

Review Article

Nanomaterials-Based Approaches for the Modulation of Sodium Bicarbonate Cotransporters

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HCO_3^- and fluid secretion are major functions of all epithelia, and alterations in HCO_3^- secretion by sodium bicarbonate cotransporters are associated with many epithelial diseases, such as renal, ocular, and dental abnormalities. Electrolyte and fluid exits are synergistically mediated by the intracellular second messengers, cAMP and Ca^{2+} , and this raises the possibility that ion transporters are involved in simple secretion and more complicated forms of regulation. Evidence indicates that HCO_3^- transport is regulated by the assemblage of Na^+ - HCO_3^- cotransporters (NBCs) into complexes by multiple regulatory factors. Recently the specific regulatory functions of factors that interact with NBCe1, especially NBCe1-B, have been elucidated. In this review, I focus on the structural characteristics of electrogenic NBCe1, pathophysiology of NBCe1, and molecular mechanisms responsible for transporter regulation. Moreover I propose the possibility to apply nanomaterials combined with regulatory factors for modulating the activity of NBC transporters as a potential development of therapeutic drug.

1. Introduction

Sodium bicarbonate cotransporters (NBCs) play crucial roles in the regulation of systemic acid/base balance, the absorption and secretion of bicarbonate (HCO_3^-), and the maintenance of electrolyte homeostasis in epithelia. The NBCs are members of the Na^+ -coupled bicarbonate transporter (NCBT) superfamily, which includes electrogenic NBCs (NBCe1 and NBCe2), electroneutral NBCs (NBCn1 and NBCn2), and Na^+ -dependent Cl^- - HCO_3^- exchanger (NDCBE) [1]. Since NBC was identified functionally in kidney proximal tubules [2], NBCe1 has been identified with five splice variants NBCe1-A through NBCe1-E and categorized to three splice variants, NBCe1-A, NBCe1-B, and NBCe1-C, which differ at their N- or C-termini in human and rodents [1, 3].

NBCe1 proteins are coded by the SLC4A4 gene [4], and NBCe1-A, which is also known as kNBC1, is predominantly expressed in kidney [5] in the basolateral membrane to mediate HCO_3^- efflux [1, 6] and play a role in transepithelial HCO_3^- reabsorption. NBCe1-A mediates the apparent 1:3

cotransport of Na^+ and HCO_3^- in proximal tubules [7] but exhibits 1:2 stoichiometry in collecting ducts [1, 8]. The stoichiometry of NBCe1-A is regulated by cell type [8], cytosolic Ca^{2+} concentration [9], and PKA phosphorylation of C-terminus [10]. NBCe1-B plays a critical role by mediating basolateral HCO_3^- influx to accumulate intracellular HCO_3^- and facilitate HCO_3^- secretion to the lumen. Furthermore, it is expressed ubiquitously in basolateral membrane of epithelia and is expressed at especially high levels in pancreas (known as pNBC1) [5, 11–14]. NBCe1-C is exclusively expressed in brain (also known as bNBC1), especially in glial cells within the Purkinje cell layer [15], and has the longest amino acid sequence of the three variants [16]. Consistent with several reports, the stoichiometry of NBCe1 depends on the splice variant, cell type, and the cell environment [8, 9, 17–19]. NBCs and their derivatives are also involved in many other tissues including salivary glands [20–22], eye [23], intestine [24–26], heart [15, 27], tooth [28, 29], and airway submucosal glands cell line Calu-3 [30]. Here I discuss the characteristics and pathophysiology of electrogenic NBCe1 expressed in basolateral membrane close to blood vessel

and molecular mechanisms of regulatory factors for various potentials of nanosized drug in the modulation of ion transporters.

