Formation of Epidermal and Dermal Merkel Cells During Human Fetal Skin Development

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The origin of Merkel cells is still a matter of debate, specifically the question of whether they are derived from epithelial cells of the epidermis or from immigrated neural crest cells. As an argument for the latter hypothesis the occurrence of dermal, nerve-associated Merkel cells in human fetal skin has often been mentioned. Therefore, we analyzed the distribution of Merkel cells in the epidermis and dermis of plantar skin of human embryos and fetuses, ranging in gestational age between 7 and 17 weeks. Merkel cells were identified by immunocytochemistry on frozen sections using antibodies against simple epithelium-type cytokeratins and by electron microscopy. In the 17-week-old fetus, 17% of the total cutaneous (epidermal and dermal) Merkel cells were located in the upper dermal compartment, whereas in the 14-week-old fetus only 3.9% of the Merkel cells were dermal, including some cells that seemed to be in the process of traversing the dermal-epidermal junction. Thirteen-week-old fetuses showed even fewer dermal Merkel cells. Twelve-week-old fetuses exhibited 660 epidermal Merkel cells per 100 mm total section length, but none in the upper or deep dermis. In 7- to 9-week embryos, no Merkel cells were recognized. However, at this stage, but not in later stages, the basal cells of the plantar epidermis expressed certain simple epithelium-type cytokeratin polypeptides. These results speak against an invasion of Merkel cells or putative neural crest-derived precursor cells into the epidermis via a dermal passage. They suggest that in plantar skin Merkel cells arise, between weeks 8–12, from precursor stages of epithelial cells of the early fetal epidermis which still express simple epithelium-type cytokeratins. The results further suggest that in subsequent stages of skin development some epidermal Merkel cells detach from the epithelium and migrate into the upper dermis where some of them may associate with small nerves. J Invest Dermatol 87:779–787, 1986

The origin of Merkel cells, the neuroendocrine cells of the epidermis, and the hair follicles during fetal skin development, is still a matter of debate. The 2 major hypotheses discussed are, on the one hand, the origin from epithelial cells of the epidermis and, on the other hand, an immigration of cells derived from the neural crest (for reviews see [1,2]). The finding, in certain species, of forms that appear to be "intermediate" in morphology between keratinocytes and Merkel cells [3–6], the detection of cytokeratins, i.e., the epithelial type of intermediate-sized filament (IF) proteins [7–12], and various other experimental findings (e.g. [13,14]) seem to support the notion that Merkel cells derive from epithelial cells present in the fetal epidermis.

However, the cytokeratin filaments of Merkel cells are composed of polypeptides different from those constituting the tonofilaments of keratinocytes [7] and thus their composition cannot be considered evidence for a histogenic relationship between these two cell types. The theory of the derivation of Merkel cells from the neural crest and their immigration along peripheral nerves into the epidermis and the outer root sheath of the hair follicle has been mainly supported by reports of the occurrence, in early fetal dermis, of Merkel cells that seemed to be free and were assumed to be "on their way" from the neural crest to the epidermis [1,15–19]. By immunohistochemistry using antibodies specific for cytokeratins of Merkel cells, we have recently demonstrated abundant Merkel cells in the upper dermis of fetal plantar skin [7] that were closely associated with nerve fibers, as well as some Merkel cells that apparently were in the process of penetrating the dermal-epidermal boundary. In fetal week 17, the earliest stage of that study, approximately 83% of the Merkel cells were located within the epidermis whereas 17% appeared to be located in the dermis. While these findings would be compatible with the "immigration hypothesis," they do not exclude a migration of epidermally derived Merkel cells in the opposite direction, i.e., from the epidermis into the dermis.

The present study has been undertaken to obtain further insight into Merkel cell formation by analyzing the Merkel cell distribution in epidermis and dermis of earlier development stages.

