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Diversification and Specialization of Touch Receptors in Skin

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Our skin is the furthest outpost of the nervous system and a primary sensor for harmful and innocuous external stimuli. As a multifunctional sensory organ, the skin manifests a diverse and highly specialized array of mechanosensitive neurons with complex terminals, or end organs, which are able to discriminate different sensory stimuli and encode this information for appropriate central processing. Historically, the basis for this diversity of sensory specializations has been poorly understood. In addition, the relationship between cutaneous mechanosensory afferents and resident skin cells, including keratinocytes, Merkel cells, and Schwann cells, during the development and function of tactile receptors has been poorly defined. In this article, we will discuss conserved tactile end organs in the epidermis and hair follicles, with a focus on recent advances in our understanding that have emerged from studies of mouse hairy skin.

Skin is our body's protective covering and our largest sensory organ. Unique among our sensory systems, the skin's nervous system gives rise to distinct sensations, including gentle touch, pain, itch, warmth, and cold. These distinct percepts are initiated by an impressive array of somatosensory neurons, whose sensory axons, called afferents, densely innervate the skin (Fig. 1). We rely on sensory inputs from the skin to interact with objects in our environment and to avoid harm.

Our sense of touch enables us to perform numerous behaviors that rely on fine motor skills, including typing, feeding, and dressing ourselves. Touch is also important for social exchange, including pair bonding and child rearing (Tessier et al. 1998; Feldman et al. 2010). Infants deprived of touch stimuli display developmental and cognitive deficits (reviewed in Kaffman and Meaney 2007; Ardiel and Rankin 2010). For example, premature babies show delayed development and growth but this can be improved by 45 minutes of daily touch stimulation. Cognitive deficits in touch-deprived rodent pups persist through adulthood, highlighting the importance of touch during development.

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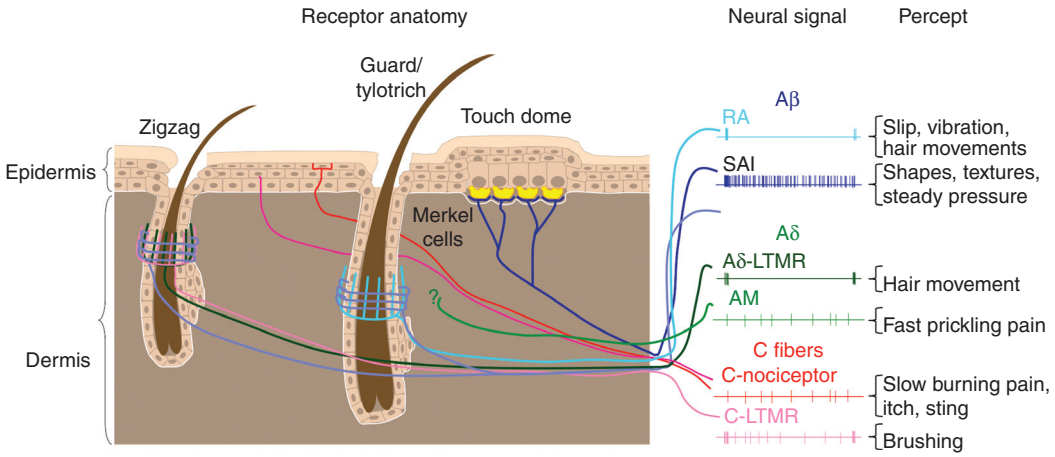

Figure 1. Touch receptors of hairy skin. A diverse group of mechanosensory afferents innervate the hairy skin of mammals. The schematic depicts anatomically distinct end organs (*right*), which give rise to neural signals with distinct patterns of activity (*center*). These different classes of sensory neurons initiate the perception of different cutaneous sensations (*left*). Aβ afferents (blue shades), which have thick myelin sheaths, are gentle-touch receptors that display rapidly adapting (RA) or slowly adapting (SA) responses to touch. In hairy skin, RA afferents form lanecolate endings around hair follicles. Slowly adapting type I (SAI) afferents innervate Merkel cells (yellow) clustered in touch domes. Aδ afferents (green shades), which have thin myelin sheaths, include Aδ low-threshold mechanoreceptors (LTMRs) and A-mechanonociceptors (AM), whose morphological end organs have not been identified. C-afferents (magenta shades) include C-LTMRs that innervate hair follicles as well as pruritoceptors and nociceptors that innervate the epidermis. (Modified from Bautista and Lumpkin 2011.)

