Acid-sensing ion channels (ASICs) are proton-gated cation channels that are widely expressed in both the peripheral and central nervous systems. ASICs contribute to a variety of pathophysiological conditions that involve tissue acidosis, such as ischemic stroke, epileptic seizures and multiple sclerosis. Although much progress has been made in researching the structure-function relationship and pharmacology of ASICs, little is known about the trafficking of ASICs and its contribution to ASIC function. The recent identification of the mechanism of membrane insertion and endocytosis of ASIC1a highlights the emerging role of ASIC trafficking in regulating its pathophysiological functions. In this review, we summarize the recent advances and discuss future directions on this topic.

Introduction

Acid-sensing ion channels (ASICs) are a proton-gated subgroup of the degenerin/epithelial Na$^+$ channel (DEG/ENaC) family of cation channels, which are trimeric protein complexes composed of different combinations of subunits. To date, 6 ASIC isoforms (ASIC1a, 1b, 2a, 2b, 3 and 4) arising from 4 genes (Accn1, 2, 3 and 4) have been identified. ASICs are expressed in both the peripheral and central nervous systems. ASIC1a, 2a and 2b are the major isoforms in the brain and spinal cord; whereas the expression of ASIC1b and ASIC3 is restricted to peripheral sensory neurons. As the key receptors for extracellular protons, ASICs have been implicated in many pathophysiological processes related to acidosis, such as pain, ischemic stroke, and fear/anxiety-related psychiatric disorders. The function of ASICs in these processes depends on the number of channels on the cell surface. Thus, the dynamic control of surface ASICs under normal and pathological conditions is currently being researched.

The number and function of receptors on the plasma membrane is partially determined by the dynamic trafficking processes, which include sorting and forward trafficking of receptors from the endoplasmic reticulum (ER) through the Golgi apparatus to the plasma membrane; endocytosis of surface receptors; resorting of receptors following endocytosis; recycling of receptors back to the plasma membrane; and targeting receptors for degradation. Elucidating the detailed molecular mechanisms that govern ASIC trafficking will improve our understanding of their pathophysiological functions in the brain.

Recent Advances in ASIC Trafficking

Defects in trafficking cause the dysfunction of ion channels, and ultimately lead to a variety of disorders. ENaCs share substantial homology with ASICs. Disruption of ENaC endocytosis, which is primarily regulated by Nedd4–2, an E3 ubiquitin ligase, has been shown to be involved in Liddle syndrome. However, it is not yet known whether the same trafficking pathways regulate ASICs or if other mechanisms are involved. Cumulative evidence indicates that the function of these channels can be increased or decreased by modulating the level of trafficking-related proteins or mutating their trafficking motifs, both of which are discussed below.

PICK1 and ASIC trafficking

Protein-interacting with C kinase-1 (PICK1) regulates the trafficking of multiple membrane proteins, and is an established ASIC binding partner that binds to the C-terminus of ASICs via its PDZ domain. It has long been speculated that PICK1 plays a role in the trafficking of ASICs. Recent evidence has shown that the genetic disruption of PICK1 leads to a decreased plasma membrane level of ASIC1 and ASIC2a, which attenuates the function of ASICs in mouse cortical neurons. This work indicates a possible regulatory role of PICK1 in ASIC trafficking. Further supporting evidence shows that overexpression of PICK1 increases the surface level of ASIC1a and ASIC1a-mediated acidotoxicity via interactions with the PICK1 BAR and lipid binding domain. However, more details regarding the exact process of PICK1-mediated ASIC trafficking are yet to be elucidated. PICK1 can facilitate either endocytosis or exocytosis of its binding partners, depending on the distribution of these proteins in different pools and the nature of the stimulation. For instance, PICK1 increases the surface expression of dopamine transporters (DATs) and enhances DAT uptake activity, which is similar to the effects of PICK1 on ASICs. In contrast, overexpression of PICK1 decreases the surface expression of AMPA receptors through calcium-dependent endocytosis. A model that...
incorporates these differences is that PICK1 may maintain an intracellular reserve pool of membrane proteins, which engages in exchanging with cell surface proteins in a regulated manner. It would be interesting to determine whether PICK1-mediated trafficking of ASICs is regulated by a similar mechanism.