2. Pathophysiology of NBCe1

Cells regulate electrolyte composition and intracellular pH via the transport of H^+ and HCO_3^- . Vectorial transport in epithelia and altered ion secretion, especially of HCO_3^- , are associated with a wide range of dysfunctions and diseases [31, 32]. Metabolic changes caused by ischemia and reperfusion induce intracellular acidosis due to the generation of H^+ , which activates Na^+-H^+ exchanger (NHE) and NBC and subsequently increases intracellular Na^+ concentrations [33]. Accordingly, transporter mutations cause many types of diseases. For example, the hyperactive NBCe1 during reperfusion leads to Na^+ and Ca^{2+} overloading and myocardial damage [33], whereas impaired sodium reabsorption caused by gentamicin-induced nephropathy is probably due to the downregulation of sodium transporters, such as NBC and NHE3, suggesting decreased activity of sodium transporters in rat proximal nephrons [34]. Furthermore, inactivating mutation of NBCe1 was observed to be associated with severe proximal renal tubular acidosis accompanied by ocular abnormalities [35–37] and severe growth retardation [36]. The maintenance of NBCe1 activity may be essential for the homeostasis of ocular tissues abundantly expressing NBCe1 [38]. Abnormal surface expression of NBCe1-B may cause migraine, which suggests that defective functions of NBCe1 are associated with pathophysiologic effects in the brain [39]. Moreover, NBCe1-A and NBCe1-B are involved in insulin secretion by rat pancreatic islet cells [40]. Insulin-mediated tyrosine kinase enhances Na^+ absorption by stimulating NBCe1 in renal proximal tubules [41]. For this reason, hyperinsulinemia could be a risk factor of hypertension via the activation of NBCs. In tooth ameloblasts and papillary layer cells, the expression of NBCe1 depends on developmental stage [42]. Furthermore, the altered expression of NBCe1 is associated with the maturation of enamel, which suggests a critical evaluation of the functions of transporters in tooth mineralization is required.

3. Splice Variants of NBCe1 in Human

NBCe1-A and NBCe1-B share 93% homology. They differ at N-termini; that is, the 41 N-terminus of NBCe1-A is replaced by 85 amino acids in the B variant. The C variant differs at its C-terminus in which 46 amino acids of the A and B variants are replaced with 61 amino acids. In the NBCe1-B variant, of the 85 amino acids, 50% are charged residues whereas in the A variant only 22% of these amino acids are charged. Although all the three variants have similar ion and voltage dependencies and plasma membrane expression patterns in oocytes [43], the transporter activity of NBCe1-A is much higher than those of the other two variants. This higher activity of NBCe1-A is due to its unique amino terminus and not due to its plasma membrane expression differences or differences in voltage/ion dependencies [43]. It has been

addressed that N-termini of NBCe1-B and NBCe1-C variants would be included autoinhibitory domains (AID) [1, 43, 44]. The minor isoforms NBCe1-D and NBCe1-E are deleted a 27 bp segment within the cytosolic N-termini [3]. The physiological significance of three variants has been determined to be unclear. The cytosolic C-terminus is known to have important roles in membrane expression of NBCe1 transporter including interactions with cytosolic carbonic anhydrase II (CA II) [45, 46]. Vince et al. addressed the fact that CA II binds to the acidic DADD motif on the Cl- HCO_3^- exchanger AE1. The C-termini of all the three NBCe1 splice variants have two similar DADD motifs [47]. CA II interacts with NBCe1-A/B in vitro [48]. Although CA II is adjacent to the C-terminus of NBCe1-A, it fails to enhance NBCe1-A activity in oocytes [49].

The C-terminus of NBCe1 is beyond the scope of this review and will not be discussed here. According to its unique N-terminal amino acid sequences, several authors have examined the involvements of regulatory or binding factors [13, 50–53]. However, this review focuses on N-termini of NBCe1 and interaction with potential regulatory factors.

4. Roles of Potential Regulatory Factors on the Regulation of NBCe1-B

4.1. IRBIT. Inositol 1, 4, 5-trisphosphate (IP_3) receptor (IP_3R) binding protein released with IP_3 , called IRBIT, was first identified by Mikoshiba's group [54]. IRBIT binds IP_3R in the resting state and dissociates from IP_3R in the stimulated state. Mikoshiba et al. attempted to identify the molecules targeted by IRBIT and focused on an immunoprecipitated protein. The sequence of extracted protein matched that of NBCe1 protein, and IRBIT was found to bind the NBCe1-B specifically but not the A variant [55]. Subsequently, they focused on the N- and C-termini of NBCe1-B for IRBIT binding because it was considered that the cytosolic domain of NBCe1-B might contain a region that interacts with IRBIT, which is a cytosolic protein. Surprisingly, their pull-down assay revealed that the 85 amino acids' sequence of the N-terminus NBCe1-B is sufficient to bind IRBIT. To identify the IRBIT binding region in the N-terminus of NBCe1-B, they prepared deletion mutants encoding different regions of the N-terminus. This terminus possesses a cluster of negatively charged residues (regions 2–24) and a cluster of positively charged residues (regions 37–59) [56]. Deletion mutants were found to bind IRBIT when both positive and negative charged clusters were present. The authors suggested that IRBIT to NBCe1-B binding might require the 3D structure of the N-terminus of NBCe1-B [55]. On the other hand, Yang et al. [13] showed deletion of PEST domain was enough to prevent IRBIT to NBCe1-B binding. This domain is a peptide sequence containing many glutamic acids and is negatively charged. The charged nature of this cluster indicates that cluster interacts with the negatively charged PEST domain of IRBIT. In addition, another member of the Na^+ -derived HCO_3^- transporters such as NBCn1-A has an N-terminal domain similar to that of NBCe1-B, which revealed that its activity was modulated by IRBIT [50].

