

The Cystic Fibrosis Transmembrane Regulator (CFTR) in the Kidney*

MARCELO M. MORALES¹, DORIS FALKENSTEIN² and ANÍBAL GIL LOPES¹

¹Instituto de Biofísica Carlos Chagas Filho

Universidade Federal do Rio de Janeiro, CCS - Bloco G 21949-900 – Rio de Janeiro, RJ, Brazil

²Instituto de Biologia, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil.

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*contributed by ANÍBAL GIL LOPES***

ABSTRACT

The cystic fibrosis transmembrane regulator (CFTR) is a Cl^- channel. Mutations of this transporter lead to a defect of chloride secretion by epithelial cells causing the Cystic Fibrosis disease (CF). In spite of the high expression of CFTR in the kidney, patients with CF do not show major renal dysfunction, but it is known that both the urinary excretion of drugs and the renal capacity to concentrate and dilute urine is deficient. CFTR mRNA is expressed in all nephron segments and its protein is involved with chloride secretion in the distal tubule, and the principal cells of the cortical (CCD) and medullary (IMCD) collecting ducts. Several studies have demonstrated that CFTR does not only transport Cl^- but also secretes ATP and, thus, controls other conductances such as Na^+ (ENaC) and K^+ (ROMK2) channels, especially in CCD. In the polycystic kidney the secretion of chloride through CFTR contributes to the cyst enlargement.

This review is focused on the role of CFTR in the kidney and the implications of extracellular volume regulators, such as hormones, on its function and expression.

Key words: CFTR, kidney, nephron, chloride channel.

INTRODUCTION

In mammals, the kidneys are responsible for the maintenance of the extracellular sodium chloride (NaCl) concentration that regulate the extracellular fluid volume (ECFV) and blood pressure. Sodium and chloride are reabsorbed along the nephron, reaching over 99% of the filtered load under low salt diets. Chloride, the predominant anion in the glomerular ultrafiltrate, is reabsorbed along the nephron either by trans or paracellular pathways (Berry & Rector 1991). Transcellular transport of

Cl^- involves several membrane proteins including the channels.

Numerous chloride channels have been discovered in a variety of animal and plant cells and their modulation and involvement in physiological processes are widely described in the literature. Some of these channels have been cloned and mutations in their genes are associated with genetic diseases (Jentsch 1994, Lehmann-Horn & Jurkat-Rott 1999, Rojas 1996 & Sasaki *et al.* 1994). One of these diseases is cystic fibrosis (CF), a common lethal autosomal recessive disorder, caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which encodes a multifunctional integral membrane protein expressed in a variety of epithelia, including the renal tubules (Rior-

This paper is dedicated to the memory of Prof. Carlos Chagas Filho as a sign of love and friendship.

