Atlante A. J Rare Dis Res Treat (2016) 1(1): 23-29
www.rarediseasesjournal.com

Journal of Rare Diseases Research & Treatment

Mini Review Open Access

Mitochondria and Cystic Fibrosis Transmembrane Conductance Regulator Dialogue: Some News.

Maria Favia[1] and Anna Atlante[2*]

[1]Department of Biosciences, Biotechnology and Biopharmaceutics - University of Bari, Via E. Orabona 4, 70126, Bari, Italy
[2]Institute of Biomembrane and Bioenergetics - CNR, Via G. Amendola 165/A, 70126, Bari, Italy

Article Info

Article Notes
Received: June 27, 2016
Accepted: July 19, 2016

***Correspondence:**
Anna Atlante, Institute of Biomembrane and Bioenergetics, CNR Via G. Amendola 165/A, 70126, Bari, Italy, Tel: +39(080)5443364 – Fax: +39 (080) 5443317
E-mail: a.atlante@ibbe.cnr.it

Keywords
Cystic Fibrosis Transmembrane Conductance Regulator
Oxidative phosphorylation
Reactive Oxygen Species
Glutathione
Mitochondria

ABSTRACT

Cystic fibrosis is a progressive, genetic disease that causes persistent lung infections and limits the ability to breathe over time. It results from different possible mutations in the CFTR gene, which encodes the CFTR chloride channel, a protein that controls the movement of salt and water in and out of your body's cells. It follows that the abnormal channel function of the expressed protein on the secretory cell membrane determines the clinical phenotype in its classical form. Novel and more recent studies on mitochondrial bioenergetics - aiming to rediscover a possible role of mitochondria in this disease - provide a springboard for upcoming research to further understand the molecular mechanisms responsible for the involvement of mitochondria in CF and identify the protein/s primarily responsible for the F508del-CFTR-dependent mitochondrial alterations. Here, we review these CFTR-driven mitochondrial defects, thus revealing potential new targets for therapy.

Introduction

Worldwide the research on mitochondria is feverish because they are considered decisive for the role played in both health and disease. Research on mitochondria rages because if we learn to know them better, to protect them and treat them, maybe we can live longer and in greater health. Every single human cell contains thousands of mitochondria which fulfil a multitude of essential cellular functions, ultimately reciprocally dependent on the production of ATP and reactive oxygen species (ROS)[1]. The production of ATP over ROS (or vice versa) ultimately depends on metabolite availability and oxidation, electron transfer through the respiratory chain, electron chemical proton gradient (ΔμH+) formation, ADP availability, adenine nucleotide translocator (ANT) activity and mitochondrial structure and morphology[2-4]. If maintained at low enough concentrations, ROS serve as signalling molecules; in excess, ROS are detrimental. Therefore, by controlling the types and levels of ROS, mitochondria play a major role in cellular redox homeostasis. It is clear that when mitochondria fail, less and less energy is generated within the cell; cell injury and even cell death follow. The dysregulation of redox balance can lead to acute and/or long-term oxidative or reductive stresses that are associated with many abnormalities in disease processes, including Cystic Fibrosis (CF)[5-6].

CF, a lethal autosomal recessive disorder, is classically characterized by obstructive lung disease, pancreatic insufficiency and elevated sweat chloride values[7]. These manifestations are

the consequence of abnormal epithelial cell transport of electrolytes caused by dysfunction of the CF transmembrane conductance regulator (CFTR).

Although the first discoveries on mitochondria function in CF date back to over 30 years ago[8], to date still little is known about the role of mitochondria in this insidious disease. This scarcity of information is due primarily to the fact that since CF is caused by mutations in the gene encoding the CFTR protein, major research is essentially centred on this mutated protein[9-10].

Here we review the CFTR-driven mitochondrial defects - with particular attention to functional ones - including those reported in more recent studies, which overall constitutes an extremely necessary and essential starting point to identify areas needed for further research aimed at understanding the molecular mechanisms responsible for the involvement of mitochondria in CF. Future perspectives are also considered.

