SEMINARS IN
NEPHROLOGY

The Sodium Bicarbonate Cotransporter: Structure, Function, and Regulation

Angelito A. Bernardo, Christian M. Bernardo, Doris Joy Espiritu, and Jose A. L. Arruda

The role of the Na^+-coupled HCO_3^- transporter (NBC) family is indispensable in acid-base homeostasis. Almost all tissues express a member of the NBC family. NBC has been studied extensively in the kidney and plays a role in proximal tubule HCO_3^- reabsorption. Although the exact function of this transporter family on other tissues is not very clear, the ubiquitous expression of NBC family suggests a role in cell pH regulation. Altered NBC activity caused by mutations of the gene responsible for NBC protein expression results in pathophysiologic conditions. Mutations of NBC resulting in important clinical disorders have been reported extensively on one member of the NBC family, the kidney NBC (NBC1). These mutations have led to several structural studies to understand the mechanism of the abnormal NBC1 activity.
Semin Nephrol 26:352-360 © 2006 Elsevier Inc. All rights reserved.

KEYWORDS sodium bicarbonate cotransporters, pRTA, acid base balance, targeting, membrane

Acid-base balance is essential for life. All cellular, tissue, and organ functions are sensitive to pH changes. The kidney plays an important role in the maintenance of acid-base balance through several mechanisms. These include bicarbonate reabsorption and regeneration, and ultimately acid excretion.

Under normal conditions, the kidney filters approximately 4,320 mEq of bicarbonate per day in human beings. The majority of the filtered bicarbonate is reabsorbed at the proximal tubule through the coordinated action of sodium hydrogen exchanger (NHE3) at the apical membrane and a member of the bicarbonate transporter superfamily, sodium bicarbonate cotransporter (NBC1) at the basolateral membrane. The remaining bicarbonate is reabsorbed at the thick ascending limb and the collecting tube through the action of the other members of the bicarbonate transporter superfamily. Therefore, abnormal function of the bicarbonate transporters in the kidney as a result of either abnormalities in hormonal regulations or mutations of the gene responsible for normal expression in the appropriate membrane will result in pathophysiologic conditions.

Advances in molecular and cellular biology have provided new understanding on the structure, function, and regulation of the bicarbonate transporter superfamily. This review focuses only on one subfamily of the bicarbonate transporter family, the Na^+-coupled bicarbonate transporters, specifically NBC1. Clinical conditions caused by abnormal NBC function also are summarized.

The Na^+-Coupled HCO_3^- Transporter (NBC) Family

The NBC family consists of at least 4 NBC isoforms, each with different variants and a couple of sodium-dependent Cl−/HCO3− transporters. The first NBC activity was described in the renal proximal tubule of the salamander (*Ambystoma tigrinum*).[1] Subsequent studies showed NBC activity in the rat proximal tubule[2,3] and in the basolateral membrane of the rabbit renal proximal tubules.[4,5] Additional studies described the presence of electrogenic NBC activity in the *Necturus* proximal tubule.[6] Although first described in the kidney, NBC also is expressed in other cell types. These include NBC expression in bovine corneal endothelial cells and in the frog retina[7,8]; in the basolateral membrane of oxyntic cells of the gastric fundus,[9] hepatoma cells, and hepatocytes[10,11]; brain and neurons[12]; and in the leech glial cells and rat hippocampus.[13,14] NBC also is expressed in the heart, lung, pancreas, and epididymis.[15-18] The function of NBC in other tissues remains to be clarified, but presumably it serves to regulate cell pH.

From the Department of Medicine, Section of Nephrology, and the Department of Physiology and Biophysics, University of Illinois at Chicago, Chicago, IL; and the Jesse Brown VA Medical Center, Chicago, IL.
Address reprint requests to Doris Joy D. Espiritu, PhD, UIC Section of Nephrology (M/C 793), 820 S. Wood St, CSN, Chicago IL 60612-7378. E-mail: dorisjoy@uic.edu

 0270-9295/06/$-see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.semnephrol.2006.07.008

Table 1 NBC Genes, Isoforms, Chromosomal Loci, Variants, and Organ Distributions

Isoform	Gene	Conductance	Chromosome Locus	Variants/Alternate Names	Expression
NBC1	SLC4A4	Electrogenic	4q21	kNBC1 (NBC1a, NBCe1A)	Human renal proximal tubules, corneal endothelium, ciliary epithelium, trabecular meshwork, lens epithelium
					Rat eye, brain, renal S_1 and S_2 segments
				pNBC1 (NBCe1-B, NBC1b, dNBC1, rb1NBC, hhNBC)	Human pancreatic duct
					Human corneal endothelial cells, ciliary epithelium, trabecula, lens epithelium
					Bovine endothelium
					Rat eye, pancreas, liver duodenum, epididymis, salivary gland, kidneys
NBC2	SLC4A7	Electroneutral	3p22	rb2NBC (NBCe1c) NBCn1A–E, muscle NBC3	Rat brain
					Human skeletal muscle, salivary gland
					Rat and rabbit connecting duct, cortical and medullary collecting duct
					Rat aorta, salivary glands
					Murine duodenum
NBC3	SLC4A8	Electrogenic	12	NDCBE	Brain, kidney, adrenal gland, spinal cord, bone marrow, other tissues
NBC4	SLC4A5	Electrogenic?	2p13	NBC4a–f	NBC4a-human heart, testes, liver, spleen
				NBCe2C	NBC4b-human heart
NCBE	SLC4A10	Electroneutral?	2q23–q24	NCBE-B	Human brain

NBC1

The first NBC (aNBCe1-A) was cloned by Romero et al[19] in 1997 in *Ambystoma tigrinum*. Burnham et al[20] later cloned the human kidney NBC. This was followed by cloning the NBC ortholog from rat.[21] An inwardly directed NBC variant was cloned from the pancreas (pNBC or NBCe1-b)[22] and from the heart and the brain (hhNBC).[23]

NBC2

NBC2 was first cloned in human retina[24] and later was found to be expressed in other organs. A splice variant also was cloned from human skeletal muscle, which originally was called *muscle NBC3*.[25] A rat ortholog, identified from rat smooth muscle referred to as *NBCn1* also was cloned.[26]

NBC3/NDCBE

An isoform of Na^+-coupled HCO3− transporters is referred as *NBC3*. This isoform appeared to have 3 transcripts.[27] The large transcript was identified from human brain library.[28] The intermediate transcript and the small transcripts are expressed in neurons and other tissues. Functional studies in oocytes showed NBC3 is a sodium-dependent Cl^-/HCO_3 exchanger and also is called *NDCBE*.[29]

NBC4

NBC4 is believed to be another member of the Na^+-coupled HCO_3^- transporter family cloned from the heart and is expressed abundantly in liver, testes, and spleen.[30]

Sodium Chloride Bicarbonate Exchanger

A new member of the Na^+-coupled HCO_3^- transporters family is a sodium chloride bicarbonate exchanger (NCBE). NCBE was cloned from insulin-secreting cell complementary DNA library using human kidney NBC1.[31] NCBE has an absolute requirement for Na^+ and HCO_3^-, but does not require Cl^-.