Acute itch and pain are warning signals. Pain alerts us to noxious mechanical, chemical, and thermal stimuli that have the potential to damage skin tissue. Moreover, under conditions of inflammation or injury, skin displays a hypersensitivity to touch and temperature that encourages us to protect injured areas. Although the evolutionary advantage of itch is not fully understood, this sensation might provide protection by alerting us to the presence of insects that have the potential to transmit disease. Itch sensation involves complex signaling between keratinocytes, immune cells, and sensory neurons that innervate the epidermis (Liu and Ji 2013; Wilson et al. 2013).

In chronic pain and itch, these unpleasant sensations persist beyond the threat of tissue injury. These chronic states accompany numerous pathophysiological conditions, leading to pain triggered by gentle touch (allodynia), enhanced sensitivity to noxious mechanical or thermal stimuli (hyperalgesia), and unrelieved itch (Gilron et al. 2006; Liu and Ji 2013). These are prevalent complaints in developed countries. Chronic pain is estimated to afflict more than 30% of Americans (Johannes et al. 2010). Moreover, unrelieved itch is one of the most common reasons for dermatological consult (Summery 2009).

Among the skin's protective functions, our understanding of cutaneous sensations has lagged compared with barrier and immune functions. Recent studies of mouse models have advanced our knowledge of the interactions between skin and the nervous system that drives sensation. Here, we focus on two mammalian skin regions that are specialized for conveying touch stimuli to the nervous system—the touch dome and the hair follicle. For additional insights into mechanosensory transduction, nociception, and itch, we refer the reader to excellent recent reviews (Basbaum et al. 2009; Chalfie 2009; Jeffry et al. 2011; Patel and Dong 2011; Liu and Ji 2013).

MAMMALIAN SKIN IS INNERVATED BY DISTINCT TYPES OF SENSORY NEURONS

Cutaneous sensory afferents display a diversity of developmental programs, molecular receptors, anatomical specializations, and neural signals, which allow them to trigger distinct sensations (Fig. 1). At the molecular level, different classes of cutaneous sensory neurons are specified by combinatorial expression of transcription factors and distinct neurotrophin dependencies (reviewed in Liu and Ma 2011; Lallemend and Ernfors 2012). Moreover, they express different receptors that can respond selectively to chemicals, temperatures, or physical forces (Lumpkin and Caterina 2007; Rice and Albrecht 2008). When these sensory receptors are activated, they lead to membrane potential changes that trigger discrete neural signals in the form of action potential trains with unique patterns of activity. These neural signals are then processed by spinal cord and brain circuitry to produce distinct percepts.

Sensory afferents can be distinguished anatomically based on their sensory terminals, or end organs, in the skin (Fig. 1). Unmyelinated afferents have free nerve endings that terminate in protrusions between epidermal keratinocytes. These include pruritoceptors, which trigger itch; nociceptors, which evoke painful sensations; and thermoreceptors, which respond to skin heating or cooling. In addition to their afferent function, many of these neurons serve an efferent role to modulate skin cells under conditions of inflammation or injury. When excited by a painful or itch-producing stimulus, peptidergic sensory neurons can release signaling molecules, such as substance P, calcitonin gene-related peptide (CGRP), and inflammatory mediators, from their free nerve endings. Thus, the complex interplay of neurons and skin cells is an integral component of skin function.