Cystic Fibrosis. Brief description

CF is a relatively common genetic disorder in the Caucasian population: people with CF tend to have a shorter-than-normal life span. In the 1950s, many children with CF died before attending elementary school; now, many CF adults reach middle age and are predicted to get older in view of advances in medical management.

CF is caused by various mutations in a gene on chromosome 7 encoding the CFTR protein, which functions as a chloride channel within a number of epithelial tissues[11-13]. Mutations of the CFTR gene reduce the channel function of the protein leading to an altered fluid and electrolyte composition of secretions, thereby resulting in their increased viscosity which is responsible for progressive obstruction and fibrosis of various organs[14]. The most frequent mutation associated with CF is the deletion of phenylalanine 508 of the CFTR (F508del-CFTR)[13]. The mutated CFTR channel is not fully

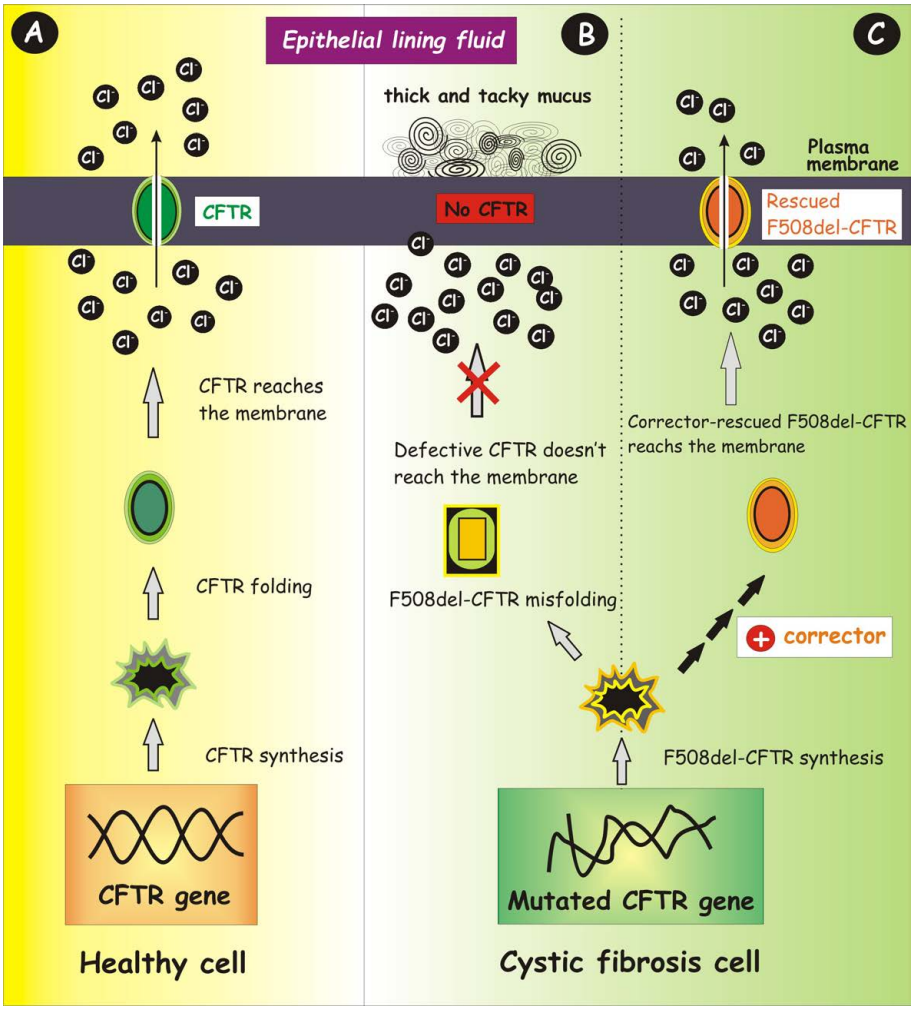

Figure 1: CFTR function in cell. In A, normal CFTR channel protein reaches the membrane and mediates Chloride (Cl-) flux across the plasma membrane; in B, mutated CFTR channel protein (F508del-) doesn't reach the plasma membrane, then preventing Cl- ion movement; in C, Corrector rescued F508del-CFTR reaches the plasma membrane, where it facilitates Cl- ion movement, albeit with lower efficiency with respect to the control, i.e. A.

glycosylated thus impairing the achievement of the plasma membrane and consequently its function in epithelial cells (Figure 1). In addition to chloride, the CFTR channel is able to transport bicarbonate[6] and also glutathione (GSH), so participating to its homeostasis[15]. Extensive research on the CFTR mutation has shed light on the ways in which this gene is vital to normal human development.

