



Review Article

CFTR activity and mitochondrial function [☆]Angel Gabriel Valdivieso ^a, Tomás A. Santa-Coloma ^{a,b,*}^a Institute for Biomedical Research (BIOMED CONICET-UCA), Laboratory of Cellular and Molecular Biology, School of Medical Sciences, Pontifical Catholic University of Argentina (UCA), Buenos Aires, Argentina^b The National Research Council of Argentina (CONICET), Buenos Aires, Argentina

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ABSTRACT

Cystic Fibrosis (CF) is a frequent and lethal autosomal recessive disease, caused by mutations in the gene encoding the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR). Before the discovery of the *CFTR* gene, several hypotheses attempted to explain the etiology of this disease, including the possible role of a chloride channel, diverse alterations in mitochondrial functions, the overexpression of the lysosomal enzyme α -glucosidase and a deficiency in the cytosolic enzyme glucose 6-phosphate dehydrogenase. Because of the diverse mitochondrial changes found, some authors proposed that the affected gene should codify for a mitochondrial protein. Later, the CFTR cloning and the demonstration of its chloride channel activity turned the mitochondrial, lysosomal and cytosolic hypotheses obsolete. However, in recent years, using new approaches, several investigators reported similar or new alterations of mitochondrial functions in Cystic Fibrosis, thus rediscovering a possible role of mitochondria in this disease. Here, we review these CFTR-driven mitochondrial defects, including differential gene expression, alterations in oxidative phosphorylation, calcium homeostasis, oxidative stress, apoptosis and innate immune response, which might explain some characteristics of the complex CF phenotype and reveals potential new targets for therapy.

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Introduction

Cystic Fibrosis (CF) is one of the most severe and frequent hereditary diseases [1]. It is the main cause of chronic lung damage and exocrine pancreatic insufficiency in the first three decades of life [2]. Other organs and all exocrine glands are also affected to a greater or lesser extent [3].

Lowe and May have described CF as a genetic recessive disorder back in 1949 [4,5]. However, the affected gene was not discovered until 1989, when the team led by Lap-Chee Tsui [6] cloned the *CFTR* gene (Cystic Fibrosis Transmembrane Conductance Regulator) and found a deletion of three base pairs in both copies of the gene [6–8]. The deletion causes the loss of a phenylalanine residue at position 508 of the CFTR protein ($\Delta F508$) [6]. Experiments of expression then demonstrated that CFTR was a chloride channel [9–16], as it was suspected for decades [17–32] and intuitively known for many centuries [1,33,34].

Today, more than 1900 mutations have been described for the *CFTR* gene (Cystic Fibrosis Mutation Database; www.genet.sickkids.on.ca), although the $\Delta F508$ mutation is the most abundant in CF patients, with an occurrence of approximately 66 % [35,36]. It is noteworthy that a clear relationship between genotype and phenotype could not be demonstrated in CF [2]. This is because the different degrees and high variability of the parameters studied in CF reflect the interaction of diverse factors, including genetic and environmental influences, infectious events and differences in treatments [37].

CFTR is an integral membrane glycoprotein frequently located in the apical membrane of the epithelial cells; it is also present in non-epithelial cells from blood, brain, heart, liver, kidney and other tissues [38–42]. In addition to chloride, the CFTR channel is able to transport bicarbonate [43] and glutathione [44]. On the other hand, the possible role of CFTR as an ATP channel has been controversial [45–54].

The CFTR channel belongs to the superfamily of ABC (ATP Binding Cassette) transporter proteins. The protein includes two nucleotide-binding domains (NBD1 and NBD2) that hydrolyze ATP to regulate the channel activity [55]. In addition, an intracytoplasmic regulatory domain (domain R) is activated by protein kinase A (PKA) phosphorylation to control the opening of the channel [16]. Thus, the chloride transport activity of CFTR is a cyclic AMP-regulated process, a feature that differentiates CFTR from the other chloride channels. The kinases PKC [56] and SRC also regulate the CFTR channel activity [57]. Actually, all molecules or pathways capable of modulating cAMP levels contribute to CFTR activation, including epinephrine, isoproterenol, carbachol, phosphodiesterase inhibitors [58] and G proteins, among other factors [59]. The CFTR protein also forms a macromolecular complex with several proteins, interacting either directly or indirectly [60,61]. Some interactions involve PDZ domain-containing proteins [60,62,63].

