Mechanisms of ENaC Regulation and Clinical Implications

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ABSTRACT

The epithelial Na⁺ channel (ENaC) transports Na⁺ across tight epithelia, including the distal nephron. Different paradigms of ENaC regulation include extrinsic and intrinsic factors that affect the expression, single-channel properties, and intracellular trafficking of the channel. In particular, recent discoveries highlight new findings regarding proteolytic processing, ubiquitination, and recycling of the channel. Understanding the regulation of this channel is critical to the understanding of various clinical phenomena, including normal physiology and several diseases of kidney and lung epithelia, such as blood pressure (BP) control, edema, and airway fluid clearance. Significant progress has been achieved in this active field of research. Although ENaC is classically thought to be a mediator of BP and volume status through Na⁺ reabsorption in the distal nephron, several studies in animal models highlight important roles for ENaC in lung pathophysiology, including in cystic fibrosis. The purpose of this review is to highlight the various modes and mechanisms of ENaC regulation, with a focus on more recent studies and their clinical implications.


The epithelial Na⁺ channel (ENaC) is expressed at the apical plasma membrane in many epithelial tissues throughout the body, including principal cells in the distal nephron of the kidney and epithelial cells in the urinary bladder, lung airway, distal colon, and ducts of salivary and sweat glands.1 In the kidney, filtered Na⁺ exits the urinary space of the collecting duct by crossing the apical plasma membrane through ENaC, which is the rate-limiting step for salt reabsorption in this segment. Working in conjunction with a basolateral Na⁺/K⁺-ATPase, this channel regulates salt reabsorption and plays a major role in the control of total-body salt and water homeostasis and BP.1,2 In airway epithelial cells, ENaC activity is an important modulator of airway surface liquid clearance. The physiologic importance of this channel is illustrated by naturally occurring ENaC mutations and conditions that cause increased or decreased ENaC activity, such as Liddle syndrome, type I pseudohypoaldosteronism (PHA-I), cystic fibrosis (CF), and high-altitude pulmonary edema.

Since the cloning of ENaC,3,4 major advances have been made in our understanding of the structure and molecular characteristics of the channel. ENaC is composed of three structurally related subunits, termed α-, β-, and γ-ENaC, which are each 85 to 95 kD in size in their unmodified state; however, glycosylation, proteolytic cleavage, and other posttranslational modifications play very important roles in the regulation of ENaC activity and expression (see next section). Each subunit shares approximately 30 to 40% sequence identity with the others and has two presumed membrane-spanning domains, a large extracellular loop, and intracellular N- and C-termini (Figure 1).16–6 ENaC is a member of a gene superfamily that includes genes identified in Caenorhabditis elegans based on mutations that result in mechanosensation defects (mec5) or neurodegeneration (degs)5,7,8 acid-sensing ion channels (ASIC)9,10 and mechanosensitive cation channels present in skin and on cochlear hair cells.11–15 Recent crystallographic data obtained on the related ASIC1 channel suggest ENaC most likely exists functionally as an α, β, γ heterotrimer at the plasma membrane (Figure 1)16; however, it is conceivable that ENaC subunit composition inside cells and at the plasma membrane is not necessarily fixed.17–19

ENaC REGULATION

Given the need for rapid, dynamic changes in salt and water reabsorption and secretion, it is not surprising that ENaC is regulated by a variety of extrinsic and intrinsic factors. The diverse pathways that are important in controlling ENaC activity ultimately impinge on...
one or more of several functional modes of channel regulation, which include the regulation of channel expression/synthesis, intracellular channel trafficking, and single-channel properties such as open probability ($P_o$).1,20

**Extrinsic Factors**

**Hormonal.**

Epithelial Na$^+$ transport is regulated by the action of the volume-regulatory hormones aldosterone, arginine vasopressin (AVP), and atrial natriuretic peptide (ANP), as well as other hormones such as insulin and endothelin.1,20 Increased apical targeting of ENaC subunits, although induced primarily by aldosterone-induced mineralocorticoid receptor (MR) action, also occur through MR-independent mechanisms. In addition, chronic AVP treatment upregulates distinct ENaC subunits, while not affecting subcellular localization of ENaC, as seen acutely with second messengers of the AVP response. Hormonal regulation of ENaC occurs through receptor-mediated modulation of intracellular signaling pathways involving various kinase cascades, such as stimulation of serum and glucocorticoid-regulated kinase (SGK1) or inhibition of extracellular signal–regulated kinase (ERK) in the case of aldosterone, protein kinase A for AVP and ANP regulation, phosphatidylinositol 3-kinase–dependent signaling for insulin, and SRC family kinases in the endothelin regulatory pathway.