**The role of the ASIC extracellular domain in channel maturation and trafficking**

The large extracellular domain of ASICs (~318 of the 528 residues in ASIC1a) has led to the speculation that it may have additional functions besides sensing protons. The trafficking of membrane proteins is tightly controlled by post-translational modification and protein maturation. As the most common type of modification, glycosylation through the secretory pathway, plays an important role in the maturation and trafficking of proteins within the cell. Jing et al. carried out studies to assess the role of N-glycosylation in the biogenesis and surface expression of ASICs. They found that the surface fraction of ASIC1a in the mouse brain contains a higher percentage of EndoH-resistant mature N-linked glycans than cytoplasmic ASIC1a, which indicates that mature ASIC1a is preferentially transported to the cell surface. Furthermore, they found that the extracellular asparagine site at 393 (Asn393; Fig. 1), but not those at other sites, was preferentially processed in middle-to-late Golgi; whereas mutation of Asn393 (N393Q) reduced ASIC1a maturation and surface expression. Importantly, inhibition of glycosylation with tunicamycin or by N393Q mutation reduced ASIC1a dendritic targeting; moreover, the N393Q mutation caused ASIC1a to be resistant to acidosis-induced spine loss. These findings suggest that glycosylation of ASICs has an important role in regulating synaptic morphogenesis and determining long-term consequences in tissue acidosis. Consistent with a previous study, the Asn393 site, located between the α6 and α7 helices in the crystal structure, is conserved among all ASICs. In addition to conventional trafficking signals that are composed typically of short linear peptide sequences, the tertiary structure, within the extracellular domain of ASICs, can form a signal patch for trafficking. In support of this hypothesis, Jing et al. showed that mutations of Tyr71 (Y71G) and Trp287 (W287G; Fig. 1), involved in the TM1-thumb interaction, decreased the surface expression and dendritic targeting of ASIC1a. In a separate study, a highly conserved salt bridge at the extracellular loop (D107-R153 of rat ASIC3, and D107-R160 of human ASIC1a; Fig. 1), which stabilizes a rigid signal patch, was found to be critical for surface expression of ASICs. These data indicate that both the post-translational modification sites and tertiary structure within the extracellular domains regulate ASIC trafficking.

**The emerging role of ASIC1a dynamic trafficking**

Our recent studies have demonstrated the molecular mechanism of ASIC1a dynamic trafficking and its pathophysiological role (Fig. 2). We found that application of brain-derived neurotrophic factor (BDNF) upregulates ASIC1a channel activity in cultured mouse spinal dorsal horn (SDH) neurons and that ASIC1a is required for sustained BDNF-induced mechanical hyperalgesia. BDNF sensitizes ASIC1a function through enhancing its forward trafficking and surface expression via the downstream tropomyosin-related kinase B (TrkB)-phosphoinositide 3 kinase (PI3K)-protein kinase B (PKB/Akt) cascade and phosphorylation of the cytoplasmic residue Ser25 of ASIC1a. Moreover, this enhancement is required for BDNF-mediated hypersensitivity of SDH nociceptive neurons and central mechanical hyperalgesia in rat and mouse models. We further demonstrated that this process was abolished by intrathecal application of a peptide representing the N-terminal region of ASIC1a encompassing Ser25. These results reveal a novel mechanism underlying ASIC1a forward trafficking, and indicate that targeting specific trafficking process of pain-facilitating receptors may more efficiently treat chronic pain. In the future, it will be interesting to examine whether this regulatory signaling pathway of ASICs is involved in other physiological or pathological conditions.

