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Mechanisms of sensory transduction in the skin

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Sensory neurons innervating the skin encode the familiar sensations of temperature, touch and pain. An explosion of progress has revealed unanticipated cellular and molecular complexity in these senses. It is now clear that perception of a single stimulus, such as heat, requires several transduction mechanisms. Conversely, a given protein may contribute to multiple senses, such as heat and touch. Recent studies have also led to the surprising insight that skin cells might transduce temperature and touch. To break the code underlying somatosensation, we must therefore understand how the skin's sensory functions are divided among signalling molecules and cell types.

The pleasant sensation of a gentle breeze or the painful experience of touching a hot stove are initiated by somatosensory neurons that innervate our skin. The peripheral terminals of these neurons, whose cell bodies are found in trigeminal and dorsal root ganglia (DRG), transduce sensory stimuli into action potentials that propagate to the central nervous system (Fig. 1).

Cutaneous sensory neurons, which are remarkably diverse, are broadly classified as Aβ-, Aδ- or C-fibres on the basis of degree of myelination and the speed at which action potentials travel along afferent fibres[1] (Fig. 1). They can be further classified according to sensory modality[1]. For example, thermoreceptors respond to warming or cooling of the skin, whereas touch receptors respond to pressure, stretch or hair movement. In addition to these neurons that respond to innocuous touch and temperatures, sensory neurons known as nociceptors initiate painful sensations. Many nociceptors are polymodal neurons that are activated by various types of sensory stimulus. The sensitivity of nociceptors to sensory stimulation can be altered by signalling pathways engaged during injury or inflammation. Sensations of pain, temperature or itch can also be evoked when endogenous or exogenous chemicals (such as histamine and menthol) activate cutaneous sensory neurons.

Here we review new findings on the cellular and molecular events that underlie somatosensation. Recent work has uncovered a number of ion channels that are candidate transducers of temperature and touch in the skin (Table 1). Attempts to nail down the roles of these ion channels *in vivo* have exposed some overlapping functions, and have suggested that additional transduction mechanisms remain to be discovered. These studies also offer the intriguing possibility that non-neuronal skin cells can directly sense touch and temperature changes. With knowledge of at least some of the factors involved in hand, the next challenge is to decode the skin's strategy for representing distinct stimuli.

Thermosensation

Mammals can discriminate temperatures ranging from extreme cold (about –10 °C) to extreme heat (about 60 °C). Different temperatures produce subjectively distinct psychophysical perceptions and objectively distinct behavioural responses. Correspondingly, different subpopulations of thermosensitive C- or Aδ-fibres encode skin temperature over different ranges[1]. Interestingly, the thermal responsiveness of sensory neurons is recapitulated in dissociated neurons that lack their peripheral endings, which has proved to be invaluable for discovering candidate transduction molecules[2]. Clues to the molecular basis of thermosensation have arisen from the recent identification of temperature-activated ion channels. Almost all of these belong to the transient receptor potential (TRP) family of cation channels[3]. These channels, which are divided into seven subfamilies, typically have six transmembrane domains, a pore region and cytoplasmic amino and carboxy termini, and assemble as functional tetramers[3]. TRP channels have a bewildering array of biophysical properties and physiological functions. Intriguingly, many participate in sensory signalling[3]. In mammals, thermally sensitive TRPs are each tuned to a distinct temperature range and most are expressed in cutaneous sensory neurons or other cell types in skin[4,5] (Table 1).

Heat transduction

Among the earliest proteins implicated in heat transduction was TRP vanilloid 1 (TRPV1). This protein was identified as the molecular target of capsaicin, the main pungent component of spicy peppers[2]. When capsaicin or other related 'vanilloid' chemicals contact the skin or mucous membranes, they activate TRPV1, which is highly expressed on nociceptive Aδ- and C-fibres, to evoke a sensation of pain[2]. Remarkably, simply heating TRPV1-expressing cells (or membrane patches derived from them) to more than 42 °C is also sufficient to evoke a robust cationic current[2]. *In vitro*, responses to heat and capsaicin are well correlated in dissociated nociceptive neurons[2]. Genetic ablation of TRPV1 in mice eliminates capsaicin responsiveness as well as most heat-activated currents in these cells[2]. *In vivo*, *Trpv1* disruption results in prolonged latencies of heat-evoked paw and tail withdrawal behaviour[2]. Importantly, however, these behavioural deficits are only partial, and are observed only at relatively high temperatures (above 50 °C)[2]. These and other data[6,7] indicate that TRPV1 is involved in, but cannot solely account for, acute thermal nociception in healthy skin. By contrast, TRPV1 seems to be a major contributor to the enhanced thermal responsiveness observed after cutaneous inflammation[2,8]. Thus, the importance of TRPV1 to thermal nociception varies according to context.

Another heat-gated TRP channel, TRPV2, is strongly expressed in a population of somatosensory neurons with characteristics of Aδ-nociceptors, but is also expressed in other neuronal and non-neuronal cells[2]. Upon heterologous expression, TRPV2 is activated by very high temperatures (above 52 °C), a pattern also observed in some Aδ-fibres *in vivo*

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and a subset of heat-sensitive DRG neurons *in vitro*[2]. These properties suggest a role for TRPV2 in the transduction of painfully hot temperatures, although supporting evidence *in vivo* has yet to emerge.

