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Role of epithelial sodium channel-related inflammation in human diseases

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The epithelial sodium channel (ENaC) is a heterotrimer and is widely distributed throughout the kidneys, blood vessels, lungs, colons, and many other organs. The basic role of the ENaC is to mediate the entry of Na^+ into cells; the ENaC also has an important regulatory function in blood pressure, airway surface liquid (ASL), and endothelial cell function. Aldosterone, serum/glucocorticoid kinase 1 (SGK1), shear stress, and posttranslational modifications can regulate the activity of the ENaC; some ion channels also interact with the ENaC. In recent years, it has been found that the ENaC can lead to immune cell activation, endothelial cell dysfunction, aggravated inflammation involved in high salt-induced hypertension, cystic fibrosis, pseudohypoaldosteronism (PHA), and tumors; some inflammatory cytokines have been reported to have a regulatory role on the ENaC. The ENaC hyperfunction mediates the increase of intracellular Na^+, and the elevated exchange of Na^+ with Ca^{2+} leads to an intracellular calcium overload, which is an important mechanism for ENaC-related inflammation. Some of the research on the ENaC is controversial or unclear; we therefore reviewed the progress of studies on the role of ENaC-related inflammation in human diseases and their mechanisms.

KEYWORDS

epithelial sodium channel, inflammation, hypertension, cardiovascular stiffening, cystic fibrosis, colitis, tumor

1 Introduction

The epithelial sodium channel (ENaC) is non-voltage-gated and amiloride-sensitive epithelial Na^+ channel (1). The classic ENaC is composed of α, β, and γ subunits; the α subunit can be replaced by the δ subunit in non-renal tissues (2). The most important function of the ENaC is to maintain the physical and cellular Na^+ homeostasis by

mediating Na^+ reabsorption in the kidneys, colon, lungs, and skin. ENaC dysfunction is associated with a variety of diseases: ENaC overexpression in the kidneys manifests as increased blood volume and hypertension (3), impaired ENaC in the colon manifests as inflammation of intestinal mucosa and diarrhea (4), and dysfunction of the ENaC in the lungs leads to pneumonia and respiratory distress (5). The expression and activity of the ENaC are regulated by a variety of factors; hormones such as renin-angiotensin-aldosterone system (RAAS), insulin, and vasopressin can maintain Na^+ metabolic homeostasis by regulating the ENaC. The self-inhibitory effect of Na^+ on the ENaC is an important piece of negative feedback, as the regulation of the ENaC by mechanical signals is critical in vascular smooth muscle cells (6).

ENaC activation leads to an increased influx of Na^+, which in turn provides potential energy for cellular material exchange. Increased Na^+/Ca^{2+} exchanges lead to elevated intracellular Ca^{2+}, which activates Ca^{2+}-related inflammatory signaling pathways (7). Activated ENaC promotes K^+ efflux, and increased K^+ efflux activates NOD-like receptor family pyrin domain containing 3 (NLRP3) inammasome, which can activate immune cells and promote inflammatory cytokine expression (8). Increased intracellular Na^+ promotes the inward flows of glucose and glutamine, which facilitate tumor growth and migration. Increased intracellular Na^+ promotes isolevuglandin (IsoLG)-adduct formation and oxidative stress, leading to T-cell activation (9). ENaC-mediated inflammation has an important role in the development of hypertension, vascular sclerosis, pneumonia, cystic fibrosis, nephritis, ulcerative colitis, and tumors. Recently, ENaC activates immune system has been widely reported, while some inflammatory cytokines also have a modulatory effect on the ENaC. In this review, we discuss the roles and mechanisms of ENaC-related inflammation in human diseases.

2 The epithelial sodium channel

2.1 Structure

The sequences of ENaC subunits and degenerin (DEG) from the nematode *Caenorhabditis* elegans are similar, so they are named the DEG/ENaC family, which also includes the mammalian acid-sensing ion channel (ASIC) (10). Canonical ENaC is a heterotrimer composed of α, β, and γ subunits; the δ subunit can replace the α subunit to form a heterotrimer in non-renal tissues (2). The δβγ channel is less sensitive to proteolytic activation (11) and has a higher IC50 for amiloride than the αβγ channel (12); the δ subunit can also be found in primates and xenopus but is not expressed in mice or rats (13–15). Non-canonical ENaC is composed of two subunits or only homomeric subunits; apart from homomeric γENaC, all non-canonical ENaCs are amiloride sensitive and mediate Na^+ absorption in oocytes (2). The α, β, γ, and δ subunits are separately encoded by SCNN1A, SCNN1B, SCNN1G, and SCNN1D, respectively (16).

ENaC subunits have two transmembrane domains, intracellular N and C termini, and a large extracellular domain. The ion selectivity filter can specifically discriminate Na^+; the filter is located in the middle of the transmembrane domains (17). The extracellular domain has protease cleavage sites, which can eliminate the inhibitory effects of the ENaC; it plays an important role in regulating ENaC activation (18, 19). The N-terminal ubiquitylation of the α and γ subunits is related to ENaC endocytosis and degradation (20); both the HGxxR sequence in the N-terminal and the PPPxY sequence in the C-terminal have regulatory effects on the ENaC. Mutations in the HGxxR sequence or the PPPxY sequence leading to abnormal function of ENaC are associated with the occurrence of Liddle syndrome (21) and pseudohypoaldosteronism (PHA) (22).

