In every organism, cells and tissues are continuously exposed to diverse internal and environmental stimuli that are counteracted by cellular homeostatic functions [1]. In diseased states, these stimuli become extreme and are referred to as stresses [2, 3]. Internal stresses are usually elicited by damaged proteins as the result of genetic mutations [4-8] or posttranslational modifications [9, 10]. External or environmental stresses include infections, toxins, radiation, smoke, hypoxia, and extreme temperatures [11-13]. Cells respond to stresses by initiating complex signaling mechanisms, SRPs, which developed to eliminate either the stressor or the damaged cells. Depending on the insult, the responses can be organelle specific, such as the ER stress response (UPR) and mitochondrial UPR, or generalized, such as the ISR that is activated primarily by cytosolic stresses, but has significant interactions with the UPR [14]. Although SRPs regulate physiological functions such as synaptic function [15] and plasma cell differentiation [16], chronic activation of SRPs, or the inability of cells to recover from stresses, leads to disease development in different organs [17]. These include, but are not limited to neurological [18, 19], metabolic [20], cardiovascular [21], airway [22-24], and kidney [25] diseases. During the past two decades, the molecular mechanisms of cellular stress responses and their contribution to human disorders have been identified and summarized in excellent reviews [11, 13, 26-31].

In this review article, we provide an overview of CF and summarize our present understanding of the most prevalent stressors and SRPs that may contribute to the pathogenesis of this genetic disorder. Considering that SRPs are not always pathogenic but function to maintain cellular homeostasis under physiological conditions, we also review experimental CF treatment approaches that are intended to interfere with cellular homeostatic processes for therapeutic benefit. Importantly, while inhibiting some SRP may be beneficial in reducing the pathological changes, enhancing others may be necessary to improve CFTR expression and function.

**Keywords:** cystic fibrosis, stress responses, pathogenesis, inflammation

**1 Introduction**

In every organism, cells and tissues are continuously exposed to diverse internal and environmental stimuli that are counteracted by cellular homeostatic functions.
2 CYSTIC FIBROSIS

2.1 Cause

CF is a monogenic, autosomal recessive, genetic disorder caused by mutations in the 180 kb, cystic fibrosis transmembrane conductance regulator (CFTR) gene, localized to the long arm of chromosome 7 that encodes the 1480 amino acid long CFTR protein [32-34]. Though mutations in the CFTR gene cause CFTR protein damage and consequential chloride and bicarbonate transport defects, severe infections and inflammation significantly contribute to CF pathogenesis (for review: [35]). The CFTR protein, a chloride [36-38] and bicarbonate [39-42] channel, is primarily expressed on the apical surface of epithelial cells lining the ducts of exocrine secretory glands, airways, and gastrointestinal (GI) tract. Defects in CFTR lead to altered excretory function and pathological changes in multiple organs with differing severity, illustrating that a single gene defect can lead to variable clinical symptoms [43].

Traditionally, CFTR mutations were classified into four [44], then six groups (Figure 1) based on their impact on the synthesis, intracellular trafficking, and function of the CFTR protein [45]. A more recent classification, referred to as theratyping, intends to include the complex, molecular/cellular phenotypes of CF alleles as well as the responses of specific mutations to presently available corrector and potentiator compounds [46]. Although ~2000 mutations have been identified in CFTR, deletion of phenylalanine at the 508 position is the most frequent and contributes to > 90% of CF cases. Other mutations are often linked to specific geographical regions and only few have a frequency above 1% (listed in the CFTR Mutation Database, http://www.genet.sickkids.on.ca/cftr/). CFTR is an ATP-binding cassette C (ABCC7) transporter, containing an N-terminal intracellular tail, 12 transmembrane segments, two nucleotide domains, and a regulatory domain [47]. The majority of the CFTR protein is localized to the cytosolic side of the membrane and the folding of the large cytosolic domains is primarily cotranslational [48].

2.2 Frequency

According to the Cystic Fibrosis Foundation patient registry, more than 30,000 patients in the United States and over 70,000 patients worldwide are living with CF. It occurs in ~1 of 2500 births among people with European ancestry, but the carrier frequency is 1 in 25 individuals, making it the most common life-limiting monogenetic disorder in this demographic group (https://www.cff.org/Research/Researcher-Resources/Patient-Registry/).