Different factors regulate CFTR expression. Cell differentiation in Caco-2 cells induces CFTR up-regulation; the same effect was not observed in T84 cells [64]. In addition, cAMP up-regulates CFTR mRNA levels [65] through a variant cAMP response element (CRE) present at position -48 to -41 of the CFTR promoter [66]. On the other hand, INF- γ [67], TNF- α [67] and progesterone [68] are able to down-modulate CFTR expression. IL-1 β modulates CFTR expression of T84 cells in a biphasic way [69]. The CFTR mRNA levels are up-regulated when the cytokine concentration is

near 1 ng/ml (≈ 6 fM) and down-modulated at higher concentrations. This biphasic response involves at least two different mechanisms: NF- κ B accounts for the stimulation of CFTR mRNA levels at low concentrations of IL-1 β (around and below 1 ng/ml) [70] whereas AP-1 appears to be involved in the down-modulation observed at higher concentrations of this cytokine (2–5 ng/ml and higher) [70,71]. Interestingly, IL-1 β has been found in sputum from CF children at high concentrations, between 2.8 and 32 ng/ml [72]. At these concentrations, according to the results obtained in T84 cells [69], the CFTR should be strongly down-modulated. Other modulators of CFTR include protein kinase C (PKC), protein tyrosine kinases (PTKs) and phospholipase C (PLC) [69], as well as steroid hormones [73–76], nitric oxide [77–80], hyperosmolarity [81], vasoactive intestinal peptide (VIP) [82,83], c-Src tyrosine kinase (SRC) [57], with-no-lysine [K] 4 kinase (WNK4) [84], casein kinase 2 (CK2) [85] and spleen tyrosine kinase (SYK) [85].

In addition to its CFTR-chloride transport activity, CFTR indirectly regulates the expression of different CFTR-dependent genes, such as *SRC* and *MUC1* [86], *MT-ND4* [87], *CISD1* [88], *RANTES* [89], and other genes involved in inflammation or metabolic functions [90–93]. It is noteworthy that two of these genes, *MT-ND4* and *CISD1*, encode for mitochondrial proteins having a reduced gene expression in CF cells [87,88,94–107]. Since ND4 (encoded by mitochondrial *MT-ND4*) is a key subunit for the activity of mitochondrial Complex I (mtCx-I), the early work of Burton L. Shapiro and colleagues [108–113] regarding possible mitochondrial failures in CF was rethought. Subsequent work of our laboratory demonstrated that indeed the activity of mtCx-I was reduced in CFTR defective cells [87,94,96,97,99]. Later, the mtCx-I failure and other alterations found in the pioneer work of Shapiro and colleagues, including glutathione and calcium metabolism [112–122], were recently confirmed by other laboratories. Here we review the earlier work and the recent findings on CFTR-induced mitochondrial alterations, and their possible pathophysiological consequences.

Initial findings involving mitochondrial alterations in CF

Irena Antonowicz, from the laboratory of Harry Shwachman at Harvard, studied several mitochondrial and lysosomal enzymes in cultures of lymphoid cells obtained from CF patients [123]. They found only alterations in the lysosomal α -glucosidase (which degrades glycogen) without any changes detected in the three mitochondrial enzymes tested: succinate dehydrogenase (succinate-coenzyme Q reductase (SQR) or respiratory Complex II), glutamate dehydrogenase (GLDH), and malate dehydrogenase (MDH). From these results, the authors concluded that CF might be a lysosomal disorder [123] (unfortunately the authors did not measure NADH dehydrogenase). On the other hand, Congdon and Littlewood found a glucose 6-phosphate dehydrogenase (G6PD or G6PDH) deficiency in CF [124], although this observation was not further explored.

During the decade before the cloning of *CFTR*, Shapiro and Feigl reported the existence of different mitochondrial abnormalities in CF [108–113,115,117,125]. First, in 1979, based on previous work from other laboratories [126–130], they found alterations on calcium uptake and oxygen consumption in mitochondria isolated from fibroblasts of CF patients [113]. In the same year, they found alterations in the optimal pH of mitochondrial Complex I (mtCx-I; NADH dehydrogenase, NADH:ubiquinone reductase

(H(+)-translocating), EC 1.6.5.3) and suggested that the mutant gene responsible for CF might be expressed within the mtCx-I [111]. Later, these same authors found that the increased calcium uptake by mitochondria was associated with an altered respiratory system activity [117] and found a reduced Km of mitochondrial NADH dehydrogenase in whole cell homogenates of cultured skin fibroblasts [110]. After these initial works, several studies described mitochondrial changes in CF [108,109,115,131–133], until the CFTR was cloned and found to be a chloride channel [6,7,134]. Following this important finding, the hypotheses of possible mitochondrial, lysosomal or cytosolic alterations in CF were totally disregarded. Future work mostly focused on the involvement of CFTR as a chloride channel. Few explored other areas. Among them, Picci et al. reported differences in the 2D electrophoretic patterns of mitochondrial proteins in CF [135]. Also, de Meer et al., found higher intracellular pH in CF patients in vivo, during workload [136]. More recently, Day et al. [137] found decreased glutathione levels in epithelial lining fluid of CFTR knockout mice, the last finding also in agreement with the early work of B.L. Shapiro and colleagues, regarding glutathione [119–122]. Now, by using different approaches, several authors are reporting different results in agreement with the pioneer work of Shapiro and colleagues, reinforcing the idea that mitochondrial dysfunctions are indeed present in CF, although as an indirect consequence of CFTR signaling mechanisms, yet undefined.