2.2 Distribution

The ENaC is firstly found in the apical surface of epithelial cells (23). The αβγ channel is expressed in many organs, such as in the kidneys (distal convoluted tubule, connecting tubule, collecting duct) (24), skin (keratinocyte, sweat gland) (25), vascular system (endothelium, smooth muscle) (26), lungs (alveolar cell, airway cell) (27), colon (28), and tongue (29).The δENaC has also been found in many non-renal organs, such as in the ovaries, brain, liver, lungs, heart, and vessel (13, 16, 30) (Figure 1).

2.3 Function

The ENaC is critical for epidermal differentiation. Hyperplasia, dehydration, disorder of lipid synthesis and secretion can be found in the αENaC KO mice skin, which leads to death soon after birth (31). Inhibition of the ENaC or blockage of its synthesis can significantly reduce the process of wound healing; the ENaC contributes to wound healing by its activity as a Na^+ channel and mediator of mechanotransduction (32). The ENaC's primary role in the colon is the recollection of Na^+, reducing salt loss in the feces. It is interesting to note that the ENaC is mainly expressed in the distal colon, not in the small intestine or proximal colon (33). A low-salt diet induces increased expression of β and γ subunits but not of α subunits (34). The ENaC controls Na^+ absorption in the inner ear, which is very important to maintain hearing; dysregulation of the ENaC in the hair cells can lead to hearing loss and vertigo (35). The ENaC can sense mechanical signals in the vascular system such as shear stress (36). The ENaC also has an effect on endothelial stiffness and the release of nitric oxide (NO) (37). The ENaC is critical in infant respiratory epithelium, which can help to remove fluid from the respiratory tract during fetal life; it then plays an important role in maintaining normal airway surface liquid (ASL) (38). Suppression or mutation of the ENaC leads to the development of pulmonary edema or cystic fibrosis (39); surprisingly, symptoms of ENaC overexpression are similar to those of cystic fibrosis (40), although the exact mechanism is not yet clear (Figure 1).

2.4 Regulation

There are many factors that can regulate the ENaC, including ions, mechanical signals, hormones, phospholipids, posttranslational modifications, and other proteins. The ENaC can be regulated by extracellular Na^+ and intracellular Na^+. An increase of Na^+ leads to EnaC allosteric change and reduction in channel open probability; this phenomenon is called feedback inhibition (18). Increased extracellular Na^+ leads to the downregulation of ENaC expression in renal epithelium, whereas in vascular endothelium it leads to increased ENaC expression, and the exact mechanism of the difference in responses is unclear (41). The ENaC provides a mechanosensory function in vascular endothelium and smooth muscle cells; shear stress can activate the ENaC then regulate NO release and vessel vasodilation (42). Hypovolemia or reduced glomerular filtration rate can stimulate the RAAS, further activate the ENaC, and lead to increased Na^+ reabsorption, which in turn raises blood pressure (43). Aldosterone is one of the main regulators of the ENaC; especially in the distal nephron, aldosterone binds to the mineralocorticoid receptor (44), then the complex translocates into the nucleus and promotes associated gene expression (45) (Figure 2). Insulin can reduce internalization and ubiquitylation of ENaC, phosphorylation of insulin receptor activates SGK1 kinase by phosphatidylinositol3-kinase (PI3K), which in turn modulates ENaC activity (45–47). Vasopressin increases the expression of the β and γ subunits, but fewer effects on the α subunit have been proven *in vivo* and *in vitro*; this effect may be achieved by vasopressin receptors (48). Several phospholipids have been reported to have a regulatory effect on the ENaC. Phosphatidylinositol (4, 5)-bisphosphate (PIP2) and phosphatidylinositol (3–5)-triphosphate (PIP3) have a direct positive regulatory role on the C-terminal of β and γENaC (49). Thus, many substances that have a regulatory effect on PIP2 and PIP3 can indirectly modulate ENaC activity, such as phospholipase C (49), myristoylated alanine-rich C-kinase (50), and phospholipase β3 (51).