Figure 1. Classification of CFTR defects. I. Gene deletion or a mutation leading to lack of CFTR mRNA. II. Mutations resulting in protein misfolding and ERAD. The most frequent mutation belongs to this group. III. Mutations leading to unfunctional CFTR (Chloride and bicarbonate conductance). IV. Functionally defective CFTR with residual function, causing mild CF. V. Low levels of CFTR with proper function. VI. Short half-life of the protein, caused by defects in recycling and early lysosomal degradation.
2.3 Affected organs

The airways, GI tract, pancreas, sweat glands, hepatobiliary system, and genital organs are commonly affected in CF. But the most severe, life-limiting symptoms of CF originate from persistent, recurrent airway infections and airway injury leading to bronchiectasis, respiratory, and secondary cardiac failure. Pancreatic duct obstruction and fibrosis begin in utero, resulting in exocrine pancreatic insufficiency in 90% of patients [35]. Without treatment, meconium ileus develops in ~10% of newborns with CF [49]. Diagnosis is enabled by measuring abnormally high levels of chloride (Cl⁻) and sodium (Na⁺) in the sweat, which was used as a diagnostic standard for CF before genetic testing became routine practice [50-53]. The majority (95%) of adult males with CF suffer from infertility, caused by azoospermia as a result of the absence of vas deferens (CBAVD). Additional disease manifestations include liver cirrhosis and diabetes mellitus [54]. However, it is still not fully understood how CFTR defects contribute to CF’s complex pathologies leading to a severe systemic disorder requiring continuous symptomatic treatment regimes, with frequent hospitalizations that ultimately contribute to a limited lifespan.

2.4 Life expectancy and therapy

With symptomatic therapies alone, the life expectancy of patients with CF has increased significantly during the past three decades to > 40 years for those born today despite no further advancement in therapies (https://cysticfibrosisnewstoday.com/2017/05/24/living-cf-life-expectancy/). With the support of the North American Cystic Fibrosis Foundation (NACFF), research efforts are actively being directed towards developing causative, supplementary, and symptomatic therapies for CF. Small molecular CFTR correctors assist in the folding of mutant CFTR and primarily target the most frequent, F508del mutation [55, 56]. Premature termination codon mutations (PTC) in the CFTR gene are treated with read through compounds that allow the synthesis of full length, functional CFTR [57]. CFTR potentiators are intended to enhance the activity of CFTR that is present at the cell surface [58, 59]. In addition, supportive therapeutics, designed to enhance CFTR expression, fight infections, and reduce pathological changes are also in the pipeline and provide hope for patients with CF [60-62]. Importantly, adolescents and adults with CF often suffer from multiple organ damage and even if a causative treatment that corrects the genetic defects in CFTR in newborns would be developed in the near future, tens of thousands of patients will require supportive therapies to prevent and reduce the consequences of the pathological events. Therefore, understanding the complex pathogenesis of CF is extremely important.

3 Stresses and stress response activation in cystic fibrosis

3.1 CFTR misfolding does not activate the UPR

Protein misfolding in the ER activates the UPR [63]. Therefore, it may sound logical that traditional Class II mutations (Figure 1), which result in CFTR misfolding and include the most common CFTR mutation, [64] activate the UPR. However, we must clarify that UPR activation by folding mutants occurs when the defective proteins are expressed at high levels and accumulate in the ER [65]. In contrast, F508del CFTR is expressed at very low levels, cotranslationally ubiquitinated [66], and quickly degraded by the proteasome [67, 68]. The process of ER associated degradation (ERAD) of F508del CFTR begins cotranslationally [66] and CFTR does not accumulate in the ER under conditions when the protein is endogenously expressed in cells. Significant overexpression of CFTR, or inhibition of ERAD by proteasome inhibitors are necessary to accumulate CFTR in the ER and activate the UPR [69]. Furthermore, the topology of CFTR is such that the majority of CFTR protein is localized to the cytosolic side of the ER membrane, with only short loops inside the ER [70]. Mutations that result in CFTR misfolding, such as the del mutation, are localized to the cytosolic domains. Further, endogenous CFTR expression is low, representing only a small portion of cellular proteins entering the ER and the secretory pathway. Therefore, it is unlikely that misfolding of CFTR without aggregation can cause ER stress and activate a classic UPR as the result of protein misfolding [69, 71]. Furthermore, the pathological processes that are linked to SRPs in CF are not CFTR-mutation specific, since they are similar in all CF patients, independent of the mutation.