In contrast to the regulation of ASIC surface expression, the endocytosis of ASIC channels is not well understood. Given that epithelial sodium channels (ENaCs), which have substantial homology with the ASIC family, are regulated by clathrin-dependent endocytosis, and their dysfunction leads to Liddle syndrome; we speculated that ASICs are also regulated by the same pathway. As expected, we found that ASIC1a is associated with several subunits of adaptor
protein 2 (AP2) and undergoes constitutive endocytosis in a clathrin- and dynamin-dependent manner in both mouse cortical neurons and heterologous cell cultures. We have further shown that the membrane-proximal residues LCRRG, located at the cytoplasmic C-terminus of ASIC1a, are critical for interaction with the endogenous adaptor protein complex. Endocytic pathway dysfunctions have been found in various neurodegenerative disorders, such as Alzheimer disease, lateral sclerosis, and ischemia. In light of these studies, we hypothesized that dysfunction of ASIC1a endocytosis in neurodegeneration may exacerbate acidosis-induced neuronal injury. In our in vitro model of acidosis-induced neuronal death, inhibition of ASIC1a internalization by dynasore, a small inhibitor of dynamin, strongly exacerbated the acidosis-induced death of cortical neurons from wild-type, but not from ASIC1a knock-out mice.23 Our results indicate the importance of endocytic pathways in acidosis-induced neuronal death and suggest that this regulation is mediated mainly via membrane retention of ASIC1a proteins (Fig. 2).

Constitutive Trafficking of ASICs

As membrane proteins, ASICs undergo constitutive trafficking. To date, their trafficking motifs and pathway-specific accessory proteins remain largely unknown. Investigating the constitutive trafficking cascade of ASICs will help us to understand the molecular mechanisms that regulate these channels and provide potential targets for preventing acidosis-induced cell death.30 In this section, we summarize the current knowledge about trafficking motifs and accessory proteins of ASICs that have a profound influence on their constitutive trafficking processes.

Trafficiﬁng motifs within the cytoplasmic domain of ASICs

Motifs within the cytoplasmic domains of membrane proteins play important roles in regulating their biogenesis, surface expression and trafficking through interactions with different accessory proteins.31 The type of motif varies among different trafficking pathways. For instance, the di-acidic motifs [(D/E)X(D/E)], di-hydrophobic motifs (FF, YY, LL or FY), YXXNPF and LXXLE are ER-exit signals that play a role in the transport of specific cargo from the ER exit sites31,32; whereas the KDEL, di-lysine (KK) and RXR motifs lead to ER retention32; and the di-leucine (LL) and tyrosine-based (YXXΦ, where Φ is a hydrophobic amino acid) motifs are canonical signals for clathrin-mediated endocytosis.33,34 Investigations are currently underway to unravel the trafficking motifs within ASICs. Several motifs within the cytoplasmic domains of ASIC1a are critical for its channel gating and surface expression. The N-termini of ASICs contain 2 highly conserved channel gating motifs. Mutation of the HIF motif (Fig. 1) abolished the proton-gated current density,37 without affecting the surface expression of ASIC1a. In addition, the HG motif (Fig. 1) is completely conserved among ENaC family members and mutating it reduces the open probability of ENaC channels.35,36 Although it is yet unknown whether the HG motif is also involved in the functional properties of ASICs, it is possible that the N-terminus of ASIC1a contains multiple channel gating motifs. In contrast, cumulative evidence shows that the trafficking motifs are located within the C-terminus of ASIC1a. All ASICs contain a PDZ-binding motif at the end of their C-termini that regulates ASIC surface expression and channel activity through interacting with several PDZ-domain proteins.9–11 In accordance with a previous study in which coexpression of postsynaptic density protein 95 (PSD95) and ASIC3 reduced the amplitude of ASIC3 proton-gated currents,38 mutating the PDZ-binding motif of ASIC1a (Fig. 1) increased its surface expression and current density.39 These data suggest that the regulation of trafficking by PDZ-binding proteins is conserved.
among ASICs. We then wanted to find out whether ASICs contained isoform-specific trafficking motifs. By thoroughly scanning the C-terminus of ASIC1a, we found that the membrane-proximal residues LCRRG, at the cytoplasmic C-terminus, are critical for surface expression (unpublished data) and responsible for the interaction with AP2, which regulates the constitutive endocytosis of ASIC1a in both mouse cortical neurons and heterologous cell cultures. Consistent with our observation, Jing et al. showed that mutating the positively-charged amino acids that overlap the LCRRG motif (from RRGK to AAGA), or deleting these residues, significantly reduced ASIC1a surface expression and proton-gated current density. Among ASIC isoforms in higher vertebrates, the LCRRG motif is unique for ASIC1a/1b, indicating that these residues act as an ASIC1a/1b-specific regulatory motif through recruiting distinctive trafficking machineries. In addition, mutating the KEAKR motif (from KEAKR to AEAAG), located next to the LCRRG motif of ASIC1a (Fig. 1), has similar effects. These data suggest that the K/R motif on the C-terminus of ASIC1a plays a critical role in the regulation of channel trafficking. Because the total protein level of ASIC1a in wild-type and RRGK/KEAKR mutants remains unchanged, it appears that these mutations do not affect the stability of the protein or protein degradation pathways. The ASIC1a C-terminal juxtamembranous motif is localized for optimal interaction with the membranous protein dynamin and the AP2 complex. It will therefore be interesting to identify the binding partners and elucidate the exact functions of these cytosolic K/R motifs in future studies.

