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Merkel cells and touch domes: More than mechanosensory functions?

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Abstract

The touch dome is an innervated structure in the epidermis of mammalian skin. Composed of specialized keratinocytes and neuroendocrine Merkel cells, the touch dome has distinct molecular characteristics compared to the surrounding epidermal keratinocytes. Much of the research on Merkel cell function has focused on their role in mechanosensation, specifically light-touch. Recently, more has been discovered about Merkel cell molecular characteristics and their cells of origin. Here we review Merkel cell and touch dome biology, and discuss potential functions beyond mechanosensation.

Keywords

Merkel cell; touch dome; mechanosensation; immune; endocrine

Merkel cells and touch domes in mammalian skin

In the time since their discovery in 1875 by Friedrich Merkel (1), Merkel cells (MCs) have garnered attention for their distinct morphology and putative sensory function. MCs are described in many species including reptiles, fish, and mammals, where they are found in the basal layer of hairy skin, glabrous skin, and some mucosal epithelia (2). Ultrastructurally, MCs are characterized by dense-core granules, indented nuclei, and desmosomal connections to neighboring keratinocytes (KCs). On their basal surface, MCs associate with sensory nerve endings. In some parts of the skin, MCs are surrounded by morphologically distinct columnar KCs at the base of a stratified squamous epithelium that is thicker than the surrounding epidermis. This specialized epidermal structure was named a touch dome (TD, or haarscheibe) based on its speculated function (3). Keratin 8 (K8) and Keratin 18 (K18) are established markers for MCs in late fetal and adult skin. Keratin 20 (K20) is also a highly specific marker for MCs in the skin. The hair follicle keratin, Keratin 17 (K17), is a marker for TD KCs (4, 5). Table 1 summarizes reported markers for MC and TD KCs.

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Merkel cell and touch dome keratinocyte progenitors originate from epidermal cells

Where MCs originate is important to MC biology. The identification of MCs in subepidermal embryonic mesenchyme initially led to the hypothesis that they arise from migrating neural crest progenitors (6). This hypothesis was widely accepted after a transgenic model utilizing *Wnt1-Cre* to fate map neural crest derived cells described labeled MCs in mouse vibrissae (7). However, conditional knockout of *Atoh1*, a transcription factor essential in MC development, using Wnt1-Cre resulted in no effect on MCs. In contrast, a K14-Cre driven deletion of Atoh1 in epidermal keratinocyte derivatives led to a loss of MCs, suggesting MCs are derived from a keratinocyte lineage rather than a neural crest origin (8). Early studies characterizing cytokeratin expression in human embryonic skin also suggested that MCs arise from epidermal epithelial precursors (4, 9), and xenografts of human embryonic skin onto nude mice further supported the idea that MCs rise from epidermal precursor cells (10). Recently, lineage-tracing experiments showed that MCs originate from K14-expressing epidermal progenitors (11). Consistent with an epidermal origin for MC, CD200+ basal cells sorted from touch domes in dissociated mouse skin were able to reconstitute touch domes when grafted onto a host mouse (12). Additional studies showed that K17+ epidermal progenitors maintain both MCs and KCs during TD homeostasis (13). The identification of MC and TD progenitors has greatly advanced our understanding of TD biology. However, the question still remains as to whether a single, multipotent progenitor gives rise to both MCs and TD KCs, or if there are distinct lineage-specific K17+ progenitors maintaining the two TD cell types.

Merkel cells are required for light-touch sensation

Many types of cutaneous mechanoreceptors endow human skin with a tactile discrimination approaching 10 nm (14). Since their discovery, a sensory function for MCs has been inferred based on their synapse-like contact with nerve endings. Merkel cells *in vitro* and *in vivo* are activated by mechanical stimuli (15), including hypotonic-induced cell swelling, supporting the hypothesis that MCs function as mechanoreceptors (16). Genetic ablation of MCs in the context of maintained TD morphology and innervation, determined that MCs are essential for light-touch responses in isolated skin preparations (17). Additional studies revealed that MCs express presynaptic molecules essential for synaptic vesicle release, as well as neuroactive substances. A recent review discusses the numerous potential neurotransmitters found in MCs (18). The details of sensory transduction by the MC-neurite complex are still unclear, and the involvement of individual neurotransmitters in MC touch-evoked responses remains to be elucidated. Now that lineage specific Cre lines are available, conditional knockout studies to determine the critical factors should be forthcoming.

