Adhesion GPCRs as a Putative Class of Metabotropic Mechanosensors

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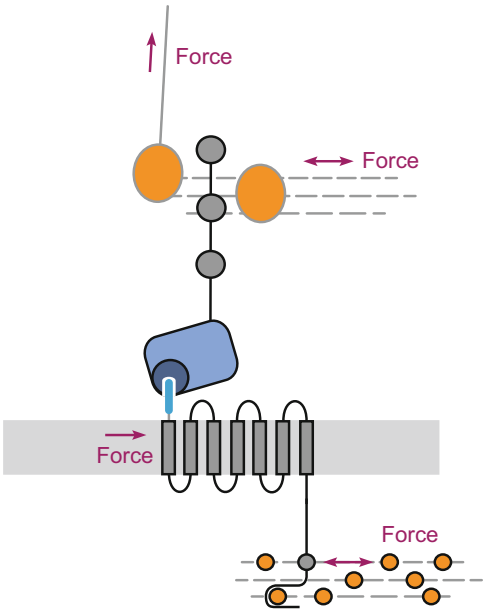
Graphical Abstract



Adhesion GPCRs as mechanosensors. Different aGPCR homologs and their cognate ligands have been described in settings, which suggest that they function in a mechanosensory capacity. For details, see text

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Contents

Abstract

G protein-coupled receptors (GPCRs) constitute the most versatile superfamily of biosensors. This group of receptors is formed by hundreds of GPCRs, each of which is tuned to the perception of a specific set of stimuli a cell may encounter emanating from the outside world or from internal sources. Most GPCRs are receptive for chemical compounds such as peptides, proteins, lipids, nucleotides, sugars, and other organic compounds, and this capacity is utilized in several sensory organs to initiate visual, olfactory, gustatory, or endocrine signals. In contrast, GPCRs have only anecdotally been implicated in the perception of mechanical stimuli. Recent studies, however, show that the family of adhesion GPCRs (aGPCRs), which represents a large panel of over 30 homologs within the GPCR superfamily, displays molecular design and expression patterns that are compatible with receptivity toward mechanical cues (Fig. 1). Here, we review physiological and molecular principles of established mechanosensors, discuss their relevance for current research of the mechanosensory function of aGPCRs, and survey the current state of knowledge on aGPCRs as mechanosensing molecules.

Keywords

Adhesion GPCR • Mechanosensor • Mechanosensation

1 General Overview of Mechanosensation

Each cell in our body is constantly exposed to a multitude of mechanical cues emanating from cell movements, hydrostatic pressure, shear stress exerted by fluids, or compressive and tensile forces of various origins. In order to react to mechanical conditions, these need to be (1) conveyed to mechanosensitive

molecules (a process termed *mechanotransmission*; Fig. 2). (2) These molecular mechanosensors perceive force application through conformational changes (*mechanoreception* or *mechanosensing*). (3) Force-dependent changes in mechanosensor structure are finally handed over to intracellular signaling cascades that are not necessarily force dependent per se, including metabotropic effectors and transcriptional pathways, which finally shape the cellular response to the mechanical change (*mechanoresponse*) [1]. Here, we will concentrate on the role of aGPCRs in the process of mechanoreception.

Mechanosensors frequently constitute integral membrane proteins, and it is commonly accepted that mechanical forces that impinge onto the cell surface affect local and global membrane tension. Thus far, a number of molecules have been attributed with a function in mechanoreception, among them ion channels, cell surface receptors (e.g., integrins, cadherins/selectins), and, more recently, G protein-coupled receptors (GPCRs).

2 Established Mechanosensors

Mechanosensors evolved different receptive strategies to reliably perceive, integrate, and convey mechanical information into the cell. Even though detailed molecular knowledge of the mechanotransduction cascade is, for many mechanosensors, still unknown, an understanding of the receptive strategies of these molecules will help define to what extent aGPCRs serve as metabotropic mechanosensitive devices. Thus, the following section delineates potential mechanisms that underlie mechanotransduction and provides an overview of established mechanosensors.

2.1 Molecular Models of Mechanosensation

Two models currently encompass how mechanical strain is transmitted onto mechanosensors. The "tethered" model is based on the concept that surface molecules are anchored to intra- and/or extracellular components via molecular springs, which convey mechanical forces to membrane integral mechanosensors (e.g., TMC, extracellular; see Sect. 2.2.5 NOMPC, intracellular; see Sect. 2.2.3). Alternatively, in the "membrane" model, mechanosensitivity is shaped by the lateral pressure profile [2] at the receptor/bilayer interface promoting conformational changes of mechanoreceptive proteins. Given that a cell's response to force is signified by its mechanical context by means of the surrounding extracellular matrix (ECM), neighboring cells, and the mechanical properties of the cell itself, it is reasonable to assume that both mechanisms are employed in parallel to ensure reliable integration of physical forces.

2.2 Ionotropic Mechanosensors

Guharay and Sachs were the first to discover that skeletal muscles in chick express an ion channel that can be activated by membrane stretch [3, 4]. After that, several years passed until the first mechanosensitive channel genes, *mscL* and *mscS*, were identified and cloned from prokaryotes [5–7]. In *Bacteria* and *Archaea*, mechanosensitive channels are primarily involved in detecting osmotically induced cell swelling to regulate turgor [6, 8].

A large number of mechanosensitive channels were identified in eukaryotic cells [9] and, based on their ion permeability, can be divided into two classes: excitatory cation-selective ion channels and inhibitory depolarization-gated ion channels. We will briefly discuss examples for both groups below. Furthermore, a novel ion channel family—transmembrane channel-like 1 and 2 (TMC1/TMC2)—was recently identified.

2.2.1 Piezo

Vertebrate Piezo1 and Piezo2 (or Fam38A and Fam38B) channel subunits comprise large membrane proteins with 14 predicted membrane-spanning segments [10]. Heterologous expression of Piezo conveys mechanosensitivity to a mechanically insensitive cell [11]. Furthermore, functional ion channels could be reconstituted from Piezo proteins in liposomes [12]. Thus, ectopically expressed Piezo appears to form mechanosensitive ion channels independent from cytoskeletal elements implying that the channel activating tension originates from the membrane [11–13].

Mammalian *Piezo 1*/*Piezo 2* was detected in the lung, bladder, colon, and skin. *Piezo 2* was additionally enriched in dorsal root ganglia (DRGs) [11], where it acts as a mechanotransducer to regulate the perception of tactile stimuli [14, 15]. Similarly, the *piezo2b* homolog plays a role in zebrafish touch sensation [16]. Moreover, Piezo1 was assigned roles in the regulation of erythrocyte cell volume and vascular development in zebrafish and mouse, respectively [17–19]. The sole Piezo homolog in *Drosophila* (*dmpiezo*) produces, similar to its vertebrate counterpart, mechano-dependent ion currents and is required for the perception of noxious mechanical stimuli in vivo. Interestingly, Piezo appears to act in parallel to Pickpocket (PPK), which belongs to the (DEG)/ENaC family, to regulate mechanical nociception in *Drosophila* larvae [20].

2.2.2 DEG/ENaC Channel

The DEG/ENaC channel family was named after their first members, degenerins (*mec-4 and deg-1*) and epithelial sodium channel (ENaC) from *C. elegans* and mammals, respectively [21–24]. DEG/ENaC channels are expressed in different tissues across a large range of phyla, are usually Na^+-selective, and appear to be activated by a wide spectrum of stimuli including mechanical force [25]. Two transmembrane domains (N- and C-termini intracellular) connected by a large extracellular loop define the protomer architecture of DEG/ENaC proteins, which can form both homo- and heteromeric ion channels [26–28].

The first identified eukaryotic genes involved in touch sensation, *mec-4* and *mec-10* (*mec*hanosensory abnormal) [29], were uncovered through forward genetic screens in *C. elegans*, in which mutants were probed for their ability to respond to gentle body touch conveyed through a defined set of touch receptor neurons [29–31]. Genetic, biochemical, functional, and morphological analyses implicate four MEC proteins (MEC-4, MEC-10, MEC-2, MEC-6) to compose mechanosensory channel complexes [32–34]. The pore-forming subunits are presumably contributed by MEC-4 and MEC-10 [23, 32, 35, 36]. Interestingly, the local lipid milieu appears to influence the function of this mechanosensory complex [33, 37–39], suggestive of a membrane stretch-mediated gating mechanism.

2.2.3 TRP Channels

Transient receptor potential (TRP) channels are involved in recognizing a broad range of mechanical and chemical stimuli [40]. Each TRP channel gene belongs to one of seven subfamilies [TRPC (classical), TRPV (vanilloid), TRPM (melastatin), TRPN (NOMPC), TRPA (ANKTM1), TRPML (mucolipin), and TRPP (polycystin)] [41] and encodes a channel subunit with at least six transmembrane-spanning segments and intracellular N- and C-terminal regions with subfamily-specific domain layout [42]. Four subunits assemble into functional homo- or heteromeric ion channels, commonly nonselective for cations and permeable to Ca^{2+} [41, 43].

Mechanosensitivity has been reported for a number of TRP channel subunits; however, to what extent these proteins are directly involved in mechanotransduction remains to be resolved for many family members. Interestingly, TRP channels were also identified as partners of GPCRs and aGPCRs in this context.

For example, TRPC6 is a downstream target of a mechanosensitive GPCR responsible for mediating myogenic vasoconstriction in response to elevated intraluminal pressure [44]. Further, mouse sensory neurons express TRPC1, TRPC3, and TRPC6 [45]. *Trpc3*/*Trpc6* double knockout mice display altered responses to tactile stimuli. These mutants also exhibit pronounced hearing impairments and vestibular defects consistent with TRPC3 and TRPC6 expression in cochlear and vestibular hair cells [45]. Recent work indicated that TRPC1, TRPC3, TRPC6, and TRPC5 heteromultimerize to contribute to cutaneous and auditory mechanosensation. Moreover, these TRP channel subunits were proposed to contribute indirectly to cochlear mechanotransduction [46].

Further, members of the TRPN family have been associated with the perception of mechanical stimuli in *Drosophila* (no receptor potential; NOMPC) [47, 48], hearing in zebrafish (TRPN1) [49], and proprioception in *C. elegans* (TRP-4) [50]. NOMPC localizes to the ciliary tips of mechanosensory neurons of the Johnston's organ and chordotonal organs in *Drosophila* [51, 52]. NOMPC can be directly mechanically activated and confers mechanosensitivity to otherwise insensitive cells, rendering NOMPC a bona fide mechanotransduction channel [53, 54]. Recent data indicate that the 29 ankyrin repeats of NOMPC's N-terminus constitute a molecular spring that conveys forces generated by the

cytoskeleton to modulate ion channel gating [55, 56]. However, loss of *nompC* does not completely abolish fly hearing [47], suggesting the existence of additional transducer molecules [57]. Alternatively, NOMPC may sensitize or adjust the mechanosensory complex for mechanical input [58]. Interestingly, genetic analysis suggests that the aGPCR dCIRL/latrophilin modulates NOMPC activity in sensory chordotonal neurons [59] (see Sect. 3.2).

