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Review

c- Src and its role in cystic fibrosis

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ABSTRACT

Cystic fibrosis (CF) is a lethal inherited disease produced by mutations in the gene encoding the CFTR chloride channel. Loss of function in the CFTR gene is associated with a not much noticed increased expression and activity of the non-receptor protein-tyrosine kinase c-Src. CF is therefore the result from the loss of CFTR chloride transport function and its consequences, including a chronic and excessive c-Src signaling. On the other hand, c-Src, encoded by the *SRC* gene, is involved in diverse signaling mechanisms that regulate key cellular functions such as cell proliferation, apoptosis, oxidative stress, inflammation, and innate immunity. These c-Src-regulated cellular functions are also affected in CF; however, studies exploring a direct role of c-Src in the regulation of these cellular functions in CF are yet scarce and often controversial. Here we describe the c-Src regulation and functions, with emphasis in those altered in CF, and describe the role of CFTR as a "signaling molecule" that negatively modulates c-Src expression and activity. It is also discussed the emerging role of intracellular Cl^- and IL-1β as intermediate signaling effectors between CFTR and c-Src.

Contents

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1. The protein tyrosine kinase c-Src

c-Src, encoded by *SRC*, was the first oncogene to be discovered (Bishop, 1983; Brown and Cooper, 1996; Thomas and Brugge, 1997). It belongs to the c-Src family of non-receptor protein tyrosine kinases (SFKs), which comprises at least nine members in vertebrates, including Fgr, Fyn, Src, Yes, Hck, Lyn, Lck, Blk, and Yrk (Le and Bast, 2011).

1.1. Regulatory mechanism of c-Src

This kinase has complex mechanisms of regulation; the most frequent are illustrated in Fig. 1. Under basal conditions, 90–95% of c-Src is phosphorylated at Tyr-530 (the numbers correspond to the human sequence; Tyr-529 corresponds to Tyr-530 after the N-terminal Met is removed) (Zheng et al., 2000). Phosphorylation of Tyr-530 is performed either by CSK (C-terminal c-Src Kinase) or CHK (CSK homologous kinase), allowing for an intermolecular interaction of the phosphorylated Tyr-530 with the SH2 domain that stabilizes a silent conformation of the enzyme (Roskoski, 2005). Thus, in resting cells, the c-Src enzyme possesses an inactive closed state. Upon different cellular stimuli, c-Src is activated through dephosphorylation of Tyr-530 (Zheng et al., 2000) by several cytoplasmic and transmembrane phosphotyrosine phosphatases (Roskoski, 2005). Upon stimulation, c-Src initiates an intermolecular autophosphorylation process at Tyr-419 (Tyr-418 after the N-terminal Met is removed), which allows for the opening of the catalytic site, thus inducing the kinase activity of the SH1 domain (Roskoski, 2004). One form of c-Src activity termination occurs as a consequence of CHK interacting non-catalytically with the active Tyr-419-c-Src to form a stable and inactive CHK:c-Src complex. Then, CHK phosphorylates Tyr-530 and dissociates from the complex once c-Src adopts the inactive conformation. On the other hand, CDK5 phosphorylates Ser-75, which targets c-Src for ubiquitin-dependent degradation (Pan et al., 2011). Other possible sites of phosphorylation and dephosphorylation exist (Roskoski, 2005), which reveal a complex scenario of regulatory mechanisms for c-Src.

c-Src is also regulated through its binding to tyrosine-phosphorylated proteins, via the SH2 domain (Songyang et al., 1993). This binding results in c-Src activation, which in turn phosphorylates the interacting proteins, allowing the amplification of the corresponding signaling pathways (Okada, 2012), as occurs with epidermal growth factor receptor (EGFR) (Biscardi et al., 1999; Osaki et al., 2011; Singh et al., 2012). The interaction between c-Src and EGFR synergizes cell responses to EGF (Irwin et al., 2011; Maa et al., 1995; Wilson et al., 1989). A similar synergic effect results from the interaction of platelet-derived growth factor receptors (PDGFR) with c-Src (Kypta et al., 1990).

In addition, GPCR receptors indirectly modulate c-Src activity, though PKA, which phosphorylates CSK and in turn phosphorylates Tyr-530 of c-Src, inhibiting c-Src's activity (Baker et al., 2006; Cornez and Tasken, 2010). PKA can also activate c-Src phosphorylating its Ser-17 (Beristain et al., 2015; Schmitt and Stork, 2002). Also, epithelial cells under mechanical o molecular stress can release ATP, which activates P2RY2 (a purinergic GPCR receptor) through a Gq/11 → PLC → PKC and IP3 pathway, increasing the intracellular Ca^{2+} and PKC activity, which in turn activate AKT and c-Src (Wang et al., 2015). Increasing the intracellular levels of Ca^{2+} using ionomycin or the PKC activity using PMA also resulted in c-Src activation (Hodges et al., 2007; Wang et al., 2015). Calmodulin (CaM) alone or bound to Ca^{2+} activates c-Src, although Ca^{2+} by itself has an inhibitory effect on c-Src activity (Stateva et al., 2015). On the other hand, Ca^{2+} activates Ca^{2+}-dependent isoforms of PKC (cPKCs) (Luo and Weinstein, 1993), which in turn activate c-Src (Li et al., 2013). PKC phosphorylates c-Src in Ser-12 and Ser-48, modifications that are required for enhanced beta-agonist stimulation in cells overexpressing c-Src (Moyers et al., 1993). P2Y2R can also induce transactivation of EGF receptors (p-Try845) through dual oxidase 1 (DUOX1)-dependent activation of c-Src, involving oxidation of cysteine residues within the c-Src molecule (Giannoni and Chiarugi, 2014; Sham et al., 2013); other intracellular pathways that generate reactive oxygen species (ROS) may activate c-Src in the same way (Giannoni and Chiarugi, 2014).

The c-Src kinase is also modulated by signaling pathways activated by heterotrimeric G protein-coupled receptors (Malarkey et al., 1995) modulated by mechanical stress (Han et al., 2005; Shahidullah et al., 2015), ion channel activities –indirectly, i.e. the Cl^- channel CFTR (Massip Copiz, 2015) and the Ca^{2+} channel CaV1.3 (Samak et al., 2011)- or through the c-Src's C-terminal amino acid sequence Gly-Glu-Asn-Leu (GENL) acting as a ligand for PDZ domains (Baumgartner et al., 2008). Additional mechanisms of signaling that determine increased c-Src activity include the pathways of IL-1β (and other cytokines), PDGF (Cheng et al., 2010; Davis et al., 2006; Wu et al., 2008; Yang et al., 2015) and EGFR/integrin signaling through a c-Src:FAK complex (McLean et al., 2005).

