This Week's Citation Classic®

Hashimoto K & Tarnowski W M. Some new aspects of the Langerhans cell. *Arch. Dermatol.* 97:450-64, 1968.
[Tufts University School of Medicine and Dermatology Research Laboratories, New England Medical Center Hospitals, Boston, MA]

Electron microscopic study of Langerhans cells in the human skin—under diseased conditions—demonstrated that the cells undergo mitosis within the epidermis, migrate from the dermis into the epidermis or vice versa, form Birbeck's granules as endocytotic organelles by infolding of the cell membrane, and contain lysosomes. The epidermal Langerhans cells constitute a self-perpetuating "intraepidermal phagocytic system" to which dermal histiocytes are added from time to time to transform into Langerhans cells. [The SCI® indicates that this paper has been cited in over 165 publications.]

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When this paper was published, the epidermal Langerhans cells (L-cells) were regarded as effete melanocytes. In the previous year (1967) Bill Tarnowski and I[1] had discovered that the proliferating histiocytes in the skin lesions of infantile histiocytosis-X (Letterer-Siwe's disease) are L-cells. This indirectly corrected the previous misinterpretation by F. Basset and J. Turiaf[2] that particles in pulmonary histiocytosis-X cells are probably viral in nature. If histiocytes of this tumor contain Birbeck's granules (B-granules) and, therefore, are identified with L-cells, we reasoned, the L-cells of the normal epidermis could be of histiocyte/macrophage lineage.

To prove this hypothesis the first task was to deny melanocyte connection. While we successfully accumulated circumstantial evidence (finding that many skin tumors having no melanocytes contain L-cells and that L-cells were indeed detected in the dermis where no melanocytes exist), we found several interesting phenomena. L-cells were seen crossing the dermo-epidermal junction, breaking the basal lamina. This established that, unlike epidermis-fixed melanocytes, L-cells can communicate between the dermis and epidermis. L-cells in the middle stages of mitosis were observed in the epidermis. This proved that they can self-reproduce independently from melanocytes. The L-cell periphery had numerous villi or cell membrane projections; these folded upon the cell membrane and the narrow space in between produced a B-granule. This suggested that extracellular materials could be engulfed into the granule and, thus, that B-granules are endocytotic organelles. This hypothesis was diametrically opposed to the theory of Golgi derivation of B-granules.

I found the basement membrane crossing of L-cells just before midnight one night; it was too late for my evening snack at Boston City Hospital, where I used to go for an affordable dinner, or for the free night snack from Tufts Medical School. I continued to work with excitement and observed L-cell mitosis around 2 a.m. I left a note on the RCA-3G electron microscope for Tarnowski, who was working on the endocytosis aspect, that I had made historic discoveries. Since the RCA-3G did not have a liquid-nitrogen cooling device, it had become overheated and its specimen holder was untouchably hot. I returned home to Brockton, Massachusetts, around 5 a.m. after developing the plates and confirming the publishable quality of these pictures. It was a very hot, muggy August night, and I could not sleep because of the weather and the excitement.

This paper contained so many new findings, new interpretations, and new hypotheses that subsequent investigators must have quoted it both affirmatively and negatively. Some ignored it, I believe, intentionally.

Subsequent works by us and others have proven that the L-cell is indeed a selective phagocyte[3,4] and that the B-granule is an endocytotic organelle.[5,6] Self-reproduction in the normal and posttraumatic epidermis[7] has been demonstrated abundantly with newer methodologies. No one asserts any longer that the L-cell is even remotely related to the melanocyte. Significantly, this work was done before the establishment of fetal development of L-cells from bone marrow or the recognition of the L-cell as the primary antigen-processing cell.

1. **Tarnowski W M & Hashimoto K.** Langerhans' cell granules in histiocytosis X: the epidermal Langerhans' cell as a macrophage. *Arch. Dermatol.* 96:298-304, 1967. (Cited 125 times.)
2. **Basset F & Turiaf J.** Identification par la microscopie électronique de particules de nature probablement virale dans les lesions granulomateuses d'une histiocytose "X" pulmonaire (Electron microscopy for identification of particles [probably viral] in pulmonary histiocytosis X granulomatous lesions). *C.R. Acad. Sci.* 261:3701, 1965. (Cited 150 times.)
3. **Hashimoto K.** Langerhans' cell granule: an endocytotic organelle. *Arch. Dermatol.* 104:148-60, 1971. (Cited 75 times.)
4. **Shelley W B & Juhlin L.** Langerhans cells form a reticulo-epithelial trap for external contact antigens. *Nature* 261:46-7, 1976. (Cited 185 times.)
5. **Takahashi S & Hashimoto K.** Derivation of Langerhans cell granules from cytomembrane. *J. Invest. Dermatol.* 84:469-71, 1985.
6. **Takigawa M, Iwatsuki K, Yamada M, Okamoto H & Imamura S.** The Langerhans cell granule is an adsorptive endocytic organelle. *J. Invest. Dermatol.* 85:12-5, 1985.
7. **Miyauchi S & Hashimoto K.** Epidermal Langerhans cells undergo mitosis during the early recovery phase after ultraviolet-B irradiation. *J. Invest. Dermatol.* 88:703-8, 1987.

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