Nevertheless, SRP activation has been demonstrated in CF tissues [14, 72-74], raising questions about the causes (stressors); types (UPR, ISR); origin (epithelial cells, inflammatory cells); severity, and the mechanisms through
which SRPs contribute to the pathological changes in CF. Understanding the causes and contribution of SRPs to the CF phenotype is crucial because SRPs are becoming potential therapeutic targets [20, 75-77], providing a unique opportunity to develop SRP modulators (inhibitors and activators) as supportive therapies for CF. However, while enhancing some SRPs in order to change the protein folding environment to promote CFTR expression would be beneficial, SRPs that exacerbate inflammation and contribute to tissue remodeling can be harmful. Therefore, further studies are necessary to determine the optimal type of intervention at different stages of CF. Herein we summarize pathological changes in CF and their relationship to SRPs.

3.2 The CF tissue Environment and SRP Activation

The respiratory epithelium and submucosal glands play a critical role in immune responses as structural and physiological barriers, as well as a site for cytokine production, recruitment of innate and adaptive immune cells, or conducting a crosstalk with fibroblasts to regulate extracellular matrix deposition [78, 79]. CFTR expression and function are crucial to maintaining the epithelial milieu [80]. Therefore, changes in epithelial cell functions, consequent to CFTR deficiency, can induce stress and affect numerous pathological processes. In addition to epithelia, CFTR function is necessary for proper macrophage [81, 82], neutrophil [83, 84], dendritic cell [85], and T lymphocyte [86] functions. Consequently, CFTR dysfunction may result in dysregulation of signaling pathways, including SRPs as well as tissue homeostasis in general. Although our understanding of these complex processes is incomplete, review of the experimental data below reveals important connections between SRPs, inflammatory responses, and pathological changes in CF.

3.3 The hyperinflammatory state in the lungs of CF patients

In newborns with CF, prior to bacterial, fungal, or viral infections, the airway epithelium has been described as a hyperinflammatory state [87-92]. This implies that inflammatory signaling pathways are activated in CF tissues as the result of CFTR functional deficiency, but prior to infections. Thus, it is difficult to assess the hyperinflammatory state in newborns. Moreover, the widely available rodent models of CF do not fully resemble the disease phenotype observed in CF patients [93, 94]. To overcome this difficulty, porcine models of CF with disrupted CFTR genes [95] that also carry the F508del mutation [96, 97] have been introduced thereby representing human conditions more closely [98, 99]. Yet, studies on the inflammatory responses of newborn CF and non-CF pig airways following exposure to heat-killed Staphylococcus aureus, in vivo and in vitro have determined that inflammatory markers were similar in CF and littermate, wild type animals. In contrast, transcriptome analysis revealed that CF pigs showed diminished host defense responses, compared to their non-CF littermates with activated apoptotic pathways and concomitant suppression of ciliary and flagellar biosynthetic pathways. Therefore, the transcriptome profiling suggested that acute inflammatory responses are dysregulated in the airways of newborn CF pigs [100]. Comparative studies between CF mice and pigs revealed that airway acidification, which occurs in humans and CF pigs, but not in CF mice, contributes to host defense abnormalities. With the introduction of rat [101, 102] and ferret [103, 104] models, the opportunities to study the hyperinflammatory phenotype have grown, yet there is no consensus concerning the cause and consequences of this phenotype. Understanding SRP activation in the tissues of multiple animal models with different mutations in CFTR will help to delineate the significance of SRPs in CF pathogenesis.

Early studies have demonstrated that the hyperinflammatory state is represented by enhanced IL-8 secretion in submucosal glands of CF patients both in vitro and in vivo, resulting from persistent NF-κB pathway activation [105, 106]. IL-8 is a potent chemotactic factor that recruits neutrophils and macrophages and is an important player in acute inflammation [107]. Therefore, IL-8 can initiate a neutrophil-driven inflammatory phenotype in CF [108]. In addition, this acute inflammatory phenotype is combined with reduced anti-inflammatory responses in CF patients [109]. In general, these early events, combined with diminished airway surface liquid secretion, lead to a loss of proper anti-bacterial responses, reduced mucociliary clearance, and defective opsonization capacities [91] (Figure 2).