**Mechanical and Cytoskeletal Activity.**

There is growing evidence that ENaC is a mechanosensitive channel. Mechanosensitivity of ENaC is not unexpected given its close phylogenetic relationship to other, more recognized mechanosensitive channels such as Mecs and Degr. Indeed, ENaC subunits are found in nonepithelial tissues and mediate mechanosensation. For example, ENaC activation by mechanical stress or cell swelling remains controversial; however, laminar shear stress induced by fluid flow under physiologically relevant conditions elegantly activates ENaC in isolated rabbit collecting ducts in vivo and in ENaC-expressing Xenopus oocytes. Shear force–induced ENaC activation is mediated by an increase in $P_o$ and is not affected by changes in [Ca$^{2+}$] or membrane trafficking. It has been proposed that large extracellular loops of ENaC function as antennae that are deflected by shear stress, transducing flow stimuli to the channel gating region. Finally, the cytoskeleton regulates ENaC, as the COOH-terminus of α-ENaC interacts directly with the actin cytoskeleton, and ENaC activity is enhanced by actin-disrupting agents.

**Proteolytic Cleavage.**

There has been a recent flurry of investigations into the regulation of ENaC activity through cleavage by intracellular and extracellular proteases. The first observation that ENaC is regulated by endogenous serine proteases was made using Xenopus A6 collecting duct cells, in which it was found that the general protease inhibitor aprotinin partially blocks amiloride-sensitive Na$^+$ uptake. Expression cloning was used to identify channel-activating peptide 1, also called prostatin, as a factor that augments ENaC currents when coexpressed in oocytes. Similar effects are observed through addition of trypsin in mouse collecting duct M-1 cells. Masilamani et al. found direct biochemical evidence for cleavage, showing the apparent molecular weight of the γ subunit shifts from approximately 85 to approximately 70 kD in rats treated with aldosterone or a low-salt diet.

ENaC activation by proteolytic cleavage was elegantly shown through patch-clamp studies to confer dramatic increases in single-channel $P_o$ of previously “near-silent” channels at the plasma membrane. At approximately that time, it was reported that furin, a member of the pro-protein convertase family, thought to reside in the trans-Golgi network, was important in cleaving the α subunit at two sites and the γ subunit at one site in the extracellular loops (ECL). Furin-mediated cleavage of α-ENaC activates ENaC by releasing an inhibitory peptide from the ECL. Furin–dependent proteolysis of α-ENaC activates the channel by relieving Na$^+$ self-inhibition (see Intrinsic Factors be-

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Figure 1. ENaC architecture: Structural features of the epithelial sodium channel. As predicted by Jasti et al., ENaC may exist as a heterotrimer with a single α, β, and γ subunit. Each subunit has two membrane-spanning domains (M1 and M2) with intracellular N- and C-termini. The β and γ subunits each contain a canonical “PY” motif in their COOH-termini. See text for details.
low), thereby increasing Na\(^+\) transport at higher extracellular Na\(^+\) concentrations.\(^{84}\) Recently, it was also shown that prostanin, likely present in the extracellular apical compartment, also cleaves γ-ENaC at a site in the ECL near furin cleavage sites, which as with the dual furin cleavage sites in α-ENaC, releases an inhibitory peptide that further activates ENaC.\(^{55}\) Proteolysis of the channel per se is not strictly necessary for activation, because deletion of these inhibitory tracts in α and γ subunits is sufficient to enhance channel activity without any cleavage. Moreover, addition of the inhibitory peptides to wild-type ENaC confers inhibition of the channel.\(^{53,56}\)

Both processed (complex glycosylated with cleaved subunits; active) and nonprocessed (noncleaved; inactive) forms of ENaC subunits exist in cells and tissues expressing endogenous ENaC.\(^{17,51,57}\) Inactive, near-silent channels at the cell surface are probably uncleaved and may serve as a channel pool that can be activated by extracellular proteases. Recent evidence suggests the extent of ENaC proteolysis is dependent on channel residency time in the plasma membrane, because channels with mutations that block ubiquitin-dependent endocytosis remain on the surface longer, have an increased proportion of mature (cleaved) subunits, and have a correspondingly higher activity.\(^{58}\) At least another level of regulation exists as a result of the presence of endogenous protease inhibitors, such as protease nexin 1.\(^{39}\) Indeed, recent studies suggest the proteolytic state of ENaC subunits reflect a net balance between the expression of activating proteases and protease inhibitors.\(^{60}\) ENaC regulation by proteases and protease inhibitors is likely to be physiologically significant in several organs, including lung and kidney. Of note, this balance may play an important role in the pathogenesis of CF lung disease (see the Clinical Correlations section).