Whereas nociceptors and pruritoceptors have free nerve endings, most tactile afferents have terminal specializations that shape mechanosensory responses so that different features of a tactile stimulus are represented in their neural firing patterns (de Garavilla et al. 2001; Rice and Albrecht 2008; Gardner et al. 2013). For example, a surprising variety of rapidly adapting afferents innervate hair follicles to respond to brushing, stroking, or air movements (Li et al. 2011). SA afferents respond to steady pressure by producing discharges throughout skin stimulation. The best characterized of these is the SA type I (SAI) afferent, which forms complexes with Merkel cells located in the stratum basale of the epidermis. Other types of SA afferents also innervate skin; however, their end organs have not been identified in mice. Although the correspondence between an end organ and its neural firing pattern has traditionally been correlative, recent studies have begun to identify molecular markers that can be used to reliably distinguish afferent subtypes in mouse skin (Loewenstein and Rathkamp 1958; Woodbury and Koerber 2007; Bourane et al. 2009; Luo et al. 2009; Seal et al. 2009; Li et al. 2011; Abraira and Ginty 2013).

Cutaneous afferents can also be classified based on the speed with which they conduct action potentials, which is set by their degree of myelination (Brown and Iggo 1967; Rice and Albrecht 2008; Gardner et al. 2013). Aβ afferents are rapidly conducting fibers that have large axonal diameters and thick myelin sheaths. C fibers, which have thin, unmyelinated afferents, are the slowest class. Aδ fibers, which have fine axonal diameters and thin myelin sheaths, display intermediate conduction velocities. Although there are many exceptions, most nociceptors, pruritoceptors, and thermoreceptors are classified as Aδ or C fibers. Most tactile afferents, or low-threshold mechanoreceptors (LTMRs), fall into Aβ or Aδ categories. A notable exception is C-LTMRs, a class of unmyelinated, LTMRs that abundantly innervate hairy skin and respond to gentle brushing (Olausson et al. 2010; Vrontou et al. 2013). These afferents have been proposed to mediate social aspects of touch that contribute to pair and maternal bonding (Olausson et al. 2010).

MERKEL CELL–NEURITE COMPLEXES IN TOUCH DOMES

Merkel cell–neurite complexes respond to pressure and encode an object's spatial features,

such as shapes and edges (Johnson 2001). These complexes are located in skin areas specialized for high tactile acuity, including glabrous fingerpads, vibrissal follicles, and touch domes, which are high-sensitivity areas of hairy skin (Fig. 2).

In the hairy skin of rodents and humans, touch domes (TDs) are specialized structures in the epidermis that consist of unusual columnar keratinocytes juxtaposed to Merkel cells (Fig. 2) (Pinkus 1902; Smith 1977; Moll et al. 1996b; Halata et al. 2003; Reinisch and Tschachler 2005). TDs are asymmetric, crescent-shaped structures that are typically associated with tylotrich (guard) hair follicles. In the adult mouse, Merkel cell clusters are polarized to the caudal side of tylotrich hairs and this polar organization has recently been shown to require Frizzled6 signaling (Chang and Nathans 2013). In human skin, TDs are most abundant on the trunk and about half are associated with hair follicles (Orime et al. 2013). Histological studies suggest that human TDs are innervated by multiple types of sensory afferents (Reinisch and Tschachler 2005). A recent study found that human TDs range in diameter from ~50 to 500 μm and contain 65–265 Merkel cells (Orime et al. 2013). In adult mice, TDs are somewhat smaller, containing ~5–40 Merkel cells in a cluster ≤100 μm in diameter (Lumpkin et al. 2003; Lesko et al. 2013). Although the molecular and cellular basis for the designation and patterning of touch dome cells during skin development remains poorly understood, recent evidence shows that touch dome keratinocytes share similar keratin markers with hair follicle keratinocytes (Doucet et al. 2013), indicating that TDs may be designated in the hair placode during morphogenesis.

