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〈教育セミナー〉

第43回教育セミナー（2018）・「健やかな肌を保つ―エイジングケア最前線―」

メラニン合成酵素およびメラノソーム輸送の分子機構
―輸送阻害に着目した美白剤開発―

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Molecular Mechanisms of Melanogenic Enzyme Transport and Melanosome Transport: Development of New Cosmetics That Inhibit Transport Machineries

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Abstract

Melanin pigments play a pivotal role in protecting our body from harmful ultraviolet radiation, but their excess deposition often causes freckles and skin spots. To prevent undesirable melanin deposition, it is important to understand the molecular mechanisms of formation, maturation, and transport of melanosomes, specialized organelles that synthesize and store melanin in melanocytes. Melanosomes are formed and matured at the perinuclear region of melanocytes (step 1). In this step, melanogenic enzymes such as tyrosinase and tyrosinase-related protein 1 (Tyrp1) are transported to immature melanosomes by several protein complexes such as BLOC-1–3 complexes and a complex composed of small GTPases Rab32/38, their effector Varp, and v-SNARE VAMP7. Mature melanosomes are first transported from the perinucleus to the cell periphery by microtubule-dependent motors such as Kif5b (*i.e.*, Rab1A/SKIP/Kif5b complex) (step 2) and then transported to just beneath the plasma membrane by an actin-dependent motor myosin-Va (*i.e.*, Rab27A/Slac2-a/myosin-Va complex) (step 3). The melanosomes anchored to the plasma membrane are finally transferred to neighboring keratinocytes or hair matrix cells through dendrites of melanocytes (step 4) to achieve skin and hair pigmentation. Recent advances in molecular biology techniques have allowed us to dissect the molecular machineries regulating each melanosome transport step. For example, knockdown of Varp by specific siRNAs or overexpression of Varp in melanocytes inhibits transport of melanogenic enzymes to immature melanosomes, which leads to a hypopigmentation phenotype in cultured melanocytes. On the other hand, functional ablation of Rab27A or its effector Slac2-a inhibits actin-based melanosome transport, which leads to a perinuclear melanosome aggregation phenotype (*i.e.*, typical phenotype observed in melanocytes from Griscelli syndrome patients). Thus, screening and identification of new substances or plant extracts that inhibit (or promote) the function of these transport machineries will enable us to develop new cosmetics for skin whitening (or new drugs that prevent gray hair) in the future.

Key words: melanosome transport, melanogenic enzymes, Rab small GTPases, melanocyte, keratinocyte.