As CF is a multi-system disease, an aggressive combination of specific therapies is required to treat the disease symptoms. Surprisingly, a novel drug class, i.e. CFTR corrector, widely used in laboratory research, could revolutionise CF treatment, together with respiratory and nutritional therapies. The fundamental premise of CFTR corrector therapy for CF is that by addressing the basic defect underlying CF will result in clinical benefit[16]. CFTR correctors are principally targeted at F508del cellular misprocessing. In particular, they do not correct errors in the CFTR gene itself (as with gene therapy), but rather, errors that occur from transcription onwards, i.e. they are able to overcome the inefficient folding of the mutant protein defect and to improve F508del trafficking, thus allowing chloride to move properly in and out of cells lining the lungs and other organs (Figure 1).

Early and latest studies concerning mitochondrial alterations in CF

Even if to date there have been very few studies on the possible functional link between mitochondrial defects and CF[5-8,17-24], the first suspicions that mitochondrial lesions occur in CF dates back to 1979 with weak hints of Complex I (mtCx-I) impairment[7,17-20,25]. Using cultured fibroblast cells from CF and control patients, Shapiro and collaborators have reported that CF cells showed more oxygen consumption and were more sensitive to the mtCx-I inhibitor rotenone than normal cells[8]. In the same time, altered optimal pH and Km values for the NADH dehydrogenase, the enzyme of mtCx-I, were also found[8]. Later, Santa-Coloma's group found a CFTR-mediated down-regulation of MT-ND4 in CF, a gene encoding for ND4, a mtCx-I subunit essential for its assembly and activity[6,26], thus endorsing the hypothesis that the activity of mtCx-I may be reduced in CF cells. Further, more recently, Santa-Coloma's group observed that autocrine IL-1β has a major role in the reduction of the mCx-I activity observed in cultured CF cells or cells with impaired CFTR activity (IB3-1, Caco-2/pRS26 cells). Interestingly, the IKK inhibitor III, the IL-1β blocking Ab or the IL-1RN, were able to fully restore the mCx-I activity, and to produce a significant reduction in the ROS levels, to near basal values for cellular ROS levels[27].

Altered kinetics also for cytochrome c oxidase (COX) resulting in increased Km have been reported in CF fibroblast by Lenaz's group[28]. Later, Antigny et al.[22] observed that the mitochondria network is fragmented in F508del-CFTR cells and the mitochondrial Ca^{2+} uptake is reduced, compared to healthy cells, proposing that these defects are the consequence of mitochondrial membrane depolarization leading to a deficient mitochondrial Ca^{2+} uptake.

Another very interesting aspect - that requires insights - is that on the role of mitochondria in decoding the Ca^{2+} signal that regulates their activity and determines their cellular fate. Rimessi et al.[29] showed the supplementary role of mitochondria as drivers of the *P. aeruginosa*-dependent inflammatory process in CF cells and demonstrate that mitochondria are critical targets of the 'proinflammatory' Ca^{2+} signal, thus considering mitochondrial Ca^{2+} signalling to have a critical role in inflammasome induction, NLRP3 recruitment and the exacerbated *P. aeruginosa*-dependent inflammatory response in CF cells.

