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Mishima Y. Macromolecular changes in pigmentary disorders.
Arch. Dermatol. **91**:519-57, 1965.
[Dept. Dermatology, Wayne State Univ. Sch. Medicine, Detroit, and Veterans Admin. Hosp., Dearborn, MI]

This was the first full study to delineate changes occurring in functioning macromolecules, such as melanosomes, within melanogenic compartments of pigment cells in their dysfunctional and neoplastic disease status. The evidence presented in the paper covered the following three subjects: 1) melanosome polymorphism; 2) intracellular localization of tyrosinase in disturbed melanogenesis-albinism; and 3) cellular nevi: subcellular and cytochemical characteristics with reference to their origin. [The *SCI*® indicates that this paper has been cited in over 135 publications, making it one of the ten most-cited papers for this journal.]

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"Shortly after my arrival in the US in the summer of 1958, following my clinical training in dermatology at the University of Tokyo Hospital, I met Hermann Pinkus who, through his perception and gentle brilliance, inspired me to venture into a new era of macromolecular pathology.

"The era of electron microscopy in biomedical sciences had just begun. The level of precision and reliability of this newly developed, highly sensitive technique became good enough to apply intricate, complex problems of biological and clinical changes occurring in human cell systems.

"The melanocyte is a cell which has distinct biological characteristics, specific enzyme systems, unique subcellular organization, location, and functions. The melanocyte undergoes numerous and diverse pathological changes which can profitably be classified into three categories of pigmentary disorders. The first and largest group is neoplasia of the pigment cell; the second group includes those disorders caused by hypofunctional melanocytes; and the third group of pigmentary disorders is characterized by the hyperfunction of melanocytes.

"In these disorders, production, excretion, and degradation of melanosomes results in characteristic pathological skin color changes. To delineate pathogenesis and cause of pigmentary disorders, basic knowledge of melanogenesis is essential.

"Fortunately, around that time, melanogenesis at the macromolecular level became increasingly clarified. Before that time, melanin was considered to be synthesized within the mitochondria which disagreed with the newly discovered melanosome concept. However, based on electron microscopic as well as biochemical evidence, this dispute was soon resolved, the melanosome concept was accepted, and it was found that melanin biosynthesis proceeds in specific cytoplasmic organelles, melanosomes, which are considered to be formed in the Golgi apparatus or smooth ER under genetic control.

"Thus, I began investigation on the basis of this new melanosome concept of melanogenesis. First, we found specific melanosome polymorphism occurring in all three types of pigmentary disorders. These findings can be used as criteria in the diagnosis of pigmentary disorders and also for the further investigation of their pathogenesis.

"Secondly, active tyrosinase was found to be present within melanosomes of human and certain animal albino melanocytes, in which melanization could be induced *in vitro* with the addition of the appropriate substrate and/or hormonal stimuli.

"Thirdly, subcellular and enzymic characteristics of various cellular nevi and resulting malignant melanoma, as well as other melanotic tumors, were disclosed with reference to their pathogenesis and developmental ontogeny.

"These discoveries resulted in my receiving the first prize in the Annual Essay Contest of the American Dermatological Association in the summer of 1964.

"I believe this paper has been highly cited because it was the first to throw light on the macromolecular changes within pigment cells which lead to their disorders.

"This has further led us to clarify various regulatory mechanisms[1-3] of melanogenesis at the macromolecular level. One of our recent findings is the integral role of glycosylation[4,5] for maturation of tyrosinase and its accepting function by premelanosomes."

1. **Mishima Y, Imokawa G & Ogura H.** Functional and three-dimensional differentiation of smooth membrane structures in melanogenesis. (Klaus S N, ed.) *Biologic basis of pigmentation*. Basel: S. Karger, 1980. p. 277-90.
2. **Imokawa G & Mishima Y.** Isolation and biochemical characterization of tyrosinase-rich GERL and coated vesicle in the melanin synthesizing cells. *Brit. J. Dermatol.* **104**:160-78, 1981.
3. **Mojamder M, Ichihashi M & Mishima Y.** Effect of DOPA-loading on glutathione-dependent 5-S cysteinyldopa genesis in melanoma cells *in vitro*. *J. Invest. Dermatol.* **78**:224-6, 1982.
4. **Imokawa G & Mishima Y.** Loss of melanogenic properties in tyrosinases induced by glycosylation inhibitors within malignant melanoma cells. *Cancer Res.* **42**:1994-2002, 1982.
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