Review

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Merkel cells and neurons keep in touch

Seung-Hyun Woo[1], Ellen A. Lumpkin[2], and Ardem Patapoutian[1]

[1] Howard Hughes Medical Institute, Molecular and Cellular Neuroscience, The Scripps Research Institute, La Jolla, CA 92037, USA
[2] Departments of Dermatology & Physiology and Cellular Biophysics, Columbia University, New York, NY 10032, USA

The Merkel cell–neurite complex is a unique vertebrate touch receptor comprising two distinct cell types in the skin. Its presence in touch-sensitive skin areas was recognized more than a century ago, but the functions of each cell type in sensory transduction have been unclear. Three recent studies demonstrate that Merkel cells are mechanosensitive cells that function in touch transduction via Piezo2. One study concludes that Merkel cells, rather than sensory neurons, are principal sites of mechanotransduction, whereas two other studies report that both Merkel cells and neurons encode mechanical inputs. Together, these studies settle a long-standing debate on whether or not Merkel cells are mechanosensory cells, and enable future investigations of how these skin cells communicate with neurons.

Merkel cell–neurite complexes in skin

We depend on our sense of touch to gather information about the world around us and to accomplish skilled movements. Our ability to experience the richness of our tactile environment relies on touch receptors present in the skin. Touch receptors express mechanically activated (MA) ion channels that detect and convert mechanical stimuli into electrical signals. These electrical signals are then delivered to the central nervous system (CNS), where they are processed and interpreted as touch sensations.

The sensory neurons that initiate touch sensation are called low threshold mechanoreceptors (LTMRs). LTMRs terminate in skin and are classified as Aβ, Aδ, or C fibers, based on their degree of myelination and action potential conduction velocities [1–3]. Both hairy and hairless skin areas contain discrete sets of LTMRs, and different types of LTMRs detect specific tactile modalities [4]. For example, lanceolate nerve endings in hair follicles respond to hair movement [5,6], whereas Pacinian and Meissner's corpuscles in hairless skin areas respond to vibrations of various frequencies [7–9]. The Merkel cell–neurite complex is a LTMR present in both skin types that is thought to be important for mediating gentle touch [3,10,11]. Interestingly, the Merkel cell–neurite complex consists of two distinct, but closely associated cell types: Aβ sensory neurons, and epithelial cells known as Merkel cells.

Merkel cells are a rare population of epithelial cells present in skin of most vertebrates [12]. First identified by Friedrich Sigmund Merkel in 1875, these cells were originally described as 'Tastzellen' (touch cells) because their close association with nerve fibers led Merkel to presume that they function in touch sensation [11]. Merkel cells are indeed found in touch-sensitive areas of the skin, such as fingertips, lips, and specialized spots in hairy skin called touch domes [10,11,13,14], and they are also found in abundance in mammalian whisker follicles [15]. Among epithelial cells, Merkel cells are unique because they form close contacts with Aβ sensory neurons at the epidermal–dermal junction [10,15]. The contacts between Merkel cells and afferent terminals are proposed to be anatomically similar to synaptic contacts [16–20].

In 1969, Iggo and Muir provided the first functional evidence to implicate Merkel cell–neurite complexes in touch reception. By recording from touch-sensitive neurons in cat hairy skin, they demonstrated that a particular type of slowly adapting (SA) discharge was evoked by mechanical stimulation of touch domes, where Merkel cell–neurite complexes localize [10]. They found that pressure applied to a touch dome produced long-lasting action potential trains characterized by an irregular firing pattern with a large variation in interspike intervals, and they categorized this firing pattern as SA type I (SAI) [10]. SAI afferents are proposed to encode fine details of objects because of their high spatial resolution and sensitivity to object features such as points, edges, and curvature [21].

Based on these findings, Merkel cell–neurite complexes are thought to be the touch receptors that initiate SAI responses of Aβ afferents for tactile discrimination of shapes and textures [10,22]; however, the precise functions of Merkel cells and Aβ SAI sensory afferents during touch transduction have been debated [4,15,22]. A key question is: which cell type is responsible for transducing mechanosensory stimuli into electrical signals? The answer to this question is not immediately obvious because the nervous system has devised two strategies for encoding sensory stimuli into neuronal signals. Sensory transduction can be accomplished either by primary sensory neurons or by epithelial-derived secondary sensory cells. For example, olfactory neurons [23] and most cutaneous LTMRs [4] are primary sensory neurons that both mediate sensory transduction and conduct neuronal impulses to the CNS. In other cases, such as taste receptor cells [24] and mechanosensory hair cells of the inner ear [25,26], sensory transduction is accomplished by epithelial-derived cells that release neurotransmitters to activate afferent neurons, which then convey sensory information to the CNS.

Corresponding authors: Lumpkin, E.A. (eal2166@columbia.edu); Patapoutian, A. (ardem@scripps.edu).
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For the Merkel cell–neurite complex, a case can be made for either primary or secondary sensory cells. Because all other LTMRs are primary sensory neurons, it stands to reason that Aβ SAI afferents might also be mechanosensitive. By contrast, a number of suggestive anatomical and developmental parallels have been observed between Merkel cells and the hair cells of the inner ear. They are both epithelial-derived cells innervated by sensory neurons [27,28]. Moreover, they express the same developmental transcription factors including atonal homolog 1 (Atoh1), an essential transcription factor for development of both Merkel cells and hair cells [29–32]. Do Merkel cells, like hair cells, also function as mechanosensory cells?