The function of Merkel cells in the epidermis has been debated for decades. A long-held model posits that Merkel cells are mechanosensory cells that transduce touch and activate SAI afferents through synaptic transmission (Iggo and Muir 1969; Tachibana and Nawa 2002; Haeberle and Lumpkin 2008). Consistent with this model, several groups have shown that Merkel cells are activated by mechanical stimuli, such as cell swelling and membrane stretch (Chan et al. 1996; Haeberle et al. 2008; Boulais et al. 2009). Moreover, parallels are notable between Merkel cells and other mechanosensory receptor cells, such as hair cells of the inner ear. For exam-

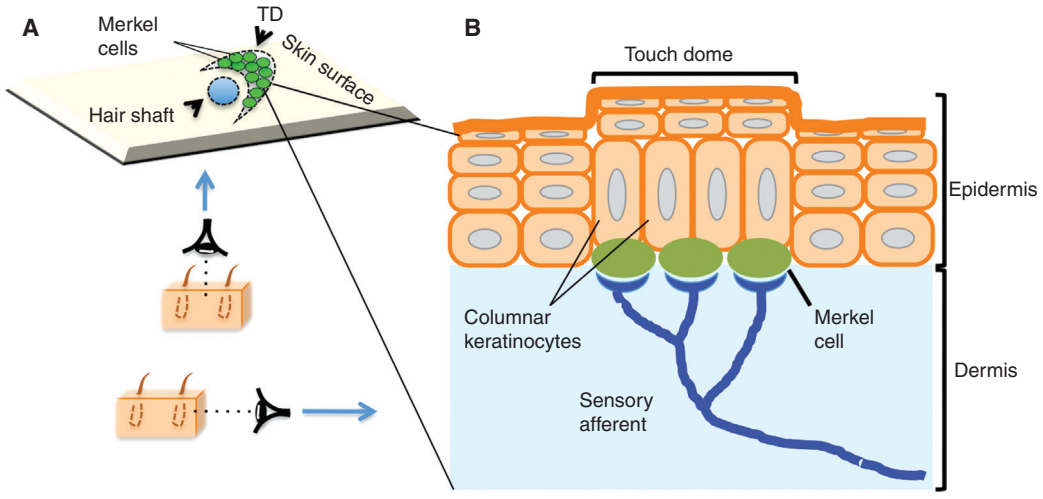

Figure 2. Position and structure of touch domes in mice. (*A*) Overhead view schematic illustrates that touch domes (TDs) are asymmetrical crescent-shaped structures that are polarized to the caudal side of tylotrich (guard) hairs in the pelage skin. (*B*) Sagittal view schematic illustrating the key cellular and structural elements of the touch dome including unusual columnar keratinocytes juxtaposed with mature Merkel cells, which are innervated by SAI sensory afferents.

ple, these cell types express a common complement of transcription factors, including Brn3c, Gfi1, Sox2, and mammalian atonal homolog 1 (*Atoh1)* (Xiang et al. 1997; Ben-Arie et al. 2000; Leonard et al. 2002; Wallis et al. 2003; Haeberle et al. 2004; Badea et al. 2012; Lesko et al. 2013). *Atoh1* is required for developmental specification of both hair cells and Merkel cells (Bermingham et al. 1999; Maricich et al. 2009; Van Keymeulen et al. 2009). A second hypothesis is that Merkel cells are accessory cells that serve as mechanical filters or release neuromodulators to shape the firing patterns of touch-sensitive SAI afferents (Gottschaldt and Vahle-Hinz 1981). A two-receptor site model, which posits that Merkel cells and sensory terminals contribute to different aspects of the SAI response, has also to be proposed (Yamashita and Ogawa 1991). Finally, the presence of noninnervated Merkel cells in some epithelia suggests that Merkel cells might participate in neuroendocrine rather than sensory functions (reviewed in Eispert et al. 2009).

Consistent with an active role in touch reception, a substantial body of histological and molecular evidence indicates that Merkel cells make synaptic-like contacts with sensory afferents (Haeberle et al. 2004; Hitchcock et al. 2004; Nunzi et al. 2004). Moreover, Merkel cells have small dense-core vesicles that contain neurotransmitters, including glutamate, ATP, serotonin, and a multitude of neuropeptides (Hartschuh et al. 1979, 1983; Alvarez et al. 1988; Gauweiler et al. 1988; Hartschuh and Weihe 1988; Garcia-Caballero et al. 1989; Toyoshima and Shimamura 1991; English et al. 1992; Fagan and Cahusac 2001; Tachibana and Nawa 2002; Haeberle et al. 2004; Hitchcock et al. 2004). A direct demonstration that Merkel cells release these neurotransmitters to convey sensory information to SAI afferents is still lacking. Alternatively, Merkel cells could release these substances in a paracrine fashion to modulate the development or function of neurons, keratinocytes, or other skin cells.