Differential expression of genes in Cystic Fibrosis

Back in 1994, as an approach to explain the diverse phenotypic characteristics of CF, we hypothesized that perhaps the CFTR activity could indirectly affect the expression of several genes. This hypothesis was tested by applying the method of differential display [138]. First, it was necessary to find a way to avoid the frequent false positive/negative signals of this method. Initially we use T84 colon carcinoma cells treated with the phorbol ester 12-O-tetradecanoylphorbol-13-acetate (TPA), a drug that down-modulates CFTR mRNA levels [139]. Since it was difficult to determine which effects were due to TPA or CFTR, we later changed the model system by using instead CFDE cells (derived from a CF patient) and the same cells ectopically expressing wt-CFTR (CFDE/6RepCFTR cells). The hypothesis was correct, and we found several CFTR-dependent genes [86,140,141]. Some spots of the differential display corresponded to unknown genes. One spot overexpressed in CFDE cells (CF cells) was studied in detail; its cDNA sequence corresponded to the SRC/c-Src tyrosine kinase. Thus, the mRNA and protein expression of SRC/c-Src was found increased in CFDE cells (CF cells). Since SRC/c-Src was known to regulate several mucins, we tested the expression of MUC1, and found that this mucin was also upregulated in CFDE cells, under SRC/c-Src modulation. These results suggested that SRC/c-Src might constitute a bridge between the CFTR failure and mucin overexpression, at least in the case of MUC1 and CFDE cells [86]. Interestingly, the effects occurred as a primary failure of CFDE cells, in the absence of any bacterial infection.

Almost in parallel, by using microarrays, Srivastava [90,91,93], Galvin [92], Eidelman [142], Pollard [143] and colleagues found several differentially expressed genes in CF cells. In addition, Ichikawa et al. [144] studied the differential expression of genes in the cell line A549, derived from lung pneumocytes, exposed to *Pseudomonas aeruginosa*, thus analyzing differential gene expression in response to bacterial–host interaction. Interestingly, Xu et al. found differential expression of 54 RNAs, corresponding to genes that influence gene transcription, inflammation, intracellular trafficking, signal transduction, and ion transport, including the CEBP δ transcription factor and IL-1 β [145,146], both

modulators of CFTR transcription [69,70,147]. More recently, Ogilvie et al. have studied the differential expression of genes in CF by using the Illumina HumanRef-8 Expression BeadChips [148]. They conclude that CF and non-CF nasal and bronchial epithelium are transcriptionally distinct. Also, the CF nasal epithelium, with 15 differentially expressed genes, was not a good surrogate for the lung epithelium that has 863 differentially expressed genes. In addition, these cells showed a distinct pattern of enriched pathways, being inflammation pathways predominant in bronchial cells, whereas the pathways controlling amino acid metabolism were predominant in nasal epithelial cells [148]. Lately, antibody microarrays were used instead of DNA microarrays to identify differentially expressed proteins as possible serum biomarkers for CF [93,149].

After characterizing SRC/c-Src and MUC1 as CFTR-dependent genes, we decided to study two additional spots of the differential display, which contrary to SRC/c-Src and MUC1 were down-modulated in CFDE cells. Surprisingly, both spots resulted in genes encoding for mitochondrial proteins: *CISD1* (a nuclear DNA-encoded gene) [88,98,101,103,105,107,150–152] and *MT-ND4* (a mitochondrial DNA-encoded gene) [87,100,102,104,106,141,153–155]. These results are discussed with more detail in the next two sections.

CISD1 expression in CF cells

As mentioned above, a differential display (DD) obtained in 2002 from CFDE cells (CF cells) and CFDE/6RepeCFTR (CF corrected cells) showed a cDNA spot that contrary to SRC had a reduced expression in CF cells. It was isolated, cloned and sequenced from a cDNA DD spot of 477 bp derived from CFDE cells. Initially, we called this gene *CFTR-RG2* (CFTR-regulated Gene 2), since it was the second CFTR-dependent cDNA isolated and sequenced in our laboratory [150]. Then, in 2004, to assign a name related to its possible function, it was called *KLPx*, since we found sequence similarities to kinesin motor proteins [107]. Then we realize that the kinesin motor region was absent and therefore we preferred to call it *ZCD1*, owing to the presence of a Zn finger-like motif, the CDGSH motif [105], defined in a previously annotated sequence obtained by Zhao M. et al. from hematopoietic stem/progenitor cells (AF220049; unpublished). The mRNA corresponding to the *ZCD1* sequence from CFDE cells was finally annotated in GenBank as “Homo sapiens zinc finger CDGSH-type domain 1 (*ZCD1*) mRNA” (accession number AY960578 and AAY32336 for the deduced protein).

