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The Nature and Origin of the Melanin Macroglobule*

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The melanin macroglobule (MMG), formerly called "macromelanosome," is a cytoplasmic spherical granule formed in the melanocyte, varying in size from one to several microns, much larger than normal ellipsoidal melanosomes.

Although ultrastructural features of MMG have been adequately described in the past, there has been a disagreement about the formation process of MMG. In order to further elucidate the nature and origin of MMG, electron microscopic studies were conducted in several pigmentary disorders. Our findings included: (1) The most remarkable characteristics of MMG are (a) the pleomorphism of their internal structure and (b) the variation of their size. (2) MMG do not represent true melanosomes but unique forms of autolysosomes resulting from the fusion of autophagosomes (containing various numbers of melanosomes) with primary and/or secondary lysosomes. (3) MMG are retained within melanocytes or transferred to keratinocytes and to Langerhans cells in the epidermis, and to macrophages in the dermis in any of their developmental stages. After transfer, MMG can fuse with other heterolysosomes and probably increase in size in these cells.

We regard melanosome complexes as but one step in an autophagic process within melanocytes which can, on occasion, produce MMG as residual bodies.

The term "macromelanosome" [1] (or giant melanosome [2]) has been used to designate a specific type of very large spherical melanosome formed in the melanocyte that has been observed in various human [1–20] and animal [21–24] pigmentary disorders since its discovery by electron microscopy in café-au-lait macules of neurofibromatosis [1]. To explain the genesis of macromelanosomes, Konrad et al [2] initially postulated that they were formed from an aberrant pathway in the morphogenesis of the melanosome. Recently, however, several investigators have indicated the possibility that macromelanosomes are formed through autophagic processes [6–8,20,21], although the precise mechanisms remain to be established. Most recently, it has been postulated that melanocytes being coded in aberrant melanogenesis will synthesize abnormal spherical vacuoles, which are enlarged by numerous accumulations of vesiculoglobular bodies (VGB), and during the accumulations of VGB, normal melanosomes may be incorporated into the precursor granules of macromelanosomes and degraded to participate in the formation of the matrix under certain pathologic conditions [15,19].

The present studies were conducted in an attempt to further define the accurate morphologic characteristics of the macromelanosome with the use of serial sections combined with high-voltage electron microscopy, scanning electron microscopy, and cytochemistry, and also to investigate more precisely the mechanism for the formation of macromelanosomes as well as their relationship to other cytoplasmic organelles. The results reported here indicate that the large pigmented granules termed "macromelanosomes" do not represent true melanosomes but unique forms of autolysosomes. Therefore, inasmuch as these granules are not simply large melanosomes but unique forms of autolysosomes, we propose the term "melanin macroglobule" (MMG) to replace all the former designations for these large pigmented granules.

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Abbreviations:
- dopa: dihydroxyphenylalanine
- E.C.R.P.E.: embryonic chick retinal pigment epithelium
- GERL: Golgi endoplasmic reticulum–lysosome complexes
- MC: melanosome complex
- MMG: melanin macroglobule
- SEM: scanning electron microscopy
- SV: spherical vacuole
- TEM: transmission electron microscopy
- VGB: vesiculoglobular body

MATERIALS AND METHODS

Biopsy specimens were obtained from (1) café-au-lait macules of neurofibromatosis (14 patients), (2) X-linked ocular albinism (2 patients), (3) the pigmented macules in nevus spilus (2 patients), (4) dysplastic melanocytic nevus (2 patients), and (5) compound melanocytic nevus (3 patients). Split-dopa preparations were used simultaneously in the half-divided specimen to survey the number of MMG in café-au-lait macules, X-linked ocular albinism, and nevus spilus. Café-au-lait macules containing significant numbers of MMG per unit area were selectively chosen and examined (14 out of 26 patients).

Conventional Transmission Electron Microscopy (TEM)

The tissues were fixed in a mixture of 2.5% glutaraldehyde and 2% paraformaldehyde solution at 4°C for 2–6 h and then postfixed in 2% osmium tetroxide at 4°C for 2 h. All the fixatives were diluted in 0.1 M cacodylate buffer at pH 7.4. Fixed tissues were dehydrated in a graded ethanol series, passed through propyleneoxide, and embedded in Epon 812. Ultrathin sections, cut serially with diamond knives on a Porter-Blum MT-2 microtome, were mounted either on a 200-mesh grid or on a 0.4 × 0.2 mm slot grid covered by Formvar substrates and then double stained with uranyl acetate and lead citrate solutions. They were observed with a Zeiss EM 109 operated at 80 kV.