1.2. Relevant cellular functions modulated by c-Src

Fig. 2 illustrates most relevant cellular functions modulated by c-Src. Its overexpression and activation is involved in cancer cell proliferation and tumor growth (Elsberger et al., 2010). A high c-Src activity is associated with metastatic potential and poor prognosis (Summy and Gallick, 2003; Wiener et al., 2003). In cancer, it plays an important role in angiogenesis and vascular permeability (Park et al., 2007; Schenone et al., 2007), regulating pro-angiogenic factors, like VEGF (Ellis et al., 1998). Its activation also leads to increased IL-8 (Dudez et al., 2008; Trevino et al., 2005), which participates, among other functions, in angiogenesis.

SFKs are also involved in many cellular processes of normal cells. Thus, c-Src is involved in cell proliferation and intercellular communication by regulating gap junction proteins (also called connexins) (Geletu et al., 2012; Giepmans et al., 2001). It also participates in cross-talk interactions between proteins in different molecular pathways (Peng et al., 2012), including the focal adhesion kinase (FAK) (Guan, 2010; Ishida et al., 1999), EGFR (Maa et al., 1995; Tice et al., 1999) and G proteins (Ma et al., 2000) pathways. c-Src is also implicated in cell cycle progression (Marcotte et al., 2012) and apoptosis (Chan et al., 2010). Although c-Src is ubiquitously expressed, it is abundant in neurons, having a role in neuron proliferation and differentiation (Parsons and Parsons, 2004). In particular, c-Src upregulates the activity of *N*-methyl-D-aspartate (NMDA) receptors and other ion channels of CNS (Kalia et al., 2004; Salter and Kalia, 2004). c-Src is also involved in the regulation of mitogen-activated protein kinase (MAPK/ERK) and phosphatidyl-inositol-3-kinase (PI3K) activation, modulating the equilibrium between survival and apoptosis (Kauffmann-Zeh et al., 1997; Yao and Cooper, 1995).

It should be pointed out here that, for simplicity, only a small subset of all possible interrelationships between c-Src and cell functions are shown in Fig. 2 (out of ~4000 entries found in Pathway Studio database v.10). Important for the focus of this review, although many of the cellular processes modulated by c-Src are also affected in cystic fibrosis, only in few cases has a direct role of c-Src been studied so far. Among them are those related to MUC1 expression (Gonzalez-Guerrico et al., 2002), gap junction regulation (Chanson and Suter, 2001; Dudez et al., 2008; Huang et al., 2003a), and *P. aeruginosa* invasion (Esen et al., 2001), effects which will be discussed with more detail below.

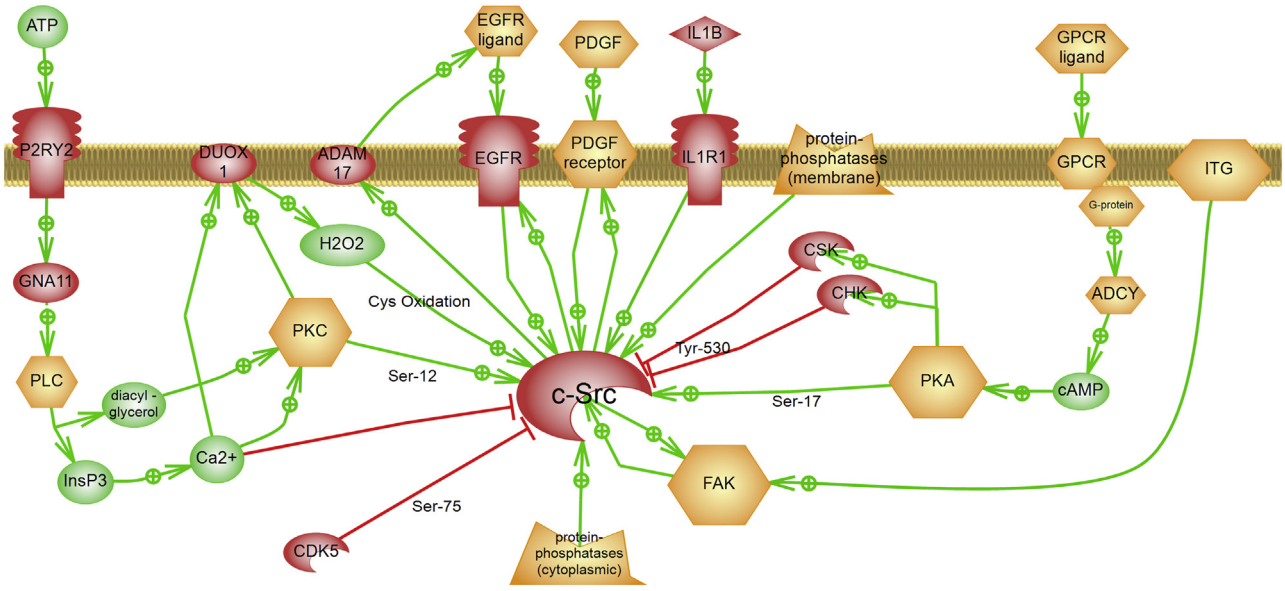

Fig. 1. Regulatory mechanisms for c-Src. The graphic was made by using the Pathway Studio (PS) software v.10 (Elsevier). For simplicity, from a total of 3940 interactions found between c-Src and other entities in the PS database (containing 2 million interactions), only the most significant for this review are illustrated. The green arrows indicate stimulation and the red T-shaped lines inhibition. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