The Na^+-coupled HCO_3^- transporter family members are summarized in Table 1.

Expression of NBC in the Kidney

Early functional studies showed the presence of the NBC activity in the S1 and S2 segments of the rabbit renal proximal tubules.[2,3,32,33] Immunocytochemical analysis localized the NBC in the rat and rabbit kidneys. Antibodies raised against the rat kidney NBC detected strong staining of the basolateral membranes of the S1 and S2 segments of the proximal tubules in the superficial cortex and midcortical

region of rat kidney.[33] Indirect immunofluorescence microscopy using polyclonal antibodies to a fusion protein containing the COOH terminal 108 amino acids of rat kidney NBC revealed the labeling of the basolateral membranes in the proximal tubules in rats and rabbits.[34] In situ hybridization studies using pNBC messenger RNA probes localized the pancreatic sodium bicarbonate cotransporter in the terminal and straight portion of the S2 segment, but not the S1 or S3 segment in rabbit proximal tubule.[35] Immunolocalization studies showed that NBC is expressed strongly in the inner stripe of the outer medulla, and expressed weakly in the outer stripe of both the outer and inner medulla. Immunoelectron microscopy of rat kidney slices showed exclusive labeling of the basolateral domains of the thick ascending limbs in the inner stripe of the outer medulla. In vitro microperfusion studies revealed functional evidence for the electroneutral apical NBC3 (an isoform of NBCn1) in the type A intercalated cells in the rabbit outer medullary collecting duct inner stripe.[36-38] Immunoelectron microscopy studies of rat kidney showed that NBC3 is localized in the rat connecting tubules, and cortical, outer medullary, and the initial inner medullary collecting ducts.[39] The same group also provided proof that NBC3 colocalized with the vacuolar H-adenosine triphosphatase in the type A intercalated cells of the rabbit collecting duct.[40] Immunoelectron microscopic studies also showed strong labeling of the apical membrane, intracellular vesicles, tubulocisternal organelles, and subapical domains of type A intercalated cells, as well as in the basolateral membranes of type B intercalated cells.[39]

Structure and Function

Members of the Na^+-coupled HCO_3^- transporter family are either electroneutral or electrogenic depending on the isoforms. The renal NBC1 is electrogenic. It transports 3 HCO_3^- with 1 Na^+ from the cell to the blood.[3] Further investigation in the rabbit basolateral membrane vesicles by $^{22}Na^+$ uptake showed a stochiometry of 1 Na^+:1CO_3^{-2}:1 HCO_3^- compatible with 3 base equivalent per 1 Na^+.[5,41] The pancreatic and the heart NBC1 variant transport 2 HCO_3^- per 1 Na^+ from the blood into the cell.

The stoichiometric profile of the NBC1 provides an interesting paradigm of interaction and interdependence of structure and function. In the mouse, phosphorylation of Ser^{982} in renal NBC1 changes the stoichiometry from $3HCO_3^-$:$1Na^+$ to $2HCO_3^-$:$1Na^+$.[42] Site-specific mutation of kNBC1 Ser^{982} showed the importance of this residue in the protein kinase A (PKA)-induced stoichiometric shift. Indeed, when Ser^{982} was mutated, it was postulated that there was alteration in electrostatic forces necessary for HCO_3^- binding and/or phosphorylation.[43-45] The difference in stoichiometry between the renal NBC1 and the pancreatic NBC1 is not dependent on NBC1 variant's primary structure but lies on the cell type where it is expressed. Gross et al[44] showed that renal NBC1 behaves similar to pancreatic NBC1 variant when expressed in pancreatic cells. The only difference between the renal NBC1 and the pancreatic NBC1 variant is that the first 41 amino acids at the N-terminal of renal NBC1 are replaced with 85 distinct amino acids in pNBC1.

Earlier studies on the structure-function relationship of NBC involved the use of chemical probes such as 4,4′-diisothiocyanostilbene-2,2′-disulfonic acid (DIDS), 4,4′-dinitrostilbene-2,2′-disulfonic acid, fluorescein isothiocyanate, and harmaline. Inhibition by the disulfonic stilbenes, DIDS, and 4,4′-dinitrostilbene-2,2′-disulfonic acid was initially a criteria used for identification of the cotransporter.[2,46] The mechanism of inhibition by disulfonic stilbenes was shown to occur at the CO_3^{-2} interaction site of the cotransporter. Molecular analysis disclosed a putative DIDS binding motif KMIK and KLKK, which is responsible for this interaction.[47,48] By using the specific probes fluorescein isothiocyanate and phenylisothiocyanate, which bind the α amino acid and ϵ amino groups, respectively, we have shown these structural determinants are required for full NBC activity.[49] Harmaline, a competitive inhibitor of NBC1, specifically binds at the Na^+ site.[41] NBC also may be affected by agents that may modify amino acid residues necessary for functional activity. We provided the first evidence that chemical agents that modify the tyrosine, sulfhydril, as well as carboxyl groups, inhibited NBC activity. Endoglycosidase F and H, and N-glycosidase and O-glycanase, which may modify glycosylation sites on NBC, significantly inhibited cotransporter activity.[50] Recent studies showed that glycosidase F shifted down the molecular weight of NBC from 130 kd to 116 kd, whereas endoglycosidase F_2, or H or D glycosidase, had no effect on the molecular weight of the cotransporter. This suggests that the NBC may possess tri- or tetra-antennary N-linked glycosylation. Mutational analyses indicated that glycosylation occurred at N593, N597, and N617 on the third extracellular loop, and is consistent with the predicted consensus N-linked glycosylation sites.[51,52]

