Piezo Proteins: Regulators of Mechanosensation and Other Cellular Processes

Piezo proteins have recently been identified as ion channels mediating mechanosensory transduction in mammalian cells. Characterization of these channels has yielded important insights into mechanisms of somatosensation, as well as other mechanosensitive processes such as sensing of shear stress, particularly in the vasculature, and regulation of urine flow and bladder distention. Other roles for Piezo proteins have emerged, some unexpected, including participation in cellular development, volume regulation, cellular migration, proliferation, and elongation. Mutations in human Piezo proteins have been associated with a variety of disorders including hereditary nephropathy, critical for all mammalian cells, has been linked to stretch-activated ion channels (SACs) (1, 2). Mechanosensation, the conversion of mechanical forces to biological signals, is a fundamental physiologic process mediating mechanosensory transduction in mammalian cells. Piezo1 and Piezo2 proteins, encoded by the Piezo1/FAM38A and Piezo2/FAM38B genes, respectively, were recently identified as mechanically activated (MA) ion channels in the murine neuroblastoma cell line N2A in an siRNA screen (3, 4). They have subsequently been shown to induce MA cationic currents in numerous eukaryotic cell types, connecting mechanical forces to biological signals. Piezo proteins are predicted to be large integral membrane proteins with 24–40 transmembrane domains, making them the proteins with the largest number of transmembrane domains (Fig. 1) (4). Initially described as an essential component of an MA ion channel (4), Piezo1 was later shown to possess an ion-conducting pore (3). Piezo1 forms homotetramers, but whether the complex contains one or four pores is unknown (3).

Piezo1 and Piezo2, ~2500 and 2800 amino acids long, respectively, share ~50% identity. Piezo homologues are found in organisms as diverse as plants, protozoa, and invertebrates. Phylogenetic analyses suggest that in vertebrates, Piezo1 diverged from Piezo2, as most lower organisms carry a single Piezo protein, whereas vertebrates have two (Fig. 2 and supplemental Fig. 1). The exception is pathogenic protozoa, where homologues of Piezo are present in two groups genetically distinct from mammalian Piezo1 and Piezo2 (5). Multiplespecies sequence alignments of evolutionarily distant protozoa, amoeba, plant, insect, and vertebrate Piezos reveal a remarkably conserved motif, the PFEW domain, hypothesized to be involved in channel conductance or gating (Fig. 3). Most mutations associated with human disease occur in this domain (see below).

In mice and humans, many mRNA isoforms from different cell types have been identified for both Piezo loci. Whether these isoforms are translated and/or are of functional significance is unknown. Piezo1 is broadly expressed with high levels in skin, bladder, kidney, lung, endothelial cells, erythrocytes, and periodontal ligament cells (6). Piezo2 is most prominently expressed in sensory trigeminal ganglia (TG) and dorsal root ganglia (DRG), Merkel cells, lung, and bladder (4, 7–9).

Electrophysiological Properties of Piezo Channels

Piezo1 and Piezo2 mediate nonselective cationic MA currents, with rapid desensitization during the static phase of the stimulus (Fig. 4A). Single-exponential fits to the desensitization component shows that at ~40 mV, Piezo1 and Piezo2 desensitize with $\tau \approx 32$ and 16 ms, respectively. Unlike peak amplitude, desensitization time is voltage-dependent and increases at positive potential (4). Experiments in heterologous systems show the absence of a systematic relationship between Piezo1- and Piezo2-mediated current amplitude and desensitization kinetics (4, 10–12), suggesting that the two parameters can be studied independently.

Following a complete desensitization, Piezo1 cannot be efficiently opened by the application of the same or larger force without first returning the initial stimulus to baseline (11). Complete recovery from desensitization takes hundreds of mil-
FM1-43 effectively inhibits both Piezo2-dependent and Piezo2-independent MA current in neurons from dorsal root ganglia (26). Similarly, GsMTx4 has many off-targets (27), perhaps due to its general mechanism of action via the lipids of the plasma membrane (28).

