Review series

The cell biology of **touch**

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The sense of touch detects forces that bombard the body's surface. In metazoans, an assortment of morphologically and functionally distinct mechanosensory cell types are tuned to selectively respond to diverse mechanical stimuli, such as vibration, stretch, and pressure. A comparative evolutionary approach across mechanosensory cell types and genetically tractable species is beginning to uncover the cellular logic of touch reception.

Force sensing is fundamental to development and survival of multicellular organisms. Cells are barraged by an array of forces, including pressure, stretch, flow, and sound waves. To cope with this diversity, specialized mechanosensory cells have evolved to be extraordinarily sensitive, selective, and fast (Chalfie, 2009). Forces that impinge upon the skin are encoded by touch receptors.

Touch is essential for myriad behaviors that range from avoiding bodily harm to social exchange. From *Caenorhabditis elegans* to mammals, species propagation relies on touch-dependent mating behaviors (Barr and Sternberg, 1999; Selden, 2004). In mammals, touch is also necessary for successful child rearing—cognitive development is stunted in touch-deprived infants (Kaffman and Meaney, 2007). Touch receptors in our fingertips are important for fine tactile acuity, which allows us to manipulate objects with high precision. We depend on this skill for countless tasks ranging from mundane (typing an e-mail) to transcendent (playing a Mozart concerto). Although indispensable in daily life, the sense of touch can be devastating in disease or injury, when dysregulation of sensory signaling leads to *touch hypersensitivity* and chronic pain (Gilron et al., 2006).

Among Aristotle's five primal senses, touch remains the least understood at the cellular level. Over the past three decades, genetic screens in *C. elegans* and *Drosophila melanogaster* have identified a plethora of molecules required for touch sensation. Recent work has begun to uncover mechanisms through which these molecules control force sensitivity. By comparison, the analysis of touch reception in mammals is in its infancy. Here, we introduce commonly used model systems, review emerging cell biological principles that govern touch sensitivity and highlight open questions in the field. *Mechanotransduction* in other cell types and *sensory modalities* has been covered in recent excellent reviews (Kung, 2005; Chalfie, 2009). Italicized terms are defined in Box 1.

A medley of mechanoreceptors

Mammalian touch receptors. A rich variety of somatosensory neurons innervate our skin to initiate the senses of touch and pain (Fig. 1). Discriminative touch is mediated by light-touch receptors, which are activated by innocuous mechanical stimuli. For example, lanceolate endings respond to hair movements, Pacinian corpuscles and Meissner's corpuscles are vibration receptors that convey textural information, and Merkel cell–neurite complexes encode an object's spatial features such as edges and curvature. The perception of pain is evoked by *nociceptors*, which are free nerve endings that respond to noxious stimuli. In addition to these broad categories, numerous classes of somatosensory neurons can be distinguished based on their functional properties and innervation patterns.

Somatosensory neurons share a basic body plan. Their somata are clustered in trigeminal ganglia, near the base of the skull, or dorsal root ganglia (DRG) nestled in each vertebra. Each somatosensory neuron has an axon, called a *sensory afferent*, which serves as a cellular cable that propagates electrical impulses, or action potentials, from the body to the central nervous system. The peripheral branches of these afferents, which innervate the skin and other organs, transduce sensory stimuli into action potentials.

In the skin, many peripheral afferents terminate in complex *end organs* whose structures shape their responses to force. For example, Pacinian corpuscles are lamellae-encased *rapidly adapting afferents* that fire selectively at the onset and offset of

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Abbreviations used in this paper: Deg/ENaC, degenerin/epithelial Na^+ channel; DRG, dorsal root ganglion; *mec*, mechanosensory abnormality; Nomp, no mechanoreceptor potential; SAI, slowly adapting type I; TRP, transient receptor potential.

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Box 1. Glossary of mechanosensory terms

Touch hypersensitivity. A heightened sensory response to force stimuli, which can accompany inflammation, injury, or disease.

Mechanotransduction. Conversion of a force into a cellular signal.

Sensory modality. A specific aspect of a stimulus that is encoded by a sensory receptor cell. Examples of primary sensory modalities include touch, pain, hearing, and taste. Examples of touch modalities include vibration, stretch, and pressure.

Nociceptor. A somatosensory neuron activated by noxious mechanical, thermal, or chemical stimuli.

Sensory afferent. A somatosensory neuron's bifurcating axon. Peripheral branches innervate skin and internal organs, whereas central branches innervate spinal cord and hindbrain.

End organs. The specialized terminals of peripheral afferents that transduce sensory stimuli into action potentials.

Rapidly adapting afferent. Light-touch receptors that respond at the onset and offset of a sustained mechanical stimulus. These receptors respond robustly to vibration.

Adaptation. A change in neuronal output to a constant sensory input.

Mechanical threshold. The amount of force necessary to evoke a response in a given mechanosensory receptor cell.

Slowly adapting afferent. Light-touch receptors that fire throughout a sustained mechanical stimulus.

Hair cells. Mechanosensory receptor cells of the vertebrate inner ear and lateral line organs that mediate hearing and balance.

Proprioceptors. Sensory neurons that monitor limb position to govern coordinated movements. These sensory receptors innervate joints and specialized muscle fibers.

Receptor potential. The change in membrane potential that occurs when a sensory stimulus activates transduction channels.

Osmosensitive channels. Membrane proteins gated by differential changes in the solute concentration (osmolarity) of a cell's extracellular and intracellular environments.

Stereocilia. In vertebrate hair cells, specialized microvilli that are sites of mechanosensory transduction.

Hemidesmosome. Junctional complex between an epithelial cell and the basal lamina.

Paracrine signaling. The ability to communicate with surrounding cells through the secretion of bioactive compounds.

a sustained touch (Fig. 1). These lamellae act as mechanical filters to govern *adaptation* (Loewenstein and Mendelson, 1965); however, recent work suggests that they also release neurotransmitters to shape sensory responses (Pawson et al., 2009). Another rapidly adapting receptor, the Meissner's corpuscle, is innervated by three distinct types of sensory afferents, which highlights the complexity of touch-sensitive end organs (Paré et al., 2001).

Along with morphology, electrophysiological properties can be used to group touch receptors (Fig. 1). Afferents are broadly classified as Aβ, Aδ, or C-fibers by the speed of action-potential propagation, which is set by myelin thickness. They can be further distinguished by *mechanical threshold*, adaptation, firing pattern, and modality, or the mechanical stimulus to which they best respond. Most Aβ afferents, which are thickly myelinated, have low mechanical thresholds and are therefore likely to be light-touch receptors. Most unmyelinated C-fiber and thinly myelinated Aδ afferents are thought to be nociceptors based on their high mechanical thresholds and projection patterns to the central nervous system (for review see Smith and Lewin, 2009). Others, including down hair, or D-hair, afferents and low-threshold C-fibers, display mechanical thresholds below the nociceptive range. Although the function of low-threshold C-fibers is not known, they have been proposed to contribute to touch hypersensitivity after injury (Seal et al., 2009) or to an affective, or emotional, component of touch (Olausson et al., 2002; Löken et al., 2009).

Developmental studies have begun to define transcription factors and growth factor pathways that underlie the diversity of touch-receptive afferents (Fig. 1; Luo et al., 2007). For example, some nociceptors require nerve growth factor (NGF) and its receptor TrkA for postnatal survival. Other nociceptors express *Runx1,* a transcription factor, and *Ret*, a receptor for glial-derived neurotrophic factor family members. Sensory neurons distinguished by the transcription factor *MafA* and early *Ret* expression innervate hair follicles, Pacinian corpuscles and Meissner's corpuscles (Bourane et al., 2009; Luo et al., 2009).

Most Merkel cell–neurite complexes require neurotrophin-3 (NT-3) and its receptor TrkC for postnatal survival (Airaksinen et al., 1996). These exquisitely sensitive touch receptors mediate *slowly adapting* type I (SAI) responses (Yoshioka et al., 2001; Woodbury and Koerber, 2007). To properly encode touch stimuli, SAI afferents require the presence of Merkel cells, which are putative sensory cells (Maricich et al., 2009). In striking parallel to *hair cells,* which are mechanosensory receptors in the inner ear (Schwander et al., 2010), Merkel cells are vertebrate epithelial specializations whose development depends on the transcription factor Atonal 1 (Atoh1; Maricich et al., 2009; Morrison et al., 2009; Van Keymeulen et al., 2009).

Transgenic mice have been engineered to express markers in subsets of touch receptor cells, including light-touch receptors (Hasegawa and Wang, 2008; Bourane et al., 2009; Luo et al., 2009), Merkel cells (Lumpkin et al., 2003), low-threshold C-fibers (Q. Liu et al., 2007; Seal et al., 2009), and C-nociceptors (Stirling et al., 2005; Zylka et al., 2005). Most available markers label multiple touch-receptor classes; however, as the list continues to grow, genetically encoded markers will be a gateway to defining the molecular differences that dictate unique responses in touch-receptor subtypes (Zhang et al., 2002; Haeberle et al., 2004).

***C. elegans* touch receptors.** In the tiny nematode *C. elegans,* a repertoire of force-evoked behaviors is initiated by mechanosensory neurons, which comprise ∼10% of the entire nervous system (Fig. 2 A; Goodman, 2006). Touch initiates avoidance behaviors, which include speeding up to escape posterior stimuli, and backing up or head turning to avoid anterior touch. Gentle body touch is transduced by touch receptor neurons that extend neurites along the animal's length (Fig. 2 A, blue; Sulston et al., 1975; Chalfie and Sulston, 1981). Harsh prodding