High-Voltage Electron Microscopy

The specimens were cut serially in 2000 Å thickness and examined in a Hitachi H-800 TEM at 200 kV, using a goniometer stage.

Scanning Electron Microscopy (SEM)

Some tissues were fixed, dehydrated and dried by the critical point method from carbon dioxide. They were finally covered with gold and carbon using IBV type of sputtering coater. The preparations were observed in a Hitachi S-700 SEM at 20 kV.

Cytochemical Investigations

Preparation of tissue: Tissues obtained from 7 café-au-lait macules, 2 dysplastic nevi, and 3 compound nevi were fixed in a dilute, cacodylate-buffered half-strength Karnovsky's fixative at 4°C for 30–90 min. After the buffered rinse, tissues were sliced and prepared for the enzyme localization.

Tyrosinase activity: Tissues were incubated in 0.1% L-dopa solution

(dihydroxyphenylalanine) diluted in 0.1 M phosphate buffer at pH 7.4 at 37°C for 2 h and then incubated in the same solution at 4°C overnight.

Acid phosphatase activity: Tissues were incubated at pH 5.0 for 30–60 min in the medium containing sodium β-glycerophosphate as a substrate according to the modified method of Gomori's technique [25]. Controls consisted of incubations that either lacked a substrate or included 0.02 M sodium fluoride as an enzyme inhibitor.

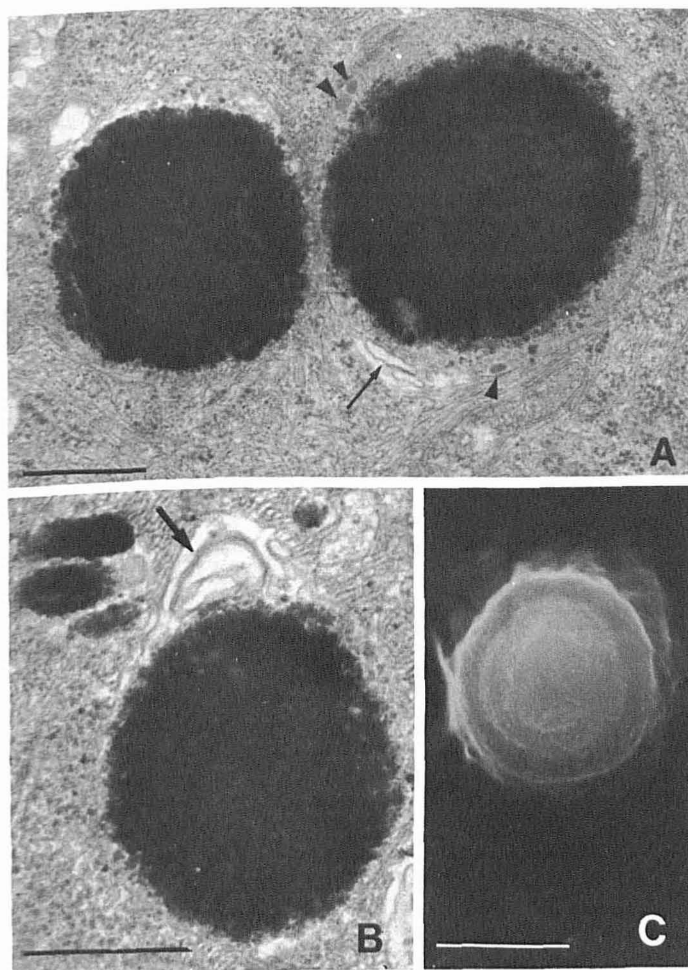


FIG 1. Electron micrographs of melanin macroglobules (MMG). *A*, Typical appearances of MMG. Note the presence of microvesicles and tubular structure (*arrow*) in the cortex of the MMG. *Arrowheads* indicate relatively large microvesicles. *Bar* = 0.5 μm. *B*, Myelinoid structure seen in the cortex of the MMG (*arrow*). *Bar* = 0.5 μm. *C*, SEM image of MMG. Three or four concentric layers are visible. *Bar* = 1.0 μm.