In addition to the alterations in epithelial functions, it has been reported that toll-like receptor (TLR) signaling, which plays a key role in innate immune responses, is enhanced in CFTR-deficient murine macrophages. This is likely caused by the inefficient trafficking and degradation of TLR4 by the lysosome and consequently, TL4-dependent excess proinflammatory cytokine production by macrophages.
The same study showed that TLR4 responses were also elevated in CF patient-derived alveolar macrophages, suggesting that these responses remain activated even after patients were exposed to environmental stressors and chronic infections [110]. Subsequent studies have identified ezrin mislocalization [111], a component of the CFTR cell surface signaling complex [112], as a link between CFTR and TLR signaling. Lack of CFTR causes ezrin mislocalization and this contributes to the TLR-4 trafficking defect, leading to persistent TLR-4 activation in CF macrophages [111]. As a connection to SRPs, enhanced TLR-4 signaling activates the inositol-requiring enzyme 1α (IRE1α)/X-box binding protein 1 (XBP1) pathway of the UPR, but without activating the ATF6 and PERK pathways and leads to additional activation of inflammatory genes in murine macrophages [113, 114], providing a strong mechanistic connection between the hyperinflammatory state in CF and SRP activation (Figure 3). Supporting this, it has been shown that the IRE1α/XBP1 pathway is activated in alveolar macrophages isolated from CF patients [71, 73]. However, these reports from CF macrophages are in contrast with those demonstrating reduced TLR signaling in CF airway epithelial cells, as well as reduced TLR4 expression in tissue sections from CF lungs [115].

To provide additional mechanistic explanation for the hyperinflammatory state in CF prior to infections, a recent study has stated that the C-terminal tail of CFTR directly binds to the N-terminal of the tumor suppressor phosphatase and tensin homolog (PTEN) and that this interaction is necessary for PTEN membrane localization. The results indicate that CFTR and PTEN binding is important, both in epithelial and immune cells [116]. Notably, in addition to governing cell proliferation by the regulation of phosphatidylinositol-3-kinase (PI3K), PTEN also plays a pivotal role in host defense against bacterial infections, but the molecular mechanisms by which PTEN elicits this function are not fully understood [117]. In the studies by Riguelme et al., PTEN immune signaling and \textit{P. aeruginosa} killing were both reduced in cells carrying different classes of CF mutants and only the presence of CFTR in the plasma membrane, but not its function, was required for PTEN cell surface localization and immune signaling. In addition, the authors concluded that CFTR and PTEN interaction was necessary to suppress...
NF-κB signaling [116], providing additional mechanistic explanation for persistent NF-κB signaling prior to infections in the CF lungs [105, 106] (Figure 4).

The above examples support the findings that NF-κB signaling and pro-inflammatory responses are elevated in CF tissues, prior to infections. However, in addition to these mechanisms, activation of SRPs by external and internal stressors can also exacerbate NF-κB signaling and pro-inflammatory responses, as we discuss later (Figure 5). Notably, to study the molecular mechanisms underlying the hyperinflammatory state in CF, most studies used CFTR deficient murine cells [118, 119], blood mononuclear cells [110], alveolar macrophages [73], or epithelial cells, isolated from CF patients. These cells were obtained most likely after the patients were exposed to infectious agents and other stressors such as hypoxic conditions (adolescents or adults) [120-122].

3.4 Infections

As mentioned previously, CFTR dysfunction leads to reduced levels and altered content of the airway surface liquid [123, 124]. This environment influences the colonization as well as internalization of pathogens: exacerbating inflammatory cytokine production by airway epithelial cells [88]. Importantly, many pathogens express TLR ligands, also referred to as pathogen associated molecular patterns (PAMPs) [125] on their surface, which have been reported to cause ER stress and activate the UPR [126]. It has also been demonstrated that airway infections and inflammation initiates the expansion of ER Ca²⁺ stores [127-129], leading to ER stress and UPR activation [29]. Additionally, infiltrating neutrophil cells generate high levels of reactive oxygen species (ROS) such as H₂O₂, superoxide (O₂⁻), hydroxyl free radical (OH), and hypochlorous acid (HClO⁻). These substances cause irreversible lung damage [130] and have been shown to activate the UPR [131, 132].