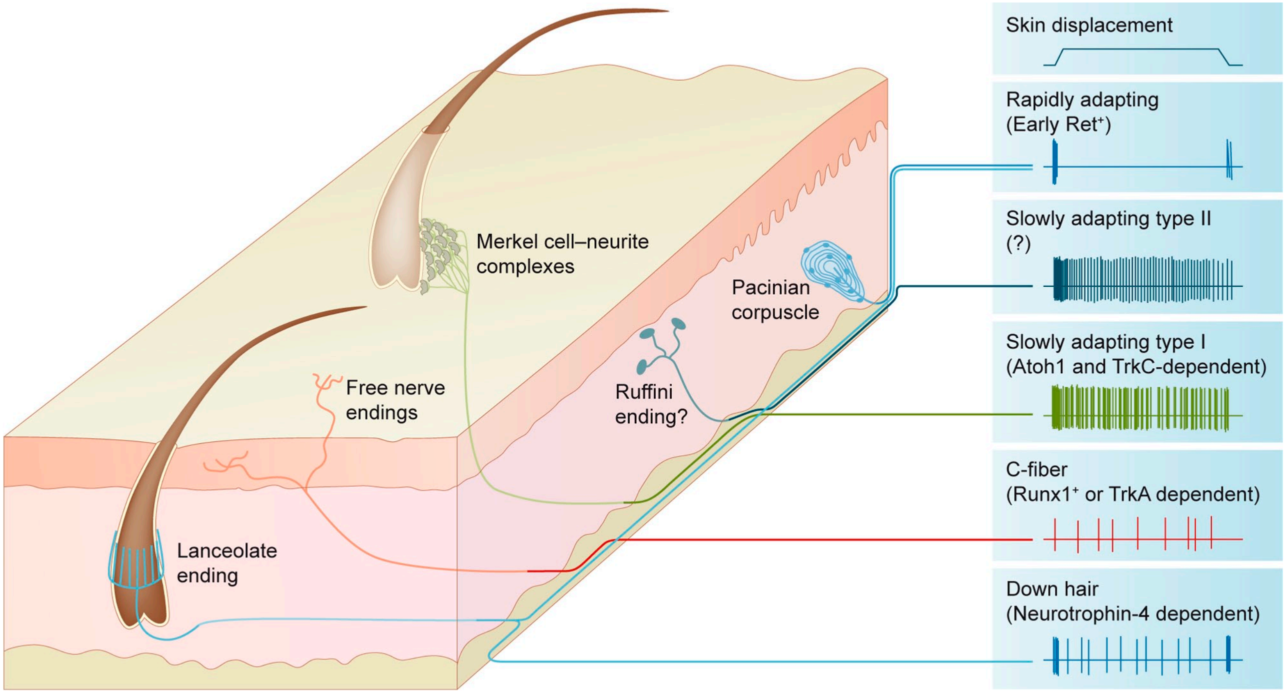

Figure 1. **Touch receptors in mammalian skin.** Touch-sensitive afferents that innervate mammalian skin display morphological, functional, and developmental diversity. As shown, lanceolate endings, Merkel cell–neurite complexes, Ruffini endings, and free nerve endings innervate hairy skin. These receptors have unique neuronal outputs, making classification feasible by electrophysiological recording from intact tissue. Lanceolate endings serve as rapidly adapting or down hair afferents. The latter are exceptionally sensitive light-touch receptors that depend on Neurotrophin-4 for proper development (Stucky et al., 1998). Merkel cell–neurite complexes mediate slowly adapting type I (SAI) responses, which are characterized by an irregular firing pattern during sustained pressure (Wellnitz et al., 2010). Although their presence in different species is debated, Ruffini endings have been proposed to mediate stretch-sensitive slowly adapting type II (SAII) responses (Chambers et al., 1972). Developmental pathways have not yet been defined for these receptors. Free nerve endings, which abundantly innervate the epidermis, include nociceptors and low-threshold C-fibers (Seal et al., 2009). Pacinian corpuscles are lamellar vibration receptors that produce rapidly adapting responses. In glabrous skin of the palms and fingertips, Pacinian corpuscles, rapidly adapting Meissner's corpuscles (not depicted), Merkel cell–neurite complexes, and free nerve endings make up the majority of touch receptors.

is detected by distinct neurons with elaborate sensory dendrites that tile the body wall (Fig. 2 A, red; Way and Chalfie, 1989; Chatzigeorgiou et al., 2010). Ciliated mechanosensory neurons innervating the nose mediate touch and physically sense food particles, which impacts foraging behaviors (Fig. 2 A, green; Kaplan and Horvitz, 1993; Sawin et al., 2000; Li et al., 2006; Kindt et al., 2007). Mating behaviors rely on ciliated male-specific neurons called sensory rays (Fig. 2 A, orange; Liu and Sternberg, 1995; Barr and Sternberg, 1999; T. Liu et al., 2007).

Thanks to a wealth of tools for analyzing the *C. elegans* nervous system, mechanotransduction is best understood in this organism. Central to this success, Chalfie and colleagues devised a simple behavioral assay for gentle-body touch and screened for genetic mutations that selectively caused mechanosensory abnormality (*mec*) without impairing locomotion (Sulston et al., 1975; Chalfie and Sulston, 1981; Chalfie and Au, 1989). Additional studies have dissected responses to nose touch and harsh body touch (Way and Chalfie, 1989; Colbert et al., 1997; Hart et al., 1999; Chatzigeorgiou et al., 2010). To delineate the cellular basis of mechanosensation, laser ablation has been used to pinpoint neurons required for touch-evoked behaviors. Additionally, anatomical reconstructions have mapped connectivity to define neural networks that link touch sensation to behaviors. Moreover, mechanosensory molecules can be assigned to signaling pathways with physiological approaches, including in vivo imaging and electrophysiology (Fig. 2 B).

***Drosophila* mechanosensory neurons.** Mechanosensory genes in *Drosophila* have been identified through forward genetic screens for insensitivity to gentle touch, noxious stimuli, and mating song (Kernan et al., 1994; Eberl et al., 1997; Tracey et al., 2003). Like worms and mammals, flies have a sizable assortment of mechanosensory neurons essential for survival (for review see Kernan, 2007; Smith and Lewin, 2009). In addition to touch receptors, *Drosophila* require auditory receptors to distinguish mating songs, wing strain gauges to fly and *proprioceptors* to coordinate their six legs. Even in a cushy laboratory setting, mechanosensory mutants perish because they are completely uncoordinated.

The fly's body is studded with type I ciliated mechanosensory receptors such as chordotonal organs and bristles (Fig. 2; Kernan, 2007). Chordotonal organs, which are stretch receptors attached to the skin, or cuticle, make up the fly's ear and contribute to proprioception. Bristles serve as the principal proprioceptors and touch receptors. These mechanosensory organs are generally innervated by one sensory neuron, which extends a sensory cilium into overlying structures (Fig. 2 C). Bristles act as levers to transmit force to the cilium attached at its base by the dendritic cap. This compresses the ciliary membrane against the tubular bundle, an array of microtubules at the dendrite's core. The resulting compression is the putative gating stimulus for mechanotransduction channels, which carry cation-selective, adapting currents remarkably similar to those of vertebrate hair cells (Fig. 2 D).

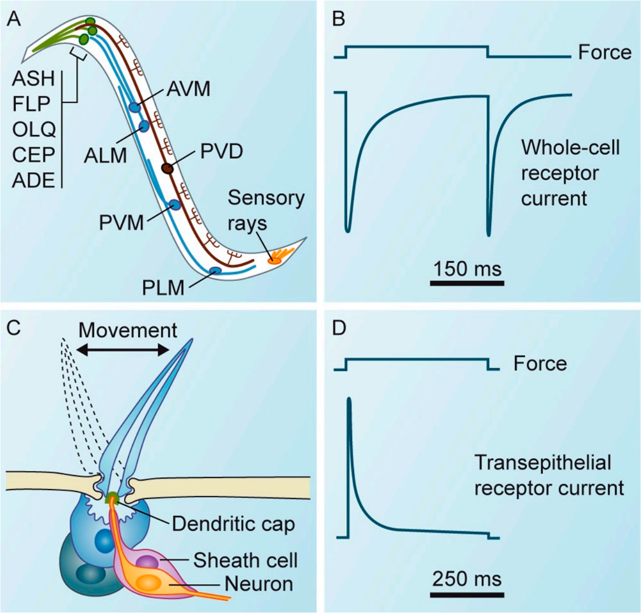

Figure 2. **Mechanosensory transduction in *C. elegans* and *Drosophila*.** (A) Mechanosensory neurons of *C. elegans* include gentle body touch neurons (blue), multidendritic harsh-touch neurons (red), ciliated neurons (green) required for nose-touch (ASH, FLP, and OLQ) or proper foraging behaviors (CEP, ADE, and PDE [not indicated]), and ciliated male-specific neurons (orange). For paired neurons, only one is shown. The branching menorahs of the PVD cell cover both sides of the worm, but only one side is shown for clarity. (B) An idealized mechanosensory current from PLM, a body touch neuron, is shown below the corresponding force stimulus. Force conveyed directly through contact with the body wall is sufficient to depolarize touch-sensitive neurons. This current is carried by MEC-4 transduction–channel complexes. (C) *Drosophila* bristle morphology. Bristle movement deforms the dendritic sheath of the mechanosensory neuron, which leads to neuronal excitation. (D) Bristle mechanoreceptor currents are recorded extracellularly in a transepithelial configuration, causing the current to appear opposite from *C. elegans* touch receptors; however, both currents are excitatory. Bristle drawing adapted with permission from Jarman, 2002.

Type II mechanosensory neurons are nonciliated neurons that innervate the cuticle (Kernan, 2007). Their multidendritic morphology is reminiscent of mammalian somatosensory neurons and *C. elegans* harsh body-touch receptors (Chatzigeorgiou et al., 2010; Oren-Suissa et al., 2010; Smith et al., 2010). Like mammalian nociceptors, at least some of these neurons sense harsh touch and noxious heat (Tracey et al., 2003; Zhong et al., 2010).

Touchy ion channels

Ion channels are key components of the transduction cascades that convert stimulus energy into membrane potential changes. In most cases, the resulting *receptor potential* triggers action potentials that transmit sensory information with high fidelity (Fig. 3). Although transduction channels are known for most mammalian sensory modalities, those that underlie touch and hearing have proven astonishingly difficult to identify. In invertebrates, leading candidates fall into the degenerin/epithelial Na$^+$ channel (Deg/ENaC) and transient receptor potential (TRP) families.

Models of force gating. In mechanosensory cells, transduction channels are thought to be directly gated by force because of their sub-millisecond response times (Corey and Hudspeth, 1979; Walker et al., 2000; O'Hagan et al., 2005; Kang et al., 2010). Like bacterial *osmosensitive channels* (Box 2), eukaryotic mechanotransduction channels might be stretch-sensitive channels gated by membrane forces (Kung, 2005; Lumpkin and Caterina, 2007). In some mechanosensory cells, transduction channel gating is proposed to require links to the cytoskeleton or extracellular matrix (ECM). Such tethers might couple directly to transduction channels, as they do for mechanosensitive integrins. Alternatively, tethers could control membrane deformation around a stretch-sensitive channel. The tether model is supported by a wealth of genetic and biophysical studies in hair cells (Assad et al., 1989; Vollrath et al., 2007; Schwander et al., 2010).

Deg/ENaC channels. The best characterized eukaryotic mechanotransduction channel is the MEC-4 complex, which transduces gentle body touch in *C. elegans* (Fig. 4; Chalfie, 2009). The Deg/ENaC subunits MEC-4 and MEC-10 form the core of this multiprotein complex (Goodman et al., 2002). Channel activity is dramatically enhanced by the accessory subunits MEC-6 and MEC-2, stomatin domain proteins that bind cholesterol (Chelur et al., 2002; Goodman et al., 2002; Huber et al., 2006; Brown et al., 2008). These are essential components, as mutations in each disrupt touch-evoked behaviors. The *unc-24* gene encodes a second stomatin domain protein that colocalizes with the MEC-4 complex. Because *unc-24* mutations only impair touch responses on a sensitized genetic background, this molecule participates in, but is not required for, touch reception (Zhang et al., 2004).

Although heterologously expressed MEC-4 complexes have not been shown to be force sensitive, compelling evidence argues that they mediate native mechanotransduction currents. Electrophysiology and in vivo imaging showed that mutations in *mec-4*, *mec-6*, and *mec-2* abolish transduction without disrupting other cellular functions (Suzuki et al., 2003; O'Hagan et al., 2005). Moreover, point mutations in *mec-4* and *mec-10* alter ion selectivity of native channels (O'Hagan et al., 2005). With a bona fide transduction channel in hand, the next challenge is to develop a mechanistic understanding of force gating.

