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HISTOLOGICAL STUDY

The importance of Merkel cells in the development of human fingerprints

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ABSTRACT
Human Merkel cells (MCs) were first described by Friedrich S. Merkel in 1875 and named "Tastzellen" (touch cells). Merkel cells are mainly located in the basal layer of the epidermis and are concentrated in touch-sensitive areas. Their density varies among different anatomical sites. Increased concentration was observed in the palms of hands with a predominance in the finger pads and also in the soles and toes. They can be classified according to the function as mechanoreceptive, endocrine, and chemo-sensitive cells. In the development of primary ridges which establish the future fingerprint patterns is assumed that Merkel cells have a significant importance in this process. At about the 7th week EGA, they first time appear in the volar skin and start to occupy the place of future primary ridges at 10 weeks EGA. It will be interesting to study their presence or absence in individuals suffering with abnormal dermatoglyphics and also to study whether the skin diseases associated with altered dermatoglyphics display some deviation regarding the distribution and density of MCs in primary ridges *(Fig. 2, Ref. 40).* Text in PDF *www.elis.sk*
KEY WORDS: Merkel cells, development, primary ridges, fingerprints, CK-20.

Introduction

Merkel cells (MCs) are post-mitotic, neuroendocrine cells predominantly present in the epidermis of vertebrates (6, 37). In 1875, Friedrich Sigmund Merkel, a German anatomist and histopathologist was first who described these interesting cells and referred them to as "tastzellen" or "touch cells/corpuscles" as they were found to form clusters connected with nerve endings in the glabrous skin (28). MCs are rare cells that occupy the basal layer of the epidermis and depending on anatomical locations, they cluster with differing densities and different patterns (25, 29). In glabrous skin, MCs are irregularly arranged in rete ridges (15) while clusters of MCs are observed around sweat glands (32). Finger pads, palms of hands, and soles and toes display an increased concentration of MCs as these sites represent highly sensitive areas of the glabrous skin (17). In hairy skin, MCs are observed within specific structures called "touch domes" which are surrounded by morphologically distinct group of columnar keratinocytes (40). MCs of touch domes are arranged into a crescent shape between hair follicles (20).

Structurally, characteristic features of both epidermal cells and neural crest derived cells are attributed to MCs. Resemblance between MCs and epidermal cells results from the presence of desmosomes which provide a connection with neighbouring keratinocytes and expression of specific markers, including keratin 8, 18, 19, and 20. Therefore, it was believed that MCs are derived from the skin (9, 30, 35). Conversely, formation of synapse-like connection with nerve fibre endings is typical for cells of neural origin. Moreover, the cytoplasm of MCs near the junction with a neurite contains numerous dark granules which resemble presynaptic vesicles expressing various synaptic markers and neurotransmitters (7, 27). Observations of MCs in the dermis (16) favoured hypothesis of neural origin of MCs as the dermis is a site of migration of neural crest cells before they invade the epidermis. Probably the best results pointing to the neural origin of MCs come from studies with quail-chick grafts (14) and lineage tracing experiments with transgenic mice (36), according to which avian and mammalian MCs are derived from neural crest cells. However, in 2009 two independent experiments proved the epidermal origin of MCs. They showed that after knocking-out of *Atoh1* in the neural crest, this had no effect on the development of MCs while its conditional deletion from the epidermis ceases production of MCs in touch domes (31, 39). Thus, basal stem cells of the epidermis give rise not only to differentiated keratinocytes but to MCs too (39).

According to Lucarz and Brand (26), MCs include groups of cells with different functions. The mechanoreceptive function of intraepithelial MCs is provided by microvilli which help to detect tissue deformations (13, 26). The endocrine function is supported by the presence of granules displaying similarities to dense-core granules of members of the amine precursor uptake and decarboxylation system (APUD) which are filled with various hormones and polypeptides (26). Moreover, MCs are thought to play an important role in the development of hair follicles and

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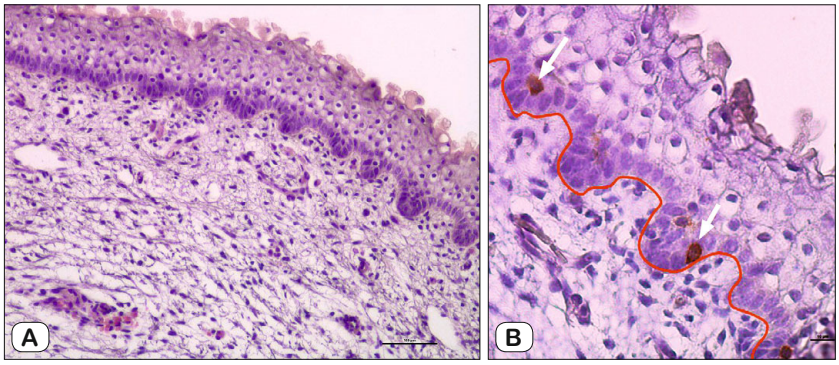