A role for Merkel cells in peripheral nerve development

Studies in human embryonic plantar skin showed most MCs initially lack innervation, and the MC-neurite complex appears later in development, suggesting that MCs attract the nerves that innervate them (19). Similar studies in developing mice confirmed that MCs are specified days prior to being innervated, further suggesting MCs may have a target role for

certain type I sensory nerve fibers during embryogenesis (20). Other studies further established that both the location and early differentiation of MCs in the epidermis are independent of nerves, but are instead linked to the development of tylotrich (guard) hair follicles (21). The fact that MCs express neuroactive substances that can modulate neuronal cell fate determination also supports the notion that MCs play a regulatory role for peripheral nerves (18). However, even though MCs are the ultimate target for innervation, there is some evidence that the MCs themselves may not be necessary to attract incoming nerve branches to the TD. When MCs are ablated via *Atoh1* deletion, TD morphology is maintained and innervation appears unaffected (17). Moreover, in *K14-Cre;Sox2*$^{floxed/floxed}$ mice where MC number is decreased because of ablation of *Sox2* in MC progenitors, TD innervation is not affected (22). Thus, factors in the TD, independent of differentiated MCs, may provide the necessary trophic signals to attract sensory nerves.

Heterogeneity of the Merkel cell population

Early morphologic observations and more recent molecular studies both suggest that subpopulations exist among MCs. Studies in early human embryonic skin found mainly round to oval MCs, with infrequent MCs having short dendrites (4). It has also been observed that dendritic MCs (DMCs) are usually not innervated but most oval MCs (OMC) are innervated (23). Later studies showed that the number of OMCs per TD remains steady over time, whereas the number of DMCs fluctuates concomitantly with the hair cycle (24, 25). Although it is intriguing to speculate that non-innervated DMCs may be a dynamic population of functionally distinct non-sensory MCs, it may be that DMCs are newly differentiated MCs that have yet to be innervated and take on an oval morphology. Interestingly, immunostaining studies observe that MCs do not all share the same molecular signatures. Differential expression of villin, N-CAM, NGF-R, neurofilaments, chromogranin A, and pancreastatin are found among MCs, demonstrating molecularly distinct populations of MCs coexist in the skin (26-28). Presently, the functional implications of the different morphological and molecular subtypes of MCs remain unknown.

Merkel cells in the skin neuroendocrine system

Merkel cells form complexes with sensory nerve afferents, and they possess typical neuroendocrine features including dense core granules and the expression of chromogranin A (29), chromogranin B (30), and synaptophysin (31). Importantly, they synthesize an array of neuroactive polypeptides/hormones such as vasoactive intestinal peptide (VIP), calcitonin gene-related peptide (CGRP) (32), neuroendocrine protein B2 (33), prepro-orexin and orexin receptors (34), serotonin (35, 36), and somatostatin (37). The presence of these signal ligands strongly suggests some form of paracrine or autocrine signaling within the skin. MCs directly contact TD KCs, and VIP is known to enhance keratinocyte proliferation (38), thus MCs may be endocrine regulators of the surrounding epidermis. MCs may also affect dermal fibroblasts by producing substance P, a peptide that can activate skin fibroblast proliferation (30, 39). However, the neuropeptides produced by MCs have diverse functions in other systems, and it remains to be seen how they function and what their targets are in the skin. It is likely they influence the local fibroblast, keratinocytes, immune cells and vasculature, in addition to their partner neurons. This would be similar to the diverse

functions of neuroendocrine cells in other organs. Intriguingly, neuropeptide release from MCs can be calcium independent (40), suggesting it may be a separate process from the Ca^{2+}-dependent neurotransmitter release thought to be involved in mechanosensation.

Merkel cells in the cutaneous immune system

Potential immunoregulatory functions of MCs and TDs have not been rigorously studied. The finding of robust CD200 expression in MC and TD KCs (12) raises a question about an unrevealed role in immunity. CD200 is a transmembrane protein that signals through the CD200 receptor (CD200R) to attenuate inflammatory reactions and promote immune tolerance. CD200 is normally expressed on thymocytes, T and B lymphocytes, neurons, and endothelial cells (41, 42), and CD200R is expressed on cells of the monocyte/macrophage lineage and T lymphocytes (43). CD200 is also highly expressed on KCs of the murine hair follicle outer root sheath (ORS) (44), and skin lacking CD200 is highly susceptible to hair follicle-associated inflammation and immune-mediated alopecia (45). Significant perifollicular inflammation is also observed in syngeneic grafts of CD200-deficient mouse skin (46). Thus, CD200 expression in the TD is likely to represent a second immune privileged compartment in the skin.