Previously, in 1999, Zhao et al. from the Chinese National Human Genome Center at Shanghai had annotated a 636 bp cDNA sequence obtained from hematopoietic stem/progenitor cells as “Homo sapiens uncharacterized hematopoietic stem/progenitor cells protein MDS029” (AF220049, unpublished). They also annotated the deduced protein sequence (AAY32336), defining the region 55.93 as “ZnF_CDGSH” a “CDGSH-type zinc finger”, using the conserved domain database CDD [156]. They also mentioned the SMART signaling domain [157] smart00704, assigning an unknown function to it. Since these results were unpublished and further details are not available, it is not clear who actually defined the CDGSH-type zinc finger, which corresponds today to a superfamily of proteins (CDD cl02748: zf-CDGSH superfamily). In addition, Strausberg et al. [158] annotated the *CISD1* sequence as C10orf70 (which stand for “chromosome 10 open reading frame 70”) during the generation and analysis of more than 15,000 full-length human cDNA sequences (ORFs) from the human genome, which was sequenced one year before [159].

In parallel, in studies linked to diabetes published in 2003, Colca et al. [161] identified a pioglitazone binding protein from bovine brain and rat liver mitochondria. Pioglitazone, an

antidiabetic drug, also binds to the nuclear peroxisome proliferator-activated receptor gamma (PPAR- γ), which is an important target for antidiabetic drugs [160]. The sequence was obtained by using nanospray LC–mass spectroscopy (MS/MS) and N-terminal sequencing confirmed the sequence; it was named mitoNEET [161].

Finally, when the crystal structure was determined by other laboratories [162–164], instead of the predicted Zn^{2+} , a [2Fe2S] cluster was found within the ZCD1 molecule [162–166]. In consequence, the official HUGO symbol (www.genenames.org) was finally agreed as “CISD1” (Z was eliminated and “IS” was added, which stands for Iron Sulfur binding motif). It is noteworthy that recent evidences suggest that Zn^{2+} can also bind to CISD1 and even may replace the [2Fe2S] cluster in *E. Coli* cultures [167]. In consequence, Zn^{2+} might also bind to CISD1 in mammalian cells in addition to [2Fe2S]. A direct measurement of Fe^{2+} and Zn^{2+} content of CISD1 isolated from mammalian cells or tissues might indicate in which proportion these ions bind to CISD1 and under which circumstances.

Although the exact function of this protein is unknown yet, it has been shown that mitoNEET/CISD1 is a mitochondrial specific binding protein receptor for pioglitazone [161] and similar drugs [168]. Co-immunoprecipitation assays suggested that mitoNEET/CISD1 was associated with proteins that belong to the mitochondrial complex I (mtCx-I), among other mitochondrial proteins [161]. The protein was also proposed to be a modulator of the oxidative capacity of cells [166], a sensor of the intracellular redox state [164,169,170], and a mediator for the transference of a [2Fe–2S] cluster to apoproteins [169,171]. We found that an eGFP-CISD1 chimera was mainly located in mitochondria after 24 h of transfection, suggesting that its primary location and function was indeed mitochondrial [88]. However, the mechanisms involved in all these possible functions, the targets of these functions, and their relevance for the mitochondrial and cellular functioning, remain to be established. The mechanisms by which CFTR controls *CISD1* expression and down-modulation in CF cells [88], and the possible consequences for the cellular pathophysiology, are still unknown.

MT-ND4 expression in CF cells

The second gene found reduced in CF cells, *MT-ND4*, encodes for ND4, one of the seven subunits (ND1 to ND7) of the mitochondrial Complex I (mtCx-I) [172]. The mammalian mtCx-I is a holoenzyme comprising 45 subunits that constitute a complex of approximately one MDa. This complex is the entry point of electrons for the oxidative phosphorylation system (OXPHOS system) [173]. ND4 subunit constitutes a fundamental component for the assembly and correct activity of mtCx-I [172,174–180]. Thus, a *MT-ND4* mutation in Leber's Hereditary Optic Neuropathy disease (LHON) determines a low efficiency in the NADH oxidation due to a mtCx-I failure [172,179,181]. The reduced expression of *MT-ND4* found in CF cells suggested that the activity of mtCx-I might be reduced in CF cells, and, as it will be discussed below, we later found that the activity of these mitochondrial complexes was indeed reduced in CF cells or in cells with impaired CFTR activity (inhibitors, iRNA, etc.).