The *C. elegans* TRPV proteins OSM-9 and OCR-2 form heteromeric channel complexes in sensory neurons that respond to touch and hyperosmolarity [60–62]. Consequently, loss of function of *osm-9* results in worms that are less sensitive to osmotic and mechanical challenges [60, 62]. *Drosophila* encodes TRPV proteins, INACTIVE and NANCHUNG, that are mutually required for the assembly of heteromultimeric channels involved in fly hearing and possibly auditory mechanotransduction [57, 58, 63, 64]. Epistatic analysis implicated NANCHUNG function in a mechanosensory signaling pathway together with the aGPCR latrophilin/CIRL [59].

Finally, TRPP homologs TRPP2 (polycystin 2 or PC2) and TRPP3 (polycystic kidney disease 2-like 1, PKD2L2) have been associated with mechanosensation. TRPP2 forms a receptor-ion channel complex with polycystin 1 (PC1, TRPP1) [65, 66], which localizes to primary cilia of renal epithelial cells and endothelial cells [67–70]. PC1 does not belong to the TRP channel family; it contains 11 -transmembrane-spanning regions and a large extracellular N-terminal domain that promotes cell-cell and cell-matrix interactions [71, 72] (see also [73]). The TRPP2/PC1 complex mediates Ca^{2+} transients in response to ciliary deflections induced by luminal shear stress [67, 68, 74]. Intriguingly, filamin A cross-links TRPP2 and the actin cytoskeleton to regulate stretch-activated cation channels (SACs) involved in cardiovascular pressure sensing [70]. Furthermore, TRPP2 forms ciliary mechanosensitive sensors with TRPV4 to transduce mechanical stress [75].

2.2.4 K_{2P} Channels

K_{2P} channels are comprised of four transmembrane-passing segments, two pore-forming regions, and intracellular N- and C-terminal portions. They assemble into hetero- and homodimeric ion channels. TWIK-related K^+ channels (TREK) and TWIK-related arachidonic acid-stimulated K^+ channel (TRAAK) are membrane tension-gated channels characterized by low mechanical threshold and a broad range of tension activation [76].

TREK-1 and TREK-2 are widely expressed within the central and peripheral nervous systems as well as nonneuronal tissues such as the cardiovascular system, lung, colon, and kidney. By contrast, TRAAK expression appears to be confined to neuronal tissues [77]. In the nervous system, K_{2P} channels are physiologically relevant as they contribute considerably to cell hyperpolarization, which balances/counteracts depolarization-induced action potentials, thereby shaping the electrical response to mechanical force. For example, TRAAK activity counteracts activation of Piezo to curtail action current generation in cultured neuroblastoma cells [78]. Further, TRAAK/TREK and mechanosensitive cation channels are coexpressed in sensory neurons of DRGs [79]. Deletion of *Traak*, *Trek-1*, or

Trek-2 genes in mice renders them hypersensitive to mechanical challenge [80, 81], which is in line with the notion that K_{2P} channels set the mechanical threshold for action potential generation [76]. Evidence for the physiological relevance of TREK-1 in mechanosensation outside the nervous system has emerged as well. Polycystins play a role in force-dependent apoptosis of renal epithelial cells, a function that was shown to rely on the opening of TREK-1 [82]. TREK-1 is enriched in the bladder, uterus, and colon where it regulates stretch-induced contraction of smooth muscle cells [83].

2.2.5 Transmembrane Channel-Like 1 and 2 Proteins

Recently, the transmembrane channel-like 1 and 2 (TMC1 and TMC2) proteins emerged as novel components required for auditory and vestibular mechanosensation in mammals [84–86]. The *Tmc* gene family encodes proteins with at least six transmembrane regions flanked by intracellular N- and C-terminal portions [87] reminiscent of TRP channel proteins. However, TMC proteins do not share sequence homologies with known ion channels [85, 88], even though recent work indicated that *C. elegans tmc-1* assembles into nonselective cation channels when heterologously expressed [89]. Several lines of evidence implicate TMC proteins as key components of the hair cell transduction complex. First, consistent with the mRNA expression pattern [90], TMC1 and TMC2 fusion proteins localize to stereocilia of the inner ear hair cells [86]. Second, mutations of the human *Tmc1* gene have been associated with dominant and recessive nonsyndromic sensorineural hearing deficits [84]. Similarly, dominant and recessive mutations of mouse *Tmc1* result in animals that exhibit defective hearing (*Beethoven*) and deafness (*dn*), respectively [84, 91]. Third, in mice, loss of function of *Tmc1* or *Tmc2* deprives hair cells of mechanosensory responses [90, 92]. Fourth, robust apical FM1-43 dye or gentamicin uptake reported for wild-type hair cells was abolished in the absence of TMC1 and TMC2 [90, 93, 94]. Fifth, expression of either TMC1 or TMC2 rescues loss of hair cell mechanosensitivity displayed by homozygous null mutants [90]. Sixth, protocadherin-15 (PCDH15) together with cadherin-23 forms extracellular tethers (called tip links), which connect adjacent pairs of stereocilia and transmit hair cell bundle deflection-based mechanical forces to mechanosensors [95, 96]. Strikingly, recent work uncovered a direct interaction between PCDH15 and TMC1 as well as TMC2 in fish and mouse [97, 98].

Taken together, these results suggest that TMC proteins are strong candidates for the long sought-after mechanosensitive channel required for mechanotransduction in mammalian hair cells [85].

2.3 Integrins and Cadherins

Cell adhesion enables the generation of mechanical tissue cohesion as well as cell-cell and cell-matrix communication vital for a myriad of physiological processes. But how do cells sense the mechanical context of their microenvironment (e.g., extracellular matrix or adjacent cells), and how are these signals translated into

cellular responses? Based on structural and functional properties, integrins and cadherins have been associated with mechanosensation in this vein.

2.3.1 Integrins

Integrins constitute a large family of glycoprotein receptors that bridge cell-cell contacts (cell adhesion) and interconnect intra- and extracellular matrices (ECMs) in metazoans. Integrins exist as heterodimers comprised of non-covalently bound α- and β-subunits, which are combined to form more than 20 distinct, functionally nonredundant receptor variants [99, 100].

Integrin heterodimers are inserted into the plasma membrane through a single transmembrane domain per protomer. The large extracellular domain (ECD) mediates interactions with ECM components (e.g., collagens, fibronectins, or laminins) and adjacent receptors [e.g., vascular cell adhesion molecule-1 (VCAM-1) and intercellular cell adhesion molecule (ICAM)] [100, 101]. The short intracellular domain (ICD) interacts, via cytoplasmic adaptors, with cytoskeletal elements to modulate local actin polymerization and global cytoskeletal dynamics [102, 103]. This molecular layout allows integrins to mechanically interlink the cell's exterior and interior providing the backbone for mechanical stress-induced assembly of focal adhesions (FA) [104–107], stimulation of signaling pathways, and gene transcription [108–110].

Importantly, integrins possess the capacity to confer signals in an "outside-in" or "inside-out" fashion associated with different biological ramifications. "Outside-in" signaling is based on the interaction of integrin ECDs with ECM molecules or opposing cellular receptors. These engagements provide information about ECM rigidity as well as adjacent cell/tissue geometry, which in turn regulate cellular growth, differentiation and apoptosis, cell polarity, and formation of focal adhesion complexes [105, 111–114]. During "inside-out" signaling, intracellular activators such as kindlins or talins associate with integrin ICDs to induce conformational changes that alter the affinity to extracellular ligands ("integrin activation"). Hence, this signaling mode affects cell adhesion and migration as well as ECM assembly [102]. Interestingly, the ionotropic Piezo1/Fam38A channel subunit was shown to induce integrin activation through an R-Ras-dependent mechanism [115].

In sum, integrin-based adhesion complexes are fit to perceive and integrate external forces into the preexisting cellular mechanical context to balance the ECM resistance according to tension forces generated by the cytoskeleton.

2.3.2 Cadherins

Cadherins are a large group of cell surface receptors that mediate Ca^{2+}-dependent cell adhesion [116]. The cadherin family includes a vast number of cell surface molecules; however, classical cadherins (E-, N-, P-cadherins) and the related desmosomal cadherins are, thus far, the best characterized. They feature cadherin repeat-containing ECDs, a single membrane-spanning region, and ICDs which interact with β-catenin (classical cadherins), γ-catenin (desmosomal cadherins), and components of the cytoskeleton [117].

Cadherins engage in ECD-dependent homo- and heterophilic interactions that may mediate adhesive and selectivity functions, respectively [118]. For example, force measurements uncovered that cadherins establish three spatially distinct bonds at different ECD regions that possess varying kinetic and mechanical properties [119, 120]. In contrast, ICDs associate with F-actin via catenin/vinculin interactions [121–124]. This structural setup allows cadherin complexes to act as mechanosensors that actively sense and transduce exogenous and endogenous mechanical fluctuations to trigger biochemical changes that direct cell responses [125]. Strikingly, the tensile force administered to an adhesion site is directly proportional to ECM stiffness [126].

Several lines of evidence support the role of cadherin-based adhesive junctions in mechanotransduction. First, cell-cell junctions undergo force-dependent remodeling not only in vitro but also in vivo [127, 128]. In *Drosophila* and *C. elegans*, cytoskeletal-provoked tension at cadherin junction coincides with a decline in junction expansion in various developmental processes. For example, the association of the actomyosin apparatus with cadherin junctions is a prerequisite for contraction-driven apical constriction during *C. elegans* gastrulation. A similar mechanism has been reported for ventral furrow formation in *Drosophila* [129]. Intriguingly, recent work demonstrated that during germ band extension in *Drosophila*, junction shrinkage appeared to result from tension-generated cadherin accumulation, which was counteracted by cadherin endocytosis [130]. Second, the mechanics of intercellular junctions (e.g., cell traction, adhesion strength, and junction rigidity) change according to the mechanical environment [122, 131–134].

In *Drosophila*, junctional mechanics are regulated in a forward loop that controls cadherin levels with respect to actomyosin density to enable adequate tissue morphogenesis [130, 135].

Taken together, cadherin complexes probe their environment for tensional changes to preserve the mechanical integrity of cellular junctions and to regulate morphogenesis and homeostasis [136–139].

2.4 Metabotropic Mechanosensors

GPCRs are biosensors vital for the transduction of light, olfactory and gustatory stimuli, as well as neurotransmitters and hormones into biochemical signals and thus shape a multitude of physiological processes [140]. Based on this perception profile, GPCRs were classically considered chemoreceptors. However, in recent years, mounting evidence suggests that mechanical forces can also be perceived through GPCRs. Therefore, GPCRs most likely constitute polymodal sensors with both chemoreceptive and mechanoreceptive properties.

The first mechanosensitive GPCR identified was the angiotensin II type 1 receptor (AT_1R), which mediates functions in preload-induced cardiac hypertrophy in vitro and in vivo. In contrast to autocrine-mediated vasoconstriction, activity of AT_1R is brought about independently of angiotensin II and facilitates intracellular signaling through $G_{q/11}$ proteins [141, 142]. In addition to this

pathophysiological function, intraluminal pressure stimulates AT_1Rs located in the arterial blood vessels causing myogenic vasoconstriction, a mechanism referred to as the Bayliss effect [44]. Mounting evidence implicates PLC kinases in mechano-dependent signaling pathways, which may subsequently trigger activation of ionotropic TRPC channels (see Sect. 2.2.3) to set arterial myogenic tone [44, 141, 143, 144].

Strikingly, AT_1R undergoes mechanically induced conformational changes that stabilize the seventh transmembrane domain near the agonist-binding pocket, a molecular organization that is different from that induced by agonist and inverse agonist signaling [145–147], suggesting stimulus modality-dependent signaling modes of this GPCR.