*Invited paper

**Member of the Academia Brasileira de Ciências

Correspondence to: Aníbal Gil Lopes

E-mail: agilopes@biof.urfj.br

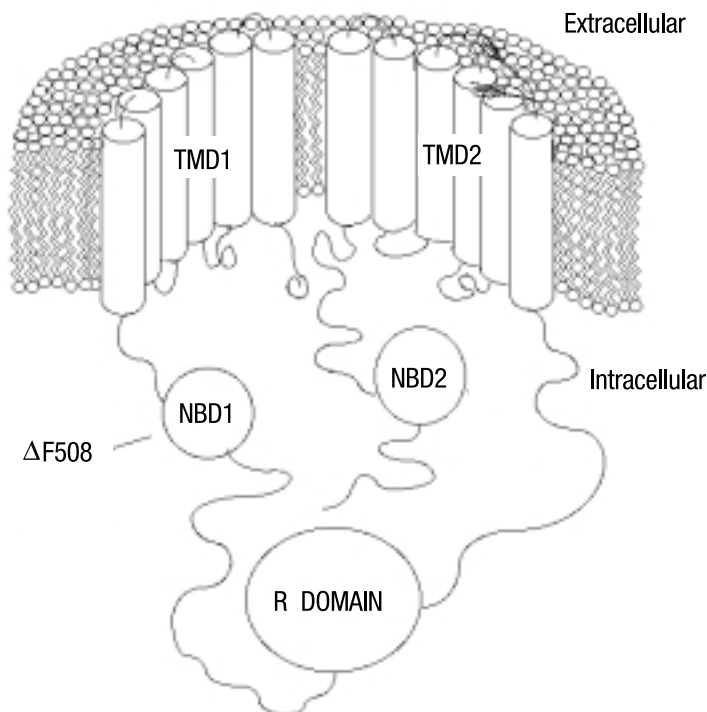


Fig. 1 – Predicted two-dimensional structure of the CFTR protein. The CFTR domains shown are: TMD1 and TMD2-transmembrane-spanning domains 1 and 2, respectively; R domain-regulatory domain; NBD1 and NBD2-nucleotide-binding domains 1 and 2, respectively. The most common mutation, $\Delta F508$, is found in NBD1. Figure modified from Ref. Collins *et al.* (1990).

dan 1993 & Rommens *et al.* 1989). The CFTR gene, identified in the q21-31 region of chromosome 7 (Riordan *et al.* 1989), encodes a protein of 165-kD containing 1480 amino acids. CFTR is a member of the ATP binding cassette family (ABC) of integral membrane proteins composed of two transmembrane domains (TMDs) and two nucleotide binding domains (NBDs), separated by a larger regulatory domain (R) containing multiple phosphorylation sites (Riordan 1993, Foskett 1998) (Figure 1). CFTR is a 3'5'-cyclic monophosphate, (cAMP)-activated Cl^- channel that modulates a series of intracellular functions by a complex process involving both phosphorylation by 3'5'-cAMP-dependent protein kinase A (PKA) and the inter-

actions of ATP with the nucleotide-binding domain (Anderson & Welsh 1992 & Morales *et al.* 1999). Besides the chloride transport function, CFTR plays an important role in intracellular vesicular acidification (Barasch *et al.* 1991), protein processing and traffic (Morris & Frizzell 1994), secretion of ATP (Winter *et al.* 1994) and control of the epithelium sodium channel (ENaC), the renal secretory K^+ channel (ROMK-2) and the outwardly rectifying chloride channel (ORCC) (Ismailov *et al.* 1996, McNicholas *et al.* 1996, Sttuts *et al.* 1995 & Schwiebert *et al.* 1995). The CFTR has a voltage dependent low-conductance for chloride (9 pS), and is found mainly on the apical membrane of secretory as well as absorptive epithelia (Berger *et al.* 1991).

In cystic fibrosis, the Cl^- channel function of CFTR is defective and more than 600 different mutations in the gene have been described, the $\Delta F508$ mutation being the most common (Tsui & Buchwald 1991). Cystic fibrosis is characterized by accumulation of thick mucus in the airway epithelia and in pancreatic and sweat ducts. These disturbances usually result in pancreatic insufficiency, increase in sweat Cl^- concentration, male infertility, intestinal and airway obstructions (Davies *et al.* 1996). The airways manifestations are the main cause of CF patient mortality. Secretory cells from the airways epithelia present a defective chloride ion transport through the apical membrane, which results in Na^+ and water hyperabsorption, thickening of the mucus and dehydration of the airways (Rojas 1996, Riordan 1993, Davies *et al.* 1996). Mutations in CFTR impair mucociliary clearance in the lung, which facilitates bacterial infection that results in a cycle of inflammation, tissue damage and finally lung insufficiency (Boat *et al.* 1989).

In spite of the injury in several organs, patients with cystic fibrosis do not develop major renal dysfunction although they have reduced renal excretion of NaCl and decreased capacity to dilute and concentrate urine (Donckerwolcke *et al.* 1992, Stenvinkle *et al.* 1991). These patients also have an enhanced excretion of penicillin and aminoglycosides in urine (Bates *et al.* 1997, Strandvik *et al.* 1989). The impaired salt reabsorption by the kidney could be related to changes in the extracellular fluid volume caused by excessive losses of NaCl in sweat and feces. However, decreased NaCl renal excretion might also result from a primary defect in renal function caused by mutations in CFTR.

