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ENVIRONMENTAL MODIFICATION OF THE SHAPE OF PIGMENT-PRODUCING CELLS

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Abstract. With fluorescence-histochemical methods (FIF method) pigment-producing cells were investigated in benign and malignant skin lesions. Here, pigment cells appear predominantly dendritic, whilst they are separated from each other by keratinocytes, cells of hair follicles, or cells of sebaceous glands. In lentigo maligna melanoma, superficial spreading melanoma as well as in nodular melanoma and some metastases of these melanomas, the tumour cells can show a dendritic pattern under special environmental situations. It is, therefore, assumed that the shape of tumour cells in melanomas is more closely dependent on their particular environment and other modifying factors than on a different histogenesis.

Key words: Melanocytes; Malignant melanoma; Seborrheic wart; Pigmented basal cell epithelioma; Histogenesis; Formalin-induced fluorescence

In the opinion of many investigators, malignant melanomas develop from melanocytes (2, 10, 20), whereas others believe nevus cells to be the origin of melanomas (1). Mishima (12, 13), however, proposes a dualistic theory of histogenesis for malignant melanoma, based on electron microscopical, histochemical and light microscopical findings. According to this theory, lentigo maligna melanoma has a melanocytogenic origin, while superficial spreading melanoma and nodular melanoma develop from nevus cells (14). These findings have been supported by some investigators (8, 11), but rejected by others (7, 19). Our fluorescence-histochemical and enzyme-histochemical results (15–17) lead rather to the conclusion that malignant melanoma develops only from melanocytes, since melanocyte-like dendritic cells could be found in all types of malignant melanomas, when exposed to special environmental situations.

MATERIAL AND METHODS

A total of 90 primary tumours and 16 lymph node metastases as well as skin metastases of various types of malignant melanomas were investigated. The primary lesions were classified according to Clark et al. (2). 43 lesions were superficial spreading melanomas (SSM), of which 16 showed nodular tumour growth. 17 tumours were primary nodular melanomas (NM), whereas 30 could be classified as lentigo maligna melanomas (LMM). The lymph node metastases had developed from all three types of melanoma. Only the skin metastases of SSM and NM could be investigated.

In addition, six seborrheic warts and four pigmented basal cell epitheliomas were also examined. All tumour specimens were frozen at the temperature of liquid nitrogen and freeze-dried. Fluorescence-microscopical investigations were carried out according to Falck et al. (4) (formalin-induced fluorescence, FIF method). With regard to methodological details, see Paul et al. (16). Structures showing yellow-green fluorescence are believed to contain precursors of melanin.

RESULTS

Special attention was given to the shape of the pigment cells, in particular their dendritic pattern. Normal melanocytes are evenly distributed in the basal layer of the epidermis. They are regularly shaped and their relative short and stout dendrites are directed towards the prickle-cell layer. The fluorescence intensity of the melanocytes increased primarily in the epidermal parts next to the superficial spreading melanoma and near the junctional nevus cell nests.

In seborrheic warts, cell bodies of melanocytes often contact the basal lamina, while very long dendrites run towards the corneal layer. In tangential sections, the cell bodies of melanocytes seem to be evenly distributed throughout the tissue (Fig. 1*a*).

In pigmented basal cell epithelioma, however, pigment cells can intermingle with strands or whorls of tumour cells. Here, they are mostly irregular in arrangement and in shape. Their dendrites are arranged in parallel. Within whorls of tumour cells, the dendrites of melanocytes are circularly arranged