This paucity of data essentially concerning the involvement of disrupted mitochondrial function in CF led us to more fully explore mitochondrial bioenergetics in cells homozygous for F508del CFTR with an added value, never before investigated, that of determining if the CFTR corrector mediated rescue of F508del-CFTR could involve corrections in the bioenergetics dynamics. So, it is of a few months ago the paper by Atlante et al.[30], showing that some steps of oxidative phosphorylation (OXPHOS), such as ANT-dependent ADP/ATP exchange, oxygen consumption, mitochondrial membrane potential (Δψ) generation and both mtCx-I and COX activities are impaired in CF cells while both ROS production and mitochondrial membrane lipid peroxidation increase (Figure 2). Importantly, treatment with the CFTR correctors, i.e. VX-809 and TMA[31-32], which increase the amount of functional CFTR at the cell surface and per se are without any direct effect on the main mitochondrial activities, partially restored the mitochondrial function in CF cells. Doubtless, one of the outstanding problems in the role played by mitochondria in disease processes concerns cellular ATP production, mostly by OXPHOS, and its utilization. ATP reaches the cytosol, via the ANT, and becomes available for various cellular processes. A decrease (about 50%) in the transport efficiency of the ANT occurs in CF cells, strongly prevented in the cells treated with the CFTR correctors[30]. As ANT-dependent ATP availability in the cytosol regulates CFTR channel activity gating[33], it follows that the activity of the ADP/ATP translocator, in concert with cytosolic enzymes that consume ATP, is critical in CF by playing a decisive role in the maintenance of cytosolic ATP levels.

Furthermore, confirming previous tips[5-8, 17-20], Atlante et al. have shown that mitochondria from CF cells are defective in NADH utilization by mtCx-I, measured both as mitochondrial oxygen consumption and Δψ generation[30]. It is known that when a mitochondrial defect is attributed to mtCx-I, it can arise from i) a loss of Complex I activity, ii) an increase in its