The requirement for Merkel cells in touch has been tested using transgenic mice and photoablation (Ogawa 1996; Halata et al. 2003). Attempts to remove Merkel cells via photoablation or enzymatic digestion have produced conflicting results, with loss of SA touch responses in some studies but not others (Diamond et al. 1988; Ikeda et al. 1994; Mills and Diamond 1995; Senok et al. 1996a,b). Because it is difficult to completely ablate Merkel cells without also damaging sensory terminals with these methods, other groups have turned to transgenic approaches. In mutant mice lacking the *p75* neurotrophin receptor, TDs have normal complements of Merkel cells at birth but most are lost postnatally. Electrophysiological recordings showed that these mutants have touch-evoked responses similar to those of wild-type mice (Kinkelin et al. 1999), indicating that Merkel cells are not necessary to produce slowing adapting touch responses. One caveat is that the presence of TDs was not confirmed in the receptive fields of these afferents; therefore, it is possible that these responses reflected the activity of SA neurons other than SAI afferents (Wellnitz et al. 2010). By contrast, in *Atoh1* conditional knockout mice, Merkel cells fail to form during development but TDs are still innervated by sensory afferents (Maricich et al. 2009). Merkel cell knockout mice show a selective loss of SAI responses in electrophysiological recordings and a loss of texture preference in behavioral assays (Maricich et al. 2009, 2012). Thus, these results suggest that Merkel cells play an integral role in touch-evoked SAI responses (Maricich et al. 2009). Because Merkel cells never develop in these mice, these studies do not distinguish between a developmental requirement, a mechanosensory function, or an accessory role. Thus, further studies are needed to define the function of Merkel cells in touch reception.

Merkel cells express numerous neuronal proteins (Halata et al. 2003; Haeberle et al. 2004), which is consistent with the notion that the developmental origin of the Merkel lineage is the neural crest. This idea was initially supported by cell-lineage tracing studies identifying Wnt1-expressing neural crest stem cells as the Merkel-cell site of origin (Szeder et al. 2003). More recently, two reports comparing murine lineage tracing models using a neural crest Cre driver (Wnt1Cre) or an epidermal Cre driver (K14Cre) indicated that Merkel cells are derived

from the proliferative keratinocyte layer (Krt14-expressing) of skin rather than Wnt1 progenitors in the neural crest (Morrison et al. 2009; Van Keymeulen et al. 2009). In support of these findings, conditional deletion of *Atoh1* in K14Cre mice was shown to abolish Merkel cell development, whereas the same mutation using Wnt1Cre mice had no effect (Morrison et al. 2009).

Although we understand very little about the signaling pathways that designate a Merkel fate in keratinocyte stem cells, recent studies have begun to unravel transcription factors other than *Atoh1* that are required for Merkel cell differentiation. Conditional deletion of Sox2, a marker of Merkel cells (Haeberle et al. 2004; Driskell et al. 2009; Lesko et al. 2013), via K14Cre mice leads to depletion of Merkel cells in the epidermis (Bardot et al. 2013; Lesko et al. 2013). Interestingly, Sox2 signaling appears to be upstream of Atoh1 and is suppressed by Ezh1 and Ezh2 histone methyltransferase enzymes (Bardot et al. 2013).

