Cell in Focus: The Merkel Cell - a review

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Abstract

Merkel cells are specialized group of cells in the skin and oral mucosa that are important for neural programming of light touch stimuli with a controversial origin. Immunohistochemical analysis of MCs has identified the expression of specific cytokeratins. This article throws light on the histological, embryological and pathological aspects of Merkel cell.

Key words: Merkel cell, Mechanoreceptor, Nerve ending

Introduction

Merkel cells (MC) or tactile cells or touch corpuscles are slowly adapting cutaneous mechanoreceptors[1] clustered around Merkel nerve endings in glabrous[2] and hairy skin[3]. They were first described by Friedrich Sigmund Merkel in 1875[2] and termed as "Tastzellen or touch cells" and as "Merkel'sche Tastzellen" and "Merkel'sche Tastko¨rperchen" to indicate their function as mechanoreceptors[4]. Later the prefix "Tast-" was omitted, and the cells were termed as Merkel cells. This term has also been used for cells of similar appearance but without contact to nerve terminals[5].

MCs are more numerous in the sun-exposed skin than in covered skin. They are found most commonly in the basal layer of the epidermis in specialized groupings called haarscheiben [or touch domes/ hair disks/tastflecke] often at the tips of rete ridges. Increased density is noted in the palmar aspect of hands, especially the finger pads, feet and plantar aspects of the toes. The lips, buccal mucosa and hard palate contain slightly less MCs.

MCs are oval shaped, measuring 10-15 μm in the long axis, with a large, pale and lobulated nucleus with few nucleoli and dense-cored granules of 80-120nm in diameter. Intermediate filaments occasionally form tonofibril-like aggregate around the nucleus and neurofilaments. The cell surface shows spine-or microvilli-like projections which interdigitate with the surrounding keratinocytes. The desmosomes of MCs are much smaller than those of keratinocytes. Cytoplasmic membrane is seen in close apposition with axonal terminal, with areas of synaptic membrane specialization[6] (Fig 1). Accumulation of large (50-110nm) dense-core vesicles are seen near the junction with the nerve fiber[1]. The complex of MC and a sensory axon terminal has been called Merkel's corpuscle[7], 'Merkel cell-neurite complex[8] or 'Merkel ending'[9]. The nerve terminal is packed with mitochondria and optically clear vesicles[8].

Since their discovery[3] conflicting evidences prevail concerning their developmental origin: (i) the neural crest and (ii) the epidermal origin[10].

The neural crest cell origin is related to the excitability of these cells with the property to synthesize neuropeptides and express presynaptic molecules and proneural transcription factors like the neural crest-derived cells[11]. In addition, Grim and Halata (2000)[12] have speculated, on the basis of results of