Thus far, eight additional putative mechanosensitive $G_{q/11}$ protein-coupled receptors have been described [148]. For example, time-resolved fluorescence microscopy of endothelial cells unveiled that mechanical strain causes a ligand-independent rise in bradykinin 2 receptor (B_2R) activity [149]. The authors suggest that, similar to AT_1R, conformational alterations of B_2R are due to tension-based properties of the lipid bilayer. However, it remains unclear if mechanical stimulation of B_2R is causally linked to effective G protein coupling. Another interesting example of a potential mechanosensitive GPCR derives from type 1 parathyroid hormone receptor (PTH_1R) essential for Ca^{2+} homeostasis in osteoblasts [150, 151]. Bone formation and bone mass regulation rely on the availability of parathyroid hormone (PTH) and mechanical loading, signal modalities proposed to converge at PTH_1R [151]. Evidence for a role in mechanoreception was also reported for dopamine receptor type 5 (D_5R) and formyl peptide receptor (FPR_1), which are both, similar to PTH_1R, excitable through fluid flow-generated shear stress in endothelial cells and neutrophils, respectively [152, 153]. Interestingly, D_5R localizes to primary cilia in vitro and in vivo and regulates their length through cofilin and actin polymerization. In addition, the authors report that ciliary sensitivity to fluid shear stress can be modified through chemosensory properties of the receptor [152]. Furthermore, electrophysiological recordings unveiled hypotonicity-dependent responses of heterologously expressed vasopressor receptors, ET_A endothelin receptor (ET_AR) and V_{1A} receptor ($V_{1A}R$), as well as H_1 histamine receptor (H_1R) and M_5 muscarinic acetylcholine receptor (M_5R) [44].

3 Adhesion GPCRs in Mechanosensation

A novel intriguing line of evidence for the mechanoreceptive role of GPCRs derives from the large family of aGPCRs, which stand out from canonical GPCRs because of their structural and functional profile as well as the conspicuous lack of soluble ligands [154]. Thus, are aGPCRs particularly prone to sense mechanical cues?

Three members of the aGPCR class, GPR56/ADGRG1, GPR126/ADGRG6, and latrophilin/CIRL/ADGRL, have been recently suggested to be involved in mechanosensation (Fig. 1) [59, 155, 156]. Like canonical GPCRs, aGPCRs possess a seven-transmembrane helix region (7TM) that can intracellularly couple to

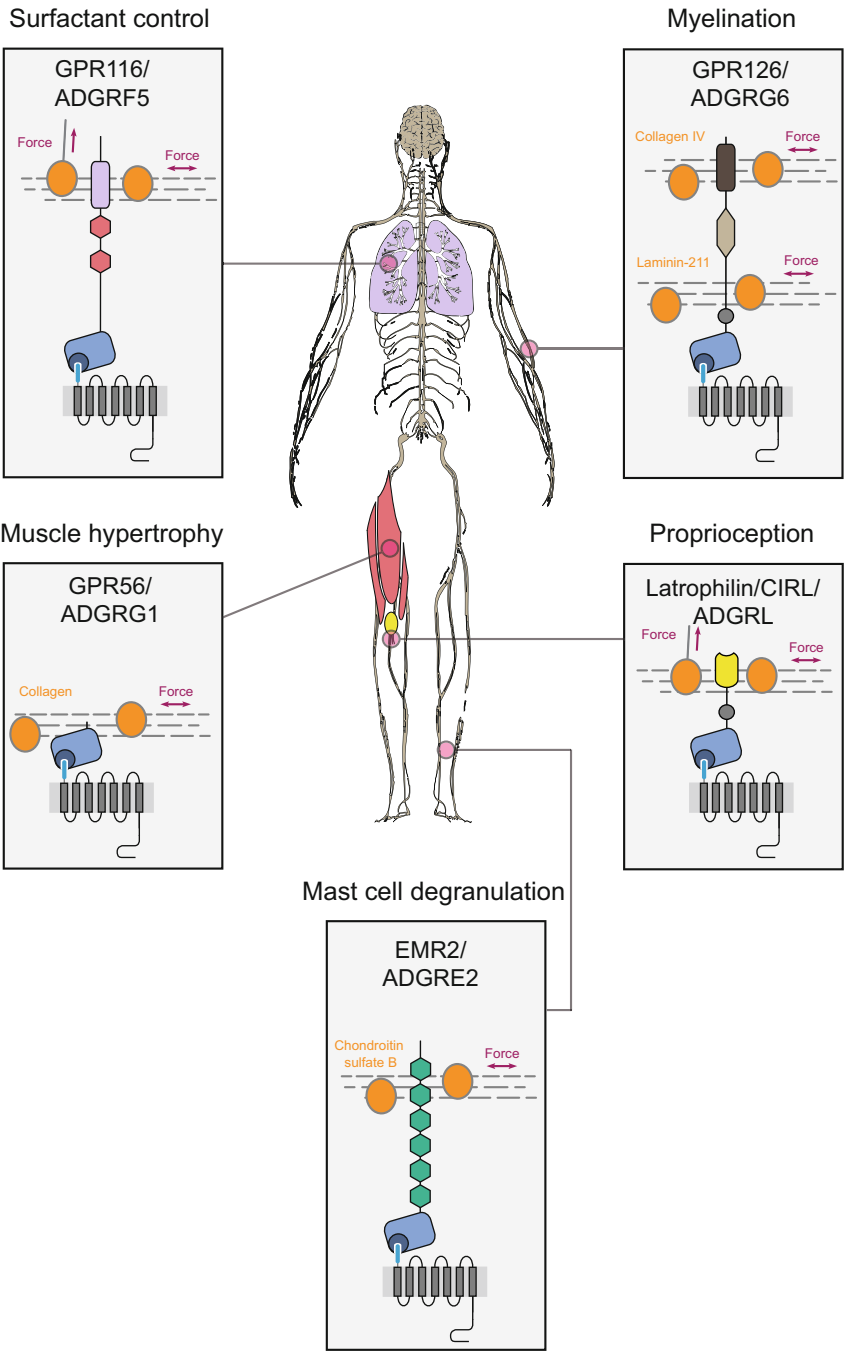

Fig. 1 Adhesion GPCRs as mechanosensors. Different aGPCR homologs and their cognate ligands have been described in settings, which suggest that they function in a mechanosensory capacity. For details, see text

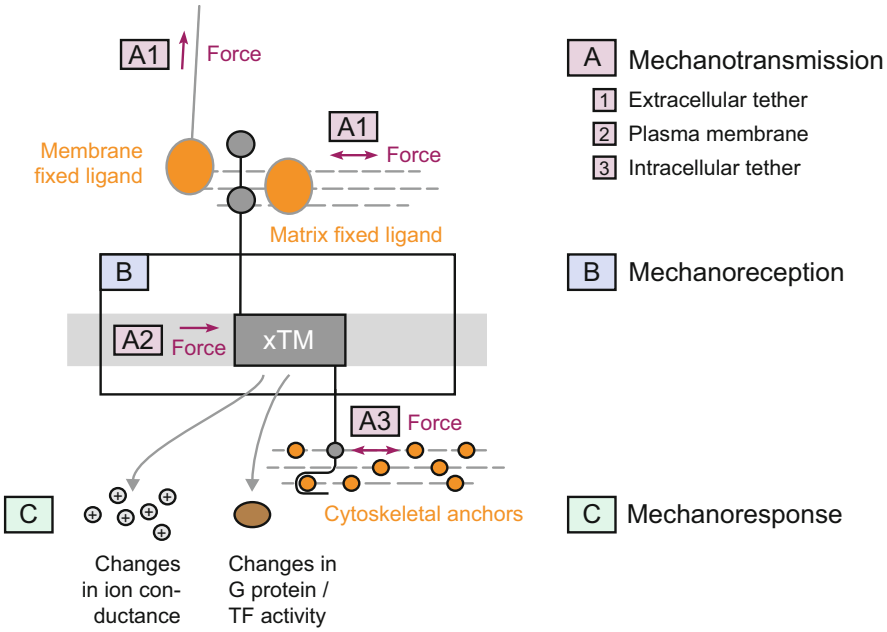

Fig. 2 Principal elements of mechanotransduction. The process of mechanotransduction can be grossly divided into three steps. (**a**) Mechanotransmission (indicated in *light pink*) that, according to current models, can be conveyed through extracellular or intracellular tethers and/or the plasma membrane. (**b**) Mechanosensation (*blue*), perceived through force-dependent conformational changes of membrane integral sensor proteins (*gray*). (**c**) Mechanoresponse (*green*), which induces changes in cell physiology (e.g., ion channel conductances, metabolic states, or modulation of transcriptional activity). xTM = variable number of transmembrane helices depending on the mechanosensor protein architecture (TRP channels, 6TM; aGPCR, 7TM; polycystin 1, 11TM; Piezo, 14TM)

heterotrimeric G proteins capable of triggering a multitude of signaling cascades that determine cellular responses (Fig. 2; see [157, 158]).

Further, aGPCRs possess large extracellular N-termini, which for many aGPCRs contain domains that are involved in cell-cell or cell-matrix adhesion [154] (see also [159]). Uniquely, the N-termini of many aGPCRs can be separated from the 7TM through an autoproteolytic event catalyzed by the GPCR proteolytic site (GPS) motif [160, 161], which is part of a much larger protein fold (GPCR autoproteolysis-inducing (GAIN) domain) [162]. Receptor cleavage is thought to occur early in the secretory pathway during protein maturation and generates an N-terminal fragment (NTF) and C-terminal fragment (CTF), which are predicted to traffic together to the cell surface where they are located as non-covalently bound heterodimers (Fig. 3; see also [73, 159]).