Because Merkel cells are postmitotic cells (Vaigot et al. 1987; Merot and Saurat 1988; Moll et al. 1996c; Woo et al. 2010), an epidermal progenitor pool would presumably be required to maintain this lineage during epidermal homeostasis. Indeed, a phenotypically distinct population of columnar keratinocytes residing in TDs possesses bipotent progenitor capacity, as evidenced by their ability to contribute to mature Merkel and squamous epidermal lineages during homeostasis and under regenerative conditions (Woo et al. 2010). Recently, a mouse model has been reported that targets touch dome columnar keratinocytes, while excluding mature Merkel cells, with a tamoxifen-inducible Cre recombinase ($CreER^{T2}$) under the regulatory control of the cytokeratin Krt17 locus (Doucet et al. 2013). Lineage studies in $Krt17CreER^{T2}$ transgenic mice showed that Merkel cells are genetic descendants of $Krt17^{+}$ touch dome keratinocytes and that the pool of Merkel cells in the touch dome is turned over every 2 months in murine skin during homeostasis (Doucet et al. 2013). Interestingly, there does not appear to be any remarkable overlap between the touch dome niche and other niches in the remainder of the epidermis, indicating that the touch dome might represent a distinct stem cell pool in the interfollicular epidermis (Doucet et al. 2013).

Our understanding of the cellular basis for the maintenance of Merkel cell homeostasis is highly relevant for two pathological skin conditions: Merkel cell carcinoma (MCC), which features an overproduction of neoplastic Merkel cells, and age-related loss of tactile acuity, which is associated with a loss of Merkel cells. MCC is a highly aggressive tumor that arises in the skin (Toker 1972) and consists of neoplastic cells expressing neuroendocrine markers and transcription factors similar to those of normal Merkel cells (Harms et al. 2013). Although MCCs are relatively rare compared with other types of nonmelanoma skin cancer, the incidence of MCC cases has tripled over the last decade with less than half of MCC patients surviving 5 years following detection of lymph node involvement (Hodgson 2005). MCC incidence is at least 10-fold greater in human immunodeficiency virus (HIV) and organ transplant patients as well as patients exposed to ultraviolet radiation (Lunder and Stern 1998; Penn and First 1999; Engels et al. 2002), indicating that immune suppression may be a critical risk factor for MCC. A previously unidentified polyoma virus, Merkel cell polyoma virus (MCV), was found in 80% of MCC cases (Feng et al. 2008) suggesting that opportunistic MCV infection plays a causal role in the formation of MCC; however, the pathogenesis of MCC remains poorly defined.

One issue clouding our understanding of MCC pathogenesis stems from conflicting reports addressing whether MCC actually arises from Merkel cells that have undergone oncogenic transformation (Gould et al. 1985; Kanitakis et al. 1998; Sidhu et al. 2005). Numerous neuronal proteins expressed by normal Merkel cells are also featured in MCC cells, supporting the idea of a Merkel cell origin for MCC. On the other hand, Merkel cells are postmitotic cells (Vaigot et al. 1987; Merot and Saurat 1988; Moll et al. 1996a) making them an unlikely candidate as a MCC cell of origin. In addition, the mature Merkel cell pool has a relatively fast (2 months) rate of turnover in adult murine skin (Doucet

et al. 2013), which raises the possibility that an epidermal keratinocyte stem cell pool may be an origin for MCC.

INNERVATION OF HAIR FOLLICLES

Hair follicles are a major component of the pilosebaceous unit, which performs a number of functions in the skin including production of hair fibers and oil, induction of angiogenesis, serving as a reservoir for pigment-producing and immune cells, and participation in wound healing. Recently, the hair follicle has gained more attention for its role in touch sensation. The displacement of hairs by innocuous mechanical stimuli activates LTMRs housed in a piloneural collar that is located in the isthmus and upper bulge regions of the hair follicle (Figs. 1 and 3). The terminals of inner piloneural afferent populations align with the neck of the hair follicle in a longitudinal direction forming palisades of lanceolate nerve endings, and outer populations innervate in a circumferential pattern (Munger and Ide 1988; Halata 1993).