**Intrinsic Factors**

**ENaC Trafficking.**

Several new communications shed light on how ENaC traffics to and from the plasma membrane. Composite channels made of multiple ENaC subunits are synthesized and modified along the biosynthetic pathway en route to the apical plasma membrane.\(^{51,52,61,62}\) ENaC is retrieved from the plasma membrane in clathrin-coated vesicles\(^{63,64}\) and may then be shuttled to the lysosome for degradation or recycled back to the plasma membrane.\(^{65}\)

Only a minority of ENaC channels reside in the apical plasma membrane,\(^{66-68}\) but ENaC surface expression may be rapidly increased. Stimulation of apical ENaC by cAMP is demonstrable in cells,\(^{66}\) but the origin of these channels is still controversial. Lu et al.,\(^{67}\) using live-cell imaging and immunocytochemistry with overexpressed ENaC in polarized MDCK cells, posited that a large pool of synthesized, intact channels rest in a sub-apical compartment available for rapid transit to the apical membrane. Conversely, an elegant study by Butterworth et al.,\(^{68}\) examining endogenous channels in mouse polarized cortical collecting duct (CCD) cells, argued that a recycling pool of channels is responsible for rapid replenishment of Na\(^+\) transport. Several other studies also addressed apical insertion of ENaC. A small portion of ENaC channels in CCD cells are resident within lipid rafts, and this pool may be part of the biosynthetic pathway.\(^{69}\) In addition, heat-shock proteins, known to promote apical expression of the CFTR Cl\(^-\) channel, stimulate plasma membrane insertion of ENaC.\(^{70,71}\) Similarly, other components of the biosynthetic pathway that alter biogenesis of ENaC have now been identified.\(^{72,73}\)

Surface ENaC is internalized, but its paths and modes of degradation are still not clear. In CCD cells, ENaC is endocytosed through clathrin-coated pits into early endosomes within minutes.\(^{64}\) This process is dependent on ENaC binding to epsin through phosphoinositides at the plasma membrane.\(^{74}\) Overexpressed ENaC has also been localized separately to recycling endosomes and late endosomes.\(^{67}\) Saxena et al.,\(^{75-79}\) contended that ENaC is present in multiple endocytic compartments, which are coordinated by sorting machinery, including syntaxin 1A as well as several Rab GTPases. Several studies using heterologous expression suggested that ENaC is sorted to lysosomes for degradation, but other studies of endogenous ENaC have demonstrated only proteasomal degradation.\(^{80-82}\)

**Nedd4-2 and ENaC Ubiquitination/Deubiquitination.**

Liddle syndrome is caused by one of several mutations in the COOH-terminal tails of β- or γ-ENaC\(^{83}\) and is responsible for gain-of-function of these channels (see the Clinical Correlations section). These mutations uniformly decrease interaction with the ubiquitin-protein ligase Nedd4-2.\(^{84}\) Several recent discoveries regarding Nedd4-2 and ENaC are noteworthy: Nedd4-2 ubiquitinates surface ENaC,\(^{85}\) this ubiquitination is necessary but not sufficient for endocytosis of the channel,\(^{85,86}\) disruption of this interaction primarily affects internalization of the channel,\(^{67}\) and ubiquitination of the channel marks it for degradation.\(^{80,85}\) As a potent inhibitor of sodium transport, the cellular pathways that affect ENaC through regulation of Nedd4-2 are also well documented. Three primary mechanisms include phosphorylation, feedback inhibition by intracellular Na\(^+\), \(^{87}\) and dietary sodium intake (likely through aldosterone).\(^{88}\)

ENaC is mono- or polyubiquitinated (linked chains of ubiquitin) at multiple residues.\(^{72,83,85}\) Interpretation of various studies is complicated because some are performed using cultured cells that endogenously express ENaC or are modified to overexpress the channel. A recent study by Weimuth et al.\(^{82}\) suggested ENaC, similar to other membrane proteins, is monoubiquitinated at the cell surface, which targets ENaC for lysosomal degradation.\(^{65}\) Conversely, polyubiquitinated ENaC may be derived from the large proportion of synthesized channels that never reach the apical membrane and are targeted for proteosomal degradation. Biochemical studies to date have not been able to discern whether either of these modes of regulation can distinguish between mature or immature ENaC (i.e., proteolytically cleaved or uncleaved channels) and
whether ubiquitin ligases other than Nedd4-2 are involved.