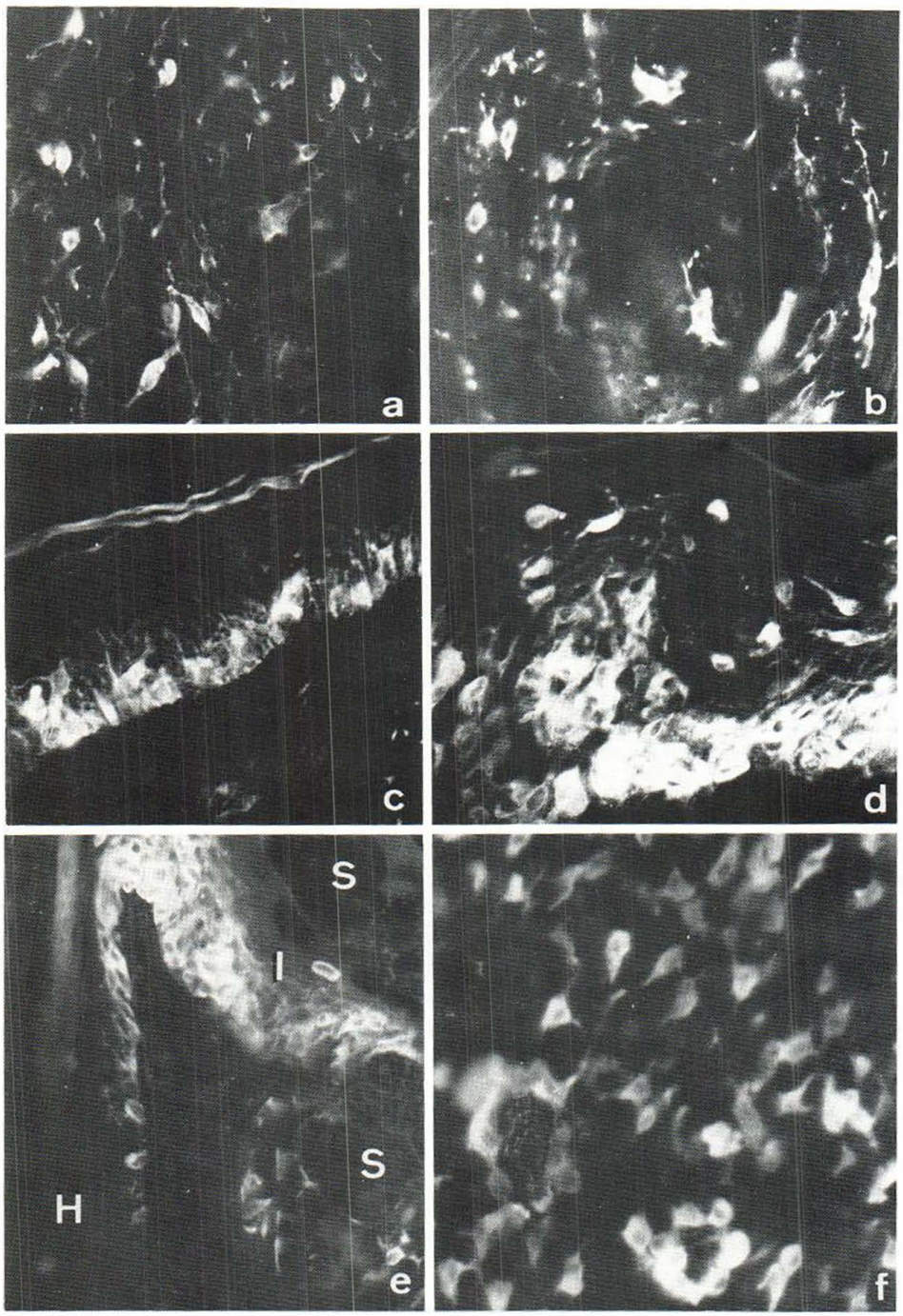

Fig. 1 a–f. Dendritic pigment cells in various tissues: (*a*) seborrheic wart; (*b*) pigmented basal cell epithelioma; (*c*) lentigo maligna; (*d*, *e*) superficial spreading melanoma; (*f*) lymph node metastasis of nodular melanoma. In (*e*), dendritic cells are arranged along hair follicle (*H*) and scattered in a sebaceous gland (*S*). Melanoma cells invading the infundibulum (*I*) of a sebaceous gland. Formalin-induced fluorescence. ×250.

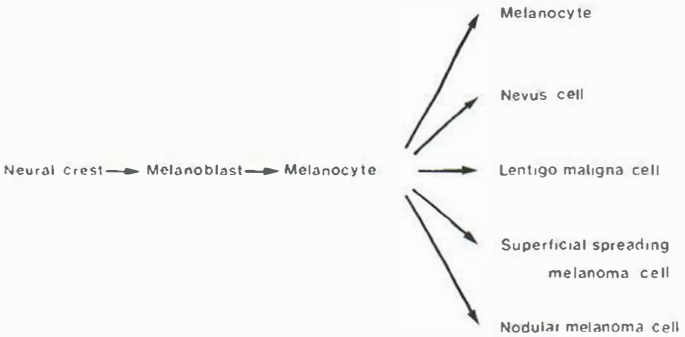

Fig. 2. Possible differentiations of melanocytes according to the particular environmental and other modifying factors.