Accessory proteins of ASICs

Several lines of evidence have shown that accessory proteins can regulate the constitutive trafficking of ASICs (summarized in Table 1). Although we are continually adding to our knowledge of ASIC accessory proteins, some questions remain unclear. Further in vitro evidence of the binding and regulatory effects of these accessory proteins on ASICs under various pathophysiological conditions is needed. For example, understanding which interactions happen in vivo, which trafficking processes involved, and what’s the pathophysiological consequence will undoubtedly advance our understanding of the pathophysiological role of ASICs.

Regulated Trafficking of ASICs

It is now well documented that membrane proteins, especially ion channels, receptors, and transporters, expressed at the surface, undergo both constitutive and regulated trafficking, which act cooperatively to achieve homeostasis and/or plasticity in response to different environmental changes. Indeed, dynamic regulation of the rate of either insertion or retrieval (or both) of integral membrane proteins in response to stimuli embodies the strategic regulation of their surface expression. Examples of receptors and transporters whose trafficking is modulated by stimuli or neuronal activity are the G protein-activated inwardly rectifying K+ channels, dopamine D2 receptors, ENaCs, cystic fibrosis transmembrane conductance regulator, as well as ionotropic ligand-gated receptors such as AMPA receptors, NMDA receptors, GABA receptors, and the purinergic receptor P2X4. Interestingly, several studies have demonstrated that regulated trafficking is also commonly used by ASICs for modulation of their physiological function. In this section, we will discuss the regulatory pathways of ASIC trafficking and its pathophysiological roles, with particular emphasis on ASIC1a.

The insulin pathway

Insulin depletion has been shown to increase ASIC1a surface expression and proton-gated current density, without affecting ASIC2a, in cultured neurons and Chinese hamster ovary cells. Cerebral ischemia results in reduced blood flow and delivery of insulin to the damaged brain region, and therefore the effect of insulin on ASIC1a expression observed in vitro is relevant to the pathogenesis of the stroke. However, more evidence is needed to elucidate the underlying mechanism. Insulin activates the insulin receptor (IR) tyrosine kinase, which results in the activation of several signaling pathways, including P13K/Akt, mitogen-activated protein kinase, and Cbl/CAP pathway. Insulin

Table 1. Accessory proteins that regulate trafficking of ASICs

| Accessory proteins | ASIC isoforms | Interaction sites | Surface expression | Refs |
|--------------------|---------------|------------------|--------------------|------|
| Annexin II/p11     | 1a            | N-terminus       | ↑ by overexpression| 66. |
| AP2µ2              | 1a            | C-terminal LCRRG motif | ↑ by overexpression | 23. |
| Dynamin1           | 1a            | NR               | ↑ by inhibition    | 23. |
| Hsc70              | 2a            | NR               | ↑ by knockdown     | 67,68|
| Lin7b              | 3             | C-terminal PDZ-binding motif | ↑ by overexpression | 38. |
| NHERF              | 3             | C-terminal PDZ-binding motif | ↑ by overexpression | 69. |
| PICK1              | 1a, 2a        | C-terminal PDZ-binding motif | ↑ by overexpression | 38,70|
| PSD-95             | 2a, 3         | C-terminal PDZ-binding motif | ↓ by overexpression | 1a: NR |
| Stomatins, STOML3  | 1a, 2a, 3     | NR               | ↑ by overexpression | 71-73|
| SGK1.1             | 1             | NR               | ↓ by activation    | 52. |