Two other TRPV subfamily members, TRPV3 and TRPV4, can also be activated by heat, as well as by chemical and osmotic stimuli[4,5]. TRPV4 exhibits an apparent threshold of about 27–34 °C, whereas that of TRPV3 is about 32–39 °C. These traits, combined with their expression in skin, make TRPV3 and TRPV4 candidate participants in the perception of warmth. As discussed below, the most prominent cutaneous expression of these channels is in epithelial cells rather than neurons. Support for roles for TRPV3 and TRPV4 in thermosensation has come from behavioural analyses of *Trpv3*- and *Trpv4*-null mutant mice. Both mutants exhibit abnormal thermal-selection behaviour when presented with a range of warm but non-painful floor temperatures. Furthermore, in pain-related thermal withdrawal assays, *Trpv3*-null mice show an acute thermosensation phenotype similar to that of *Trpv1*-null mice, with longer withdrawal latencies at temperatures above 50 °C. By contrast, *Trpv4*-null mice exhibit a slight increase in withdrawal latency only at 45–46 °C. Together, these findings argue in favour of differential but possibly overlapping roles for TRPV1–4 in heat perception.

Three additional TRP channels, TRPM2, TRPM4 and TRPM5, can also be activated by warm temperatures[4,9]; however, evidence for their expression in skin is lacking.

Cold transduction

After the identification of TRPV channels as candidate heat transducers, a key question was whether cold transduction might also occur through TRP channels. This was quickly answered with the identification of TRPM8, an ion channel activated by either modest cooling from normal skin temperature (about 32 °C) to temperatures below about 30 °C, or menthol and other chemicals that produce a cooling sensation[10,11]. In addition, TRPM8 is expressed almost exclusively in a subpopulation of C-fibres[10,11]. These features make TRPM8 an excellent candidate cold receptor, although this hypothesis remains to be tested *in vivo*.

Some cold-responsive dissociated sensory neurons respond only to temperatures below 20 °C. One possible explanation for this behaviour has come from the characterization of TRPA1 (ref. 12), a member of the TRP ankyrin subfamily that is expressed in a subset of TRPV1-positive nociceptors[12,13]. Ankyrin repeats — structural motifs found on many proteins, including some TRP channels — are thought to participate in protein–protein interactions. TRPA family members contain a relatively large number of these repeats (TRPA1, for example, has 18). TRPA1 can be activated by a host of pungent chemicals containing allyl and reactive sulphur groups, such as those found in mustard oil or garlic, and by other irritants, such as acrolein[14,15]. Some investigators have also reported that TRPA1 can be activated by the cold at less than 18 °C (refs 12, 16), prompting the suggestion that TRPA1 contributes to TRPM8-independent cold transduction.

Two *in vivo* studies have provided some support for this idea by reporting deficits in acute cold transduction or inflammation/injury-induced cold hypersensitivity in *Trpa1*$^{-/-}$ mice[17] and in rats treated with TRPA1-antisense oligonucleotides[18]. However, other studies have questioned these findings. First, some investigators have been unable to reproduce cold activation of heterologously expressed TRPA1 (refs 14, 19). Second, in a separate study, dissociated sensory neurons from another *Trpa1*-disrupted mouse line exhibited no discernable deficits in cold transduction, and the mice showed no differences in behavioural responses to cold temperatures[20]. The basis for the discrepancies between these studies is unclear; however, the examination of different types of cold hypersensitivity, the use of male versus female mice, and differential strategies for gene disruption or knockdown might all be contributing factors. A definitive evaluation of the contributions of TRPA1 to cold transduction must therefore await further studies.

The involvement of TRP channels in thermosensation is not confined to mammals. In *Drosophila*, four different TRPA subfamily channels participate in thermally evoked behaviours[4] (Table 1). As in mammals, the functions of these channels seem to segregate over different temperature ranges and result in different outputs[4,5].

Non-TRP ion channels might also participate in cutaneous cold signalling. For example, whether or not cold exposure triggers the firing of sensory neurons might be influenced by potassium channels, some of which exhibit strong temperature sensitivity[21].

Mechanotransduction

A diversity of mechanosensitive neurons innervate the skin[1] (Fig. 1). Many have complex endings, some of which are associated with specialized cells in the skin. Light touch is mediated predominantly by Aβ afferents with low mechanical thresholds. The perception of painful touch is initiated by high-threshold C- and Aδ-nociceptors that can be polymodal or solely mechanoreceptive. C-fibres sensitive to gentle touch have been described in several species, including humans, in whom they have been proposed to contribute to social interactions such as maternal bonding[22].