**Molecular Properties of Piezo1**

Incorporation of purified Piezo1 into an asymmetric lipid bilayer triggers electrical activity suppressed by the application of 50 μM RuR to the “extracellular” side of the bilayer. In proteoliposomes, Piezo1 conducts K⁺ and Na⁺ without preference, but whether purified Piezo1 conducts divalent ions and/or retains mechanosensitivity is unclear (3). Perhaps mechanosensitivity depends on the interaction with a regulator protein, such as stomatin-like protein 3 (STOML3), which interacts with both Piezo1 and Piezo2 and positively regulates channel activity (12), or it could be an intrinsic property of the channel, similar to that reported for the bacterial mechan gated channels MscS and MscL (29) and the eukaryotic two-pore potassium channels of the TREK group (30, 31). When compared side-by-side, Piezo1 activation requires a similar change in membrane tension as MscL (13), suggesting that lipid tension alone is, in principle, sufficient to gate Piezo1.

**Biological Aspects of Piezo1**

**Role of Piezo1 in Vascular Biology**

Piezo1 appears to function in endothelial cell types under both static and shear stress conditions. Germ line homozygous Piezo1 knock-out mice exhibited embryonic lethality at midgestation with disorganized and decreased yolk sac vasculature (32, 33). Embryos demonstrated growth retardation, pericardial effusion, and defects in vascular formation. Mice with endothelium-specific disruption of Piezo1 also exhibited embryonic lethality, with abnormal vessel formation and perturbed endothelial cell organization and alignment (32). Mice haploinsufficient for Piezo1 in endothelial cells were viable, with endothelial abnormalities in mature vessels. In Piezo1-depleted human umbilical vein endothelial cells (HUVECs) under static conditions, there was a total reduction in eNOS protein, decreased vascular endothelial growth factor (VEGF)-evoked phosphorylation of Ser-1177, a critical enhancer of eNOS activity, and suppression of endothelial cell migration, suggesting that Piezo1 drives endothelial cell migration through eNOS in the absence of shear stress (32).

Piezo1 also acts as an endothelial sensor of blood flow, promoting endothelial cell organization and alignment in the direction of flow (32, 33). Shear stress in HUVECs led to a change in subcellular localization of Piezo1, from a broad distribution under static conditions to accumulation at leading apical lamellipodia. Piezo1-depleted HUVECs exhibited defective alignment and elongation of endothelial cells in response to laminar shear stress as well as defective migration of cells toward VEGF. In wild type HUVECs under similar conditions, GsMTx4 disrupted the alignment of cells in the direction of

**Pharmacological Regulation of Piezo1 and Piezo2**

Piezo1 and Piezo2 are pharmacologically orphaned, with only a small number of nonspecific inhibitors available. Ruthenium Red (RuR) and gadolinium (Gd³⁺) reversibly block Piezo1 and Piezo2 current in C2C12 cells (4). RuR blocks murine Piezo1 at IC₅₀ 5.4 μM only when applied from the extracellular side, but fails to block the Drosophila Piezo orthologue (3). Another small molecule blocker, FM1-43, inhibits human Piezo2 current at 15 μM (15), but whether the block is reversible is unclear. In HEK293 cells, ~80% of peak Piezo1 current is reversibly inhibited by both l-‐enantiomers and d-‐enantiomers of GsMTx4, a peptide from tarantula venom (16). GsMTx4 is effective against Piezo1 at low micromolar concentrations and inhibits the channel only when applied from the extracellular side (10, 17, 18). GsMTx4 acts as a gating modifier shifting the midpoint of activation to higher pressure values (17). Whether GsMTx4 is effective against Piezo2 is unclear; in DRG neurons, GsMTx4 fails to suppress rapidly desensitizing MA currents (19) thought to be mediated by Piezo2 (4, 20).

None of these inhibitors are Piezo-specific. RuR and Gd³⁺ are known as efficient blockers of various types of ion channels in native cells and heterologous systems (21–25), whereas
shear stress, whereas both GsMTx4 and RuR blocked cell migration toward VEGF. Application of shear stress to endothelial cells evoked Piezo1-dependent currents with calcium influx followed by activation of calpain-2 activity. Protease activation, via proteolytic cleavage of the actin cytoskeleton and focal adhesion proteins, led to the spatial reorganization and alignment of endothelial cells to the polarity of the applied force (32).