For several aGPCRs, a cryptic tethered ligand, termed the *Stachel* sequence, has been described, which acts as a potent agonist for downstream signaling [163–166] (Fig. 3; see also [157, 158]). Yet, crystal structures of aGPCR GAIN domains

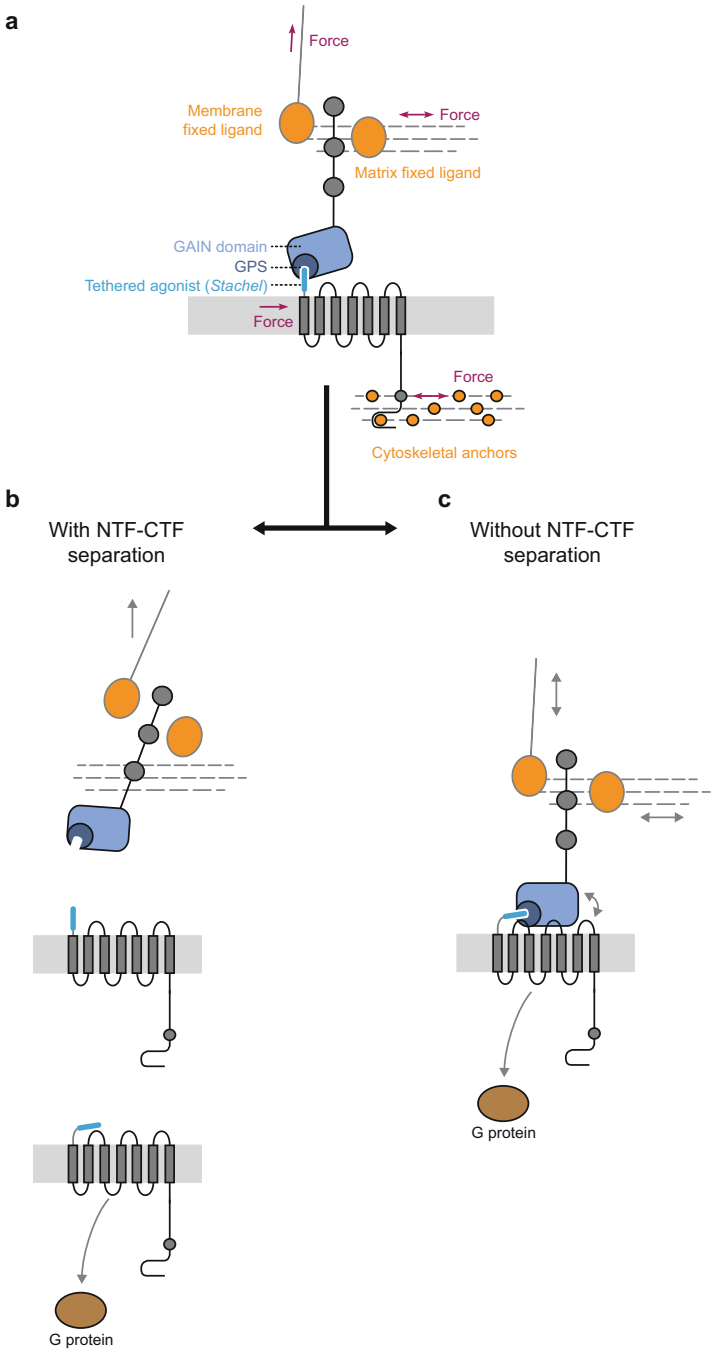

Fig. 3 Sequence of putative events during aGPCR-mediated mechanotransduction. (**a**) aGPCRs are subjected to mechanical force through their adhesive ECDs, at the level of the membrane, or through intracellular anchors. (**b**) Depending on whether the receptor is autoproteolyzed and

demonstrate that the *Stachel* sequence is deeply buried between two β-sheets [162], suggesting that the tethered agonist, at least for some aGPCRs, may not be readily exposed. How, then, might the *Stachel* sequence "escape" the ensconcement of the GAIN domain β-sheets in order to confer a signal to the receptor's 7TM stretch? Recent studies suggest that mechanical activation may be at play, which could induce conformational changes within the GAIN domain or complementary portions of the receptor to liberate the *Stachel* sequence and to allow receptor activation (Fig. 3).

3.1 GPR126/ADGRG6

As described in [167], myelin is the multilamellar sheath generated by specialized glial cells called Schwann cells in the peripheral nervous system and oligodendrocytes in the central nervous system. In the peripheral nervous system, GPR126 couples to $G\alpha_s$ and elevates cAMP in Schwann cells to initiate myelination (Fig. 1) [155, 163, 168–171]. The *Stachel* sequence of GPR126 is a potent agonist to trigger cAMP elevation, and analysis of zebrafish mutants has recently provided evidence that *Stachel*-mediated signaling is critically important in vivo. Liebscher and colleagues generated a new mutant allele of *gpr126*, $gpr126^{stl215}$, in which two amino acids essential for signaling were precisely deleted from the *Stachel* sequence. In vitro analysis demonstrated that this mutant receptor could be cleaved and that it trafficked appropriately to the cell surface, although it was incapable of signaling via cAMP. Accordingly, in vivo, $gpr126^{stl215}$ mutant Schwann cells could not initiate myelination [163]. This work suggested a model in which *Stachel*-mediated activation of Gpr126 is required for cAMP elevation and subsequent myelin initiation.

To determine how the *Stachel* sequence of GPR126 might be exposed during Schwann cell myelination, Petersen and colleagues investigated the relationship between one GPR126 binding partner, laminin-211, and GPR126 signaling [155] (discussed further in [167]). Laminin-211 is a heterotrimeric protein encoded by *Lama2*, *Lamb1*, and *Lamc1* genes [172], and like GPR126, laminin-211 is required for Schwann cell development and myelination [173]. Overexpression of *lama2* in zebrafish rescues myelination in *gpr126* hypomorphic mutants in a cAMP-dependent manner, suggesting that laminin-211 activates $G\alpha_s$ signaling.

Fig. 3 (continued) present as an NTF/CTF heterodimer at the cell surface, force transmission may separate the NTF from the CTF, thereby exposing the cryptic tethered agonist that interacts with the 7TM domain and triggers intracellular responses. (**c**) Several aGPCRs cannot be autoproteolytically cleaved, yet they appear to harbor a *Stachel* sequence that can stimulate receptor activity. This indicates that the tethered agonist can interact with the 7TM domain even if it remains associated with GAIN domain, possibly through conformational changes of the GAIN domain that render the agonist accessible. Note that this scheme illustrates putative intramolecular interactions between GAIN/*Stachel* and the 7TM region of aGPCRs; however, intermolecular interactions are conceivable as well

Intriguingly, addition of laminin-211 to GPR126 in heterologous cell systems suppressed cAMP elevation under standard culture conditions and elevated cAMP levels under dynamic conditions (vibration or shaking) [155]. These data can be reconciled by observations from related aGPCRs, noted above, that the *Stachel* sequence is buried, not exposed, between two β-sheets of the GAIN domain [162]. The *Stachel* sequence is so deeply buried that significant structural changes might be required for *Stachel*-mediated receptor activation to occur (Fig. 3). In vitro analyses of mutant receptors demonstrated that laminin-211 addition facilitates greater GPR126 activation than dynamic forces alone and that dynamic force signaling requires the *Stachel* sequence to activate GPR126.

These in vitro findings suggested that laminin-211 enhances GPR126 structural changes to allow for *Stachel*-mediated signaling, and the overexpression studies in zebrafish demonstrated that increased *lama2* levels can drive Gpr126-dependent myelination. What physical forces might laminin-211 impart upon GPR126 in vivo? Interestingly, laminin-211 polymerization is known to be essential for Schwann cell development; $Lama2^{dy2j}$ mouse mutants have a spontaneous mutation that leads to aberrant splicing and deletion of the laminin α2 polymerization domain, and these mice have defects in Schwann cell development and myelination [174–176]. To test if laminin α2 polymerization could be an activating force on Gpr126, reminiscent of physical forces in vitro, Petersen and colleagues engineered a non-polymerizable Lama2 overexpression construct to mimic the $Lama2^{dy2j}$ mouse mutation. Unlike wild-type *lama2*, the polymerization-defective *lama2 (dy2j)* was not sufficient to rescue myelination defects in hypomorphic *gpr126* zebrafish mutants [155].

In summary, the in vitro studies suggested the possibility that GPR126 might be sensitive to mechanical force, while the in vivo studies implicated laminin-211 polymerization as a potential source to transmit forces and stimulate mechanosensation in vivo.

3.2 Latrophilins/ADGRL1–ADGRL3

Contemporaneous work in *Drosophila* has even more strongly implicated an aGPCR in mechanosensation, as latrophilin/CIRL was shown to shape the response of chordotonal sensory neurons by determining the sensitivity of certain mechanosensors in a cell-autonomous manner [59]. Chordotonal neurons are peripheral, compound mechanosensory neurons in *Drosophila*, which perceive mechanical signals such as sound, touch, and muscle stretch [47, 52, 177]. Latrophilin/CIRL is robustly expressed in these cells (unpublished data) suggestive of a function in this cell type. Indeed, analyses of a newly engineered *dCirl* null allele revealed many interesting phenotypes consistent with a role for latrophilin/CIRL in mechanosensation. *dCirl* mutant larvae exhibited aberrant crawling patterns, and although locomotion is a complex behavior controlled by both motor outputs and peripheral sensory inputs, this defect could be partially rescued by chordotonal neuron-specific expression of *dCirl*. Moreover, *dCirl*

mutant larvae were also less responsive to gentle touch (touch perception is a known function of the chordotonal organ), and this phenotype could only be suppressed by chordotonal neuron-specific re-expression of this aGPCR [59]. Interestingly, the morphology of chordotonal neurons is grossly normal in *dCirl* null mutants, suggesting that latrophilin/CIRL is required specifically for the function of these neurons and not for their development or morphology.

To elucidate the potential role of latrophilin/CIRL in mechanosensation, Scholz and colleagues directly applied mechanical stimulation (vibration stimuli) to the cap cells of the chordotonal organ and simultaneously recorded action currents from chordotonal neurons. While *dCirl* mutant neurons maintained spontaneous activity in the absence of vibration stimuli, the mutant neurons displayed significantly lower action current frequencies across the entire tested vibration spectrum. Compound mutant analyses also demonstrated that *dCirl* genetically interacts with TRP channels, known as mechanosensor molecules of *Drosophila* chordotonal neurons [59] (see also Sect. 2.2.3).

All in all, these studies establish that latrophilin/CIRL can modulate the sensitivity of neuronal mechanosensation (Fig. 1). Given that several cell-specific rescue experiments demonstrate that *dCirl* functions cell autonomously in chordotonal neurons, likely via CTF signaling, it will be interesting to determine if and how *Stachel* sequence signaling modulates these functions of latrophilin/CIRL in mechanosensation (Fig. 3).

3.3 GPR56/ADGRG1

The role of aGPCRs as mechanosensors also extends beyond the nervous system. Skeletal muscle can respond to multiple stimuli, including mechanical tension, which is a potent regulator of muscle mass. In myotubes, a splice isoform of the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) induces muscle hypertrophy. Interestingly, overexpression of PGC-1α increases *Gpr56* expression, and GPR56 overexpression also induces muscle hypertrophy dependent on $G\alpha_{12/13}$ signaling. Resistance exercise causes muscle hypertrophy, but this phenotype is attenuated in *Gpr56* mutant mice [156] (see also [178]). These results collectively highlight a potential role for Gpr56 in sensing muscle fiber size, which could be mediated by mechanical sensitivity to stretch (Fig. 1).

Furthermore, in the central nervous system, GPR56 is required for proper cortical development (i.e., cortical folding), which has been directly linked to mechanosensation [179]. GPR56 and other aGPCRs including GPR114/ADGRG5 and GPR97/ADGRG3 are also highly expressed on lymphocytes [180]; it is tempting to speculate that signaling via these aGPCRs might be affected during the rolling and extravasation behaviors characteristic of these cells.

3.4 Mechanosensation by Other Adhesion GPCRs

These recent studies implicating Gpr126, latrophilin/CIRL, and GPR56 as putative mechanosensitive receptors raise the interesting and obvious question as to whether other aGPCRs might share this mechanosensitive property.

Indeed, one splice variant of GPR114 is sensitive to mechanical stimulation [166], although it is not yet clear in what physiological context this receptor may partake in mechanoreception. In addition, recent reports implicate *EMR2*/*ADGRE2* in vibratory urticaria [181], an autosomal dominant disorder that is signified by hives and systemic manifestations in response to cutaneous vibration. Interestingly, mast cells express EMR2, and mechanosensing through this receptor appears to depend on the stability between the NTF and CTF heterodimer of EMR2. A human mutation in the GAIN domain destabilizes this interaction and conceivably results in increased receptor activity upon mechanical challenge, which ultimately leads to massive mast cell degranulation [181]. Moreover, observations from previous studies on several aGPCRs can be interpreted in the light of these new insights to support a unifying model of mechanical susceptibility of this receptor class.