A further roll for MCs in regulating the immune system is implicated by their relationship with Langerhans cells (LC), dendritic antigen presenting cells that reside in the epidermis (47). MCs are known to interact with LCs in the skin (48). Hair follicles normally function as portals for LCs to enter the epidermis (49), however the portals for LCs into glabrous skin are unknown. It is possible that the dense clusters of MCs in acral skin allow LC to enter the hairless epidermis. At the same time, MCs produce CGRP, a neuropeptide that can inhibit antigen presentation by LCs (50).

MCs may also be involved in modulating inflammatory responses in the skin. Normal MCs produce met-enkephalin, which can enhance immune responses at low doses and suppress responses at high doses (20, 51). In addition, MCs can react to histamine or activation of the osmoreceptor TRPV4 by releasing VIP (40), which can decrease the production of pro-inflammatory cytokines (52). In psoriasis, MC numbers are higher in lesional skin than in normal skin (53). Moreover, MC expression levels of neuropeptides such as somatostatin, which is thought to be involved in skin immunology, are also different between psoriatic lesions and controls (54). The MC hyperplasia observed in psoriasis implies that MCs respond to, and possibly regulate, pathological skin inflammation. Occasionally, leukocytes are observed closely abutting DMCs, suggesting another potential functional linkage with the immune system (23). TD KCs also potentially contribute to regulating epidermal immunity by expression of K17, which can function to polarize the cutaneous inflammatory response (55). Taken together, these features of MCs and TD KCs predicate their potential involvement in cutaneous immunity.

Other hypothetical functions

Although little has been done to substantiate non-sensory functions of MCs and TDs in the skin, it seems probable that some additional functions will be found. In addition to the proposed functions discussed above, some highly speculative roles for MCs have been put

forward (56). These include: (1) Involvement in magnetoreception, as MCs occasionally contain transferred melanosome which magnetite. (2) Involvement in fingerprint formation, as MCs cluster at the base of epidermal ridges in glabrous skin. (3) Proposing that efferent neural signals drive MCs to generate electromagnetic fields for telekinesis. (4) Suggesting that the their broad distribution and possible multimodality sensing allows MCs to transmit environmental information to oocytes to alter epigenetic imprinting. (5) Determination of hair form, as MCs are found in hair follicles and proliferate synchronously with the hair cycle. It should be noted that some of the observations upon which these fanciful hypotheses are based have not been widely accepted.

Conclusions and perspectives

Early studies of MC and TD ultrastructure predicted a role in somatosensation for the innervated neuroendocrine cells and their specialized epidermal niche. Since then, MC involvement in light touch sensation has been demonstrated in a number of experimental systems. Modern molecular characterizations have furthered our understanding of MC and TD biology (Figure 1). Recently, transgenic mice have allowed for the identification of epithelial MC progenitors, and now offer genetic tools that will allow for mechanistic studies of MC function.

A number of MC characteristics suggest functions beyond mechanosensation. Apparent molecular and structural heterogeneity among MCs is consistent with functionally distinct subpopulations of MCs. As MCs produce a number of secreted signaling factors, it is likely that they act as endocrine regulators in the skin. The precise nature and targets of such endocrine regulation remain to be elucidated. It is also likely that MCs interact with the cutaneous immune system. MCs and TD KCs express a number of known immunoregulators, and it will be interesting to learn how MCs contribute to immune responses.

Investigating MCs is an important aspect of cutaneous biology. There is also tremendous clinical and translational interest in Merkel cell carcinoma (MCC), a highly aggressive skin cancer that might originate from mutant MCs or MC progenitors. Although knowledge of MC and TD biology could contribute to understanding MCC, the inability to culture normal MCs currently limits their *in vitro* study. The identification of MC precursors *in vivo* will hopefully accelerate our understanding of TD homeostasis, and will provide insight into the conditions needed to culture MCs. Thus, research into MC biology contributes to our understanding of mechanosensation and the neuro-cutaneous interface, and could also provide insights into the endocrine regulation of the skin, the cutaneous immune system, and the formation of skin cancer.

