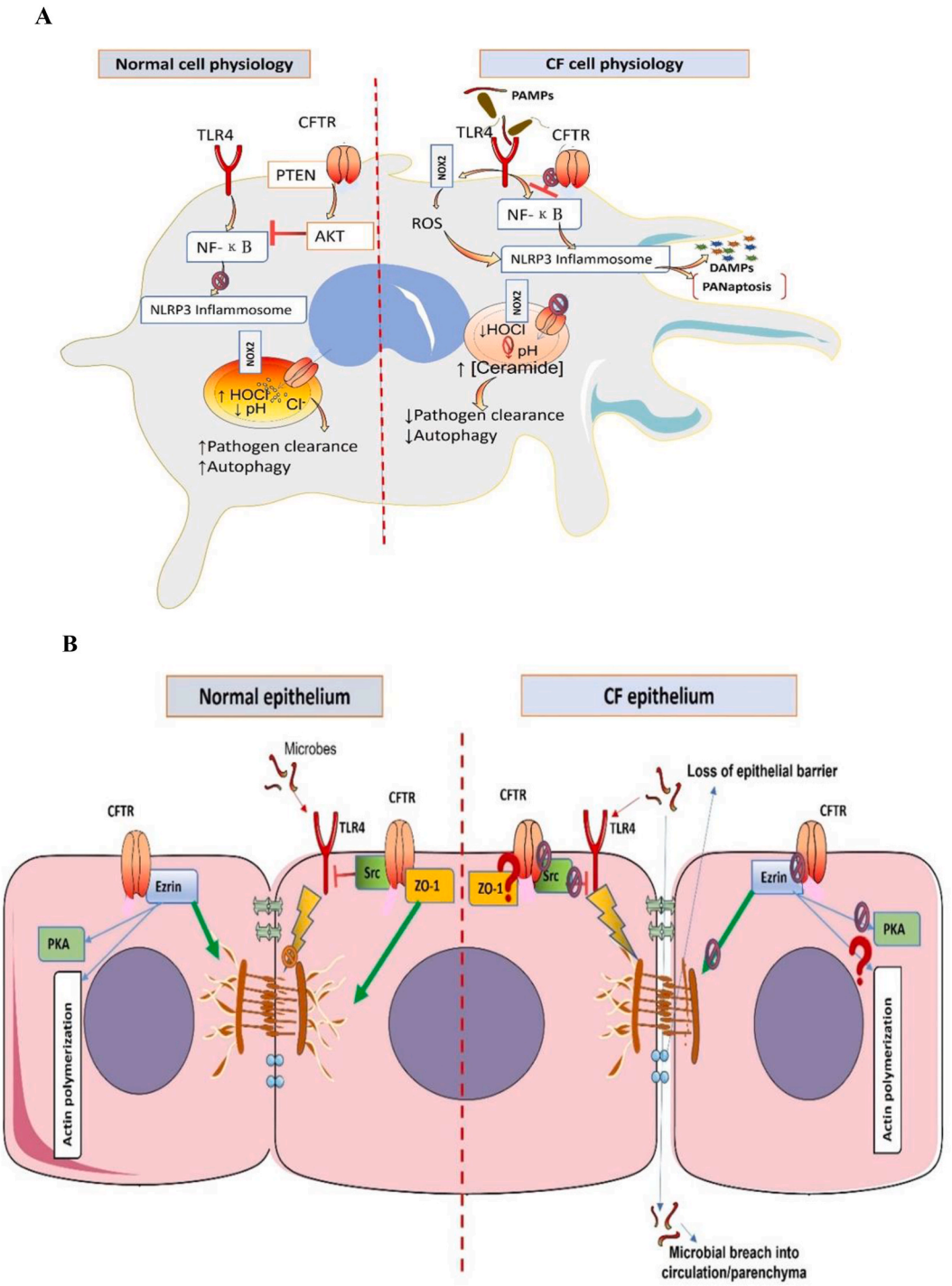

Fig. 2. Pathophysiological effects of dysfunctional CFTR at cellular level. CFTR-induced physiological changes common to all cell types (including leukocytes, **2A**), and those specific for epithelial and endothelial cells (**2B**) are shown. Phosphatase and tensin homologue (PTEN) associates with CFTR to suppress TLR4/NF-κB signaling and inflammosome activation. CFTR regulates Cl^- levels in the lumen of lysosomes to establish an acidic environment and produce HOCl upon NOX2 activation for effective oxidative burst. CFTR also facilitates endotoxin tolerance, ciliary movement, and epithelial barrier maintenance through its interaction with Src kinase, ZO-1, and Ezrin. In CFTR dysfunction, compromised lysosomal acidification results in reduced pathogen clearance and impaired autophagy. Further, loss of epithelial barrier function obliterates endotoxin tolerance in epithelial cells, where microbial breach of the epithelial barrier orchestrates elevated PRR-mediated signaling followed by leukocyte infiltration in the parenchyma or even sepsis when microbes enter the circulation.

vast mucus layer is shredded off continuously by ciliary movement in the lungs or bolus movement in the gut and replenished by newly secreted mucins, which ensures that the foreign bodies are not just stopped but also expelled from the system [12,15].

2.2. The role of CFTR

The nature of mucus is an important determinant of CF pathogenesis since thickened mucus that resists expulsion by mucociliary action becomes the root cause for the incidence of infections [13,15,19]. CFTR plays a critical role in maintaining the nature of mucosal barrier, both directly and indirectly. It aids in mucin secretion, unfolding, and polymerization for mucus formation through its conductance of HCO_3^-. It also establishes a water-rich environment for mucus spreading by facilitating ion channels, especially limiting ENaC activity (to limit Na^+ intake) as well as aquaporin-mediated water transport towards the mucosal surface [2,16,20,21]. Overall, the abundance of Na^+ combined with the action of aquaporins enriches water content of the mucus. In this manner, CFTR ensures fluidity of the airway surface liquid and thereby regulates mucosal thickness [5,10,22]. Therefore, dysfunctional CFTR would result in the loss of airway surface liquid eventually leading to thickening of mucus secretion as in the case of CF (Fig. 1).