Mitochondrial complex I and Cystic Fibrosis

As mentioned in the previous section, we found a down-regulation of *MT-ND4* in CF, a gene encoding for ND4, a mtCx-I subunit essential for its assembly and activity [100]. The CFTR-mediated down-modulation of *MT-ND4* found in CF cells was in agreement with the early findings of Shapiro et al., showing that the activity of mtCx-I was affected in CF cells [108,110,111]. The results obtained and the previous work by other laboratories

prompted as to measure the mtCx-I activity in CF cells. Consistent with the earlier observations, we found a decreased mtCx-I activity in cells derived from trachea of CF patients (CFDE and IB3-1 cells) when compared to the same cells ectopically expressing wild type CFTR (wt-CFTR) (CFDE/6RepCFR and S9, respectively) [87,94,97,99]. This was also found in colon carcinoma cells (T84 and Caco-2), which express high levels of endogenous wt-CFTR, treated either with pharmacological inhibitors of CFTR activity or RNAi [87,94,97,99]. The decreased activity of mtCx-I found in CF cells might be a consequence of the MT-ND4 down-regulation induced by CFTR mutations or inhibition [100]. In agreement with these findings, Kelly-Aubert et al. have recently reported a decrease in mtCx-I activity in CF cells as compared to cells rescued by ectopic expression of wt-CFTR, and also by using a *CFTR*-knockout mice [182]. These authors suggested that the observed reduction in the specific activity of mtCx-I was caused by oxidation because of the oxidative stress originated in reduced glutathione levels [182]. Altogether, these observations suggest that the mtCx-I activity is altered in CF. The possible mechanisms involved in regulation of mtCx-I by CFTR (CFTR \rightarrow mtCx-I) are unknown yet.

Altered Ca^{2+} homeostasis in mitochondria

Recently, Antigny et al. have reviewed the changes occurring in calcium homeostasis and calcium signaling in CF [183]. Donnell et al., back in 1961, were perhaps the first to show alterations of calcium homeostasis in CF [184]. They found evidences of calcium deposition and signs of reparative fibrosis in the bowel of CF patients. Then, Marmar et al. showed altered calcium in parotid gland secretions [185] and Blomfield et al., reported hypersecretion of zymogen granules in the submandibular saliva, with elevated calcium concentrations [186]. Since these initial reports, many investigators found alterations in calcium secretion and homeostasis in CF. Later, Shapiro and Lam [114], based on previous observations from different laboratories [126–130], found increased intracellular calcium concentration ($[Ca^{2+}]_i$) in fibroblasts derived from CF patients. Feigal et al. also found an increased mitochondrial Ca^{2+} uptake attributed to alterations in oxidative phosphorylation [115,117].

More recently, in contrast to the earlier observations of Feigal and Shapiro, Antigny et al. have found a decreased mitochondrial Ca^{2+} uptake in CF airway epithelial cells ($\Delta F508$ homozygous) [187]. The reason for this discrepancy is unknown. In addition, they observed a fragmentation of mitochondria and a decrease of the mitochondrial membrane potential ($\Delta\Psi_{mit}$) in CF cells as compared to control cells. These changes in mitochondrial Ca^{2+} homeostasis were linked to a decreased mitochondrial membrane potential ($\Delta\Psi_{mit}$), which in turn occurs owing to changes in the oxidative phosphorylation [187].

Among several intracellular pathways activated by calcium, it has been reported that increased $[Ca^{2+}]_i$ may lead to activation of NF- κ B (“Nuclear Factor Kappa B”) and its proinflammatory effects [188,189]. Thus, the rise in $[Ca^{2+}]_i$ observed in CF cells may induce or at least contribute to the increased NF- κ B activation seen in these cells. As discussed below, the increased oxidative stress in CF also contribute to activation of NF- κ B.

Diverse processes affected in CF and related to mitochondrial pathways

Oxidative stress

Reactive oxygen species (ROS) levels are increased in airway diseases, including CF [182,190–197]. CF cells also show higher

sensibility to oxidative stress caused by environmental factors, such as ozone [198] and air pollution [199], or infections [200]. The origin and consequences of high ROS levels are not fully understood. Cleeter et al. suggest that a defect in mtCx-I may lead to an increased ROS yield, which in turn further affect mtCx-I activity [201]. On the other hand, Esposito et al. have shown that inhibition of the OXPHOS system in Ant1(tm2Mgr) (-/-) mice, lacking the heart/muscle isoform of the adenine nucleotide translocation protein Ant, increase ROS levels. Interestingly, in the same work, as a compensation response, increased levels of manganese superoxide dismutase (Mn-SOD or SOD2) were also observed [202]. They concluded that, if the antioxidant defenses are not enough to deal with high ROS levels, then increased mtDNA damage might occur. Similar results were obtained by Lian and Godley in human RPE cells [203]. The increased mtDNA damage may in turn further reduce the OXPHOS system activity, producing a vicious cycle that results in additional ROS generation [204,205].