Further evidence for the importance of ENaC ubiquitination comes from two studies that highlighted reversal of the ubiquitination process (de-ubiquitination) as another mode of ENaC regulation. In CCD cells, Usp-45, a de-ubiquitinating enzyme, is potently up-regulated by aldosterone and reverses the inhibitory effects of Nedd4-2 on ENaC retrieval.\cite{98,99} UCH-L3 is also identified in CCD cells to de-ubiquitinate ENaC and enhance rapid recycling of ENaC to the apical plasma membrane.\cite{100} UCH-L3 is localized to early endosomes, arguing that it plays a direct role in modifying Nedd4-2–dependent, ubiquitinated ENaC upon retrieval from the plasma membrane.

\section*{Na\textsuperscript{+} Self-Inhibition and Feedback Inhibition}

ENaC activity is regulated by changes in both extracellular and intracellular [Na\textsuperscript{+}]. A fast change (over seconds) in channel activity as a result of changes in extracellular [Na\textsuperscript{+}] is known as Na\textsuperscript{+} self-inhibition.\cite{101} This process is steeply temperature dependent, and treatment with external trypsin blunts the self-inhibition effect, suggesting intrinsic channel cleavage relieves Na\textsuperscript{+} self-inhibition.\cite{102} Additional work by Sheng et al.\cite{103} identified key ECL histidine residues that modulate Na\textsuperscript{+} self-inhibition, which are interestingly located near furin cleavage sites in the α and γ subunits of ENaC (see Intrinsic Factors above). Noncleaved channels have a low intrinsic $P_o$ that results from enhanced channel inhibition by external Na\textsuperscript{+}.\cite{104}

Feedback inhibition, a slower change (over hours) in channel activity caused by increased intracellular [Na\textsuperscript{+}], was first described in 1961 by MacRobbie and Ussing.\cite{105} Epithelial cells exposed to inhibitors of the Na\textsuperscript{+}/K\textsuperscript{+}-ATPase did not swell from continued Na\textsuperscript{+} influx. Recent investigations demonstrated that increases in Na\textsuperscript{+} influx leading to elevated intracellular [Na\textsuperscript{+}] indirectly downregulate ENaC activity.\cite{106} Gain-of-function Liddle mutations in ENaC may operate by decreasing feedback inhibition, thereby enhancing ENaC activity.\cite{107,108} Nedd4-mediated ubiquitination, altered in the Liddle phenotype, mediates this effect.\cite{109} Thus, acute changes in [Na\textsuperscript{+}] affect open probability, whereas chronic changes in [Na\textsuperscript{+}] affect trafficking.

Both self-inhibition and Na\textsuperscript{+} feedback are likely important physiologically in limiting Na\textsuperscript{+} absorption under conditions of high salt delivery, thereby mitigating large changes in intracellular [Na\textsuperscript{+}] and epithelial cell volume.\cite{110,111} In addition, Kellenberger et al.\cite{112} described that the effects of Liddle mutants on ENaC trafficking occur only in the presence of high Na\textsuperscript{+} influx; that is, wild-type and Liddle mutant channels had equivalent ENaC activity when incubated in a low-Na\textsuperscript{+} bath. This finding could explain why patients with Liddle syndrome lack respiratory manifestations, because broad ranges in luminal airway [Na\textsuperscript{+}] are not as evident as in the distal nephron.

\section*{Phosphorylation}

Phosphorylation of ENaC was first described by Shimkets et al.\cite{113} as a possible mode of its hormone-mediated regulation. Aldosterone- and insulin-mediated regulation of ENaC occurs through SGK1-mediated inhibition of Nedd4-2.\cite{114,115} Since these initial discoveries, a complex array of kinases has been shown to regulate ENaC directly and indirectly. For the purposes of this review, only recent discoveries are discussed.