CFTR AND KIDNEY

Several studies have demonstrated the presence of CFTR in the kidney, and its mRNA has been detected in all nephron segments by reverse transcription PCR (Riordan *et al.* 1989, Morales *et al.* 1996). CFTR was detected in proximal tubule, thin limbs of Henle's loop, and luminal membrane of distal

tubule, cortical collecting duct, and the inner medullary collecting duct by immunocytochemistry (Crawford *et al.* 1991). Patch-clamp analysis has also confirmed its presence in proximal and distal tubules and in cortical and inner medullary collecting ducts (Husted *et al.* 1995, Letz & Korbmacher 1997, Stanton 1989, Segal *et al.* 1993). CFTR is highly expressed during the early stages of kidney development. At gestational age of 12 weeks kidney CFTR is confined to the apical membrane of the ureteric bud derived collecting tubule, and its presence in proximal tubule cytoplasm is first seen at 16 weeks of gestation (Devuyst *et al.* 1996).

CFTR IN PROXIMAL TUBULE

Although immunolocalization studies indicate an apical expression of CFTR in the proximal tubules (Crawford *et al.* 1991), patch clamp studies localize its activity at the basolateral membrane (Segal *et al.* 1993). The function of CFTR in proximal tubules is uncertain because the reabsorption of NaCl in this segment of the nephron is increased in CF, rather than decreased as would be expected if CFTR mediates Cl^- absorption (Bates *et al.* 1997, Stenvinkle *et al.* 1991). The increase in CF kidney Cl^- reabsorption could be associated with the reduced extracellular volume fluid or with a reduced NaCl reabsorption in the thick ascending limb of Henle and distal tubule, both found in CF (Donckerwolcke *et al.* 1992, Strandvik *et al.* 1989).

On the other side, in CF the defective CFTR channel causes an increase in penicillin and aminoglycosides excretion in the proximal tubule. One hypothesis for this phenotype is that the abnormal CFTR decreases Cl^- reabsorption, which increases Cl^- in the tubular lumen. This Cl^- will move into the cell in exchange for those drugs, which increase their clearance (Woodland *et al.* 1998).

CFTR IN HENLE'S LOOP AND DISTAL NEPHRON SEGMENTS

The mRNA for CFTR was found in the thin ascending limbs of Henle's loop, but no protein was identified in this nephron segment by immunolocalization

or patch clamp studies (Crawford *et al.* 1991, Devuyt *et al.* 1996). The CFTR protein has not been detected in the thick ascending limbs of Henle's loop by immunocytochemistry, although in patch clamp studies a Cl^- channel with a low conductance (9 pS), dependent of ATP and Mg^{++} , was found in the basolateral membrane (Berger *et al.* 1991). This channel was denominated pseudo CFTR, since it is still functional in CFTR knockout mice (Marvaio *et al.* 1998).

Distal convoluted tubule CFTR was detected by immunolocalization and patch clamp studies in the apical membrane. Probably Cl^- is secreted into the luminal fluid through CFTR in response to the electrochemical gradient generated by the Na/Cl cotransporter. CFTR in this segment may also facilitate HCO_3^- secretion by mediating the recycling of Cl^- through the Cl^-/HCO_3^- exchanger in the apical membrane (Tauc *et al.* 1996, Rubera *et al.* 1999). CFTR protein was not found in the connecting tubule, in the α and β intercalated cells of collecting ducts or in the outer medullary collecting duct (OMCD) (Crawford *et al.* 1991, Todd-Turla *et al.* 1996).

CFTR IN COLLECTING DUCTS

In cortical collecting ducts (CCD) the CFTR protein was only identified in the apical membrane of the principal cells. There are experimental evidences that Cl^- absorption in this nephron segment is through the paracellular pathway following the electrochemical gradient (Koeppen & Stanton 1992). However, depending of the electrochemical driving force for Cl^- movement across the apical membrane CFTR channel, this ion could either be absorbed or secreted (Ling *et al.* 1994). This Cl^- movement is dependent on Na^+ absorption through the ENaC channel and may be controlled by hormones like aldosterone and arginine-vasopressin (Duong Van Huyen *et al.* 1998).

