Summary

Cutaneous pigmentation is the outcome of exquisite interactions among various cell types in the skin, the best described of which are the interactions between epidermal melanocytes and keratinocytes, and between melanocytes and dermal fibroblasts. Melanocytes are the site of melanin synthesis, and keratinocytes are the recipients of melanosomes, melanin-containing organelles. The wide variation in constitutive pigmentation among humans is caused by enormous differences in the rate of synthesis of the two forms of melanin, eumelanin and pheomelanin, and the rate of transfer of melanosomes to keratinocytes. Cutaneous pigmentation is regulated by a wide array of factors, some of which are endocrine, and many are paracrine and/or autocrine. Many of those factors regulate constitutive pigmentation and also participate in the ultraviolet radiation (UVR)- or inflammation-induced hyperpigmentation. There is convincing evidence that the tanning response to UVR exposure is mediated by a spectrum of locally produced cytokines and growth factors, such as α-melanocyte-stimulating hormone (α-MSH) and adrenocorticotropic hormone (ACTH), and endothelin-1 (ET-1). Currently, more is known about the regulation of melanin synthesis than about the control of melanosome transfer. Only in the past few years...
was significant progress made in defining some of the molecular aspects and genes involved in the latter process. The significance of cutaneous pigmentation lies in its principal role in photoprotection against the carcinogenic effects of UVR. Numerous epidemiological and clinical studies have concluded that the incidence of UVR-induced skin cancer correlates inversely with constitutive pigmentation and the ability to tan. An important role of some of the paracrine/autocrine factors, such as nerve growth factor (NGF), stem cell factor (SCF), ET-1, α-MSH, or ACTH, is to protect melanocytes from stress-induced apoptosis, e.g., that induced by exposure to UVR. This survival effect is of tremendous importance given the significance of the melanocyte in photoprotection and its limited capacity to proliferate and self-renew. It is plausible that at least some of those factors might link the survival pathways to the DNA repair pathways in melanocytes. If this is the case, then the ability of melanocytes to respond to those survival factors might be a determinant of skin cancer, particularly melanoma, susceptibility.

**Key Words:** Human melanocytes; endocrine factors; paracrine factors; autoimmune factors; facultative pigmentation; constitutive pigmentation; photoprotection.

**SKIN PIGMENTATION: THE OUTCOME OF MELANIN SYNTHESIS AND DISTRIBUTION IN THE EPIDERMIS**

Melanocytes are cells that are specialized in the synthesis of melanin(s), the pigment that provides the skin and hair with their distinctive coloration. In humans, the vast majority of melanocytes reside in the epidermis and within the hair follicles, and some are present in other anatomical sites, mainly the eyes and inner ear. To date, most of the current knowledge about the regulation of human pigmentation is either based on studies of human epidermal melanocytes, or extrapolated from studies on follicular melanocytes in other mammals, mainly mice. In general, epidermal and follicular melanocytes are considered to be similar in the manner they are regulated. However, these two melanocyte populations differ in several aspects, including their life span, interaction with the surrounding epithelial and mesenchymal cells, and responses to environmental factors, particularly ultraviolet radiation (UVR).

In humans, skin pigmentation is the outcome of the synthesis of melanin by epidermal melanocytes and the distribution of melanin to surrounding keratinocytes (1). In the human epidermis, melanocytes comprise less than 10% of the entire epidermal cell population, whereas keratinocytes are the major structural cells. Melanocytes interact physically via their dendrites with the neighboring keratinocytes. Melanin-containing melanosomes are transferred along the dendrites of melanocytes to keratinocytes, and this donation of melanosomes is critical for normal skin pigmentation. The physical interaction of melanocytes with keratinocytes has led to the concept of the epidermal melanin unit, which underscores the importance of communication between these two cell types for normal pigmentation (2). Keratinocytes have a high self-renewal capacity and undergo a well-defined differentiation program that culminates in apoptotic-like cell death (3). In contrast, melanocytes in the epidermis are generally highly differentiated and slowly proliferating, and have a poor ability to regenerate. The significance of the melanocytes lies in their role in photoprotection against the damaging effects of UVR, the worst of which is skin cancer; hence, it is crucial to maintain their survival in the epidermis (4,5).

The wide diversity of skin color in humans is caused by the extensive variation in constitutive pigmentation, which, in turn, is determined by three main factors: the rate of synthesis of melanin by melanocytes, the relative amounts of eumelanin (the brown-black pigment) and pheomelanin (the red-yellow pigment) synthesized by melanocytes, and the number and size of melanosomes and the rate of their transfer to keratinocytes (1,6,7). In dark skin, melanosomes are larger and more numerous than in light skin, and