ERK2 and casein kinase 2 (CK2) directly phosphorylate the COOH-termini of β- and γ-ENaC and promote Nedd4-2-mediated ENaC internalization.\cite{116,117} Protein kinase C (PKC), which may be stimulated through extracellular purinergic receptor activation, inhibits both ENaC $P_o$ and surface expression by signaling through the mitogen-activated protein kinase/ERK pathway.\cite{118,119} A recently discovered functional polymorphism in the COOH-terminal tail of human α-ENaC also prompted investigation of its regulation by kinase-mediated changes in ENaC trafficking.\cite{120} The COOH-terminal tail of α-ENaC is regulated by CK1 or PKC-δ to increase insertion of channels in the plasma membrane.\cite{121,122} SGK1 also directly phosphorylates and stimulates α-ENaC.\cite{123} The G-protein–coupled receptor kinase GRK2, which is implicated in cases of human hypertension, disrupts Nedd4-2–ENaC interaction by direct phosphorylation of the COOH-terminal tail of β-ENaC.\cite{124}

Kinases that indirectly regulate ENaC trafficking are also noteworthy. 1kB kinase–β interacts with ENaC to upregulate cell surface expression and Na\textsuperscript{+} current in CCD cells.\cite{125} With No lysines [K] (WNK1) was recently demonstrated to alter SGK1 activity and hence stimulate ENaC. Akt (similar to SGK1) also disrupts ENaC–Nedd4-2 binding and hence stimulates ENaC-mediated Na\textsuperscript{+} current in response to insulin.\cite{126} Protein kinase A was shown previously to inhibit Nedd4-2\textsuperscript{Δ} (similar to SGK1) but has also now been suggested to modulate tyrosine kinase activity to increase apical expression of ENaC.\cite{127} Protein kinase D also rapidly promotes insertion of ENaC into the plasma membrane.\cite{128} The metabolic sensor AMP-activated kinase (AMPK), which is sensitive to a host of external stimuli and intracellular energy stores, indirectly inhibits ENaC surface expression by promoting an interaction between Nedd4-2 and ENaC.\cite{129,130} Interestingly, phosphatidylinositol 3-kinase influences both ENaC trafficking (through SGK1 and/or Akt) and $P_o$.\cite{131}

These myriad signaling pathways demonstrate a complex regulatory network that directly and indirectly influences ENaC surface expression and $P_o$. Such mechanisms are likely operative in acute, subacute, and chronic changes in ENaC regulation. Further study is warranted to determine how many of these pathways alter Na\textsuperscript{+} transport in vivo.

\section*{Metabolic Depletion and pH.}

It has long been recognized that inhibition of cellular metabolism through depletion of metabolic substrates\cite{132,133} and hypoxia\cite{134,135} inhibits apical Na\textsuperscript{+} channel activity in epithelia, but the underlying mechanisms involved in this inhibition are unclear. Several ion transport proteins are downregulated by depletion of energy substrates, particularly ATP. The metabolic sensor AMPK is
implicated in several of these transport proteins, reviewed elsewhere.\textsuperscript{124} We propose that AMPK plays an important role in this ENaC-metabolism coupling process and represents another mode of intrinsic regulation of the channel. Intracellular acidification also inhibits \(\alpha\)-ENaC, and intracellular alkalinization stimulates ENaC activity through an increase in \(P_e\).\textsuperscript{125,126} Hypoxia also has direct effects on expression of ENaC subunits and activity in rodent airway epithelial cells.\textsuperscript{127,128} Further clinical correlations of these phenomena are warranted to ascertain their physiologic or pathophysiologic importance. A schematic working model of the regulation of ENaC by various signaling pathways is shown in Figure 2.

**Clinical Correlations**

The importance of ENaC is underscored by continued discoveries of the relevance of ENaC activity in renal, gastrointestinal, and pulmonary physiology (Figure 3).

