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REVIEW ARTICLE

Keratinocytes regulate the function of melanocytes

Tomohisa Hirobe*

Fukushima Project Headquarters, National Institute of Radiological Sciences, Chiba, Japan

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ABSTRACT

Mammalian keratinocytes compose the bulk of the epithelium, undergo keratinization, and form the dead superficial layer of the skin. These superficial keratinized cells are continuously replaced by cells derived from mitotic cells in the lowest layer of the epidermis (i.e., the basal layer). Melanocytes locate in the basal layer and do not keratinize; however, they can produce melanin pigments. Melanin is accumulated in small granules called melanosomes. The melanosomes are transported to dendrites from which the melanosomes are transferred to keratinocytes. Epidermal invaginations such as keratinocytes and melanocytes extend to the dermis to form hair follicles. In addition to these two cells, dermal fibroblasts are also required for the formation of hair follicles. The homeostasis of the epidermis and hair follicle is primarily regulated by the cellular interaction between keratinocytes and melanocytes. Keratinocytes stimulate melanocyte functions such as proliferation, differentiation, melanogenesis, and dendritogenesis. Using the techniques of tissue culture, biochemistry, and molecular biology, factors that have been derived from keratinocytes are hormones, growth factors, and cytokines such as α-melanocyte-stimulating hormone, adrenocorticotrophic hormone, basic fibroblast growth factor, nerve growth factor, endothelins, granulocyte-macrophage colony-stimulating factor, stem cell factor, leukemia inhibitory factor, and hepatocyte growth factor. These keratinocyte-derived paracrine factors have a key role in regulating melanocyte function through receptor-mediated signaling pathways, followed by maintaining epidermal and hair follicular homeostasis.

Introduction

The skin is the largest organ in mammals. It covers the surface of the body and consists of three main layers: the surface epidermis, the subjacent dermis, and the subcutaneous tissue (the lowest layer). An important function of the skin is to protect an animal's body from external stimuli. The skin consists primarily of three cell types: keratinocytes, melanocytes, and fibroblasts. Keratinocytes compose the bulk of the epithelium, undergo keratinization, and form the dead superficial layer of the skin. These superficial keratinized cells continuously desquamate from the surface and are replaced by cells derived from mitotic cells in the lowest layer of the epidermis (i.e., the basal layer). The higher level cells are successively displaced by the population of new cells below them. As they move upwards, they elaborate keratin and accumulate it in the cytoplasm, and finally the cells are mostly occupied by keratin.[1]

Melanocytes, which are pigment-producing cells, are originally derived from neural crest cells in the embryonic skin. Neural crest cells migrate from the dorsal to ventral side and localize all over the body. Melanoblasts, which are a precursor of melanocytes, differentiate from the neural crest cells, proliferate, and colonize the epidermis in the embryonic stage. In the epidermis, the melanocytes locate in the basal layer and do not keratinize, but they can produce melanin pigments.[2] Mammalian hair forms from hair follicles derived from hair germ cells that begin as an epidermal invagination, and include keratinocytes, melanoblasts, and melanocytes.[2] The dermis, which consists of fibroblasts, forms a thickening beneath the epidermis and the end of the invagination surrounds the thickening. The dermal thickening develops into a dermal papilla, and the surrounding part of the invagination forms the hair bulb.[2–4] The lower half of the hair bulb is called a hair matrix, and numerous functional melanocytes are localized there.[2] Keratinocyte stem cells[5] and melanocyte stem cells[6] locate in the bulge area of hair follicles (i.e., at the site of attachment of the

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* Corresponding author. Fukushima Project Headquarters, National Institute of Radiological Sciences, 4-9-1 Anagawa, Inage-ku, Chiba 263-8555, Japan.
E-mail address: thirobe@nirs.go.jp.

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arrector pili muscle). They produce new proliferating and differentiating keratinocytes and melanocytes.

Recent studies using tissue culture, biochemistry, and molecular biology techniques demonstrate that keratinocytes regulate epidermal and hair follicular melanocyte functions such as proliferation, differentiation, melanogenesis, and dendritogenesis. This article reviews studies on the regulation of melanocyte function by keratinocytes and discusses in detail the mechanism of regulation.

Structure and function of the epidermis

The epidermis is a histologically stratified squamous epithelium and constantly requires renewal from birth to death. An important role of the epidermis is to protect the skin from many types of environmental stresses such as exposure to bacteria; viruses; chemicals; UV radiation; ionizing radiation; electromagnetic waves; and physical, thermal, and mechanical injuries (i.e., barrier function). Keratinocytes compose the bulk of the epidermis, undergo differentiation (i.e., keratinization), and form a dead superficial layer on the skin (this layer is called the "keratinized layer" or "cornified layer").[2] A function of keratinocytes is to produce keratin and filaggrin, which are involved in regulating the barrier function. The renewal of the epidermis is supported by the proliferation and differentiation of keratinocytes (i.e., epidermal homeostasis primarily depends on a balance between the proliferation and differentiation of keratinocytes).[2]