Several studies also showed that acetazolamide, a carbonic anhydrase inhibitor, inhibited HCO_3^- reabsorption in the proximal tubule.[53,54] It also has been shown that the some Asp residues were involved in the carbonic anhydrase (CA) II binding. It is hypothesized that CA II interaction is necessary for the stoichiometric shift in the cotransporter.[55,56] Colocalization of NBC1 with CA IV in the basolateral membranes of proximal tubules implied a functional and physical interaction between the 2.[57] Mutagenesis studies revealed that G767 is the site of interaction between NBC1 and CA IV.[58]

Previous studies of other members of the bicarbonate superfamily, anion exchangers (AEs), have provided insights on the role of the NH2 and the COOH termini on structure and function of the exchangers.[59-63] The N-terminus of NBC1 contains conserve amino acids found in AE2 necessary for pH sensing and contains a stretch of conserve amino acids found in AE1 necessary for interaction with other cytoplasmic loops of AEs in erythrocyte.[59] The N-terminus also is important for cytoskeletal protein binding and dimerization and is necessary for membrane insertion and activity.[59]

The C-terminus of NBC1 is very hydrophilic and is believed to be involved in protein-protein interaction and targeting to the plasma membrane.[56] It contains 15 consecutive positively charged residues and an acidic motive LDSDNDD.

Recent studies from our laboratory showed that the N- and the C-termini are not necessary for NBC1 targeting to the basolateral membrane because in the absence of either terminus, NBC1 is expressed in the basolateral membrane. However, both the N- and the C-termini play a distinct role in NBC1 activity.[64] Truncation of either the N- or the C-termini completely abolished NBC1 activity. The C-terminus is the primary determinant for NBC1 stability in the basolateral membrane. Truncation of the entire C-terminus caused increased endocytosis and mistargeting to the apical membrane. These results support the study of Li et al,[65] which showed that truncation of the last 23 amino acid mistargets NBC1 to the apical membrane.

We also reported an interesting determinant for NBC1 activity involving the possible interaction of the C- and N-termini of NBC1. By using co-immunoprecipitation and nickel (II) nitrilotriacetic acid (Ni-NTA) pull-down assay, we were able to detect a possible interaction of the N- and the C-termini. Most importantly, this interaction increased stability of the C-terminus–truncated NBC1 in the basolateral membrane and restored NBC1 activity.[64]

The transmembrane region contains amino acids predicted to be a potential determinant for HCO3− and Na+ permeation.[66]

Regulation

The NBC1 that is the main isoform in the kidney is regulated by hormones and other stimuli. NBC1 activity is upregulated by acidosis,[67,68] angiotensin II (AII),[69,70] carbachol,[71] glucocorticoid,[72] and insulin.[71] It also is known that NBC1 activity is decreased in metabolic alkalosis[67] and parathyroid hormone.[73] Cyclic adenosine monophosphate (cAMP) inhibits NBC1 activity through its effect in PKA.[74]

Studies performed in our laboratory investigated the mechanism of regulation of NBC1 stimulation by CO_2. We have shown that several enzymes mediate the acidic upregulation of NBC1 by 10% CO_2. Phosphatidylinositol 3-kinase, proline-rich tyrosine kinase, Src family kinases (SFKs) all play a role in increasing NBC1 activity by acidosis.[70,75,76] Other NBC isoforms expressed in the outer medullary collecting duct and thick ascending limb also have been shown to increase activity in response to acute intracellular acidification.[36]

The mechanism of maintenance of metabolic alkalosis in the setting of K^+ deprivation had been shown to be caused by an increase in NBC1 messenger RNA, protein expression, and activity in the renal proximal tubule cells and other bicarbonate transporters in medullary thick ascending limb (mTAL) tubule and inner medulla.[77]

The mechanism of increased NBC1 activity in the presence of AII also was elucidated in our laboratory. We have shown that the effect of AII is by the inhibition of adenyl cyclase through a G_i-coupled mechanism and through protein kinases.[78] AII stimulation of NBC activity is mediated by angiotensin II receptor type I (AT_1) receptor with subsequent activation of the Src family tyrosine kinase and the mitogen-activated protein kinase (MAPK).[70] AII also stimulates NBC1 activity by promoting NBC trafficking/translocation to the plasma membrane through a microtubule-dependent pathway.[79,80] Similar requirements for SFK/MAPK and Ras coupling is required for cholinergic stimulation of NBC1. SFK, Ras, and the classic MAPK pathway couple muscarinic-receptor activation to increased Na-HCO_3 cotransport activity in renal epithelial cells.[70]

Parathyroid hormone (PTH) decreased bicarbonate reabsorption in the renal proximal tubule through inhibition of NBC1 and NHE. It is postulated that this may be owing to a phosphatidylinositol-dependent mechanism.[81] Studies performed in our laboratory showed that this inhibition is mediated by Gsα, Gq, and calcium calmodulin kinase pathways.[73] We also have shown that in human proximal tubule cells, the interaction of NBC1 with Gsα mediates the inhibitory effects of PTH on cotransporter.[82] Likewise, we showed that the acute inhibitory effects of PTH involves serine/threonine phosphorylation[83] of NBC1 mediated by PKA. Additional experiments performed in our laboratory suggest that PTH also may inhibit NBC activity by promoting clathrin-dependent endocytosis and subsequent degradation of the cotransporter through lysosomal and proteasomal pathways.[84,85]

The cAMP-PKA system also inhibits both transporters.[86,87] Independent studies indicated that limited proteolysis of specific protein fractions dissociated NBC and NHE activities from regulation by PKA, and this regulatory response could be restored by a dissociable regulatory factor.[88,89]

The isolation and cloning of a cofactor for cAMP-mediated inhibition of Na^+-H^+ exchanger, Na^+ hydrogen exchanger regulatory factor (NHERF),[88] provided a possible link for the parallel regulation. NHERF transfection in BSC-1 cells devoid of endogenous NHERF resulted in lower basal level of NBC activity. cAMP stimulation further enhanced the inhibition of NBC activity, an effect not seen in wild-type controls.[89] Although NHERF forms a signal complex with ezrin, PKA, and NHE3, leading to phosphorylation of NHE3, the interaction between NHERF and NBC1 has not been detected. We suggested that cAMP-mediated inhibition of NBC is the result of a biochemical modification of the NBC1 transporter by a process that requires NHERF, but not through direct interaction of NBC1 and NHERF itself.