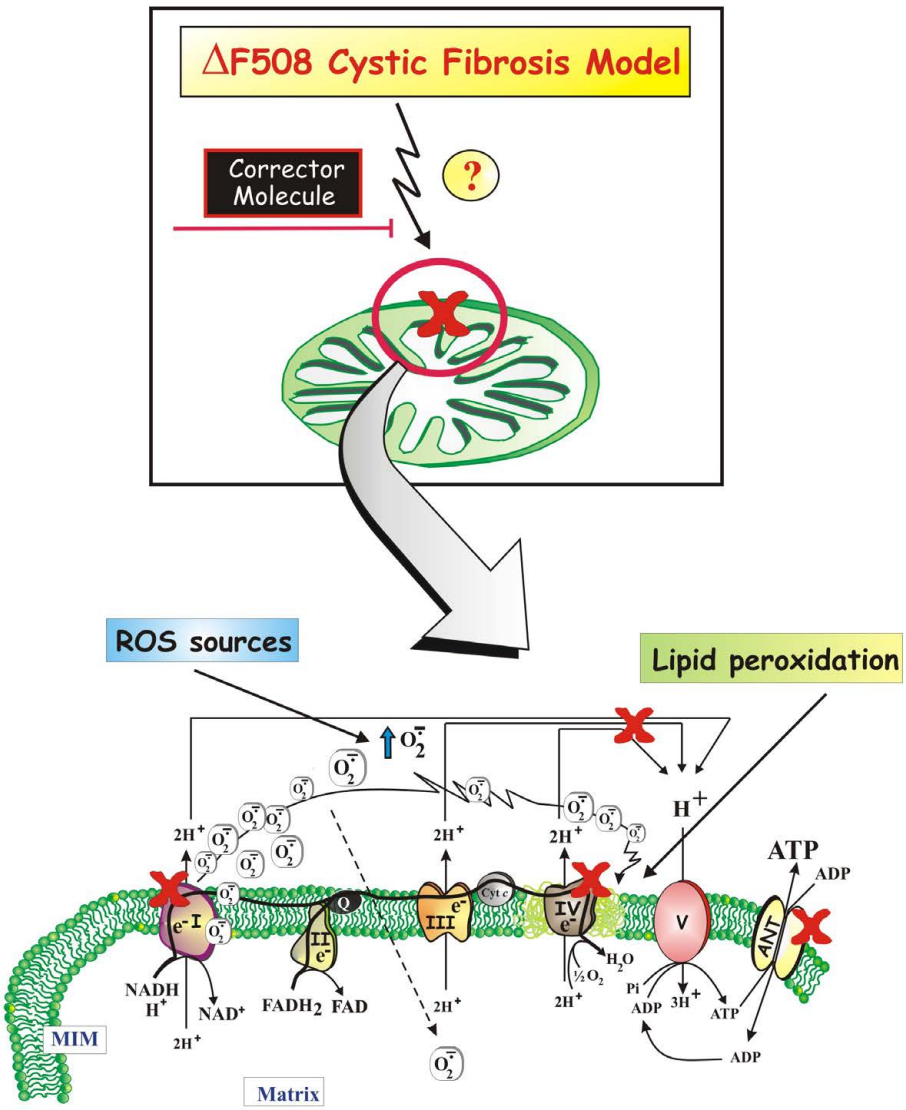

Figure 2: Mitochondrial targets in a F508del Cystic Fibrosis model. F508del CF is associated to mitochondrial dysfunction, rescued in a CFTR corrector-dependent manner.

ROS production or iii) both, thus attributing to mtCx-I a role in inducing oxidative stress. Thus, in this respect, an innovative finding was highlighted: the rotenone-sensitive mtCx-I -dependent ROS production increases in CF, thus suggesting that the mitochondrial defect attributed to mtCx-I arises from both a loss of activity and an increase in ROS production (Figure 2). Concerning this, Kelly Aubert[5] observed that the decrease in the mtCx-I activity of CF cells and CFTR knockout mice was reverted to healthy values by treating cells with GSH monoethylester, a membrane permeable analogue of GSH proved to be able in increasing mitochondrial GSH (mGSH) levels in several cellular models[34-36]. Further, consistently with this, the existence of mitochondrial oxidative stress in lungs from CFTR-knockout mice has been confirmed by both an increase in the oxidation of mitochondrial DNA and a loss of aconitase activity[37].

Importantly, in addition to the defect of mtCx-I, Atlante et al.[30] also observed a functional defect in Complex IV (i.e. COX), confirming the finding[28] of about 30years ago, according which there was a significant increase of the Km of COX for cytochrome c in CF fibroblasts, but this without providing the possible mechanism for the change in kinetics. The activity of COX, a multi-subunit protein complex embedded in the inner mitochondrial membrane, is strongly dependent on the membrane lipid environment. So, since mitochondrial ROS production and membrane lipid peroxidation increase in CF cells, Atlante et al.[30] have suggested that ROS-mediated damage of the membrane microenvironment may be responsible for inhibition of Complex IV. A note very important and exciting in this context is the finding that treatment of CF cells with the CFTR correctors partially restores the mitochondrial

function as well it reduces the extent of membrane lipid peroxidation in CF cells (Figure 2).

Future Perspectives

The novel information on mitochondrial bioenergetics in CF reported in Atlante et al.[30], together with the restorative action provided by the CFTR correctors, strongly suggest the profound interaction dynamics between CFTR, mitochondrial (patho)physiology and ROS.

Currently, we cannot provide any molecular mechanism underlying how CFTR dysfunction affects so many parameters of mitochondrial function, let alone how corrector-induced increased CFTR cell surface expression is able to repair these mitochondrial dysfunctions. However, we are confident and with clear ideas on how to proceed in research concerning the existing dialogue between mitochondria and CFTR in CF.

Here, we briefly design the research issues on which we're already working: i) one of these regards GSH; ii) the other, the ANT.

i. As a drop of GSH levels in lung epithelial lining fluid has been reported in CF[38,39], we are putting in the spotlight the GSH level, both mitochondrial and cytosolic forms, the GSH-dependent enzymes and all that concerns it in-order-to establish and understand the link between mitochondrial impairment, low GSH levels and defective F508del-CFTR. The reason for this is because cell redox balance within a cell - mainly influenced by the ratio between reduced GSH and its oxidized form - is regulated by complex processes, which converge exclusively upon mitochondria. Concerning this, that a link exists between GSH and mitochondria is demonstrated by the fact that a decrease in the mtCx-I activity of CF cells and CFTR knockout mice was reverted to control values by treating cells with GSH monoethylester[5], a membrane permeable analogue of GSH proved to be effective in increasing mGSH levels in several cellular models[34-36].