Subsequent processing: After being rinsed in the same buffer, the tissues were postfixed in 1% osmium tetroxide at 4°C for 1 h. Then, they were dehydrated and embedded in Epon 812. For scrutiny for acid phosphatase reaction products, sections were first observed without staining. After confirmation of the reaction products, the staining was added.

RESULTS

Morphologic and Cytochemical Properties of MMG in the Melanocyte

The ultrastructural features regarding the morphology of MMG observed in biopsies from all the pigmentary disorders were essentially similar. MMG were generally spherical or rarely ovoid and measured approximately 1–6 μm in diameter. They were frequently located in the cell body, often indenting the nuclei. Rarely, relatively small MMG were found in the dendritic process. They were frequently surrounded by (10 nm) intermediate filaments (Fig 1*A*). Usually, they consisted of (a) electron-dense amorphous substances with diffusely scattered electron-lucent microvesicles, about 400 Å in diameter, in the core and (b) of electron-dense fine particles accompanied by numerous less electron-dense microvesicles, 400–500 Å in diameter, in the cortex at varying depths. Some microvesicles with moderately electron-dense grains inside were found to reach up to 800 Å in diameter (Fig 1*A*). Tubular and/or myelinoid structures were occasionally observed in the cortex (Fig 1*A*,*B*). SEM observations revealed clearly that a certain type of MMG consisted of 3 or 4 concentric layers (Fig 1*C*). However, it was often possible to detect different configurations of the same MMG, when serial sections were analyzed, combined with high-voltage electron microscopy. As can be clearly seen in Fig 2*A*,*B*, electron-lucent microvesicles are not prominent when the MMG is cut at its greatest diameter, while they are more visible when the MMG is cut at its edge. In addition, electron-dense ellipsoidal and/or ovoid substances were occasionally seen within the peripheral or even in the central area (Fig 3*A*, *B*). The fusion of the MMG with melanosome complexes as well as the other MMG was frequently observed (Fig 4*B*). Furthermore, it was also found that the MMG did not appear to have any particular internal structure as defined by its size.

The presence of acid phosphatase activities was demonstrated in MMG of any size and internal structure. Fine or coarse opaque grains of reaction products were located mainly in the peripheral zone (Fig 4*A*). However, rarely, reaction products were discerned to be few in number, presumably suggesting low levels of enzyme activities. Occasionally, spherical vacuoles containing acid phosphatase reaction products were encountered in the vicinity of the MMG (Fig 4*A*). Controls showed no dense homogeneous reaction products.

Reaction products of dopa-oxidase (tyrosinase) were detected mainly in Golgi endoplasmic reticulum–lysosome complexes (GERL), some coated vesicles, and premelanosomes. However,

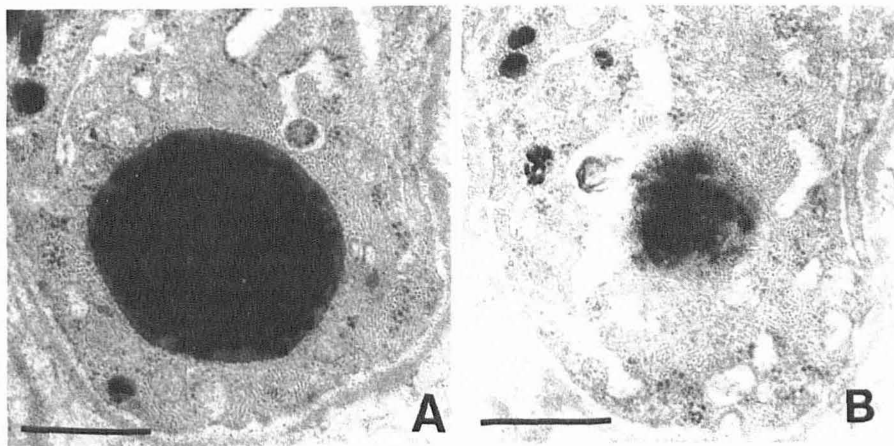


FIG 2. Serial profiles of the same MMG (high-voltage electron microscopy). Electron-lucent microvesicles are not prominent when the MMG is cut at its greatest diameter (*A*), while they are visible when cut at its edge (*B*). *Bar* = 1 μm.

it seemed to be very difficult to determine unequivocal reaction products of tyrosinase within MMG. As far as we could observe, there appeared to be no differences in the density of MMG following the incubation in dopa, and almost none of the reaction products was demonstrated in the cortex (Fig 5).