Posttranslational modifications have an important modulatory effect on the ENaC. Nedd4-2 (neural precursor cell expressed developmentally downregulated protein 4-2) can promote specific lysine residues ubiquitination in the N-terminal regions of α and γENaC, ultimately promoting ENaC endocytosis and degradation (52). Dexamethasone promotes ENaC expression by regulating DNA methylation, which may be a potential therapeutic mechanism for cystic fibrosis (53). Extracellular signal-regulated kinase (Erk) has been reported to phosphorylate PY motifs in βENaC, rapidly modulating ENaC activity (54). Deubiquitylating enzymes (DUBs and USPs) can reduce α and γENaC ubiquitylation and internalization enhance ENaC stability and activity (55). N- and C-terminal regions on β or γENaC can be palmitoylated on specific cysteine residues, which can reduce channel open possibility (this is one of the mechanisms of Na^+ self-inhibition (56)). Proteases can activate ENaC by cleaving inhibitory fragments; for example, golgi-resident protease furin can release inhibitory fragments in α and γENaC, and prostasin and low-dose trypsin can also activate ENaC

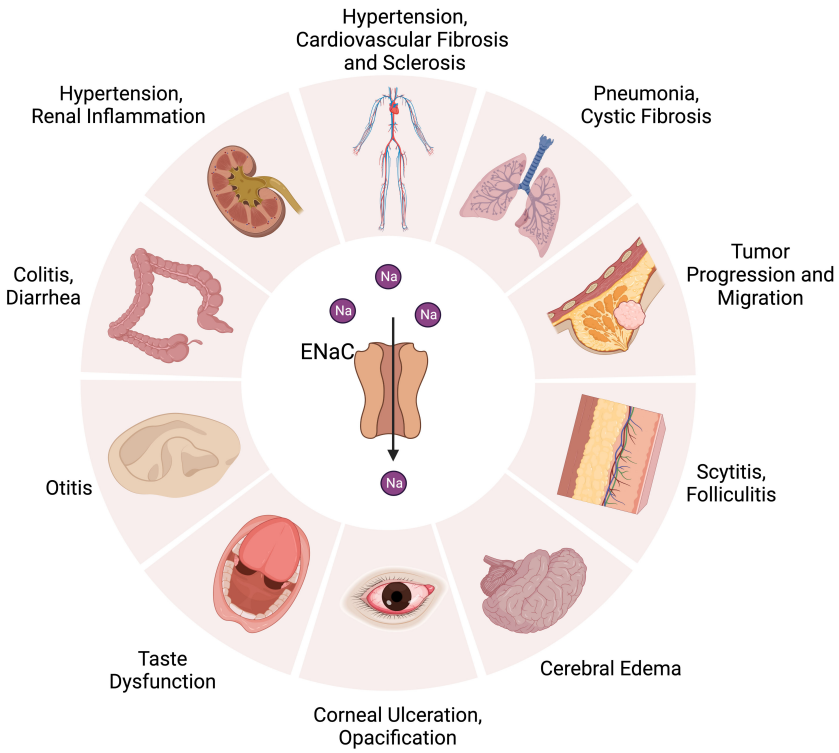

FIGURE 1
Distribution of ENaC in organs and related diseases. ENaC is associated with hypertension, cardiovascular fibrosis and sclerosis in the cardiovascular system. In the kidney, colon, and skin, ENaC affects water absorption by regulating Na+ transport, which is related to the development of hypertension, diarrhea, renal inflammation, colitis, scytitis and folliculitis. ENaC dysfunction is associated with pneumonia, cystic fibrosis, taste dysfunction, otitis, cerebral edema, corneal ulceration and opacification. ENaC also has an important role in the progression and metastasis of tumor.

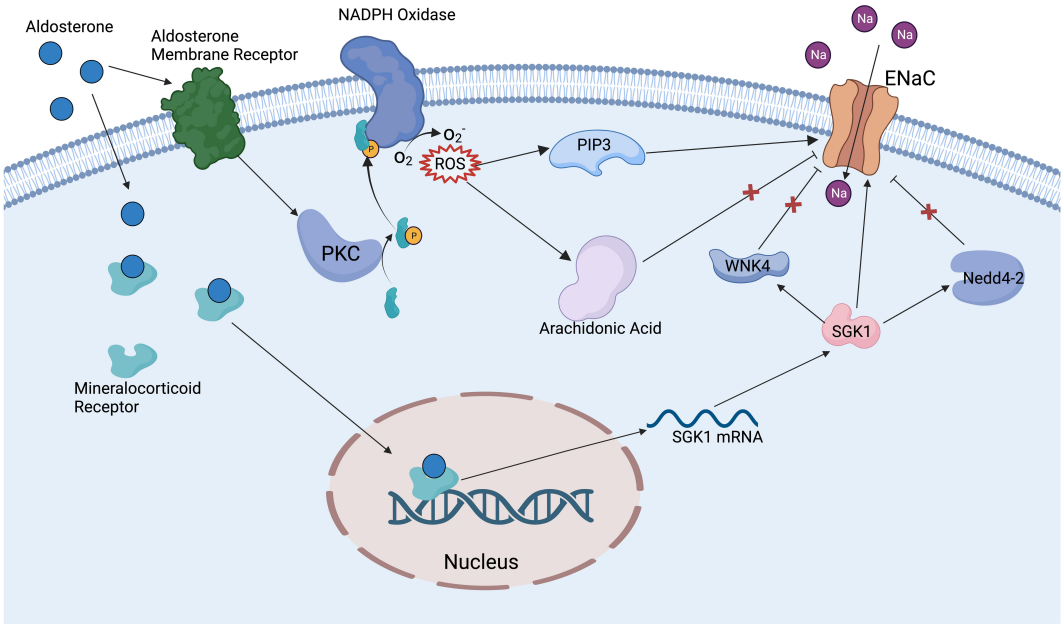

FIGURE 2
Mechanism of aldosterone regulating ENaC. Aldosterone binds to mineralocorticoid receptors in the cytoplasm and promotes the expression of SGK1. SGK1 can deregulate the inhibition of ENaC by WNK4 and Nedd4-2 ubiquitinates, also can directly activate ENaC. Aldosterone binds to aldosterone receptors on the cell membrane to activate PKC and NADPH oxidase, then promotes the production of ROS. ROS activates ENaC via PIP3 and relieves the inhibition of ENaC by the arachidonic acid metabolic pathway.