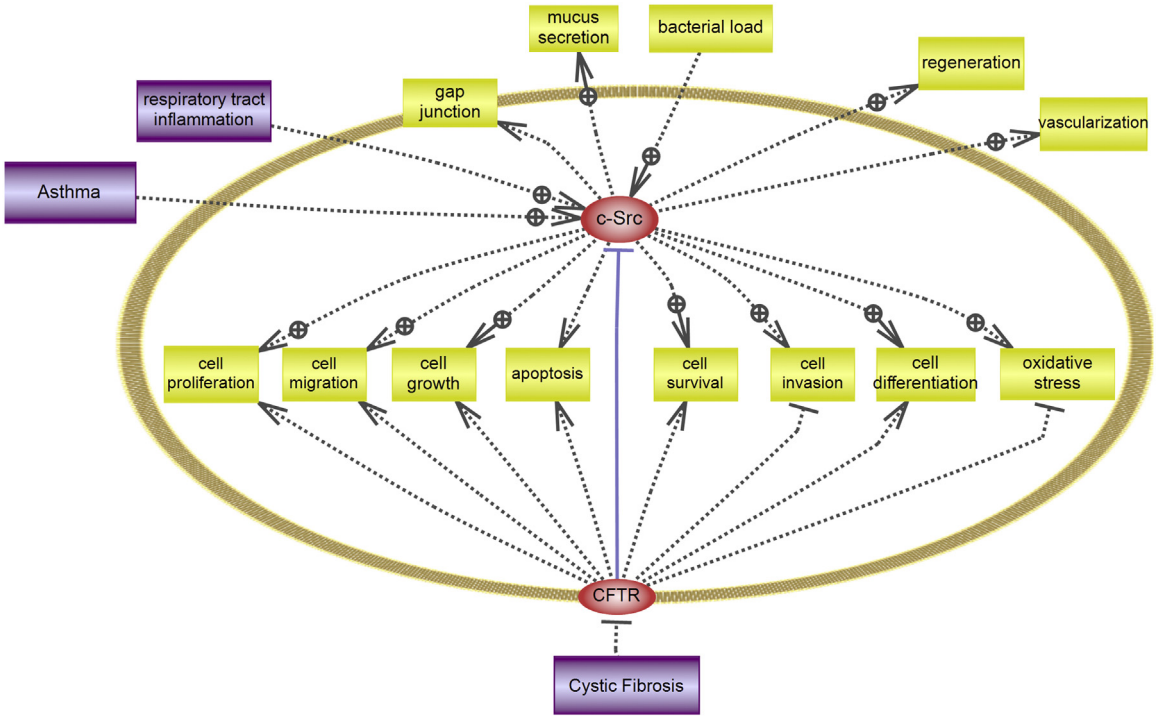

Fig. 2. Different cellular and tissue functions modulated by c-Src**.** This figure illustrates different cellular functions modulated by c-Src, in vivo or in vitro, in model systems others than cystic fibrosis (CF), such those of asthma and respiratory tract inflammation. Noteworthy, although all these functions were also found altered in CF, only in few cases a role of c-Src in these altered functions have been studied or postulated for CF cells. Further studies are needed to better understand the possible role of c-Src on these effects.

1.3. Inflammation and c-Src

The inflammatory signalings involved in airway pulmonary diseases, including the role of SFKs, have been previously reviewed in detail (Lee and Yang, 2013). In human airway smooth muscle cells, TNF-α or IL-1β, through c-Src, induce the expression of inflammatory targets, which include the vascular cell adhesion molecule-1 (VCAM-1) and the intercellular adhesion molecule-1 (ICAM-1) (Lee and Yang, 2012). In addition, c-Src regulates a COX-2/PGE2/IL-6-dependent airway inflammation via NADPH oxidase/ROS (Lin et al., 2010). TNF-α, in human mucoepidermoid lung carcinoma cells, in addition to activating NIK (NF-κB inducing kinase) via TRAF6, can also activate c-Src via PKC (Huang et al., 2003c). In addition, in mesangial cells, stimulated with IL-1β, c-Src increases basal and stimulated NO production via tyrosine phosphorylation of IκBα and consequent NF-κB activation (Jalal and Kone, 2006). These are

only a few examples of the numerous studies in which c-Src modulates receptors or signaling cascades involved in inflammation. In conclusion, c-Src signaling is crucial to the inflammatory process.

1.4. Mucins and c-Src

Mucins have important physiological and physiopathological roles, covering many different diseases, especially infections and cancer (Tarang et al., 2012). Different interrelationships between c-Src and mucins were extensively reported in studies related to cancer cell proliferation (Van Seuningen et al., 2001).

Mucins are high molecular weight glycoproteins. Their complex oligosaccharide side chains are attached to the protein backbone through *O*-glycosidic linkages (Mall, 2008). Mucins can be either soluble (constituting mucus gels) or membrane-bound proteins (MUC1 and MUC4 are the best characterized membrane-bound mucins) (Jonckheere and Van Seuningen, 2010). Both types of mucins have the function to protect the epithelial surfaces. This characteristic was recognized long ago in the pioneer work of Claude Bernard, who compared the mucins from stomach with the porcelain protecting a pot (Bernard, 1856). The transmembrane mucins are expressed on the apical cell surface of epithelial cells in different organs (Mall, 2008). They participate in cell-cell and cell-matrix interactions (Chaturvedi et al., 2007), in cell signaling (Abdullah and Davis, 2007; Funes et al., 2006; Nadel, 2007), and in the regulation of biological properties of cancer cells (Bruyere et al., 2011; Fang et al., 2009).

Mucins glycosylation (both *N*-glycosylation and *O*-glycosylation) occurs in the Golgi apparatus. A family of enzymes called *N*-acetylgalactosaminyl transferases (GalNac-Ts) initiate *O*-glycosylations. Gill and colleagues observed that c-Src regulates *O*-glycosylation of mucins through redistribution of the GalNac-Ts from the Golgi to the ER, increasing initiation of *O*-glycosylation (Gill et al., 2010). c-Src also participates in gastric mucins secretion triggered by beta-adrenergic GPCR (G protein-coupled receptor) activation. In this pathway, EGFR is a convergence point in which c-Src kinase is required for its transactivation (Slomiany and Slomiany, 2005). The same signaling pathway was observed for the modulation of salivary mucin secretion (Slomiany and Slomiany, 2004b). The four gel-forming mucin genes MUC2, MUC5AC, MUC5B and MUC6 are clustered on the p15 arm of chromosome 11 and their expression is also under c-Src regulation, through activation of the Src/Ras/MAPK/pp90rsk cascade, leading to NF-κB activation (Van Seuningen et al., 2001). The expression of these 11p15 mucin genes is regulated by pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α), pleiotropic cytokines (multifunctional cytokines, such as IL-4, IL-9, IL-13, affecting different cells types), bacterial products (e.g. LPS), growth factors (among others EGF and TGF-α), platelet activating factor (PAF), retinoids, and hormones (Van Seuningen et al., 2001). Among transcription factors involved in regulation of gel-forming mucins are ATF-1, CREB and RAR-α; their expression is also regulated by epigenetic mechanisms (Van Seuningen et al., 2001; Yamada et al., 2011).