Autophagy

Autophagy is a natural process by which cells degrade or recycle damaged or unneeded proteins, organelles, and pathogens. The mechanisms of autophagy and their relationship with disease are becoming of high interest [206]. Luciani et al. showed that the CFTR failure in CF induces autophagy inhibition, since defective CFTR upregulates ROS and tissue transglutaminase (TG2), which in turn drive the cross-linking of beclin 1 [195]. This process favors the accumulation of beclin 1 in aggresomes, resulting in a decreased degradation of these juxtannuclear inclusion bodies that appear as a response to misfolded proteins [207]. Rescuing cells from autophagy through beclin 1 overexpression, cystamine or antioxidants, results in improved CFTR transport and reduced ROS formation and inflammation [195,208]. Abdulrahman et al. observed similar results rescuing autophagy by using the immunosuppressant drug rapamycin on CFTR Δ F508 mouse macrophages [209]. Thus, the excessive intracellular accumulation of defective CFTR observed in CF cells seem to be a consequence of autophagy inhibition and aggresome accumulation [195,208]. Targeting autophagy might be a useful strategy for CF therapy [210].

Glutathione

The higher sensitivity to oxidative stress in CF might be associated with several factors that affect the redox balance and the susceptibility to high ROS levels. One of these factors is the ratio between reduced and oxidized glutathione. Reduced glutathione is the most abundant antioxidant inside cells and the ratio between its reduced and oxidized form reflects the redox state and health of cells. A deficient extracellular glutathione (eGSH) transport that cause an imbalance between reduced glutathione and oxidized glutathione (GSH/GSSG) outside cells has been linked to the low CFTR activity found in CF [44,211–213]. This deficiency in eGSH transport might decrease the antioxidant protection of the extracellular space against oxidative stress. In addition, lower mitochondrial GSH (mGSH) levels were found in CFTR-knockout mice (CFTR -/-), and in tracheal cells from CF patients, accompanied with increased ROS production [193]. Recently, other authors have confirmed a decreased mGSH levels in CF that occurs in the absence of a defect in the transport of GSH through mitochondria [182]. Furthermore, these authors reported a decrease in the mtCx-I activity of CF cells and CFTR-knockout mice that was reverted to control values by treating cells with GSH monoethyl ester (GSH-EE) [182]. GSH-EE is a membrane permeable analog of GSH proved to be effective to

increase mGSH levels in several cellular models [214–216]. This reactive, as well as other antioxidant compounds that allow increased mGSH levels, might be potentially useful for CF therapy [182].

Peroxiredoxin

In addition to GSH levels, other components of the antioxidant defense mechanism are affected in CF. It is noteworthy that the enzyme peroxiredoxin 6 (Prdx6, EC 1.11.1.15), which plays an important role in the defense against oxidative damage in lung [217–219], has a decreased expression and activity in CFTR-knockout mice [217]. This enzyme uses GSH as electron donor to reduce hydrogen peroxide (H₂O₂), fatty acid hydroperoxides and phospholipid hydroperoxides [220]. Although the mechanism responsible for decreased Prdx6 expression in CF is unknown, these results are in agreement with the general idea of a redox imbalance and higher susceptibility to oxidative damage in CF.

Superoxide Dismutases (SODs)

Another factor that affects the redox balance is the level and activity of superoxide dismutases (SOD, EC 1.15.1.1). SOD enzymes are key components of the cellular defense system against the production of the free radical superoxide (O₂⁻), by dismutation of O₂⁻ in oxygen (O₂) and hydrogen peroxide (H₂O₂). A decreased protein expression of Cu/Zn-SOD (SOD1, cytosolic localization) and Mn-SOD (SOD2, mitochondrial localization) was found in pancreatic and tracheal cells derived from CF patients, without changes in their activities [192]. By the contrary, a decrease in the activity of extracellular SOD (EC-SOD/SOD3) was observed in CF cells, without changes in its protein expression level [192]. These results are in agreement with previous work in which a decrease in the SOD activities was found in plasma of CF patients [221]. They are also in agreement with a decrease in the Cu/Zn-SOD activity of blood cells (mononuclear cells and polymorphonuclear cells) from CF patients [222,223]. The diminished extracellular SOD activity, together with the diminished eGSH, could produce a misbalance in the extracellular redox state, affecting the structure and function of many membrane and extracellular proteins.