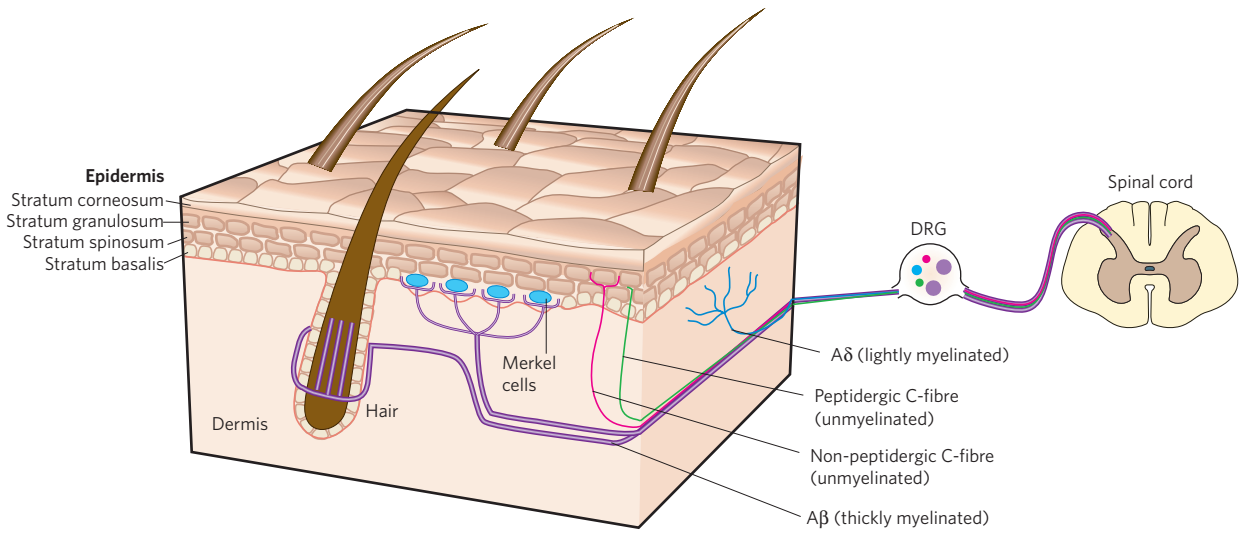

Figure 1 | Diversity of somatosensenory neurons in the skin. The skin is innervated by somatosensory neurons that project to the spinal cord. Aβ-fibres, such as those that innervate Merkel cells and those around hair shafts, are though to be touch receptors. Aδ-fibres and C-fibres include thermoreceptors and nociceptors. Aδ-fibres terminate in the dermis. Peptidergic and non-peptidergic C-fibres terminate in different epidermal layers[59] and have different projection patterns to the spinal cord[60].

Despite intensive efforts to discover molecules that initiate touch sensation in mammals, the transduction mechanisms are largely unknown. The conceptual framework guiding these efforts posits that transduction channels are directly activated by mechanical stimuli[23]. Indeed, mechanical gating might be a general model for ion channels[24]. Stretch-sensitive channels are gated by forces in the membrane bilayer[23] (Fig. 2a). These channels can been activated experimentally by applying pressure to a membrane patch to deform the bilayer. They are found in a broad range of bacterial and eukaryotic cell types and fall into structurally distinct ion-channel families[23].

An alternative direct-gating model proposes that channels are tethered to the cytoskeleton or extracellular matrix, and that tension between these linkages controls channel gating (Fig. 2b). It is not clear whether tethers couple directly to channel domains or whether they modulate membrane forces around a stretch-sensitive channel. The tether model emerged from biophysical studies of auditory and vestibular hair cells[25]; however, genetic screens for mechanosensory mutants in *Drosophila* and *Caenorhabditis elegans* have identified a plethora of molecular candidates that fit this model[26].

A third possibility is that transduction channels are coupled to mechanically sensitive proteins through signalling intermediates (Fig. 2c). For example, in *C. elegans* polymodal sensory neurons, transduction-channel activation might require the production of lipid metabolites[27], as described below. One limitation of indirect mechanisms is that they are intrinsically slower than direct mechanical gating. In fact, direct gating was first proposed for hair cells because of their remarkable transduction speed (about 40 μs)[28]. Similar arguments have been made for *C. elegans* body touch neurons[29] and *Drosophila* bristles[30]; however, their reported latencies (about 200–500 μs) are similar to the delay between presynaptic calcium entry and postsynaptic responses at room temperature (200–600 μs)[31]. Because this delay is sufficient to accommodate vesicle fusion, transmitter diffusion and activation of ligand-gated ion channels, this timescale alone cannot rule out indirect coupling models.

DEG/ENaC channels

The molecular basis of touch has been most extensively characterized in *C. elegans* body touch neurons[26]. Electrophysiology[29] and *in vivo* imaging[32] have provided direct evidence that the transduction channel is a complex of the degenerin/epithelial Na^+ channel (DEG/ENaC) subunits MEC-4 and MEC-10, and two accessory subunits (MEC-2 and MEC-6). Although touch-evoked behaviours depend on specialized microtubules and extracellular proteins, these specialized microtubules are not essential for transduction-channel gating[29].

On the basis of striking *mec* phenotypes, roles for *mec*-related molecules in mammalian touch reception have been tested. Mutant mice lacking a *mec-2*-related protein, stomatin-like protein 3 (SLP3), show a marked loss of touch sensitivity *in vitro* and *in vivo*[33]. Thus, SLP3 seems to be essential for mechanotransduction in a subset of cutaneous touch receptors. By contrast, similar studies indicate that three mammalian DEG/ENaC isoforms (Table 1) — the acid-sensing ion channels (ASICs) — might not have direct roles in mechanotransduction, and instead might modulate sensory signalling. In the skin, ASIC2 and 3 localize to the peripheral terminals of putative touch receptors; however, genetic disruption of ASIC subunits alters only modestly the touch-evoked responses of a few cutaneous afferent subtypes[34]. Importantly, mechanical thresholds are not affected. Unexpectedly, mice expressing a