1.5. Mucin hypersecretion and c-Src

Since c-Src regulates the expression of most mucins, this protein kinase should have an important role in controlling the hypersecretion of mucins, which constitutes an important mechanism of defense against infections. However, there are only a few studies so far linking c-Src, mucins, and infections. In NCIH292 (airway epithelial cell line) and HM3 (colon epithelial cell line) cells, *P. aeruginosa*-induced mucin overproduction requires the activation of nuclear factor NF-κB (p65/p50) via a c-Src-dependent Ras-MAPK-pp90rsk pathway (Li et al., 1998). The activated NF-κB in turn binds to a site in the 5′-flanking region of the MUC2 gene inducing its transcription (Li et al., 1998). A different c-Src-related mitogen-activated protein kinase pathway (MAPK p44/42, also known as extracellular signal-regulated kinase 1 and 2, ERK1/2) is involved in the rhinovirus-induced mucin hypersecretion in cultured human airway epithelial cells (rhinovirus produce the common cold) (Inoue et al., 2006). In contrast, the LPS of *Helicobacter pylori* induces gastric tissue inflammation and dedifferentiation, which eventually leads to gastric cancer (Song et al., 2013), by a process which is accompanied by inhibition of gastric mucin (Slomiany and Slomiany, 2004a) (instead of hypersecretion). In this regard, agonists of peroxisome-proliferator-activated receptor gamma (PPARγ) negatively regulate genes associated with inflammation in human monocytes (Jiang et al., 1998). In addition, PPARγ and its activation of phosphatidylinositol 3-kinase (PI3K) are important regulators of mucosal responses to bacterial infections. In cultured human gastric mucosal cells, PPARγ activation with the agonist ciglitazone suppresses the *Helicobacter pylori* induced inhibition of mucin synthesis, involving a c-Src kinase-dependent epidermal growth factor receptor (EGFR) transactivation (Slomiany and Slomiany, 2004a). The LPS-induced reduction in mucin synthesis results in apoptosis, caspase-3 activity and nitric oxide (NO) generation (Slomiany and Slomiany, 2004a). However, activation of PPARγ not always overrides LPS stimulation of proinflammatory cytokines (Jiang et al., 1998). A similar mechanism was observed with other bacterial species, such as *Porphyromonas gingivalis* (Slomiany and Slomiany, 2004c). Thus, it appears that c-Src may be an important modulator of inflammation and mucin hypersecretion during the development of infections.

2. Cystic fibrosis

Cystic fibrosis (CF) or mucoviscidosis is a lethal autosomal recessive disease (Quinton, 2010; Riordan, 2008). The main characteristics of this disease are the presence of abundant and sticky mucus (which clogs glandular ducts, airways and intestine), pulmonary and pancreatic inflammation, pulmonary fibrosis, and recurrent lung infections, which eventually lead to organ failure (Shamsuddin and Quinton, 2014; Wang et al., 2014). The gene responsible for the disease, the cystic fibrosis transmembrane conductance regulator or *CFTR*, was identified and cloned in 1989 (Riordan et al., 1989). Later, it was found to function as a cAMP-activated chloride channel (Anderson et al., 1991a,b; Bear et al., 1991; Collins, 1992; Rich et al., 1990), in agreement with the already known alterations of chloride transport in CF and its cAMP-dependency (Bijman, 1989; Chen et al., 1989; de Jonge, 1989; Jetten et al., 1989; Kopelman et al., 1989). CFTR is a transmembrane glycoprotein, member of the superfamily of ABC (ATP Binding Cassette) transporter proteins. It has two membrane spanning domains (MSD 1 and MSD 2) that forms the channel, two nucleotide-binding domains (NBD1 and NBD2) that hydrolyze ATP to regulate the channel activity (Schwiebert et al., 1999) and a regulatory domain (R), which is activated by PKA phosphorylation, and controls the opening of the channel (Rogan et al., 2011). This R domain is unique among ABC transporters. CFTR appears to function not only as a regulated chloride channel (Schwiebert et al., 1999); it may be also involved in the transport of bicarbonate (Chan et al., 2006; Poulsen et al., 1994; Smith and Welsh, 1992), glutathione (Kogan et al., 2003) and ATP (Egan, 2002). It is yet a controversial issue whether or not CFTR transports these additional anions directly or indirectly through other channels (Egan, 2002).

Several cellular functions have been found altered in CF, including apoptosis (Soleti et al., 2013), autophagy (Mayer et al., 2013; Nakahira et al., 2014; Villella et al., 2013), redox balance (Ziady and Hansen, 2014), inflammation (Cohen-Cymberknoh et al., 2013), innate immunity (Hartl et al., 2012), mitochondrial functions

(Valdivieso and Santa-Coloma, 2013), and mucin expression and secretion (Kreda et al., 2012). Noteworthy, in other diseases and cellular models c-Src has an important role in regulation of these functions. However, as previously mentioned, in CF, the possible role of c-Src in these functions remains mostly unexplored.

2.1. Bacterial infections in cystic fibrosis and c-Src activity

The principal microorganisms involved in CF lung infections are *Pseudomonas aeruginosa* (Hoiby, 2011), and to a lesser extent *Staphylococcus aureus* (Besier et al., 2007; Wong et al., 2013) and *Haemophilus influenzae* (Starner et al., 2006). *P. aeruginosa* is able to persist many years in CF lungs due to the formation of biofilms (Haley et al., 2012). Many of the strains that constitute the Burkholderia cepacia (Pseudomonas cepacia) complex (Bcc), which are highly resistant to antibiotic treatments, also produce biofilms (Silva et al., 2011). Together with *P. aeruginosa*, *B. cepacia* causes severe lung infections in CF patients, producing in the long-term irreversible and extensive tissue damage. This damage often leads to lung transplantation as the only possible solution (Olland et al., 2011). Once the chronic disease and damage is established, the decay in the lung performance year after year is constant and irreversible. For this reason, early management of the disease is very important to diminish and perhaps even eliminate the long-term consequences (Grasemann and Ratjen, 2013).