Invertebrate Deg/ENaC channels are also required for responses to harsh touch. In *Drosophila*, *pickpocket* is expressed in type II multidendritic neurons that serve as nociceptors (Adams et al., 1998; Hwang et al., 2007). Disrupting *pickpocket* expression impairs harsh touch–evoked behaviors (Zhong et al., 2010). Similarly, the expression of *mec-10* and *degt-1* in *C. elegans* multidendritic neurons is required for avoidance of harsh prodding (Chatzigeorgiou et al., 2010). Collectively, these findings indicate that Deg/ENaC channels function in touch sensation across species and modalities.

A number of *mec*-related molecules are expressed in mammalian DRG neurons and their possible roles in touch reception have been examined in knock-out mice (Fig. 3). Disruption of a distant *mec-2* relative, stomatin-like protein-3 (SLP3), causes behavioral deficits in texture discrimination and loss of mechanosensitivity in a subset of mouse touch receptors (Wetzel et al., 2007). Although these SLP3-dependent sensory neurons have yet to be identified, this intriguing result points to a conserved role for stomatin domain proteins in touch. In contrast, only

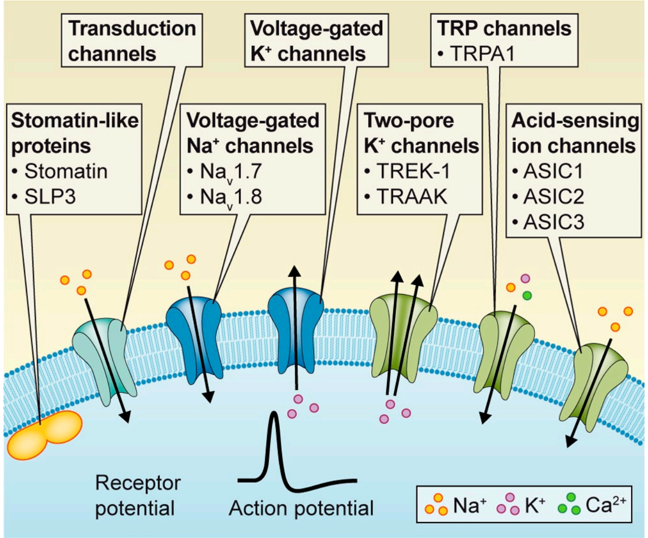

Figure 3. **Molecules that govern touch sensitivity in mammalian somatosensory neurons.** Classes of ion channels that transduce or modulate touch sensitivity are listed in bold. Listed below are genes that have been implicated in mammalian touch responses or pathologies by genetic studies. Transduction channels (cyan) convert force into receptor currents, which then trigger action potentials by opening voltage-activated sodium and potassium channels (blue). This signal travels to the brain to alert the organism of force stimuli. Touch sensitivity is also dictated by ion channels that modify the signal or set membrane excitability (green). Touch deficits result from mutations in voltage-activated sodium channels (Nassar et al., 2004; Cox et al., 2006), two-pore potassium channels (encoded by KCNK genes), ASIC subunits, which are encoded by amiloride-sensitive cation channel (ACCN) genes, and TRP channels, such as TRPA1. Stomatin-domain proteins (yellow) alter touch sensitivity in some mammalian sensory neurons (Martinez-Salgado et al., 2007; Wetzel et al., 2007).

subtle changes in touch-evoked responses result from disrupting mammalian DEG/ENaC isoforms called acid-sensing ion channels (ASICs; encoded by amiloride-sensitive cation channel [ACCN] genes; Price et al., 2000, 2001; Drew et al., 2004). Thus, these channels might modulate rather than transduce mechanosensory information in mammals (Fig. 3). Alternatively, these modest phenotypes may reflect redundant gene function.

TRP channels. TRP channels are a diverse class of cation channels implicated in a wide variety of physiological processes, including numerous sensory modalities. In *C. elegans*, the TRP vanilloid (TRPV) isoforms *osm-9* and *ocr-2* are expressed in ciliated mechanoreceptors, and their mutations impair nose-touch avoidance, hypertonicity, and chemical stimuli (Colbert et al., 1997; Tobin et al., 2002; Kahn-Kirby and Bargmann, 2006). These proteins colocalize in sensory cilia. Their ciliary localization is interdependent; therefore, these isoforms likely form heteromers. A role for *osm-9's* mammalian orthologue TRPV4 in mechanotransduction has also been proposed; however, TRPV4 disruption has only modest effects on touch thresholds (Liedtke and Friedman, 2003; Suzuki et al., 2003). Interestingly, the related *Drosophila* TRPV isoforms, *nanchung* (*nan*) and *inactive* (*iav*), are required for hearing but not touch (Kim et al., 2003; Gong et al., 2004).

PKD-2 is another *C. elegans* TRP channel that localizes to sensory cilia (Barr et al., 2001). This channel is expressed in male-specific neurons. Mating defects result from mutations in this gene and its partner, the PKD-1 homologue *lov-1*.

Box 2. Ancient mechanotransduction channels

Although mechanotransduction exists in myriad forms in metazoans, mechanical senses originated in unicellular organisms. The first to evolve was osmosensation, which allows a cell to maintain membrane integrity when confronted with varying aqueous environments. In fact, the most extensively characterized mechanotransduction channels are the Msc channels of *Escherichia coli* (MscL, MscS, and MscM), which act as emergency release valves to expel solutes in the presence of hypotonic external solutions (Berrier et al., 1996). This quick response prevents lysing as a result of increased osmotic pressure inside the cell.

Although Msc channels are not conserved in vertebrates, homologues are present in members of *Archaea* (Kloda and Martinac, 2001). The only eukaryotic homologues of Msc channels are found in plants. These MscS-like (MSL) channels are likely to perform similar functions to their bacterial counterpart by allowing plants to correct for improper cellular turgor (Peyronnet et al., 2008).

TRPN1, which is encoded by the *no mechanorecptor potential C* (*nompC*) gene, was the first candidate mechanotransduction channel identified in *Drosophila.* Mutant flies exhibit defects in touch, hearing, and proprioception (Kernan et al., 1994; Walker et al., 2000). Because these mutants have severely reduced mechanotransduction currents in bristles, TRPN1 is an excellent candidate for a touch transduction channel (Walker et al., 2000). Consistent with this hypothesis, TRPN1 localizes to the distal tips of sensory dendrites in chordotonal and bristle mechanoreceptors (Cheng et al., 2010; Lee et al., 2010). This channel is also expressed in a subset of multidendritic neurons that may function as proprioceptors (Cheng et al., 2010). In a noteworthy parallel, the *C. elegans* TRPN1 orthologue TRP-4 is expressed in putative proprioceptors and in ciliated mechanosensory neurons involved in foraging behavior (Li et al., 2006). An exciting recent study demonstrates that mechanotransduction currents in these ciliated neurons require functional TRP-4. Furthermore, TRP-4 pore mutations alter the biophysical properties of native transduction currents. Together, these findings strongly support the notion that TRPN1 is a mechanosensory transduction channel in invertebrates. Mammals have apparently adopted a different molecular strategy for touch transduction: TRPN1 homologues are expressed in mechanosensory cells in *C. elegans,* zebrafish, and amphibians, but they are not found in mammalian genomes (Walker et al., 2000; Sidi et al., 2003; Shin et al., 2005; Li et al., 2006).

TRPA isoforms are also involved in touch reception. For example, *Drosophila painless* is required for behavioral responses to harsh prodding and noxious heat (Tracey et al., 2003). *C. elegans trpa-1* mutants display defects in nose-touch and foraging behaviors (Kindt et al., 2007). Mammalian TRPA1 is likely to modulate the responsiveness of touch-sensitive nociceptors during inflammation (Fig. 3; Lumpkin and Caterina, 2007; Kwan et al., 2009).

Touch-evoked currents in cultured DRG neurons. Although the molecular identities of mammalian mechanotransduction channels remain mysterious, touch-evoked currents have been studied in cultured DRG neurons (McCarter et al., 1999). In subsets of DRG neurons these currents have different ion selectivities, which suggests that they are carried by discrete ion channel isoforms (Drew et al., 2002; Hu and Lewin, 2006; Rugiero et al., 2010). Like touch receptors in vivo,

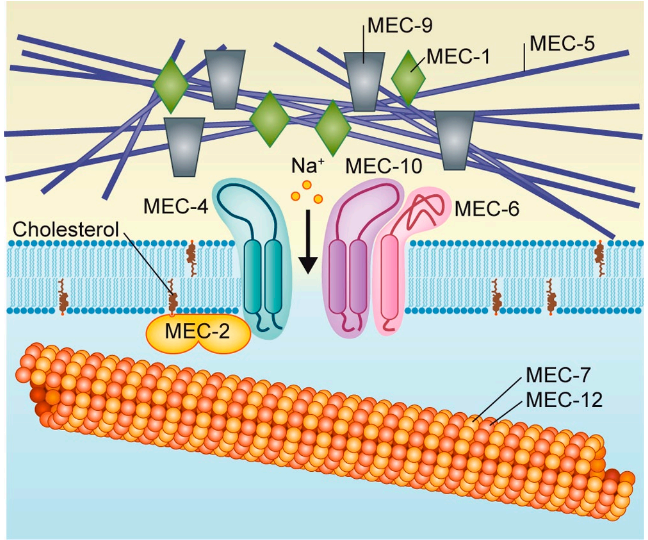

Figure 4. **A molecular model of touch—the MEC-4 complex.** The MEC-4 complex of *C. elegans* body-touch neurons has been the focus of three decades of research. MEC-4 and MEC-10 are Deg/ENaC isoforms that serve as pore-forming subunits. Functional channels likely contain two MEC-4 subunits and one MEC-10 subunit (Hong and Driscoll, 1994; Jasti et al., 2007). MEC-2 and MEC-6 are accessory subunits that enable channel activity. MEC-2 is a stomatin-like protein located in the inner leaflet of the membrane, whereas MEC-6 is a paraoxonase-like transmembrane protein (Chelur et al., 2002). Mechanotransduction also requires a specialized extracellular matrix, consisting of MEC-5, a collagen isoform, and MEC-1 and MEC-9, both with multiple EGF repeats. MEC-7 and MEC-12 are tubulin monomers that form 15-protofilament microtubules required for touch sensitivity.

cultured DRG neurons display a variety of adaptation profiles (Rugiero et al., 2010). Unlike hair cells, adaptation in cultured DRG neurons is Ca^{2+} independent. Collectively, these studies suggest that mechanotransduction in mammalian cells is mediated by distinct molecular mechanisms. An exciting recent study has identified a novel ion channel class, the piezo family, which is required for touch-evoked currents in cultured DRG neurons (Coste et al., 2010). How these touch-evoked responses in vitro relate to mechanotransduction in vivo is an important, open question.

Additional ion channels shape touch sensitivity. Signaling pathways downstream of transduction govern touch sensitivity by altering membrane excitability (Fig. 3; Foulkes and Wood, 2008). Loss-of-function mutations in *SCN9A*, which encodes $Na_V1.7$, a nociceptor-specific voltage-activated Na^+ channel, cause a dramatic loss of sensitivity to painful stimuli in humans and mice (Nassar et al., 2004; Cox et al., 2006). Conversely, gain-of-function mutations in this gene lead to pain hypersensitivity. Increased touch responsiveness has also been observed in mice lacking two-pore K^+ channels, which set resting membrane potentials (Nöel et al., 2009). Related two-pore K^+ channels are proposed to be the molecular targets of sanshool, a compound found in Schezuan peppercorns that activates touch receptors and induces a tingling sensation in humans (Lennertz et al., 2010). Although intensive efforts remain focused on identifying mammalian mechanotransduction channels, these studies underscore the possibility that other sensory molecules may be targets for therapeutic development.