Clinical Importance

The unique and the ubiquitous expression of NBC in different tissues indicates its vital physiologic role. Any disruption in cotransporters' expression or functional activity may result in abnormality in function. The first reported mutations in SLC4A4 gene (gene encoding NBC1 protein) involved the R510H and R298S mutations (Table 2). The patients had short stature and ocular abnormalities caused by bilateral glaucoma, cataracts, and band keratopathy. They had systemic acidemia, proximal renal tubular acidosis, and hypokalemia, as well as increased serum amylase levels. However, they had no symptoms of pancreatitis. NBC functional activity was decreased to 55% of normal. The inactivation of NBC1 found in the corneal endothelium may have caused an

Table 2 Human Mutations of the SLC4A4 (NBC1) Causing Proximal RTA

Mutation	Explanation	Clinical and laboratory characteristics	Comments
R298S	Arginine to serine at position 298	Short stature, mental retardation, glaucoma, cataracts, band keratopathy, proximal RTA, hypokalemia, increased amylase level but no clinical signs of pancreatitis	55% decrease in NBC activity, autosomal recessive, significant surface expression in oocytes
R510H	Arginine to histidine at position 510	Short stature, glaucoma, cataracts, band keratopathy, hypokalemia, proximal RTA, increased amylase level but no clinical signs of pancreatitis	57% decrease in NBC activity, autosomal recessive, faint patchy expression in oocytes
Q29X	Cytosine to thymine transition at nucleotide 234 forms stop codon at codon 29, leading to truncated NBC1 that lacks 1007 aa	Short stature, mental retardation, glaucoma, proximal RTA, amylase level not reported, hypokalemia	Complete loss of NBC activity
2311ΔA	Single nucleotide deletion resulted in a frame shift at codon 721	Short stature, glaucoma, band keratopathy, no mental retardation, increased amylase level but no clinical signs of pancreatitis, proximal RTA, renal biopsy examination showed mild focal sclerosis, tubulointerstitial fibrosis with decreased glomerular filtration rate, calcification in basal ganglia, grey matter, white matter, frontal region	Complete loss of NBC activity, loss of surface expression in oocytes
T485S	Threonine to serine at position 485	Short stature, band keratopathy, cataracts, delayed development, proximal RTA, amylase level not measured	Complete loss of NBC activity, faint patchy surface expression in oocytes
S427L	Serine to leucine at position 427	Short stature, normal intelligence, poor dentition, cataracts, corneal opacity, glaucoma, proximal RTA, normal amylase level	90% decrease in NBC activity, normal cell surface expression in oocytes
A799V	Alanine to valine at position 799	Short stature, mental retardation, band keratopathy, cataracts, glaucoma, proximal RTA, amylase level not measured	85% decrease in NBC activity, significant surface expression in oocytes
R881C	Arginine to cysteine at position 881	Short stature, delayed development, glaucoma, cataracts, proximal RTA, increased amylase level but no clinical signs of pancreatitis	60% decrease in NBC activity, significant surface expression in oocytes

increase in HCO_3^--induced calcium deposition in the corneal stroma leading to band keratopathy. NBC1 also has been shown to modulate the trabecular cells and cilliary muscle function, which is important for aqueous humor secretion and flow.[90,91] High doses of K citrate and Na citrate given early markedly improved growth, although acidosis was not corrected completely.[92]

Another homozygous mutation, Q29X, was described in a patient who had short stature, proximal renal tubular acidosis, mental retardation, and bilateral glaucoma. She did not have cataract or band keratopathy.[93] The nonsense mutation located in the unique 5′-end of kNBC1 led to a truncated kNBC1 deficient in 1,007 NH_2 terminus amino acids. This mutation resulted in a complete loss of function of kNBC1, without any effect on pNBC1.[94] Another missense mutation, S427L, was reported in another patient. The child had normal intelligence, proximal renal tubular acidosis, bilateral glaucoma, and cataracts, as well as abnormal dentition. The mutant NBC had 10% activity as compared with wild-type NBC.[95] Three new homozygous mutations of the NBC1 were described recently, namely T4853, A799V, and R881C. The functional activities of A799V and R881C were 15% to 40% of wild type, whereas T485S mutation is completely devoid of activity in oocytes. The patients with the earlier-described mutations have severe proximal renal tubular acidosis, short stature, mental retardation, glaucoma, cataracts, and band keratopathy.[96] A mutation caused by a single nucleotide deletion 2311ΔA resulted in a frame shift at codon 721 to form the stop codon TGA, resulting in the mutant phenotype. This mutant has no measurable NBC1 activity or

surface expression in oocytes. Clinically, the patient had normal intelligence, but had growth retardation, band keratopathy, cataracts, and glaucoma. He had systemic acidemia and proximal renal tubular acidosis.[97]

NBC promotes the reabsorption of Na^+ into the blood may expand the extracellular volume, contributing to blood pressure increases.

A susceptibility gene for hypertension has been localized to a chromosome in close proximity to the NBC gene SLC4A5. This proximity may suggest an association and possible role of NBC in the pathogenesis of hypertension and thus requires further study.[98] It also has been shown that dysregulation of the NBC through a defective dopamine 1–receptor signaling mechanism may play a role in the development of high blood pressure in spontaneously hypertensive rats,[99] again implying a role of NBC in increased blood pressure.

NBC1 also is implicated in an acute rejection model in rat kidney transplantation leading to acid-base and electrolyte abnormalities. NBC1 expression and function were upregulated in an acute rejection model whereas NHE3 did not change. It is suggested that modulation of function of sodium bicarbonate transporter may play a role in acute kidney allograft rejection, but the mechanism responsible is not known. This interesting observation requires further study.[100]

Hypoxic insults to the central nervous system as in obstructive sleep apnea/hypoventilation syndrome may produce neurosensory problems. In mouse models of chronic hypoxia, kNBC1 and pNBC1 expression were decreased, especially in the hippocampus. It is suggested that the downregulation of these transporters may reflect adaptive response to injury or may be part of a cascade of events causing neuronal damage.[101] In another study, an electrogenic NBC variant was cloned in the rat brain. This clone is similar to the pNBC from pancreas but differs in the 5′ untranslated and the NH2 terminus coding region of the kNBC1 that was studied in an ischemia model of injury. The protective role of this variant was investigated in an oxygen-glucose deprivation ischemic model in astrocytes. Neuronal injury was prevented by inhibiting NBC in this model, suggesting a possible role of the sodium bicarbonate cotransporter.[102]