Other Cytoplasmic Organelles Considered to Be Associated with the MMG in the Melanocyte

The cytoplasmic organelles described below were observed in close relation to the MMG in every biopsy specimen.

Melanosome complexes (MC): Careful examinations of each biopsy specimen always revealed MC within some melanocytes. MC were membrane-delimited bodies ranging from 0.3 to more than 6 μm in diameter and contained various numbers of ellipsoidal melanosomes. Microvesicles were clearly seen in significant numbers within MC in a well-fixed specimen (Fig 6). Some MC revealed the cortical shells similar to those of the MMG. The following observations seemed to represent the formation and degradation processes of MC. In the early formative stage, melanosomes to be digested were surrounded possibly by a 2-layered membrane system (Fig 7*A*). Then, distinct outer membranes of melanosomes and one of the surrounding membranes disappeared to form a single membrane-bound MC (Fig 6). With the advance of degradation, the outline of phagocytized melanosomes became obscured, concomitant with the appearance of electron-dense fine particles and less electron-dense microvesicles, and gradually MC came to resemble MMG (Fig 7*B,C*). Obviously, it is difficult to distinguish some MC from MMG based on the internal structure. Since there were frequent fusions of MC with MMG, pleomorphic internal structures were occasionally noted (Fig 7*D*). Acid phosphatase activities were demonstrated generally at high levels within MC.

Spherical vacuoles (SV): SV, ranging from 0.3–0.6 μm, consisted of granular or amorphous materials of moderate electron density, usually without lamellar or filamentous structures. Sometimes, these vacuoles contained small numbers of microvesicles and electron-dense fine substances which possibly were melanin moieties. Acid phosphatase activities were found in some of the SV, indicating that these SV could be lysosomes (Fig 4*A*). Dopa-oxidase reaction products appeared to be negative in these vacuoles.

Melanosomes: Melanosomes were also observed in the melanocyte with or without MMG and showed various degrees of melanization according to their stages of maturation. Interestingly, in the case of melanocytes of café-au-lait macules, acid phosphatase activities were demonstrable in some of the Stage III and most of the Stage IV melanosomes, while the activities could be hardly detected in most of the Stage I and II melanosomes. As had been pointed out [26], these melanosomes revealed a certain number of microvesicles.

Other autophagic vacuoles: Rarely, autophagic vacuoles containing membranous or flocculent structures were observed. Microvesicles indistinguishable from those of the MMG were also present in these vacuoles (Fig 8*A,B*).

The Occurrence of MMG in Other Cells

The MMG were transferred to keratinocytes, Langerhans cells, and macrophages. However, the MMG within these cells were relatively small in size, ranging from 1–2 μm, indicating that large MMG may be hard to be transferred.

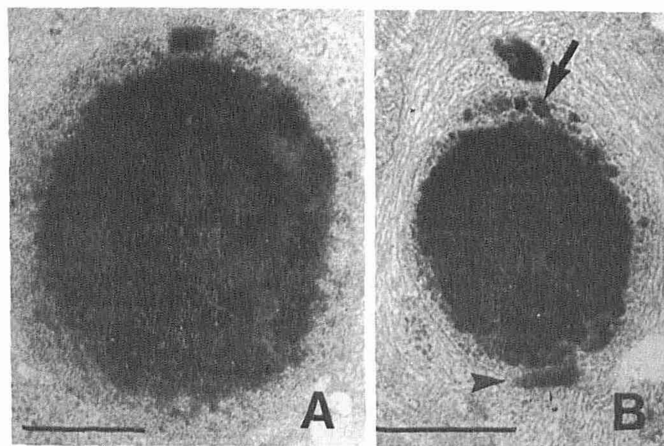


FIG 3. *A*, Note the presence of several normal sized melanosomes in the center of the granule. *Bar* = 0.5 μm. *B*, The ellipsoidal melanosome (*arrowhead*) as well as ovoid electron-dense substances (*arrow*) are present in the outer zone of the MMG. *Bar* = 0.5 μm.