In the murine lung, loss of *Gpr116*/*Adgrf5* causes reduced surfactant uptake, leading to massive and pathological accumulations of surfactant lipids and proteins in the alveolar space [182–184] (see also [185]). Given that surfactant is essential to temper lung surface tension to allow for effortless lung expansion during inhalation, it is enticing to speculate that GPR116 is involved in monitoring lung tension (Fig. 1).

Similar to the expression of dCIRL in mechanosensory cells, GPR98/VLGR/ADGRV1 localizes to inner ear hair cells [186], where it is involved in proper development of the cochlear organ of Corti [187]. In the future, it will be interesting to determine the exact role of GPR98 during auditory mechanotransduction in these cells.

4 Conclusions

In sum, ionotropic mechanosensors are distributed throughout various organ systems across different species where they assure mechanosensory responses with latencies on millisecond timescales, rather atypical for metabotropic mechanosensors. Interestingly, however, in some instances these responses appear to be adjusted through the activity of GPCRs, which begs the question if ionotropic and metabotropic mechanosensors form functional units to enable reliable mechanotransduction.

aGPCRs regulate a multitude of physiological processes signified by the capacity to sense mechanics in different cellular contexts, which could explain the participation of aGPCRs in various, seemingly unrelated, biological phenomena. The structural and functional layouts of aGPCRs potentially reflect their optimization for the perception of mechanical forces, rather than a general sensitivity to a range of multiple sensory stimuli known for other GPCR families. Another

interesting aspect will be to unveil the signaling cascades through which aGPCRs influence ionotropic mechanotransduction processes and whether ion channels and GPCRs form functional mechanosensory units. Further research efforts will clarify the physiological and pharmacological properties underlying the mechanobiological roles of aGPCRs.

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References

1. Hoffman BD, Grashoff C, Schwartz MA (2011) Dynamic molecular processes mediate cellular mechanotransduction. Nature 475:316–323. doi:10.1038/nature10316
2. Cantor RS (1997) Lateral pressures in cell membranes: a mechanism for modulation of protein function. J Phys Chem B 101:1723–1725. doi:10.1021/jp963911x
3. Guharay F, Sachs F (1984) Stretch-activated single ion channel currents in tissue-cultured embryonic chick skeletal muscle. J Physiol 352:685–701
4. Guharay F, Sachs F (1985) Mechanotransducer ion channels in chick skeletal muscle: the effects of extracellular pH. J Physiol 363:119–134
5. Sukharev SI, Blount P, Martinac B, Blattner FR, Kung C (1994) A large-conductance mechanosensitive channel in E coli encoded by mscL alone. Nature 368:265–268. doi:10.1038/368265a0
6. Levina N, Tötemeyer S, Stokes NR, Louis P, Jones MA, Booth IR (1999) Protection of Escherichia coli cells against extreme turgor by activation of MscS and MscL mechanosensitive channels: identification of genes required for MscS activity. EMBO J 18:1730–1737. doi:10.1093/emboj/18.7.1730
7. Perozo E, Rees DC (2003) Structure and mechanism in prokaryotic mechanosensitive channels. Curr Opin Struct Biol 13:432–442
8. Ajouz B, Berrier C, Garrigues A, Besnard M, Ghazi A (1998) Release of thioredoxin via the mechanosensitive channel MscL during osmotic downshock of Escherichia coli cells. J Biol Chem 273:26670–26674
9. Kung C (2005) A possible unifying principle for mechanosensation. Nature 436:647–654. doi:10.1038/nature03896
10. Ge J, Li W, Zhao Q, Li N, Chen M, Zhi P et al (2015) Architecture of the mammalian mechanosensitive Piezo1 channel. Nature 527:64–69. doi:10.1038/nature15247
11. Coste B, Mathur J, Schmidt M, Earley TJ, Ranade S, Petrus MJ et al (2010) Piezo1 and Piezo2 are essential components of distinct mechanically activated cation channels. Science 330:55–60. doi:10.1126/science.1193270
12. Coste B, Xiao B, Santos JS, Syeda R, Grandl J, Spencer KS et al (2012) Piezo proteins are pore-forming subunits of mechanically activated channels. Nature 483:176–181. doi:10.1038/nature10812
13. Gottlieb PA, Sachs F (2011) Piezo1: properties of a cation selective mechanical channel. Channels (Austin) 6:214–219. doi:10.4161/chan.21050
14. Woo SH, Ranade S, Weyer AD, Dubin AE, Baba Y (2014) Piezo2 is required for Merkel-cell mechanotransduction. Nature 509:622–626
15. Coste B, Murthy SE, Mathur J, Schmidt M, Mechioukhi Y, Delmas P et al (2015) Piezo1 ion channel pore properties are dictated by C-terminal region. Nat Commun 6:7223. doi:10.1038/ncomms8223

16. Faucherre A, Nargeot J, Mangoni ME, Jopling C (2013) Piezo2b regulates vertebrate light touch response. J Neurosci 33:17089–17094. doi:10.1523/JNeurosci0522-13.2013
17. Faucherre A, Kissa K, Nargeot J, Mangoni ME, Jopling C (2014) Piezo1 plays a role in erythrocyte volume homeostasis. Haematologica 99:70–75. doi:10.3324/haematol.2013.086090
18. Li J, Hou B, Tumova S, Muraki K, Bruns A, Ludlow MJ et al (2014) Piezo1 integration of vascular architecture with physiological force. Nature 515:279–282. doi:10.1038/nature13701
19. Ranade SS, Qiu Z, Woo SH, Hur SS (2014) Piezo1, a mechanically activated ion channel, is required for vascular development in mice. Proc Natl Acad Sci U S A 111(28):10347–10352. doi:10.1073/pnas.1409233111
20. Kim SE, Coste B, Chadha A, Cook B, Patapoutian A (2012) The role of Drosophila Piezo in mechanical nociception. Nature 483:209–212. doi:10.1038/nature10801
21. Canessa CM, Horisberger JD, Rossier BC (1993) Epithelial sodium channel related to proteins involved in neurodegeneration. Nature 361:467–470. doi:10.1038/361467a0
22. Canessa CM, Schild L, Buell G, Thorens B, Gautschi I, Horisberger JD et al (1994) Amiloride-sensitive epithelial Na^+ channel is made of three homologous subunits. Nature 367:463–467. doi:10.1038/367463a0
23. Driscoll M, Chalfie M (1991) The mec-4 gene is a member of a family of Caenorhabditis elegans genes that can mutate to induce neuronal degeneration. Nature 349:588–593. doi:10.1038/349588a0
24. Lingueglia E, Voilley N, Waldmann R, Lazdunski M, Barbry P (1993) Expression cloning of an epithelial amiloride-sensitive Na^+ channel. A new channel type with homologies to Caenorhabditis elegans degenerins. FEBS Lett 318:95–99
25. Kellenberger S, Schild L (2002) Epithelial sodium channel/degenerin family of ion channels: a variety of functions for a shared structure. Physiol Rev 82:735–767. doi:10.1152/physrev.00007.2002
26. Askwith CC, Wemmie JA, Price MP, Rokhlina T, Welsh MJ (2004) Acid-sensing ion channel 2 (ASIC2) modulates ASIC1 H^+-activated currents in hippocampal neurons. J Biol Chem 279:18296–18305. doi:10.1074/jbc.M312145200
27. Baron A, Voilley N, Lazdunski M, Lingueglia E (2008) Acid sensing ion channels in dorsal spinal cord neurons. J Neurosci 28:1498–1508. doi:10.1523/JNEUROSCI.4975-07.2008
28. Benson CJ, Xie J, Wemmie JA, Price MP, Henss JM, Welsh MJ et al (2002) Heteromultimers of DEG/ENaC subunits form H^+-gated channels in mouse sensory neurons. Proc Natl Acad Sci U S A 99:2338–2343. doi:10.1073/pnas.032678399
29. Chalfie M, Sulston J (1981) Developmental genetics of the mechanosensory neurons of Caenorhabditis elegans. Dev Biol 82:358–370
30. Sulston J, Dew M, Brenner S (1975) Dopaminergic neurons in the nematode Caenorhabditis elegans. J Comp Neurol 163:215–226. doi:10.1002/cne.901630207
31. Chalfie M, Au M (1989) Genetic control of differentiation of the Caenorhabditis elegans touch receptor neurons. Science 243:1027–1033
32. Goodman MB, Ernstrom GG, Chelur DS, O'Hagan R, Yao CA, Chalfie M (2002) MEC-2 regulates C. elegans DEG/ENaC channels needed for mechanosensation. Nature 415:1039–1042. doi:10.1038/4151039a
33. Zhang S, Árnadóttir J, Keller C, Caldwell GA, Yao CA, Chalfie M (2004) MEC-2 is recruited to the putative mechanosensory complex in C. elegans touch receptor neurons through its stomatin-like domain. Curr Biol 14:1888–1896. doi:10.1016/j.cub.2004.10.030
34. Chelur DS, Ernstrom GG, Goodman MB, Yao CA, Chen L, O'Hagan R et al (2002) The mechanosensory protein MEC-6 is a subunit of the C. elegans touch-cell degenerin channel. Nature 420:669–673. doi:10.1038/nature01205
35. Huang M, Chalfie M (1994) Gene interactions affecting mechanosensory transduction in Caenorhabditis elegans. Nature 367:467–470. doi:10.1038/367467a0