through a similar mechanism (57). WNK lysine deficient protein kinase 1 (WNK1) has been proven to activate the ENaC by SGK1 pathway (58), while WNK4 has an inhibitory effect on the ENaC (59) (Figure 2). Amiloride hydrochloride is a specific inhibitor of the ENaC, with an IC50 of 1μM, and is widely used in clinical treatments and in the basic research of the ENaC (60).

2.5 Effect on other ions and channels

The ENaC's fundamental function is to regulate the transport of Na^+; increased intracellular Na^+ can further influence other ions and channels (41). ENaC mediates the influx of Na^+, which is pumped out of cells via the Na^+/K^+-ATPase (NKA) (61). Reabsorbed Na^+ can create the driving force to excrete K^+ through apical secretory K^+ channels (62, 63); these are important pathways for K^+ excretion, but the ability of ENaC to directly secrete k^+ is limited, because ENaC is more (>100-fold) selective to Na^+ than K^+ (12). The ENaC has been shown to interact with the HCO_3^-/Cl^- exchanger and to some extent can affect blood HCO_3^- and Cl^- levels (64, 65). The ENaC mediates increased intracellular Na^+ and facilitates the exchange of Na^+ with Ca^{2+} through the Na^+–Ca^{2+} exchanger (NCX), which causes a Ca^{2+} overload and further activates downstream signaling pathways (7, 8). Some hormones or kinases have regulatory effects on multiple ion channels, which may lead to the ENaC indirectly affecting other ions and channels, as both SGK1 and aldosterone have effects on the ion channels of Na^+, K^+, Ca^{2+}, and Cl^- (66, 67). Reports about the effects of the ENaC on other ions and channels are lacking, and therefore need further study.

Pendrin is a Cl^-/HCO_3^- exchanger that can be seen in the intercalated cells. The function of ENaC is downregulated in pendrin-null kidney (68). In H^+/K^+-ATPase type 2 (HKA2)-null mice, the expression of α and γENaC, pendrin are upregulated, but the expression of Na^+/Cl^- cotransporter (NCC) is downregulated (69). The ENaC has a regulatory effect on the NCC, and γENaC knockout leads to impaired excretion of K^+ and increased NCC activation (70). ZIP2/SLC39A2 is a splice isoform of the Zn^{2+} importer, and when inversely correlated with intracellular Zn^{2+} can induce ENaC expression and activation in cystic fibrosis (71). HKalpha2 is one of the H^+/K^+ ATPase subunits in the colon, and decreased ENaC-mediated Na^+ reabsorption has been observed in HKalpha2 homozygous knockout mice (72). The cystic fibrosis transmembrane conductance regulator (CFTR) can mediate Cl^- and HCO_3^- efflux. Na^+ enters cells through the ENaC and is pumped out by NKA; this generates a transepithelial electrical gradient of Cl^-, which is absorpted into cells by CFTR, and decreased Cl^- in cytosolic increases ENaC expression and Na^+ reabsorption (73, 74). Na^+/H^+ exchanger (NHE3), bumetanide-31 sensitive Na^+/K^+-$2Cl^-$ transporter (NKCC2), NCC, and the ENaC work together in the kidneys to regulate the reabsorption and secretion of Na^+ and K^+ (75).

3 Role of epithelial sodium channel-related inflammation

3.1 Epithelial sodium channel-related inflammation in cardiovascular system

High salt exposure increases Na^+ entry into cells through the ENaC, and increased intracellular Na^+ acts as a driving force to promote NCX for Ca^{2+} exchange in antigen-presenting cells (APCs). Elevated intracellular Ca^{2+} increases ROS production and activates

NLRP3 inflammasome, leading to T-cell activation and the release of inflammatory cytokines, which promotes Na^+ reabsorption and hypertension (7). Increased Na^+ leads to IsoLG-adduct formation and the expression of tumor necrosis factor (TNF)α, interleukin (IL)-6, and IL-1β. IsoLG-adducts as neoantigens can activate T cells (9), while the inhibition of NADPH-oxidase reduces monocyte activation and IsoLG-adduct formation (76) (Figure 3). It has been found that αENaC is overexpressed in neutrophils in hypertensive patients (77). SGK1 in APCs mediates high salt-induced expression, and the assembly of α and γENaC promotes the expression of IL-1β and the formation of IsoLG-adducts in salt-sensitive hypertension. Less endothelial dysfunction and blunted hypertension have been found both in SGK1 knockout mice and mice with application of SGK1 inhibitors (78).

