

Epithelial sodium channel (ENaC) in GtoPdb v.2025.4

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Abstract

Overview

Epithelial sodium channels (ENaC) are located on the apical membrane of epithelial cells in the kidney tubules, lungs, respiratory tract, male and female reproductive tracts, sweat and salivary glands, placenta, colon, and several other organs [10, 17, 26, 25, 57]. In these epithelia, Na⁺ ions enter epithelial cells from the extracellular fluid *via* ENaC and are subsequently pumped out into the interstitial fluid by the Na⁺/K⁺-ATPase on the basolateral membrane [49]. Because sodium is a major electrolyte in the extracellular fluid (ECF), the osmotic changes caused by sodium flux are accompanied by parallel water movement [7]. Thus, ENaC plays a central role in regulating ECF volume and blood pressure, primarily through its function in the kidney [51]. The expression of ENaC subunits- and therefore its activity- is controlled by the renin-angiotensin-aldosterone system and other factors involved in electrolyte homeostasis [51, 36].

Genetic studies of systemic pseudohypoaldosteronism type I revealed that ENaC activity depends on three essential subunits encoded by three separate genes encoding homologous proteins [12, 26]. Within the wider protein superfamily that includes ENaC, the first crystal structure determined was that of ASIC, which revealed a trimeric structure with a large extracellular domain anchored in the membrane by a bundle of six transmembrane helices (two per subunit) [3, 30]. The first 3D structure of human ENaC was determined using single-particle cryo-electron microscopy at 3.7Å resolution [45], later improved to 3.0Å [46]. These structures confirmed that ENaC has a quaternary structure similar to ASIC. ENaC assembles as a heterotrimer, with α -, γ -, and β -subunits arranged in clockwise order when viewed from above [13]. In contrast to ASIC1, which can form a functional homotrimer, ENaC is only fully functional as a heterotrimer composed of either $\alpha\beta\gamma$ or $\delta\beta\gamma$ [33]. Recently, Houser and Baconguis co-expressed human δ , β , and γ and determined the structures of complexes using single-particle cryoelectron microscopy. The structures showed that β and γ positions are conserved among the different complexes while the α position in the $\alpha\beta\gamma$ trimer is occupied by either δ or another β [29].

In the respiratory and female reproductive tracts, large regions of the epithelium consist of multiciliated cells with a microtubule-based cytoskeleton. In these cells, ENaC is distributed along the entire length of the cilia [19]. This localization substantially increases ENaC density on the cell surface and enables precise regulation of periciliary fluid osmolarity throughout its depth [19]. In the *vas deferens* of the male reproductive tract, the luminal surface is covered with microvilli and stereocilia supported by actin bundles [57]. In these cells, both ENaC and the aquaporin AQP9 are localized to the projections as well as to the basal and smooth muscle layers [57]. In contrast, CFTR- the chloride channel defective in cystic fibrosis- is confined to the apical cell surface but is absent from cilia and microvilli [19, 57]. Collectively, ENaC function regulates epithelial fluid volume, which is essential for mucociliary clearance in the respiratory tract, gamete transport, fertilization, implantation, and cell migration [19, 44, 26].

Genes and Phylogeny

The human genome contains four homologous genes (*SCNN1A*, *SCNN1B*, *SCNN1G*, and *SCNN1D*) encoding the α -, β -, γ -, and δ -ENaC subunits, respectively [11, 40, 55, 62]. These subunits share 23–34% sequence identity and <20% identity with ASIC subunits [26]. Genes encoding all four ENaC subunits are present in bony vertebrates, except in ray-finned fishes, which have lost them entirely. The mouse genome has also lost *SCNN1D*, the gene for δ -ENaC [21, 26]. The α -, β -, and γ -ENaC genes are present in jawless vertebrates (*e.g.*, lampreys) and cartilaginous fishes (*e.g.*, sharks) [26].

Methylation analysis of the 5'-flanking regions of *SCNN1A*, *SCNN1B*, and *SCNN1G* in human cells

revealed an inverse correlation between gene expression and DNA methylation, suggesting epigenetic transcriptional control of ENaC genes [48].

Channel biogenesis, assembly and function

ENaC subunit expression is regulated primarily by aldosterone and by numerous other extracellular and intracellular factors [51, 35, 47]. Most studies indicate that expression of the three subunits is not tightly coordinated [9]. However, transport of the subunits to the membrane requires all three intact subunits, and even a single missense mutation can reduce the number of assembled channels on the cell surface [18].

ENaC is constitutively active, meaning Na^+ flow does not require an activating factor. Thus, heterologous cells expressing ENaC (*e.g.*, human cRNAs in *Xenopus* oocytes) must be maintained in amiloride-containing solutions to block channel activity. ENaC activity is then measured by replacing the bath with amiloride-free solution. The channel alternates between two states: 1) open and 2) closed. The probability of ENaC being open is referred to as open probability (P_o). ENaC regulation involves two key parameters: (1) membrane channel density and (2) open probability [31, 33]. Open probability is markedly reduced by extracellular Na^+ in a process known as sodium self-inhibition [4, 28, 59].