NBC contributes 30% to the control of intracellular pH regulation in cardiac Purkinje cells, and 50% in ventricular myocytes.[15,103] Intracellular pH may modulate Ca^+ and Na fluxes affecting cardiac rhythm and contractility.[104,105] In the ischemia reperfusion model of injury, inhibition of hhNBC by specific antibody significantly protects systolic and diastolic functions during reperfusion.[106] Another recent study suggests that the hhNBC blockade may reduce ischemic Na+ overload.[107]

Tumor propagation and growth are enhanced by an acidic milieu.[108] NBC1 activity has been shown to promote cell migration of transformed epithelial cells, which is a requirement for tumor spread.[109] Increased expression of NBC1 has been reported in renal cell carcinoma. It is postulated that NBC1 may be involved in creating a microenvironment that may enhance tumor spread and aggressiveness.[110]

NBC3 and NBC4 also play a role of clinical importance. Targeted disruption of NBC3 (SLC4A7) in the mouse caused blindness and hearing defects similar to that of Usher's syndrome, which is characterized by degeneration of the sensory and auditory receptors. NBC4 (SLC4A5) is implicated in Alström syndrome.[111] The syndrome is a rare genetic disease characterized by cardiomyopathy, sensorineural hearing loss, retinopathy, truncal obesity, hypogonadism, diabetes mellitus, and asthma.[112]

In summary, cellular, tissue and organ functions are impacted by any abnormality of these transporters. The sodium bicarbonate cotransporter plays an indispensable role in the regulation of intracellular pH. Abnormalities in NBC function caused by mutations or hormonal regulation affect several organ systems, leading to important clinical consequences.

References

1. Boron WF, Boulpaep EL: Intracellular pH regulation in the renal proximal tubule of salamander basolateral HCO_3^- transport. J Gen Physiol 81:53-94, 1983
2. Alpern RJ: Mechanism of basolateral membrane $H^+/OH-/HCO_3^-$ transport in the rat renal proximal tubule. J Gen Physiol 86:613-636, 1985
3. Yoshitomi K, Burckhardt BC, Fromter E: Rheogenic sodium-bicarbonate cotransport in the peritubular cell membrane of rat renal proximal tubule. Pflugers Arch 405:360-366, 1985
4. Biagi BA, Sohtell M: Electrophysiology of basolateral bicarbonate transport in the rabbit renal proximal tubule. Am J Physiol 250:F267-F272, 1986
5. Soleimani M, Grassl SM, Aronson PS: Stoichiometry of Na^+-HCO_3^- cotransport in basolateral membrane vesicles isolated from rabbit renal cortex. J Clin Invest 79:1276-1280, 1987
6. Lopes AG, Siebens AW, Giebisch G, et al: Electrogenic Na^+/HCO_3^- cotransport across the basolateral membrane of isolated perfused *Necturus* proximal tubule. Am J Physiol 253:F340-F350, 1987
7. Jentsch TJ, Keller SK, Koch M, et al: Evidence for coupled transport of bicarbonate and sodium in cultured bovine corneal endothelial cells. J Membr Biol 81:189-204, 1984
8. Hughes BA, Adorante JS, Miller S, et al: Apical electrogenic Na+/HCO_3^- cotransport. A mechanism for HCO_3^- absorption across the retinal pigment epithelium. J Gen Physiol 94:125-150, 1989
9. Curci S, Deblis L, Fromter E: Evidence for rheogenic sodium bicarbonate cotransport in the basolateral membrane of oxyntic cells in frog gastric fundus. Pflugers Arch 408:497-504, 1987
10. Weintraub WH, Machen TE: pH regulation in hepatoma cells: Roles for Na-H exchanger and Cl-HCO_3^- and Na-HCO_3^- cotransport. Am J Physiol 257:G317-G327, 1989
11. Gleeson D, Smith ND, Boyer JL: Bicarbonate dependent and independent intracellular pH regulatory mechanism in the rat hepatocytes. J Clin Invest 84:312-321, 1989
12. Schmitt BM, Berger UV, Douglas RM, et al: Na/HCO3 cotransporters in rat brain: Expression in glia, neurons, and choroids plexus. J Neurosci 20:6839-6848, 2000
13. Deitmer JW, Schlue WR: An inwardly directed electrogenic sodium bicarbonate cotransporter in leech glial cells. J Physiol 411:179-194, 1989
14. Bevensee MO, Apkon M, Boron WF: Intracellular pH regulation in cultured astrocytes from rat hippocampus. Electrogenic Na^+/HCO_3^- cotransport. J Gen Physiol 110:467-483, 1997
15. Lagadic-Gossmann D, Buckler KJ, Vaughan-Jones RD: Role of bicarbonate in pH recovery from intracellular acidosis in the guinea-pig ventricular myocyte. J Physiol 458:361-384, 1992
16. Lubman RL, Chao DC, Crandall ED: Basolateral localization of Na(+)-HCO3− cotransporter activity in alveolar epithelial cells. Respir Physiol 100:15-24, 1995
17. Jensen LJ, Schmitt BM, Berger UV, et al: Localization of sodium bicar-