Possible pathophysiological consequences

Apoptosis

Except for one work [224], different investigators have found increased apoptosis in CF [191,192,198,199,225–228]. Although several studies suggest that apoptosis in CF is a consequence of the recurrent bacterial infections [225,226,228], others suggest that apoptosis in CF is a primary defect that occurs even in the absence of bacterial infections [191,192,227,229]. In infected human conjunctiva epithelial Chang cells, apoptosis mediated by mitochondrial alterations was induced after infection with *P. aeruginosa*. These alterations include mitochondrial depolarization, enhanced ROS production, release of cytochrome c, and activation of c-Jun N-terminal kinases (JNKs) [200]. On the other hand, in JME cells (CF Δ F508CFTR nasal epithelial cells), the homoserine lactone C12 rapidly activates apoptosis. However, no differences were seen between JME cells and CFTR corrected JME cells after C12 treatment, suggesting that CFTR is not an important modulator of C12-induced apoptosis [228]. It should be pointed-out, however, that corrected JME cells ectopically express wt-CFTR under the control of a foreign promoter, thus possible feedbacks on its own promoter are missing.

Other studies suggest that the increased apoptosis in CF might be related to a decrease in the antioxidant protection system, which may contribute to self-perpetuate the inflammatory process characteristic of CF [191,192,199]. In particular, Rottner et al. reported a marked sensitivity of CF cells to start apoptosis linked to activation of the NF- κ B pathway, suggesting that the secretion of proinflammatory cytokines from these cells promote apoptosis [227]. Recently, a link between the high level of the oxidative stress and apoptosis has been attributed to a decrease in the antioxidant defenses, caused by reduced activity and expression of superoxide dismutase (SOD) enzymes [192]. Hence, a tendency to increased apoptosis mediated by the mitochondrial pathway seems to occur in CF cells, probably exacerbated upon bacterial infections.

Chronic inflammation

Chronic lung inflammation is an important characteristic of the CF phenotype [230,231]. Yet, it is difficult to define and distinguish primary defects due to the CFTR failure from secondary defects that occur after bacterial infections. It is even more difficult to determine their relative weight in defining the CF phenotype or its clinical manifestations.

In early studies, several cytokines were found to be elevated in sputum obtained from CF patients, including IRAP, IL-1 α , IL-1 β , IL-6, and TNF- α [232,233]. In addition, in neutrophils from CF patients, IL-8 was found at high levels and its receptors down-modulated [234]. After these initial studies, several reports suggest elevated concentrations of cytokines, chemokines (small cytokines) and other inflammatory mediators in CF patients [72,235–250].

The role of Interleukin-1, neutrophil elastase and lipopolysaccharide to regulate inflammation in CF has been reviewed by Carroll et al. [251]. Studying possible modulators of CFTR expression, we found that IL-1 β was able to modulate CFTR expression in a biphasic way. At low concentrations (< 1 ng/ml) IL-1 β up-regulates CFTR mRNA levels [69] through NF- κ B [70,71].

However, at concentrations over 2.5 ng/ml (between 2.3 and 32 ng/ml were found in CF children [72]), the IL-1 β effect was the contrary, inducing a down-regulation of CFTR expression. The mechanism involved in this second phase was not fully defined yet and might involve the AP-1 transcription factor [71], as occurs with TNF- α , which down-modulates CFTR mRNA by increasing its degradation through the AP1 pathway [252–255]. These results suggest that CF children, having high concentrations of IL-1 β and TNF- α , should have a strong down-modulation of CFTR, which together with the low levels of Δ F508-CFTR able to reach the cell membranes in CF cells, might constitute a negative loop with profound consequences for the disease. In addition, CFTR negatively regulates NF- κ B-mediated innate immune response [256], establishing an additional loop between CFTR and NF- κ B (CFTR|NF- κ B→CFTR). In addition to its effects on CFTR, IL-1 β reduces the mtCx-I activity in human chondrocyte cells [257] and its mRNA was found elevated in cells with impaired CFTR activity [95,258,259]. Therefore, IL-1 β might be an important piece of the CFTR → mitochondrial signaling.

Following these initial studies, additional cytokines were found increased in CF, including IL-8 [259–265] and IL-17 [266–270]. The increased concentrations of different cytokines might be responsible for the abundant neutrophil recruitment observed in CF and drive the activation of transcription factors such as the nuclear factor- κ B (NF- κ B) [271,272] and the activator protein 1 (AP-1) [273], increasing in turn the inflammatory response with the consequent tissue damage. Now, numerous studies support the concept that alterations in the inflammatory process are present in CF [247,264,274–278].