Interestingly, the *P. aeruginosa* invasion to the airway epithelium cells induces and requires the activation of the tyrosine kinases c-Src and c-Fyn; the activation of these kinases seems to be crucial for the internalization of *P. aeruginosa* into the epithelial cells (Esen et al., 2001). Asialo GM1(de Bentzmann et al., 1996), MUC1 (Kato et al., 2010; Lu et al., 2006) and CFTR act as surface receptors for these bacteria, although CFTR is responsible for their internalization and clearance from lungs (Pier et al., 1997). Lyn, another member of the Src family of tyrosine kinases, is also involved in *P. aeruginosa* internalization (Kannan et al., 2006; Lepanto et al., 2011). Binding of *P. aeruginosa* to cells also triggers NF-κB activation (DiMango et al., 1998). Resistance to *P. aeruginosa* chronic lung infection requires CFTR-modulated IL-1β release and signaling through its receptor, and this release and signaling is deficient in CFT1 cells, which have impaired CFTR activity (Reiniger et al., 2007). Noteworthy and in contrast, we have observed that a saturating autocrine IL-1β loop is present when the CFTR activity is affected in cultured CF cells or in Caco-2 cells treated with CFTR shRNA, and that only wild-type (wt) CFTR cells have a response to IL-1β, measured as NF-κB activation, ROS production and mitochondrial Complex I inhibition (Clauzure et al., 2014). Thus, the lack of response to IL-1β observed in cells with impaired CFTR activity is probably due to the presence of a saturating IL-1β autocrine signaling.

The recurrent pulmonary infections that suffer CF patients by *P. aeruginosa* and other bacteria are characterized by an overactive and destructive inflammatory response (Cohen and Prince, 2012). Through Toll-like Receptors (TLRs), *P. aeruginosa* activates many signaling pathways responsible for the inflammatory and immune response (McIsaac et al., 2012). One of *P. aeruginosa*'s secreted exoproducts, the exoenzyme S (Exo S), activates in monocytes TLR2 and TLR4 signaling, thus stimulating proinflammatory cytokines production (Epelman et al., 2004); NF-κB, Erk1/2, and c-Src kinase pathways are involved in these effects (Epelman et al., 2008). Interestingly, SFKs are present within the detergent-resistant membrane microdomains (DRM or lipid rafts) where ExoS directly binds and induces its phosphorylation (Epelman et al., 2008).

It has also been reported that bacterial stimuli in epithelial cells activate a TLR-mediated response that results in ATP secretion and P2YR activation. This signaling mechanism triggers DUOX1 activation. In turn, the intracellular production of H_2O_2 by DUOX1 induces a ligand-independent activation of EGFR or the activation of an upstream tyrosine kinase such as c-Src, with the consequent activation of the NF-κB and AP-1 pathways, leading to IL-8 production and secretion (Sham et al., 2013).

There is evidence that c-Src is involved in the regulation of gap junction channels (Cx43) when mediators of inflammation are present (Huang et al., 2003a,b). During the course of an inflammatory response, gap junction channels close to reduce the intercellular diffusion of signaling molecules and the recruitment of neighboring cells (Chanson and Suter, 2001). When CFTR is dysfunctional, both TNF-alpha signaling (Huang et al., 2003b) and c-Src-signaling are altered (defective c-Src stimulation in response to medium renewal), resulting in the persistence of gap junction connectivity in CF airway cells (Dudez et al., 2008; Huang et al., 2003a).

2.2. CFTR-dependent genes

For a few years after the CFTR was cloned (Riordan et al., 1989), most of the work focused on possible cytoplasmic/membrane effects of its transport activity (Bear et al., 1991; Cheng et al., 1990). Little was known regarding CFTR regulation. At that time, we thought that the complex CFTR phenotype might be the result of changes in the expression of a set of CFTR-dependent genes and CFTR-modulating genes. By using differential display to test this hypothesis, we initially studied lymphocytes from blood samples of a family with CF children. However, the high intrinsic variability, possible due to different treatments and distinct genetic modifiers, prompted us to change the approach and use CF cell lines instead. Since it was known that the phorbol ester TPA was able to reduce CFTR expression (Trapnell et al., 1991), we decided to study first the differential expression of genes in TPA-treated cells (Cafferata et al., 1995). We observed several TPA-dependent gene products. One cDNA fragment was isolated from the gel, purified and cloned (Cafferata et al., 1996). The sequence was later completed and named "Homo sapiens orphan G protein-coupling receptor PEIG-1 mRNA" (PEIG stand for "phorbol ester induced gene 1"; AF506289). Noteworthy, two years later, also using differential display, Cheng and Lotan found a retinoic-acid inducible gene that encoded a putative G protein-coupled receptor (RAIG1), possessing identical sequence (Cheng and Lotan, 1998). Later, other members of this family were identified (Brauner-Osborne et al., 2001; Brauner-Osborne and Krogsgaard-Larsen, 2000; Robbins et al., 2000). Thus, *PEIG-1*, *RAIG1* or *GPRC5A* are the same gene. Interestingly, *PEIG-1/RAIG1/GPRC5A* has been characterized as a putative tumor-suppressor gene by Ye et al. (Ye et al., 2009), associated with survival in human lung adenocarcinomas (Kadara et al., 2010) and with Chronic Obstructive Pulmonary Disease (COPD) and lung inflammation through NF-κB induction (Barta et al., 2012; Chen et al., 2010; Fujimoto et al., 2012). This NF-κB activation may be related to the autocrine IL-1β loop that we found in cells with impaired CFTR function, which is responsible for the increased NF-κB signaling (Clauzure et al., 2011, 2013, 2012, 2014, 2010).

After that initial work, we realized that characterizing all the TPA-depending genes to identify possible CFTR-related genes using differential display would be a formidable task, with a high risk of finding CF unrelated false positives. Therefore, we changed the strategy and began looking for genes that might be directly (or indirectly) under CFTR control, by comparing the differential gene expression of CF and CF-corrected cells, incubated or not in the presence of CFTR inhibitors. To avoid a possible bias in the results (due to clonal selection or other nonspecific effects), only the spots corresponding to CF corrected cells incubated in the presence of CFTR inhibitors and that reversed the signal towards the pattern of CF cells were considered positive. In this way, we found that the CFTR chloride transport activity regulated the expres-