MATERIALS AND METHODS

Tissues Fourteen normal human embryos and fetuses were obtained during iatrogenic abortions performed for medical and

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Abbreviations:
FITC: fluorescein isothiocyanate
IF: intermediate-sized filaments
NF-L: small neurofilament polypeptide
NF-M: medium-sized neurofilament polypeptide
TRITC: tetramethylrhodamine isothiocyanate
nonmedical reasons. The gestational age, as estimated by the size of the uterus, as well as the crown–rump length, the heel–toe length standards [20], and the menstrual age, ranged between week 7–17 of gestation (7 weeks, 1 case; 8 weeks, 2 cases; 9 weeks, 1 case; 12 weeks, 1 case; 13 weeks, 5 cases; 14 weeks, 1 case; 15 weeks, 2 cases; 17 weeks, 1 case). Tissue samples from foot soles were excised immediately after removal and frozen in isopentane that had been precooled in liquid nitrogen; in some cases, samples were also fixed in glutaraldehyde for electron microscopy.

**Immunofluorescence Microscopy** Indirect immunofluorescence microscopy was carried out on approximately 5 μm-thick cryostat sections cut vertical to the epidermal surface and fixed in acetone – 20°C [21]; 8 μm- or 10 μm-thick cryostat sections were used for counting of Merkel cells. The following primary antibodies were used: (1) monoclonal antibody CK 2 specific for the simple epithelium-type cytokeratin no. 18 [22] of the human cytokeratin catalog [23] which in the epidermis selectively labels Merkel cells [7]; (2) monoclonal murine antibody RGE 53 also specific for cytokeratin no. 18 [24]; (3) a guinea pig antisera reacting with cytokeratin no. 18 and “IT-protein” [25] but not with other keratin polypeptides (R. Moll, S. Winter, and W. W. Franke, unpublished data); (4) monoclonal murine antibody Kfk 8.60 which is specific for cytokeratin polypeptides nos. 10/11 occurring in terminally differentiating keratinocytes [26]; (5) murine monoclonal antibody KA 1 specific for cytokeratin filaments of stratified squamous epithelial and myoepithelial cells [27]; (6) murine monoclonal antibody PKK 1 reacting with several cytokeratin polypeptides including nos. 8, 18, and 19 [28]; (7) murine monoclonal antibody K, 8.1 specific for the simple epithelium-type cytokeratin no. 8 (R. Hazan and W. W. Franke, unpublished data); (8) monoclonal murine antibody A 53/B/A 2 specific for cytokeratin no. 19 which occurs in various simple and some stratified epithelia [29]; (9) rabbit antibodies against the small neurofilament polypeptide NF-L [30]; (10) rabbit antibodies against the medium-sized neurofilament polypeptide NF-M [31]; and (11) monoclonal murine antibodies NR-4 [32] and 2F11 [33] specific for the small neurofilament polypeptide NF-L.

As secondary antibodies, fluorescein isothiocyanate (FITC)-coupled, tetramethylrhodamine isothiocyanate (TRITC)-coupled, or Texas Red-coupled goat antibodies to total immunoglobulins of mouse, guinea pig, or rabbit were used (obtained from Medac or Dianova, Hamburg, F.R.G.). Double label immunofluorescence microscopy was performed by simultaneously applying both primary antibodies and subsequently, after washing, FITC-coupled secondary antibodies against immunoglobulins of the species of the first antibodies, together with TRITC-coupled or Texas Red-coupled secondary antibodies directed against immunoglobulins of the other species.

**Electron Microscopy** For electron microscopy of ultrathin sections, small samples of planar skin were fixed in buffered glutaraldehyde, dehydrated, embedded in epoxy resin, and sectioned as previously described [7, 34]. Three fetuses of weeks 7–8, 13, and 15 were studied. From each fetus 3 different samples taken at random were fixed, embedded, and sectioned at intervals >10 μm, totaling an average epidermal length of ~500 μm per block, i.e., 1.5 mm cumulative epidermal length per fetal stage.

**Morphometric Analyses** Numerical analyses of Merkel cells were performed on immunofluorescence microscopy slides made from serial 8–10 μm-thick frozen sections vertical to the surface, which were incubated with antibodies against cytokeratin no. 18 (see also [7]). For the specimens of the 17-week-old fetus in which glandular ridges were already developed, the sections were approximately vertical to these ridges. Every third section of a section series was used for counting of Merkel cells. Cells positive for cytokeratin no. 18 were registered when the nucleus-containing cell body was identified in the section, whereas sections through the cell processes or partial cross sections with areas smaller than half of the nuclear diameter were disregarded. Epidermal and dermal Merkel cells were counted separately. The epidermis and the dermis were identified in the sections using phase contrast microscopy. The length of the epidermis taken for the counting of Merkel cells was measured at the microscope using a graded ocular eyepiece.

