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A novel player in the field: Merkel disk in touch, itch, and pain

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Introduction

Mammalian skin, comprising both hairy and glabrous skin, is innervated by various types of low-threshold mechanoreceptors (LTMRs), which renders skin into a mechanosensitive organ [1]. Based on the degree of axonal myelination and conduction velocity, LTMRs are further divided into C-, Aδ- and Aβ-LTMRs. Electrophysiological recordings from those LTMRs have revealed unique action potential firing patterns upon discriminative mechanical stimuli. Although great strides have been made in the past decades to identify LTMRs that are specifically involved in the genesis of tactile sensations [2, 3], their anatomical and physiological properties remain largely unknown. Light touch sensation is encoded by Merkel cell-neurite complex which is composed of slowly adapting type I (SAI) cutaneous Aβ-LTMRs and skin-derived Merkel cells. Recent exciting studies have begun to understand how Merkel cell-neurite complex is involved in the generation of touch, itch and pain.

Merkel cell-neurite complex

First identified by Friedrich Sigmund Merkel in 1875, Merkel cells were described to form cluster structure in the basal layer of the epidermis and make synaptic contacts with Aβ fibers expressing neurofilament heavy polypeptide (NFH). This specialized epidermal structure, which was termed as Merkel cell-neurite complex or Merkel disk, produces long-lasting SAI discharge with an irregular firing pattern upon sustained indentation [4, 5] and conveys the tactile sensations about curvature, edge and shape of subjects [6-8]. Although the neural crest was originally thought to be the progenitor of Merkel cells [9, 10], emerging evidence strongly suggest that Merkel cells are derived from epithelial progenitor cells in the skin epidermis that express both Keratin17 (K17) and the transcriptional regulator atonal homolog 1 (*Atoh1)* [11, 12]. More interestingly, although genetic ablation of touch dome

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cells disrupted the maintenance of Merkel cells and the innervation of touch domes by NFH^+ fibers, the K17-expressing keratinocytes but not Merkel cells are required for maintaining innervation of the Merkel cell-neurite complex [13, 14].

Physiological functions of Merkel disk

Merkel disk has been implicated in touch sensation for decades [15-18]. However, the precise cellular and molecular mechanisms remain elusive due to a lack of selective genetic tools. Until recently, elegant studies using *ex vivo* skin-nerve preparations revealed truncated SAI afferent firing in Merkel cell-deficient mice while selective activation of Merkel cells using optogenetic approaches was sufficient to evoke SAI afferent firing [19]. More strikingly, epidermal-specific knockout mice lacking the mechanosensitive *Piezo2* channels displayed compromised SAI firing in the static phase in response to sustained mechanical stimuli and partial loss of touch sensation as reflected by a reduction in paw withdrawal response in von Frey test [20]. Combined, these results suggest that Merkel cells and associated Piezo2 channels are essential for gentle touch sensation in mice.

A two-receptor model was subsequently proposed to elucidate the coordination between Merkel cells and SAI afferents in touch sensation: Piezo2 channels expressed by the SAI afferent directly sense the mechanical force and initiate action potential firing in the dynamic phase while Merkel cells mediate sustained firing during static displacement [19, 21, 22]. However, how Merkel cells convey the sustained mechanical input and initiate static firing remains controversial. Molecular profiling assays showed that Merkel cells express presynaptic molecules and may regulate the activities of innervating SAI afferents through releasing excitatory neurotransmitters such as 5-hydroxytryptamine (5-HT), norepinephrine (NE), and glutamate (Glu) [15]. Patch-clamp recordings showed that only 5-HT but not other neurotransmitters (including ATP, Glu, NE, etc) elicited SAI impulses in nerve bundles attached with whisker hair follicle [23]. In marked contrast, another recent study demonstrated that NE but not 5-HT or dopamine evoked action potentials in the SAI afferents in *ex vivo* skin-nerve preparations [24]. Thus, whether Merkel cell-neurite complex is formed by serotonergic or adrenergic synapses needs further confirmation. Notably, besides 5-HT and NE, other Merkel cell-related neurotransmitters and synaptic components were barely studied.

The unique distribution pattern of Merkel disk endows Merkel cell-associated synaptic machinery multiple potentials in modulating the functions of other skin resident cells, immune cells, and sensory nerve endings. For example, substance P (SP) released by Merkel cells may directly activate keratinocytes to promote proliferation in wound healing [25]; On the other hand, Merkel cell-derived calcitonin gene-related peptide (CGRP) may inhibit immune cells recruitment and modulate immune function [26].

Merkel disk in itch

Although our sense of touch is essential to social communication and spatial awareness, under pathological conditions such as aging and dry skin lightly stroking or gently poking the skin evokes itch sensation, a phenomenon known as “alloknesis” which is a major

medical problem for those suffering from chronic itch. However, whether and how Merkel cells contribute to the genesis of alloknesis remain poorly understood. Recently, we showed for the first time that alloknesis associated with aging and dry skin is correlated with a loss of Merkel cells in the skin. Furthermore, both Merkel cells and associated Piezo2 channels are required to constitutively suppress alloknesis under normal condition as genetic ablation of either Merkel cell or Merkel cell-specific Piezo2 is sufficient to produce alloknesis [27]. Surprisingly, Merkel cell deficiency does not affect acute scratching induced by intradermal injections of the itch-inducing meditators, such as chloroquine (CQ) and histamine, suggesting that Merkel cells are dispensable for acute chemical itch. These findings potentially identify a novel therapeutic target for treating chronic itch-associated alloknesis.