3. Dysfunctional CFTR and cystic fibrosis

CFTR which had been earlier known to be present only on the plasma membrane, has recently been reported on the membranes of lysosomes, endosomes, *trans*-Golgi network, peroxisomes, and the ER with their presence on mitochondria, nuclear membrane, and other organelles still largely unknown. While CFTR plays a critical role in maintaining the acidic environment of lysosomes, it is essential for the generation of reactive species of oxygen, nitrogen, and chlorine (ROS, RNS, and RCS) in the peroxisomes [10,23,24]. On the plasma membrane, as mentioned before, CFTR regulates the conductance of Cl^- and other small anions across the membrane to maintain ionic and water balance both within the cell and in the extracellular apical surface. The absence of normal CFTR function leads to perturbations in basic cellular processes, such as mucus secretion, ciliary movement, cellular integrity, autophagy, cellular metabolism, oxidative burst, protein chlorination, pathogen clearance, endotoxin tolerance, and cell death among others [6,10,11,25] (Fig. 2A). Moreover, consequences of the absence of basal CFTR function varies between different cell types in terms of its metabolism, location, and function. Cells being fundamental units of the body, the outcome could vary widely from tissue to tissue and from organ to organ depending on the type, number, and location of CFTR-expressing cells present [26,27]. Since all organ systems are interconnected, CF patients often manifest the overall pathophysiological outcome [2,19].

Reduction or complete loss of CFTR function on the apical membrane of epithelial cells lining the lungs, biliary, and gastrointestinal tracts leads to mucus thickening driving the onset of CF pathophysiology. Also, loss of CFTR disturbs the integrity of epithelia due to reduced gap junctions and ciliary activity [18,24,28–30]. As mucus thickening makes it difficult for their clearance, it gets stuck on the surface for an unusually long period of time thereby favouring invasion of microbes into the epithelium followed by PAMP-dependent hyperactivation of innate immune signaling in epithelial cells and infiltrated innate immune cells through inflammasome activation due to NF-kB and redox imbalance (Fig. 2B). This results in excessive release of proinflammatory cytokines and DAMPs within the epithelial tissue to further aggravate systemic inflammatory response [25,31–33]. In antigen-presenting cells (APCs) and innate immune cells (especially macrophages), loss of CFTR function results in reduced Cl^- influx into phagosomes hindering the production of RCS which is essential for oxidative burst and phagocytosis [34–36]. CFTR loss leads to impaired endotoxin tolerance in a pre-CF state since CFTR is known to directly regulate Src kinase and subsequent p38 activation. This further aids in sustaining prolonged type 1 immune response and hence the inflammatory milieu [37–39]. Reduced CFTR expression results in impaired NADPH oxidase (NOX) activity and limited ROS production thereby preventing immune cells from effectively killing the pathogens as evidenced in murine macrophages. In the epithelial cells and alveolar macrophages of mice and humans, it was found that the absence of CFTR leads to accumulation of ceramide in the vesicles including lysosomes which could greatly impact lysosomal pH and autophagy [23,35]. While direct evidence is lacking for the role of CFTR dysfunction leading to ceramide accumulation in the mitochondrial membrane, unlike that described for lysosomes, it rather seems reasonable from previous studies that point toward a correlation between higher incidence of mitochondrial dysfunction and ROS generation in CF. With reduced CFTR expression, the pH of lysosomes was found to be increased resulting in the loss of acidic environment that is much required for lysosomal function. Of note, increased cytosolic Cl^- levels may render fusion of endosomes with lysosomes, and could lead to serious outcomes, like impaired autophagy, impaired lysosomal killing of phagocytosed pathogens, ineffective oxidative burst, lysosomal leakage, and loss of synergistic crosstalk between apoptosis and necroptosis [40–42]. Although the extent of impact of CFTR dysfunction on NETosing neutrophils is not known, it seems obvious that impaired NOX activity and bacterial killing could certainly diminish the process of effective NETosis. Loss of CFTR expression in neurons of mice have been demonstrated to raise the cytosolic concentration of Cl^- *via* limiting extracellular release, which is a well-known trigger for Na^+/K^+ hyperactivation and thus neuronal conductance. Although it is tempting to speculate an altered neuronal autophagy and microglial activity in CF pathogenesis and an ensuing neural degeneration, more research is warranted to establish the significance of CFTR on neuroinflammation and cognitive impairment.

3.1. The respiratory system

The lungs, comprising of several different levels of architecture from the bronchi to alveoli, is the most affected organ which is at the centre of both morbidity and mortality due to CF. The lungs have about a billion alveoli that are rich in blood capillaries. The epithelial cells lining the airways are equipped with hair-like projections called cilia which synchronously move back and forth to expel

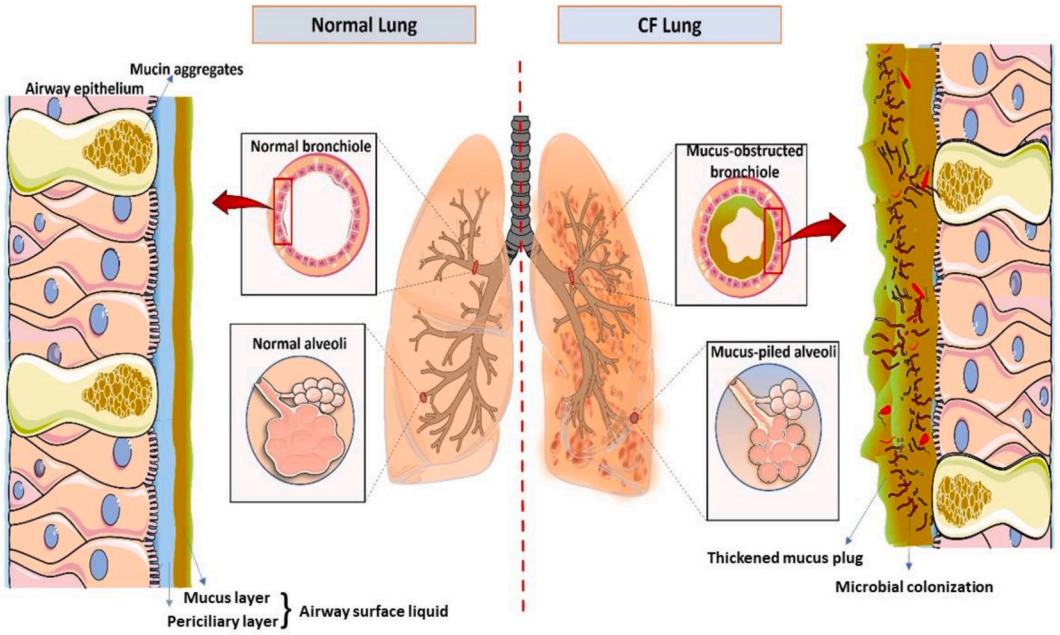

Fig. 3. Pathophysiological manifestation of CF in the lungs. In normal lungs, mucociliary clearance ensures that no microbes are hoarding the airways. In CF lungs, loss of airway surface liquid, defective mucin unfolding, mucus condensation, and loss of mucociliary activity contribute to accumulation of mucus within the airways thus favouring colonization of microbes, with infiltration of leukocytes and heightened NETosis contributing to tissue destruction and fibrosis.