Innate immunity

A central question is whether the mitochondrial defects found in CF are strong enough to influence innate immunity and, in the long-term, favor lung bacterial infections. Initial works in models of viral infection connected mitochondria, apoptosis and innate

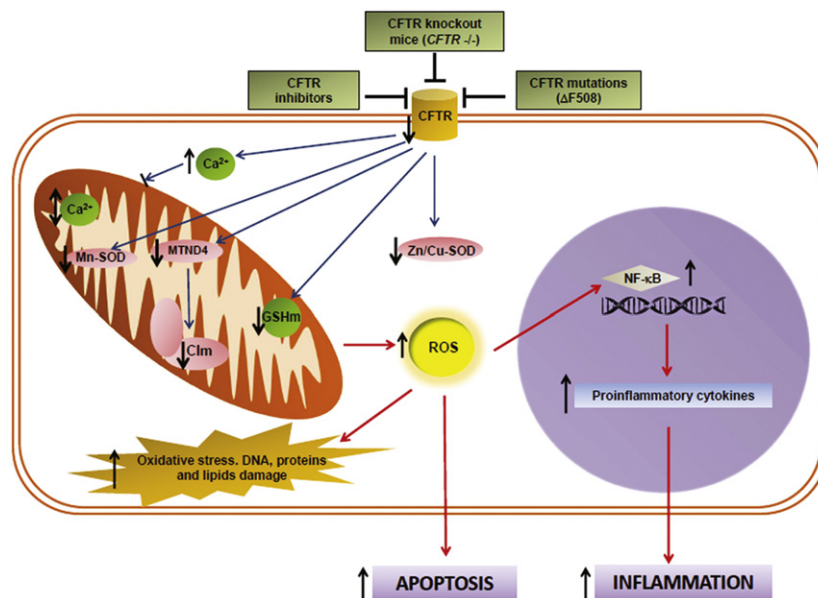


Fig. 1. Representative scheme for mitochondrial alterations in CF. The effects of a CFTR failure on ROS production, apoptosis and inflammation are shown, together with the main relationships between mitochondrial activity and antioxidant defense system in CF. CFTR inhibition or mutation leads to mitochondrial alterations that produce an imbalance in the antioxidant defense system and an impairment of the OXPHOS system, inducing an excessive ROS production by mitochondria. The noxious effects of ROS include DNA, protein and lipids damage, apoptosis and inflammation, the latter due to ROS-induced NF- κ B. Also, the CFTR failure induces an alteration in calcium homeostasis for the mitochondria. All these effects suggest an important role of the mitochondria in defining at least some of the phenotypic characteristics of CF. The vertical black arrows indicate the net effect of a CFTR failure. The red connectors illustrate positive interactions and the black ones (-) inhibition. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

immunity [279–282]. Then, death receptors (DDs) have been recognized as modulators of immune and inflammatory responses [283]. Also, it has been shown that exacerbated inflammation might impair the function and structure of mitochondria [284]. More recently, studies on pattern recognition receptors (PRRs), including Toll-like receptors (TLRs) and cytosolic Nod-like receptors (NLRs), have become important players in the innate immune and inflammatory responses [285,286]. These studies led to the characterization of the “inflammasome”, a macromolecular complex that uses NLRs as scaffold proteins, which recruits and activates inflammatory caspases, essential mediators of inflammation and cell death responses. The activation of caspases directly connects to the mitochondrial apoptotic pathways [285]. Mitochondria, in turn, play a very important role in modulation of the cell death pathway during defense against bacterial infections [287]. In addition, the process of autophagy [288–290] and the production of ROS [291,292] became new players in defining innate immunity. Even more, mitochondria by itself, once released from damaged cells, can trigger an acute inflammatory response [293]. Thus, mitochondria emerges as a fundamental piece of the innate immune response [294–297], modulating the inflammasome-mediated production of proinflammatory cytokines [298]. Dysfunctional mitochondria generate ROS and induce the NLRP3 inflammasome activation [299,300]. On the other hand, autophagy negatively regulates the NLRP3 inflammasome [299]. In consequence, the role of autophagy [195,208,209,301–305] and the inflammasome [303,306,307] both have increased relevance in CF research.

Concluding remarks

Fig. 1 summarizes the mitochondrial abnormalities found in CF cells or tissues. Among them, differential expression of genes or proteins, alterations on calcium homeostasis, membrane potential, increased ROS, and reduced Complex I activity, all appear to occur in mitochondria due to the CFTR failure. These mitochondrial effects in turn induce changes in the ratio of reduced/oxidized glutathione, trigger apoptotic events, and produce inflammatory responses that affect innate immunity. These alterations might influence the phenotype or clinical manifestations of CF and have profound pathophysiological consequences.

A complete understanding of these interactions, their mechanisms of action and the relative importance of each pathway, will help to better define the CF phenotype and clinical manifestations, and to find possible new targets for CF therapy. Thus, the role of CFTR in regulating mitochondrial functions, in particular de OXPHOS pathway, and the role of mitochondria in modulating the inflammatory process, and their possible effects on innate immunity, are issues of increasing interest in CF research.

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