4.2. Phosphatidylinositol 4,5-Bisphosphate (PIP2). Phospholipids are ubiquitous and act as powerful signaling molecules. Beyond its classic functions, such as acting as a precursor for inositol triphosphate (IP_3) and diacylglycerol, several reports have showed that phosphatidylinositol 4,5-bisphosphate (PIP2) activates diverse processes, including K_{ATP} channel [57, 58] and NHE1 [59]. More recently, inside-out macropatch experiments showed PIP2 stimulated NBCe1-A activity in xenopus oocytes [44]. In the presence of poly-D-lysine or neomycin, only small PIP2-induced inward current was elicited, but PIP2-induced inward current was reestablished after removing neomycin [44]. These data represent the fact that the positive N-terminus clusters of NBCe1-B and -C variants may interact with PIP2 to inhibit automodulation of AID domain. PIP2 hydrolysis indirectly stimulates NBCe1-B and NBCe1-C by increasing IP_3 and Ca^{2+} , which are involved in kinase such as staurosporine-sensitive kinase [60]. Although sites that interact with PIP2 have been reported for several transporters, such as transient receptor potential canonical and P2X channels [61–63], the specific binding site in PIP2 has not been determined. Analysis of the PIP2-binding region of PH domain-containing proteins indicated that the presence of basic amino acids is needed to interact with the anionic head group of PIP2. In the NCBT family, the potential [K- X_n -K/R-K] sequence, characterized by phosphoinositide-binding motif [64], was found to be a conserved cluster of positively charged residues. PIP2 and IRBIT activate NBCe1-B in a nonadditive manner due to interaction with the same site within the AID [50]. Not only activity of NBCe1-B but also activities of other ion channels such as K_{ATP} channel and NHE1 can be modulated by the PIP2. It can be considered new therapeutic approaches for pathology of ion channels.

4.3. Mg^{2+} , Polyvalent Cation, and Other Cytosolic Factors. Mg^{2+} plays an indispensable role in diverse biological functions, which include modulations of the activities of enzymes, ion channels, and transporter, and is the second-most abundant intracellular ion after potassium [65, 66]. Mg^{2+} can reduce ion channel currents by blocking channels in a voltage-dependent manner [67] and also associates with the negative charges of phosphoinositides by electrostatic interaction [68]. Recently, intracellular Mg^{2+} was observed to inhibit NBCe1-B currents voltage-independently in cloned NBCe1-B expressing mammalian cells and native bovine parotid acinar cells, whereas N-terminus truncated NBCe1-B mutant was less sensitive to Mg^{2+} than the wild type [51]. In addition to regulatory role of IRBIT on NBCe1-B, the coexpression of AHCYL2 (adenosylhomocysteine hydrolase-like protein 2 or long IRBIT) also reduces affinity for intracellular Mg^{2+} and subsequent inhibition of NBCe1-B currents in HCO_3^- -depleted conditions [52]. This means that IRBIT, long IRBIT, and Mg^{2+} can be considered potential secondary effectors of NBCe1-B. As mentioned above, polyvalent cations such as neomycin also inhibit recombinant and native currents. These findings may provide clues regarding interaction between Mg^{2+} and clustered negative charged amino acids of

N-terminus by electrostatic mechanism directly or indirectly. Further studies are needed to prove this hypothesis. Several other cytosolic regulatory or membrane bound factors including actin or enzymes for the cytoskeletal elements may be involved in the regulation of NBC transporters.

4.4. Intracellular Cl^- Interacting Motifs. Cl^- is a major anion and involves numerous cellular functions responsible for fluid and electrolytes homeostasis. Cl^- concentration varies and is determined by the activity of several ion transporters/channels such as ClC Cl^- transporter [69], Cl^-/HCO_3^- exchanger [70], and CFTR [31, 71]. Recently, the regulatory role of intracellular Cl^- was addressed in electrogenic NBC transporters through the complex modulation of activity [72]. Resting NBCe1-B is inhibited by high intracellular Cl^- concentration. The regulatory effect of intracellular Cl^- on electrogenic NBC is mediated by Cl^- interacting GXXXX motifs. The NBCe1-B is mediated by two GXXXX motifs, one of which is unmasked by IRBIT in autoinhibitory module to interact with high affinity for Cl^- . During the resting state of intracellular Cl^- which is between 5 and 60 mM [73], an activity of NBCe1-B modestly operates at around 40% of highest activity, whereas nonphysiological concentration of Cl^- at 140 mM inhibited NBCe1-B activity by around 60%. In the presence of IRBIT, high affinity Cl^- interacting GXXXX site of NBCe1-B is released and observed. Complicated modulation, modulation of IRBIT in AID, or different affinity of Cl^- addresses the fact that NBCe1-B senses different range of Cl^- and has several functional roles as well as saving energy [72]. In addition, sequence analysis of other transporters revealed that K^+-Cl^- cotransporter KCC, Na^+-Cl^- cotransporter NCC, $Na^+-K^+-Cl^-$ cotransporter NKCC, epithelial Na^+ channel ENaC, and solute carrier family 26A (SLC26A) transporters also possess GXXXX motif. Further studies will be required to characterize and determine any potential Cl^- regulation to these transporters.