36. O'Hagan R, Chalfie M, Goodman MB (2004) The MEC-4 DEG/ENaC channel of Caenorhabditis elegans touch receptor neurons transduces mechanical signals. Nat Neurosci 8:43–50. doi:10.1038/nn1362
37. Getz GS, Reardon CA (2004) Paraoxonase, a cardioprotective enzyme: continuing issues. Curr Opin Lipidol 15:261
38. Huber TB, Schermer B, Muller RU, Hohne M, Bartram M, Calixto A et al (2006) Podocin and MEC-2 bind cholesterol to regulate the activity of associated ion channels. Proc Natl Acad Sci U S A 103:17079–17086. doi:10.1073/pnas.0607465103
39. Barnes TM, Jin Y, Horvitz HR, Ruvkun G (1996) The Caenorhabditis elegans behavioral gene unc-24 encodes a novel bipartite protein similar to both erythrocyte band 7.2 (stomatin) and nonspecific lipid transfer protein. J Neurochem 67(1):46–57
40. Clapham DE (2003) TRP channels as cellular sensors. Nature 426:517–524. doi:10.1038/nature02196
41. Montell C (2005) The TRP superfamily of cation channels. Sci Signal 2005:re3. doi:10.1126/stke.2722005re3
42. Christensen AP, Corey DP (2007) TRP channels in mechanosensation: direct or indirect activation? Nat Rev Neurosci 8:510–521. doi:10.1038/nrn2149
43. Owsianik G, Talavera K, Voets T, Nilius B (2006) Permeation and selectivity of TRP channels. Annu Rev Physiol 68:685–717. doi:10.1146/annurev.physiol.68.040204.101406
44. Schnitzler MMY, Storch U, Meibers S, Nurwakagari P, Breit A, Essin K et al (2008) Gq-coupled receptors as mechanosensors mediating myogenic vasoconstriction. EMBO J 27:3092–3103. doi:10.1038/emboj.2008.233
45. Quick K, Zhao J, Eijkelkamp N, Linley JE, Rugiero F, Cox JJ et al (2012) TRPC3 and TRPC6 are essential for normal mechanotransduction in subsets of sensory neurons and cochlear hair cells. Open Biol 2:120068. doi:10.1098/rsob.120068
46. Sexton JE, Desmonds T, Quick K, Taylor R, Abramowitz J, Forge A et al (2015) The contribution of TRPC1, TRPC3, TRPC5 and TRPC6 to touch and hearing. Neurosci Lett 610:36–42. doi:10.1016/j.neulet.2015.10.052
47. Eberl DF, Hardy RW, Kernan MJ (2000) Genetically similar transduction mechanisms for touch and hearing in Drosophila. J Neurosci 20:5981–5988
48. Walker RG, Willingham AT, Zuker CS (2000) A Drosophila mechanosensory transduction channel. Science 287:2229–2234
49. Sidi S, NompC TRP (2003) Channel required for vertebrate sensory hair cell mechanotransduction. Science 301:96–99. doi:10.1126/science.1084370
50. Li W, Feng Z, Sternberg PW, Xu XZS (2006) A C. elegans stretch receptor neuron revealed by a mechanosensitive TRP channel homologue. Nature 440:684–687. doi:10.1038/nature04538
51. Lee J, Moon S, Cha Y, Chung YD (2010) Drosophila TRPN(=NOMPC) channel localizes to the distal end of mechanosensory cilia. PLoS One 5(6), e11012
52. Cheng LE, Song W, Looger LL, Jan LY, Jan YN (2010) The role of the TRP channel NompC in Drosophila larval and adult locomotion. Neuron 67:373–380. doi:10.1016/j.neuron.2010.07.004
53. Yan Z, Zhang W, He Y, Gorczyca D, Xiang Y, Cheng LE et al (2013) Nature 493:221–225. doi:10.1038/nature11685
54. Gong J, Wang Q, Wang Z (2013) NOMPC is likely a key component of Drosophila mechanotransduction channels. Eur J Neurosci 38:2057–2064. doi:10.1111/ejn.12214
55. Liang X, Madrid J, Gärtner R, Verbavatz J-M, Schiklenk C, Wilsch-Bräuninger M et al (2013) A NOMPC-dependent membrane-microtubule connector is a candidate for the gating spring in fly mechanoreceptors. Curr Biol 23:755–763. doi:10.1016/j.cub.2013.03.065
56. Zhang W, Cheng LE, Kittelmann M, Li J, Petkovic M, Cheng T et al (2015) Ankyrin repeats convey force to gate the NOMPC mechanotransduction channel. Cell 162:1391–1403. doi:10.1016/j.cell.2015.08.024

57. Göpfert MC, Albert JT, Nadrowski B, Kamikouchi A (2006) Specification of auditory sensitivity by Drosophila TRP channels. Nat Neurosci 9:999–1000. doi:10.1038/nn1735
58. Lehnert BP, Baker AE, Gaudry Q, Chiang A-S, Wilson RI (2013) Distinct roles of TRP channels in auditory transduction and amplification in Drosophila. Neuron 77:115–128. doi:10.1016/j.neuron.2012.11.030
59. Scholz N, Gehring J, Guan C, Ljaschenko D, Fischer R, Lakshmanan V et al (2015) The adhesion GPCR latrophilin/CIRL shapes mechanosensation. Cell Rep. doi:10.1016/j.celrep.2015.04.008
60. Tobin DM, Madsen DM, Kahn-Kirby A, Peckol EL (2002) Combinatorial expression of TRPV channel proteins defines their sensory functions and subcellular localization in C. elegans neurons. Neuron 35(2):307–318
61. Kaplan JM, Horvitz HR (1993) A dual mechanosensory and chemosensory neuron in Caenorhabditis elegans. Proc Natl Acad Sci U S A 90(6):2227–2231
62. Colbert HA, Smith TL, Bargmann CI (1997) OSM-9, a novel protein with structural similarity to channels, is required for olfaction, mechanosensation, and olfactory adaptation in Caenorhabditis elegans. J Neurosci 17:8259–8269
63. Kim J, Chung YD, Park D-Y, Choi S, Shin DW, Soh H et al (2003) A TRPV family ion channel required for hearing in Drosophila. Nature 424:81–84. doi:10.1038/nature01733
64. Gong Z, Son W, Chung YD, Kim J, Shin DW, McClung CA et al (2004) Two interdependent TRPV channel subunits, inactive and Nanchung, mediate hearing in Drosophila. J Neurosci 24:9059–9066. doi:10.1523/JNeurosci.1645-04.2004
65. Hanaoka K, Qian F, Boletta A, Bhunia AK, Piontek K, Tsiokas L et al (2000) Co-assembly of polycystin-1 and -2 produces unique cation-permeable currents. Nature 408:990–994. doi:10.1038/35050128
66. Yu Y, Ulbrich MH, Li M-H, Buraei Z, Chen X-Z, Ong ACM et al (2009) Structural and molecular basis of the assembly of the TRPP2/PKD1 complex. Proc Natl Acad Sci U S A 106:11558–11563. doi:10.1073/pnas.0903684106
67. Nauli SM, Alenghat FJ, Luo Y, Williams E, Vassilev P, Li X et al (2003) Polycystins 1 and 2 mediate mechanosensation in the primary cilium of kidney cells. Nat Genet 33:129–137. doi:10.1038/ng1076
68. Nauli SM, Kawanabe Y, Kaminski JJ, Pearce WJ, Ingber DE, Zhou J (2008) Endothelial cilia are fluid shear sensors that regulate calcium signaling and nitric oxide production through polycystin-1. Circulation 117:1161–1171. doi:10.1161/CIRCULATIONAHA.107.710111
69. AbouAlaiwi WA, Takahashi M, Mell BR, Jones TJ, Ratnam S, Kolb RJ et al (2009) Ciliary polycystin-2 is a mechanosensitive calcium channel involved in nitric oxide signaling cascades. Circ Res 104:860–869. doi:10.1161/CIRCRESAHA.108.192765
70. Sharif-Naeini R, Folgering JHA, Bichet D, Duprat F, Lauritzen I, Arhatte M et al (2009) Polycystin-1 and -2 dosage regulates pressure sensing. Cell 139:587–596. doi:10.1016/j.cell.2009.08.045
71. Wilson PD (2004) Polycystic kidney disease: new understanding in the pathogenesis. Int J Biochem Cell Biol 36:1868–1873. doi:10.1016/j.biocel.2004.03.012
72. Harris PC, Torres VE (2009) Polycystic kidney disease. Annu Rev Med 60:321–337. doi:10.1146/annurev.med.60.101707.125712
73. Nieberler M, Kittel RJ, Petrenko AG, Lin H-H, Langenhan T (2016) Control of adhesion GPCR function through proteolytic processing. In: Langenhan T, Schöneberg T (eds) Adhesion G protein-coupled receptors: molecular, physiological and pharmacological principles in health and disease. Springer, Heidelberg
74. Praetorius HA, Spring KR (2001) Bending the MDCK cell primary cilium increases intracellular calcium. J Membr Biol 184:71–79
75. Köttgen M, Buchholz B, Garcia-Gonzalez MA, Kotsis F, Fu X, Doerken M et al (2008) TRPP2 and TRPV4 form a polymodal sensory channel complex. J Cell Biol 182:437–447. doi:10.1083/jcb.200805124

76. Brohawn SG (2015) How ion channels sense mechanical force: insights from mechanosensitive K2P channels TRAAK, TREK1, and TREK2. Ann N Y Acad Sci 1352:20–32. doi:10.1111/nyas.12874
77. Noël J, Sandoz G, Lesage F (2014) Molecular regulations governing TREK and TRAAK channel functions. Channels (Austin) 5:402–409. doi:10.4161/chan.5.5.16469
78. Brohawn SG, Su Z, MacKinnon R (2014) Mechanosensitivity is mediated directly by the lipid membrane in TRAAK and TREK1 K^+ channels. Proc Natl Acad Sci U S A 111:3614–3619. doi:10.1073/pnas.1320768111
79. Enyedi P, Czirják G (2010) Molecular background of leak K^+ currents: two-pore domain potassium channels. Physiol Rev 90:559–605. doi:10.1152/physrev.00029.2009
80. Alloui A, Zimmermann K, Mamet J, Duprat F, Noël J, Chemin J et al (2006) TREK-1, a K+ channel involved in polymodal pain perception. EMBO J 25:2368–2376. doi:10.1038/sj.emboj.7601116
81. Heurteaux C, Guy N, Laigle C, Blondeau N, Duprat F, Mazzuca M et al (2004) TREK-1, a K+ channel involved in neuroprotection and general anesthesia. EMBO J 23:2684–2695. doi:10.1038/sj.emboj.7600234
82. Peyronnet R, Sharif-Naeini R, Folgering J, Arhatte M (2012) Mechanoprotection by polycystins against apoptosis is mediated through the opening of stretch-activated K2P channels. Cell Rep 1:241–250
83. Sanders KM, Don KS (2006) Two-pore-domain potassium channels in smooth muscles: new components of myogenic regulation. J Physiol 570:37–43. doi:10.1113/jphysiol.2005.098897
84. Kurima K, Peters LM, Yang Y, Riazuddin S, Ahmed ZM, Naz S et al (2002) Dominant and recessive deafness caused by mutations of a novel gene, TMC1, required for cochlear hair-cell function. Nat Genet 30:277–284. doi:10.1038/ng842
85. Pan B, Géléoc GS, Asai Y, Horwitz GC, Kurima K, Ishikawa K et al (2013) TMC1 and TMC2 are components of the mechanotransduction channel in hair cells of the mammalian inner ear. Neuron 79:504–515. doi:10.1016/j.neuron.2013.06.019
86. Kurima K, Ebrahim S, Pan B, Sedlacek M, Sengupta P, Millis BA et al (2015) TMC1 and TMC2 localize at the site of mechanotransduction in mammalian inner ear hair cell stereocilia. Cell Rep 12:1606–1617. doi:10.1016/j.celrep.2015.07.058
87. Keresztes G, Mutai H, Heller S (2003) TMC and EVER genes belong to a larger novel family, the TMC gene family encoding transmembrane proteins. BMC Genomics 4:24. doi:10.1186/1471-2164-4-24
88. Labay V, Weichert RM, Makishima T, Griffith AJ (2010) Topology of transmembrane channel-like gene 1 protein. Biochemistry 49:8592–8598. doi:10.1021/bi1004377
89. Chatzigeorgiou M, Bang S, Hwang SW, Schafer WR (2013) tmc-1 encodes a sodium-sensitive channel required for salt chemosensation in C. elegans. Nature 494:95–99. doi:10.1038/nature11845
90. Kawashima Y, Géléoc GSG, Kurima K, Labay V, Lelli A, Asai Y et al (2011) Mechanotransduction in mouse inner ear hair cells requires transmembrane channel-like genes. J Clin Invest 121:4796–4809. doi:10.1172/JCI60405
91. Vreugde S, Erven A, Kros CJ, Marcotti W, Fuchs H, Kurima K et al (2002) Beethoven, a mouse model for dominant, progressive hearing loss DFNA36. Nat Genet 30:257–258. doi:10.1038/ng848
92. Beurg M, Kim KX, Fettiplace R (2014) Conductance and block of hair-cell mechanotransducer channels in transmembrane channel-like protein mutants. J Gen Physiol 144:55–69. doi:10.1038/ng848
93. Gale JE, Marcotti W, Kennedy HJ, Kros CJ, Richardson GP (2001) FM1-43 dye behaves as a permeant blocker of the hair-cell mechanotransducer channel. J Neurosci 21:7013–7025
94. Marcotti W, Van Netten SM (2005) The aminoglycoside antibiotic dihydrostreptomycin rapidly enters mouse outer hair cells through the mechano-electrical transducer channels. J Physiol 567:505–521
95. Kazmierczak P, Sakaguchi H, Tokita J (2007) Cadherin 23 and protocadherin 15 interact to form tip-link filaments in sensory hair cells. Nature 449(7158):87–91. Abstract