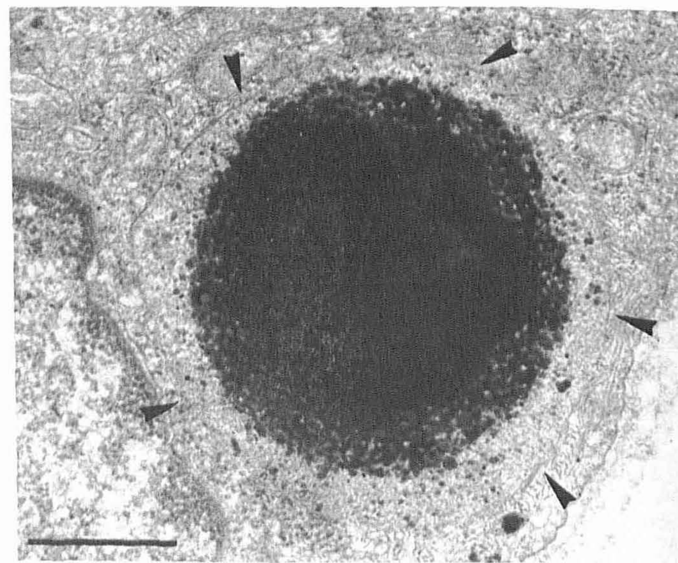


FIG 5. Electron micrographs of dopa oxidase (tyrosinase) reaction. Reaction products are hardly demonstrated in the outer zone of the MMG. *Bar* = 0.5 μm.

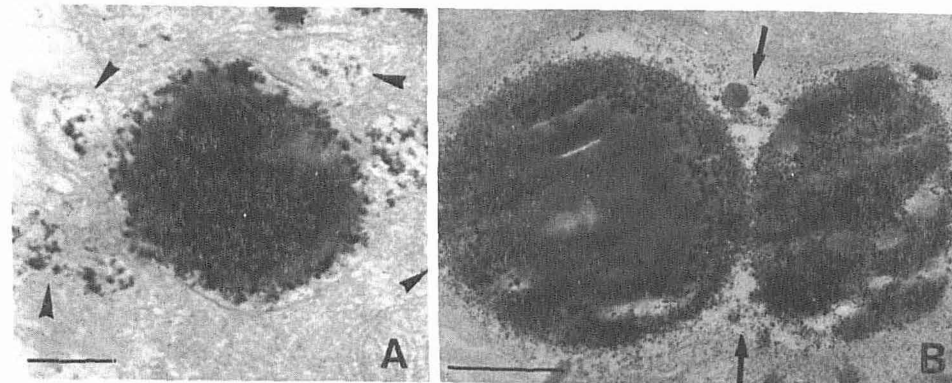


FIG 4. Electron micrographs of acid phosphatase reaction. Reaction products are demonstrated as dense or fine opaque grains mainly in the outer zones of the MMG. Spherical vacuoles containing reaction products are seen in the vicinity of the MMG (*arrowheads*) (*A*). Note the fusion of the MMG with the melanosome-complex (*arrows*) (*B*). No stain. *A*, *Bar* = 0.5 μm. *B*, *Bar* = 1.0 μm.

Keratinocyte. The basal keratinocytes bearing principally MC often contained MMG which were usually singly dispersed but occasionally showed the fusion with MC. Rarely, MMG were observed within the stratum corneum. In addition, large MC, some of which had a close resemblance to the MMG, were occasionally found (Fig 9*A*).

Langerhans cell: Very rarely, Langerhans cells in the vicinity of MMG-bearing keratinocytes or melanocytes were found to contain the MMG, which also showed the fusion with other lysosomes (Fig 9*B*).

Dermal melanophage (macrophage bearing MC): Melanophages sometimes contained MMG that were found to exist singly or were enclosed within large phagocytic vacuoles containing a variable number of degraded melanosomes or other cellular components. MMG in these cells showed high levels of acid phosphatase activities as well as MC.