bonate cotransporter (NBC) protein and messenger ribonucleic acid in rat epididymis. Biol Reprod 60:573-579, 1999
18. Zhao H, Star RA, Muallem S: Membrane localization of H+ and HCO3− transporters in the rat pancreatic duct. J Gen Physiol 104: 57-85, 1994
19. Romero MF, Hediger MA, Boupaep EL, et al: Expression cloning and characterization of a renal electrogenic Na^+/HCO_3^- cotransporter. Nature 387:409-413, 1997
20. Burnham CE, Amlal H, Wang Z, et al: Cloning and functional expression of a human kidney Na^+/HCO_3^- cotransporter. J Biol Chem 272:19111-19114, 1997
21. Romero MF, Fong P, Berger UV, et al: Cloning and functional expression of rNBC an electrogenic Na^+- HCO_3^- cotransporter from rat kidney. Am J Physiol 274:F425-F432, 1998
22. Abuladze N, Lee I, Newman D, et al: Molecular cloning, chromosomal localization, tissue distribution, and functional expression of the human pancreatic sodium bicarbonate cotransporter. J Biol Chem 273: 17689-17895, 1998
23. Choi I, Romero MF, Khandoudi N: Cloning and characterization of human heart electrogenic Na^+- HCO_3^- cotransporter isoform (hhNBC). Am J Physiol 276:C576-C584, 1999
24. Ishibashi K, Sasaki S, Marumo F: Molecular cloning of a new sodium bicarbonate cotransporter cDNA from human retina. Biochem Biophys Res Commun 246:535-538, 1998
25. Pushkin A, Abuladze N, Lee I, et al: Cloning, tissue distribution, genomic organization, and functional characterization of NBC3, a new member of the sodium bicarbonate cotransporter family. J Biol Chem 274:16569-16575, 1999
26. Choi I, Aalkjaer C, Boulpaep EL, et al: An electroneutral sodium/bicarbonate cotransporter NBCn1 and associated sodium channel. Nature 405:571-575, 2000
27. Amlal H, Burnham CE, Soleimani M: Characterization of Na+/HCO-3 cotransporter isoform NBC-3. Am J Physiol 276:F903-F913, 1999
28. Nagase T, Ishikawa K, Suyama M, et al: Prediction of the coding sequences of unidentified human genes. XI. The complete sequences of 100 new cDNA clones from brain which code for large proteins in vitro. DNA Res 5:277-286, 1998
29. Grichtchenko II, Choi I, Zhong X, et al: Cloning, characterization and chromosomal mapping of a human electroneutral Na^--driven Cl−HCO3− exchanger. J Biol Chem 261:8778-8783, 2001
30. Pushkin A, Abuladze N, Newman D, et al: Cloning, characterization and chromosomal assignment of NBC4, a new member of the sodium bicarbonate cotransporter family. Biochim Biophys Acta 1493:215-218, 2000
31. Wang CZ, Yano H, Nagashima K, et al: The Na+-driven Cl−/HCO3− exchanger. Cloning, tissue distribution, and functional characterization. J Biol Chem 275:35486-35490, 2000
32. Geibel, Giebisch G, Boron WF: Basolateral sodium-coupled acid-base transport mechanisms of the rabbit proximal tubule. Am J Physiol 257:F790-F797, 1989
33. Maunsbach AV, Vorum H, Kwon TH, et al: Immunoelectron microscopic localization of the electrogenic Na^+/HCO_3^- cotransporter in rat and *ambystoma* kidney. J Am Soc Nephrol 1:2179-2189, 2000
34. Schmitt BM, Biemesderfer D, Romero MF, et al: Immunolocalization of electrogenic Na^+-HCO_3^- cotransporter in mammalian and amphibian kidney. Am J Physiol 276:F27-F38, 1999
35. Abuladze N, Lee I, Newman D, et al: Axial heterogeneity of sodium bicarbonate cotransporter expression in the rabbit proximal tubule. Am J Physiol 274:F628-F633, 1998
36. Yip K-P, Tsuroaka S, Schwartz GJ, et al: Apical H^+/base transporters mediating bicarbonate absorption and pH_i regulation in the OMCD. Am J Physiol 283:F1098-F1104, 2004
37. Vorum H, Kwon TH, Fulton C, et al: Immunolocalization of electroneutral Na-HCO_3 cotransporter in rat kidney. Am J Physiol 279: F901-F909, 2000
38. Praetorius J, Buozinova EV, Kim XH, et al: NBCn1 is a basolateral Na^+:HCO_3^- cotransporter in rat kidney inner medullary collecting ducts. Am J Physiol 286:F903-F912, 2004
39. Kwon TH, Pushkin A, Abuladze N, et al: Immunoelectron microscopic localization of NBC3 sodium bicarbonate cotransporter in rat kidney. Am J Physiol 278:F327-F336, 2000
40. Pushkin A, Yip KP, Clark I, et al: NBC expression in rabbit collecting duct: Colocalization with vacuolar H-ATPase. Am J Physiol 277: F974-F981, 1999
41. Soleimani M, Aronson PS: Ionic mechanism of Na-HCO^-_3 cotransport in rabbit renal basolateral membrane vesicles. J Biol Chem 264: 18302-18308, 1989
42. Gross E, Hawkins K, Pushkin A, et al: Phosphorylation of Ser^{982} in kNBC1 shifts the HCO_3^-:Na^+ stoichiometry from 3:1 to 2:1 in proximal tubule cells. J Physiol 537:659-665, 2001
43. Gross E, Hopfer U: Activity and stoichiometry of Na:HCO_3 cotransport in immortalized proximal tubule cells. J Membr Biol 152:245-252, 1996
44. Gross E, Abuladze N, Pushkin A, et al: The stoichiometry of the electrogenic sodium bicarbonate cotransporter pNBC1 in mouse pancreatic duct cells is $2HCO_3^-$:$1Na^+$. J Physiol 531:375-382, 2001
45. Gross E, Abuladze N, Pushkin A: The HCO_3^-:Na^+ stoichiometry of pNBC1 is organ specific. J Am Soc Nephrol 11:1299, 2000
46. Grassl SM, Aronson PS: Na^+/HCO_3^- cotransport in basolateral membrane. J Biol Chem 261:8778-8783, 1986
47. Gross E, Kurtz I: Structural determinants and significance of regulation of electrogenic Na^+-HCO_3^- cotransport stiochiometry. Am J Physiol 283:F876-F887, 2002
48. Okubo K, Kang D, Hamasaki N, et al: Red blood cell band 3, lysine 539, and lysine 851 react with the same H_2DIDS. J Biol Chem 269: 1918-1926, 1994
49. Stim J, Bernardo AA, Kear FT, et al: Renal cortical basolateral Na^+/HCO_3^- cotransporter II: Detection of conformational changes with fluorescein isothiocyanate labeling. J Membr Biol 140:39-46, 1994
50. Bernardo AA, Kear FT, Arruda JAL: Renal cortical Na^+/HCO_3^- cotransport VI: The effect of chemical modification on cotransporter activity. J Membr Biol 158:49-57, 1997
51. Choi I, Lihui H, Rojas JD, et al: Role of glycosylation in the renal electrogenic Na^+-HCO_3^- cotransporter NBCe1. Am J Physiol 284: F1199–F1206, 2003
52. Romero MF, Boron WF: Electrogenic Na^+/HCO_3^- cotransporters cloning and physiology. Annu Rev Physiol 61:699-723, 1999
53. Burg M, Green M: Bicarbonate transport by isolated perfused rabbit proximal convoluted tubules. Am J Physiol 233:F307-F314, 1977
54. Cogan MG, Maddox DA, Warnock DG, et al: Effect of acetazolamide in bicarbonate reabsorption in the proximal tubule of the rat. Am J Physiol 237:F447-F454, 1979
55. Gross E, Pushkin A, Abuladze N, et al: Regulation of the sodium bicarbonate cotransporter kNBC1 function: Role of Asp(986), Asp(988) and kNBC1-carbonic anhydrase II binding. J Physiol 544: 679-685, 2002
56. Pushkin A, Abuladze N, Gross E, et al: Molecular mechanism of kNBC1-carbonic anhydrase II interaction in proximal tubule cells. J Physiol 559:55-65, 2004
57. Tsuruoka S, Swenson ER, Petrovic S, et al: Role of basolateral carbonic anhydrase in proximal tubular fluid and bicarbonate absorption. Am J Physiol 280:F146-F154, 2001
58. Alvarez B, Loiselle FB, Supuran CT, et al: Direct extracellular interaction between carbonic anhydrase IV and the human NBC1, sodium/bicarbonate cotransporter. Biochemistry 42:12321-12329, 2003
59. Kanki T, Young MT, Sakaguchi M, et al: The N-terminal region of the transmembrane domain of human erythrocyte band 3. Residues critical for membrane insertion and transport activity. J Biol Chem 278: 5564-5573, 2003
60. Toye AM, Bruce LJ, Unwin RJ, et al: Band 3 Walton, a C-terminal deletion associated with distal renal tubular acidosis, is expressed in the red cell membrane but retained internally in kidney cells. Blood 99:342-347, 2002
61. Toye AM, Banting G, Tanner MJ: Regions of human kidney anion exchanger 1 (kAE1) required for basolateral targeting of kAE1 in polarised kidney cells: Mis-targeting explains dominant renal tubular acidosis (dRTA). J Cell Sci 117:1399-1410, 2004