**Kidney.** ENaC gain-of-function mutations in patients with Liddle syndrome lead to volume expansion, hypertension, hypokalemia, low aldosterone levels, and metabolic alkalosis.\textsuperscript{83,129–131} ENaC loss-of-function mutations are found in patients with PHA-I, a disorder characterized by volume depletion, hypotension, and hyperkalemia.\textsuperscript{132–134} Recent molecular studies also implicated ENaC in PHA-II, but this has not been confirmed \textit{in vivo}.\textsuperscript{135}

The importance of ENaC in the genesis of essential hypertension has also been explored in subsets of the population. Several studies showed single-nucleotide polymorphisms (SNP) and sensitivity to amiloride associated with hypertension among African-American individuals\textsuperscript{136–139} (reviewed elsewhere\textsuperscript{140}). The most detailed correlation between SNP and ENaC function is the Thr663Ala polymorphism in \(\beta\)-ENaC. This variant is more common among white individuals and segregates with a lack of hypertension among African-American individuals.\textsuperscript{106} The amino acid substitution may be a site for threonine phosphorylation by either PKC-\(\delta\) or CK1\textsuperscript{107,108} to regulate the intracellular trafficking of the channel. Despite these attempts to correlate the molecular mechanisms of a given SNP with BP, different investigators have reached differing conclusions about the significance of this mutation, demonstrating the difficulty in proving a cause-and-effect relationship in ENaC polymorphisms for essential hypertension.

Pathophysiologic implications of ENaC trafficking in diabetes and fluid overload states were examined recently in animal models. Insulin increases apical targeting of distinct ENaC subunits after acute treatment. Chronic hyperinsulinemia is associated with antinatriuresis, but increased ENaC activity in models of type II diabetes has not yet been demonstrated.\textsuperscript{141} Two models of hyperinsulinemia and hypertension in mice reveal a role for insulin-dependent SGK1 activation and ENaC-mediated sodium reabsorption.\textsuperscript{142,143} Increased apical targeting of ENaC subunits is seen in sodium avid states such as certain models of nephrotic syndrome or cirrhosis.\textsuperscript{144–146}

![Figure 2. Modes of ENaC regulation. The various mechanisms of ENaC regulation can be divided into extrinsic and intrinsic mechanisms. Extrinsic regulation of the channel may be due to hormone activation, mechanical stretch, and/or proteolytic cleavage. Intrinsic regulation may be due to intracellular trafficking, ubiquitination, various kinases, sodium, and metabolic substrates. Several examples of each are delineated in the text.](image)

![Figure 3. Clinical correlations of ENaC regulation. ENaC has been well characterized as a regulator of volume status and BP, but more recent studies have demonstrated its role in edema formation and gastrointestinal and respiratory disorders, including CF, neonatal respiratory distress syndrome, and high-altitude pulmonary edema.](image)
DISCUSSIONS

None.

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Colon.
Inhibition of sodium and chloride absorption in the colon is important for diarrheal disorders such as CF and ulcerative colitis. Decreased expression of ENaC subunits in human biopsy samples from patients with colitis is a mechanism, but further studies are warranted.

Lung.
The importance of ENaC in the regulation of airway surface liquid volume is suggested by the finding that loss-of-function mutations in PHA-I are associated with neonatal respiratory distress syndrome. The mechanism of respiratory distress is believed to be increased pulmonary edema from decreased Na+ absorption through alveolar ENaC. Hypoxemia decreases ENaC expression in nongenetic forms of this disorder among premature infants. In addition to effects on surfactant production, dexamethasone may resolve this condition by counteracting hypoxia-induced decreases in ENaC. Decreased ENaC activity in the lung is also seen in patients susceptible to high-altitude pulmonary edema. A potential therapeutic role for ENaC modulation in the acute respiratory distress syndrome is also being explored.

A direct role of ENaC in pulmonary edema is seen in rodents. Mice carrying null alleles for α-ENaC are unable to clear fluid from their airways at the time of birth and died within 40 h after delivery from lethal respiratory distress syndrome. Conversely, gain of ENaC function as a result of loss of its normal regulation by CFTR in the airways of patients with CF is a major contributing factor in the pathogenesis of CF airway disease. Indeed, a β-ENaC transgenic lung mouse model revealed overexpression of ENaC is sufficient to recapitulate the CF lung phenotype of decreased airway surface liquid volume and increased airway inflammation.

CONCLUSIONS

ENaC activity has several physiologic and pathophysiologic implications, and its regulation is complex. Several extrinsic and intrinsic motifs are now known in this regulatory network, and, most recently, exciting discoveries in cellular and animal models have been made in the proteolytic processing and intracellular trafficking of the channel. Although several common disease states now implicate this channel, further research is needed to elucidate how these various regulators of ENaC affect human physiology.
BRIEF REVIEW

Mechanisms of ENaC Regulation


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