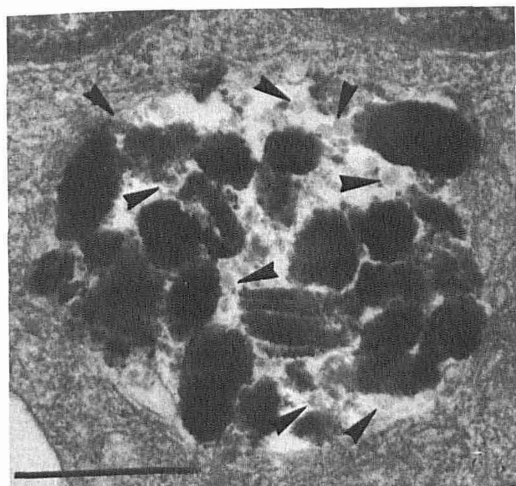
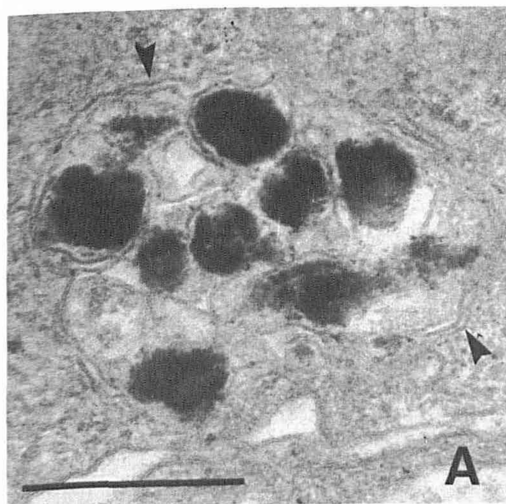


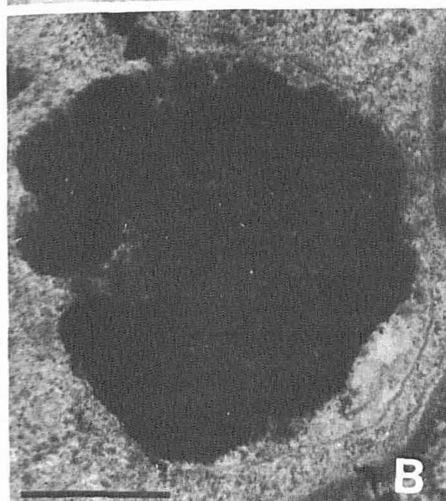
FIG 6. A typical MC. Phagocytized melanosomes still retain their normal shape. Note the presence of some microvesicles (*arrowheads*). *Bar* = 0.5 μm.

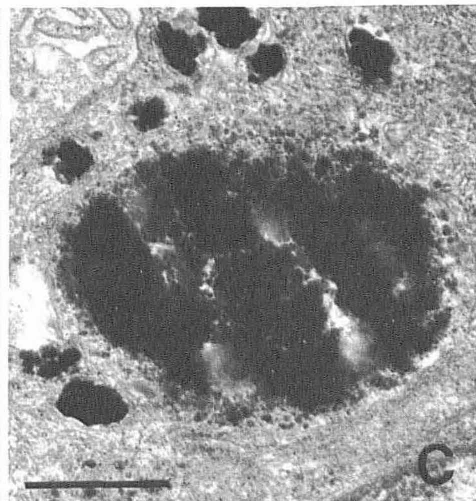
DISCUSSION

The morphologic characteristics of MMG in our studies are consistent with those described in the past [1,2]. However, with the use of serial sections combined with high-voltage electron microscopy, it has been frequently demonstrated that there is a pleomorphism in the internal structure of the same MMG. This may indicate that the previous staging and typing of MMG, suggesting a morphologic sequence in their development, may be artificial [1,2]. The occasional fusion of the MMG with other cytoplasmic organelles, including MC and SV may possibly contribute in part to the pleomorphic configuration. The other important conclusion is that the internal structure does not appear to be defined by its size.