It should be noted that while it is largely agreed that the total number of Merkel cells per touch dome decreases with age in mice [27-30], the lifespan of individual Merkel cells remains highly debated. Lineage tracing studies showed that Merkel cells were replaced every two months in touch domes [13]. Moreover, touch domes were reported to undergo a rapid remodeling and the number of Merkel cells per touch dome oscillated within hair cycles until adulthood [31]. On the other hand, other studies showed that embryonic-derived Merkel cells survived for at least 9 months and the average number of Merkel cells per touch dome remained steady in both natural and induced hair circles [32]. Moreover, it is also possible that changes in number of Merkel cells under normal development and pathological conditions such as skin inflammation might have distinct effects on sensory biology.

Of note, a recent study demonstrated that the innervation of Merkel cells by Aβ-fibers but not the number of Merkel cells is decreased in a mouse model imiquimod (IMQ)-induced psoriasis [33]. Similar to the loss of Merkel cells in the dry skin model, a reduction of the Aβ-fibers in the IMQ-induced psoriasis model also promoted mechanical itch, which was recapitulated by silencing the Aβ-fibers through TLR5-mediated entry of QX314, a membrane-impermeant lidocaine derivative that selectively blocks sodium channels when delivered intracellularly [34, 35]. Therefore, either a loss of Merkel cells in the setting of dry skin and aging or a reduction of Aβ-fibers in the IMQ-induced psoriasis can reduce the sustained SAI afferent firing which results in a disinhibition of mechanical itch. Combined, these studies highlight the critical role of the Merkel cell-neurite complex in modulating mechanical itch in the skin.

Interestingly, patients with prurigo nodularis often are associated with significantly increased number of Merkel cells when compared to control group with lichen simplex chronicus [36]. Moreover, along with the increased number of Merkel cells, expressions of neuropeptide (such as pancreatic polypeptide, somatostatin, chromogranin A) was upregulated in psoriatic lesion when compared with normal skin [37]. Although further mechanistic studies are needed to confirm if there is a causal relationship of increased number of Merkel cells and chronic itch, these observations imply that Merkel cells might be involved in the genesis of chronic itch in humans.

Although how Merkel cells modulate SAI afferent function remains to be studied, Merkel cells contain various substances that could excite afferent fibers through synaptic release machinery. 5-HT was the first to be reported to excite action potentials in NFH-positive

fibers and transmit tactile signals [23, 38]. 5-HT could also excite NFH-negative sensory neurons and mediate itch and pain sensation [39]. It will be interesting to test if Merkel cells are involved in itch and pain through releasing 5-HT under pathological conditions. Moreover, NE was also shown to excite Merkel cells innervating SAI fibers. As an inhibitory neurotransmitter revealed at the spinal cord level [40], NE may also affect the activity of inhibitory afferents at the skin level, which further support the role of Merkel cells in mechanical itch modulation. Although neurotransmitters such as CGRP, substance P, dynorphin A, and glutamate were detected in Merkel cell through immunohistochemistry staining, whether and how they affect Merkel cell-neuronal signaling are poorly understood.

Merkel disk in pain

Mechanical allodynia is a painful sensation evoked by innocuous tactile stimuli, which occurs especially under conditions of nerve damage and prolonged inflammation. Although the cellular and molecular mechanisms governing the conversion from touch to pain are not completely understood, two recent studies showed that loss of Piezo2 function in sensory neurons reduced mechanical pain in mice and, more importantly, Piezo2 loss-of-function mutations in humans rendered a loss of mechanical hypersensitivity in response to touch after inflammation [41, 42], suggesting neuronal Piezo2 is required for the development of mechanical allodynia in both humans and mice. Mechanistically, it was reported that Piezo2-mediated mechanical allodynia is dependent on the function of Epac1 (exchange factor directly activated by cAMP 1), a sensor for intracellular cyclic AMP [43]. Since the two-receptor model hypothesizes that both Piezo2-expressing Merkel cells and SAI afferents work together to mediate touch sensation, a potential role of Merkel cells in converting gentle touch to mechanical pain is strongly suggested. Theoretically, stimulation of Piezo2-expressing Merkel cells by skin inflammation and/or tissue injury might promote the production and release of pain-producing neuromediators including NE and 5-HT, which could subsequently activate and/sensitize the mechanosensitive primary sensory nociceptors in the skin and produce mechanical allodynia [44-46].

Conclusion and perspectives

Chronic itch and pain are debilitating conditions that substantially affect quality of life of affected individuals. Current treatments for both chronic itch and pain show limited efficiency but severe side effects. Skin-resident cells/structures emerge as major contributors to both initiation and maintenance of chronic itch and pain. Studies on the role of Piezo2 channels and Merkel disk in itch/pain signaling will not only shed fundamental insights into the mechanisms of itch/pain transduction but also open promising new avenues for effective treatments of chronic pain and itch.

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