Fig. 1. Sagittal section through the pad region of the foot toe of a human foetus in 8th week (A) haematoxylin and eosine, (B) Immunoperoxidase staining (using a monoclonal antibody selective for cytokeratin 20 (clone K_s20.8.) Dako. (A) In some parts the basal layer of epidermis is straight or undulated and cells are columnar, (B) CK-20 positive Merkel cells are localized between the cells of the stratum basale of the epithelium (orange arrows). The first hint of undulation of the basal layer is visible, CK-20 positive Merkel cells (orange arrows) also organizing in lines, where the primary ridges arise. Red line- undulation of basal layer of the epithelium. Original magnification a) x 100, b) x 400 (collection of human tissue from the Department of Histology and Embryology, Medical Faculty, Comenius University in Bratislava, unpublished data)

eccrine sweat glands (21). The chemosensitive function is associated with a production of active mediators involved in transfer of nociceptive signals (38). It is also believed that MCs are involved in immunity and inflammatory processes (40).

Because it was impossible to observe MCs with light microscope, an accurate identification of MCs was achieved upon implementation of antibodies against cytokeratin type 20 (CK-20) in immunohistochemistry due to their high degree of specificity for MCs (30).

Merkel cells in the development of fingerprints.

Fingerprints (dermatoglyphs) are impressions left by the friction ridges of a human finger of the hands and feet. Fingerprinting is a form of biometrics which uses physical and biological characteristics for human identification. No two people have the same fingerprints, not even identical twins. The development of primary ridges is the basis for appearing of human fingerprints (8). The formation of future fingerprints starts at about 10th week of pregnancy (2, 34). At that time two different parts form the embryonic skin: the epidermis and the underlying amorphous fibrous dermis. The epidermis consists of three different layers: the basal layer of keratinocytes at the interstice between the dermis and the epidermis, the intermediate layer, and the embryonic epidermal surface layer – the periderm (18). The primary ridge formation is initiated by rapid proliferation of basal epidermal cells which appear as epidermal folds protruding into the dermis. The formation of primary ridges continues until about 16 weeks of Estimated Gestational Age (EGA), at which time secondary ridges start to appear. Primary ridges are therefore responsible for the overall pattern of definitive fingerprints which will be permanently present on the epidermal surface from the 16th week of EGA (2).

Although it is known that primary ridges develop from proliferation sites of the basal layer cells, it is not quite understood what causes the arrangement of cell proliferations in a specific manner leading to the formation of ridges. The folding hypothesis proposed in 1883 by Kollmann and improved by Bonnevie (5) suggests that rapid proliferation of the basal layer cells causes the cells to become compressed and project downwards into the dermis. Later on, the folding hypothesis was rejected and it was suggested instead that primary ridges arise by fusion of rapidly proliferating centres of epidermal cells that increase in diameter and grow into one another (1). Nevertheless, there is no mechanism known, based on cell proliferation, leading to fingerprint patterns formation. The nerve theory suggests that developing nerves can trigger the proliferation of epidermal cells as the nerve endings appear at the sites of ridge formation prior to appearance of friction ridges (5, 11). It was even proposed that the distribution of the capillary-nerve pairs at the epidermal-dermal junction has an impact on the primary ridge alignment (3, 11). However, it is questionable how nerves and capillaries themselves can establish the alignment pattern of the developing primary ridges.

According to the latest findings, MCs are believed to be involved in creation of fingerprints. At about the 7th week of EGA, they first time appear in the volar skin and start to divide (Fig. 1). Prior to formation of primary ridges, around the 10th week of pregnancy, MCs start to occupy the same place where the primary ridges will appear (19, 21). At the same time regression of the volar pads and excessive growth of cells in the basal layer generate mechanical compressive stress in the basal layer (2, 24). Once the compressive stress is exceeded, buckling occurs and epidermal folds grow into the dermis. MCs rearrange along the lines of smallest compressive stress in ridges running in parallel. Considering the mechano-sensing function of MCs, they are believed to induce the formation of primary ridges once the pattern of MCs has been settled (23). Figure 2 summarizes the stages of the development of primary and secondary ridges with the Merkel cells involved in this process.

Discussion

Development of the papillary ridges is important to establish the future pattern of human fingerprints. There exist different theories that attempt to explain the formation of fingerprints (1, 3, 5, 11, 22, 24). A model based on buckling process, by which most common fingerprint types can be reproduced, was proposed and patterns observed in this simulated process resemble real fingerprint patterns (24). Nonetheless, there are still missing information about the factors (very first stimuli) which trigger the