62. Zhang D, Kiyatkin A, Bolin JT, et al: Crystallographic structure and functional interpretation of the cytoplasmic domain of erythrocyte membrane band 3. Blood 96:2925-2933, 2000
63. Zhu Q, Lee DW, Casey JR: Novel topology in C-terminal region of the human plasma membrane anion exchanger, AE1. J Biol Chem 278: 3112-3120, 2003
64. Espiritu DJ, Bernardo AA, Arruda JA: The role of the NH2 and the COOH termini in targeting, stability and activity of sodium bicarbonate cotransporter 1 (NBC1). Am J Physiol 291(3):F588-596, 2006
65. Li HC, Worrell RT, Matthews JB, et al: Identification of a carboxyl-terminal motif essential for the targeting of Na+-HCO-3 cotransporter NBC1 to the basolateral membrane. J Biol Chem 279:43190-43197, 2004
66. Kurtz I, Petrasek D, Tatishchev S: Molecular mechanisms of electrogenic sodium bicarbonate cotransport: Structural and equilibrium thermodynamic considerations. J Membr Biol 197:77-90, 2004
67. Akiba T, Rocco VK, Warnock DG: Parallel adaptation of the rabbit renal cortical sodium/proton antiporter and sodium/bicarbonate cotransporter in metabolic acidosis and alkalosis. J Clin Invest 80:308-315, 1987
68. Ruiz OS, Arruda JAL, Talor Z: Na-HCO_3^- cotransporter and Na-H antiporter in chronic respiratory acidosis and alkadosis. Am J Physiol 256:F414-F420, 1989
69. Geibel J, Giebisch G, Boron WF: Angiotensin II stimulates both Na(+)-H+ exchange and Na+/HCO3− cotransport in the rabbit proximal tubule. Proc Natl Acad Sci U S A 87:7917-7920, 1990
70. Robey RB, Ruiz OS, Espiritu DJ, et al: Angiotensin II stimulation of renal epithelial cell Na/HCO3 cotransport activity: A central role for Src family kinase/classic MAPK pathway coupling. J Membr Biol 187: 135-145, 2002
71. Ruiz OS, Qiu YY, Cardoso LR, et al: Regulation of the renal Na-HCO3 cotransporter: IX. Modulation by insulin, epidermal growth factor and carbachol. Regul Pept 77:155-161, 1998
72. Ruiz OS, Wang LJ, Pahlavan P, et al: Regulation of renal Na-HCO3 cotransporter: III. Presence and modulation by glucocorticoids in primary cultures of the proximal tubule. Kidney Int 47:1669-1676, 1995
73. Ruiz OS, Qiu YY, Wang LJ, et al: Regulation of the renal Na-HCO3 cotransporter: V. Mechanism of the inhibitory effect of parathyroid hormone. Kidney Int 49:396-402, 1996
74. Ruiz OS, Arruda JA: Regulation of the renal Na-HCO3 cotransporter by cAMP and Ca-dependent protein kinases. Am J Physiol 262:F560-F565, 1992
75. Ruiz OS, Robey RB, Qiu YY, et al: Regulation of the renal Na-HCO(3) cotransporter. XI. Signal transduction underlying CO(2) stimulation. Am J Physiol 277:F580-F586, 1999
76. Espiritu DJD, Bernardo AA, Robey RB, et al: A central role for Pyk2-Src interaction in coupling diverse stimuli to increased epithelial NBC activity. Am J Physiol 283:F663-F670, 2002
77. Amlal H, Habo K, Soleiman M: Potassium deprivation upregulates expression of renal basolateral Na^+:HCO_3^- cotransporter NBC1. Am J Physiol 279:F532-F543, 2000
78. Ruiz OS, Qiu YY, Wong LJ, et al: Regulation of the renal Na-HCO_3 cotransporter: IV. Mechanisms of the stimulatory effect of angiotensin II. J Am Soc Nephrol 6:1202-1208, 1995
79. Noboa OA, Espiritu DJD, Bernardo AA, et al: Angiotensin II modulates Na^+/HCO_3^- cotransporter in cultured human proximal tubule cells through a novel mechanism. J Am Soc Nephrol 11:7, 2000 (abstr)
80. Noboa OA, Espiritu DJD, Ibanez VC, et al: Microtubules play a role in stimulation of the Na^+/HCO_3^- cotransporter (NBC1) activity by angiotensin II (A II). J Am Soc Nephrol 12:59, 2001 (abstr)
81. Pastoriza-Munoz E, Harrington RM, Graber ML: Parathyroid hormone decreases bicarbonate reabsorption in the rat proximal tubule by stimulating phosphatidylinositol metabolism and inhibiting base exit. J Clin Invest 89:1485-1495, 1992
82. Damaraju R, Espiritu DJD, Noboa OA, et al: Gsα and Na^+/HCO_3^- cotransporter (NBC) interaction mediates PTH inhibition of NBC in human proximal tubule cells. J Am Soc Nephrol 11:49, 2000
83. Vernik J, Espiritu DJD, Bernardo AA, et al: PTH acutely inhibits sodium bicarbonate cotransporter (NBC) activity through serine/threonine phosphorylation. J Am Soc Nephrol 14:305, 2003
84. Espiritu DJD, Ibanez VC, Noboa OA, et al: Downregulation of NBC1 by parathyroid hormone in human proximal tubule cells (HK2) involves proteasomal and lysosomal mechanisms. J Am Soc Nephrol 12:3, 2001
85. Bernardo AA, Espiritu DJD, Arruda AL: Endocytosis of the renal sodium bicarbonate cotransporter (NBC) is mediated by a cAMP_PKA dependent pathway and clathrin coated vesicles. J Am Soc Nephrol 14:560, 2003
86. Weinman EJ, Steplock D, Bui G, et al: Regulation of renal Na^+/H^+ exchanger by cAMP-dependent protein kinase. Am J Physiol 258: F1254-F1258, 1990
87. Ruiz OS, Arruda JAL: Regulation of the renal Na-HCO_3 cotransporter by cyclic AMP and Ca-dependent protein kinases. Am J Physiol 257: F560-F565, 1992
88. Weinman EJ, Steplock D, Wang Y, et al: Characterization of a protein cofactor that mediates protein kinase A regulation of the renal brush border membrane Na^+-H^+ exchanger. J Clin Invest 95:2143-2149, 1995
89. Bernardo AA, Kear FT, Stim JA, et al: Renal cortical basolateral Na^+/HCO_3^- cotransporter III: Evidence for a regulatory protein in the inhibitory effect of protein kinase A. J Membr Biol 145:67-74, 1995
90. Usui T, Hara M, Satoh H, et al: Molecular basis of ocular abnormalities associated with proximal renal tubular acidosis. J Clin Invest 108:107-115, 2001
91. Igarashi T, Inatomi J, Sekine T, et al: Mutations in SCL4A4 cause permanent isolated proximal renal tubular acidosis with ocular abnormalities. Nat Genet 23:264-266, 1999
92. Shiohara M, Igarashi T, Mori T, et al: Genetic and long term data on a patient with permanent isolated proximal renal tubular acidosis. Eur J Pediatr 159:892-894, 2000
93. Igarashi T, Inatomi J, Sekine T, et al: Novel nonsense mutation in the Na^+/HCO_3^- cotransporter gene (SLC4A4) in a patient with permanent isolated proximal renal tubular acidosis and bilateral glaucoma. J Am Soc Nephrol 12:713-718, 2001
94. Igarashi T, Sekine T, Inatomi J, et al: Unraveling the molecular pathogenesis of isolated proximal renal subular acidosis. J Am Soc Nephrol 13:2171-2177, 2002
95. Dinour D, Chang M-H, Saton J, et al: A novel missense mutation in the sodium bicarbonate cotransporter (NBCe1/SLC4A4) causes proximal tubular acidosis and glaucoma through ion transport defects. J Biol Chem 279:52238-52246, 2004
96. Horita S, Yamada H, Inatomi J, et al: Functional analysis of NBC1 mutants associated with proximal renal tubular acidosis and ocular abnormalities. J Am Soc Nephrol 16:2270-2278, 2005
97. Inatomi J, Itorita S, Braverman N, et al: Mutational and functional analysis of SLC4A4 in a patient with proximal renal tubular acidosis. Pflugers Arch 448:438-444, 2004
98. Barkley RA, Chakravarty A, Cooper RJ, et al: Positional identification of hypertension susceptibility genes to chromosome 2. Hypertension 43:477-482, 2004
99. Kunimi M, Seki G, Hara C, et al: Dopamine inhibits the renal Na^+-HCO_3^- cotransporter in normotensive rats but not in spontaneously hypertensive rats. Kidney Int 57:534-543, 2000
100. Velic A, Hirsch JR, Bartel J, et al: Renal transplantation modulates expression and function of receptors and transporters of rat proximal tubules. J Am Soc Nephrol 15:967-977, 2004
101. Douglas RM, Xue J, Chen JY, et al: Chronic intermittent hypoxia decreases the expression of Na/H exchangers and HCO_3^- dependent transporters in mouse CNS. J Appl Physiol 95:292-299, 2003
102. Giffard R, Papadopoulos MC, van Hoof JA: The electrogenic sodium bicarbonate cotransporter: Developmental expression in rat brain and possible role in acid vulnerability. J Neurosci 20:1001-1008, 2000