Handling stress with cytoskeletal support

Like hair cells, many touch receptors have prominent cytoskeletal specializations. In invertebrates, these specializations are microtubule based. Modified cilia serve as sensory dendrites in *Drosophila* type I mechanosensory neurons, as well as in *C. elegans* nose-touch and male-specific neurons (Goodman, 2006; Kernan, 2007). Thus, sensory defects result from mutations in genes that disrupt ciliogenesis, intraflagellar transport, or ciliary protein localization (Perkins et al., 1986; Kernan, 2007; Bae et al., 2008). Although *C. elegans* body-touch receptor neurons lack sensory cilia, their mechanosensitive processes are filled with highly cross-linked, 15-protofilament microtubules (Fig. 4; Chalfie and Thomson, 1979, 1982).

Analysis of two *mec* genes demonstrates that these unique structures are essential for touch-evoked behaviors. *Mec-12* and *mec-7* encode α- and β-tubulins that form 15-protofilament microtubules (Savage et al., 1989; Fukushige et al., 1999). These genes are highly expressed in touch receptor neurons, consistent with the observation that 15-protofilament microtubules are exclusive to these cells (Chalfie and Sulston, 1981; Chalfie and Thomson, 1982; Hamelin et al., 1992; Fukushige et al., 1999). Many *mec-7* and *mec-12* mutant alleles cause 15-protofilament microtubules to be replaced by typical microtubules (Chalfie and Thomson, 1982). Mutations in these two genes also render worms touch insensitive (Chalfie and Sulston, 1981; Chalfie and Au, 1989). Based on such genetic evidence, early tether models posited that attachments between the MEC-4 complex, the cytoskeleton, and the ECM are necessary for mechanotransduction (Gu et al., 1996).

Recent physiological and structural data indicate that this model must be revised (Fig. 4). Importantly, transduction currents are attenuated, but not abolished, by *mec-7* and *mec-12* mutations. These data demonstrate that 15-protofilament microtubules, although necessary for touch-evoked behaviors, are not required for transduction channel activation (O'Hagan et al., 2005; Bounoutas et al., 2009). Moreover, functional MEC-4 complexes are unlikely to be attached to microtubules because the densities of MEC-4 puncta and juxtamembrane microtubules are not correlated, and these structures do not colocalize at the plasma membrane (Emtage et al., 2004; Cueva et al., 2007). Instead, microtubule bundles link to the plasma membrane at sites distinct from MEC-4 puncta. One candidate for these links is Echinoderm microtubule-associated protein-like protein-1 (ELP-1), which is expressed in cells that adhere to the cuticle, including body-touch receptor neurons, nose-touch neurons, and male-specific neurons (Hueston et al., 2008). Notably, disrupting *elp-1* impairs touch sensitivity.

Together, these findings suggest that the cytoskeleton impacts force sensitivity without direct attachments to the MEC-4 complex. Alternative models posit that the MEC-4 complex is a stretch-activated channel and that microtubule bundles indirectly participate in gating by altering membrane forces during channel activation or adaptation (Cueva et al., 2007; Bounoutas et al., 2009).

Along with a structural role in force sensing, wild-type microtubules are required for proper trafficking of mechanotransduction proteins. Strong loss-of-function mutations in *mec-7* and *mec-12* disrupt overall protein levels and the distribution of MEC-4 puncta (Emtage et al., 2004; Bounoutas et al., 2009). Although transduction channels must insert into the plasma membrane to activate neurons, immunoelectron microscopy indicated that about half of the MEC-4 complexes are linked to intracellular microtubules in the absence of membrane-bound vesicles (Cueva et al., 2007). This intriguing observation suggests that membrane proteins might traffic along microtubules via nonvesicular transport in touch receptor neurons.

Compared with hair cells and *C. elegans* touch receptors, little is known about the role of the cytoskeleton in vertebrate touch reception. One study of cultured DRG neurons found that cytochalasin B, which inhibits actin polymerization, attenuates mechanosensitive currents (Drew et al., 2002). Whether this effect is through alterations in the cortical cytoskeleton or microfilament-based specializations is unclear. In fact, cytoskeletal specializations have not yet been described in mammalian somatosensory afferents.

In contrast, Merkel cells have conspicuous microvilli, which are coupled to overlying epidermal cells by electron-dense filaments (Toyoshima et al., 1998). Intriguingly, these processes are enriched in espin, an actin-binding protein found in hair cell *stereocilia* and other sensory microvilli (Sekerková et al., 2004). Based on their structural similarity to stereocilia, the Merkel cell's microvilli have been proposed to be sites of mechanotransduction (Iggo and Findlater, 1984); however, functional support for this model is lacking.

Grasping the role of the matrix

Forces exerted between metazoan cells and the ECM play a fundamental role in the development and function of complex tissues (for review see Ingber, 2006). Different tissues express numerous ECM components and their receptors, most notably integrins. The ability of cells to respond appropriately to their local matrix environment is essential for cell migration, differentiation, and survival (for review see Legate et al., 2009).

The importance of ECM proteins to touch sensation is best understood in *C. elegans* touch receptor neurons. Their mechanosensitive neurites are embedded in an electron-dense ECM and surrounded by epidermal cells, which are attached to the cuticle at periodic hemidesmosomal-like structures (Emtage et al., 2004). In these neurons, touch responses require specialized ECM components as well as integrin signaling (Calixto et al., 2010).

Three *mec* genes encode essential ECM components (Fig. 4; Chalfie and Sulston, 1981; Du et al., 1996). Touch receptor neurons express MEC-1 and MEC-9, which are secreted proteins containing multiple epidermal growth factor (EGF)–like domains and Kunitz-like repeats (Du et al., 1996; Emtage et al., 2004). A unique collagen encoded by *mec-5* is produced by adjacent epidermal cells (Du et al., 1996). Interestingly, these proteins are distributed in puncta that overlap with MEC-4 complexes (Emtage et al., 2004). Mutations in these matrix-component genes disrupt the subcellular distribution of MEC-4 complexes. In contrast, the punctate localization of ECM components is unaffected by *mec-4* mutations. Together, these data suggest that the ECM properly localizes transduction channels. Based on incomplete colocalization of MEC-5 and MEC-4 complexes at the ultrastructural level, Cueva et al. (2007) have argued that MEC-5 is unlikely to function as a gating tether. Whether integrins or other linking proteins play a direct role in transduction channel activation remains to be determined.

In *Drosophila* type I sensory organs, connections between mechanosensory dendrites and the cuticle are essential for transduction (Kernan, 2007). As in *C. elegans*, mechanosensory processes are encircled by supporting cells that secrete an electron-dense ECM, termed the dendritic sheath or cap (Fig. 2 C). One component of this matrix is encoded by the *NompA* gene (Chung et al., 2001). Behaviorally, *NompA* mutants are touch insensitive and deaf. They also lack bristle mechanoreceptor responses (Kernan et al., 1994).

Three lines of evidence argue that NompA is a structural element of the dendritic cap (Chung et al., 2001). First, *NompA* mutants have disorganized dendritic caps and detached mechanosensory dendrites. Second, NompA includes a large, secreted domain that localizes to the cap. Third, this region contains a zona pellucida domain, which is commonly found in ECM proteins. In a noteworthy parallel, zona pellucida domain proteins called tectorins are major components of the tectorial membrane, which is essential for mechanical stimulation of cochlear hair cells (Killick et al., 1995). Because dendrite attachment is disrupted in *NompA* mutants, it is clear that NompA, like tectorins, plays a key structural role in mechanotransduction. Whether it also directly participates in transduction channel gating is still unclear.

Although the importance of the ECM in development of mammalian somatosensory neurons has long been recognized, a possible role in sensory transduction is only now being explored. In DRG neurons, interactions between specific integrins and the ECM promote neurite extension during development and injury-induced regeneration (Tomaselli et al., 1993; Andrews et al., 2009). An intriguing recent study implicates molecularly distinct extracellular contacts in mammalian touch reception (Hu et al., 2010). In DRG neurons in vitro, Hu et al. (2010) observed that touch-sensitive neurites are connected to laminin substrates via 100-nm proteinaceous filaments. Reminiscent of pioneering studies that revealed the Ca^{2+} sensitivity of hair cell tip links (Assad et al., 1991), a battery of treatments was tested to define those that disrupted 100-nm filaments and abolished mechanosensitivity in putative light-touch receptors. These filaments are sensitive to furin proteases but are resistant to treatments that disrupt integrins, cadherins, and glycosyl phosphatidylinositol-anchored proteins. This unique sensitivity profile indicates that 100-nm tethers are distinct from integrins as well as cadherin-based tip links in hair cells. Defining the molecular identity of these junctional proteins and determining their role in mechanotransduction will be exciting next steps.

Sensational epidermal cells

Although the epidermis's mechanical properties are key for transmitting force from the skin's surface to touch receptors, several lines of evidence suggest that epidermal cells play more than a mere structural role. In *C. elegans* touch receptor neurons, structural attachment to the cuticle is not required for touch sensitivity, as demonstrated by the touch responsiveness of *him-4* mutants that lack hemidesmosomal connections to the cuticle (Vogel and Hedgecock, 2001). Instead, the epidermis secretes essential ECM molecules that are proposed to position transduction channel complexes in sensory neurons (Emtage et al., 2004).

Mammalian epidermal cells are ideally poised to participate in somatosensory signaling (Lumpkin and Caterina, 2007). The epidermis is innervated by sensory afferents that transduce noxious mechanical stimuli (Zylka et al., 2005; Cavanaugh et al., 2009) and by Merkel cell–neurite complexes (Johnson, 2001). Keratinocytes, which are the principal cells of the epidermis, Merkel cells, and the lamellae of Pacinian corpuscles express neurotransmitters that have the potential to tune the touch sensitivity of afferents (Halata et al., 2003; Lumpkin and Caterina, 2007; Pawson et al., 2009). Although keratinocytes and sensory afferents do not form synapses, their proximity could allow rapid *paracrine signaling*.

Notably, mammalian epidermal cells express sensory ion channels implicated in mechanotransduction, such as TRPV4 and TRPA1 (Liedtke et al., 2000; Lee and Caterina, 2005; Kwan et al., 2009). Mechanically evoked firing properties of light-touch receptors are altered in TRPA1 knockout mice, leading Kwan et al. (2009) to propose that TRPA1 influences touch sensitivity through a modulatory role in keratinocytes. This model is readily testable with tissue-specific knock-outs.

In 1875, Merkel posited that his eponymous cells act as touch receptors and several lines of evidence support this notion (Merkel, 1875). Merkel cells form synaptic contacts with sensory neurons, express numerous presynaptic proteins, and are intrinsically force sensitive in vitro (Haeberle et al., 2004, 2008; Lumpkin and Caterina, 2007; Boulais et al., 2009). Moreover, Merkel cells are required for touch-evoked SAI responses (Maricich et al., 2009). In *Atoh1* knock-out mice, Merkel cells fail to develop, but SAI sensory afferents still innervate their proper receptive fields. Electrophysiological analysis of these mice revealed a complete loss of SAI responses in the absence of Merkel cells (Maricich et al., 2009). As predicted, light-touch receptors that innervate other end organs displayed normal mechanosensitivity, demonstrating that *Atoh1* is selectively required for touch responses in Merkel cell–neurite complexes. The effects of postnatal loss of Merkel cells are less clear. Some studies report that Merkel cell loss impaired SAI responses (Ikeda et al., 1994; Senok et al., 1996), whereas others found little impact on slowly adapting responses (Mearow and Diamond, 1988; Mills and Diamond, 1995; Kinkelin et al., 1999). Further studies are needed to determine whether this discrepancy is due to methodological differences. Alternatively, Merkel cells might be required for proper development but not maintenance of functional SAI afferents.