A historical view of Merkel cells

The possibility that Merkel cells are sensory cells has been a subject of debate for decades. Some studies concluded that Merkel cells are mechanosensors, whereas others concluded that SAI afferents are primary sensory receptors, and that Merkel cells are accessory cells that modulate SAI responses [29,33–38]. For example, phototoxic ablation of Merkel cells caused decreased SAI responses in one study [38], but showed no effect in another report [37]. A third group raised concerns about the effectiveness of this ablation method, as they found that the sensitivity to phototoxic destruction varied among Merkel cells, and that this method also had an adverse effect on afferent terminals [35]. Another study examined SA responses in the neurotrophin receptor *p75* knockout mice, in which Merkel cells initially develop but are lost with age [34]. *p75* knockout mice showed a normal proportion of SA responses, even after losing the majority of epidermal Merkel cells, indicating that Merkel cells are not required for touch-evoked firing in SA afferents [34]. In this study, SAI firing patterns were not analyzed in detail; therefore, it is unclear whether or not Merkel cell loss might have subtly altered SAI firing properties. Overall, these studies were not sufficient to clarify whether Merkel cells are necessary for SAI firing patterns.

More recently, complete ablation of Merkel cells was achieved in the pelage skin of mice by genetically deleting *Atoh1* [29]. In these mice, touch domes develop without Merkel cells, but are innervated by myelinated afferents [29]. These mice showed a selective and complete loss of SAI firing patterns, which indicates that Merkel cells are essential components for producing SAI responses in sensory afferents [29]. These results are consistent with the hypothesis that Merkel cells are mechanosensory receptor cells; however, two other models can also explain this phenotype. First, developmental deletion of Merkel cells might have adverse effects on Aβ SAI afferent development [4,22]. Second, the firing patterns of Aβ SAI afferents could differ in the absence of Merkel cells, leading them to be classified as non-SAI responses.

To qualify as a mechanosensory receptor cell, the candidate cell type should be mechanosensitive. Thus, more direct approaches have been used to ask whether Merkel cells are intrinsically mechanosensitive. In isolated rat whisker hair follicles, direct displacement of Merkel cells using a glass probe elicited robust Ca^{2+} influx in these cells, and this rise in Ca^{2+} was suggested to be important for synaptic transmission to the afferent nerve terminals [36]. In this setting, however, SAI afferent terminals were in contact with Merkel cells, so neuronal contribution during mechanotransduction could not be ruled out. Other groups performed similar experiments in dissociated Merkel cells to avoid this problem. In some studies, hypotonic-induced cell swelling was used as an alternative to a displacement stimulus. When dissociated Merkel cells were exposed to hypotonic solutions, a similar increase in intracellular Ca^{2+} was observed [33,39]; however, hypotonic-induced Ca^{2+} influx in Merkel cells might be a consequence of activating volume-regulatory machinery rather than mechanosensory transduction mechanisms [33].

Most LTMRs have mechanosensitive endings that terminate in skin [40,41]. A lack of definitive proof for mechanosensitivity of Merkel cells led some groups to conclude that SAI sensory neurons are primary mechanoreceptors, and that Merkel cells act as accessory cells [42,43]. Indeed, it has been argued that the response latency of SAI afferents is too short to involve synaptic transmission from Merkel cells, suggesting that the afferents must be directly mechanosensitive [44].

A third model, which posits two receptors sites, combines elements of the two previous models by proposing that both Merkel cells and Aβ SAI sensory afferents are involved in mechanotransduction [45]. Supported by pharmacological studies that altered synaptic signaling, this model hypothesizes that SAI afferents mediate the initial dynamic phase of touch responses and that Merkel cells transduce the sustained, or static, phase of touch responses [17,46,47]. The two-receptor site model can account for both the short latency of SAI firing and the presence of a synapse between Merkel cells and SAI afferents.

Merkel cells are touch-sensitive cells with Piezo2-dependent transduction channels

Recently, important advances have been made to elucidate the function of Merkel cells in touch. Three independent studies report disparate set of experiments and provide direct evidence that Merkel cell are indeed touch-sensitive cells, and that they function as essential components of touch receptors in skin.

Two studies used a combination of mouse genetics and *in vitro* and intact electrophysiological recordings to examine the role of Merkel cells during touch transduction [48,49], whereas a third study used an *ex vivo* rat whisker preparation with pharmacological manipulations to elucidate Merkel cell function [50]. As an initial step, all three studies independently provided a clear answer to the question of whether Merkel cells are cell-autonomously touch sensitive. When Merkel cells were gently displaced with a glass probe, they produced robust MA currents both *in vitro* and *ex vivo* [48–50]. The biophysical properties of these currents resembled those of Piezo2, a MA ion channel expressed in somatosensory neurons [48–51]. Consistent with this observation, all three groups demonstrated that Merkel cells preferentially expressed Piezo2 [48–50]. For the next step, the three studies took distinct approaches.

One group showed that Merkel cell activation alone is sufficient to induce action potential firing in Aβ SAI