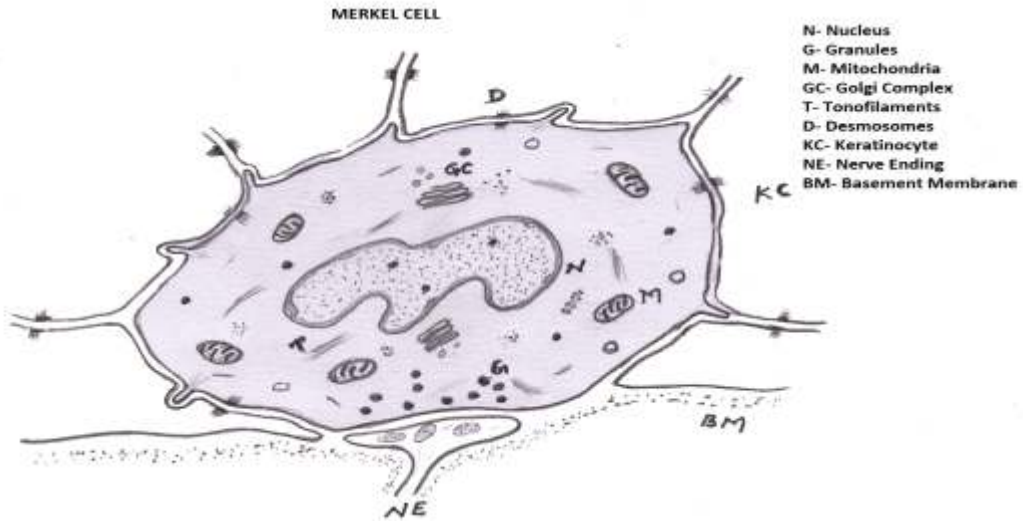

Fig 1: Schematic Representation of Merkel Cell

avian chimeric experiments, that MCs share their origin with neural elements. Strong evidence against the neural crest origin of MCs is their temporal appearance. From 8th week of IUL, Merkel cells are detectable within the epidermis in suprabasal positions. Their number and density increase dramatically in the subsequent weeks[13].

MCs are identifiable and transplantable several weeks before other neural crest derivatives such as nerve endings reach the fetal epidermis, suggesting that MCs do not originate from NCCs[14].

Contradictory to the above origin, Tweedle[15] found that MCs in the amphibian epidermis developed from embryos from which neural precursor tissues had been removed at early developmental stages. Moll et al.[16] also demonstrated that MCs developed in human epidermis xenografted on the dermis of nude mice that had been deprived of nerve elements. These findings seem to support the epidermal origin which is also supported by the fact that MCs reside in the basal layer of the epidermis and express keratins of simple epithelia like K8, K18, and K20[17]. Lineage-tracing experiments using epidermal-specific CRE[18], epidermal (Krt14C^{re}) and neural crest (Wnt1C^{re}) Cre-driver lines[19] demonstrated that MCs are derived from epidermal cells.

Identification

MCs are difficult to visualize on hematoxylin and eosin (H&E) stained sections at the light microscopic level. Merkel cells incorporate the fluorescent dye quinacrine that bind to ATP in Merkel cell granules [20].

Immunohistochemistry

MCs demonstrate both epithelial and neuroendocrine markers. The intermediate filaments stain positively for low molecular weight cytokeratins (CK) 8, 18, 19, and 20. CK20 is a highly specific marker for MCs in normal skin[21], but also demonstrate positivity for taste buds and various epithelia of the gastrointestinal tract[22].

Neuroendocrine markers such as chromogranin A, protein gene product 9.5, neuron-specific enolase, and synaptophysin, may be useful as diagnostic adjuncts[23,24,25,26]. Vasoactive intestinal polypeptide, serotonin, substance P, met-enkephalin, pancreastatin, calcitonin gene-related peptide (CGRP), somatostatin and bombesin show variable positivity[27]. Toyoshima et al. showed that an antibody against villin was an excellent marker of Merkel cells and their microvilli[28].

Functions

Many kinds of neuroactive substances were immunohistochemically detected in MC granules, the neurotransmitter in the Merkel ending has not yet been determined[10]. Furthermore, it is clear that normal and pathological oral mucosa contain many non-innervated Merkel cells with secretory processes, suggesting that MCs include heterogeneous subpopulations with different functions[29].

1) Endocrine and nervous function

The morphology of the dense-core granules is similar to the secretory granules of APUD system and hence assumed the endocrine function[30]. Merkel cells connected with nerve fibers may secrete endocrine substances via regulation of autonomic nerves. Merkel cells present in hair follicles are not nerve-associated but contain stem cells for hair growth and regeneration and exert paracrine functions during hair development. A close anatomical relationship exists between Merkel cells and Langerhans cells within the bulge area of human hair follicles [31]. With regards to this, a new concept named ''Neuroimmunocutaneous system'' was developed where numerous cel-

lular contacts between nerve fibers, cutaneous cells and immune cells allow molecular exchanges, thereby modulating the functions of epidermal and dermal cells[32]. The neuroendocrine character of Merkel cells is supported by the immunoreactivity for chromogranin A (CGA)[25] and a variety of neuropeptides[33]. Though it is difficult to distinguish between the endocrine and nervous aspects of Merkel cells it is possible that these cells may possess dual functions storing both local hormones and neurotransmitters [34].