**RESULTS**

In epidermis of plantar skin of 13- to 15-week-old fetuses only some inconspicuous thickenings of the epidermal basal cell layer were recognized by phase contrast microscopy that might correspond to developing glandular ridges (Fig 1). In immunofluorescence microscopy, antibodies to cytokeratin no. 18 stained individual cells that were scattered throughout the basal cell layers (Fig 1a–d). Often they were located at a position just above the basalmost cell layer, but in other places they reached the dermal-epidermal junction (Fig 1a–d). Such cytokeratin no. 18-positive cells had previously been identified as neuroendocrine, i.e., Merkel cells [7] (see also Fig. 3 of the present article). The Merkel cells were characterized by roundish or ellipsoid cell bodies and often exhibited slender, sometimes branched cell processes that were also decorated by antibodies to cytokeratin no. 18 and sometimes made contact with neighboring Merkel cells or the dermal-epidermal junction (Fig 1a,b; see also Fig 2j). In cross sections these cell processes appeared as small dots (e.g., Fig 1g).

In fetuses of this stage, some Merkel cells of the basal layer, which usually were devoid of processes, seemed to protrude somewhat toward the dermis (Fig 1e–h). Moreover, some Merkel cells were noted the cell bodies of which seemed to be located partly in the epidermis and partly in the dermis (Fig 1i,j). Finally, some Merkel cells appeared to be located free in the upper dermis (Fig 1k) and often seemed to be associated with dermal nerve fibers, as revealed by double immunofluorescence microscopy using neurofilament antibodies (Fig 1f). In a 14-week-old fetus, 129 mm of skin section length were quantitatively evaluated. Among 930 Merkel cells counted, 3.7% were located within the dermis (Table I). The 13-week-old fetuses also exhibited some dermal Merkel cells, but considerably fewer than were found in the 14- and 15-week-old fetuses. In later stages, i.e., 17- to 24-week-old fetuses, which have been described in detail in a preceding study [7], the glandular ridges were more clearly developed. the Merkel cells were concentrated in the ridges, and dermal Merkel cells were clearly more abundant (Table I) [7].

In foot-sole skin of a 12-week-old fetus, Merkel cells stained with antibodies against cytokeratin no. 18 were relatively frequent in— or just above—the basal layer of the epidermis which was straight and did not show any ridges (Fig 2a–e). In survey pictures, a certain spatial pattern suggestive of a segmental distribution of the Merkel cells was apparent (Fig 2a). All 860 Merkel cells counted were epidermal, and neither dermal Merkel cells nor Merkel cells crossing the dermal-epidermal junction were observed (Table I).

When antibodies against the neurofilament polypeptides NF-L and NF-M were applied in single or double label immunofluorescence microscopy, together with antibodies against cytokeratin no. 18, the Merkel cells from all fetal stages examined were found to be negative for neurofilaments (Fig 2x,d). In contrast, dermal nerve fibers were positive and some of them were in contact with the dermal-epidermal junction (Fig 2x,d). The monoclonal antibody Kfk 8.60 against cytokeratins nos. 10/11 stained the suprabasal epidermal keratinoctyes (Fig 2f) whereas the Merkel cells, as identified by staining of antibodies against cytokeratin no. 18, were negative, as were the basal keratinoctyes (Fig 2x,f). Monoclonal antibody KA1 stained the whole epidermis, including the basal layer, except for the Merkel cells (Fig 2g,h). In contrast, the Merkel cells were selectively decorated by monoclonal antibodies K, 8.1 and A53-B/A 2 against the simple epithelium-type cytokeratins nos. 8 and 19, respectively (Fig 2i,f).