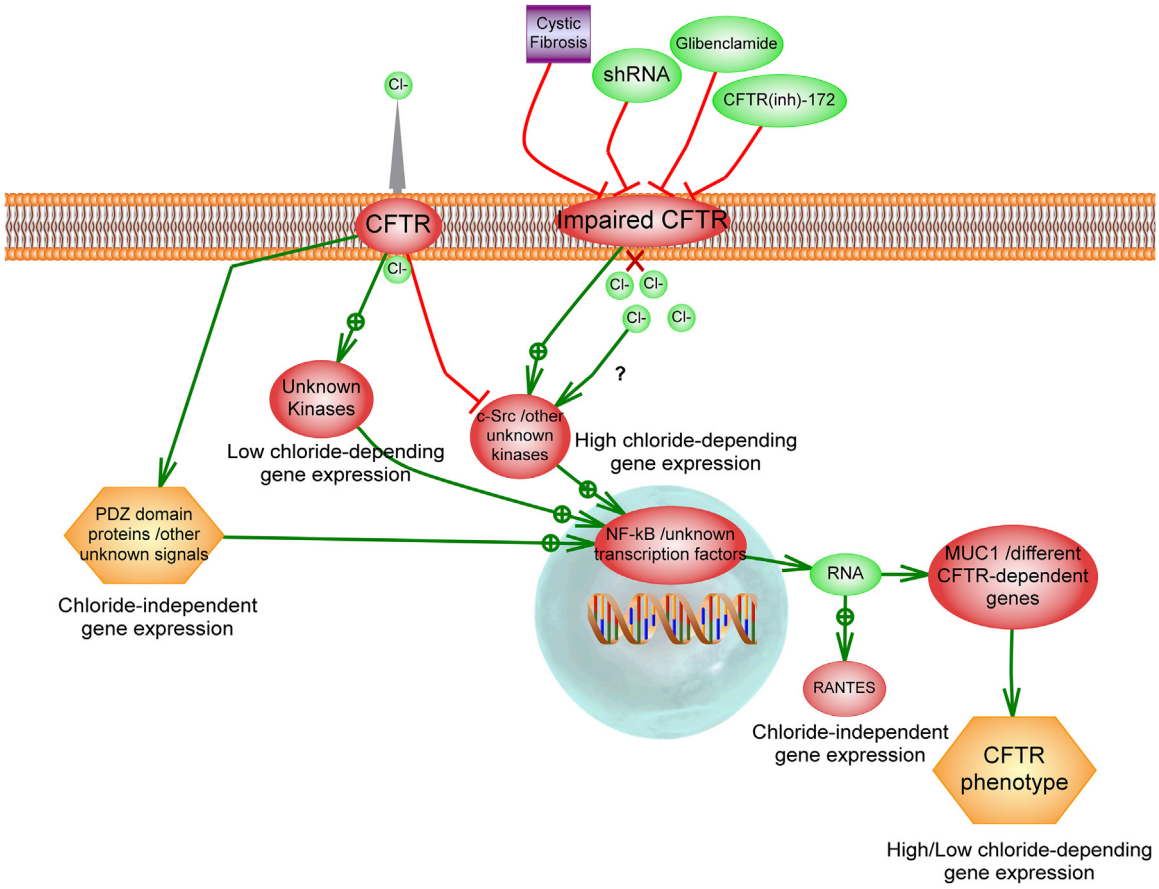

Fig. 3. CFTR-dependent genes. The existence of CFTR-depending genes has been demonstrated in the past two decades by using either differential display (Cafferata et al., 1995; Gonzalez-Guerrico et al., 2002; Taminelli et al., 2008; Valdivieso et al., 2007) or microarrays (Galvin et al., 2004; Srivastava et al., 1999). The mechanisms by which CFTR modulates these CFTR-dependent genes are largely unknown, except for MUC1 (Gonzalez-Guerrico et al., 2002) and RANTES (Estell et al., 2003). The protein-tyrosine kinase c-Src was the first signaling element found in the CFTR signaling pathway, which modulates the expression of MUC1 (Gonzalez-Guerrico, 2001; Gonzalez-Guerrico et al., 2002). Possible mechanisms involved are illustrated, including those independent of the channel activity (such as the expression of RANTES (Estell et al., 2003)) and those depending on the Cl^- transport activity of CFTR (c-Src, MUC1, MTND4 and CISD1), both signaling through putative, unknown kinase cascades (except for c-Src in MUC1 expression (Gonzalez-Guerrico et al., 2002)).

sion of several genes, including c-Src (which in turn regulated MUC1) (Gonzalez-Guerrico et al., 2002, 1999), MT-ND4 (a mitochondrial gene encoding a subunit of the mitochondrial Complex I)(Valdivieso et al., 2007), and CISD1 (a mitochondrial protein encoded in the nucleus with a yet ill-defined function)(Taminelli et al., 2008).

In parallel, other laboratories, by using microarrays, were also able to demonstrate that several genes were under CFTR-regulation (Srivastava et al., 1999, 2002; Xu et al., 2003). However, the relative importance of CFTR-dependent genes was later questioned by Zabner and colleagues, who also using microarrays found little differences in gene expression, in primary nasal differentiated cells obtained from normal and CF individuals (Zabner et al., 2005). Nevertheless, it should be taken into account that primary cells are often cultured in a semi-defined media containing FBS substitutes, which include growth factors (e.g. EGF 10 ng/ml), adhesion factors, hormones, and other factors of undisclosed composition (pituitary extracts, etc.). These serum substitutes may introduce a misinterpretation of data (Ye and Lotan, 2008). The substitutes may be ideal to growth cells rapidly, but the excessive presence of EGF and other unknown components from the "pituitary extract" or other components used in these substitutes may introduce a bias in the results. These factors may have unknown effects over cells, including the abrogation of the CFTR-expression. In fact, an extremely low CFTR expression was reported for cultured primary cells (Zabner et al., 2005). Thus, in the absence of CFTR expression, it should be expected that only a few differentially expressed genes would be found between normal and CF cells, even though the cultures corresponded to primary, well-differentiated, and polarized cells.

The CFTR signaling intermediates in the pathways that eventually lead to the expression of CFTR-dependent genes are largely unknown, with the exception of c-Src (Gonzalez-Guerrico et al., 2002), IL-1β (Clauzure et al., 2014) and Cl^- itself (Valdivieso et al., 2016). The Fig. 3 illustrates different possible ways that may result in the regulation of the steady-state levels of mRNA corresponding to CFTR-dependent genes.