### Piezo1 in Erythrocytes

Based on its role in hereditary xerocytosis (HX, see below), numerous roles have been suggested for Piezo1 in the erythrocyte. It has been suggested that Piezo1 plays a previously unrecognized role in erythrocyte volume regulation, with HX erythrocytes gradually becoming dehydrated during repeated cycles of travel through the microcirculation, associated with changes in oxygenation/deoxygenation (34). A potential role in regulating a stretch-activated calcium pathway has also been suggested (35–38). Local deformations in the erythrocyte membrane transiently activate a calcium permeability pathway, leading to increased intracellular calcium, with activation of potassium currents through the calcium-sensitive Gardos channel and activation of secondary anion currents through other channels (39). Circulatory shear stress has been suggested to cause reversible increases in erythrocyte calcium permeability (36, 40). Erythrocyte aging has been associated with alterations in membrane permeability for calcium (41–43). Localized membrane deformation has been associated with increased calcium in the process of apical alignment in the initial steps of malaria invasion (42). Thus Piezo1 is an excellent candidate for the unidentified stretch-induced cation pathway in the erythrocyte that plays critical roles in erythrocyte aging, malaria invasion, and circulatory shear stress.

It has also been suggested that Piezo1 may act as an osmoreceptor in erythrocytes and other cells. Volume sensing, a poorly understood process in vertebrate cells, has been linked to stretch-activated currents induced by changes in cell volume (44). As soon as the Piezo proteins were identified, they were candidates for cellular osmosensors (45). GsMTx4 inhibits both mechanically activated currents and whole-cell regulatory volume decreases in NRK-49 cells, indicating a potential role for Piezo1 in volume homeostasis (46). Knockdown of Piezo1 and its homologues in zebrafish erythroid cells led to development of macrocytic anemia, sphere-shaped circulating erythrocytes with disrupted membranes, and swollen nuclei (47). These results are intriguing, suggesting that Piezo1 not only may participate in volume regulation but also may have a role in maintaining the structural integrity of the red cell. However, because zebrafish erythrocytes do not enucleate, volume homeostatic mechanisms and membrane structure may be different from that in enucleated mammalian erythrocytes. A recent genome-wide association study of red cell indices linked mean corpuscular hemoglobin concentration, a factor influenced by erythrocyte hydration, to single nucleotide polymorphism (rs10445033) in the Piezo1 gene locus, explaining 8% of the phenotypic variance of mean corpuscular hemoglobin concentration (48).

### FIGURE 3. A highly conserved region in Piezo proteins

Multiple sequence alignment of Piezo proteins reveals a highly conserved region across species in the COOH terminus of Piezo proteins from plants to humans. This absolutely conserved region, the PFEW motif, is shown with amino acids comprising this motif shaded.