(Fig. 1*b*). In the above-mentioned skin lesions, the appearance of melanocytes is altered, but they still retain their characteristic shape.

Dendritic cells could also be observed in cases of lentigo maligna. In the flat parts of this lesion, as long as the atypical pigment cells were still lying intra-epidermally, they were of differing size and possessed long and irregularly branched dendrites. In these cases the basal layer of the epidermis consisted almost completely of atypical pigment cells (Fig. 1*c*). These cells retained their dendritic pattern as long as they did not concentrate to pseudonests, even when they were arranged in the basal parts of the atrophic epidermis in several layers. When forming pseudonests, the cells seemed to lose their dendritic pattern. This became especially evident in the nodular region of the lentigo maligna melanoma, where the tumour cells had lost all those characteristics observed in the intra-epidermal areas. Nodular regions of LMM could not always be distinguished from nodular parts of SSM or from primary nodular melanoma.

In cases of superficial spreading melanoma, the tumour cells are mostly round or oval in shape. This pattern of tumour cells could also be observed when single cells were located within the inflammatory infiltration or within the epidermis. In some tumour areas, however, tumour cells were diffusely scattered within the acanthotic epidermis, displaying long and strongly fluorescing dendrites. (Fig. 1*d*). In other cases, however, where the fluorescence intensity of the tumour cells was very weak, single strongly fluorescing cells with clearly visible dendrites were seen in some tumour cell nests. Pigment cells also showed a dendritic pattern in SSM, when arranged in a palisade manner along hair follicles or scattered among cells of sebaceous glands (Fig. 1*e*).

In the nodular melanoma, the histological pattern was even more uniform than in SSM. In this tumour, dendritic cells were only scattered between unbranched tumour cells which are mainly bunched together.

Tumour cells of lymph node metastases also showed a rather uniform pattern, in which short dendrites of tumour cells were also occasionally visible. In one case of lymph node metastases of a nodular melanoma, nearly all cells were dendritic (Fig. 1*f*). They were not bunched together but were instead separated from each other by non-fluorescing lymphoid cells.

DISCUSSION

By using fluorescence histochemical methods (FIF), the shape of pigment-producing cells can be visualized in detail. In this way it can be clearly determined if these cells are dendritic. Dendritic cells of rather regular shape and branching can be shown not only in seborrheic warts but also in pigmented basal cell epithelioma (3, 18). In all these cases, the pigment cells are evenly distributed throughout the tissue which is of epidermal origin. When the melanocytes in seborrheic warts are compared with those of pigmented basal cell epithelioma, it can be stated that in the latter tumour the melanocytes are more irregularly branched. In pigmented basal cell epithelioma, the dendrites of the pigment cells are arranged parallel, and in a circular fashion in cylindrical or spherical tumour parts. This parallel arrangement of the dendrites may indicate the direction of cell growth within the tumour. In the same sense, the direction of the dendrites in normal epidermis can be best understood, because both the direction of growth of

epidermis cells and the direction of dendrites are towards the corneal layer.

Surprisingly, in rare cases, single dendritic cells could also be detected in nests of melanoma cells. Why those cells remain dendritic seems difficult to explain, for we recently found (17) that melanoma cells lose their dendrites, become round or oval in shape, and bunch together with other melanoma cells when contact with epidermis cells is lost. Because these dendritic cells are very large, they might be single dendritic tumour cells rather than displaced normal melanocytes.

It is only under special conditions that tumour cells of malignant melanoma appear dendritic, e.g. when they are not crowded together and when they remain in contact with keratinocytes or with cells of epidermal origin. This becomes most evident in lentigo maligna, where in flat regions nearly all atypical pigment cells are dendritic; in nodular regions, however, these characteristic signs can be completely lost, as the cells bunch together and lose contact with the epidermis. Even in some cases of SSM, tumour cells can be dendritic if they are loosely arranged between keratinocytes, while in neighboring tumour cell nests, dendrites are no longer visible.

A dendritic pattern of pigment cells can also be observed in a SSM which invades a sebaceous gland. On the other hand, these cells might instead be induced melanocytes with strong fluorescence, as they can normally be found in sebaceous glands too (5).

The assumption that the shape of tumour cells is not invariable in one and the same tumour type seems strongly supported by the finding of numerous dendritic tumour cells in a lymph node metastasis of a nodular melanoma, where the primary had shown very few dendritic cells. This finding could be explained easily by the fact that these tumour cells are evenly distributed within the metastasis and separated from each other by non-fluorescing lymphoid cells.