Table 1 | Proposed mechanosensory and thermosensory transduction channels

Identity	Family	Proposed physical modality	Additional activators	Temperature range	Sensory neuron or skin expression	Species
TRPA1	TRPA	Thermal, mechanical	Isothiocyanates, Ca^{2+}, icilin	<18 °C	C-fibres	Mammals
Painless	TRPA	Thermal, mechanical	Isothiocyanates	n.a.	Multidendritic neurons	*Drosophila*
TRPA	TRPA	Thermal	None known	>24–29 °C	Subset of central neurons	*Drosophila*
Pyrexia-PA	TRPA	Thermal	None known	>40 °C	Multidendritic and other neurons	*Drosophila*
Pyrexia-PB	TRPA	Thermal	None known	>37 °C	Multidendritic and other neurons	*Drosophila*
TRPC1	TRPC	Mechanical	Receptor-operated, store-operated?	n.a.	Mechanosensory neurons	*Xenopus*, mammals
TRPM8	TRPM	Thermal	Menthol, icilin	<28 °C	C-fibres	Mammals
TRPN1	TRPN	Mechanical (audition)	None known	n.a.	Hair cells	*Danio rerio, Xenopus*
NOMPC	TRPN	Mechanical (audition, touch, proprioception)	None known	n.a.	Chordotonal organs, bristles	*Drosophila*
TRP-4	TRPN	Mechanical (touch, proprioception)	None known	n.a.	Ciliated sensory neurons and interneurons	*C. elegans*
TRPV1	TRPV	Thermal, osmotic	Capsaicin, protons, endocannabinoids, diphenyl compounds	>42 °C	C- and Aδ-fibres, keratinocytes	Mammals
TRPV2	TRPV	Thermal, osmotic, mechanical	Diphenyl compounds	>52 °C	Aδ- and Aβ-fibres, immune cells	Mammals
TRPV3	TRPV	Thermal	Camphor, carvacrol, diphenyl compounds	>34–39 °C	Keratinocytes, C-fibres	Mammals
TRPV4	TRPV	Thermal, osmotic	PUFAs, 4αPDD, epoxyeicosatrienoic acids	>27–34 °C	Keratinocytes, Merkel cells, Aδ- and C-fibres	Mammals
OSM-9/OCR-2	TRPV	Thermal, osmotic	PUFAs, G-protein-coupled receptors	n.a.	Polymodal and chemosensory neurons	*C. elegans*
NAN/IAV	TRPV	Mechanical (audition, proprioception)	Osmotic	n.a.	Chordotonal neurons	*Drosophila*
ASIC1	DEG/ENaC	Mechanical (touch)	Protons	n.a.	Aδ-, Aβ- and C-fibres	Mammals
ASIC2	DEG/ENaC	Mechanical (touch)	Protons	n.a.	Aδ- and Aβ-fibres	Mammals
ASIC3	DEG/ENaC	Mechanical (touch, nociception)	Protons	n.a.	Aδ- and Aβ-fibres	Mammals
MEC-4/MEC-10	DEG/ENaC	Mechanical (touch)	None known	n.a.	Body touch neurons	*C. elegans*
TREK-1	2P K^+ channel	Thermal, mechanical	Lipids, protons	n.a.	Aδ- and C-fibres, Aβ-fibres?	Mammals

dominant-negative *Asic3* mutation are hypersensitive to acute mechanical and chemical stimuli[35].

TRPN and TRPA channels

Like the *mec* genes, *Drosophila* NOMPC (TRPN1) was identified as a candidate transduction channel in a genetic screen for touch-insensitive animals[30]. TRPN channels have unusually large N-terminal domains with 29 ankryin repeats. *Drosophila nompC* mutants show defects in hearing, touch and proprioception. Moreover, the *C. elegans* TRPN1 homologue *trp-4* is expressed in mechanosensory neurons[30,36] and has been proposed to function in proprioception on the basis of the conspicuous locomotory defects of *trp-4* mutants[36].

In *Drosophila* auditory antennae and vertebrate hair cells, mechanical stimuli initiate two processes that govern auditory sensitivity: electrical excitation that triggers downstream neuronal signalling and mechanical amplification that increases sensitivity at particular sound frequencies. Interestingly, *nompC* mutations in *Drosophila* partly reduce mechanically evoked neuronal signals in bristles[30] and antennae[37] but completely eliminate mechanical amplification in antennae[38]. Because the transduction machinery is an essential part of the amplification feedback loop, these results suggest that NOMPC directly participates in transduction but that it cannot be the only transduction channel in these neurons.

The vertebrate homologue of NOMPC, TRPN1, is expressed in mechanosensory hair cells in some fish and amphibians[39,40] but is not present in the genomes of reptiles, birds or mammals. Hair cells contain a cluster of mechanically sensitive microvilli, known as stereocilia, and a single true cilium, the kinocilium. The latter is not required for mechanotransduction, although it is probably important for the development or stimulation of stereocilia *in vivo*. In zebrafish hair cells, RNA-interference knockdown of *trpn1* eliminates mechanically evoked potentials[39]. Surprisingly, the channel's predominant localization to kinocilia[39,40] indicates that it might not directly mediate transduction. Collectively, these studies point towards a phylogenetically conserved role for TRPN channels in mechanosensory signalling; however, TRPN subunits might also have roles other than transduction.

The intriguing phenotypes of TRPN mutants focused attention on TRPA1 because it is the only mammalian TRP channel with an extended ankryin domain and it is expressed in nociceptors[12,13,19] and hair cells[19,41]. Interestingly, one *Drosophila Trpa* isoform, *painless*, is required for withdrawal from harsh prodding[42]. By contrast, *Trpa1*$^{-/-}$ mice have been reported to show small[17] or no[20] deficits in acute touch sensitivity, indicating that TRPA1 is not essential for mechanotransduction in somatosensory neurons. Although RNA-interference-mediated knockdown suggested TRPA1 to be a promising candidate in hair-cell transduction[41], *Trpa1*$^{-/-}$ mice have normal auditory responses[17,20] and hair-cell transduction currents[17]. Together, these results indicate that mammalian TRPA1 has a minor role in the acute transduction of mechanical stimuli; however, the *Trpa1*-knockout studies demonstrated that this channel is crucial for the hypersensitivity to both touch and heat that accompanies skin inflammation by mustard oil as well as the heat hypersensitivity caused by bradykinin. Thus, TRPA1 may be an excellent target for new therapeutics for pain hypersensitivity.