A high-sodium diet (>150 mM) increases ENaC expression and promotes vascular endothelial cell stiffness and dysfunction (79). The ENaC is a key molecule of endothelial dysfunction in cardiovascular fibrosis and stiffening; activation of the ENaC on vascular endothelial cells increases oxidative stress and endothelial cell permeability, leading to impaired NO release and the formation of an inflammatory microenvironment (80). Aortic endothelium stiffness and dysfunction is reduced in αENaC knockout mice, including decreased endoplasmic reticulum stress and oxidative stress, and reduced endothelium permeability and expression of proinflammatory cytokines; endothelium NO synthase is also activated (81). Estrogen activates ENaC via SGK-1 in vascular endothelial cells, leading to a higher risk of arterial stiffening in women, which can be reduced by amiloride (82). Knockdown of αENaC in endothelial cells leads to a decrease of cortical stiffness; conversely, αENaC overexpression leads to an increase of cortical stiffness in vascular endothelial cells and promotes oxidative stress and inflammation in aortic tissues (83); this effect is related to AMP-activated protein kinase α (AMPKα) and sirtuin 1-mediated endothelial NO synthase (eNOS) activation (84). A high-fat diet leads to activation of ENaC-mediated inflammation and increases secretion of TNFα, IL-1β, IL-6, vascular cell adhesion molecule (VCAM)-1 and intracellular adhesion molecule (ICAM)-1, which in turn leads to endothelial dysfunction and vascular sclerosis. Benzamil is a specific inhibitor of ENaC that can reduce the inflammation induced by a high-fat diet (85).

The ENaC increases cardiac endothelium permeability, promotes macrophage recruitment and M1 polarization, and leads to ventricular fibrosis and remodeling in female mice. Amiloride can attenuate the impaired left ventricular initial filling rate and relaxation time (86). The ENaC causes endothelium-dependent relaxation impairment in mice aorta through the ROS/COX-2-mediated SGK-1/Nedd4-2 signaling pathway; blocking the ENaC facilitates attenuation of hyperhomocysteinemia-induced cardiovascular system disease (79).

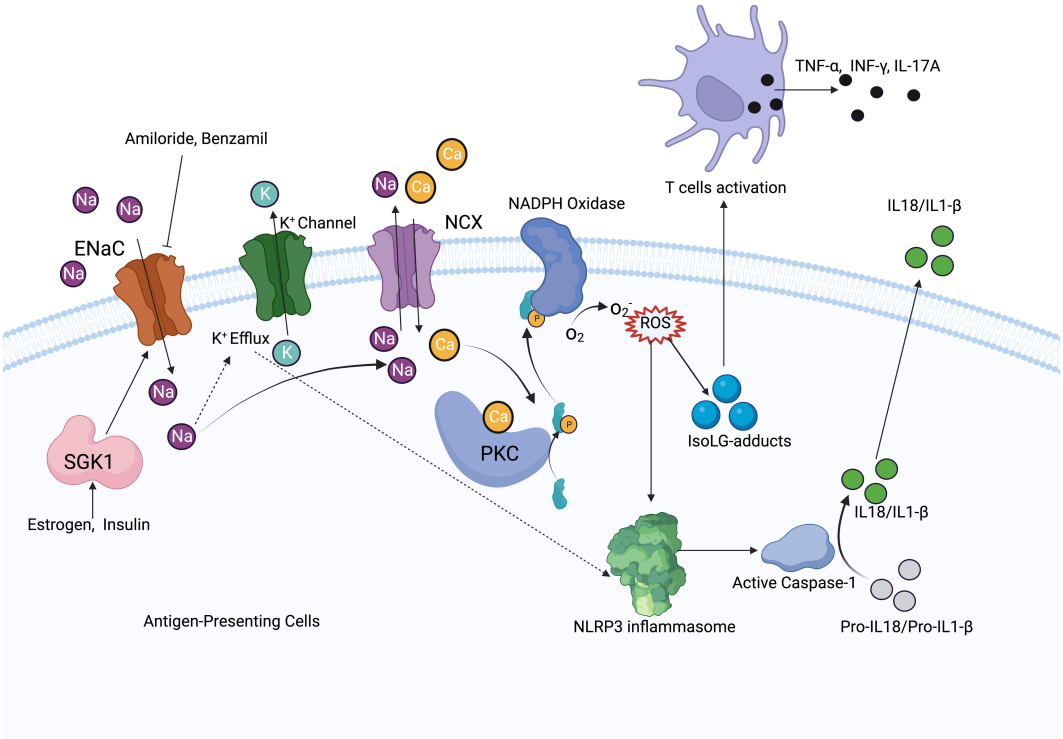

FIGURE 3
Mechanism diagram of ENaC activating immune system. In antigen-presenting cells, ENaC mediates Na^+ influx, which increases Na^+ exchange with $Ca2^+$ via NCX. Elevated intracellular $Ca2^+$ activates PKC and NADPH oxides to increase ROS production. ROS activates the NLRP3 inflammasome and promotes IsoLG-adducts formation, meanwhile, increased intracellular Na^+ promotes K^+ efflux, which also activates the NLRP3 inflammasome. NLRP3 inflammasome increases IL-1β, IL-18 production by activating caspase-1, IsoLG-adducts promotes T cells activation. ENaC expression is regulated by SGK1, while estrogen and insulin have regulatory effects on SGK1.