microbes and debris along with mucus [24,43,44]. In CF, mucus thickening as a result of dysfunctional CFTR is attributed to the loss of airway surface liquid and delayed mucus clearance, and *vice versa*. Loss of mucociliary activity along with mucus thickening allows microbes to come in contact with surface epithelium resulting in the activation of pattern recognition receptors (PRRs) and the ensuing pathogen-associated molecular pattern (PAMP) response in these cells [25,33,45]. These events lead to loss of ciliary activity, release of antimicrobial mediators like defensins, and inflammatory mediators like cytokines, chemokines, and damage-associated molecular patterns (DAMPs) [13,24,46] (Fig. 3). It should be noted that, once PAMP-mediated inflammatory response is initiated at a specific site, it ripples out to nearby epithelial cells and parenchymal tissue as well as endothelium of capillaries with the aid of DAMP response [4,13]. Also, allergen/pollutant accumulation, pathogen entry, and DAMP response would lead to activation of alveolar dendritic cells and subsequent orchestration of T cell activation in lymphoid organs. Thus, inflammatory response culminates in endothelial activation and leukocyte infiltration into the parenchyma and the site of pathogen entry [26,47].

The DAMPs and proinflammatory cytokines in affected tissues prime conversion of most of the infiltrated immune cells towards proinflammatory phenotypes. Infiltrated neutrophils undergo degranulation, pyroptosis, and/or formation of neutrophil extracellular traps (NETs) by a process referred to as NETosis. Monocytes polarize into M1 macrophages, $CD4^+$ T cells into Th1/Th17 cells, while invariant natural killer (iNK) T cells and $CD8^+$ T cells undergo degranulation of reactive species and tissue destructing enzymes like perforins and granzymes [48–50]. A minor population of infiltrated neutrophils and monocytes (polarized into M2 macrophages) are channelized to phagocytose the invaded microbes. However, due to impairment in oxidative burst and lysosome-mediated pathogen digestion resulting from CF-associated dysfunctional CFTR, neutrophils and macrophages are only capable of establishing and amplifying the DAMP-mediated proinflammatory response but unable to effectively clear invaded pathogens as seen in normal individuals [33,35,51,52]. Once proinflammatory milieu spreads throughout the lung tissue, the resulting inflammatory response mainly through purinergic signaling further leads to complete loss of mucus clearance along with hypersecretion of mucin vesicles by the goblet cells as demonstrated in mouse models [17,22,46]. Also, the abundantly released ROS even with impaired cellular oxidative burst potentially remodels thickened mucus into a more condensed form by means of aberrant disulphide bridges between cysteine residues of mucins [53,54]. All of this leads to microbial colony establishment and biofilm formation usually due to *Pseudomonas aeruginosa* and non-typical *Hemophilus influenza* in the lungs of mice and humans [6,52]. Furthermore, thickened mucus and biofilm together could effectively shield bacteria from NETs, leukocyte attack, and other antibacterial factors like complements and immunoglobins since their movement inside the mucus is restricted due to increased viscosity and loss of fluidity [55].

It should be pointed out that the biofilm component of *Pseudomonas aeruginosa* (alginate) and the apoptotic bodies of epithelial cells are potent inducers of T2 immunity *via* M2 polarization and Th2 phenotype switching [13,52,56,57]. This might possibly explain why lungs of CF patients are also overcrowded with T2 immune cells at the same time. Yet, proinflammatory milieu from heightened leukocyte infiltration and subsequent conversion into T1 immune cells outweigh T2 immunity by a huge margin. This helps with the understanding of CF pathophysiology as inflamed air sacs swell up with thickened mucus, necrotic fluid, and inflammatory T1 immune cells as is the case with pneumonia, whereas fibroblasts infiltrating the parenchyma further destruct lung tissue by depositing excessive

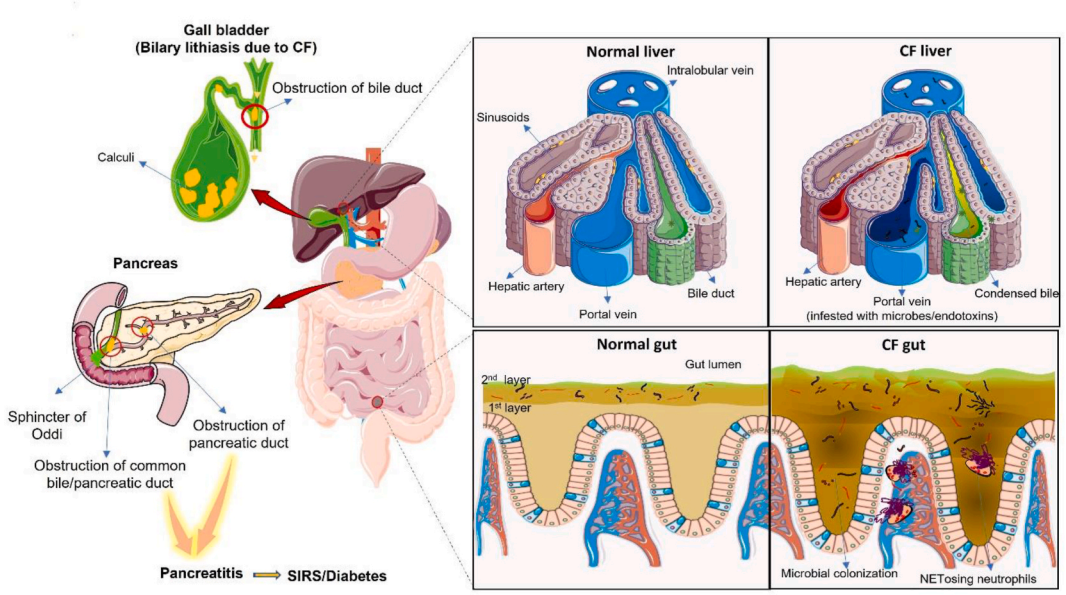

Fig. 4. Pathophysiological manifestations of CF in the gut, pancreas, and liver. Under normal conditions, gut microbiome is maintained within the outer mucosal layer whereas in CF, they breach into the leaky epithelium and stir an innate immune response involving NETosis that could influence liver physiology by transfer of DAMPs, microbes, and PAMPs into the hepatic portal system. Also, obstruction of the bile duct by gall stones further aggravates liver cirrhosis, while obstruction of the pancreatic duct or common bile/pancreatic duct by the mucus plug results in pancreatitis.