It is also important to look at the role of SRPs in CF pathogenesis from the invader’s side since they play important role in exacerbating SRPs. Antibiotics are not capable of eradicating infections since a minor population of pathogens are highly tolerant to antibiotics and can turn into dormant, persister cells that re-establish infections [133, 134]. The significance of persisters in CF is obvious, considering that pathogens such as P. aeruginosa form biofilms in CF patients and therefore are protected from the immune system, providing an additional opportunity for the development of persisters. Indeed, it has been reported that antibiotic treatment during chronic infections with P. aeruginosa in CF patients causes

![Figure 3. TLR signaling and IRE1/XBP1 activation in CF macrophages. Under physiological conditions, when CFTR is present, it binds to TLR-4 through ezrin and is directed to the lysosome for degradation in macrophages (left). In the lack of CFTR, TLR-4-ezrin interactions and lysosomal targeting are damaged, leading to chronic TLR activation that can induce the IRE1/XBP1 pathway of the UPR. XBP1s can directly activate IL-6, TNF and IL-1 transcription.](image-url)
the development of high-persister populations (HIP) [135]. One of the mechanisms that can induce persister development is the activation of bacterial SRPs, such as the SOS stress response, which leads to changes in their gene expression profile [133, 136, 137]. Although whether or not changes in bacterial gene expression can initiate or exacerbate host SRPs has not been determined, such mechanisms may provide additional opportunities for the activation of epithelial SRPs.

### 3.5 Pollution

According to the World Health Organization, 9 in 10 people worldwide breath polluted air and pollution has become an important cause of human diseases and death (http://www.who.int/airpollution/en/). Therefore, the mechanisms and level by which pollution contributes to CF pathology is of great interest to patients and their families. Indeed, it has been reported that CF patients who live in polluted areas are more likely infected with *Pseudomonas aeruginosa* or *Burkholderia cepacia* (for review: [138] and have more pulmonary exacerbations that are defined by the NACFF as respiratory symptoms that need immediate treatment. Importantly, pulmonary exacerbations contribute significantly to the decline of respiratory function, measured by forced expiratory volume (FEV1) in CF patients [139]. In addition to providing a favorable environment for infections, inhaled pollutants can alter the protein folding homeostasis, referred to as proteostasis and activate the UPR as well as the ISR [11, 23].

### 3.6 Connection between pro-inflammatory responses and SRPs

As discussed in the previous sections, multiple feedback-type connections exist between inflammatory responses
and stress responses in different tissues (for review: [31]). Based on the findings reviewed herein, these mechanisms are likely to contribute to the development of the CF phenotype as well. Enhanced TLR-4 signaling during the early stages of CF can activate the IRE1/XBP1 arm of the UPR not only in macrophages, but in other cells as well [113, 114] (Figure 3). Activation of the IRE1α pathway of the UPR leads to the splicing of the XBP1 mRNA and production of the XBP1’s transcription factor that directly activates tumor necrosis factor (TNF) and interleukin-6 (IL6) transcription [113]. Activated IRE1α may also form a complex with TNF receptor-associated factor 2 (TRAF2) and induce Jun N-terminal kinase (JNK) phosphorylation, increasing pro-inflammatory gene expression through the activator protein 1 (AP1) transcription factor. In addition, the IRE1α–TRAF2 complex may recruit IκB kinase (IKK), which phosphorylates IκB, leading to its degradation and the release of nuclear factor-κB (NF-κB) that moves to the nucleus to induce inflammatory genes [140]. Likewise, NF-κB pathway activation may also occur through the PERK-eIF2α translational inhibition mechanism resulting in reduced IκB and NF-κB levels [141]. In this scenario, the shorter life span of IκB allows NF-κB translocation to the nucleus to promote the expression of inflammatory genes [142]. Further, ATF4, the transcription factor that is produced through the PERK pathway or other kinases activated through the ISR, can directly activate the IL6 promoter [143] and enhance inflammation. ATF6α, induces NF-κB signaling via AKT

Figure 5. Communications between SRPs and inflammatory responses. Multiple feedback-type pathways between the UPR and inflammatory responses are depicted. A: TLR-4 signaling activates the IRE1/XBP1 pathway. B: ATF6 activates the acute phase response and the NF-κB pathway through AKT phosphorylation. C: IRE1 activation leads to inflammasome and NF-κB activation. D: The PERK pathway can activate inflammasome and pro-inflammasome and pro-inflammatory cytokine production.
phosphorylation and CREBH-mediated mechanisms of acute phase response (APR) activation [143]. Regulated IRE1α-dependent decay (RIDD) of miR-17, targeting the thioredoxin-interacting protein (TXNIP) mRNA, allows higher expression of TXNIP that activates the NLRP3 inflammasome with increased IL-1β secretion. TXNIP can also be induced through the PKR-like ER kinase (PERK)-activating transcription factor 5 (ATF5) pathway to induce inflammasome production (Figure 5).