| Species          | Amino Acid Sequence                                      |
|------------------|----------------------------------------------------------|
| Human 1          | FRLVPFLVELRAVMDWVWTDTTLSLSSWMC                          |
| Human 2          | FRLVPFLTELRAVMDWVWTDTTLSLSSWIC                          |
| Macaca 1         | FRLVPFLVELRAVMDWVWTDTTLSLSSWMC                          |
| Macaca 2         | FRLVPFLTELRAVMDWVWTDTTLSLSSWIC                          |
| Mouse 1          | FRLVPFLVELRAVMDWVWTDTTLSLSSWMC                          |
| Mouse 2          | FRLVPFLTELRAVMDWVWTDTTLSLSSWIC                          |
| Dog 1            | FRLVPFLVELRAVMDWVWTDTTLSLSSWMC                          |
| Dog 2            | FRLVPFLTELRAVMDWVWTDTTLSLSSWIC                          |
| Rat 1            | FRLVPFLVELRAVMDWVWTDTTLSLSSWMC                          |
| Rat 2            | FRLVPFLTELRAVMDWVWTDTTLSLSSWIC                          |
| Frog 1           | FRLVPFLVELRAVMDWVWTDTTLSLSSWMC                          |
| Frog 2           | FRLVPFLTELRAVMDWVWTDTTLSLSSWIC                          |
| Zebrafish 1      | FRLVPFLVELRAVMDWVWTDTTLSLSSWMC                          |
| Zebrafish 2      | FRLIPFLTELRAVMDWVWTDTTLSLSSWIC                          |
| C. elegans       | FMNIPFLFELRTAIDWTWDTSMPLDFFNF                           |
| Drosophila       | YMQIPFLYELRTILDWVCDIDSTMTIFDWLK                         |
| Arabidopsis      | YRALPFYELRCVLDSCTATTSLTMYDVLK                           |
| Trypanosoma A    | YRCLPFLEIRVTDTVKEKSLHLDNYLK                             |
| Trypanosoma B    | YRCLPFLEIRVTDTVKEKSLHLDNYLK                             |

**Hydropobicity**

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**MINIREVIEW:** Piezo Proteins

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Role of Piezo1 in Cell Migration, Proliferation, and Elongation

Piezo1 was shown to participate in integrin activation, suggesting a non-MA role for Piezo1. Knockdown of Piezo1 in lung epithelial cells decreased cell adherence and promoted cell migration (50). Because it is down-regulated in many small cell lung cancer cell lines, loss of Piezo1 has been suggested to play a role in increased cell migration and distant metastases in lung cancer (50). In contrast, knockdown of Piezo1 in gastric tumor cell lines was associated with decreased cell migration (51). These studies, along with those from endothelial cells, implicate a role for Piezo proteins in cell migration, proliferation, and elongation.

Biological Aspects of Piezo2

Mechanosensation provides a necessary means of communication of an organism with its environment through the largest organ in the body of mammals, the skin. Dysregulation of somatosensory mechanosensitivity leads to peripheral neuropathies, which, in most cases, have no effective treatment. These conditions include diabetic neuropathy, peripheral vascular disease, and post-chemotherapy neuropathies. The cause of somatosensory dysfunction in most neuropathies is poorly understood. In many cases, it appears to involve aberrant sensitivity to mechanical force at the level of cutaneous mechanoreceptors or primary afferent neurons. Mechanical allodynia, associated with several neuropathies, is the disease where normally innocuous stimuli are perceived as excruciatingly painful (52). No specific treatments are available beyond palliative measures. Exemplary of these disorders is trigeminal neuralgia (53), a debilitating condition manifested as severe facial pain provoked by light touch, likely caused by aberrant mechanosensitivity of the trigeminal nerve. Despite decades of research, the molecular mechanism(s) through which we sense mechanical inputs remains poorly defined. Mechanosensitivity is the least understood of our senses at cellular and molecular level (54–56).

Piezo2 participates in the recognition of light touch and noxious stimuli at the level of both primary afferents and somatosensory components of cutaneous mechanoreceptors (see below). However, these processes require further investigation. It appears likely that Piezo2 alone is not sufficient to mediate the multitude of mechano-evoked phenomena observed in neural and somatic cells involved in cutaneous mechanotransduction. For instance, in somatosensory neurons, Piezo2 is responsible only for the rapidly desensitizing MA current (4, 20). In Merkel cells, conditional knockdown of Piezo2 is insufficient to recapitulate the effect of complete Merkel cell ablation (8). Therefore, other mechano-gated ion channels are likely to exist in both neural and somatic components of the mechanotransducing system.