96. Sakaguchi H, Tokita J, Müller U, Kachar B (2009) Tip links in hair cells: molecular composition and role in hearing loss. Curr Opin Otolaryngol Head Neck Surg 17:388. doi:10.1097/MOO.0b013e3283303472
97. Maeda R, Kindt KS, Mo W, Morgan CP, Erickson T, Zhao H et al (2014) Tip-link protein protocadherin 15 interacts with transmembrane channel-like proteins TMC1 and TMC2. Proc Natl Acad Sci U S A 111:12907–12912. doi:10.1073/pnas.1402152111
98. Beurg M, Xiong W, Zhao B, Müller U (2015) Subunit determination of the conductance of hair-cell mechanotransducer channels. 2015. Proc Natl Acad Sci U S A 112(5):1589–1594. doi:10.1073/pnas.1420906112
99. Hynes R (1987) Integrins: a family of cell surface receptors. Cell 48:549–554. doi:10.1016/0092-8674(87)90233-9
100. Hynes RO (2002) Integrins: bidirectional, allosteric signaling machines. Cell 110:673–687
101. Plow EF, Haas TA, Zhang L, Loftus J, Smith JW (2000) Ligand binding to integrins. J Biol Chem 275:21785–21788. doi:10.1074/jbc.R000003200
102. Shattil SJ, Kim C, Ginsberg MH (2010) The final steps of integrin activation: the end game. Nat Rev Mol Cell Biol 11:288–300. doi:10.1038/nrm2871
103. Campbell ID, Humphries MJ (2011) Integrin structure, activation, and interactions. Cold Spring Harb Perspect Biol 3(3):a004994
104. Balaban NQ, Schwarz US, Riveline D, Goichberg P, Tzur G, Sabanay I et al (2001) Force and focal adhesion assembly: a close relationship studied using elastic micropatterned substrates. Nat Cell Biol 3:466–472. doi:10.1038/35074532, Abstract
105. Galbraith CG, Yamada KM, Sheetz MP (2002) The relationship between force and focal complex development. J Cell Biol 159(4):695–705
106. Wang N, Butler J, Ingber D (1993) Mechanotransduction across the cell surface and through the cytoskeleton. Science 260:1124–1127. doi:10.1126/science.7684161
107. Choquet D, Felsenfeld DP, Sheetz MP (1997) Extracellular matrix rigidity causes strengthening of integrin–cytoskeleton linkages. Cell 88(1):39–48
108. Meyer CJ, Alenghat FJ, Rim P, Fong JH-J, Fabry B, Ingber DE (2000) Mechanical control of cyclic AMP signalling and gene transcription through integrins. Nat Cell Biol 2:666–668. doi:10.1038/35023621, Abstract
109. Chen J, Fabry B, Schiffrin EL, Wang N (2001) Twisting integrin receptors increases endothelin-1 gene expression in endothelial cells. Am J Physiol Cell Physiol 280:C1475–C1484
110. Riveline D, Zamir E, Balaban NQ, Schwarz US, Ishizaki T, Narumiya S et al (2001) Focal contacts as mechanosensors: externally applied local mechanical force induces growth of focal contacts by an mDia1-dependent and rock-independent mechanism. J Cell Biol 153:1175–1186. doi:10.1083/jcb.141.2.539
111. Lo CM, Wang HB, Dembo M, Wang Y (2000) Cell movement is guided by the rigidity of the substrate. Biophys J 79(1):144–152
112. Chen CS, Mrksich M, Huang S, Whitesides GM, Ingber DE (1997) Geometric control of cell life and death. Science 276(5317):1425–1428
113. Dike LE, Chen CS, Mrksich M, Tien J, Whitesides GM, Ingber DE (1999) Geometric control of switching between growth, apoptosis, and differentiation during angiogenesis using micropatterned substrates. Dev Biol 35:441–448
114. Parker KK, Brock AL, Brangwynne C, Mannix RJ, Wang N, Ostuni E et al (2002) Directional control of lamellipodia extension by constraining cell shape and orienting cell tractional forces. FASEB J 16(10):1195–1204
115. McHugh BJ, Buttery R, Lad Y, Banks S (2010) Integrin activation by Fam38A uses a novel mechanism of R-Ras targeting to the endoplasmic. J Cell Sci 123(1):51–61. doi:10.1242/jcs.056424
116. Nose A, Tsuji K, Takeichi M (1990) Localization of specificity determining sites in cadherin cell adhesion molecules. Cell 61:147–155

117. Shapiro L, Weis WI (2009) Structure and biochemistry of cadherins and catenins. Cold Spring Harb Perspect Biol 1:a003053. doi:10.1101/cshperspect.a003053
118. Prakasam AK, Maruthamuthu V, Leckband DE (2006) Similarities between heterophilic and homophilic cadherin adhesion. Proc Natl Acad Sci U S A 103:15434–15439. doi:10.1073/pnas.0606701103
119. Leckband D, Prakasam A (2006) Mechanism and dynamics of cadherin adhesion. Annu Rev Biomed Eng 8:259–287. doi:10.1146/annurev.bioeng.8.061505.095753
120. Shi Q, Maruthamuthu V, Li F, Leckband D (2010) Allosteric cross talk between cadherin extracellular domains. Biophys J 99:95–104. doi:10.1016/j.bpj.2010.03.062
121. Desai R, Sarpal R, Ishiyama N, Pellikka M, Ikura M, Tepass U (2013) Monomeric α-catenin links cadherin to the actin cytoskeleton. Nature 15:261–273. doi:10.1038/ncb2685
122. le Duc Q, Shi Q, Blonk I, Sonnenberg A, Wang N, Leckband D et al (2010) Vinculin potentiates E-cadherin mechanosensing and is recruited to actin-anchored sites within adherens junctions in a myosin II-dependent manner. J Cell Biol 189:1107–1115. doi:10.1083/jcb.201001149
123. Yonemura S, Wada Y, Watanabe T, Nagafuchi A, Shibata M (2010) alpha-Catenin as a tension transducer that induces adherens junction development. Nature 12:533–542. doi:10.1038/ncb2055
124. Yonemura S (2011) A mechanism of mechanotransduction at the cell-cell interface: emergence of α-catenin as the center of a force-balancing mechanism for morphogenesis in multicellular organisms. Bioessays 33:732–736. doi:10.1002/bies.201100064
125. Leckband DE, de Rooij J (2014) Cadherin adhesion and mechanotransduction. Annu Rev Cell Dev Biol 30:291–315. doi:10.1146/annurev-cellbio-100913-013212
126. Saez A, Buguin A, Silberzan P, Ladoux B (2005) Is the mechanical activity of epithelial cells controlled by deformations or forces? Biophys J 89:L52–L54. doi:10.1529/biophysj.105.071217
127. Liu Q-S, Zhang J, Liu M, Dong W-G (2010) Lentiviral-mediated miRNA against liver-intestine cadherin suppresses tumor growth and invasiveness of human gastric cancer. Cancer Sci 101:1807–1812. doi:10.1111/j.1349-7006.2010.01600.x
128. Barry AK, Wang N, Leckband DE (2015) Local VE-cadherin mechanotransduction triggers long-ranged remodeling of endothelial monolayers. J Cell Sci 128:1341–1351. doi:10.1242/jcs.159954
129. Roh-Johnson M, Shemer G, Higgins CD, McClellan JH, Werts AD, Tulu US et al (2012) Triggering a cell shape change by exploiting preexisting actomyosin contractions. Science 335:1232–1235. doi:10.1126/science.1217869
130. Levayer R, Lecuit T (2013) Oscillation and polarity of E-cadherin asymmetries control actomyosin flow patterns during morphogenesis. Dev Cell 26:162–175. doi:10.1016/j.devcel.2013.06.020
131. Tabdili H, Langer M, Shi Q, Poh Y-C, Wang N, Leckband D (2012) Cadherin-dependent mechanotransduction depends on ligand identity but not affinity. J Cell Sci 125:4362–4371. doi:10.1242/jcs.105775
132. Ladoux B, Anon E, Lambert M, Rabodzey A, Hersen P, Buguin A et al (2010) Strength dependence of cadherin-mediated adhesions. Biophys J 98:534–542. doi:10.1016/j.bpj.2009.10.044
133. Dufour S, Mège R-M, Thiery JP (2014) α-Catenin, vinculin, and F-actin in strengthening E-cadherin cell–cell adhesions and mechanosensing. Cell Adh Migr 7:345–350. doi:10.4161/cam.25139
134. Thomas WA, Boscher C, Chu Y-S, Cuvelier D, Martinez-Rico C, Seddiki R et al (2013) α-Catenin and vinculin cooperate to promote high E-cadherin-based adhesion strength. J Biol Chem 288:4957–4969. doi:10.1074/jbc.M112.403774
135. Lecuit T, Lenne P-F, Munro E (2010) Force generation, transmission, and integration during cell and tissue morphogenesis. Annu Rev Cell Dev Biol 27:157–184. doi:10.1146/annurev-cellbio-100109-104027