extracellular matrix to cause fibrosis [24,58,59]. Of note, early-stage thickened mucus is sufficient to establish a hypoxic environment which would only get worse with inflammatory response (NETosis and mucus hypersecretion) mediated by bacterial colonization and airway obstruction due to a hyperthickened mucosal biofilm resulting from aggregated *S*–S linked mucins and NETs (mid-stage), and finally with fluid accumulation due to complete loss of vascular and epithelial integrity resulting from excessive cell death (end-stage) [6,13,44,48]. In fact, hypoxia does play a major role in modulating the immune response in CF. On one hand, it potentially favours NK cell-mediated tissue destruction (since hypoxia is known to downregulate MHC I, a suppressor of NK cell engagement) and on the other hand, it favours Th2 immunity following extensive fibroblast infiltration, proliferation, and activity (mainly *via* IL-10 and TGF-β signaling) ultimately resulting in pneumonia-like tissue remodelling and fibrosis [60–64]. Taken together, accumulation of immune-modified mucus, immune-mediated tissue destruction, and immune-mediated fibrosis lead to a continuous source of initiators of proinflammatory signals, decreased number of air sacs, and decreased pulmonary air transactions, respectively [15,44,65,66].

Therefore, what started off as a local inflammatory reaction at pathogen contact site on the surface epithelium, persistent and lasting bacterial colonization due to a malfunctioning immune system, mucus thickening, and bacterial colonization in the biofilm all lead toward CF pathophysiology as PAMP-mediated inflammatory response initiates a tissue damage-dependent DAMP response, which now favours emergence of a systemic inflammatory response [10,13,67].

3.2. The digestive system

Loss of CFTR also affects normal functioning of the digestive system. Modulation of Cl^- concentration is vital for maintaining the composition of saliva, gastric juice, mucus, and commensal microbiota as well as processes, like food digestion, nutrient absorption, and excretion [68–71]. And since Cl^- transport is predominantly controlled by CFTR, complications due to an ineffective digestive system is quite inevitable in CF (Fig. 4).

3.2.1. Salivary glands

In the acini of human salivary glands which contain secretory cells, acetylcholine-mediated secretion of zymogens (α-amylase) from serous cells and aldosterone-induced secretion of mucins from seromucous cells to form primary saliva is facilitated by the co-ordinated activities of aquaporin 5 and ion channels, mainly Cl^- and HCO_3^- on the apical and luminal surfaces [72,73]. Absence of CFTR on serous cell membrane facing the lumen results in reduced influx of Cl^- from lumen into the cells coupled with reduced efflux of HCO_3^- from cells into the lumen. This limits the release of Na^+, Cl^-, and water through apical surface into the luminal duct. Later in the ductal cells of mice and humans, the absence of CFTR on apical membrane instead of releasing HCO_3^- and absorbing NaCl results in reduced uptake of Cl^- and increased resorption of HCO_3^-, Na^+, and water into the cells [69,72,74]. The net result is a reduction in the volume of saliva by 15 times (of the usual 1.5 L), which is now of thickened/hypertonic nature [75]. It has been reported that such a phenomenon also occurs during sepsis and from elevated proinflammatory cytokines during systemic inflammatory response in mouse models [76,77]. Since changes in the salivary constituents, like electrolytes, lactoferrin, amylase, lipase, kallikrein, lysozymes, DAMPs,

and IgA among others in CF is not well studied, it is worth exploring.

3.2.2. Gastrointestinal tract

Unlike lungs, the gastrointestinal tract is made up of four layers, namely mucosa (innermost), submucosa, muscularis propria, and serosa, and lacks ciliary activity on its inner mucous (epithelial) layer. The loose, mobile outer mucous (muscular) layer often enriched with microbiome is continuously cleared by shear forces generated by the moving luminal contents. Entry of microbes into the inner mucous layer and subsequent formation of biofilm from microbial colonization on the epithelial surface is limited by the rapid turnover of mucus along with epithelial cells [13,15]. Yet breaching by microbes, especially mucus-degrading microbes or microbial molecules into inner mucous layer occurs very often, which is managed by continuous secretion of mucin 2 from the goblet cells to form the stratified mucous layer. This replaces the entire inner mucous layer in a matter of hours whereby invading microbes are pushed away from the epithelial surface [15,17]. Even if microbes make contact with the epithelium, PAMP response (*via* TLR/Myddosome/inflammasome or TLR/PIDDosome) elicited within these cells would activate nearby epithelial and goblet cells [38,47,49,78,79]. Activated epithelium facilitates entry of leukocytes, mainly neutrophils, from Peyer's patches into the lumen which undergoes NETosis with NETs acting as a barrier as well as a trap for the microbes. Also in mice and humans, activated goblet cells hyperexocytose mucin in order to sequester free or trapped microbes into the mucus plug which later gets carried into the lumen [15,78,80–82]. This defence mechanism is especially important in regions of crypt opening, where a single sentinel cell in each crypt opening guards intestinal stem cells from microbes by activating nearby goblet cells to secrete MUC2 *via* Ca^{2+} signaling from TLR activation [17,83].

In the absence of CFTR, gut surface epithelial cells malfunction in a manner similar to airway surface epithelial cells, where mucus thickening, microbial invasion, and immune response become inevitable leading to CF-related pathology in the gut [15,78]. Due to mucus obstruction and altered mucus nature, inner mucous membrane of CF patients always remains permeable to microbes which colonize in the mucous biofilm. While the lung is mostly colonized by a single microbial species, the intestine (and mucous biofilm) is usually colonized by several different microbes due to the presence of thousands of species in the gut [15,84]. Colonized microbes act as a continuous source of PAMP signals for the activation of surface epithelial cells, sentinel cells, and ultimately immune cells in Peyer's patches through conductance of PAMP/DAMP response in mucosa-associated lymphoid tissue, where active inflammatory response and breakdown of epithelial barrier result in excessive NETosis, mucus thickening, loss of intestinal stem cells, reduced bowel movement, altered microbiome, hampered nutrient absorption (including short-chain fatty acids), and malfunctional excretion [80,83,85]. In addition to eliciting inflammasome activation upon direct contact with TLRs of epithelial cells, altered microbiome could also facilitate desialylation and breakdown of membrane and other secreted glycoproteins (including mucins) by producing enzymes, like sialidases, fucosidases, proteases, and sulfatases thus favouring mucus breakdown and microbial breaching [86]. Since, immune cells and complement system recognize any protein as self or non-self primarily through sialylation and fucosylation patterns of these proteins, manifestation of desialylation and defucosylation of membrane and soluble proteins (mainly immunoglobulins) results in heightened innate immune response *via* abrogation of Siglec-mediated signaling, and also leads to complement activation upon contact of sialidase/fucosidase with blood thus augmenting the inflammatory signaling process [65,86]. Also, loss of commensal bacteria that are capable of synthesizing short-chain fatty acids from dietary fibres in the gut of CF patients could result in mired activation of Nrf2/Sirt1 resulting in uncorroborated anti-oxidant and anti-inflammatory responses [87,88]. Noteworthily, 10% of newborns with CF have mucus obstruction only in the gut (and not in the lungs) since their gut is colonized by microbes even before birth, where a diverse microbiome similar to that of an adult exists [89–93]. This clearly demonstrates that gut may be the first organ to be affected by dysfunctional CFTR where the severity of CF could be determined by the extent of microbial infection and PRR-mediated signaling.