Another key question is whether Merkel cell synapses are excitatory or whether they release neuromodulators that tune the sensitivity of touch-receptive afferents. Functional studies that blocked synaptic transmission have led to conflicting models (Fagan and Cahusac, 2001; Halata et al., 2003; Cahusac et al., 2005; Cahusac and Senok, 2006; Cahusac and Mavulati, 2009). Surprisingly, immunostaining has localized several neurotransmitter receptors to Merkel cells rather than to their SAI afferents (Beiras-Fernández et al., 2004; Cahusac et al., 2005; Tachibana and Nawa, 2005; Tachibana et al., 2005). These findings suggest that neurotransmitters may act on Merkel cells themselves. Thus, the role of Merkel cells in touch reception remains to be determined.

What we do and don't know

Touch is a complex sense comprising a diversity of modalities, and we have just begun to glimpse the underlying cellular principles. Common themes have emerged from histological, physiological, and behavioral studies of genetically tractable organisms.

First, mechanosensory signaling relies on specialized cellular morphologies. Across invertebrate and vertebrate species, noxious touch is transduced by free nerve endings. In contrast, light-touch receptors display a range of morphologically complex end organs. These are largely microtubule based in invertebrate neurons. Elucidating the role of cytoskeletal proteins in vertebrate touch reception awaits future studies.

Second, tissue mechanics and nonsensory cells shape responses to mechanical stimuli. Recent studies propose that human tactile acuity is influenced by skin mechanical properties such as fingertip size, epidermal stiffness, and the spacing of fingerprint ridges (Gerling and Thomas, 2008; Peters et al., 2009; Scheibert et al., 2009). For many light-touch receptors, elaborate accessory structures govern tuning and sensitivity. Epidermal cells provide structural attachments, secrete specialized ECM components, and might affect touch-evoked responses through the release of neuroactive compounds. The question remains as to whether Merkel cells and keratinocytes actually transduce mechanical stimuli or whether they play a modulatory role.

Third, excitatory ion channels are central to touch reception. All of the invertebrate mechanotransduction channels identified through unbiased genetic screens fall into the Deg/ENaC and TRP channel families. Understanding their mechanisms of force gating will require biophysical insights such as high-resolution protein structures. In vertebrate mechanosensory cells, an emerging picture indicates that the molecular details of transduction differ substantially. Intensive studies of mammalian Deg/ENaC and TRP channels have failed to demonstrate a fundamental role for these channels in cutaneous mechanotransduction, although they modulate touch responsiveness. The modest touch deficits of knock-out mice might reflect the genetic redundancy of transduction channels, the functional overlap of touch-receptor cells that use distinct transduction mechanisms, or the involvement of novel ion channels, such as the piezo family. Distinguishing between these possibilities will require techniques borrowed from the invertebrate playbook, including selective markers for different touch receptors, feasible approaches for recording transduction currents, innovative behavioral assays for tactile discrimination, and unbiased molecular screens in mammals and zebrafish (Granato et al., 1996; Ribera and Nüsslein-Volhard, 1998; Low et al., 2010). These approaches hold promise for unraveling the molecular complexity of touch, which is an essential step in dissecting the neuronal code of this enigmatic sense.

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References

Adams, C.M., M.G. Anderson, D.G. Motto, M.P. Price, W.A. Johnson, and M.J. Welsh. 1998. Ripped pocket and pickpocket, novel *Drosophila* DEG/ENaC subunits expressed in early development and in mechanosensory neurons. *J. Cell Biol.* 140:143–152. doi:10.1083/jcb.140.1.143

Airaksinen, M.S., M. Koltzenburg, G.R. Lewin, Y. Masu, C. Helbig, E. Wolf, G. Brem, K.V. Toyka, H. Thoenen, and M. Meyer. 1996. Specific subtypes of cutaneous mechanoreceptors require neurotrophin-3 following peripheral target innervation. *Neuron.* 16:287–295. doi:10.1016/S0896-6273(00)80047-1

Andrews, M.R., S. Czvitkovich, E. Dassie, C.F. Vogelaar, A. Faissner, B. Blits, F.H. Gage, C. ffrench-Constant, and J.W. Fawcett. 2009. Alpha9 integrin promotes neurite outgrowth on tenascin-C and enhances sensory axon regeneration. *J. Neurosci.* 29:5546–5557. doi:10.1523/JNEUROSCI.0759-09.2009

Assad, J.A., N. Hacohen, and D.P. Corey. 1989. Voltage dependence of adaptation and active bundle movement in bullfrog saccular hair cells. *Proc. Natl. Acad. Sci. USA.* 86:2918–2922. doi:10.1073/pnas.86.8.2918

Assad, J.A., G.M. Shepherd, and D.P. Corey. 1991. Tip-link integrity and mechanical transduction in vertebrate hair cells. *Neuron.* 7:985–994. doi:10.1016/0896-6273(91)90343-X

Bae, Y.K., J. Lyman-Gingerich, M.M. Barr, and K.M. Knobel. 2008. Identification of genes involved in the ciliary trafficking of *C. elegans* PKD-2. *Dev. Dyn.* 237:2021–2029. doi:10.1002/dvdy.21531

Barr, M.M., and P.W. Sternberg. 1999. A polycystic kidney-disease gene homologue required for male mating behaviour in *C. elegans*. *Nature.* 401:386–389.

Barr, M.M., J. DeModena, D. Braun, C.Q. Nguyen, D.H. Hall, and P.W. Sternberg. 2001. The *Caenorhabditis elegans* autosomal dominant polycystic kidney disease gene homologs lov-1 and pkd-2 act in the same pathway. *Curr. Biol.* 11:1341–1346. doi:10.1016/S0960-9822(01)00423-7

Beiras-Fernández, A., R. Gallego, M. Blanco, T. García-Caballero, C. Diéguez, and A. Beiras. 2004. Merkel cells, a new localization of prepro-orexin and orexin receptors. *J. Anat.* 204:117–122. doi:10.1111/j.1469-7580.2004.00266.x

Berrier, C., M. Besnard, B. Ajouz, A. Coulombe, and A. Ghazi. 1996. Multiple mechanosensitive ion channels from *Escherichia coli*, activated at different thresholds of applied pressure. *J. Membr. Biol.* 151:175–187. doi:10.1007/s002329900068

Boulais, N., J.P. Pennec, N. Lebonvallet, U. Pereira, N. Rougier, G. Dorange, C. Chesné, and L. Misery. 2009. Rat Merkel cells are mechanoreceptors and osmoreceptors. *PLoS One.* 4:e7759. doi:10.1371/journal.pone.0007759

Bounoutas, A., R. O'Hagan, and M. Chalfie. 2009. The multipurpose 15-protofilament microtubules in *C. elegans* have specific roles in mechanosensation. *Curr. Biol.* 19:1362–1367. doi:10.1016/j.cub.2009.06.036

Bourane, S., A. Garces, S. Venteo, A. Pattyn, T. Hubert, A. Fichard, S. Puech, H. Boukhaddaoui, C. Baudet, S. Takahashi, et al. 2009. Low-threshold mechanoreceptor subtypes selectively express MafA and are specified by Ret signaling. *Neuron.* 64:857–870. doi:10.1016/j.neuron.2009.12.004

Brown, A.L., Z. Liao, and M.B. Goodman. 2008. MEC-2 and MEC-6 in the *Caenorhabditis elegans* sensory mechanotransduction complex: auxiliary subunits that enable channel activity. *J. Gen. Physiol.* 131:605–616. doi:10.1085/jgp.200709910

Cahusac, P.M., and S.C. Mavulati. 2009. Non-competitive metabotropic glutamate 1 receptor antagonists block activity of slowly adapting type I mechanoreceptor units in the rat sinus hair follicle. *Neuroscience.* 163:933–941. doi:10.1016/j.neuroscience.2009.07.015

Cahusac, P.M., and S.S. Senok. 2006. Metabotropic glutamate receptor antagonists selectively enhance responses of slowly adapting type I mechanoreceptors. *Synapse.* 59:235–242. doi:10.1002/syn.20236

Cahusac, P.M., S.S. Senok, I.S. Hitchcock, P.G. Genever, and K.I. Baumann. 2005. Are unconventional NMDA receptors involved in slowly adapting type I mechanoreceptor responses? *Neuroscience.* 133:763–773. doi:10.1016/j.neuroscience.2005.03.018

Calixto, A., D. Chelur, I. Topalidou, X. Chen, and M. Chalfie. 2010. Enhanced neuronal RNAi in *C. elegans* using SID-1. *Nat. Methods.* 7:554–559. doi:10.1038/nmeth.1463

Cavanaugh, D.J., H. Lee, L. Lo, S.D. Shields, M.J. Zylka, A.I. Basbaum, and D.J. Anderson. 2009. Distinct subsets of unmyelinated primary sensory fibers mediate behavioral responses to noxious thermal and mechanical stimuli. *Proc. Natl. Acad. Sci. USA.* 106:9075–9080. doi:10.1073/pnas.0901507106

Chalfie, M. 2009. Neurosensory mechanotransduction. *Nat. Rev. Mol. Cell Biol.* 10:44–52. doi:10.1038/nrm2595

Chalfie, M., and M. Au. 1989. Genetic control of differentiation of the *Caenorhabditis elegans* touch receptor neurons. *Science.* 243:1027–1033. doi:10.1126/science.2646709

Chalfie, M., and J. Sulston. 1981. Developmental genetics of the mechanosensory neurons of *Caenorhabditis elegans*. *Dev. Biol.* 82:358–370. doi:10.1016/0012-1606(81)90459-0

Chalfie, M., and J.N. Thomson. 1979. Organization of neuronal microtubules in the nematode *Caenorhabditis elegans*. *J. Cell Biol.* 82:278–289. doi:10.1083/jcb.82.1.278

Chalfie, M., and J.N. Thomson. 1982. Structural and functional diversity in the neuronal microtubules of *Caenorhabditis elegans*. *J. Cell Biol.* 93:15–23. doi:10.1083/jcb.93.1.15

Chambers, M.R., K.H. Andres, M. von Duering, and A. Iggo. 1972. The structure and function of the slowly adapting type II mechanoreceptor in hairy skin. *Q. J. Exp. Physiol. Cogn. Med. Sci.* 57:417–445.