103. Camilion de Hurtado MC, Perez NG, Cingolani HE: An electronic sodium bicarbonate cotransport in the regulation of myocardial intracellular pH. J Mol Cell Cardiol 27:231-242, 1995
104. Vaughan RD, Spitzer KW: Role of bicarbonate in the regulation of intracellular pH in the mammalian ventricular myocytes. Biochem Cell Biol 80:579-596, 2002
105. Yamamoto T, Swietach P, Rossinni A: Functional diversity of electrogenic Na^+-HCO_3^- cotransport in ventricular myocytes from rat, rabbit and guinea pig. J Physiol 562:455-475, 2005
106. Khandoudi N, Albadine J, Philippe R, et al: Inhibition of the cardiac electrogenic sodium bicarbonate cotransporter reduces ischemic injury. Cardiovasc Res 52:387-396, 2001
107. Ten Hove M, Nederhoff MG, Van Echteld CJA: Relative contributions of Na^+/H^+ exchange and Na^+/HCO_3^- cotransport to ischemic Na^+ overload in isolated rat hearts. Am J Physiol 258:H287-H292, 2005
108. Gatenby RA, Gawlinki ET: A reaction-diffusion model of cancer invasion. Cancer Res 56:5745-5753, 1996
109. Schwab A, Kossmann H, Klein M, et al: Functional role of Na^+-HCO_3^- cotransport in migration of transformed renal epithelial cells. J Physiol 568:445-458, 2005
110. Yamada H, Yamazaki S, Moriyama N, et al: Localization of NBC-1 variants in human kidney and renal cell carcinoma. Biochem Biophys Res Commun 310:1213-1218, 2003
111. Pushkin A, Abuladze N, Newman D: Cloning, characterization and chromosomal assignment of NBC4, a new member of the sodium bicarbonate cotransporter family. Biochim Biophys Acta 1493:215-218, 2000
112. Collin GB, Marshall JD, Boerkele CF, et al: Alstrom syndrome: Further evidence of linkage to human chromosome 2p13. Hum Genet 105: 474-479, 1999