These examples support complex mechanistic links between inflammation and SRPs, and in the next section, we discuss how these contribute to the pathology of CF.

4 The consequences of stress responses in CF

4.1 CFTR expression regulation by SRPs

It has been reported that cell culture conditions, such as oxygenation [144], hypoxia [145], and reactive oxygen nitrogen species (ROS) [146] alter CFTR-expression levels in respiratory and intestinal epithelial cells, expressing CFTR endogenously. Since both hypoxia and ROS can activate the UPR (Figure 1), these observations have prompted initiation of studies to analyze the role of the UPR in CFTR expression regulation. Subsequently, it was determined that CFTR expression is reduced by the UPR at transcriptional and post-transcriptional levels [147-149]. Also, since the UPR enhances ERAD, the maturation efficiency of CFTR is also reduced when the UPR is activated [147].

More recently, it has been shown that CFTR transcription is regulated by oxidative stress [150] implying that CFTR expression reduction, or acquired CFTR deficiency by SRPs may contribute to the pathomechanism of respiratory disorders such as chronic bronchitis and COPD [148, 151]. Indeed, it has also been reported that cigarette smoke reduces CFTR expression and function [152-155] and that oxidative stress activates the UPR in smokers [156-159]. Although these studies suggest a strong connection between SRPs and acquired CFTR deficiency, further studies are necessary to understand fully the molecular mechanisms by which SRPs regulate CFTR expression. Importantly, if SRPs reduce CFTR expression in CF, in addition to the reduced expression and function caused by mutations, SRP-mediated CFTR expression inhibition can diminish the efficacy of CFTR correctors. This suggests that CF patients would benefit from supportive treatments that enhance CFTR transcriptional and processing efficiencies or the ER pool of CFTR [160], independent of the mutation.

4.2 Pathological changes in CF organs and their relations SRPs

Upper Airways: Multiple nasal polyps with mucous cysts and hyperplastic glands are frequently present in the upper airways of CF patients [161]. A proteomic study analyzing nasal polyps from CF patients has revealed an altered redox state and consequent UPR activation, as well as elevated interleukin 8 (IL-8) and leukotriene B4 (LTB4) secretion [162]. However, SRP activation is more likely the consequence of functional and structural changes in the tissue, as discussed earlier, rather than the cause of polyp development. This is supported by the finding that UPR activation inhibits cell proliferation and colon cancer development from polyps [163].

4.3 Tissue remodeling and fibrosis in the lower airways and other organs

CF is a multiorgan disorder, with pathological changes that include tissue remodeling and fibrosis [161, 164, 165]. In the lower airways the hyperinflammatory state, in combination with bacterial, viral and fungal infections, leads to excessive neutrophil infiltration and release of ROS, as well as other inflammatory mediators thus continuously activating SRPs. Lung tissue damage by neutrophil elastase, fibrosis, and remodeling lead to the development of bronchiectasis [166]. In other tissues such as the pancreas and liver, fibrosis is one of the most prevalent morphological features associated with CF [167]. Fibrosis is a common feature of many diseases such as pulmonary fibrosis, liver cirrhosis, kidney, and cardiovascular disorders and often leads to organ failure [168, 169]. There is growing evidence that SRPs contribute to tissue fibrosis through cell-type specific mechanisms (For review: [11, 170]). In epithelial tissues, more specifically in alveolar epithelial cells, UPR signaling induces mesenchymal transition [171] activating fibroblasts which deposit collagen [172, 173], induce myofibroblasts [174], macrophages [73], and T cells [170], leading to complex pathological changes in different tissues. While it is obvious that multiple agents and cellular mechanisms contribute to the complex pathology of CF, based on their central role both in physiological and pathological processes, SRPs are also likely significant contributors to CF pathology [71, 73].
4.4 Possible role of transmissible or non-cell autonomous SRPs in the development of pathological changes

As we summarized this far, SRP induction in multiple cell types such as epithelial cells, macrophages can contribute to the pathology of CF [71]. It is also evident that SRPs serve both homeostatic and pathologic functions [13, 17]. The complex role of these responses in CF pathology is further supported by the introduction of transmissible, or non-cell autonomous SRPs [175, 176] suggesting that SRPs can be transferred between cells in a tissue and elicit cell type specific responses [177, 178]. The mechanisms of intercellular stress communication are not fully understood, but it has been shown that XBP-1 can serve as cell-nonautonomous regulator of stress tolerance in C. elegans since neuronal XBP-1s activated the UPR in distal cells [179]. Evidence suggests that soluble factors transferred by exosomes is one of the mechanisms involved in stress response transfer between cells [180]. Interestingly, according to our best knowledge, no studies have analyzed intercellular stress communication in CF tissues to date. Understanding the role of intercellular stress communication to the pathogenesis of CF and the mechanisms by which stress signaling occurs between cells is imperative for the development of SRP modulators for therapeutic purposes.