TRPV channels

The first TRP channel shown to participate in mechanosensation was the *C. elegans* TRPV channel OSM-9 (ref. 43). In the polymodal sensory neuron ASH, OSM-9 and another TRPV isoform, OCR-2, co-localize to sensory cilia, which is consistent with the idea that they form heteromeric transduction channels. Like other TRPV channels, OSM-9/OCR-2 channels are thought to be polymodal, because mutations in each subunit disrupt avoidance of hypertonic, mechanical and chemical stimuli.

Although these stimuli probably activate OSM-9/OCR-2 channels through distinct signalling cascades, each cascade might involve polyunsaturated fatty acids (PUFAs)[43]. In fact, modulation by lipid metabolites is a feature of many TRP channels, including *Drosophila trp*[3]. In *C. elegans*, mutations that interfere with PUFA synthesis have been shown to compromise all three ASH-mediated sensory modalities as well as olfactory responses[27]. Conversely, exogenously applied PUFAs rapidly activate ASH and elicit avoidance behaviours in an *osm-9*-dependent manner. Together, these data suggest that PUFAs are produced through sensory transduction cascades to activate OSM-9; however, it is also possible that these lipids serve as channel modulators or provide a lipid environment that is permissive for channel function.

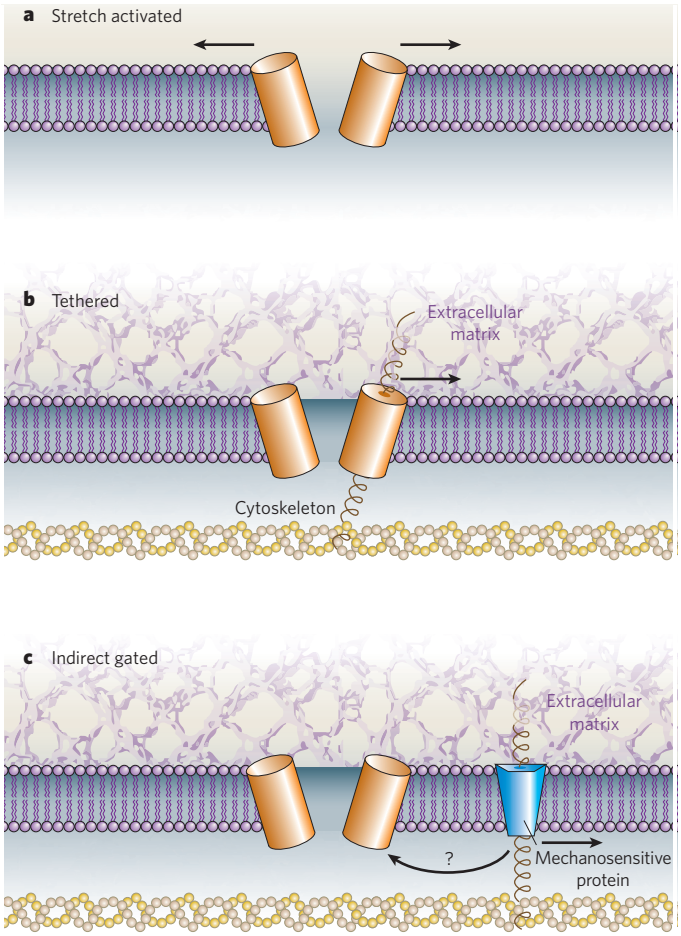

Figure 2 | Gating models of mechanotransduction channels. a, Stretch-activated ion channels open when forces (horizontal arrows) in the lipid bilayer change, for example, owing to alterations in bilayer tension or curvature. **b**, In sensory cells, mechanically gated channels are proposed to require links to extracellular or cytoskeletal proteins. Displacements that change the tension on these links open the channel. These links could directly transmit force to the channel protein (as depicted) or could control the membrane forces around stretch-sensitive channels. **c**, Another possibility is that a mechanosensitive protein regulates ion-channel opening through a signalling intermediate. Such hypothetical transduction proteins might require tethers (as depicted) or might respond to changes in the lipid bilayer.

The two *Drosophila* TRPV isoforms, *nanchung* (*nan*) and *inactive* (*iav*), are essential for sensory signalling because mutations in either gene abolish sound-evoked neuronal activity in auditory antennae[44,45]. Moreover, NAN and IAV are activated by hypotonic challenge in heterologous cell types, which suggests that they can transduce mechanical stimuli. Like OSM-9/OCR-2, NAN and IAV co-localize to sensory cilia of mechanoreceptive neurons[44,45]. Surprisingly, a green-fluorescent-protein-tagged version of IAV was found only in the proximal cilium[44], which is at odds with the hypothesis that mechanically gated channels are tethered at ciliary tips. Moreover, whereas *nompC* mutations abolish mechanical amplification in auditory antennae, *nan* and *iav* loss-of-function mutations actually increase amplification[38]. This suggests that NAN and IAV are not part of the mechanically activated transduction complex. An alternative model that can reconcile these findings is that

mechanically sensitive proteins indirectly activate NAN/IAV channels to effect downstream signalling (Fig. 2c). One speculative model is that NAN/IAV, like OSM-9/OCR-2, are activated by fatty acid metabolites, although such signalling might not be fast enough to account for fly auditory transduction[37,44].