3.2.3. Pancreas

Pancreas serves both as an exocrine gland that secretes digestive enzymes from acini into the duodenum as well as an endocrine gland that secretes hormones from islets into the circulation. The pancreatic juice consists of water and about 200 different proteins and ions, mainly HCO_3^-, Na^+, Cl^-, and K^+, that all play a vital role in mediating digestion, stomach acid neutralization, cell growth, and immunity [94]. Upon vagal stimulation, acinar cells secrete zymogens and other digestive enzymes, like phospholipase A2, amylase, nuclease, and proteases including elastase along with release of protons into the acini (pH 6.8). Later when duodenum receives chyme from the stomach, it releases secretin and cholecystokinin, both of which have control over pancreatic function. Secretin increases secretion of HCO_3^- from ductal cells into the ductules to about six times the plasma HCO_3^- concentration, while cholecystokinin regulates the flow of acidic fluid containing digestive enzymes from acini through the HCO_3^--rich lumen resulting in an increase in fluid pH to 8.0, which is released into the pancreatic duct and later drained into duodenum to neutralize stomach acid to facilitate the activity of digestive enzymes [95,96].

The most common manifestation of CFTR dysfunction in the pancreas is duct obstruction by stones or viscid mucus, where loss of flow of bile salts and pancreatic juice into the duodenum results in improper digestion/absorption (pancreatic insufficiency), although severe inflammatory response from autolysis (pancreatitis) leading to systemic inflammatory response syndrome (SIRS) and diabetes could occur [4,97–99]. Also, hindered autophagy due to failed lysosome acidification contributes to diabetes and other metabolic disorders [42]. On one hand, CFTR maintains the pH of pancreatic juice by facilitating HCO_3^- secretion from SLC26A3 of luminal cells while on the other hand, it maintains the nature of mucus by facilitating aquaporin-mediated hydration and limiting ENaC-mediated Na^+ absorption [95,99]. Mucus obstruction in the pancreatic duct would lead to accumulation of digestive enzymes within pancreas for a prolonged period of time to mediate autolysis of pancreatic tissue resulting in the release of excessive DAMPs and the accompanying inflammatory response [97]. Unlike lungs and gut where the severity of CF pathology is due to PRR-mediated signaling from bacterial infections, the manifestation in pancreas is exclusively due to PRR signaling mediated by DAMPs generated from autolysis

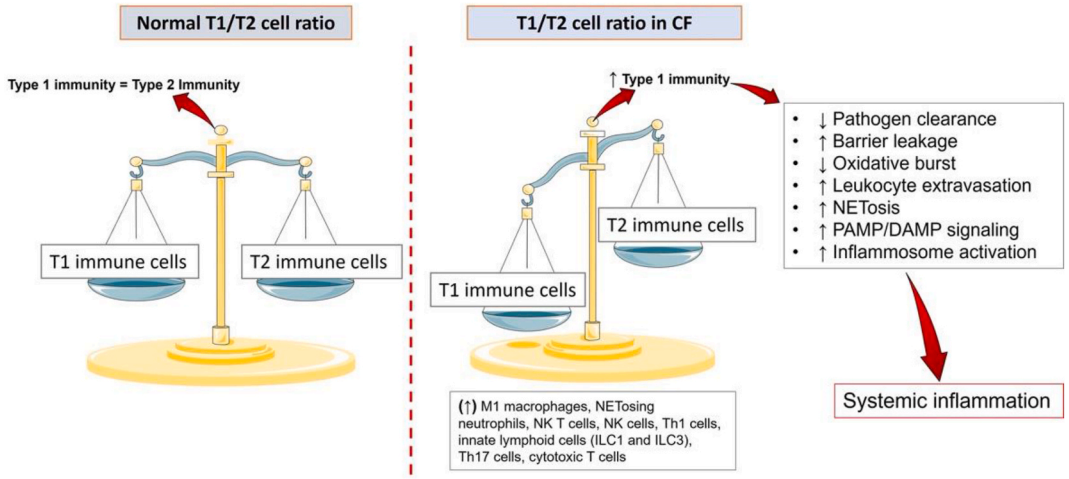

Fig. 5. T1/T2 immune cell ratio switching in circulation and parenchyma of organs in CF. Due to elevated PAMP response and the release of proinflammatory cytokines in CF, innate immune cell hyperactivation in blood occurs where the infiltrated monocytes, neutrophils, and $CD4^+$ T cells become polarized into proinflammatory type 1 immune cells (M1 macrophage/NETosing neutrophil/Th1 cells) leading to decreased T1/T2 immune cell ratio within parenchyma. This switch in ratio culminates in the release of more proinflammatory cytokines into the circulation to accelerate the systemic inflammatory response.

[97,98].

Apart from life-threatening inflammatory responses that occur rarely in pancreas and liver, pancreatic insufficiency along with bile obstruction and de-neutralized stomach acid affects almost all CF patients, where the process of digestion and absorption, especially that of fats and fat-soluble vitamins like vitamin K is compromised depending on severity leading to altered microbiome (acidophilic microbes), retarded growth due to malabsorption, and impaired blood vessel integrity due to hypocoagulable blood [72,97,98,100]. In newborns, reduction in fecal elastase 1 due to pancreatic insufficiency serves as a diagnostic marker since lung infections are unlikely, and also neonatal biopsies are not done for ethical reasons [101].