ii. In view of the fact that mitochondrial ANT-dependent ATP availability in the cytosol serves to gate CFTR channel activity, it follows that the activity of ANT is critical in CF. In this regard, we cannot exclude that the ANT impairment occurring in CF cells[30] is due i) to ROS-dependent oxidation of thiol group/s of the carrier, present at the active site of ANT and oriented toward the external hydrophilic phase, and/or ii) to changes in mitochondria configuration from the orthodox to a condensed form, an alteration that may modify thiol groups of membrane protein/s against oxidation by ROS. This consistently with the observation that ROS can regulate protein function thorough modification/s of specific thiol(s) of a protein or of its surrounding lipid environment[40]. So, that being said, the possibility that thiol groups on the matrix surface of the ANT may trigger the mechanism responsible of the mitochondrial permeability transition pore opening in CF cannot be excluded.

Needless to say that further exploration of mechanism underlying mitochondrial function in CF may open new possible avenues for therapeutics. Will see some good!

Schematic representation of the mitochondrial respiratory chain

Oxidation of respiratory substrates leads to reduction of coenzymes to NADH and $FADH_2$. Ubiquinone (Q) shuttles electrons from both Complexes I and II to Complex III, while cytochrome c (cyt c) shuttles electrons from Complex III to Complex IV. Molecular oxygen (O_2) is the terminal electron acceptor. Protons ($2H^+$) are pumped out by Complexes I, III and IV creating a proton electrochemical potential gradient. The resulting proton gradient drives both the exchange of ADP/ATP via the ANT and the synthesis of ATP from ADP and inorganic phosphate (Pi) by Complex V.

Mitochondrial targets in CF are marked with X

i) ANT and Complex I are inhibited; $\Delta\psi$ generation decreases; ii) production of ROS at Complex I is exacerbated; iii) COX is inhibited through ROS-induced damage to mitochondrial lipids, such as cardiolipin. In particular, the mitochondrial defect attributed to Complex I arises from both a loss of activity and an increase in ROS production; whereas Complex IV is impaired through Complex I-dependent ROS production and membrane lipid peroxidation in CF cells.

Main abbreviations

I, Complex I or NADH-ubiquinone oxidoreductase; II, Complex II or succinate-ubiquinone oxidoreductase; III, Complex III or ubiquinone–cytochrome-c oxidoreductase; IV, Complex IV or cytochrome-c oxidase; V, Complex V or FoF1 ATP synthase; ANT, adenine nucleotide translocator; MIM, mitochondrial inner membrane.

Acknowledgments

This research was supported by Italian Cystic Fibrosis Research Foundation

FFC#1/2015 Project: "Relationship between mitochondria and F508del-CFTR in Cystic Fibrosis" to A.A.

Conflict of Interest statement.

The authors declare no conflicts of interest.

References

1. Mailloux RJ, Jin X, WillmoreWG. Redox regulation of mitochondrial function with emphasis on cysteine oxidation reactions. Redox Biol. 2013 Dec 19; 2: 123-39.

2. Brown GC, Borutaite V. There is no evidence that mitochondria are the main source of reactive oxygen species in mammalian cells. Mitochondrion. 2012 Jan; 12(1): 1-4.

3. Korshunov SS, Skulachev VP, Starkov AA. High protonic potential actuates a mechanism of production of reactive oxygen species in mitochondria. FEBS Lett. 1997 Oct 13; 416(1): 15-8.

4. Pouvreau S. Superoxide flashes in mouse skeletal muscle are produced by discrete arrays of active mitochondria operating coherently. PLoSOne. 2010 Sep 28; 5(9). pii: e13035.

5. Kelly-Aubert M, Trudel S, Fritsch J, Nguyen-Khoa T, Baudouin-Legros M, Moriceau S, Jeanson L, et al. GSH monoethylester rescues mitochondrial defects in cystic fibrosis models. Hum Mol Genet. 2011 Jul 15; 20(14): 274559.

6. Valdivieso AG, Santa-Coloma TA. CFTR activity and mitochondrial function. Redox Biol. 2013 Feb 5; 1: 190-202.

7. Mickle JE, Macek M Jr, Fulmer-Smentek SB, Egan MM, Schwiebert E, Guggino W, Moss R, et al. A mutation in the cystic fibrosis transmembrane conductance regulator gene associated with elevated sweat chloride concentrations in the absence of cystic fibrosis. Hum Mol Genet. 1998 Apr; 7(4): 729-735.