136. Maître J-L, Heisenberg C-P (2013) Three functions of cadherins in cell adhesion. Curr Biol 23:R626–R633. doi:10.1016/j.cub.2013.06.019
137. Andreeva AV, Han J, Kutuzov MA, Profirovic J, Tkachuk VA, Voyno-Yasenetskaya TA (2010) T-cadherin modulates endothelial barrier function. J Cell Physiol 223:94–102. doi:10.1002/jcp.22014
138. Groschwitz KR, Hogan SP (2009) Intestinal barrier function: molecular regulation and disease pathogenesis. J Allergy Clin Immunol 124:3–20. doi:10.1016/j.jaci.2009.05.038, quiz 21–2
139. Gumbiner BM (2005) Regulation of cadherin-mediated adhesion in morphogenesis. Nat Rev Mol Cell Biol 6:622–634. doi:10.1038/nrm1699
140. Bockaert J, Pin JP (1999) Molecular tinkering of G protein-coupled receptors: an evolutionary success. EMBO J 18:1723–1729. doi:10.1093/emboj/18.7.1723
141. Schnitzler MY, Storch U, Gudermann T (2011) AT1 receptors as mechanosensors. Curr Opin Pharmacol 11:112–116
142. Zou Y, Akazawa H, Qin Y, Sano M, Takano H, Minamino T et al (2004) Mechanical stress activates angiotensin II type 1 receptor without the involvement of angiotensin II. Nat Cell Biol 6:499–506. doi:10.1038/ncb1137
143. Jarajapu YPR, Knot HJ (2002) Role of phospholipase C in development of myogenic tone in rat posterior cerebral arteries. Am J Physiol Heart Circ Physiol 283:H2234–H2238. doi:10.1152/ajpheart.00624.2002
144. Osol G, Laher I, Kelley M (1993) Myogenic tone is coupled to phospholipase C and G protein activation in small cerebral arteries. Am J Physiol Heart Circ Physiol 265:H415–H420
145. Farrens DL, Altenbach C, Yang K, Hubbell WL (1996) Requirement of rigid-body motion of transmembrane helices for light activation of rhodopsin. Science 274(5288):768–770
146. Karnik S, Gogonea C, Patil S, Saad Y, Takezako T (2003) Activation of G-protein-coupled receptors: a common molecular mechanism. Trends Endocrinol Metab 14:431–437. doi:10.1016/j.tem.2003.09.007
147. Yasuda N, Miura S-I, Akazawa H, Tanaka T, Qin Y, Kiya Y et al (2008) Conformational switch of angiotensin II type 1 receptor underlying mechanical stress-induced activation. EMBO Rep 9:179–186. doi:10.1038/sj.embor.7401157
148. Storch U, Mederos y Schnitzler M, Gudermann T (2012) G protein-mediated stretch reception. Am J Physiol Heart Circ Physiol 302:H1241–H1249. doi:10.1152/ajpheart.00818.2011
149. Chachisvilis M, Zhang Y-L, Frangos JA (2006) G protein-coupled receptors sense fluid shear stress in endothelial cells. Proc Natl Acad Sci U S A 103:15463–15468. doi:10.1073/pnas.0607224103
150. Mannstadt M, Jüppner H, Gardella TJ (1999) Receptors for PTH and PTHrP: their biological importance and functional properties. Am J Physiol 277:F665–F675
151. Zhang Y-L, Frangos JA, Chachisvilis M (2009) Mechanical stimulus alters conformation of type 1 parathyroid hormone receptor in bone cells. Am J Physiol Cell Physiol 296:C1391–C1399. doi:10.1152/ajpcell.00549.2008
152. Abdul-Majeed S, Nauli SM (2011) Dopamine receptor type 5 in the primary cilia has dual chemo- and mechano-sensory roles. Hypertension 58:325–331
153. Makino A, Prossnitz ER, Bunemann M, Wang JM, Yao WJ, Schmid-Schoenbein GW (2006) G protein-coupled receptors serve as mechanosensors for fluid shear stress in neutrophils. Am J Physiol Cell Physiol 290:C1633–C1639. doi:10.1152/ajpcell.00576.2005
154. Langenhan T, Aust G, Hamann J (2013) Sticky signaling-adhesion class G protein-coupled receptors take the stage. Sci Signal 6:re3. doi:10.1126/scisignal.2003825
155. Petersen SC, Luo R, Liebscher I, Giera S, Jeong S-J, Mogha A et al (2015) The adhesion GPCR GPR126 has distinct, domain-dependent functions in Schwann cell development mediated by interaction with laminin-211. Neuron 85:755–769. doi:10.1016/j.neuron.2014.12.057

156. White JP, Wrann CD, Rao RR, Nair SK, Jedrychowski MP, You JS et al (2014) G protein-coupled receptor 56 regulates mechanical overload-induced muscle hypertrophy. Proc Natl Acad Sci U S A. doi:10.1073/pnas.1417898111
157. Liebscher I, Schöneberg T (2016) Tethered agonism: a common activation mechanism of adhesion GPCRs. In: Langenhan T, Schöneberg T (eds) Adhesion G protein-coupled receptors: molecular, physiological and pharmacological principles in health and disease. Springer, Heidelberg
158. Kishore A, Hall RA (2016) Versatile signaling activity of adhesion GPCRs. In: Langenhan T, Schöneberg T (eds) Adhesion G protein-coupled receptors: molecular, physiological and pharmacological principles in health and disease. Springer, Heidelberg
159. Araç D, Sträter N, Seiradake E (2016) Understanding the structural basis of adhesion GPCR functions. In: Langenhan T, Schöneberg T (eds) Adhesion G protein-coupled receptors: molecular, physiological and pharmacological principles in health and disease. Springer, Heidelberg
160. Lin H-H, Chang G-W, Davies JQ, Stacey M, Harris J, Gordon S (2004) Autocatalytic cleavage of the EMR2 receptor occurs at a conserved G protein-coupled receptor proteolytic site motif. J Biol Chem 279:31823–31832. doi:10.1074/jbc.M402974200
161. Krasnoperov VG, Bittner MA, Beavis R, Kuang YN, Salnikow KV, Chepurny OG et al (1997) alpha-Latrotoxin stimulates exocytosis by the interaction with a neuronal G-protein-coupled receptor. Neuron 18:925–937. doi:10.1016/S0896-6273(00)80332-3
162. Araç D, Boucard AA, Bolliger MF, Nguyen J, Soltis SM, Südhof TC et al (2012) A novel evolutionarily conserved domain of cell-adhesion GPCRs mediates autoproteolysis. EMBO J 31:1364–1378. doi:10.1038/emboj.2012.26
163. Liebscher I, Schön J, Petersen SC, Fischer L, Auerbach N, Demberg LM et al (2014) A tethered agonist within the ectodomain activates the adhesion G protein-coupled receptors GPR126 and GPR133. Cell Rep 9:2018–2026. doi:10.1016/j.celrep.2014.11.036
164. Stoveken HM, Hajduczok AG, Xu L, Tall GG (2015) Adhesion G protein-coupled receptors are activated by exposure of a cryptic tethered agonist. Proc Natl Acad Sci U S A. doi:10.1073/pnas.1421785112
165. Demberg LM, Rothemund S, Schöneberg T, Liebscher I (2015) Identification of the tethered peptide agonist of the adhesion G protein-coupled receptor GPR64/ADGRG2. Biochem Biophys Res Commun 464:743–747. doi:10.1016/j.bbrc.2015.07.020
166. Wilde C, Fischer L, Lede V, Kirchberger J, Rothemund S, Schöneberg T et al (2015) The constitutive activity of the adhesion GPCR GPR114/ADGRG5 is mediated by its tethered agonist. FASEB J. doi:10.1096/fj.15-276220
167. Sigoillot SM, Monk KR, Piao X, Selimi F, Harty BL (2016) Adhesion G protein-coupled receptors in the nervous system: from synapse and dendrite morphogenesis to myelination. In: Langenhan T, Schöneberg T (eds) Adhesion G protein-coupled receptors: molecular, physiological and pharmacological principles in health and disease. Springer, Heidelberg
168. Monk KR, Naylor SG, Glenn TD, Mercurio S, Perlin JR, Dominguez C et al (2009) A G protein-coupled receptor is essential for Schwann cells to initiate myelination. Science 325:1402–1405. doi:10.1126/science.1173474
169. Monk KR, Oshima K, Jörs S, Heller S, Talbot WS (2011) Gpr126 is essential for peripheral nerve development and myelination in mammals. Development 138:2673–2680. doi:10.1242/dev.062224
170. Glenn TD, Talbot WS (2013) Analysis of Gpr126 function defines distinct mechanisms controlling the initiation and maturation of myelin. Development 140:3167–3175. doi:10.1242/dev.093401
171. Mogha A, Benesh AE, Patra C, Engel FB, Schöneberg T, Liebscher I et al (2013) Gpr126 functions in Schwann cells to control differentiation and myelination via G-protein activation. J Neurosci 33:17976–17985. doi:10.1523/JNEUROSCI.1809-13.2013
172. Feltri ML, Wrabetz L (2005) Laminins and their receptors in Schwann cells and hereditary neuropathies. J Peripher Nerv Syst 10:128–143. doi:10.1111/j.1085-9489.2005.0010204.x

173. Monk KR, Feltri ML, Taveggia C (2015) New insights on Schwann cell development. Glia 63:1376–1393. doi:10.1002/glia.22852
174. Colognato H, Yurchenco PD (1999) The laminin alpha2 expressed by dystrophic dy(2J) mice is defective in its ability to form polymers. Curr Biol 9:1327–1330
175. Yang D (2005) Coordinate control of axon defasciculation and myelination by laminin-2 and -8. J Cell Biol 168:655–666. doi:10.1083/jcb.200411158
176. Xu H, Christmas P, Wu XR, Wewer UM, Engvall E (1994) Defective muscle basement membrane and lack of M-laminin in the dystrophic dy/dy mouse. Proc Natl Acad Sci U S A 91:5572–5576
177. Eberl DF (1999) Feeling the vibes: chordotonal mechanisms in insect hearing. Curr Opin Neurobiol 9:389–393. doi:10.1016/S0959-4388(99)80058-0
178. White JP (2016) Control of skeletal muscle cell growth and size through adhesion GPCRs. In: Langenhan T, Schöneberg T (eds) Adhesion G protein-coupled receptors: molecular, physiological and pharmacological principles in health and disease. Springer, Heidelberg
179. Budday S, Steinmann P, Kuhl E (2015) Physical biology of human brain development. Front Cell Neurosci 9:257. doi:10.3389/fncel.2015.00257
180. Peng Y-M, van de Garde MDB, Cheng K-F, Baars PA, Remmerswaal EBM, van Lier RAW et al (2011) Specific expression of GPR56 by human cytotoxic lymphocytes. J Leukoc Biol 90:735–740. doi:10.1189/jlb.0211092
181. Boyden SE, Desai MS, Cruse G, Young ML, Bolan HC, Scott LM et al (2016) Vibratory urticaria associated with a missense variant in ADGRE2. N Engl J Med 374(7):656–663. doi:10.1056/NEJMoa1500611
182. Bridges JP, Ludwig M-G, Mueller M, Kinzel B, Sato A, Xu Y et al (2013) Orphan G protein-coupled receptor GPR116 regulates pulmonary surfactant pool size. Am J Respir Cell Mol Biol 49:348–357. doi:10.1165/rcmb.2012-0439OC
183. Yang MY, Hilton MB, Seaman S, Haines DC, Nagashima K, Burks CM et al (2013) Essential regulation of lung surfactant homeostasis by the orphan G protein-coupled receptor GPR116. Cell Rep 3:1457–1464. doi:10.1016/j.celrep.2013.04.019
184. Fukuzawa T, Ishida J, Kato A, Ichinose T, Ariestanti DM, Takahashi T et al (2013) Lung surfactant levels are regulated by Ig-Hepta/GPR116 by monitoring surfactant protein D. PLoS One 8:e69451. doi:10.1371/journal.pone.0069451
185. Ludwig M-G, Seuwen K, Bridges JP (2016) Adhesion GPCR function in pulmonary development and disease. In: Langenhan T, Schöneberg T (eds) Adhesion G protein-coupled receptors: molecular, physiological and pharmacological principles in health and disease. Springer, Heidelberg
186. McMillan DR, Kayes-Wandover KM, Richardson JA, White PC (2002) Very large G protein-coupled receptor-1, the largest known cell surface protein, is highly expressed in the developing central nervous system. J Biol Chem 277:785–792. doi:10.1074/jbc.M108929200
187. McGee J, Goodyear RJ, McMillan DR, Stauffer EA, Holt JR, Locke KG et al (2006) The very large G-protein-coupled receptor VLGR1: a component of the ankle link complex required for the normal development of auditory hair bundles. J Neurosci 26:6543–6553. doi:10.1523/JNEUROSCI.0693-06.2006