Electron microscopy confirmed the identification of Merkel cells in the basal compartment of the fetal epidermis (Fig 3). As best recognized by immunofluorescence microscopy, cell bodies...
Figure 1. Immunofluorescence microscopy of plantar skin of 14-week-old human fetus. 

(a) Monoclonal antibody RGE 53 against cytokeratin no. 18 stains several Merkel cells situated in or above the basal cell layer. 

(b) Guinea pig antibodies against cytokeratin no. 18 showing decoration of Merkel cells in suprabasal position extending thin processes. Only one Merkel cell (arrow) has contact to the basal lamina. 

(c and d) Phase contrast pictures corresponding to (a) and (b), respectively. 

(e through h) Antibodies against cytokeratin no. 18 (e, RGE 53; g, guinea pig antibodies) showing Merkel cells in basal position protruding toward the dermis (arrows; f and h are phase contrast pictures corresponding to e and g, respectively). 

(i and j) Guinea pig antibodies against cytokeratin no. 18, showing a Merkel cell positioned half in the epidermis and half in the dermis (arrow; j is the phase contrast picture to i). 

(k and l) Double immunofluorescence microscopy showing, in the upper dermis, a solitary Merkel cell positive for antibody RGE 53 against cytokeratin no. 18 (k) but negative for the rabbit antibodies against neurofilament protein NF-L (l); the neurofilament antibodies stain, however, nerve fibers closely associated with the dermal Merkel cell. 

Small bars denote the dermal-epidermal junction. D = dermis. Bars represent 50 μm.
Table I. Quantitative Aspects of Merkel Cells in Human Fetal Plantar Skin

<table>
<thead>
<tr>
<th>Fetal Age (weeks)</th>
<th>Length of Epidermis Analyzed in Sections (mm)</th>
<th>Numbers of Epidermal Merkel Cells*</th>
<th>Numbers of Dermal Merkel Cells*</th>
<th>Numbers of Merkel Cells per Millimeter Epidermis in Section</th>
<th>Percentage of Dermal Merkel Cells</th>
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<td>17</td>
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<td>140</td>
<td>29</td>
<td>6.8</td>
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*As detected by immunofluorescence microscopy using antibodies against cytokeratin no. 18.

Figure 2. Immunofluorescence microscopy of plantar skin of 12-week-old human fetus. a, Survey micrograph showing positive staining with antibody CK 2 against cytokeratin no. 18 of Merkel cells exclusively within the epidermis. b, Phase contrast picture corresponding to (a). c and d, Double immunofluorescence microscopy using antibody CK 2 against cytokeratin no. 18, which stains epidermal Merkel cells (c), counterstained with rabbit antibodies against the neurofilament polypeptide NF-M, which stains dermal nerve fibers (d). e and f, Double immunofluorescence microscopy, demonstrating that Merkel cells identified by guinea pig antibodies against cytokeratin no. 18 (e) are negative with antibody K8 8.60, which stains suprabasal keratinocytes (f). g and h, Double immunofluorescence microscopy, showing that Merkel cells positive for guinea pig antibodies against cytokeratin no. 18 (g) are not decorated by antibody KA1, which stains all keratinocytes (h). i, A Merkel cell selectively stained by antibody K, 8.1 against cytokeratin no. 8. j, A Merkel cell selectively positive for antibody A53-B/A2 specific for cytokeratin no. 19. Small bars denote the dermoeipidermal junction. Bars represent 50 μm.
Figure 3. Electron microscopy of plantar epidermis of 13-week-old human fetus. a, Survey electron micrograph showing a small section of a Merkel cell (arrows) containing dense-cored granules, situated above the layer of the tonofibril (TF)-containing basal keratinocytes. Small arrows denote the basal lamina. b, Small cytoplasmic process of a Merkel cell containing numerous dense-cored neurosecretory granules (arrowheads) situated in a widened space between 2 keratinocytes which appears to be lined by a mucus-like substance. D = desmosome connecting the process with the adjacent keratinocyte. TF = tonofibril. Small arrows denote the basal lamina. c, Detail of a Merkel cell containing neurosecretory granules (arrowheads) of variable size (65–150 nm diameter). A small desmosome (D) connects this cell with the adjacent basal keratinocyte. TF = tonofibrils. d, Merkel cell with neurosecretory granules (arrowheads) and intermediate filaments (IF) arranged in loose and random pattern. Bars represent 0.5 μm.