3.2.4. *Liver*

Unlike other organs, liver gets affected at a later stage secondary only to intestinal and pancreatic complications [11,102]. About 80–90% of bile along with dietary polyphenols and other components, like endotoxins, short-chain fatty acids, and trimethylamine (derived from microbiota) absorbed from the intestine is returned to liver through the hepatic portal system [103,104]. If gut homeostasis is lost as in the case of CF, the resulting microbial dysbiosis would lead to passage of endotoxins, and in critical cases microbes into hepatic portal system to upset the liver *via* PAMP/DAMP response [103,105]. Also, the hepatocytes actively endocytose and process xenobiotics with the help of phase I and II enzymes as well as phase 3 transporters, which could be later released into the bloodstream if hydrophilic or bile fluid if hydrophobic [106]. So, bile fluid stored in the gall bladder could contain endotoxins and hydrophobic xenobiotics along with cholesterol, salts, and bile acids [107–109]. It is important to maintain bile flow without any obstruction in order to avoid liver damage and excessive fibrosis from inflammatory consequences due to pervasive PRR-mediated signaling [10]. Hence, it is crucial to maintain its pH and fluidity as it crosses through cholangiocytes before getting released into the gall bladder, in the absence of which gall stone formation and biliary obstruction occurs resulting in cholestasis [110,111].

Cholestasis would lead to accumulation of toxic bile over the biliary epithelium within liver and gall bladder resulting in damage to the epithelium at first before progressing to chronic liver dysfunction/fibrosis [38,104,112]. Since cholangiocyte CFTR in the bile duct is essential for maintaining bile pH and viscosity (*via* HCO_3^- release), the incidence of cholestasis becomes inevitable in CF patients [104,111,113]. On the other hand, due to loss of intestinal epithelial integrity and microbial dysbiosis from dysfunctional CFTR, microbes breach into the liver through hepatic portal vein paving way for PAMP-mediated endothelial activation and extensive leukocyte infiltration, where release of DAMPs including ATP facilitates purinergic signaling to amplify the inflammatory response [66,103,104,114]. This would mediate bile release independent of CFTR, thereby nullifying the benefit of bile secretion impairment due to diminished cholic acid signaling resulting from dysfunctional CFTR [104,115,116]. Accordingly, liver failure due to prolonged inflammatory milieu/fibrosis or acute liver damage ensues depending on the extent of microbial infection/PRR-mediated signaling.

Similarly in the lumen of hepatic duct, CFTR is essential for mucus homeostasis and secretion of HCO_3^-, Na^+, and water from cholangiocytes in response to secretin/protein kinase A, whereby secreted bile acids from the liver are solubilized, liquefied, and neutralized before entering gall bladder [104,111,116]. Ions and water molecules are absorbed from the bile fluid in response to acetylcholine secretion where CFTR plays a key role in stopping bile fluid from getting too concentrated inside gall bladder. CFTR dysfunction results in mucus thickening in the hepatic duct and reduction in bile fluid volume leading to obstruction in its flow into the gall bladder [104,111,113].

CFTR dysfunction contributes to the accumulation of cytosolic Cl^- [99,117]. Increase in the levels of cytosolic Cl^- and ClO^- (generated from free myeloperoxidase) is responsible for histone chlorination [118]. We speculate that histone chlorination could

hinder its net electronegative charge from aiding in DNA condensation leading to histone eviction and chromatin decondensation thus favoring both suicidal and vital NETosis. Myeloperoxidase, free from azurophilic granules are enriched both in cytosolic and nuclear portions of neutrophils from the mucus of CF patients. Interestingly, these neutrophils were found to be actively undergoing NETosis within the mucus, abetting our speculation [119]. Recently, gallstone formation was attributed to NETosis, and in fact, NETs were found to be a major component of gallstones, others being cholesterol and mucins [120]. Moreover, hyperinfiltration of neutrophils and excessive NETosis are hallmarks of CF pathophysiology due to elevated PRR-mediated signaling from PAMP/DAMP response [59] (Fig. 5). Of note, mucus production from tuft cells of the gall bladder could also contribute to gallstone formation in CF by increasing the viscosity of bile fluid due to altered pH and massive dehydration [83,91].

Hence, loss of CFTR function leads to hyperconcentration of already concentrated/insolubilized bile acids resulting in gallstone formation, which in part, is accompanied by excessive NETosis involving CFTR-deficient neutrophils upon inflammatory PRR-mediated signaling following pathogen intrusion. Thus, CFTR is vital for limiting gallstone formation as evidenced from higher incidence of gallstones among CF patients [111]. Also, CFTR loss facilitates mucus plugging upstream of sphincter of Oddi limiting bile flow into the duodenum through common bile and pancreatic ducts even in the presence of cholecystokinin stimulus. This obstruction of bile flow in the ducts would eventually result in sustained inflammatory response, portal vein hypertension (rarely), and ultimately scarring and damaging of the liver (cirrhosis) [38,72,91,97,98,121].

3.3. The reproductive system

Although CF affects both male and female reproductive systems, most severe outcomes are commonly observed only in males [1, 122]. Upon development, sperms from the testes move to epididymis from where mature sperms reach the ejaculatory duct following mixing with seminal fluid, and finally urethra before ejaculation. Like any other duct, vas deferens also secretes mucins forming the mucus layer which is vital to facilitate sliding of sperms through the duct. Because of mucus obstruction in the vas deferens which occurs in about 95% of CF patients, sperms do not make their way to the ejaculatory duct thus making the person infertile, although 90% of CF males produce sperms. Less than 5% of CF males lack vas deferens right from birth which is referred to as congenital bilateral absence of vas deferens. Thus, 95–98% of males with CF become infertile with some of them even becoming sterile [122–125].

Unlike males, most CF females do not face major reproductive problems, although a small number of them have issues getting pregnant. The upper tract with the ovaries, fallopian tubes, uterus, and the endocervix and the lower tract, consisting of the ectocervix and vagina forms the female reproductive system. A mid-transformation zone between these tracts demarcates an immunologically active region where a stratified squamous epithelium narrows down to a single layer of columnar epithelium, a seemingly target for pathogenic invasion. The CFTR harboring epithelial cells of the endocervical layer secrete cervicovaginal mucus that lines the cervical canal through the vaginal cavity and hosts a commensal microflora that could be likened to the gut microbiota, the former being lactobacilli dominant [126]. This microbial population, in addition to lowering vaginal pH, has been argued to be locally activating and regulating a complement-mediated inflammatory response during pregnancy and parturition, thus competitively inhibiting pathogenic entry. In a plethora of ways reflecting the airway and other epithelial tissues discussed thus far, a scanty and heavily dehydrated mucosal barrier in CF females allows easier infection specifically by sexually acquired parasites, including herpes simplex virus type 2 (genital herpes), hepatitis B virus, human papillomavirus (cervical cancer/genital warts) and mainly, human immunodeficiency virus (AIDS). Again, CFTR dysfunction and the severity of CF serves as a critical determinant of pathogenic invasion, PRR-mediated activation of neutrophils and macrophages by PAMPs, altered inflammatory milieu as the mucosal barrier is breached and systemic dissemination is initiated [127].