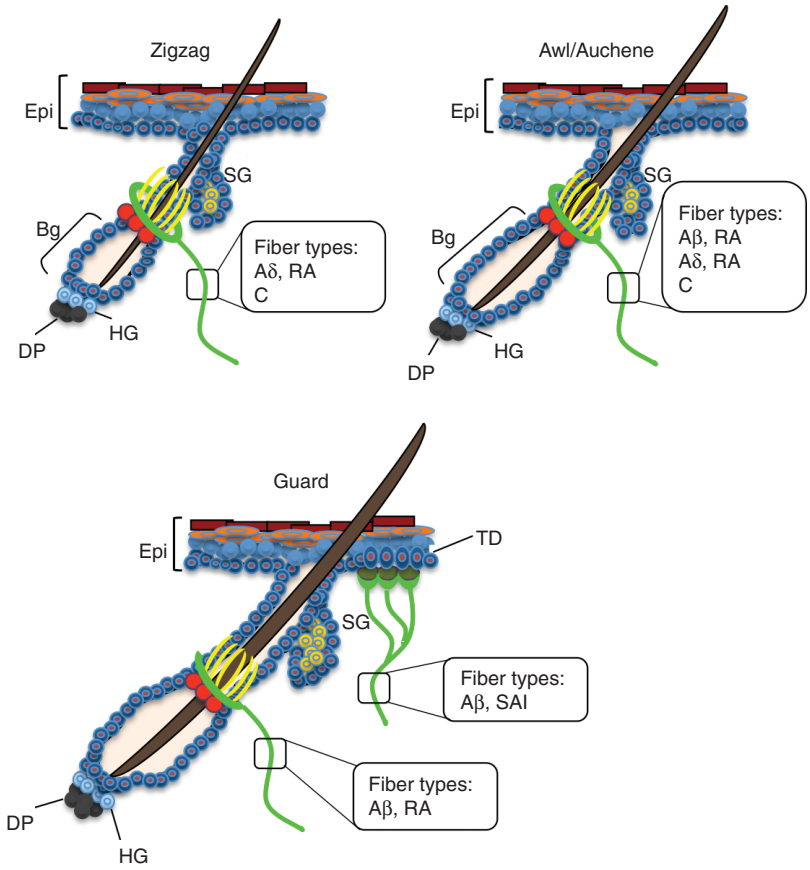

Figure 3. Schematic representation of the structural components of the piloneural collar mechanoreceptor. Sensory projections from dorsal root ganglion neurons innervate the isthmus/upper bulge region of hair follicles in the pelage skin in circumferential (CF) and longitudinal (LF) patterns. The terminal endings of these sensory afferents are tightly associated with the upward processes of terminal Schwann cells (tSCs; red). Both the fibers and tIISC processes are associated with the outer root sheath keratinocytes in the hair follicle. The four types of pelage follicles, zigzag, awl, auchene, and guard, and the accompanying afferent combinations are shown. Bg, bulge; CF, circumferential fibers; IFE, interfollicular epidermis; Is, isthmus; LF, lanceolate fibers; SG, sebaceous gland.

Whereas histological data indicate that at least five distinct populations of sensory neurons localize to the piloneural collar (Millard and Woolf 1988), recent studies using sparse genetic labeling have revealed that the repertoire of sensory receptors innervating mouse hairy skin is even more complex (Li et al. 2011; Badea et al. 2012; Wu et al. 2012; reviewed in Abraira and Ginty 2013). For example, at least 10 morphologically distinguishable types of sensory afferents innervate mouse dorsal skin at postnatal day 21 (Wu et al. 2012). Many of the sensory neurons that innervate hair follicles express the transcription factor Brn3b and are derived from early *Ret*-positive sensory neurons during embroyonic development (Bourane et al. 2009; Luo et al. 2009; Badea et al. 2012). In some cases, an individual sensory afferent innervates only a single hair follicle, whereas other afferents innervate hundreds of hair follicles spanning a skin area of up to $\sim$7 mm^2 (Li et al. 2011; Wu et al. 2012). The complicated composition of the piloneural collar might allow the hair follicle to discriminate between subtle differences in mechanical force or the duration of stimulation.