containing the nucleus (not shown) as well as cytoplasmic processes of Merkel cells (Fig 3a, b) were often seen at positions immediately above the basal keratinocyte layer (Fig 3a). Higher magnification revealed numerous dense-cored neurosecretory granules in the cytoplasm of Merkel cell bodies and processes (Fig 3b–d). Small, although typical desmosomes connected the Merkel cells with the adjacent keratinocytes which were also identified by their densely packed bundles of tonofilaments (Fig 3b, c). In contrast to the keratinocytes, the Merkel cells did not show densely fasciated tonofilament bundles but their IF appeared in rather loose and often random arrangements (Fig 3d). We did not observe cells containing both tonofilaments and neurosecretory granules, i.e., cells that would correspond to “transitional cells” [6,14].

In plantar skin of 7- to 9-week-old fetuses, the epidermis was relatively straight and consisted of 2–3 cell layers. The upper cell layer contained some partly rounded, proplugging cells typical of the periderm (Fig 4a–d). In immunofluorescence microscopy, both the basal epidermal cell layer and the periderm layer were stained by the cytokeratin antibody PKK 1 (Fig 4a). In contrast, the antibodies against cytokeratin no. 18 used in this study, i.e., CK2 and RGE 53, selectively stained the upper periderm layer, while the basal layer was negative (Fig 4b). As another cytokeratin no. 18 recognizing monoclonal antibody (K5 18.18) did react with
When deeper regions of the fetal plantar skin of the various stages were examined by immunofluorescence microscopy with antibodies against cytokeratin no. 18, positive cells could not be detected in any of the specimens, while thick bundles of neurofilament-positive nerve fibers were present in this tissue (not shown).

**DISCUSSION**

We have previously shown that, in plantar skin of human fetuses and adults, Merkel cells are relatively frequent and are immunocytochemically recognized—and distinguished from keratinocytes—by antibodies specific for cytokeratin no. 18 [7]. Similar immunocytochemical results have been reported for Merkel cells in various other locations and in other species [8,9,11,12]. This is confirmed by our present immunocytochemical demonstration that in early fetal epidermis individual cells that are selectively positive for cytokeratin no. 18 correspond to typical Merkel cells as recognized by electron microscopy. Characteristic morphologic features of these cells include their near-basal location, slender cytoplasmic processes, and dense-core neuroendocrine vesicles.

Electron microscopic findings of single Merkel cells situated in the dermis of human fetal skin, together with observations of Merkel cells that seem to pass the dermal-epidermal junction, are commonly taken as evidence in support of the hypothesis that Merkel cells originate from neural crest-derived cells which invade the epidermis [1,15-19]. Using immunocytochemistry with antibodies against cytokeratin no. 18 as a specific probe for the detection of Merkel cells in epidermis [7-9,11], we also found variable proportions of Merkel cells in the upper dermis of plantar skin of human fetuses of 17 weeks and older as well as individual Merkel cells at the level of the basal lamina which showed extensions into both the dermal and the epidermal compartment. These findings suggest that during fetal development Merkel cells migrate from one compartment to the other but they do not allow a decision on the direction of this migration. Therefore, we have studied plantar skin of earlier fetal stages.

Our results show that dermal Merkel cells and Merkel cells in transit between the dermal and epidermal compartments exist rarely, if at all, in early stages of skin development, i.e., up to week 12. From week 13 on, a detectable proportion of the Merkel cells was located in the upper dermis, and this proportion appeared to increase, at least until week 17. If these dermal Merkel cells would be on their way from the neural crest to the epidermis, one would expect more dermal and fewer epidermal Merkel cells to occur in earlier fetal stages and an absence of epidermal Merkel cells in the earliest stages in which neuroendocrine cells of the skin are detected. However, our data show that the opposite is true and strongly suggest that the dermal Merkel cells originate in the epidermal compartment and migrate into the dermis. The frequency of mitotic divisions of epidermal and dermal Merkel cells during the developmental period studied is not known. However, the occurrence and frequency of such divisions in either compartment would not bear on the histogenetic pathway proposed.