In conclusion, dendritic, melanocyte-like pigment cells are to be found in all three types of malignant melanoma; the tumour cells retained their ability to form dendrites, according to their particular environmental conditions. Moreover, it should be remembered that the degree of differentiation of tumour cells and their special surface pattern may also influence their shape, as has been observed in cultured cells (6, 9). Because in certain circumstances the original melanocyte-like dendritic pattern can be found in all three types of melanoma, a unitarian histogenesis from melanocytes is conceivable (Fig. 2).

REFERENCES

1. Allen, A. C.: A reorientation on the histogenesis and clinical significance of cutaneous nevi and melanomas. Cancer *2:* 28, 1949.
2. Clark, W. H. Jr, From, L., Bernardino, E. A. & Mihm, M. C.: The histogenesis and biologic behavior of primary human malignant melanomas of the skin. Cancer Res *29:* 705, 1969.
3. Deppe, R., Pullmann, H. & Steigleder, G. K.: Dopa-positive cells and melanin in basal cell epithelioma (BCE). Arch Dermatol Res *256:* 79, 1976.
4. Falck, B., Hillarp, N.-Å., Thieme, G. & Torp, A.: Fluorescence of catecholamines and related compounds condensed with formaldehyde. J Histochem Cytochem *10:* 348, 1962.
5. Ito, K., Sato, S., Nishijima, A., Hiraga, K., Hidano, A. & Kukita, A.: Melanogenic melanocytes in human sebaceous glands. Experientia *32:* 511, 1976.
6. Kitano, Y.: Effects of melanocyte stimulating hormone and theophylline on human melanocytes in vitro. Arch Dermatol Res *255:* 163, 1976.
7. Klingmüller, G., Reuter, G., Rodermund, O. E. & Schmöckel, C.: Die Submikroskopie des malignen Melanoms. Dermatol Wschr *156:* 308, 1970.
8. Klug, H. & Günther, W.: Ultrastructural differences in human malignant melanomata. An electron microscopical study. Br J Dermatol *86:* 395, 1972.
9. Lipkin, G. & Knecht, M. E.: Contact inhibition of growth is restored to malignant melanocytes of man and mouse by a hamster protein. Exp Cell Res *102:* 341, 1976.
10. Lund, H. Z. & Kraus, J. M.: Melanotic tumors of the skin. *In* Atlas of the Tumor Pathology, Sect. I (Armed Forces Institute of Pathology), 1962.
11. Lupulescu, A., Pinkus, H., Birmingham, D. J., Usndek, H. E. & Posch, J. L.: Lentigo maligna of the fingertip. Clinical, histological and ultrastructural studies of two cases. Arch Dermatol *107:* 717, 1973.
12. Mishima, Y.: Macromolecular changes in pigmentary disorders. Arch Dermatol *91:* 519, 1965.
13. Mishima, Y.: Changes in the current concepts of malignant melanoma. Curr Probl Dermatol *3:* 51, 1971.
14. Mishima, Y. & Matsunaka, M.: Macromolecular pathology of pagetoid melanoma. *In* Pigment Cell, vol. 1., p. 292. Karger, Basel, 1973.
15. Paul, E.: Histochemical findings in different types of malignant melanoma: Biological and clinical significance. Arch Dermatol Res *254:* 159, 1975.
16. Paul, E., Hartwig, H.-G., Möller, W. & Illig, L.: Fluorescenzhistochemische Untersuchungen und mikrofluorometrische Analysen an pigmentbildenden Tumoren der Haut. (Unter besonderer Be-

rücksichtigung der Melanom-Theorie von Mishima). Arch Dermatol Res *253:* 125, 1975.
17. Paul, E. & Illig, L.: Melanin-producing cells and histogenesis of malignant melanoma. Arch Dermatol Res *257:* 163, 1976.
18. Szodoray, L.: Die Rolle der Melanocyten bei einzelnen Hautgeschwülsten. Zentralbl Allg Pathol *103:* 81, 1962.
19. Thies, W. & Scherowsky, U.: Prognose des malignen Melanoms in Abhängigkeit vom Entstehungsmodus. Arch Dermatol Forsch *244:* 210, 1972.
20. Trapl, J., Paleček, L., Ebel, J. & Kučera M.: Tentative new classification of melanoma of the skin. Acta Dermatovener (Stockholm) *46:* 443, 1966.

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