4.5 Altering cellular homeostasis (proteostasis) to increase CFTR expression levels and improve structure as experimental therapeutic approaches for CF

One of the homeostatic functions of the UPR is to enhance the protein folding and trafficking capacity of the cells by increasing chaperone expression and other components of the secretory pathway [63]. Interestingly, prior to the recognition of this important homeostatic function of the UPR and based on the observation that intracellular trafficking of CFTR is defective [64], altering the protein trafficking environment of cells expressing the mutant CFTR became an experimental therapeutic approach for CF. As examples, low temperature (27°C) culture of cells [181], treatment with glycerol, [182], 4-phenylbutyrate (4PBA) [183, 184] named chemical chaperones at the time, as well as organic solutes [185, 186] helped to deliver some functional F508del CFTR to the cell surface. Because CFTR is subjected to ERAD [187] selective inhibition of ERAD was another attempt to rescue CFTR [188].

However, proteasome inhibition causes ER stress leading to UPR-mediated cell death thus proteasome inhibitors are used in cancer therapeutics to influence cell survival and proliferation proteins [189-192], suggesting that their use in CF may not be beneficial. Altering cellular protein homeostasis, or proteostasis, in order to overcome the trafficking defect of a single membrane protein may not serve as the best approach. Since proteostasis is a vital homeostatic system that controls the physiological development and functions of eukaryotic cells, deficiencies or significant changes in proteostasis can lead to a variety of human disorders [193]. Having said that, identification of endogenous proteostasis components with at least some specificity to CFTR mutants may help to identify checkpoints for intervention without compromising cellular functions in general. Indeed, an interesting study has demonstrated that reducing the expression of Aha1, an Hsp90 co-chaperone led to the rescue of CFTR. The authors concluded that the failure of CFTR to fold to an energetically favorable conformation is caused by the steady-state nature of the cellular protein folding environment, or “chaperome” [194]. A more recent study has shown that, cytosolic chaperones may alter the channel structure of F508del CFTR, closer to the native fold by remodeling gating energetics towards wild-type CFTR [195]. Notably, it is important to distinguish between chaperones that are part of the proteome and pharmacological chaperones, designed to help the intracellular processing of CFTR mutants such as F508del [196].

Focusing on SRPs and CF, interaction between the listed experimental therapeutic approaches that alter cellular proteostasis and SRPs is obvious since SRPs contribute to proteostasis regulation and altered proteostasis may activate SRPs. As examples, both the XBP1 [16, 197, 198] and ATF6 [199, 200] pathways of the UPR enhance the protein folding capacity of the ER, as well regulate ERAD [201, 202]. However, it is unlikely that increasing the folding capacity of the ER, or enhancing ERAD would provide significant benefits in CF. Identifying CFTR mutation-specific proteostasis components and developing therapeutic molecules that can mimic or antagonize their function in order to improve functional CFTR expression levels without affecting the proteome, in general, would be more feasible.

5 Conclusions

As reviewed herein, there are strong feedback-type regulatory mechanisms between SRPs, inflammatory
responses, and tissue remodeling such as fibrosis. Although it is often difficult to determine the cause of SRP activation, mounting experimental evidence supports a strong correlation between disease pathogenesis and SRPs. Understanding these pathological processes may lead to targeted therapeutic developments that can influence SRPs on a disease-specific manner. According to our present understanding, SRPs may contribute to CF pathogenesis through multiple mechanisms that include inhibition of CFTR expression at transcriptional and post-transcriptional levels, as well as by enhancing the severity of inflammation in the organs of CF patients. Consequently, CFTR expression inhibition reduces the levels of CFTR that is available to be corrected by mutation specific CFTR correctors and exacerbated inflammatory responses accelerate tissue remodeling. Importantly, if SRPs contribute to CF pathology, reprogramming them for therapeutic purposes could complement other, mutation specific treatment options.

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