2.3. *Mucins overexpression in cystic fibrosis and c-Src*

The possible overexpression of mucins in cystic fibrosis is also controversial. Some authors were not able to find changes in mucin expression, whereas others have shown strong evidences. The issue has been extensively reviewed (Kreda et al., 2012). In our hands, in cultured CFDE airway epithelial cells (cells derived from a CF patient), the overexpression of MUC1 was a primary response to CFTR malfunction, in which c-Src constituted a bridge connecting the CFTR activity with MUC1 expression. This was observed in cultured cells and, therefore, it is not a secondary effect due to infections; it is rather a primary defect, at least for these CF cells (Gonzalez-Guerrico et al., 2002), probably due to an intrinsic sterile

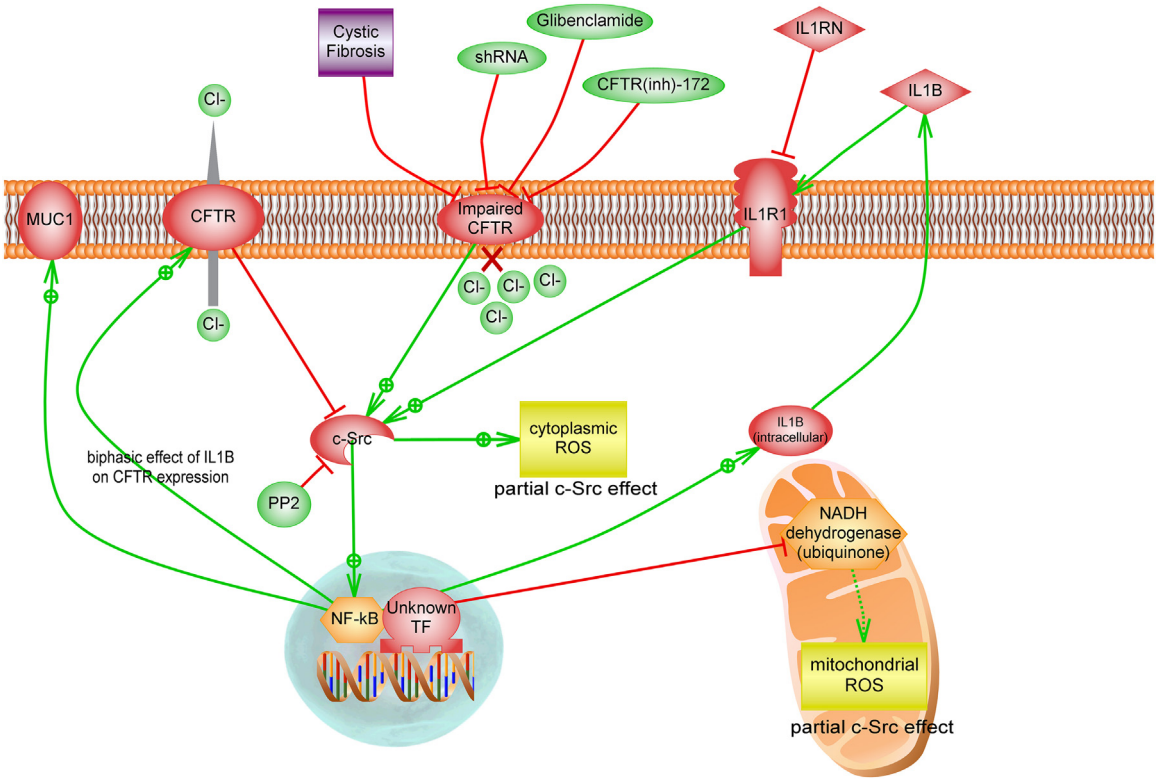

Fig. 4. CFTR as a signaling molecule. The graphic illustrates recent data related to the role of IL-1β, through an autocrine loop, in CFTR signaling. The IL-1β receptor antagonist IL1RN disrupted the IL-1β loop and normalized the ROS levels and the mitochondrial Complex I/III activity. In addition, IL-1β is upstream of c-Src in the CFTR → c-Src → MUC1 and ROS pathways. These represent initial studies. Many effectors in these pathways need to be study yet; e.g. the biphasic effect of IL-1β on CFTR expression, the role of mitochondrial Complex I in mitochondrial ROS generation, the origin of the cytoplasmic ROS, the role of the inflammasome and its regulation, and the role of Cl^- as a second messenger for CFTR.

inflammation mediated by IL-1β (Clauzure et al., 2014; Lukens and Kanneganti, 2014), as it will be discussed below.

In cell systems different from CF cells, it has been well demonstrated a role of c-Src in the regulation of the expression of several mucins (Basbaum et al., 1999; Gonzalez-Guerrico et al., 2002; Li et al., 1998; Ren et al., 2006; Van Seuningen et al., 2001). However, numerous reports argue against a possible direct role of CFTR in mucin regulation (Kreda et al., 2012); in most cases, it has been observed that CFTR activity and mucin expression are rather independent cellular functions that can be even expressed by different cells types (Kreda et al., 2012). Nevertheless, it should be taken into account that mucin-stimulating factors secreted by epithelial cells in response to the CFTR failure (i.e. IL-1β, TNF-α) may also reach distant cells through paracrine or endocrine effects. Thus, even cells lacking CFTR, such as goblet cells, may still respond to paracrine/endocrine stimulation from CFTR-responding cells, producing excessive mucins. In consequence, the CFTR failure may determine the overexpression of mucins through autocrine, paracrine, or endocrine signaling.

2.4. c-Src modulates the CFTR channel activity

One of the first links between c-Src activity and Cl^- secretion was reported in 1996 when it was observed that the activation of a c-Src/PyMT (Polyoma Middle T) pathway in colon carcinoma Caco-2 cells leads to a suppression of CFTR expression and attendant Cl^- secretion mediated by either cAMP or $[Ca_i^{2+}]$ (Davenport et al., 1996). Later, in colon carcinoma T84 cells incubated with IFN-gamma, it was observed that the inhibition of c-Src by PP2 increases Cl^- secretion (Uribe et al., 2002). On the other hand, CFTR's open probability and its voltage-dependent fast gate are dependent on tyrosine phosphorylation by c-Src (Fischer and Machen, 1996).

In an early work, we had observed that the SFKs inhibitors genistein and herbimycin A inhibited the stimulatory effect of IL-1β on CFTR expression, suggesting that at least one SFK was likely to be involved in the CFTR up-regulation induced by IL-1 β (Cafferata et al., 2000). Later, Cesaro and colleagues found a role of CFTR phospho-Tyr512 in regulating the phosphorylation of Ser511 by CK2, suggesting a cascade of events in which a SFK and CK2 act in concert to phosphorylate CFTR's Ser511 (Cesaro et al., 2013). Billet and colleagues found a role for Tyr phosphorylation in the muscarinic activation of CFTR (Billet et al., 2013), identified potential phosphorylation sites for SFKs (Billet et al., 2016), and showed that c-Src and proline-rich tyrosine kinase 2 (Pyk2) can both stimulate CFTR activity and produce the activation of quiescent CFTR channels (Billet et al., 2015). In patch-clamp experiments, these kinases can activate CFTR to near 80% of the activation reached by using PKA (Billet et al., 2015).

2.5. CFTR as a signaling molecule

Since CFTR is a channel and not a classical signaling receptor, it does not have a typical ligand-receptor signaling mechanism. Recent evidences prompted us to suggest that CFTR may be able to signal by modulating the intracellular chloride concentration, using the chloride anion as a second messenger, modulating the expression of specific genes (Valdivieso et al., 2016). Exactly how this signal is transmitted is yet unknown.