Our findings are also in agreement with several electron microscopic observations that Merkel cells are not seen in the dermis prior to week 12 [1,15,18,35] and with cytoskeletal protein characterizations of Merkel cells. Their epithelial nature is demonstrated by the presence of desmosomes and desmosomal proteins as well as cytokeratin filaments [7-9,11,12]. On the other hand, cytoskeletal neural markers such as neurofilaments and glial filaments are absent [this study, 7-9,12,36,37] (for the occurrence of neurofilaments in some forms of the putatively Merkel cell-derived neuroendocrine tumors of the skin see [10,38,39]).

Further support for the epidermal derivation of Merkel cells is the observation of so-called transitional cells in fetal, newborn, and adult mammals of various species. These cells show features of both keratinocytes and Merkel cells and, therefore, are thought to be developing Merkel cells [40]. However, there are arguments

**Figure 4.** Immunofluorescence microscopy of plantar epidermis of 8-week-old human fetus. A, Antibody PKK1 staining the whole epidermis. B, Antibody CK2 against cytokeratin no. 18 staining the upper (periderm) layer, while the basal layer is negative and Merkel cells are not detected therein. C and D, Antibody K, 8.1 against cytokeratin no. 8 (c) and antibody A53-B/A2 against cytokeratin no. 19 (d), both staining both the periderm and the basal cell layer. E, Antibody KA1 specific for stratified squamous epithelial and myoepithelial cells also decorates both the periderm and the basal cell layer. F, Antibody Kk 8.60 against cytokeratins nos. 10/11, selectively staining foci of developing flat intermediate cells. D = dermis. The brackets denote the thickness of the epidermis. Bars represent 50 μm.
against this interpretation such as reports of transitional cells in adult but not in embryonic epidermis of birds [41]. Perhaps the most conclusive argument supporting the epidermal histogenesis of neuroendocrine cells of the skin is provided by results from experimental studies in animals. In amphibians, for example, the development of epidermal neuroendocrine cells, i.e., cells equivalent to Merkel cells, takes place even after removal of the neural crest in earlier stages of embryogenesis [13]. Moreover, in regenerating stratified squamous epithelium of the labial mucosa of adult rabbits, Merkel cells can appear as transitional cells located within the epithelium, although undifferentiated neuroectodermal tissue is not present in the adult animals [14]. Although the cytoarchitecture content clearly identifies the Merkel cells as epithelial, their complement of cytokeratin polypeptides expressed (for details see [7]) does not indicate a derivation from differentiated keratinocytes which have a very different cytokeratin polypeptide composition [cf. 7,42–45]. Therefore, a direct histogenetic relationship between basal keratinocytes and Merkel cells would have to involve a complete switch in cytokeratin polypeptide expression from stratified to simple epithelium-type components, which we consider unlikely. Our examinations of earlier fetal stages offer an alternative explanation [7; see also 11,42]. Cells of the basal epidermal layer of 7- to 9-week embryos in which Merkel cells are not yet detectable, express the simple epithelium-type cytokeratins nos. 8 and 19 [42,46] and probably also minor amounts of cytokeratin no. 18. Most likely these basal cells also express some stratified epithelium-type cytokeratins because polypeptides nos. 5 and 6 have been found in early fetal skin of other body sites from the 2-layer stage on [42] and basal cells of embryonic and fetal plantar epidermis are positive with the cytokeratin antibody KAI which recognizes cytokeratins of this group [27]. Therefore, the apparent simultaneous expression of stratified and simple epithelium-type cytokeratins in the epidermal basal cell layer of 7- to 9-week-old fetuses suggests that these basal cells include multipotent epithelial stem cells that might alternatively give rise to true keratinocytes, expressing stratified epithelium-type cytokeratins, and to Merkel cells, expressing only simple epithelium-type cytokeratins. A complex cytokeratin polypeptide pattern similar to that probably present in the very early basal cells has also been found in an embryologically and topologically related epithelium, the amnion epitheliun [47].