On the other hand, thickened cervical mucus impedes the movement of sperms towards the egg [122]. Sometimes, net physiological outcome from nutrient malabsorption, systemic inflammation, hypertension, and lung dysfunction could result in ovulation-related problems in mammals including mice and humans [122,125,128]. Premature/preterm births, terminations, and miscarriages are also prevalent among CF females, yet a correlation between CF and preeclampsia is lacking [129]. Altogether, the incidence of microbial infections in both CF males and females could be much higher than the normal population as the microbial clearance potential of leukocytes is reduced due to impaired lysosomal acidification and oxidative burst as discussed earlier. It is well-known that altered microbiota in the reproductive organs of both male and female patients worsens the incidence of urinary tract infections and even prostate and cervical cancers. Even though CFTR overexpression has been associated with cancer progression in humans [130], an association between dysfunctional CFTR in CF patients and carcinogenesis and urinary tract infections has not been documented yet.

4. Conclusion

As discussed above, CF can be considered as an inflammatory disease that originates from CFTR dysfunction. Due to loss of epithelial barrier function and defective pathogen clearance mechanisms, opportunistic pathogens, virions, and allergens gain access to the parenchymal tissues of both respiratory and digestive systems. In particular, establishment of a bacterial colony in lungs triggers PAMP-mediated inflammatory response that could potentially lead to heightened systemic inflammatory response/sepsis. This is because lungs are the major site of thrombopoiesis where an extreme manifestation of platelet mediated-NETosis becomes inevitable leading to release of excessive DAMPs into the circulation. Notably, CFTR dysfunction is capable of initiating sterile inflammatory response independent of bacterial infections. Also, inflammatory response-mediated fibrosis of the lungs and loss of alveolar numbers from CF contributes to hypoxia-associated muscle wastage, prothrombotic condition, neurodegeneration, disturbance of circadian rhythm, and pre-eminent vascular pressure among other pathological outcomes. Although disease manifestations in liver and pancreas

Table 1
Stages and immune cell signatures in CF disease progression.

CF severity and features	Early stage	Mid-stage	End stage
Immune cell signature and immune response	1) T1 < T2 2) Mild/localized PAMP response 3) Compromised phagosome activity with mild NETosis 4) No type 2 inflammation	1) T1 = T2 2) Comprehensive PAMP response 3) Severe NETosis with moderate DAMP response 4) Type 2 inflammation severity unknown	1) T1 > T2 2) Extreme PAMP response 3) Extreme NETosis with severe DAMP response 4) Type 2 inflammation severity unknown
Infection	Mild (gut)	Severe (gut, lungs)	Extreme (gut, lungs, liver)
Manifestation	Mucus thickening, microbial dysbiosis	Dysbiosis, lung infection, multi-organ fibrosis	Pneumonia, liver cirrhosis, sepsis
Systemic inflammatory response syndrome	Mild	Moderate	Severe

also impact the quality of life of CF patients, severity of the disease and disease outcome is mainly dependent on the extent of damage occurring to the lungs.

Therefore, degree of CF severity totally relies on the extent of systemic inflammatory milieu arising from host-pathogen/allergen interactions (PAMP/DAMP responses) upon microbial colonization including that of viruses like SARS-CoV2 in the lungs. Though abridged generation of HOCl, a key ROS/RCS in CF contributes towards insufficient innate immune response, persistence of PAMP-mediated signaling due to microbial intrusion aggravates NETosis and facilitates lung fibrosis, even multi-organ failure upon orchestration of severe SIRS. The occurrence of secondary outcomes, such as diabetes, vascular dysfunction, and cancer due to prolonged inflammatory milieu in CF patients is well-established, which could determine overall ailment and life expectancy due to the disease. Also, the role of type 2 inflammation in CF disease progression is not yet explored. Since Th2 immune response contributes to type 2 inflammation-associated fibrosis *via* IL-4/13-Bcell-IgE-eosinophil axis, and that Th2 immune response is elicited even at an early stage of CF, it is reasonable to contemplate involvement of type 2 inflammation (associated with Th2 cells, not to be confused with type 2 immunity) in aggravating the fibrotic condition similar to asthma. Although the contributing nature of autoimmune diseases like lupus in systemic inflammation is well-known, the reason behind elevated incidence of these diseases among CF patients remains elusive. Hence, this allows us to postulate that systemic inflammation (as seen in CF) could contribute to the incidence of autoimmune conditions early on.

After carefully assessing various factors influencing CF disease progression, we propose an association of immune cell function with CF (Table 1).

Since the role of CFTR on metabolism, hematopoiesis, stem cell exhaustion, nerve cell conduction, immunosenescence, and thrombopoiesis is still unknown, the impact of CF pathophysiology on these processes remains an enigma. Conspicuously, compensation of CFTR dysfunction by other Cl^- channels, mainly ClCs and CLICs to limit ENaC activity and HCO_3^- synthesis could explain the disparity in disease progression between two patients carrying the same mutation. However, the role of thrombopoiesis from hypertensive lung vessels in exaggerating microvascular coagulopathy and systemic inflammatory response is well-established. This implies contribution of hypertension towards the progression of CF suggesting prophylactic use of vasodilators and blood thinners as effective alternative treatment options. While antibiotics, CFTR modulators, and mucolytics (including DNAse) are in common use for the management of CF on a daily basis, immunomodulators like steroids, vasodilators like low-dose Viagra, anti-coagulants like factor V inhibitors, and NETosis inhibitors like Nec-1 could also be considered as potential therapeutic indicators for the future. In the meantime, autologous gene therapy that could replace CFTR mutants with normal copies of the CFTR gene is still fraught with several challenges.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