Chatzigeorgiou, M., S. Yoo, J.D. Watson, W.H. Lee, W.C. Spencer, K.S. Kindt, S.W. Hwang, D.M. Miller III, M. Treinin, M. Driscoll, and W.R. Schafer. 2010. Specific roles for DEG/ENaC and TRP channels in touch and thermosensation in *C. elegans* nociceptors. *Nat. Neurosci.* 13:861–868. doi:10.1038/nn.2581

Chelur, D.S., G.G. Ernstrom, M.B. Goodman, C.A. Yao, L. Chen, R. O' Hagan, and M. Chalfie. 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

Cheng, L.E., W. Song, L.L. Looger, L.Y. Jan, and Y.N. Jan. 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

Chung, Y.D., J. Zhu, Y. Han, and M.J. Kernan. 2001. nompA encodes a PNS-specific, ZP domain protein required to connect mechanosensory dendrites to sensory structures. *Neuron.* 29:415–428. doi:10.1016/S0896-6273(01)00215-X

Colbert, H.A., T.L. Smith, and C.I. Bargmann. 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.

Corey, D.P., and A.J. Hudspeth. 1979. Response latency of vertebrate hair cells. *Biophys. J.* 26:499–506. doi:10.1016/S0006-3495(79)85267-4

Coste, B., J. Mathur, M. Schmidt, T.J. Earley, S. Ranade, M. Petrus, A.E. Dubin, and A. Patapoutian. 2010. Piezo1 and Piezo 2 are essential components of distinct mechanically activated cation channels. *Science.* 2: (Epub ahead of print).

Cox, J.J., F. Reimann, A.K. Nicholas, G. Thornton, E. Roberts, K. Springell, G. Karbani, H. Jafri, J. Mannan, Y. Raashid, et al. 2006. An SCN9A channelopathy causes congenital inability to experience pain. *Nature.* 444:894–898. doi:10.1038/nature05413

Cueva, J.G., A. Mulholland, and M.B. Goodman. 2007. Nanoscale organization of the MEC-4 DEG/ENaC sensory mechanotransduction channel in *Caenorhabditis elegans* touch receptor neurons. *J. Neurosci.* 27:14089–14098. doi:10.1523/JNEUROSCI.4179-07.2007

Drew, L.J., J.N. Wood, and P. Cesare. 2002. Distinct mechanosensitive properties of capsaicin-sensitive and -insensitive sensory neurons. *J. Neurosci.* 22:RC228.

Drew, L.J., D.K. Rohrer, M.P. Price, K.E. Blaver, D.A. Cockayne, P. Cesare, and J.N. Wood. 2004. Acid-sensing ion channels ASIC2 and ASIC3 do not contribute to mechanically activated currents in mammalian sensory neurones. *J. Physiol.* 556:691–710. doi:10.1113/jphysiol.2003.058693

Du, H., G. Gu, C.M. William, and M. Chalfie. 1996. Extracellular proteins needed for *C. elegans* mechanosensation. *Neuron.* 16:183–194. doi:10.1016/S0896-6273(00)80035-5

Eberl, D.F., G.M. Duyk, and N. Perrimon. 1997. A genetic screen for mutations that disrupt an auditory response in *Drosophila melanogaster*. *Proc. Natl. Acad. Sci. USA.* 94:14837–14842. doi:10.1073/pnas.94.26.14837

Emtage, L., G. Gu, E. Hartwieg, and M. Chalfie. 2004. Extracellular proteins organize the mechanosensory channel complex in *C. elegans* touch receptor neurons. *Neuron.* 44:795–807. doi:10.1016/j.neuron.2004.11.010

Fagan, B.M., and P.M. Cahusac. 2001. Evidence for glutamate receptor mediated transmission at mechanoreceptors in the skin. *Neuroreport.* 12:341–347. doi:10.1097/00001756-200102120-00032

Foulkes, T., and J.N. Wood. 2008. Pain genes. *PLoS Genet.* 4:e1000086. doi:10.1371/journal.pgen.1000086

Fukushige, T., Z.K. Siddiqui, M. Chou, J.G. Culotti, C.B. Gogonea, S.S. Siddiqui, and M. Hamelin. 1999. MEC-12, an alpha-tubulin required for touch sensitivity in *C. elegans*. *J. Cell Sci.* 112:395–403.

Gerling, G.J., and G.W. Thomas. 2008. Fingerprint lines may not directly affect SA-I mechanoreceptor response. *Somatosens. Mot. Res.* 25:61–76. doi:10.1080/08990220701838996

Gilron, I., C.P. Watson, C.M. Cahill, and D.E. Moulin. 2006. Neuropathic pain: a practical guide for the clinician. *CMAJ.* 175:265–275.

Gong, Z., W. Son, Y.D. Chung, J. Kim, D.W. Shin, C.A. McClung, Y. Lee, H.W. Lee, D.J. Chang, B.K. Kaang, 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

Goodman, M.B. 2006. Mechanosensation. *WormBook.* 6:1–14.

Goodman, M.B., G.G. Ernstrom, D.S. Chelur, R. O'Hagan, C.A. Yao, and M. Chalfie. 2002. MEC-2 regulates *C. elegans* DEG/ENaC channels needed for mechanosensation. *Nature.* 415:1039–1042. doi:10.1038/4151039a

Granato, M., F.J. van Eeden, U. Schach, T. Trowe, M. Brand, M. Furutani-Seiki, P. Haffter, M. Hammerschmidt, C.P. Heisenberg, Y.J. Jiang, et al. 1996. Genes controlling and mediating locomotion behavior of the zebrafish embryo and larva. *Development.* 123:399–413.

Gu, G., G.A. Caldwell, and M. Chalfie. 1996. Genetic interactions affecting touch sensitivity in *Caenorhabditis elegans*. *Proc. Natl. Acad. Sci. USA.* 93:6577–6582. doi:10.1073/pnas.93.13.6577

Haeberle, H., M. Fujiwara, J. Chuang, M.M. Medina, M.V. Panditrao, S. Bechstedt, J. Howard, and E.A. Lumpkin. 2004. Molecular profiling reveals synaptic release machinery in Merkel cells. *Proc. Natl. Acad. Sci. USA.* 101:14503–14508. doi:10.1073/pnas.0406308101

Haeberle, H., L.A. Bryan, T.J. Vadakkan, M.E. Dickinson, and E.A. Lumpkin. 2008. Swelling-activated Ca2+ channels trigger Ca2+ signals in Merkel cells. *PLoS One.* 3:e1750. doi:10.1371/journal.pone.0001750

Halata, Z., M. Grim, and K.I. Bauman. 2003. Friedrich Sigmund Merkel and his "Merkel cell", morphology, development, and physiology: review and new results. *Anat. Rec. A Discov. Mol. Cell. Evol. Biol.* 271:225–239. doi:10.1002/ar.a.10029

Hamelin, M., I.M. Scott, J.C. Way, and J.G. Culotti. 1992. The mec-7 beta-tubulin gene of *Caenorhabditis elegans* is expressed primarily in the touch receptor neurons. *EMBO J.* 11:2885–2893.

Hart, A.C., J. Kass, J.E. Shapiro, and J.M. Kaplan. 1999. Distinct signaling pathways mediate touch and osmosensory responses in a polymodal sensory neuron. *J. Neurosci.* 19:1952–1958.

Hasegawa, H., and F. Wang. 2008. Visualizing mechanosensory endings of TrkC-expressing neurons in HS3ST-2-hPLAP mice. *J. Comp. Neurol.* 511:543–556. doi:10.1002/cne.21862

Hong, K., and M. Driscoll. 1994. A transmembrane domain of the putative channel subunit MEC-4 influences mechanotransduction and neurodegeneration in *C. elegans*. *Nature.* 367:470–473. doi:10.1038/367470a0

Hu, J., and G.R. Lewin. 2006. Mechanosensitive currents in the neurites of cultured mouse sensory neurones. *J. Physiol.* 577:815–828. doi:10.1113/jphysiol.2006.117648

Hu, J., L.Y. Chiang, M. Koch, and G.R. Lewin. 2010. Evidence for a protein tether involved in somatic touch. *EMBO J.* 29:855–867. doi:10.1038/emboj.2009.398

Huber, T.B., B. Schermer, R.U. Müller, M. Höhne, M. Bartram, A. Calixto, H. Hagmann, C. Reinhardt, F. Koos, K. Kunzelmann, et al. 2006. Podocin and MEC-2 bind cholesterol to regulate the activity of associated ion channels. *Proc. Natl. Acad. Sci. USA.* 103:17079–17086. doi:10.1073/pnas.0607465103

Hueston, J.L., G.P. Herren, J.G. Cueva, M. Buechner, E.A. Lundquist, M.B. Goodman, and K.A. Suprenant. 2008. The *C. elegans* EMAP-like protein, ELP-1 is required for touch sensation and associates with microtubules and adhesion complexes. *BMC Dev. Biol.* 8:110. doi:10.1186/1471-213X-8-110

Hwang, R.Y., L. Zhong, Y. Xu, T. Johnson, F. Zhang, K. Deisseroth, and W.D. Tracey. 2007. Nociceptive neurons protect *Drosophila* larvae from parasitoid wasps. *Curr. Biol.* 17:2105–2116. doi:10.1016/j.cub.2007.11.029

Iggo, A., and G.S. Findlater. 1984. Sensory receptor mechanisms. World Scientific Publishing Co., Singapore. 117–131.

Ikeda, I., Y. Yamashita, T. Ono, and H. Ogawa. 1994. Selective phototoxic destruction of rat Merkel cells abolishes responses of slowly adapting type I mechanoreceptor units. *J. Physiol.* 479:247–256.

Ingber, D.E. 2006. Cellular mechanotransduction: putting all the pieces together again. *FASEB J.* 20:811–827. doi:10.1096/fj.05-5424rev

Jarman, A.P. 2002. Studies of mechanosensation using the fly. *Hum. Mol. Genet.* 11:1215–1218. doi:10.1093/hmg/11.10.1215

Jasti, J., H. Furukawa, E.B. Gonzales, and E. Gouaux. 2007. Structure of acid-sensing ion channel 1 at 1.9 A resolution and low pH. *Nature.* 449:316–323. doi:10.1038/nature06163

Johnson, K.O. 2001. The roles and functions of cutaneous mechanoreceptors. *Curr. Opin. Neurobiol.* 11:455–461. doi:10.1016/S0959-4388(00)00234-8

Kaffman, A., and M.J. Meaney. 2007. Neurodevelopmental sequelae of postnatal maternal care in rodents: clinical and research implications of molecular insights. *J. Child Psychol. Psychiatry.* 48:224–244. doi:10.1111/j.1469-7610.2007.01730.x

Kahn-Kirby, A.H., and C.I. Bargmann. 2006. TRP channels in *C. elegans*. *Annu. Rev. Physiol.* 68:719–736. doi:10.1146/annurev.physiol.68.040204.100715

Kang, L., J. Gao, W.R. Schafer, Z. Xie, and X.Z. Xu. 2010. *C. elegans* TRP family protein TRP-4 is a pore-forming subunit of a native mechanotransduction channel. *Neuron.* 67:381–391. doi:10.1016/j.neuron.2010.06.032

Kaplan, J.M., and H.R. Horvitz. 1993. A dual mechanosensory and chemosensory neuron in *Caenorhabditis elegans*. *Proc. Natl. Acad. Sci. USA.* 90:2227–2231. doi:10.1073/pnas.90.6.2227

Kernan, M.J. 2007. Mechanotransduction and auditory transduction in *Drosophila*. *Pflugers Arch.* 454:703–720. doi:10.1007/s00424-007-0263-x