3.2 Epithelial sodium channel-related inflammation in the respiratory system

Cystic fibrosis is a multisystem disease, characterized by mutations of the CFTR gene and repeated pulmonary infections (87). The ENaC has been shown to be overactive in cystic fibrosis, resulting in increased Na^+ and water absorption from the airway lumen, eventually leading to mucus accumulation, bacterial infection, and airway inflammation (5) (Figure 4). The ENaC mediates Na^+ influx and indirectly increases K^+ efflux, which leads to NLRP3 inflammasome activation, further causing excessive IL-1β and IL-18 secretion (8). The bronchoalveolar lavage fluid has a higher number of inflammatory cytokines and chemokines, such as G-CSF, MCP-1, IL-5, and IL-6. In the βENaC overexpressed mice model, neutrophil extracellular traps were detected in the airways, even when there was no bacterial infection (88). Overexpression of βENaC increases the secretion of inflammatory cytokines and leads to conditions such as cystic fibrosis in mice; inhibition of the ENaC or NLRP3 inflammasome can improve the symptoms (8, 88) (Figure 3). βENaC transgenic mice developed chronic airway inflammation earlier than control group and had higher levels of CXC chemokines, MIP-2 and IL-13 (89). The pulmonary inflammation in mice overexpressing β and γENaC was increased, as evidenced by a significant increase in neutrophils, eosinophils, and lymphocytes (90). The application of antisense oligonucleotides to inhibit the expression of the ENaC in airway epithelial cells can reduce pulmonary inflammation (91). The ENaC is involved in pulmonary inflammation of muco-obstructive lung diseases (92) and acute respiratory distress syndrome (93); in similar molecular mechanisms, azithromycin improves obstructive lung diseases by targeting the ENaC (94).

Inflammatory cytokines can also modulate the ENaC, leading to increased pulmonary inflammation. IL-1α and IL-1β can induce αENaC expression through the NF-kB signaling pathway in mouse lung epithelial cells, where the extracellular signal-regulated kinase (ERK) and mitogen-activated protein kinase (MAPK) signaling pathway also plays a partial role (95). In small airway epithelial cells of mice injected intraperitoneally with high-mobility group box-1 protein (HMGB-1), the open probability of ENaC was increased, and the levels of IL-1β, IL-10, IL-6, IL-27, IL-17A and interferon (IFN)-β were significantly increased in the bronchoalveolar lavage fluid of these mice (96). Transforming growth factor (TGF)-β can mediate the internalization of βENaC through the TGF-β receptor 1 pathway in the alveolar epithelial cells, causing pulmonary edema in acute lung injury (97). TGF-β can inhibit the antioxidant system by internalization of the ENaC, activate the plasminogen activator inhibitor 1 (PAI-1) and NF-kB signaling pathway, and lead to inflammation and injury in the lung (98). ENaC activation can decrease ASL and increase inflammation in the airway. Resolvin D1 is a drug that can inhibit TNFα-mediated inflammation in macrophages; it also inhibits the decrease of ASL caused by ENaC activation while reducing IL-8 secretion by alveolar macrophages and enhancing the phagocytic capacity (99). Resolvin E1 regulates the expression of the ENaC and NKA through the PI3K/AKT/SGK1 signaling pathway that promotes alveolar fluid clearance and reduces inflammation in the lungs (100). T-helper cell type 2 (Th2)-