2) Mechanoreceptive function

Merkel cells act as mechanical transducers and neurotransmitters, which generate impulses in the axon terminal via ligand-gated ion channels. Mechano receptive property of palatine merkel cells is emphasized by the release of glutamate and increased intra cellular calcium concentration during mechanical stimulation[35,36]. It is generally accepted that touch domes are slowly adapting type mechanoreceptors. However, in some species Merkel cell-neurite complexes are rapidly adapting mechanoreceptors rather than slowly adapting ones[37].

3) Chemo sensitive function

Merkel cells may have a possible chemosensitive function, in particular nociceptive function. Chemosensitive sensations are mediated by free nerve endings. But no specialized sensory cells have been identified to underlie the sensations of irritation. Substance P and CGRP released from rat and monkey Merkel cell-neurite complexes are consistent with a response to irritants and are well known to be the main active mediators for transferring nociceptive signals [38].

Merkel cell-like cells

Cells of the diffuse endocrine system resemble Merkel cells that are mainly found in the epithelium of the gut and bronchial mucosa. They are referred to as cells of the APUD system[39] or paraneurons[40] which release neurotransmitters with paracrine functions. Also, in those areas where Merkel cells are usually found, pale oval cells with dense-core granules are sometimes seen in the basal layer of the epidermis or the mucosa of ectodermal origin. In contrast to Merkel cells, these cells have oval nuclei with many nuclear pores, lack any contact with nerve terminals, have few small desmosomes with surrounding keratinocytes, or hemi-desmosomes with the basal lamina and lack cytoplasmic processes. The dense core granules are close to the Golgi apparatus in that part of the cell facing the skin surface, rather than the basal lamina. Tachibana observed "dendritic Merkel cells" lacking contact with nerve terminals in the oral mucosa of rodents and man[29]. The authors suggested that the population of Merkel cells is very heterogeneous, with a wide variety of functions, including endocrine functions[10]. Clear information on their function is still lacking, and it is still unknown whether these cells belong to the same developmental lineage as those Merkel cells in contact with nerve terminals[27].

Merkel cell pathology: Merkel cell carcinoma

Merkel cell carcinoma (MCC) is a rare, aggressive and often fatal cutaneous malignancy that has a poor prognosis[41]. Otherwise known as neuroendocrine tumor, it is most frequent among immunosuppressed, arsenic, ultraviolet A and methoxslen exposed individuals[42,43].

The primary lesion of MCC is distinguished by its absence of distinctive clinical characteristics. MCC often presents as a rapidly growing, asymptomatic, reddish-blue dermal papule or nodule that develops over the course of weeks to months[41]. The mnemonic AEIOU has been used to describe its clinical appearance and demographic characteristics: asymptomatic, expanding rapidly, immune suppression, older than [50] years, ultraviolet-exposed/fair skin[44]. However, most of these tumors are likely diagnosed through a combination of vigilance, a low threshold for biopsy, and micro-

scopic evaluation, rather than by clinical findings. It occurs most commonly in the head and neck region and extremities with a predilection for periocular region[45].

MCCs are dermally based tumors composed of small uniform round blue cells arranged in anastomosing cords, bands and clusters. Their cells commonly possess ill-defined, scanty cytoplasm, and round vesicular nuclei with "salt and pepper" chromatin and frequent mitotic figures[41]. Up to 10% of MCCs contain pagetoid intraepidermal involvement and apoptotic bodies are often seen[13]. MCCs sometimes contain areas of squamotization and can occur in combination with other epithelial tumors. Nearly 40% are associated with Bowen's disease or squamous cell carcinoma. Less frequently, MCCs are found in association with BCC or eccrine tumors.