Kernan, M., D. Cowan, and C. Zuker. 1994. Genetic dissection of mechanosensory transduction: mechanoreception-defective mutations of *Drosophila*. *Neuron.* 12:1195–1206. doi:10.1016/0896-6273(94)90437-5

Killick, R., P.K. Legan, C. Malenczak, and G.P. Richardson. 1995. Molecular cloning of chick beta-tectorin, an extracellular matrix molecule of the inner ear. *J. Cell Biol.* 129:535–547. doi:10.1083/jcb.129.2.535

Kim, J., Y.D. Chung, D.Y. Park, S. Choi, D.W. Shin, H. Soh, H.W. Lee, W. Son, J. Yim, C.S. Park, et al. 2003. A TRPV family ion channel required for hearing in *Drosophila*. *Nature.* 424:81–84. doi:10.1038/nature01733

Kindt, K.S., V. Viswanath, L. Macpherson, K. Quast, H. Hu, A. Patapoutian, and W.R. Schafer. 2007. *Caenorhabditis elegans* TRPA-1 functions in mechanosensation. *Nat. Neurosci.* 10:568–577. doi:10.1038/nn1886

Kinkelin, I., C.L. Stucky, and M. Koltzenburg. 1999. Postnatal loss of Merkel cells, but not of slowly adapting mechanoreceptors in mice lacking the neurotrophin receptor p75. *Eur. J. Neurosci.* 11:3963–3969. doi:10.1046/j.1460-9568.1999.00822.x

Kloda, A., and B. Martinac. 2001. Mechanosensitive channel of Thermoplasma, the cell wall-less archaea: cloning and molecular characterization. *Cell Biochem. Biophys.* 34:321–347. doi:10.1385/CBB:34:3:321

Kung, C. 2005. A possible unifying principle for mechanosensation. *Nature.* 436:647–654. doi:10.1038/nature03896

Kwan, K.Y., J.M. Glazer, D.P. Corey, F.L. Rice, and C.L. Stucky. 2009. TRPA1 modulates mechanotransduction in cutaneous sensory neurons. *J. Neurosci.* 29:4808–4819. doi:10.1523/JNEUROSCI.5380-08.2009

Lee, H., and M.J. Caterina. 2005. TRPV channels as thermosensory receptors in epithelial cells. *Pflugers Arch.* 451:160–167. doi:10.1007/s00424-005-1438-y

Lee, J., S. Moon, Y. Cha, and Y.D. Chung. 2010. *Drosophila* TRPN(=NOMPC) channel localizes to the distal end of mechanosensory cilia. *PLoS One.* 5:e11012. doi:10.1371/journal.pone.0011012

Legate, K.R., S.A. Wickström, and R. Fässler. 2009. Genetic and cell biological analysis of integrin outside-in signaling. *Genes Dev.* 23:397–418. doi:10.1101/gad.1758709

Lennertz, R.C., M. Tsunozaki, D.M. Bautista, and C.L. Stucky. 2010. Physiological basis of tingling paresthesia evoked by hydroxy-alpha-sanshool. *J. Neurosci.* 30:4353–4361. doi:10.1523/JNEUROSCI.4666-09.2010

Li, W., Z. Feng, P.W. Sternberg, and X.Z. Xu. 2006. A *C. elegans* stretch receptor neuron revealed by a mechanosensitive TRP channel homologue. *Nature.* 440:684–687. doi:10.1038/nature04538

Liedtke, W., and J.M. Friedman. 2003. Abnormal osmotic regulation in trpv4−/− mice. *Proc. Natl. Acad. Sci. USA.* 100:13698–13703. doi:10.1073/pnas.1735416100

Liedtke, W., Y. Choe, M.A. Martí-Renom, A.M. Bell, C.S. Denis, A. Sali, A.J. Hudspeth, J.M. Friedman, and S. Heller. 2000. Vanilloid receptor-related osmotically activated channel (VR-OAC), a candidate vertebrate osmoreceptor. *Cell.* 103:525–535. doi:10.1016/S0092-8674(00)00143-4

Liu, K.S., and P.W. Sternberg. 1995. Sensory regulation of male mating behavior in *Caenorhabditis elegans*. *Neuron.* 14:79–89. doi:10.1016/0896-6273(95)90242-2

Liu, Q., S. Vrontou, F.L. Rice, M.J. Zylka, X. Dong, and D.J. Anderson. 2007. Molecular genetic visualization of a rare subset of unmyelinated sensory neurons that may detect gentle touch. *Nat. Neurosci.* 10:946–948. doi:10.1038/nn1937

Liu, T., K. Kim, C. Li, and M.M. Barr. 2007. FMRFamide-like neuropeptides and mechanosensory touch receptor neurons regulate male sexual turning behavior in *Caenorhabditis elegans*. *J. Neurosci.* 27:7174–7182. doi:10.1523/JNEUROSCI.1405-07.2007

Loewenstein, W.R., and M. Mendelson. 1965. Components of receptor adaptation in a Pacinian corpuscle. *J. Physiol.* 177:377–397.

Löken, L.S., J. Wessberg, I. Morrison, F. McGlone, and H. Olausson. 2009. Coding of pleasant touch by unmyelinated afferents in humans. *Nat. Neurosci.* 12:547–548. doi:10.1038/nn.2312

Low, S.E., J. Ryan, S.M. Sprague, H. Hirata, W.W. Cui, W. Zhou, R.I. Hume, J.Y. Kuwada, and L. Saint-Amant. 2010. *touché* Is required for touch-evoked generator potentials within vertebrate sensory neurons. *J. Neurosci.* 30:9359–9367.

Lumpkin, E.A., and M.J. Caterina. 2007. Mechanisms of sensory transduction in the skin. *Nature.* 445:858–865. doi:10.1038/nature05662

Lumpkin, E.A., T. Collisson, P. Parab, A. Omer-Abdalla, H. Haeberle, P. Chen, A. Doetzlhofer, P. White, A. Groves, N. Segil, and J.E. Johnson. 2003. Math1-driven GFP expression in the developing nervous system of transgenic mice. *Gene Expr. Patterns.* 3:389–395. doi:10.1016/S1567-133X(03)00089-9

Luo, W., S.R. Wickramasinghe, J.M. Savitt, J.W. Griffin, T.M. Dawson, and D.D. Ginty. 2007. A hierarchical NGF signaling cascade controls Ret-dependent and Ret-independent events during development of nonpeptidergic DRG neurons. *Neuron.* 54:739–754. doi:10.1016/j.neuron.2007.04.027

Luo, W., H. Enomoto, F.L. Rice, J. Milbrandt, and D.D. Ginty. 2009. Molecular identification of rapidly adapting mechanoreceptors and their developmental dependence on ret signaling. *Neuron.* 64:841–856. doi:10.1016/j.neuron.2009.11.003

Maricich, S.M., S.A. Wellnitz, A.M. Nelson, D.R. Lesniak, G.J. Gerling, E.A. Lumpkin, and H.Y. Zoghbi. 2009. Merkel cells are essential for light-touch responses. *Science.* 324:1580–1582. doi:10.1126/science.1172890

Martinez-Salgado, C., A.G. Benckendorff, L.Y. Chiang, R. Wang, N. Milenkovic, C. Wetzel, J. Hu, C.L. Stucky, M.G. Parra, N. Mohandas, and G.R. Lewin. 2007. Stomatin and sensory neuron mechanotransduction. *J. Neurophysiol.* 98:3802–3808. doi:10.1152/jn.00860.2007

McCarter, G.C., D.B. Reichling, and J.D. Levine. 1999. Mechanical transduction by rat dorsal root ganglion neurons in vitro. *Neurosci. Lett.* 273:179–182. doi:10.1016/S0304-3940(99)00665-5

Mearow, K.M., and J. Diamond. 1988. Merkel cells and the mechanosensitivity of normal and regenerating nerves in *Xenopus* skin. *Neuroscience.* 26:695–708. doi:10.1016/0306-4522(88)90175-3

Merkel, F. 1875. Tastzellen und Tastkörperchen bei den Haustehieren und beim Menschen. *Arch Mikrosk Anat.* 11:636–652. doi:10.1007/BF02933819

Mills, L.R., and J. Diamond. 1995. Merkel cells are not the mechanosensory transducers in the touch dome of the rat. *J. Neurocytol.* 24:117–134. doi:10.1007/BF01181555

Morrison, K.M., G.R. Miesegaes, E.A. Lumpkin, and S.M. Maricich. 2009. Mammalian Merkel cells are descended from the epidermal lineage. *Dev. Biol.* 336:76–83. doi:10.1016/j.ydbio.2009.09.032

Nassar, M.A., L.C. Stirling, G. Forlani, M.D. Baker, E.A. Matthews, A.H. Dickenson, and J.N. Wood. 2004. Nociceptor-specific gene deletion reveals a major role for Nav1.7 (PN1) in acute and inflammatory pain. *Proc. Natl. Acad. Sci. USA.* 101:12706–12711. doi:10.1073/pnas.0404915101

Noël, J., K. Zimmermann, J. Busserolles, E. Deval, A. Alloui, S. Diochot, N. Guy, M. Borsotto, P. Reeh, A. Eschalier, and M. Lazdunski. 2009. The mechano-activated K+ channels TRAAK and TREK-1 control both warm and cold perception. *EMBO J.* 28:1308–1318. doi:10.1038/emboj.2009.57

O'Hagan, R., M. Chalfie, and M.B. Goodman. 2005. The MEC-4 DEG/ENaC channel of *Caenorhabditis elegans* touch receptor neurons transduces mechanical signals. *Nat. Neurosci.* 8:43–50. doi:10.1038/nn1362

Olausson, H., Y. Lamarre, H. Backlund, C. Morin, B.G. Wallin, G. Starck, S. Ekholm, I. Strigo, K. Worsley, A.B. Vallbo, and M.C. Bushnell. 2002. Unmyelinated tactile afferents signal touch and project to insular cortex. *Nat. Neurosci.* 5:900–904. doi:10.1038/nn896

Oren-Suissa, M., D.H. Hall, M. Treinin, G. Shemer, and B. Podbilewicz. 2010. The fusogen EFF-1 controls sculpting of mechanosensory dendrites. *Science.* 328:1285–1288. doi:10.1126/science.1189095

Paré, M., R. Elde, J.E. Mazurkiewicz, A.M. Smith, and F.L. Rice. 2001. The Meissner corpuscle revised: a multiafferented mechanoreceptor with nociceptor immunochemical properties. *J. Neurosci.* 21:7236–7246.

Pawson, L., L.T. Prestia, G.K. Mahoney, B. Güçlü, P.J. Cox, and A.K. Pack. 2009. GABAergic/glutamatergic-glial/neuronal interaction contributes to rapid adaptation in pacinian corpuscles. *J. Neurosci.* 29:2695–2705. doi:10.1523/JNEUROSCI.5974-08.2009

Perkins, L.A., E.M. Hedgecock, J.N. Thomson, and J.G. Culotti. 1986. Mutant sensory cilia in the nematode *Caenorhabditis elegans*. *Dev. Biol.* 117:456–487. doi:10.1016/0012-1606(86)90314-3

Peters, R.M., E. Hackeman, and D. Goldreich. 2009. Diminutive digits discern delicate details: fingertip size and the sex difference in tactile spatial acuity. *J. Neurosci.* 29:15756–15761. doi:10.1523/JNEUROSCI.3684-09.2009

Peyronnet, R., E.S. Haswell, H. Barbier-Brygoo, and J.M. Frachisse. 2008. AtMSL9 and AtMSL10: Sensors of plasma membrane tension in Arabidopsis roots. *Plant Signal. Behav.* 3:726–729.