Along with its role in thermosensation, mammalian TRPV4 has been proposed to function in mechanotransduction and osmosensation[46]. Similarly to NAN and IAV, heterologously expressed TRPV4 can be activated by hypotonic solutions[47,48]. As with OSM-9, the osmotic activation of TRPV4 requires fatty acid metabolites[49]. Moreover, TRPV4 can complement some of the sensory defects of *C. elegans osm-9* mutants[46]. Although its expression in large-diameter sensory neurons and Merkel cells[47] is consistent with a role in cutaneous touch, disrupting *Trpv4* expression in mice has only modest effects on acute mechanosensory thresholds[50,51]. TRPV4 function might instead be important for inflammation-induced mechanical hypersensitivity and nociceptive responses to hypotonic solutions[52].

Two additional mammalian TRPV subunits have been implicated in mechanosensory signalling. TRPV1 is dispensable for cutaneous mechanosensation; however, this channel is required for normal stretch-evoked reflexes in the bladder[53] and for osmosensation in hypothalamic neurons[54]. Mammalian TRPV2 is a candidate mechanotransduction channel because it can be activated by hypotonic and stretch stimuli *in vitro*[55] and it is expressed in large-diameter somatosensory neurons[2].

Stretch-sensitive channels

Stretch-sensitive ion channels that are expressed in sensory neurons have also been proposed to participate in mammalian mechanotransduction. For example, the canonical TRP channel TRPC1, which is activated by membrane stretch in *Xenopus* ooctyes[56], is broadly expressed in mammalian cells, including in somatosensory neurons. In addition, the stretch-sensitive two-pore potassium channel TREK-1 seems to have a key role in acute touch: *Trek-1*$^{-/-}$ mice show markedly increased sensitivity to low-threshold mechanical stimuli, but normal sensitivity to acute heat and noxious pressure[57]. These results highlight the fact that many types of channel must work in concert to control the sensitivity of touch and pain receptors.

Roles for epidermal cells in somatosensation

Somatosensory transduction is generally thought to occur in the terminals of sensory neurons. Skin cells are often viewed as bystanders in this process, providing, at most, physical and trophic support to those nerve terminals. An emerging alternative view is that non-neuronal cells function as primary transducers of some physical and chemical stimuli and that these cells can, in turn, communicate to neighbouring somatosensory afferents.

Epithelial cells as sensory receptor cells

Two epithelial cell types are well established as mediators of sensory transduction. First, hair cells carry out the mechanotransduction that underlies auditory and vestibular function. In these cells, displacement opens transduction channels near the tips of stereocilia, causing membrane depolarization and consequent release of neurotransmitter (almost certainly glutamate) from the hair cell's synapses onto afferent auditory neurons[25] (Fig. 3a). Second, taste perception begins with chemical transduction events that occur in specialized epithelial cells in the taste buds (Fig. 3b). The signal by which taste cells communicate with afferent neurons has not been firmly established, but ATP and serotonin are strong candidates[58]. Furthermore, there is evidence for a signal relay of sorts by which tastants are initially detected by a 'receptor' epithelial cell that communicates with a neighbouring 'output' epithelial cell that, in turn, signals to the sensory afferent[58] (Fig. 3b).

Keratinocytes

Keratinocytes, the predominant cell type in the epidermis, proliferate from a basal layer located at the dermal–epidermal border and, through a coordinated programme of differentiation and apical migration, form a well-organized stratified epithelium (Fig. 1). Although much attention has been focused on the chemical and mechanical barrier functions of keratinocytes, physical protection seems to be just one role of these cells.

Three lines of evidence suggest that keratinocytes participate in the detection of physical and chemical stimuli. First, localization studies involving genetically labelled neuronal subpopulations have revealed at least two populations of sensory afferent fibres that ramify within distinct epidermal layers[59] (Fig. 1). Sensory neurons that express proinflammatory neuropeptides such as calcitonin gene-related polypeptide