Concerning the nature of MMG, it should be noted that the most remarkable characteristics are the pleomorphism of the internal structure and the variation regarding the size, since these features are quite consistent with those of lysosomes. In other words, the morphologic heterogeneity of MMG seems to be attributable in part to the fact that they represent various stages in a dynamic process of intragranular degradation of phagocytized melanosomes. Moreover, the presence of acid phosphatase activities in MMG may permit their identification







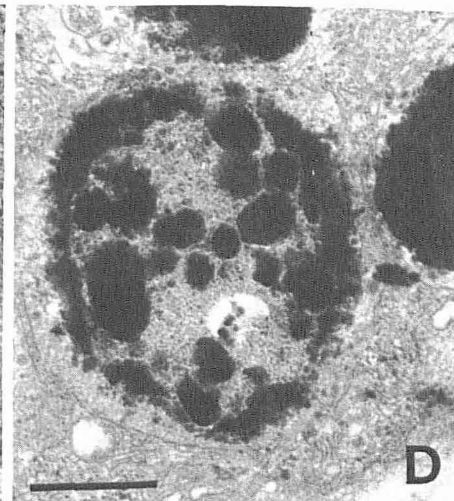


FIG 7. The formation and degradation of the MC. *A*, In the early formative stage, melanosomes are surrounded possibly by a 2-layered membrane system (*arrowheads*). Note the presence of the outer membranes of the enclosed melanosomes. *Bar* = 0.5 μm. *B and C*, With the advance of degradation, melanosomes become obscured, concomitant with the appearance of electron-fine particles and amorphous substances. *Bar* = 0.5 μm. *D*, Occasionally, highly pleomorphic configurations are observed. They may be caused by the fusions of different degradative stages of MC. *Bar* = 0.5 μm.

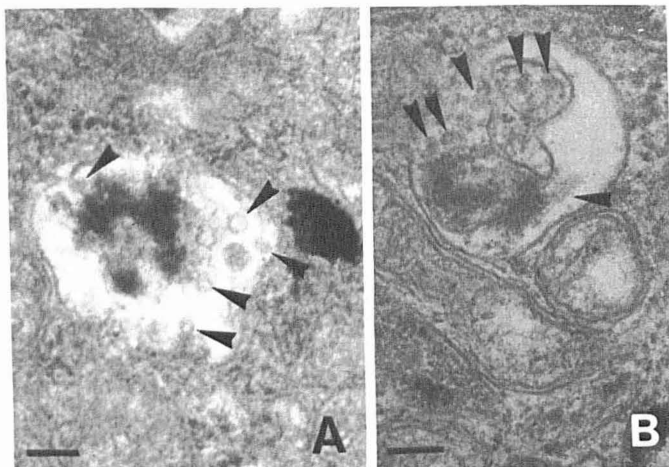


FIG 8. *A*, An autophagic vacuole containing electron-dense flocculent materials and several microvesicles (*arrowheads*). *Bar* = 0.1 μm. *B*, An autophagic vacuole containing membranous and flocculent materials probably derived from degenerated mitochondria or endoplasmic reticula. Note the presence of the microvesicles (*arrowheads*) which are indistinguishable from those of the MMG. *Bar* = 0.1 μm.

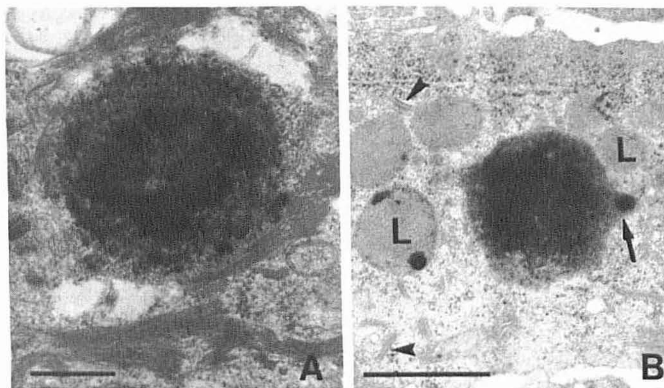


FIG 9. *A*, MMG-like granule observed in the keratinocyte. Note the presence of ellipsoidal melanosomes in the center of the granule. *Bar* = 0.5 μm. *B*, MMG in the Langerhans cell. An *arrow* points out the fusion with the other lysosome. Lysosomes (L) and Langerhans cell granules (*arrowheads*) are present as well. *Bar* = 1 μm.

as lysosomes. Low levels of activities in a few MMG may presumably depend on the degree of the consumption of acid phosphatase or on how recently MMG received the enzyme from other lysosomes [21]. With respect to tyrosinase activities, we find it difficult to determine reaction products in MMG. Although the reaction products were demonstrated in GERL, coated vesicles, and premelanosomes, we could not demonstrate definite reaction products within the cortical shells of MMG, which might be considered as the most active site of tyrosinase if MMG did, in fact, contain tyrosinase [2]. Autoradiographic studies conducted to date also have failed to demonstrate the incorporation of [^{3}H]tyrosine into MMG (only 6 MMG were examined). The principal inference derived from the cytochemical findings is that the enzymatic properties of MMG are also consistent with those of lysosomes.