Symbols: ↑, increases; ↓, decreases. Abbreviations: AP2µ2, adaptor protein 2 µ2 subunit; Hsc70, heat shock cognate protein 70; Lin7b, abnormal cell lineage 7b; NHERF, Na+/H+ exchanger regulatory factor 1; PICK1, protein interacting with C-kinase 1; PSD-95, postsynaptic density protein 95; STOML3, stomatin-like protein 3; SGK1.1, serum- and glucocorticoid-induced kinase isoform 1.1; NR, not reported.
signaling also activates serum- and glucocorticoid-induced kinase 1 (SGK1), and the brain-specific isofrom SGK1.1 decreases ASIC1a surface expression and proton-gated current density; it would therefore be interesting to investigate whether activation of SGK1.1 facilitates the endocytosis or inhibits the membrane insertion of ASIC1a in the brain. Moreover, the expression level of SGK1.1 is highly associated with neuronal activity, and it could therefore provide insights into the neuronal activity-dependent trafficking of ASICs.

The PI3K/Akt pathway

It has long been speculated that the trafficking of ASICs can be regulated under pathological conditions that relate to tissue acidosis, such as ischemic stroke, epileptic seizures and chronic pain. However, evidence shows that acidosis itself has no influence on the trafficking processes of ASICs. A possible interplay between ASICs and neurootrophins, or other mediators of pathologiival development, is worthy of investigation. Our recent work examined the interaction between neurootrophin signaling and ASIC1a channel function, as well as its significance in chronic pain, using both in vitro and in vivo approaches. Because ASIC1a is the major component of ASICs and is required for central sensitization and pain hypersensitivity in SDH neurons, we screened several neurotrophins for ASIC1a function, and found that BDNF upregulates the activity of ASIC1a via the PI3K/Akt signaling pathway. BDNF and its receptor, TrkB, have been implicated in the development of spinal central sensitization that underlies persistent pain. We found that BDNF facilitates ASIC1a membrane insertion, a process for which the Ser25 site on the ASIC1a N-terminus is crucial. Blockade of ASIC1a trafficking by peptides that mimic the Ser25 phosphorylation site attenuates pain sensitization. Our results provide novel insights into the cellular processes of BDNF/TrkB signaling-mediated central sensitization. Because activity-dependent expression and release of BDNF is essential for synaptic plasticity and fear conditioning in the CNS, it is possible that BDNF-mediated ASIC1a trafficking also plays a role in fear memory at the central nucleus where ASIC1a is robustly expressed, for example, at the lateral and basolateral nuclei of the amygdala and striatum.

Summary and Outlook

Our knowledge on the trafficking of ASICs has expanded in the past few years. However, more studies are needed to unravel the basic cell biological processes of ASICs to understand the pathophysiological role of ASICs. Future directions of ASIC trafficking studies are discussed below.

1. Imaging the trafficking and pathophysiology of ASICs in vivo. There remains a challenge to elucidate the mechanisms of ASIC trafficking between the plasma membrane and intracellular compartments with excellent spatial and temporal resolutions. To address this issue, more sensitive molecular probes and microscopy methods for ASICs should be developed. For example, pH-sensitive GFP, a superektptic pHluorin, has been demonstrated to be a powerful probe used to monitor the dynamics of several ion channels, when it is fused to their extracellular domains. In combination with total internal reflection fluorescent microscopy, it is possible to visualize the rapid appearance of surface ion channel clusters within a specific region. However, the extracellular domain of ASICs is compact, and it is therefore important to test whether a pHluorin fusion protein would work. The use of an extracellular HA-tag within ASICs would provide a good start for such studies.

2. Identifying novel physiological and pathophysiological mechanisms of ASIC trafficking. Investigations should be undertaken to address whether ASICs have isoform-specific trafficking motifs and related accessory proteins; the role of ASIC1a endocytosis in acidosis-induced neuronal death; and the contribution of ASIC trafficking to synapse development and synaptic transmission.

In summary, to understand the role of ASICs in disease more thoroughly and to explore new clinical treatments, the above issues should be addressed with a combination of traditional and the latest techniques.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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