This hypothesis of Merkel cell origin would imply that basal cells of 7- to 9-week-old fetuses may begin to produce neuroectodermal granules and also lose their tonofilaments consisting of stratified epithelium-type cytokeratins. It is not yet clear whether the expression of neuroendocrine features occurs synchronously with the cytoskeletal change to the simple epithelial cytokeratin pattern, or whether the cytoskeletal changes precede the onset of expression of neuroendocrine features. Conversely, the possible existence of precursor cells that might simultaneously express some stratified-type cytokeratins as well as the simple epithelial ones, together with neuroendocrine elements, i.e., cells that would correspond to the transitional cells described in other species [6,14,40,41,48–50], will have to be examined in future immunocytochemical experiments.

Our conclusion that Merkel cells develop from certain epithelial cells within the fetal epidermis, and not from cells immigrated from the neural crest, puts the neuroendocrine cells of the epidermis into one line with other epithelial neuroendocrine cells such as the enterochromaffin and other APUD cells of the gastrointestinal tract as well as the pancreatic islet cells for which a neural crest derivation has been excluded (for review see [51]). Thus, at present the only bona fide epithelial cell type, expressing cytokeratins, that has been proved to originate from the neuroectoderm is the calcitonin-producing ("C") cell of the thyroid gland [52; for literature see 51].

The biologic functions of epidermal and dermal Merkel cells in fetal development of mammals, as well as in postnatal life are not clear. A popular concept is that these cells represent me-chanoceptors, and this is primarily based on morphologic similarities of mammalian Merkel cells with cells present in dermal sensory corpuses of some lower vertebrates (for review see [2]). The frequent and close association of dermal Merkel cells with dermal nerves may also suggest an analogy to the dermal sensory corpuses found in a number of non-mammalian vertebrates such as the Grandy corpuses of the upper dermis of the avian hard palate, which apparently function as sensory organs in the adult animals [48,49]. The interpretation of the dermal Merkel cell–nerve complexes as rudimentary Grandy corpuses in the sense of phylogenetic relicts would explain their transient existence in fetal life. However, Saxd [41] has suggested that the avian dermal Merkel cells might differ in histogenesis from the epidermal Merkel cells of other species. Unfortunately, the cell type relationship of mammalian Merkel cells to the dermal Merkel cells of birds has not yet been demonstrated with adequate cell biologic criteria, including epithelial markers. An alternative hypothesis of Merkel cell function is that these cells, as well as the neuroendocrine epithelial cells of other epidermis (for references see [10]), produce and secrete [53] tissue hormones which induce and/or promote the local formation, growth, and differentiation of special skin structures such as, depending on the specific body site, hair follicles, eccrine sweat glands, and nerves. The products of Merkel and other neuroendocrine epithelial cells could then serve a similar function in local cell proliferation and morphogenesis as, for example, the neuropeptides described as "head activators" in lower metazoans such as in Hydra [54]. The concepts of a paracrine function of Merkel cells would also be in line with the idea that Merkel cells, specifically the epidermal ones, can act as "target structures" for outgrowing nerve fibers [55], and the disappearance of dermal Merkel cells during later fetal development [7] might then merely reflect the loss of such functions in histogenesis. A considerable reduction in the number of neuroendocrine cells during the later stages of fetal life has also been reported for the neuroendocrine ("Kutschinsky") cells of the bronchial epithelium [56] which express, among other components, bombesin, a molecule for which paracrine and autocrine functions have been reported [57].

It is still unsettled whether the neuroendocrine tumors of the skin, the so-called Merkel cell tumors, indeed developed from Merkel cells (for review see [10]). These tumors appear to develop in the dermis without a direct spatial connection to the epidermis of the epidermis and outer root sheath. The assumption that the dermal Merkel cell might be the cell of origin of Merkel cell tumors would easily overcome this apparent discrepancy. However, in adults in whom these tumors develop, dermal Merkel cells have not yet been convincingly shown, although occasional residual Merkel cells may exist in the postnatal dermis and provide a reservoir for potentially proliferative cells. At least our observation that Merkel cells, in principle, are able to migrate into the dermis may offer a new possible relationship between Merkel cells and the neuroendocrine tumors of the skin, i.e., Merkel cell tumors.

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