Contribution of Piezo2 to Mechano-activated Current in Primary Afferent Neurons

In the skin, mechanical forces are perceived by peripheral cutaneous end organs, which contain somatic cells in complex with primary afferent nerve endings. Somata of the primary afferents are located in the somatosensory ganglia, either TG, which innervate the head, or DRG, which innervate different

**Piezo1 in the Genitourinary Tract**

Piezo1 is expressed in cells of the genitourinary system, especially in renal tubular epithelial cells and in uroepithelial cells. Similar to endothelial cells, studies in Piezo1-expressing HEK293 cells demonstrated shear stress activation of Piezo1 followed by calcium influx. Knockdown of Piezo1 in basolateral proximal convoluted tubular cells reduced activity of SACs. Interestingly, Polycystin-2 interacts with Piezo1 and inhibits endogenous SACs in these cells, indicating that renal SACs depend on Piezo1 but are critically conditioned by Polycystin-2 (49). These results suggest a role for Piezo1 in detection of intraluminal pressure changes and urine flow sensing. In cultured uroepithelial cells, Piezo1 has a functional role in stretch-evoked calcium influx and ATP release, an effect blocked by GsMTx4, implicating a role for Piezo1 in detecting urothelial extension during bladder distention (18).

**Piezo1 in Osteoclastogenesis**

Static compressive loading led to Piezo1 up-regulation in human periodontal ligament cells, contributing to mechanical stress-induced osteoclastogenesis (6).
parts of the body. Primary afferents are intrinsically mechano-
sensitive, i.e. they have the ability to convert membrane stretch
into depolarizing ionic current in the absence of other tissue
components. Direct mechanical stimulation of somata or neu-
rites of dissociated DRG neurons elicits MA current that expo-
nentially desensitizes with a characteristic time constant, \( \tau \) \((21)\). \( \tau \) values serve as the basis for neuronal classification as rapidly,
intermediately, and slowly desensitizing \((4, 12, 19–22, 24, 26,
57–59)\).

Piezo2 activity has been linked to mechansensitive neurons
in DRG \((4, 15, 20, 60, 61)\) and TG \((62, 63)\). Knockdown studies
reveal that Piezo2 is responsible for a majority of the rapidly
desensitizing MA current in murine DRG neurons. Piezo2-ex-
pressing neurons, however, do not seem to belong to a single
functional subtype. Piezo2 is expressed in small-diameter
unmyelinated nociceptors expressing TRPV1 or VGLU3 and in
large-diameter myelinated neurofilament 200-positive innocu-
ous mechanoreceptors \((4, 20)\), suggesting the involvement of
Piezo2 in both painful and innocuous mechanoreception.
Intrathecal injection of Piezo2 antisense oligonucleotides into
DRG neurons elevated the threshold of sensitivity to light touch
\((15)\). Because germ line knock-out of Piezo2 leads to embryonic
lethality \((60)\), a better understanding of the contribution of
Piezo2-mediated MA current in neurons to physiological touch
responses will require behavioral analysis of animals with pri-
mary afferents lacking Piezo2.

**Role of Piezo2 in Light Touch Sensitivity**

Several studies have revealed a key role for Piezo2 in mecha-
notransduction in Merkel cells in the skin \((7–9)\). These cells are
part of the Merkel cell-neurite complexes innervated by a spe-
cific subset of primary afferents, the A\(\beta\) slowly adapting type I
low-threshold mechanoreceptors (SAI-LTMR). These com-
plexes transmit high spatial resolution and selective sensitivity
and are thought to participate in both gentle touch and the
decoding of specific object features such as form, shape, and
texture by the skin. Direct mechanical stimulation of dissoci-
ated murine Merkel cells with a glass probe evoked a rapidly
desensitizing RuR-sensitive MA current, absent after condi-
tional knock-out of Piezo2 in skin \((7, 8)\). Similarly, recordings
from Merkel cells in an *ex vivo* whisker hair follicle preparation
revealed rapidly desensitizing MA current inhibited by Gd\(^{3+}\),
RuR, anti-Piezo2 antibody, or Piezo2 shRNA knockdown \((64)\).