Adding to this complexity are the distinct hair follicle types identified in murine skin—zigzag, awl, auchene, and guard—that can be discriminated based on hair shaft thickness, length, and the presence of kinks (Fig. 3) (Schlake 2007). The discovery of selective molecular markers for different classes of hair follicle afferents has enabled a systematic analysis of the pilonural collars of these different hair follicle types (Li et al. 2011). Piloneural lanceolate endings are formed by at least three types of hair follicle sensory neurons: Aβ-LTMR, Aδ-LTMR, or C-LTMRs (Li et al. 2011). Each of these subtypes reports hair movements but they convey information to the central nervous system with different latencies. Moreover, Aβ-LTMR, Aδ-LTMR, and C-LTMRs that innervate the same skin area display overlapping but distinct central projection patterns, suggesting that their inputs are integrated by spinal cord circuitry. Remarkably, guard, awl/auchene, and zigzag follicles are innervated by unique complements of these sensory neurons in adolescent mice (P14–P30) (Fig. 3). These data suggest that each type of hair follicle represents a distinctive mechanosensory unit equipped to selectively encode specific aspects of brushing or stroking stimuli. These signals are then integrated by spinal circuits to form a cohesive representation of touch (Li et al. 2011; Abraira and Ginty 2013).

The palisade patterning of terminal nerve endings are a unique feature of the piloneural collar receptor, which appears to be influenced in part by the presence of type II terminal Schwann cells (tIISCs). A recent study reported that tIISCs are required for maintenance of mouse lanceolate endings and that these tIISCs persist following denervation (Li and Ginty 2014). These tIISCs express Nestin and S100 and display long fingerlike processes that extend upward from tIISC cell bodies and interdigitate with longitudinal fibers so that each nerve ending is tightly juxtaposed on either side with tIISC processes (Kaidoh and Inoue 2000, 2008; Woo et al. 2010). Electron microscopic studies have shown that N-cadherin-mediated adherens junctions are formed between outer root sheath (ORS) keratinocytes in the hair follicle and either tIISC processes or the terminal nerve endings themselves (Kaidoh and Inoue 2000, 2008). These data indicate that the maintenance of this receptor might rely on communication between all three cellular components. Support for this idea has come from analysis of the skin of mice lacking Vglut2, a vesicular glutamate transporter that packages excitatory glutamate into exocytic vesicles. Tissue-specific deletion of Vglut2 showed that neuron-derived glutamate plays an essential role in the development, maintenance, and mechanosensory capacity of the piloneural collar (Woo et al. 2010). These studies illustrate that terminal Schwann cells might have a key role in the function of somatosensory receptors by facilitating the positioning of sensory end organs. Collectively, these results showed that glutamate derived from sensory terminals is essential for the proper development, maintenance, and sensory function of the piloneural mechanoreceptor (Woo et al. 2012). This is the first evidence that excitatory glutamate derived from sensory neurons can regulate the differen-

tiation of glial cells in the skin. Importantly, these results confer an efferent functionality to this population of glutamatergic sensory afferents in the skin. Glutamate release from exocytic vesicles has been observed following stretch activation of mechanosensory nerve terminals innervating muscle spindles, providing a precedence for this concept in other peripheral tissues. Moreover, sensory neuron-derived Shh ligands have been shown to modulate the ability of hair follicle stem cells to respond to skin wounding (Brownell et al. 2011). Whether additional efferent factors released by sensory neurons influence skin or hair follicle homeostasis or pathological skin conditions including cancer carcinogenesis remains poorly understood.

CONCLUDING REMARKS

We are witnessing an exciting period of rapid progress in the field of cutaneous neurobiology. The combination of modern mouse genetics, neurophysiology, development, and stem cell biology has shed new light on the complex interactions between the nervous system and skin cells, as well as the intricate neuronal processes that underlie our rich sensory experiences.

As highlighted above, fascinating questions remain unanswered. What are the signaling mechanisms in keratinocytes and other skin cell types that transduce efferent signals from cutaneous sensory neurons? What are the developmental pathways that allow keratinocyte-derived Merkel cells to adopt a neuronal-like cell fate? Do epidermal Merkel cells and keratinocytes play a functional role in sensory signaling, as suggested by numerous anatomical and molecular studies? Moreover, little is known about how the nervous system adapts to the changes in skin structure and function that accompanies normal aging and environmental exposures. For example, given that follicles can produce different hair types in adult hair cycles (Chi et al. 2013), do corresponding changes in innervation occur when hair morphology switches? With modern tools in hand, the answers to these questions are now within reach.

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