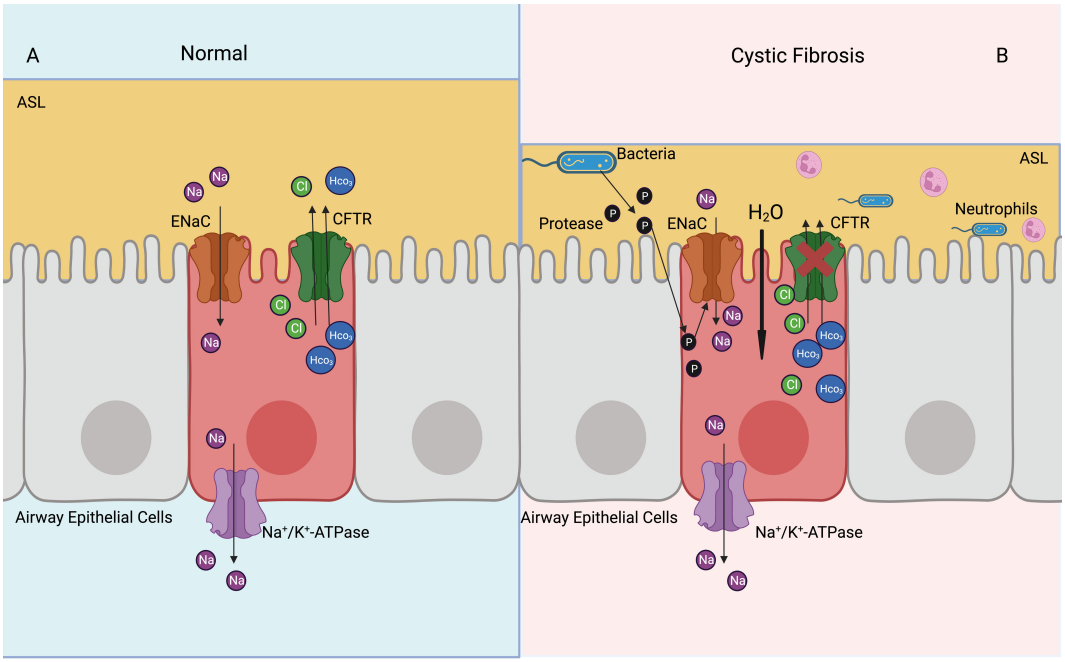

FIGURE 4
Activated ENaC exacerbates cystic fibrosis airway inflammation. **(A)** In the normal airway, ENaC mediates uptake of Na^+ in the airway epithelial cells, CFTR mediates Cl- and HCO_3- outflux, basolateral NKA expels Na^+ out of cells, thus achieving a balance of intracellular ions transport and maintaining ASL normal function. **(B)** In the cystic fibrosis airway, CFTR dysfunction leads to airway bacterial infection and ASL dehydration. Proteases released by bacteria can activate ENaC, which increases Na^+ into airway epithelial cells. Elevated intracellular osmotic pressure promotes moisture absorption, exacerbates ASL dehydration and airway inflammation.

dependent airway inflammation is related to reduced transcript levels of α, β, and γENaC (101).

Nedd4-2 inhibits the function of the ENaC by ubiquitinating lysine residues on the ENaC. Knockdown of Nedd4-2 ubiquitinates leads to increased ENaC activity and aseptic lung inflammation, which may be associated with fetal lethal lung disease (102). Upregulation of ENaC expression via the PI3K/Akt/Nedd4-2 signaling pathway can suppresse lipopolysaccharide-induced inflammation in acute lung injuries (103). Bacterial proteases contribute to increase ENaC activity, promote Na^+ uptake by airway epithelial cells, decrease ASL and mucociliary clearance of airway, and exacerbate pulmonary inflammation (57, 104) (Figure 4).

3.3 Epithelial sodium channel-related inflammation in the kidneys

RAAS activates the ENaC in the collecting duct through increased reactive oxygen species (ROS); in particular, ROS raises PIP3 and decreases inhibition of the ENaC by arachidonic acid (105) (Figure 2). Renal inflammatory cytokines IL-1β, IL-6, TNFα, TGF-β, and collagen III were increased in βENaC knockout mice, and mean arterial blood pressure was elevated (106). When treated with a high salt intake, male db/db mice (a mouse model of obesity and diabetes) show higher renal fibrosis, albuminuria, and inflammatory cytokine expressions, including IL-1b, TNFa, IL-6, and IL-17A, than female mice, which is associated with ENaC dysregulation (107). IL-6 leads to elevated α, β, and γENaC in mouse cortical-collecting duct cells, which suggests that renal inflammation may lead to natriuresis via IL-6 (108). A high salt intake induces increased α and γENaC expression. Intracellular increased Na^+ promotes IsoLG-adduct formation, leading to renal inflammation and hypertension; this process is SGK1 mediated. Inhibition of SGK1 in $CD11c^+$ cells by knockdown or pharmacological inhibition can reduce nicotinamide adenine dinucleotide phosphate oxidase and ENaC expression, which plays a protective role against renal inflammation and hypertension (78, 109). The angiotensin-converting enzyme (ACE) has an important role in regulating Na^+ absorption and diabetic renal inflammation. The ENaC expression is downregulated by 55% in ACE N-domain knockout diabetic mice compared with diabetic wild-type mice; IL-1β and TNFα are downregulated by 55% and 53%, respectively (110). TIP peptide can mimic the lectin-like domain of TNF and activate ENaC by binding α subunit. TIP peptide injected intraperitoneally into nephrotoxic serum nephritis mice reduces glomerular inflammation and proteinuria and decreases Th17 cell infiltration (111).