4.5. WNK/SPAK Kinases. The regulation of ion transporters is determined by the WNK (with-no-lysine) and the SPAK (Ste20-related proline/alanine-rich kinase) kinase pathways, which involve scaffolding interaction and phosphorylated state [73, 74]. WNK and SPAK kinases suppress fluid and HCO_3^- secretion by inhibiting the surface expression of NBCe1-B in pancreatic and parotid secretory ducts, and these pathways stabilize the resting state of secretory duct for HCO_3^- secretion by reducing the surface expressions of ion transporters, whereas IRBIT dramatically stimulates ductal fluid secretion and reverses the effects of WNKs and SPAK kinases [75]. The convergent regulation of NBCe1-B activity by IRBIT and WNK/SPAK is concentrated on the AID of its N-terminus [50]. SPAK kinase phosphorylates S65 and T49 of NBCe1-B within AID, and this T49 phosphorylation is required for regulation of NBCe1-B by SPAK. However, the regulation of the reciprocal balance of activated and inhibitory states of NBCe1-B by IRBIT and the WNK/SPAK pathways remains to be clarified.

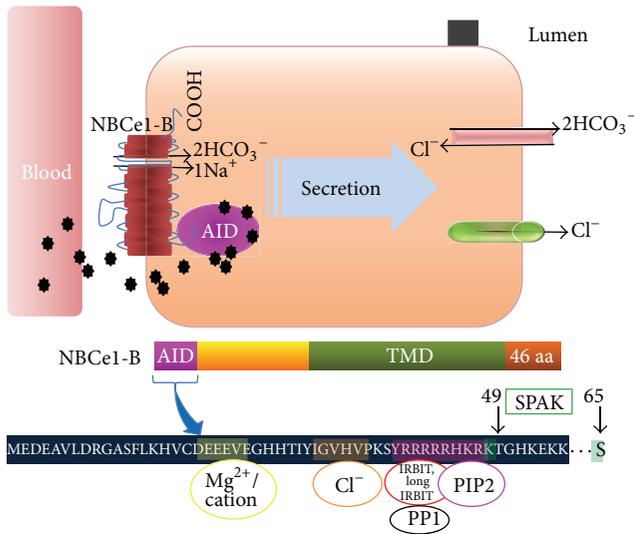


FIGURE 1: Putative regulatory factors of NBCe1 N-terminal modules. AID domain, TMD domain, and C-terminus are highlighted with magenta, green, and orange color, respectively. Binding motifs are highlighted with similar color background of regulatory factors. SPAK phosphorylation sites are highlighted with green background Tyr49 and Ser65 within N (1–85) terminus. AID: autoinhibitory domain; TMD: transmembrane domain.

5. Summary

NBCe1-B is a pivotal regulatory protein in HCO_3^- secreting epithelia, such as those of intestine, lung, pancreas, and salivary glands [31]. As indicated above, several interacting factors are involved in regulation of NBCe1-B for HCO_3^- secretion. I focused on the N-terminus of NBCe1-B based on the findings of regulatory factors, summarized and illustrated in Figure 1. It will provide particular interests to clarify secretory mechanisms and develop the treatment modalities with nanosized drug and nanomaterial-conjugated regulatory factors. While proteins or enzymes of exogenous origin are attractive for therapeutic applications, their clinical administration has been restricted to the immune response [76]. Therefore protein or enzyme based therapies critically need efficient delivery platforms that protect their degradation through encapsulated carrier platform. The development of promising platform for encapsulating functional biomolecules such as enzymes, phospholipids, and charged ions that can freely diffuse in and out through the pores of nanomaterials may be needed. Moreover the regulatory factor-recruited nanocarrier can be applicable to modulate the activity of overexpressed transporters and subsequently diminish tumor-preferred circumstances in tumorigenesis.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

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