Hyperplasia of Merkel Cells in Hyperplasia Epidermis: Which Induces Which?

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Although Merkel cell (MC) was described more than a century ago by Merkel [1], the involvement of MC within a pathologic process remains unclear. Besides the so-called MC carcinoma (neuroendocrine carcinoma of the skin), hyperplasia of MC has been observed. Gould et al. [2, 3] reported the existence of such a feature within chronically damaged actinic skin. Hyperplastic MC were distributed as basal rows and showed focal and architectural abnormalities [3]. Less frequently, these cells were observed isolated or in clusters within the stratum spinosum. We recently expanded these observations to actinic keratoses [4] of which only the hypertrophic varieties demonstrated hyperplasia of MC. Furthermore, this hyperplasia was almost restricted to those lesions with club-like epidermal proliferations. Because similar clublike proliferations where MC cluster are normal morphological patterns of some epithelia, e.g. the parakeratotic zone of the rabbit lip epithelium or the ingrowing hair follicles of the mouse skin during embryogenesis, and because such MC were also pointed out within involved skin of psoriasis [5], a situation where club-like proliferations are common, we proposed that the MC hyperplasia could result as a consequence of a specific differentiation of the epithelia. In this issue (p. 73), Wollina rises the question whether MC hyperplasia or epidermal hyperplasia triggers the other, and refers to an important study conducted by Jones and Munger [6] in opossum. Sequential events occurring in this experiment can be summarized as follows: (i) partial neurectomy; (ii) compensatory hyperplasia of the dorsal root ganglia with an increased innervation of both the dermis and the epidermis; (iii) epidermal hyperplasia, and (iv) precocious hair development. This experiment suggests to Wollina that MC hyperplasia is a prerequisite to the epidermal hyperplasia rather than a consequence. This could imply that the preexisting intraepidermal MC attract and guide the nerve endings to their final location. This would be in accordance with the hypothesis of MC target for the ingrowing nerves [7]. Unfortunately, Jones and Munger [6] did not look for MC hyperplasia during the course of epidermal changes in the skin they studied.

However, there is some evidence favoring the opposite. The sequence of events of hair development during mouse skin embryogenesis clearly shows that a follicle-like structure precedes the appearance of follicular MC [Mérot, Y.: unpubl. data]. MC are only recognisable at the 12th day of the gestation [8] when the hair follicle enters stage 2 or 3 of its development according to Davidson and Hardy's [9] classification. At that time, there is no connection between MC and the ingrowing nerve endings [10]. At least in this physiological condition, epithelial changes precede MC. But MC could still function as a target for ingrowing nerves.

Since the time we performed our study on actinic keratoses [4] , we extended our observations in other inflammatory and tumoral derma-toses. Unfortunately, no examples of skin disease could clearly favor one of the above-mentioned hypotheses rather than the other.

For example, we had the opportunity to point out a striking MC hyperplasia in a case of trichofolliculoma using the same method as in

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our study, i.e. a standard immunoperoxidase technique and a low molecular weight cytokeratin monoclonal antibody to recognize MC [4]. MC hyperplasia was again restricted to club-like or raquet-like hair follicle structures. In another case of trichofolliculoma without well-formed club-like or raquet-like structures, there was no MC hyperplasia. This MC was confirmed using a panel of different low molecular weight cytokeratin monoclonal antibodies [Mérot, Y.; Chaubert, P.; Hürlimann, J.: unpubl. data]. MC was not associated with a similar nerve ending hyperplasia. Furthermore, Jones and Munger's [6] observation could represent, at least in the first steps of events , an experimental model of some forms of prurigo nodularis Hyde, histologic features of which include a neural hyperplasia and a hyperplastic hyperkeratotic epidermis. In all but one case of nodular prurigo which we studied by immunohistochemistry, we observed a clear-cut increase of MC within the involved epidermis comparing to the adjacent normal skin. MC usually did not cluster, but were increased in number within the basal cell layer of the epidermis. However, the hyperplastic epidermis did not always show club-like or raquet-like proliferations. Furthermore, in the case without MC hyperplasia, the epidermis was only slightly hyperplastic. At least in this pathological condition, MC hyperplasia was not only restricted to clublike epidermal hyperplasia, but also to a more irregular pattern of epidermal hyperplasia. All these preliminary observations suggest that MC hyperplasia could be associated with epidermal hyperplasia, mostly when club-like proliferations predominate. However, epidermal or follicular hyperplasia could also occur without any relationship to an increase in MC number. This could perhaps mean that epidermal hyperplasia is a prerequisite of MC hyperplasia. We are now investigating a wide variety of inflammatory and tumoral dermatoses showing various patterns of epidermal hyperplasia to figure out the precise relationship between MC hyperplasia and hyperplastic epidermis.

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Synaptophysin-Like Immunoreactivity in Merkel Cells of Fetal Rat Skin

To the editor,

We would like to report on the synaptophysin-like immunoreactivity of Merkel cells in fetal rat skin at day 20 of gestation, as detected by double immunostaining [1].

Unfixed, frozen sections obtained from the barbate portion of fetal rats were first incubated with an MC-specific antikeratin antibody (RCK-102, Bio-Science Products AG), confirmed by immunoelectron microscopy [unpubl. data], and thereafter immunostained using an immunogold-silver staining technique. Washed in PBS, the sections were then incubated with a monoclonal antibody against synaptophysin (Boehringer, Mannheim). Using the ABC immunostaining technique, the final reaction product was developed with DAB.

For negative controls the antisynaptophysin antibody was replaced by PBS. Single cells, scattered in the basal layer of the epidermis, as well as cells clustered in the outer root sheath of hair follicles, stained positively with the Merkel cell-specific antikeratin antibody applied in the first step. Incubation with the antisynaptophysin antibody revealed a positive staining reaction within the cytoplasm of these cells (fig. 1). Negative controls were negative.

Fig. 1. Cells, clustered in the outer root sheath of a hair follicle in fetal rat skin at day 20 of gestation, are stained with a monoclonal antibody against synaptophysin. The DAB reaction product is found within the cytoplasm (arrows).