8. Shapiro BL, Feigal RJ, Lam LF. Mitochondrial NADH dehydrogenase in cystic fibrosis. Proc Nat Acad Sci USA 1979 Jun; 76(6): 2979-2983.

9. Brodlie M, Haq IJ, Roberts K, Elborn JS. Targeted therapies to improve CFTR function in cystic fibrosis. Genome Med 2015 Sep 24; 7: 101.

10. Haq IJ, Gray MA, Garnett JP, Ward C, Brodlie M. Airway surface liquid homeostasis in cystic fibrosis: pathophysiology and therapeutic targets. Thorax 2016 Mar; 71(3): 284-287.

11. Collins FS. Cystic fibrosis: molecular biology and therapeutic implications. Science 1992 May 8; 256(5058): 774-779.

12. Rommens JM, Iannuzzi MC, Kerem B, Drumm ML, Melmer G, Dean M, et al. Identification of the cystic fibrosis gene: chromosome walking and jumping. Science 1989 Sep 8; 245(4922): 1059-1065.

13. Riordan JR, Rommens JM, Kerem B, Alon N, Rozmahel R, Grzelczak Z, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. Science 1989 Sep 8; 245(4922): 1066-1073.

14. Rowe SM, Miller S, Sorscher EJ. Cystic fibrosis. N Engl J Med. 2005 May 12; 352(19): 19922001.

15. Ntimbane T, Comte B, Mailhot G, Berthiaume Y, Poitout V, Prentki M, et al. Cystic fibrosis-related diabetes: from CFTR dysfunction to oxidative stress. Clin Biochem Rev. 2009 Nov; 30(4): 153-177.

16. Rowe SM, Verkman AS. Cystic fibrosis transmembrane regulator correctors and potentiators. Cold Spring Harb Perspect Med. 2013 Jul 1; 3(7). pii: a009761.

17. Feigal RJ, Shapiro BL. Mitochondrial calcium uptake and oxygen consumption in cystic fibrosis. Nature 1979 Mar 15; 278(5701): 276-277.

18. Shapiro BL, Lam LF, Feigal RJ. Mitochondrial NADH dehydrogenase in cystic fibrosis: enzyme kinetics in cultured fibroblasts. Am J Hum Genet. 1982 Nov; 34(6): 846-852.

19. Shapiro BL. Mitochondrial dysfunction, energy expenditure, and cystic fibrosis. Lancet 1988 Jul 30; 2(8605): 289.

20. Shapiro BL. Evidence for a mitochondrial lesion in cystic fibrosis. Life Sci. 1989; 44(19): 1327-1334.

21. Kamdar O, Le W, Zhang J, Ghio AJ, Rosen GD, Upadhyay D. Air pollution induces enhanced mitochondrial oxidative stress in cystic fibrosis airway epithelium. FEBS Lett. 2008 Oct 29; 582(25-26): 3601-3606.

22. Antigny F, Norez C, Becq F, Vandebrouck C. CFTR and Ca signaling in cystic fibrosis. Front Pharmacol. 2011 Oct 25; 2: 67.

23. Sureshbabu A, Bhandari V. Targeting mitochondrial dysfunction in lung diseases: emphasis on mitophagy. Front Physiol. 2013 Dec 26; 4: 384. Review

24. Awasthi A, Prasad B, Kumar J. Altered Mitochondrial Function and Cystic Fibrosis. Hereditary Genetics 2015; S7: 001.

25. Valdivieso AG, Clauzure M, Marín MC, Taminelli GL, Massip Copiz MM, Sánchez F, et al. The mitochondrial complex I activity is reduced in cells with impaired cystic fibrosis transmembrane conductance regulator (CFTR) function. PLoS One. 2012; 7(11): e48059.

26. Valdivieso AG, Marcucci F, Taminelli GL, Gonzàlez-Guerrico AM, Alvarez S, Teiber ML, et al. The expression of the mitochondrial gene MT-ND4 is downregulated in cystic fibrosis. Biochem Biophys Res Commun. 2007 May 11; 356(3): 805-809.