Price, M.P., G.R. Lewin, S.L. McIlwrath, C. Cheng, J. Xie, P.A. Heppenstall, C.L. Stucky, A.G. Mannsfeldt, T.J. Brennan, H.A. Drummond, et al. 2000. The mammalian sodium channel BNC1 is required for normal touch sensation. *Nature.* 407:1007–1011. doi:10.1038/35039512

Price, M.P., S.L. McIlwrath, J. Xie, C. Cheng, J. Qiao, D.E. Tarr, K.A. Sluka, T.J. Brennan, G.R. Lewin, and M.J. Welsh. 2001. The DRASIC cation channel contributes to the detection of cutaneous touch and acid stimuli in mice. *Neuron.* 32:1071–1083. doi:10.1016/S0896-6273(01)00547-5

Ribera, A.B., and C. Nüsslein-Volhard. 1998. Zebrafish touch-insensitive mutants reveal an essential role for the developmental regulation of sodium current. *J. Neurosci.* 18:9181–9191.

Rugiero, F., L.J. Drew, and J.N. Wood. 2010. Kinetic properties of mechanically activated currents in spinal sensory neurons. *J. Physiol.* 588:301–314. doi:10.1113/jphysiol.2009.182360

Savage, C., M. Hamelin, J.G. Culotti, A. Coulson, D.G. Albertson, and M. Chalfie. 1989. mec-7 is a beta-tubulin gene required for the production of 15-protofilament microtubules in *Caenorhabditis elegans*. *Genes Dev.* 3:870–881. doi:10.1101/gad.3.6.870

Sawin, E.R., R. Ranganathan, and H.R. Horvitz. 2000. *C. elegans* locomotory rate is modulated by the environment through a dopaminergic pathway and by experience through a serotonergic pathway. *Neuron.* 26:619–631. doi:10.1016/S0896-6273(00)81199-X

Scheibert, J., S. Leurent, A. Prevost, and G. Debrégeas. 2009. The role of fingerprints in the coding of tactile information probed with a biomimetic sensor. *Science.* 323:1503–1506. doi:10.1126/science.1166467

Schwander, M., B. Kachar, and U. Müller. 2010. Review series: The cell biology of hearing. *J. Cell Biol.* 190:9–20. doi:10.1083/jcb.201001138

Seal, R.P., X. Wang, Y. Guan, S.N. Raja, C.J. Woodbury, A.I. Basbaum, and R.H. Edwards. 2009. Injury-induced mechanical hypersensitivity requires C-low threshold mechanoreceptors. *Nature.* 462:651–655. doi:10.1038/nature08505

Sekerková, G., L. Zheng, P.A. Loomis, B. Changyaleket, D.S. Whitlon, E. Mugnaini, and J.R. Bartles. 2004. Espins are multifunctional actin cytoskeletal regulatory proteins in the microvilli of chemosensory and mechanosensory cells. *J. Neurosci.* 24:5445–5456. doi:10.1523/JNEUROSCI.1279-04.2004

Selden, S.T. 2004. Tickle. *J. Am. Acad. Dermatol.* 50:93–97. doi:10.1016/S0190-9622(03)02737-3

Senok, S.S., Z. Halata, and K.I. Baumann. 1996. Chloroquine specifically impairs Merkel cell mechanoreceptor function in isolated rat sinus hairs. *Neurosci. Lett.* 214:167–170. doi:10.1016/0304-3940(96)12906-2

Shin, J.B., D. Adams, M. Paukert, M. Siba, S. Sidi, M. Levin, P.G. Gillespie, and S. Gründer. 2005. *Xenopus* TRPN1 (NOMPC) localizes to microtubule-based cilia in epithelial cells, including inner-ear hair cells. *Proc. Natl. Acad. Sci. USA.* 102:12572–12577. doi:10.1073/pnas.0502403102

Sidi, S., R.W. Friedrich, and T. Nicolson. 2003. NompC TRP channel required for vertebrate sensory hair cell mechanotransduction. *Science.* 301:96–99. doi:10.1126/science.1084370

Smith, E.S., and G.R. Lewin. 2009. Nociceptors: a phylogenetic view. *J. Comp. Physiol. A Neuroethol. Sens. Neura. Behav. Physiol.* 195:1089–1106. doi:10.1007/s00359-009-0482-z

Smith, C.J., J.D. Watson, W.C. Spencer, T. O'Brien, B. Cha, A. Albeg, M. Treinin, and D.M. Miller III. 2010. Time-lapse imaging and cell-specific expression profiling reveal dynamic branching and molecular determinants of a multi-dendritic nociceptor in *C. elegans*. *Dev. Biol.* 345:18–33. doi:10.1016/j.ydbio.2010.05.502

Stirling, L.C., G. Forlani, M.D. Baker, J.N. Wood, E.A. Matthews, A.H. Dickenson, and M.A. Nassar. 2005. Nociceptor-specific gene deletion using heterozygous NaV1.8-Cre recombinase mice. *Pain.* 113:27–36. doi:10.1016/j.pain.2004.08.015

Stucky, C.L., T. DeChiara, R.M. Lindsay, G.D. Yancopoulos, and M. Koltzenburg. 1998. Neurotrophin 4 is required for the survival of a subclass of hair follicle receptors. *J. Neurosci.* 18:7040–7046.

Sulston, J., M. Dew, and S. Brenner. 1975. Dopaminergic neurons in the nematode *Caenorhabditis elegans*. *J. Comp. Neurol.* 163:215–226. doi:10.1002/cne.901630207

Suzuki, H., R. Kerr, L. Bianchi, C. Frøkjaer-Jensen, D. Slone, J. Xue, B. Gerstbrein, M. Driscoll, and W.R. Schafer. 2003. In vivo imaging of *C. elegans* mechanosensory neurons demonstrates a specific role for the MEC-4 channel in the process of gentle touch sensation. *Neuron.* 39:1005–1017. doi:10.1016/j.neuron.2003.08.015

Tachibana, T., and T. Nawa. 2005. Immunohistochemical reactions of receptors to met-enkephalin, VIP, substance P, and CGRP located on Merkel cells in the rat sinus hair follicle. *Arch. Histol. Cytol.* 68:383–391. doi:10.1679/aohc.68.383

Tachibana, T., M. Endoh, N. Fujiwara, and T. Nawa. 2005. Receptors and transporter for serotonin in Merkel cell-nerve endings in the rat sinus hair follicle. An immunohistochemical study. *Arch. Histol. Cytol.* 68:19–28. doi:10.1679/aohc.68.19

Tobin, D., D. Madsen, A. Kahn-Kirby, E. Peckol, G. Moulder, R. Barstead, A. Maricq, and C. Bargmann. 2002. Combinatorial expression of TRPV channel proteins defines their sensory functions and subcellular localization in *C. elegans* neurons. *Neuron.* 35:307–318. doi:10.1016/S0896-6273(02)00757-2

Tomaselli, K.J., P. Doherty, C.J. Emmett, C.H. Damsky, F.S. Walsh, and L.F. Reichardt. 1993. Expression of beta 1 integrins in sensory neurons of the dorsal root ganglion and their functions in neurite outgrowth on two laminin isoforms. *J. Neurosci.* 13:4880–4888.

Toyoshima, K., Y. Seta, S. Takeda, and H. Harada. 1998. Identification of Merkel cells by an antibody to villin. *J. Histochem. Cytochem.* 46:1329–1334.

Tracey, W.D. Jr., R.I. Wilson, G. Laurent, and S. Benzer. 2003. painless, a *Drosophila* gene essential for nociception. *Cell.* 113:261–273. doi:10.1016/S0092-8674(03)00272-1

Van Keymeulen, A., G. Mascre, K.K. Youseff, I. Harel, C. Michaux, N. De Geest, C. Szpalski, Y. Achouri, W. Bloch, B.A. Hassan, and C. Blanpain. 2009. Epidermal progenitors give rise to Merkel cells during embryonic development and adult homeostasis. *J. Cell Biol.* 187:91–100. doi:10.1083/jcb.200907080

Vogel, B.E., and E.M. Hedgecock. 2001. Hemicentin, a conserved extracellular member of the immunoglobulin superfamily, organizes epithelial and other cell attachments into oriented line-shaped junctions. *Development.* 128:883–894.

Vollrath, M.A., K.Y. Kwan, and D.P. Corey. 2007. The micromachinery of mechanotransduction in hair cells. *Annu. Rev. Neurosci.* 30:339–365. doi:10.1146/annurev.neuro.29.051605.112917

Walker, R.G., A.T. Willingham, and C.S. Zuker. 2000. A *Drosophila* mechanosensory transduction channel. *Science.* 287:2229–2234. doi:10.1126/science.287.5461.2229

Way, J.C., and M. Chalfie. 1989. The mec-3 gene of *Caenorhabditis elegans* requires its own product for maintained expression and is expressed in three neuronal cell types. *Genes Dev.* 3(12A):1823–1833. doi:10.1101/gad.3.12a.1823

Wellnitz, S.A., D.R. Lesniak, G.J. Gerling, and E.A. Lumpkin. 2010. The regularity of sustained firing reveals two populations of slowly adapting touch receptors in mouse hairy skin. *J. Neurophysiol.* 103:3378–3388. doi:10.1152/jn.00810.2009

Wetzel, C., J. Hu, D. Riethmacher, A. Benckendorff, L. Harder, A. Eilers, R. Moshourab, A. Kozlenkov, D. Labuz, O. Caspani, et al. 2007. A stomatin-domain protein essential for touch sensation in the mouse. *Nature.* 445:206–209. doi:10.1038/nature05394

Woodbury, C.J., and H.R. Koerber. 2007. Central and peripheral anatomy of slowly adapting type I low-threshold mechanoreceptors innervating trunk skin of neonatal mice. *J. Comp. Neurol.* 505:547–561. doi:10.1002/cne.21517

Yoshioka, T., B. Gibb, A.K. Dorsch, S.S. Hsiao, and K.O. Johnson. 2001. Neural coding mechanisms underlying perceived roughness of finely textured surfaces. *J. Neurosci.* 21:6905–6916.

Zhang, S., J. Arnadottir, C. Keller, G.A. Caldwell, C.A. Yao, and M. Chalfie. 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

Zhang, Y., C. Ma, T. Delohery, B. Nasipak, B.C. Foat, A. Bounoutas, H.J. Bussemaker, S.K. Kim, and M. Chalfie. 2002. Identification of genes expressed in *C. elegans* touch receptor neurons. *Nature.* 418:331–335. doi:10.1038/nature00891

Zhong, L., R.Y. Hwang, and W.D. Tracey. 2010. Pickpocket is a DEG/ENaC protein required for mechanical nociception in *Drosophila* larvae. *Curr. Biol.* 20:429–434. doi:10.1016/j.cub.2009.12.057

Zylka, M.J., F.L. Rice, and D.J. Anderson. 2005. Topographically distinct epidermal nociceptive circuits revealed by axonal tracers targeted to Mrgprd. *Neuron.* 45:17–25. doi:10.1016/j.neuron.2004.12.015