No data was used for the research described in the article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Hamai, A. Hamann, M. Hamasaki, I. Hamer, Q. Hamid, E.M. Hammond, F. Han, W. Han, J. T. Handa, J.A. Hanover, M. Hansen, M. Harada, L. Harhaji-Trajkovic, J.W. Harper, A.H. Harrath, A.L. Harris, J. Harris, U. Hasler, P. Hasselblatt, K. Hasui, R. G. Hawley, T.S. Hawley, C. He, C.Y. He, F. He, G. He, R.R. He, X.H. He, Y.W. He, Y.Y. He, J.K. Heath, M.J. Hébert, R.A. Heinzen, G.V. Helgason, M. Hensel, E. P. Henske, C. Her, P.K. Herman, A. Hernández, C. Hernandez, S. Hernández-Tiedra, C. Hetz, P.R. Hiesinger, K. Higaki, S. Hilfiker, B.G. Hill, J.A. Hill, W.D. Hill, K. Hino, D. Hofius, P. Hofman, G.U. Höglinger, J. Höhfeld, M.K. Holz, Y. Hong, D.A. Hood, J.J.M. Hoozemans, T. Hoppe, C. Hsu, C.Y. Hsu, L.C. Hsu, D. Hu, G. Hu, H.M. Hu, H. Hu, M.C. Hu, Y.C. Hu, Z.W. Hu, F. Hua, Y. Hua, C. Huang, H.L. Huang, K.H. Huang, K.Y. Huang, S. Huang, S. Huang, W.P. Huang, Y. R. Huang, Y. Huang, Y. Huang, T.B. Huber, P. Huebbe, W.K. Huh, J.J. Hulmi, G.M. Hur, J.H. Hurley, Z. Husak, S.N.A. Hussain, S. Hussain, J.J. Hwang, S. Hwang, T.I.S. Hwang, A. Ichihara, Y. Imai, C. Imbriano, M. Inomata, T. Into, V. Iovane, J.L. Iovanna, R.V. Iozzo, N.Y. Ip, J.E. Irazoqui, P. Iribarren, Y. Isaka, A.J. Isakovic, H. Ischiropoulos, J.S. Isenberg, M. Ishaq, H. Ishida, I. Ishii, J.E. Ishmael, C. Isidoro, K.I. Isobe, E. Isono, S. Issazadeh-Navikas, K. Itahana, E. Itakura, A.I. Ivanov, A.K.V. Iyer, J.M. Izquierdo, Y. Izumi, V. Izzo, M. Jäättelä, N. Jaber, D.J. Jackson, W.T. Jackson, T.G. Jacob, T.S. Jacques, C. Jagannath, A. Jain, N.R. Jana, B.K. Jang, A. Jani, B. Janji, P.R. Jannig, P.J. Jansson, S. Jean, M. Jendrach, J.H. Jeon, N. Jessen, E.B. Jeung, K. Jia, L. Jia, H. Jiang, H. Jiang, L. Jiang, T. Jiang, X. Jiang, X. Jiang, Y. Jiang, Y. Jiang, A. Jiménez, C. Jin, H. Jin, L. Jin, M. Jin, S. Jin, U.K. Jinwal, E.K. Jo, T. Johansen, D.E. Johnson, G.V. W. Johnson, J.D. Johnson, E. Jonasch, C. Jones, L.A.B. Joosten, J. Jordan, A.M. Joseph, B. Joseph, A.M. Joubert, D. Ju, J. Ju, H.F. Juan, K. 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Moore, M.N. Moore, R. Mora-Rodriguez, P.I. Moreira, E. Morel, M.B. Morelli, S. Moreno, M.J. Morgan, A. Moris, Y. Moriyasu, J. L. Morrison, L.A. Morrison, E. Morselli, J. Moscat, P.L. Moseley, S. Mostowy, E. Motori, D. Mottet, J.C. Mottram, C.E.H. Moussa, V.E. Mpakou, H. Mukhtar, J.M. M. Levy, S. Muller, R. Muñoz-Moreno, C. Muñoz-Pinedo, C. Münz, M.E. Murphy, J.T. Murray, A. Murthy, I.U. Mysorekar, I.R. Nabi, M. Nabissi, G.A. Nader, Y. Nagahara, Y. Nagai, K. Nagata, A. Nagelkerke, P. Nagy, S.R. Naidu, S. Nair, H. Nakano, H. Nakatogawa, M. Nanjundan, G. Napolitano, N.I. Naqvi, R. Nardacci, D.P. Narendra, M. Narita, A.C. Nascimbeni, R. Natarajan, L.C. Navegantes, S.T. Nawrocki, T.Y. Nazarko, V.Y. Nazarko, T. Neill, L.M. Neri, M. G. Netea, R.T. Netea-Maier, B.M. Neves, P.A. Ney, I.P. Nezis, H.T.T. Nguyen, H.P. Nguyen, A.S. Nicot, H. Nilsen, P. Nilsson, M. Nishimura, I. Nishino, M. Niso-Santano, H. Niu, R.A. Nixon, V.C.O. Njar, T. Noda, A.A. Noegel, E.M. Nolte, E. Norberg, K.K. Norga, S.K. Noureini, S. Notomi, L. Notterpek, K. Nowikovsky, N. Nukina, T. Nürnberger, V.B. O'donnell, T. O'donovan, P.J. O'dwyer, I. Oehme, C.L. Oeste, M. Ogawa, B. Ogretmen, Y. Ogura, Y.J. Oh, M. Ohmuraya, T. Ohshima, R. Ojha, K. Okamoto, T. Okazaki, F.J. Oliver, K. Ollinger, S. Olsson, D.P. Orban, P. Ordonez, I. Orhon, L. Orosz, E.J. O'rourke, H. Orozco, A. L. Ortega, E. Ortona, L.D. Osellame, J. Oshima, S. Oshima, H.D. Osiewacz, T. Otomo, K. Otsu, J.H.J. Ou, T.F. Outeiro, D.Y. Ouyang, H. Ouyang, M. Overholtzer, M.A. Ozbun, P.H. Ozdinler, B. Ozpolat, C. Pacelli, P. Paganetti, G. Page, G. Pages, U. Pagnini, B. Pajak, S.C. Pak, K. Pakos-Zebrucka, N. Pakpour, Z. Palková, F. Palladino, K. Pallauf, N. Pallet, M. Palmieri, S.R. Paludan, C. Palumbo, S. Palumbo, O. Pampliega, H. Pan, W. Pan, T. Panaretakis, A. Pandey, A. Pantazopoulou, Z. Papackova, D.L. Papademetrio, I. Papassideri, A. Papini, N. Parajuli, J. Pardo, V.V. Parekh, G. Parenti, J.I. Park, J. Park, O.K. Park, R. Parker, R. Parlato, J.B. 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