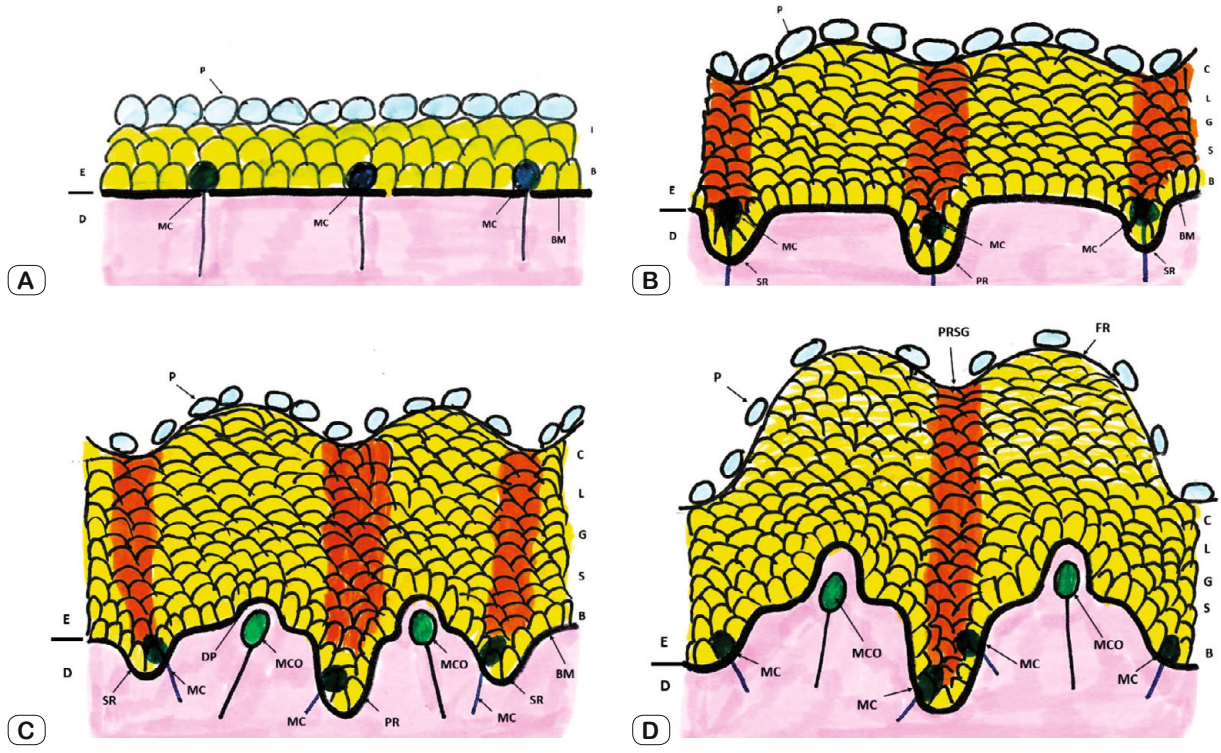

Fig. 2. Schematic picture representing the cross section of epidermis around the 8.–13. week (A) and 13.–16. week (B), (C) of the primary ridge (PR) and secondary ridge (SR) development. (D) represents fully developed and differentiated epidermis with the creation of primary ridge surface groove (PRSG). The PR growing is the cause of the epidermal layer deformation results in groove on the friction ridge apex. This PRSG are not visible until the periderm layer has reduced and detached. MCs are embedded within the basal layer and during the ridge formation are localized along the primary ridges and stimulate the stratum basale to grow conical shaped buds. Within the dermal papillae are Meissner corpuscles nerves responsible for detecting two-point discrimination, ability to discern that two nearby objects touching the skin are truly two distinct points, not one. P – periderm, E – epidermis, D – dermis, BM – basal membrane, B – basal layer, I – intermediate layer, PR – primary ridge, SR – secondary ridge, MC – Merkel cell, B – basal layer, S-spinous layer, granular layer, lucid layer, cornified layer, DP – dermal papillae, MCO – Meissner corpuscle, PRSG – primary ridge surface groove, FR – friction ridge (modified according to Bush, 2011).

primary ridges to configure in a specific manner which is unique for every individual.

Recently, a great interest was attributed to MCs and it seems that these cells could represent a missing link between the stress generated within the epidermis followed by developing patterns along the stress lines (23). Due to the fact that MCs appear in the volar skin at 7 of weeks EGA and start to occupy the place of future primary ridges at 10 weeks of EGA (19, 21), it will be interesting to study their presence or absence in individuals suffering from abnormal dermatoglyphics. Adermatoglyphia, a rare condition characterised by the absence of epidermal ridges, results from congenital or acquired causes (33). Congenitally abnormal dermatoglyphics can be categorised into 5 groups and are manifested by complete absence of ridges, inconspicuous ridges, dissociated ridges, vertically oriented ridges, or combination of ridge dissociation and vertical orientation of ridges (10, 12). The congenital form rarely manifests as an isolated disease but is usually part of a complex syndrome (33). Moreover, some genetic disorders such as Down syndrome, Turner syndrome, Klinefelter syndrome, Edwards' syndrome, Patau syndrome together with conditions affecting the overall morphology of the fingers (e.g. polydactyly, syndactyly, brachydactyly, and ectrodactyly) are also associated with abnormal fingerprints configurations (12, 33). Acquired adermatoglyphia can be further classified into dermatological and non-dermatological. Dermatological causes include various types of dermatitis, eczema, and other types of skin diseases while non-dermatological causes are related to accidents, drugs, or are associated with some medical disorders (12, 33). Although the primary cause of different types of adermatoglyphia is known, the relation of MCs to various skin diseases is basically missing. Therefore, it will be of great interest to study whether the skin diseases associated with altered dermatoglyphics display some deviation regarding the distribution and density of MCs in primary ridges.

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