Mammalian melanocytes locate in the basal layer; they do not keratinize but produce melanin pigments.[7] Melanin is produced from L-tyrosine (L-Tyr) with the aid of enzymatic reactions by tyrosinase (Tyr), Tyr-related protein (Tyrp)-1, and Tyrp2.[8] Most epidermal melanocytes migrate to the hair follicles and colonize hair matrix melanocytes in hairy general body (i.e., trunk) skin in animals. In the glabrous skin of the ear, nose, foot, and tail in animals and in human skin (except for the scalp, underarm, and pubic skin), numerous differentiated melanocytes are present in the epidermis—even in adults.[2,9] However, in the epidermis of hairy skin in mice, epidermal melanocytes exist only during the early weeks after birth.[2] In human skin, the epidermal melanin unit, which comprise keratinocytes and melanocytes, has a key role in regulating pigmentation and homeostasis of the epidermis.[9]

Structure and function of the hair follicle

Hair follicular melanocytes derived from epidermal melanocytes are highly dendritic and colonize the hair matrix. Hair matrix melanocytes secrete mature melanosomes (i.e., melanin-containing organelles) to surrounding keratinocytes.[2] Keratinocytes develop the hair cortex and medulla in which melanosomes are incorporated. In mammals, the process of morphogenesis of the hair follicle is cyclic[10] and is called the hair cycle (i.e., growth cycle).[3] The hair cycle consists of three phases: resting (i.e., telogen phase), growth (i.e., anagen phase), and regression (i.e., catagen phase). Anagen hair follicles produce hair shafts formed by fully keratinized cells and pigmented melanocytes. This deposition of mature melanosomes continues during the entire anagen phase (approximately 17 days). This phase is divided into six subphases (i.e., anagen I–VI). When cell proliferation of hair matrix keratinocytes ceases (i.e., catagen), the melanocytes also cease producing melanosomes and no further cells enter the hair shafts. This phase is followed by the telogen phase. In mice, hair growth is synchronized and proceeds in waves all over the body. This growth pattern does not occur in humans.

Hair matrix melanocytes differ from epidermal melanocytes in that hair matrix melanocytes are larger than epidermal melanocytes, possess longer dendrites, and interact with fewer keratinocytes.[2] A functional melanin unit between melanocytes and keratinocytes is established in mature hair follicles. Melanocytes locate in the basal layer of the hair matrix close to the dermal papillae and rest on the glassy membrane (i.e., the basement membrane).[2] Pigmentation is strictly coupled to the growth phase of the hair cycle (i.e., anagen III–VI).[3] Towards the end of the anagen phase, identifiable melanocytes decrease in number and the melanocytes lose their dendrites, shrink, become less pigmented, and disappear in the catagen phase.[3] Keratinocytes and melanocytes die and finally hair follicles move upwards to form a rudimentary hair germ near a sebaceous gland.[6] In the telogen phase, keratinocyte stem cells and melanocyte stem cells continue to reside in the bulge area.[6]

Regulation of melanocyte function

The main function of melanocytes is to produce melanin.[2,7,8] Melanin absorbs UV waves to prevent DNA damage to the keratinocytes. The quality and quantity of melanin present in an animal's body is determined by the differentiated state of melanocytes, melanocyte number, degree of melanogenesis, and dendricity, and by environmental factors such as the surrounding tissue environment, blood supply, UV radiation, and ionizing radiation.[2,7,8] Melanin synthesis in melanocytes is primarily controlled by Tyr, Tyrp1, and Tyrp2.[7,8,11] Tyrosinase initiates melanin synthesis by catalyzing the oxidation of L-Tyr to dopaquinone.[12] Tyrosinase-related protein-1 possesses 5,6-dihydroxyindole-2-carboxylic acid (DHICA) oxidase activity.[13] By contrast, Tyrp2 possesses dopachrome tautomerase activity,[14] which converts dopachrome to DHICA.[15] Melanocytes produce two types of melanin: brown-black eumelanin and red-yellow pheomelanin.[7,16] Differences exist in their molecular size and general properties, although these melanins arise from a common metabolic pathway in which dopaquinone is a key intermediate.[16]

Melanin synthesis occurs in specialized organelles called melanosomes.[17] Melanosome maturation is categorized into four stages: stages I and II include unmelanized immature premelanosomes, whereas stages III and IV contain melanized melanosomes.[18] In animals, coat colors are determined by the quantity and properties of melanosomes transferred to neighboring keratinocytes from hair matrix melanocytes. Melanosomes are produced in various sizes, numbers, and densities. They are passed on to the hair shaft where the final distribution patterns of the pigment are determined. This distribution determines the coat coloring of animals.[19] Eumelanin-containing melanosomes (i.e., eumelanosomes) are elliptical in morphology with longitudinal depositions of pigments in intraluminal fibrils.[20] By contrast, pheomelanin-containing melanosomes (i.e., pheomelanosomes) are spherical with granular depositions of pigments within multivesicular bodies. Agouti (*A*/—) melanocytes contain pheomelanosomes in the pheomelanin-producing stage of the anagen phase and in yellow melanocytes (lethal yellow, A^y/—; recessive yellow, $Mc1r^e$/$Mc1r^e$ or *e*/*e*).[21] Thus, the differences in melanin synthesis correspond to differences in melanosome morphology. Numerous genetic and epigenetic factors regulate melanin synthesis in melanocytes.[2,19] Among these factors, the coat color genes are the most important.[19] In mice, more than 300 genes are involved in melanocyte-proliferation and differentiation; approximately one-half of the genes have been cloned and their functions have been clarified.[22] Furthermore, epigenetic factors from the surrounding tissue environment, especially keratinocytes, are also important for regulating melanin synthesis.