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REVIEW ARTICLE

Biogenesis of pigment granules: a sensitive way to regulate melanocyte function

Vincent J. Hearing*

Pigment Cell Biology Section, Laboratory of Cell Biology, Building 37, Room 2132, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA

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Summary Pigmentation not only provides a wide range of cosmetic coloration to the skin, hair and eyes, but also provides the underlying tissue significant protection from ultraviolet (UV) damage, which can lead to photoaging and photocarcinogenesis. The melanin pigment is synthesized and deposited within a unique, membrane-bound organelle termed the melanosome. Recent advances in molecular biology and biochemistry have allowed a greater appreciation of how melanocytes generate this organelle and how its biogenesis, structure and function is regulated by the environment. Melanosomes serve as ideal models for the study of organelle biogenesis, protein trafficking, organelle movement and cell—cell interactions that occur during the transfer of melanosomes to keratinocytes. Our understanding of the mechanisms behind a wide range of human pigmentary diseases have grown remarkably as melanosomes have been unraveled.
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Contents

Abbreviations: ASP, agouti signal protein; DCT, dopachrome tautomerase; DHI, 5,6-dihydroxyindole; DOPA, 3,4-dihydroxyphenylalanine; ER, endoplasmic reticulum; ET, endothelin; GS, Griscelli syndrome; HPS, Hermansky—Pudlak syndrome; LRO, lysosome-related organelles; MSH, melanocyte stimulating hormone; OCA, oculocutaneous albinism; TYRP1, tyrosinase-related protein 1; UV, ultraviolet

* Tel.: +1 301 496 1564; fax: +1 301 402 8787.
E-mail address: hearingv@nih.gov.

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1. Introduction

Pigmentation of the skin serves a number of valuable functions, perhaps foremost among those the photoprotection of underlying tissues from ultraviolet (UV) radiation. There is a direct inverse relationship between the constitutive color of the skin and the rate of skin cancer, and those with lighter colored skin are 50× more likely to develop basal or squamous cell carcinoma and are 13× more likely to develop malignant melanoma than are those with darker skin [1—3]. Recent studies have shown that melanin not only functions as a sunscreen to absorb UV and prevent DNA damage, but that its other properties, e.g. as an antioxidant and a radical scavenger, also play important roles in protecting cells from such damage [4—6].

Melanocytes respond to a wide variety of intrinsic and extrinsic factors, produced by the environment or by neighboring cells in the skin, including UV, melanocyte stimulating hormone (MSH), agouti signal protein (ASP), endothelin 1 (ET1), dickkopf 1 (DKK1) and a wide variety of growth factors, cytokines, etc. (reviewed in [7]). My laboratory has been involved for many years in characterizing the regulation of melanocyte function, primarily at the subcellular level, and our research has gradually evolved into studies on parameters important to: (1) the production of the pigment melanin, (2) the biogenesis and maturation of the subcellular organelle in which the pigment is produced (the melanosome), (3) how melanosomes mature en route to their migration to the dendrites of the melanocytes and how they are eventually transferred to keratinocytes and (4) how the entire differentiation machinery of the melanocyte is regulated by its environment.

The pigmentation of the skin involves the cooperation of melanocytes and keratinocytes to produce melanosomes and then transfer them to keratinocytes, which then distribute them in various fashions en route to the surface of the skin. Recently, fibroblasts have also been shown to participate in the regulation of melanocyte growth and differentiation [8], and thus skin colors between races, and even on various areas of a single individual (e.g. compare skin on the palm with skin on the forearm) reflect the interactions of many epidermal and dermal components.

2. Biogenesis of the melanosome as a unique organelle

The original concept for melanosome biogenesis was proposed almost exactly 40 years ago by Seiji et al. [9]. Despite the fact that only tyrosinase had been identified as a melanogenic enzyme at that time and that they had only some early biochemical analysis and ultrastructural data to work with, they hypothesized a mechanism that remains essentially valid today as they proposed it long ago. They suggested that melanosomes were first created by relatively amorphous and spherical vesicles that blebbed from the endoplasmic reticulum (ER), which lacked tyrosinase activity and any internal structural components. Those early melanosomes were termed premelanosomes but are now referred to as Stage I melanosomes. Tyrosinase could be visualized at the ultrastructural level in 3,4-dihydroxyphenylalanine (DOPA)-positive Golgi vesicles which then trafficked to Stage I melanosomes, resulting in their transformation to elongated, fibrillar organelles which are tyrosinase-positive, and are now known as Stage II melanosomes. Melanin synthesis begins and the pigment is deposited uniformly on the internal fibrils, at which time they are termed Stage III melanosomes. In