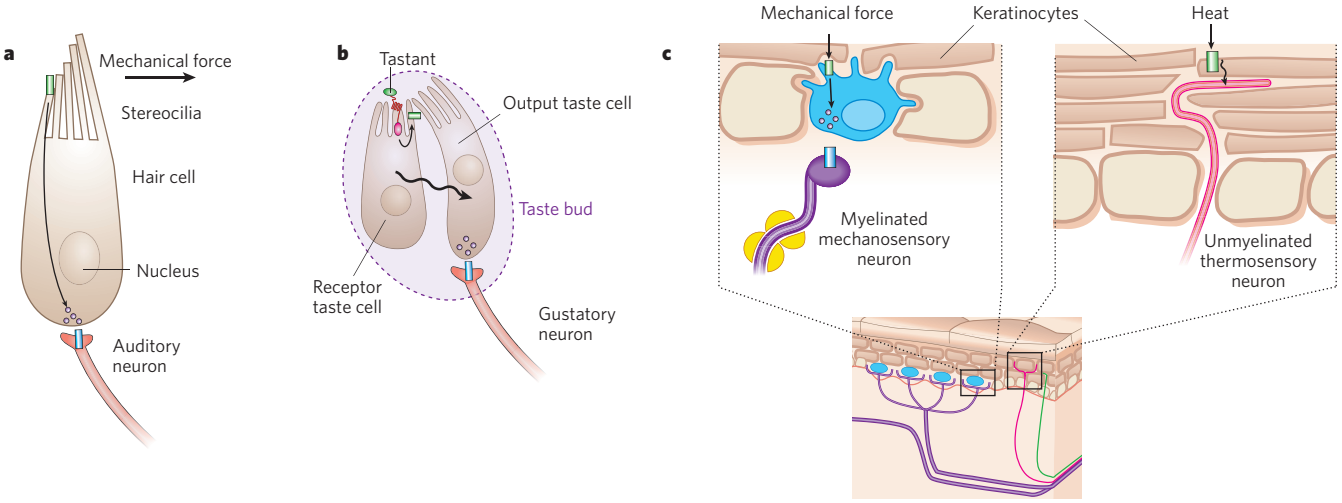

Figure 3 | Sensory transduction by epithelial cells. **a**, Hair cell of the inner ear. Mechanical deflection of stereocilia opens non-selective cation channels, which depolarize the cell to increase the rate of glutamate release onto synaptically connected auditory afferents. **b**, Taste bud epithelium. Chemical tastants activate a G-protein-coupled receptor–ion channel pathway in a 'receptor' epithelial cell, which communicates through paracrine signalling (wavy line) to an adjacent 'output' epithelial cell. The output cell releases neurotransmitter onto a synaptically connected taste afferent[58]. **c**, Proposed models for keratinocyte and Merkel cell involvement in cutaneous thermotransduction and mechanotransduction. Touch activates an unknown transduction mechanism in Merkel cells (blue, left), which are synaptically connected to cutaneous Aβ afferents. The myelin sheath of the Aβ afferent is lost as it approaches a Merkel cell. Projections from the Merkel-cell surface represent microvilli. Heat activates TRPV3 and TRPV4 ion channels (green, right) expressed in keratinocytes. Paracrine signalling from keratinocytes to adjacent afferents (wavy line) results in neuronal activation. For simplicity, direct thermotransduction and mechanotransduction by cutaneous afferents are not shown.

(CGRP) ascend through the basal epidermal layer to terminate in the next layer, the stratum spinosum. By contrast, a population of nonpeptidergic neurons that express a specific G-protein-coupled receptor, MrgD, terminate more superficially, in the stratum granulosum. These two neuronal populations also exhibit distinct projection patterns to the spinal cord and have apparently distinct sensory functions[60]. Although classical synaptic structures between keratinocytes and sensory nerve terminals have not been described, the proximity of these cell types and even close membrane–membrane apposition[61,62] provides ample opportunity for rapid paracrine communication.

A second line of evidence implicating keratinocytes in sensory signalling comes from the fact that these cells secrete numerous chemical substances capable of modulating, activating or inhibiting sensory neurons. Examples include neurotrophins, ATP, β-endorphin, interleukins and endothelin-1 (refs 63–66). Interestingly, different layers of the epidermis can release substances with different effects. Whereas superficial keratinocytes can release antinociceptive molecules such as β-endorphin, stimulation of deeper epidermal keratinocytes results in the release of pro-nociceptive endothelin-1 (ref. 67). The presence of such potentially antagonistic systems in the epidermis hints at a capacity for signal filtration or processing upstream of the nervous system.

A third fact that supports the involvement of keratinocyte function in acute sensory signalling is that they express various receptors that have been implicated in pain or temperature sensation. Some of these are receptors for the chemical substances mentioned above. In these cases, it is difficult to distinguish whether the receptors facilitate inter-keratinocyte signalling, keratinocyte–neuron signalling, or both. For example, mechanically stimulating keratinocytes *in vitro* causes ATP release and signalling through the metabotropic ATP receptor P2Y2 (ref. 66). P2Y2 activation mobilizes the release of intracellular Ca^{2+} stores, which, in turn, evokes the release of still more ATP from the stimulated keratinocytes. The result is an intercellular relay that spreads across the culture. If sensory neurons are co-cultured with keratinocytes stimulated in this way, the neurons exhibit a delayed activation through their own purinergic receptors[66]. Although this sequence of events has not been established *in vivo*, it provides a plausible picture of how a physical stimulus could result in sensory neuron excitation.

Recent data also indicate that keratinocytes might transduce thermal stimuli. For example, the warm-activated ion channels TRPV3 and TRPV4 are more readily detectable in keratinocytes than in sensory neurons[4–6]. Currents mediated by these two types of channel can be evoked by heat stimulation of cultured keratinocytes and distinguished on the basis of their kinetic profiles[4,5]. These responses can be augmented by agonists of TRPV3 or TRPV4 (camphor or 4-α-phorbol 12,13-didecanoate (4αPDD), respectively) and are eliminated by *Trpv3* or *Trpv4* disruption[4,5].

The expression of functional TRPV3 and TRPV4 in keratinocytes, coupled with the behavioural thermosensory defects in *Trpv3*- or *Trpv4*-null mutant mice provides a strong circumstantial case for the contribution of the keratinocyte-expressed channels in heat sensation. Whether — and, if so, how — stimulation of these channels results in neuronal activation has not yet been established, however. One recent study demonstrated that chemical activation of TRPV3 in keratinocytes cultured from tongue epithelium caused interleukin-1α release[65], providing validation of the idea that TRPV channel activation in keratinocytes stimulates the release of bioactive substances.

TRPV1 expression in keratinocytes has also been reported, and capsaicin can evoke the release of interleukin-8 from immortalized human keratinocytes[5]. Similarly, in the urinary bladder TRPV1 is expressed both in sensory neurons and in the urothelial cells that form the bladder luminal epithelium. In fact, TRPV1 is essential for the stretch-evoked release of ATP from the urothelium, a process that triggers afferent neuron activation and reflex contraction of the bladder[5].