It may be important to mention acid phosphatase activities in normal melanosomes. There has been conflicting evidence regarding the relationship between melanosomes and acid phosphatase activities. Melanosomes could be involved in the lysosomal system, according to studies in mouse melanoma [27, 28]. By contrast, Toda and Fitzpatrick [29] demonstrated, with the use of biochemical and cytochemical methods in embryonic chick retinal pigment epithelium (E.C.R.P.E.), that there was a clear inverse relationship between tyrosinase activities and acid phosphatase activities in melanosome fractions, and only on day 21 of E.C.R.P.E could acid phosphatase activities be detected within melanosomes, while on day 10, when most of melanosomes are already at Stage IV [30], they were not detected. Acid phosphatase activities were also reported to be negative in melanosomes of the differentiating melanocytes [31]. Our recent cytochemical study in normal human melanocytes indicated that acid phosphatase is not one of the inherent properties of melanosomes themselves, but presumbly is incorporated into melanosomes only when the process of degradation of melanosomal constituents takes place.†

On the basis of our findings, we concluded that MMG are formed through autophagic processes. The melanosomes to be digested must be separated from the other parts of the cell. One mechanism responsible for this separation is the fact that a membrane system, considered to be an element of smooth endoplasmic reticula, surrounds them and they fuse with one another [32]. The autophagosome resulting from this process then fuses with primary and/or secondary lysosomes, acquiring hydrolytic enzymes and forming an autolysosome. Within the autolysosome, ingested melanosomes are subjected to the action of a large number of hydrolytic enzymes, resulting in the breakdown of the constituents of melanosomes [33]. Ultimately, indigestible or slowly digestible substances remain within the autolysosome to form MMG. Therefore, we think that MC formed by an autophagic process within melanocytes can occasionally give rise to MMG as the end products (i.e., residual bodies). In addition, successive fusions between the autolysosomes not only provide hydrolytic enzymes but also lead to a mixture or shaking of contents among them. This may be the mechanism by which MMG can achieve the large size and pleomorphic structure. Although microvesicles may be a characteristic constituent of MMG and also one of the internal structures of melanosomes [26], their presence in MMG is not enough to support the hypothesis that MMG are true melanosomes. In fact, microvesicles are common in lysosomes (multivesicular bodies) and also could be observed in the autophagic vacuoles other than MC. It should be noted that the formation processes of MMG are similar among the disorders in our study, since Jimbow and Horikoshi [19] claimed that earlier reports identifying MMG in café-au-lait macules [1], nevus spilus [2], and X-linked ocular albinism [5] had always differentiated them from autophagocytosis of melanosomes.

Concerning the occurrence of MMG in keratinocytes, it was proposed that they were transferred from melanocytes to keratinocytes after their maturation (i.e., the end stage of autophagic processes) [1,2]. We recognized large MC which have a close resemblance to MMG. However, MMG-like granules appeared to be much larger than ordinary MC formed by transfer of normal melanosomes and have never been observed and reported elsewhere. Therefore, this finding probably indicates that MMG can be transferred in any of their developmental stages from melanocytes. MMG can also be transferred to (or engulfed by) Langerhans cells and dermal melanophages. Even in these cells, MMG can fuse with other heterolysosomes, suggesting that they may also increase in size by the accumulation of additional amounts of melanin moieties and other cellular components. The evidence that larger (more than 2 μm in diameter) MMG do not tend to be transferred smoothly indicates that they may be retained within melanocytes.

In summary, our studies of MMG have demonstrated that they are formed through autophagic processes. We could demonstrate that the morphologic and enzymatic properties of MMG are consistent with those of lysosomes.

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† H Nakagawa, AR Rhodes, TB Fitzpatrick, and Y Hori, manuscript in preparation.

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