Mechanical stimulation can be subdivided into two compo-
nents: when the probe is in the process of deforming the mem-
brane (the dynamic phase) and when the probe is held in the
extended position (the static phase). In response to such a
ramp-and-hold type of stimulation, slowly adapting type I low-
threshold mechanoreceptors transmit a well defined firing
pattern, consisting of a high-frequency response during the
dynamic phase followed by a slowly adapting response during
the static phase. Conditional knock-out of Piezo2 in Merkel
cells only modestly affected firing in the dynamic phase, but
profundely attenuated the response in the static phase, decreas-
ing the number of spikes and increasing inter-spike interval \((7,
8)\). Piezo2 knockdown in hair follicles suppressed firing at both
dynamic and static phase \((64)\). The discrepancy between these
results could be due to the different origin of Merkel cells
(touch domes in Refs. 7 and 8 versus whisker hair follicles in Ref.
64). However, it appears that Piezo2 contributes to the mecha-
nosensitivity of both neural and somatic components of the
cutaneous Merkel cell organs and that the deletion of Piezo2 in
Merkel cells leads to the inability of the sensory neurons to
transmit afferent response in the typical slowly adapting man-
ner. At the behavioral level, deletion of Piezo2 in Merkel cells
suppresses sensitivity to gentle (<1.5 g) touch by a Von Frey
filament, but does not affect sensitivity to heavier stimuli \((7)\).
Further experiments, using other types of light touch-oriented
behavioral paradigms \((65)\), are required to clarify the contribu-
tion of Piezo2 to light touch detection.

A recent study has revealed an unprecedented up-regulation
of Piezo2-expressing large-diameter neurons in TG of acutely
mechanosensitive species-tactile foraging ducks \((63)\). The skin
of the duck bill contains numerous mechanoreceptive end
organs that are innervated by primary afferents from TG. The
expansion of Piezo2-positive mechanoreceptors in duck TG,
where these cells account for up to 85% of the neuronal popu-
lation, further supports the notion of a key role for this protein
in light touch perception \((63)\).

**Role of Piezo2 in Noxious Mechanotransduction**

Co-localization of Piezo2 with small-diameter unmyelinated
nociceptors in DRG suggested a role in noxious mechanosen-
sitivity. Piezo2-mediated MA current amplitude was signifi-
cantly potentiated in cells treated with the proalgesic peptide
bradykinin (BK) and co-expressing the bradykinin receptor \(\beta2\)
\((60)\). In addition to the effect on MA current amplitude, BK
treatment prolonged desensitization, thus increasing the
amount of depolarizing charge entering the cell. This effect is
evident in Piezo2-expressing HEK293 cells and cultured DRG
neurons exhibiting the rapidly desensitizing MA current.
Physiologically, both the increase in amplitude and the prolongation
of desensitization facilitate depolarization and increase the
chance of action potential generation, signaling pain. The intra-
cellular pathways connecting BK signaling and Piezo2 include
G-protein-mediated signaling cascades, which converge on
protein kinases C and A (PKA). Piezo2 has over 30 potential
phosphorylation sites, but their functional importance awaits
clarification \((60)\).

Phosphorylation is probably not the only mechanism of
Piezo2 activity regulation. For example, cAMP, an intracellular
messenger linked to development of mechanical allodynia and
hyperalgesia, potentiates Piezo2 activity in HEK293 cells and
DRG neurons and prolongs desensitization of mouse (but not
human) Piezo2 \((15, 60)\). In addition to a direct potentiation of
PKA, cAMP triggers Epac1-dependent signaling, which has
numerous downstream effector targets, including phospho-
lipases, GTPases, and ion channels \((66)\). The involvement of
the Epac1 in a Piezo2 sensitization cascade is supported by the
finding that ectopic expression of Epac1 potentiates human
Piezo2 activation by cAMP \((15)\). Interestingly, upon the formation of
the whole-cell recording configuration, the amplitude of the
rapidly desensitizing MA current in DRG neurons and in
Piezo2-expressing HEK293 cells gradually increases. This
run-up process can be reversed by the omission of GTP from
the intracellular solution \((61)\), which further strengthens func-
tional connections between Piezo2 and G-protein signaling cascades.