Despite these findings, direct evidence for acute keratinocyte to sensory neuron signalling is lacking. Furthermore, ATP receptors and TRPV channels in keratinocytes almost certainly have other functions. For example, extracellular ATP is required for the barrier function of keratinocytes. In addition, abnormalities in hair integrity[68] or hair follicle cycling[69] have been detected in *Trpv3*- and *Trpv1*-null mice, respectively, as well as in rodents expressing a mutated form of *Trpv3* (ref. 70).

Merkel cells

Merkel cell–neurite complexes, which mediate a subset of slowly adapting responses to touch, are important for distinguishing shape, form and texture[71]. These complexes are made up of Merkel cells in close association with Aβ-afferent terminals (Fig. 3c). They are found in the basal epidermal layer of touch-sensitive areas of the skin, including glabrous skin, whisker follicles and touch domes.

Parallels identified between Merkel cells and hair cells have fuelled speculation that Merkel cells are sensory cells that transduce touch and then communicate with afferents by synaptic transmission[71] (Fig. 3c). First, both epithelial cell types seem to make synaptic contacts with sensory terminals. Second, Merkel cells contain elongated microvilli, reminiscent of the hair cell's stereocilia. In fact, Merkel cells express an espin isoform that is found only in the microvilli of sensory cells, such as hair cells, taste receptor cells and vomeronasal neurons[72]. Finally, Merkel cells and hair cells express some of the same developmental transcription factors, including mammalian atonal homologue 1 (ref. 73) and growth-factor independent 1 (ref. 74). Although these similarities are intriguing, experiments designed to determine whether Merkel cells are required for touch sensitivity have produced contradictory results[71] and so far there is no direct evidence demonstrating that Merkel cells are activated by touch.

The idea that Merkel cells are presynaptic is supported by morphological and molecular studies[71]; however, functional studies that tested the role of synaptic transmission in touch have produced conflicting results[71,75–77]. Merkel cells contain dense-core vesicles that resemble neurosecretory vesicles. Moreover, Merkel cells have membrane densities similar to those at synaptic active zones and they express piccolo, a presynaptic active-zone protein[78]. Because Merkel cells express molecules necessary for synaptic glutamate release and neuropeptide production[78], an important open question is whether Merkel cell synapses are excitatory or whether they send modulatory signals to regulate touch-sensitive neurons.

Another challenge to the simple model that Merkel cells are sensory cells is that recent immunohistochemical studies have localized a number of neurotransmitter receptors to Merkel cells but not to associated sensory neurons[76,79]. These data suggest that neurotransmitters might be released from sensory neurons or keratinocytes to signal to Merkel cells or perhaps that Merkel-cell signalling is autocrine.

Future directions

A flurry of recent work has indicated that many ion channels are in the right place and have the right properties to participate in the skin's sensory functions. These advances have uncovered recurring themes but have also provided a tantalizing glimpse of the molecular complexity of somatosensory transduction. A key challenge now is to explain the molecular logic of touch, temperature sensation and nociception.

One unifying principle is the participation of TRP channels in somatosensation. The extent to which these channels exhibit specialized versus overlapping functions remains to be clarified. Their heterogeneity might be further increased by heteromultimerization among TRP subunits or splice variants. Moreover, changes in channel expression, sensitivity or interactions might contribute to alterations in sensory perception that accompany tissue inflammation.

A second recurring theme is the polymodality of putative transduction channels, which raises the possibility that sensory integration begins at the first step of signalling. Whether and how stimuli converge to modulate ion channels *in vivo* are crucial open questions. To answer them, we must first understand how physical and chemical stimuli control channel gating. For example, an important step is to determine how force opens mechanotransduction channels, such as the MEC-4/MEC-10 complex. Structure and function studies have begun to define TRP channel domains required for activation by chemical stimuli[80,81].

Moreover, thermodynamics-based efforts have yielded some insight into thermosensitivity[82]. Nonetheless, our understanding of polymodal channel gating remains rudimentary and requires higher-resolution structural and functional studies.

A theme revealed by invertebrate systems is the molecular heterogeneity of mechanotransduction. Although vertebrate DEG/ENaC and TRP channels are currently under the greatest scrutiny as candidate transduction channels, the subtle mechanosensory defects in knockout mice suggest that there are other candidates still to be identified. It is possible that structurally unrelated mechanotransduction channels have yet to be discovered, as was highlighted by the recent finding that Ca^{2+}-release-activated Ca^{2+} channels belong to a previously unrecognized ion channel family[83]. We also need new strategies for evaluating candidate mechanotransduction channels. For example, techniques for measuring transduction currents in the skin are essential for determining whether a candidate acts directly in transduction or in signal propagation.

A final emerging concept is the role of epithelial cells in sensory transduction. A fundamental open question is whether skin cells truly act as first-line transducers of physical stimuli, or whether their expression of TRP channels reflects modulatory or non-sensory functions. If epithelial cells do mediate sensory transduction, we must discover mechanisms of signal relay and specificity between epithelial cells and neurons. For example, a molecule released from heat-activated keratinocytes must excite the correct sensory neuron subtypes and must be short-lived enough to allow discrimination of acute changes in skin temperature. For Merkel cells, the synaptic junctions with Aβ-fibres provide a mechanism for specificity and speed; however, the direction and type of signalling between Merkel cells and sensory neurons are open questions. ■

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