A key regulatory feature is that the α - and γ -subunits contain conserved extracellular serine protease cleavage sites [26]. Proteolytic cleavage by enzymes such as furin and plasmin activates ENaC [52, 34, 1].

Diseases associated with ENaC mutations

Mutations in *SCNN1A*, *SCNN1B*, or *SCNN1G* can cause partial or complete loss of ENaC activity [12, 23]. Such loss-of-function mutations are associated with systemic or multi-system autosomal recessive pseudohypoaldosteronism type I (OMIM abbreviation: PHA1B) [22, 12, 26, 64, 19, 54]. No PHA-causing mutations have been identified in *SCNN1D*. Patients with PHA experience severe salt wasting in all aldosterone target organs expressing ENaC, including kidney, sweat glands, salivary glands, and respiratory tract. In infancy and early childhood, the resulting electrolyte disturbances, dehydration, and acidosis often require recurrent hospitalization. The frequency and severity of salt-wasting episodes generally improve with age [24]. PHA1B also affects female reproductive system function [19, 6].

The ENaC carboxy-terminal region contains a short consensus sequence called the PY motif. Mutations in this motif in *SCNN1B* and *SCNN1G* are associated with Liddle syndrome, a disorder marked by early-onset hypertension [60, 5]. The PY motif is recognized by Nedd4-2, a ubiquitin ligase. Mutations that disrupt this recognition reduce ENaC ubiquitylation, leading to channel accumulation at the membrane and increased ENaC activity [53].

ENaC expression in tumors

Intracellular sodium concentrations are often elevated in cancer cells compared with normal cells, leading to the hypothesis that ENaC overexpression may contribute to metastasis [39]. However, RNA-seq analysis of ENaC genes and clinical data of cervical cancer patients from The Cancer Genome Atlas (TCGA) revealed a negative correlation with histologic grades of tumor [61]. Similarly, in breast cancer cells, overexpression or siRNA-mediated knockdown of α -ENaC showed that higher α -ENaC levels suppress cell proliferation [63]. In contrast, TCGA data showed that elevated *SCNN1A* expression correlates with poor prognosis in ovarian cancer [41]. Thus, the role of ENaC in tumorigenesis appears to be tissue-specific.

COVID-19

SARS-CoV-2 virions, the cause of COVID-19, are covered with glycosylated spike (S) proteins. These proteins bind to membrane-bound ACE2 as the first step of viral entry. Entry depends on S-protein cleavage (at Arg-667/Ser-668) by a serine protease. Anand *et al.* identified a sequence motif at this cleavage site homologous to the furin cleavage site in ENaC α [2]. A comprehensive review of COVID-19 pathophysiology suggests a role for ENaC in the early stages of infection in respiratory epithelia [20].

ENaC Inhibitors for Cystic Fibrosis

Cystic fibrosis (CF) is the most common life-limiting autosomal recessive disorder among Caucasians. CF is caused by mutations in the gene that codes for CFTR (Cystic Fibrosis Transmembrane Conductance Regulator). CFTR is a chloride and bicarbonate channel located on the apical membrane [14]. CFTR-mediated movement of Cl^- and HCO_3^- ions into the lumen also drives water flow into the lumen by osmosis. CFTR is expressed in many tissues but the most severe effect of mutated CFTR is observed in the respiratory tract in the form of airway surface liquid (ASL)

depletion which leads to mucus accumulation, inflammation and bacterial infections that lead to mortality.

Normal CFTR activity inhibits ENaC by causing a reduction in surface expression of ENaC as well as its P_o [50]. In many epithelia, ENaC and CFTR are not co-localized on the apical membrane indicating that the two channels do not directly interact [19, 56, 57]. In the absence of a functional CFTR, ENaC activity increases (also named as "hyperactivated ENaC"), leading to increased Na^+ and water absorption and consequently ASL depletion. These observations have led to the development of inhibitors targeting ENaC in the airways to ameliorate ASL dehydration [58, 43, 38]. Most of the ENaC inhibitors in development are designed for application by inhalation and improved lung retention to avoid damaging the vital activity of ENaC in other tissues [37, 16]. Despite the development of many ENaC inhibitors for CF [15], nearly all drug candidates were discontinued at Preclinical, Phase 1 or Phase 2 stage of clinical trials [38, 16, 43]. However, there is one candidate, EDT001, that is still under Phase 2 clinical trial [16]. The persistence of the scientists and the drug companies and the versatility of their approaches provide hope that an appropriate useful treatment will emerge to help CF patients.

Thus, insights into the physiological and pathological roles of ENaC across diverse tissues continue to guide the development of targeted inhibitors, with cystic fibrosis representing a prominent example where modulation of ENaC activity may translate fundamental biology into therapeutic benefit.

Contents

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Channels and Subunits

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[ENaC \$\delta\$](#)

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