Intrathecal injection of Piezo2 antisense oligonucleotides significantly attenuates Epa1-mediated allodynia in two models of chronic and neuropathic pain (15). Knockdown of Piezo2 in whisker hair follicles pre-sensitized with capsaicin injection suppresses pain responses (64). In flies, full genomic or sensory neuron-specific ablation of the Piezo orthologue leads to a severe and specific defect in noxious mechanotransduction (67). Together, these data strongly link Piezo2 function with noxious mechanosensation at physiological level. Descriptive studies identified Piezo2 in a neurochemically distinct subpopulation of corneal afferent neurons that are not polymodal nociceptors or cold-sensing neurons, suggesting that this subpopulation of pure mechano-nociceptors is an excellent candidate for transducers of noxious mechanical stimuli in the cornea (62).

Piezo Proteins and Human Disease

piezo1 and Hereditary Xerocytosis

Combining linkage analyses, SNP typing, and exome sequencing, Zarychanski et al. (68) identified PIEZO1 as the gene for HX. HX is a dominant disorder of erythrocyte dehydration with mild to moderate compensated hemolytic anemia (69). HX erythrocytes exhibit decreased total cation and potassium content not accompanied by a proportional net gain of sodium and water. Additional HX-associated PIEZO1 missense mutations have subsequently been described, primarily in residues located in the highly conserved COOH terminus (70, 71). Functional studies demonstrate a partial gain-of-function phenotype associated with many of the mutants due to generation of MA currents that inactivate more slowly than wild type (72). This indicates that there is likely increased cation permeability that leads to HX erythrocyte dehydration. Because the channel may homo-tetramerize, this delayed inactivation may be due to a dominant negative effect. In some PIEZO1 HX-associated variants, the mechanism of cellular dehydration is unknown.

Piezo2 and Neuromuscular Abnormalities

Coste et al. (72) identified two mutations in PIEZO2 in patients with distal arthrogyrosis (DA) type 5. The arthrogyrosis syndromes are a collection of disorders characterized by multiple congenital joint contractures. There is wide phenotypic variability, and numerous etiologies, inherited and acquired, have been implicated. DA5 is a dominant disorder characterized by skeletal muscle contractures, restrictive lung disease, and ophthalmoplegia. Both mutations were associated with faster recovery of PIEZO2-dependent MA currents from inactivation, whereas one was also associated with slowed inactivation (72).

McMillin et al. (73) identified 13 PIEZO2 mutations in 35 families affected by Gordon syndrome (GS), DA5, and Marden-Walker syndrome (MWS). Gordon syndrome is an uncommon dominant disorder associated with multiple contractures of the hands and feet and cleft palate. MWS is characterized by joint contractures, cleft palate, blepharophimosis, developmental delay and hindbrain malformations. All three syndromes are phenotypically similar, distinguished by a few specific characteristics. This study revealed that there is significant phenotypic and genotypic overlap between these disorders. Ten GS kindreds had PIEZO2 mutations, with nine kindreds sharing an identical mutation, R2686H. PIEZO2 mutations were found in 24 of 29 DA5 kindreds, including two kindreds with R2686H and 10 with pGlu2727del, the mutation previously identified by Coste et al. (72). One MWS kindred had a mutation in the same arginine codon as GS and DA5 kindreds, R2686H, with replacement of Arg by Cys instead of His. Although no functional studies were performed, the authors suggest that PIEZO2 mutations may disrupt a neuromuscular pathway that influences skeletal muscle development. Similar to HX-associated PIEZO1 mutations, most PIEZO2 mutations were located in the highly conserved COOH terminus, highlighting this region of Piezo proteins as a key element controlling channel desensitization.

All Piezo1 and Piezo2 mutations characterized so far are gain-of-function, strongly suggesting that the underlying cause of Piezo-linked disorders is excessive cation influx in response to mechanical stimulation. The phenotypic variability suggests different functional roles for the COOH terminus of Piezo proteins in varying cell types.

Future Directions

Since their discovery as mechanosensory transduction molecules, studies of Piezo proteins have revealed many unexpected roles beyond mechanotransduction. It will be exciting to unravel the numerous cell-, development-, and differentiation stage-specific and organism-specific roles of these proteins.

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