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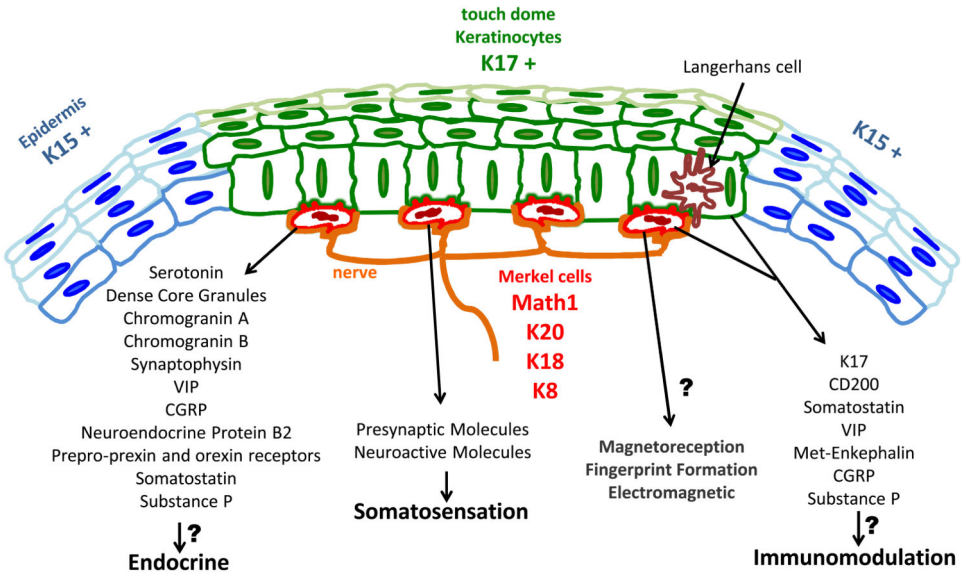

Figure 1.

Schematic of the mouse touch dome. Markers reported to be expressed in Merkel cells and touch dome keratinocytes that suggest function.

Table 1

Molecular characters of touch dome keratinocyte and Merkel cell.

Marker	Note	Ref
K18	A type I cytokeratin expressed by MCs. Usually expressed in single layer epithelial tissues with its partner K8.	(9)
K20	A type I cytokeratin expressed by MCs. K20+ MCs cells are negative for K17.	(25)
K8	At E15, K8 is restricted to scattered immature MCs in developing tylotrich follicles and the adjacent epidermis. By E16-E17, the K8+ MCs form a disc-shaped TD.	(21)
Math1/Atoh1	A basic helix-loop-helix transcription factor expressed by MCs and necessary for MC specification.	(17)
FM 1-43	Small fluorescent styryl dye taken up by MCs after systemic administration.	(17)
VGLUT2	Presynaptic protein. VGLUT2 immunoreactivity is most intense on the side of the MCs that abut sensory nerve terminals. The ionotropic receptor GluR2 that monitors glutamate release is also enriched in MCs.	(57)
Cav2.1	MCs have functional L-type and P/Q–type voltage-gated calcium channels.	(57)
Rab3c, SNAP25, piccolo, CCK8, synaptotagmin13, cholecystokinin 26-33, Synaptic vesicle protein	Among 362 MC-enriched transcripts, this list is confirmed by immunostaining. These features demonstrate that MCs are excitable cells.	(57)
Vasoactive intestinal peptide (VIP)	A neuropeptide hormone expressed by MCs. VIP can enhance keratinocyte proliferation and reduce inflammation.	(32, 38, 52)
Serotonin	A monoamine hormone expressed by MCs. Serotonin plays important roles in many biological process including neurotransmission, stress responses, and the regulation of inflammation.	(35, 36)
Sox2	All MCs express Sox2, a transcription factor expressed in adult stem cells that plays a crucial role in tissue regeneration in various organs.	(22)
CD200	A membrane glycoprotein expressed in TD KCs and MCs. CD200 attenuates inflammatory reactions and promotes immune tolerance.	(12, 58)
Tbc1d10c	Marks TD KCs.	(12)
K17	A type I cytokeratin. TD KCs prominently express K17 and show reduced K15 expression. K17 can regulate cutaneous inflammation.	(5, 55)