27. Clauzure M, Valdivieso AG, Massip Copiz MM, Schulman G, Teiber ML, Santa-Coloma TA. Disruption of interleukin-1β autocrine signaling rescues complex I activity and improves ROS levels in immortalized epithelial cells with impaired cystic fibrosis transmembrane conductance regulator (CFTR) function. PLoS One. 2014 Jun 5; 9(6): e99257.

28. Battino M, Rugolo M, Romeo G, Lenaz G. Kinetic alterations of cytochrome-c oxidase in cystic fibrosis. FEBS Lett. 1986 Apr 21; 199(2): 155-158.

29. Rimessi A, Bezzerri V, Patergnani S, Marchi S, Cabrini G, Pinton P. Mitochondrial Ca^{2+}dependent NLRP3 activation exacerbates the Pseudomonas aeruginosa-driven inflammatory response in cystic fibrosis. Nat Commun. 2015 Feb 4; 6: 6201.

30. Atlante A, Favia M, Bobba A, Guerra L, Casavola V, Reshkin SJ. Characterization of mitochondrial function in cells with impaired cystic fibrosis transmembrane conductance regulator (CFTR) function. J Bioenerg Biomembr. 2016 Jun; 48(3): 197-210.

31. Ren HY, Grove DE, De La Rosa O, Houck SA, Sopha P, Van Goor F, et al. VX-809 corrects folding defects in cystic fibrosis transmembrane conductance regulator protein through action on membrane-spanning domain 1. Mol Biol Cell. 2013 Oct; 24(19): 3016-3024.

32. Favia M, Mancini MT, Bezzerri V, Guerra L, Laselva O, Abbattiscianni AC, et al. Trimethylangelicin promotes the functional rescue of mutant F508del CFTR protein in cystic fibrosis airway cells. Am J Physiol Lung Cell Mol Physiol. 2014 Jul 1; 307(1): L48-L61.

33. Hwang TC, Kirk KL. The CFTR ion channel: gating, regulation and anion permeation. Cold Spring Harb Perspect Med. 2013 Jan 1; 3(1): a009498.

34. Fernandez-Checa JC, Garcia-Ruiz C, Ookhtens M, Kaplowitz N. Impaired uptake of glutathione by hepatic mitochondria from chronic ethanol-fed rats. Tracer kinetic studies in vitro and in vivo and susceptibility to oxidant stress. J Clin Invest. 1991 Feb; 87(2): 397-405.

35. Martensson J, Jain A, Frayer W, Meister A. Glutathione metabolism in the lung: inhibition of its synthesis leads to lamellar body and mitochondrial defects. Proc Nat Acad Sci USA 1989 Jul; 86(14): 5296-5300.

36. Martensson J, Meister A. Mitochondrial damage in muscle occurs after marked depletion of glutathione and is prevented by giving glutathione monoester. Proc Nat Acad Sci USA 1989 Jan; 86(2): 471-475.

37. Velsor LW, Kariya C, Kachadourian R, Day BJ. Mitochondrial oxidative stress in the lungs of cystic fibrosis transmembrane conductance regulator protein mutant mice. Am J Respir Cell Mol Biol. 2006 Nov; 35(5): 579-586.

38. Gao L, Kim KJ, Yankaskas JR, Forman HJ. Abnormal glutathione transport in cystic fibrosis airway epithelia. Am J Physiol. 1999 Jul; 277(1 Pt 1): L113-8.

39. Velsor LW, van Heeckeren A, Day BJ. Antioxidant imbalance in the lungs of cystic fibrosis transmembrane conductance regulator protein mutant mice. Am J Physiol - Lung Cell Mol Physiol. 2001 Jul; 281(1): L31-L38.

40. Bobba A, Amadoro G, Petragallo VA, Calissano P, Atlante A. Dissecting the molecular mechanism by which NH2htau and Aβ1-42 peptides impair mitochondrial ANT-1 in Alzheimer disease. Biochim Biophys Acta 2013 Jul; 1827(7): 848-60.