3.4 Epithelial sodium channel-related inflammation in the colon

IL-13 is increased in ulcerative colitis, which can inhibit the ENaC and SGK1 through the JAK1/2-STAT6-MAPK signaling pathways, and decreases Na^+ reabsorption in the intestinal epithelium (112). Elevated proinflammatory cytokines such as TNFα and IFNγ inhibit β and γENaC expression; therefore, reducing colonic Na^+ absorption leads to diarrhea in ulcerative colitis (113). In campylobacter jejuni-caused enteritis, β and γENaC dysfunction causes Na^+ malabsorption, which leads to diarrhea and increased immune responses, and IFNγ, TNFα, IL-13, and IL-1β expressions are increased, which is confirmed by colonic biopsy (114). Campylobacter concisus downregulates β and γENaC through the IL-32-mediated ERK1/2 signaling pathway, impairs intestinal mucosal barrier function, and leads to inflammation and diarrhea (115). Aldosterone can upregulate γENaC expression through the MEK1/2 signaling pathway; TNFα, IFNγ, and IL-15 impair the promotion of aldosterone to γENaC in lymphocytic colitis, resulting in impaired Na^+ absorption and diarrhea (116). The mechanism of reduced Na^+ absorption in non-inflamed colon is impaired γENaC, which is similar to the mechanism of lymphocytic colitis (117).

3.5 Epithelial sodium channel-related inflammation in tumors

Chronic inflammation plays an important role in tumorigenesis, a high salt intake can lead to a microenvironment of chronic inflammation in tissues, and elevated Na^+ in some tumor cells is associated with ENaC and ASIC overexpression (118). A high salt intake plays an important role in the transmembrane transport of glucose and glutamine, which helps to maintain the high active cellular state of tumor cells and promote tumor growth and metastasis (119). A high salt intake (0.15M NaCl) and IL-17 (0.1 nM) can upregulate γENaC, activate ROS, and reactive nitrogen (RNS), thus promoting the growth of breast cancer cells, and also promote inflammatory cytokine expression such as IL-6 and TNFα (120). However, some studies show that a high expression of αENaC inhibits breast cancer progression and migration, while a low expression of αENaC promotes the proliferation of breast cancer cells (121). The role of ENaC in tumor growth and metastasis has been extensively studied, but the role of ENaC-induced inflammation in tumors is lacking and needs further research.

3.6 Epithelial sodium channel-related inflammation in other areas

PHA is a multisystemic disease caused by ENaC mutations, manifesting as sweat gland duct occlusion and eccrine glands inflammation due to salt accumulation developing into miliaria rubra, folliculitis, and atopic dermatitis-like skin lesions (122). The barrier function disruption of skin epithelium leads to increased Na^+ influx through ENaC, which activates fibroblasts via the COX-2/PGE2 pathway, resulting in fibrosis and the increased secretion of inflammatory cytokines. *In vivo* experiments verified that inhibition of ENaC or COX-2 significantly reduces scar formation (123). In the conditional βENaC meibomian gland knockout mouse model, inflammatory cell infiltration is significantly increased, inflammatory cytokine (IL-1β, IL-8, IL13, and Ym1) expression is significantly higher, and the incidence of other ocular surface diseases

such as corneal opacification, ulceration, neovascularization is increased, which is one of the manifestations of PHA (124).

The ENaC is related to chronic rhinosinusitis, which manifests as significantly decreased α and βENaC mRNA levels in chronic rhinosinusitis patients (125). Lipopolysaccharide injected into the middle ear cavity can decrease ENaC expression and induce middle ear inflammation (126). Transtympanic injection of urban particulate matter leads to inflammatory cell infiltration and increased vascular space in the middle ear, along with decreased ENaC expression, which is associated with development of otitis (127). Inflammation can modulate ENaC-mediated Na^+ uptake in taste buds, IL-1β induces an increase in Na^+ transport, and, conversely, TNFα leads to a decrease in Na^+ transport through the ENaC, which is related to the modulation of taste function during disease to limit Na^+ consumption (128). Curcumin maintains tight junction proteins' integrity, promotes ENaC and NKA expression, and decreases inflammation in hypoxia-induced cerebral edema, as evidenced by decreased NF-kB and inflammatory cytokines (IL-1, IL-2, IL-18, and TNFα) and an increase in anti-inflammatory cytokine (IL-10) expression. Migration of macrophages is important for phagocytosis of pathogens and cellular debris. ENaC promotes the migration and polarization of macrophages and amiloride reduces migration of macrophages by inhibiting the ENaC. Inflammatory cytokines IFNγ and TNFα can reduce the expression of αENaC and decrease the migration of macrophages (129).

4 Conclusions

The ENaC-mediated increase of intracellular Na^+ can further promote Ca^{2+} influx and K^+ efflux; intracellular Ca^{2+} overload activates downstream inflammatory signaling pathways, which is a key pathogenic mechanism of ENaC-related inflammation. There are several posttranslational modifications that have been reported to have a regulatory effect on the ENaC, but more research is still needed to demonstrate the regulatory role of other modifications. ENaC dysfunction disrupts intracellular ion homeostasis; the role of the ENaC on other ions and channels and the consequent changes in physiological function are not well studied. Regulation of ENaC expression by extracellular Na^+ is reversed in the renal epithelium and vascular endothelium; the exact mechanism needs further investigation. The role of ENaC-related inflammation in tumor growth and migration needs further investigation.

Author contributions

YC, XY, and ZY wrote and edited the manuscript. SZ, JZ, and WG designed and guided the study. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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