Another signaling mechanism for CFTR apparently involves the solely presence of the CFTR at the cell membrane through its PDZ-interacting motif, as mentioned previously, which is a process

independent of the CFTR chloride transport activity (Estell et al., 2003; Pelaseyed and Hansson, 2011). In fact, many other possibilities for signaling exist for CFTR, including indirect effects on membrane potential, cell volume regulation, modulation of other channels and transporters (e.g. epithelial sodium channel ENaC), transport of glutathione (affecting ROS signaling and redox balance) and bicarbonate (modifying the extracellular pH which in turn may modulate signaling by pH-dependent sensors). All these areas are yet unexplored.

We have recently observed that increased c-Src expression and activity not only occurs in CFDE cells (Gonzalez-Guerrico et al., 2002) but also in HT-29 incubated with CFTR inhibitors, in IB3-1 cells (derived from a CF patient), and in Caco-2 cells (Massip Copiz, 2015). In the last cells, increased levels of c-Src were observed after CFTR knock-down (KD) with specific shRNAs (Massip Copiz, 2015; Massip Copiz et al., 2013, 2010). Interestingly, these KD Caco-2 cells recover their normal c-Src levels when cultured in the presence of the IL1R inhibitor IL1RN (anakinra, IL-1Ra). This result suggests that the previously described autocrine IL-1β signaling pathway (Clauzure et al., 2014) is responsible for the increased c-Src activity in cells with impaired CFTR activity. Therefore, IL-1β is a new element of the CFTR signaling pathway, located upstream of c-Src. This result is in agreement with results reported for other cellular models in which IL-1β, in addition to stimulate NF-κB, p38, JUN, and ERK1/2, also stimulates c-Src (Cheng et al., 2010; Davis et al., 2006; Luo et al., 2009; Wu et al., 2008). Therefore, as illustrated in Fig. 4, the presence of an autocrine IL-1β signaling seems to be the reason for the increased c-Src activity found in cells with impaired CFTR activity (Gonzalez-Guerrico, 2001; Gonzalez-Guerrico et al., 2002). These results are also in agreement with the relevant role of the inflammasome described by others in CF (Grassme et al., 2014; Iannitti et al., 2016; Rimessi et al., 2015; Tang et al., 2012).

It should be pointed out that additional signaling mechanisms for CFTR might result from interactions with other neighboring proteins sensitive to conformational changes in the CFTR molecule, for example, when the CFTR protein is present in the active conformation. In addition, some interactive conformations would be missing in a loss-of-function mutation. Thus, several possible mechanisms of direct or indirect signaling by CFTR remain to be explored in addition to those produced by changes in the intracellular Cl^- concentration.

3. Concluding remarks

Several hypotheses try to explain the different parameters found altered in CF, such as mitochondrial alterations (Valdivieso and Santa-Coloma, 2013), inflammasome activation (Grassme et al., 2014; Tang et al., 2012), IL-1β secretion (Clauzure et al., 2014; Tang et al., 2012), oxidative stress and ROS levels (Clauzure et al., 2014; Duranton et al., 2012; Galli et al., 2012; Lee and Yang, 2012; Thevenod, 2009; Valdivieso and Santa-Coloma, 2013), mucin expression (Gustafsson et al., 2012; Kreda et al., 2012), airway surface liquid (ASL) dehydration (Boucher, 2007; Gaillard et al., 2010), and susceptibility to infections (Grassme et al., 2010). Lately, the most widely accepted hypothesis regarding the possible causes for the susceptibility to lung infections in CF, namely the dehydration of the ASL (Gaillard et al., 2010), has been questioned. Instead, a new hypothesis was postulated, in which a change of the ionic composition of ASL, in particular a reduced bicarbonate secretion through CFTR leading to a lower extracellular pH, (Quinton, 2008, 2010; Shamsuddin and Quinton, 2014; Yang et al., 2013), is perhaps the main factor contributing to the increased susceptibility to infections (Awadalla et al., 2014; Bartlett et al., 2013; Meyerholz et al., 2010; Rogers et al., 2008a,b; Stoltz et al., 2010, 2013). On the other hand, it may also be that low pH and low ASL volume are both in play (Garland et al., 2013). The different hypotheses have been changing drastically and dynamically within the last twenty years. It is evident that we are yet far from a clear understanding of the mechanisms involved in all these processes, and in which way they may influence the CF phenotype and the course of the disease.

Regarding c-Src in CF, it has been demonstrated that this tyrosine kinase is involved in the mechanism that determines P. aeruginosa invasion to epithelial cells (Esen et al., 2001). In addition, c-Src has a role in regulating the fast gate of the CFTR in airway epithelial Calu-3 cells (Fischer and Machen, 1996), and in the TNF-α effects leading to reduced gap junctional communications and increased IL-8 secretion in MDCKI epithelial wt-CFTR cells, both responses impaired in mutant CFTR lacking its PDZ-interacting motif (Dudez et al., 2008). On the other hand, the possible role of c-Src in the expression of mucins in CF requires further investigation, since this is yet a controversial issue.

CFTR is not a membrane receptor and its signaling do not follow the classical ligand-receptor interaction and signaling pathways. Instead, CFTR may produce different signaling mechanisms through interacting PDZ domains, modulating other channels, using other yet unknown interactions, or modulating the intracellular Cl^- concentration. Since Cl^- acts as a second messenger modulating the expression of specific chloride-depending genes (Valdivieso et al., 2016), CFTR may indirectly act as a signaling molecule by changing the intracellular Cl^- concentration, which in turn can regulate the expression of specific genes (the same reasoning applies to GABA receptors and other channels and transporters that define the intracellular Cl^- concentration).

As illustrated in Fig. 4, initial steps in the CFTR signaling cascade that modulate CFTR-dependent genes appear to include Cl^- (Valdivieso et al., 2016), IL-1β (Clauzure et al., 2014) and c-Src (Gonzalez-Guerrico et al., 2002). Besides c-Src, other signaling pathways involved in IL-1β signaling should be also active, as occurs with NF-κB and p38, which are involved in the negative modulation of the mitochondrial Complex I and ROS in CF cells (Clauzure et al., 2014). The IL-1β pathway could be only one of many cascades modulated by Cl^- as a second messenger. Finding the different mechanisms involved in CFTR signaling should help in gaining a deeper understanding of CF pathophysiology.

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