The histopathologic differential diagnosis for MCC includes other small round blue cell tumors, such as metastatic small cell carcinoma of the lung, small cell cutaneous lymphoma, melanoma, Ewing's sarcoma, neuroblastoma, rhabdomyosarcoma, and BCC.

Treatment is done with surgical wide excision of the primary tumor, radiation therapy and chemotherapy[46]. Sentinel lymph node biopsy was advocated because of its low morbidity and provides an easy reliable way of locating occult metastasis[47].

Conclusion

Merkel cells are mechano-sensory cells that tune mammalian touch receptors. The origin and its role in growth and differentiation of skin appendages are still unclear. The functions of Merkel cells on production of tissue hormones, cytokines and growth factors and the proliferative potential of these cells may be brought to light with further studies.

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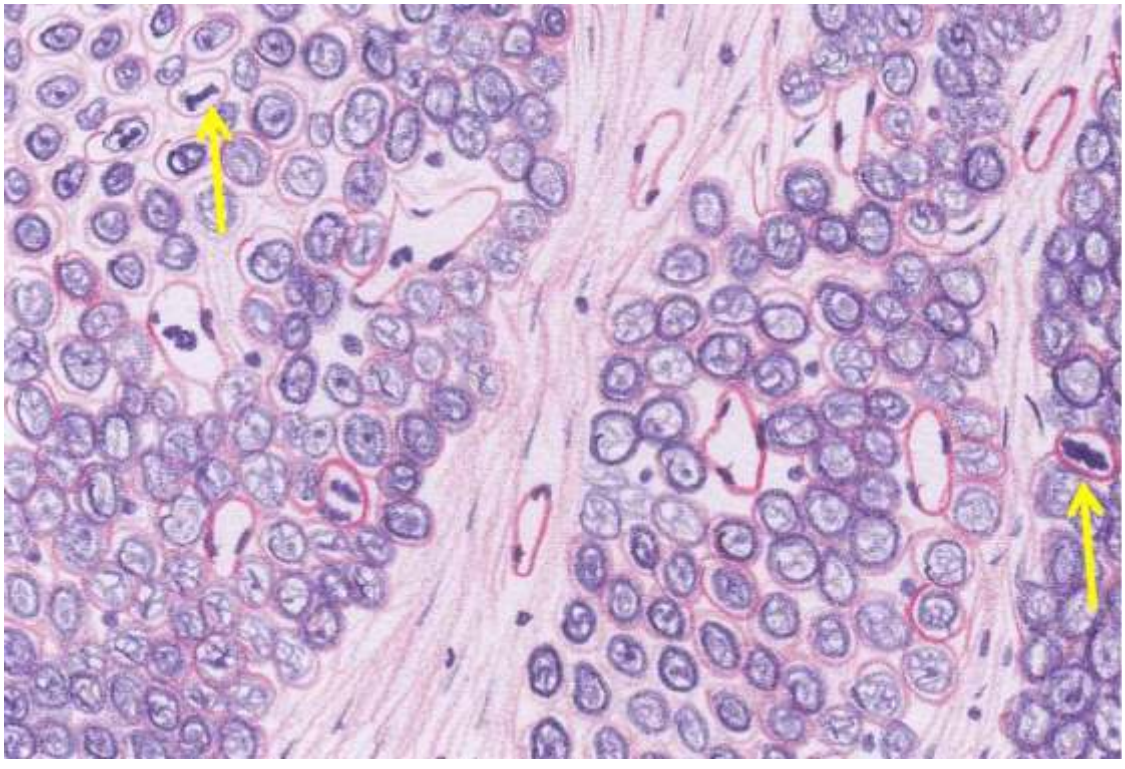

Figure 2:
Illustrated pathology: highly cellular tumor composed of small undifferentiated cells in solid sheets and fascicles. The round cells are pleomorphic with moderate cytoplasm, hyperchromatic nucleus and prominent nucleoli, mitotic figures (arrows) are evident

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