In the inner medullary collecting duct (IMCD) CFTR plays an intriguing role. The CFTR channel is expressed at the apical membrane in this nephron segment, but alternative splice form of this molecule,

the TNR-CFTR, was also found (Morales *et al.* 1996). Electrophysiological studies support the view that Cl^- secretion through the CFTR follows the electrochemical driving force across the apical membrane (Kizer *et al.* 1995, Husted *et al.* 1995). The Cl^- secretion occurs by a two step process, first involving the uptake of Cl^- across the basolateral membrane by Cl^-/HCO_3^- exchange and $Na^+/K^+/2Cl^-$ cotransport and, then, the efflux of Cl^- across the apical membrane through CFTR channel (Letz & Korbmacher 1997, Moyer *et al.* 1995, Kizer *et al.* 1995, Rocha & Kudo 1990). Arginine vasopressin (AVP) stimulates Cl^- secretion in IMCD by increasing 3'5'-cAMP which activates protein kinase A (PKA) which in turn activates CFTR channel (Moyer *et al.* 1995). The role of AVP on Cl^- secretion may be related to the fact that Na^+ secretion follows that of Cl^- , inducing natriuresis and chloruresis to maintain a normal plasma osmolality during dehydration, as observed *in vivo* in rats (Luke 1973).

TNR-CFTR, THE RENAL SPLICE VARIANT OF CFTR

TNR-CFTR, a splice variant isoform of CFTR gene is associated with specific small endosomal populations highly expressed in the renal medulla (Morales *et al.* 1996). Functional studies with TNR-CFTR, expressed in *Xenopus* oocytes or mammalian cells, showed cAMP-dependent single chloride channel properties like those of the wild type CFTR, but with lower efficiency (Morales *et al.* 1996). In medullary collecting ducts the TNR-CFTR protein and mRNA expression is present during embryonic life, increasing during fetal kidney development and reaching the highest level at birth (Devuyt *et al.* 1996). The specific function of the TNR-CFTR is not clear and does not seem to be related to chloride secretion. Because it is found in abundance in intracellular vesicles in the cytoplasmic compartment, it may be involved in vesicular trafficking.

CFTR AND POLYCYSTIC KIDNEY DISEASE (PKD)

CFTR expression and chloride channel function is normal in polycystic kidney disease (PKD), an au-

tosomal dominant genetic disease (Hanaoka *et al.* 1996, Sullivan *et al.* 1998). This renal disorder is characterized by the presence of multiple epithelial cyst with epithelial cell proliferation and apical fluid secretion. The cyst enlargement in PKD kidney is thought to involve inappropriate polarized secretion of sodium ions into the tubule lumen due to the mis-polarization of the ($Na^+ + K^+$)-ATPase pump in the cyst apical membrane (Wilson 1997). Na^+ and Cl^- contents in cyst fluid are abnormally high, and addition of cAMP to PKD cyst epithelia in culture increases fluid secretion and ATP release into the cyst fluid. These findings could be due to the CFTR, since it is well known that this channel transports both Cl^- and ATP (Sullivan *et al.* 1998) and suggest the involvement of CFTR in PKD cysts fluid secretion and enlargement.

CFTR AND OTHER CONDUCTANCES

Chloride transport by CFTR in renal epithelia represents a high-energy expenditure, since this channel requires ATP hydrolysis (Winter *et al.* 1994) and its conductance is too low (9 pS) to produce fast absorptive or secretive fluxes. One possible role for CFTR in the kidney is the activation or inhibition of other channels like ORRC, ENaC and ROMK2 (Ismailov *et al.* 1996, Wang 1999, Schwiebert *et al.* 1995, Morris 1999). It has also been shown that arginine-vasopressin (AVP) produces an increase of chloride secretion due to transcriptional enhancement in the expression of CFTR and other transporters in rat cortical collecting ducts cells (Djelidi *et al.* 1999).

Recent studies from our group showed that in homozygous Brattleboro rats, a strain of Long-Evans rats carrying an autosomal recessive mutation that results in a deficiency of arginine-vasopressin (AVP) secretion in the plasma, the expression of CFTR mRNA was low in the renal cortex and medulla but returned to normal after AVP reposition. The mRNA of CFTR was increased in the medulla of dehydrated Wistar rats and no variation was observed in the cortex. The modulation of CFTR by the main hormone involved in the regulation of body

fluid osmolality suggests that this chloride channel play a role in extracellular volume regulation (Morales M M *et al.* submitted).

CONCLUSION

The studies reviewed here show the importance of the CFTR channel in the kidney. Besides its function in chloride transport, CFTR modulates different epithelial conductances, such as channels for sodium (ENaCs), potassium (ROMK2) and chloride (ORCCs), probably by mediating ATP transport. Although very well studied in other organs, the function of CFTR is not fully understood in the kidney and further studies are crucial to understand its role in renal physiology.

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