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〈シンポジウム II〉

『光老化の予防と対策最前線』

メラニン輸送の分子メカニズム解明とその応用

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Molecular Mechanism of Melanin Transport and Its Application

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Abstract

The pigmentation of mammalian skin requires the proper formation and transport of melanosomes that specifically synthesize and store melanin pigments in epidermal melanocytes. At least six distinct transport steps are involved in this process: (step 1) the formation and maturation of melanosomes, (step 2) the long-range microtubule-dependent transport of melanosomes, (step 3) the transfer of melanosomes from microtubules to actin filaments, (step 4) the short-range actin-based transport of melanosomes, (step 5) the anchoring of melanosomes to the plasma membrane, and (step 6) the transfer of melanosomes from melanocytes to adjacent keratinocytes. The molecular mechanisms of several steps of melanosome transport have recently been revealed by the genetic analysis of pigmentary disorders in humans (e.g., Griscelli syndrome) and mice (e.g., *chocolate*) and by the biochemical analysis of the gene products responsible for these pigmentary disorders. One of the most important players in melanosome transport is small GTPase Rab27, the deficiency of which causes type 2 human Griscelli syndrome. Rab27A first regulates actin-based melanosome transport through the formation of a tripartite protein complex composed of Rab27A, its specific effector Slac2-a/melanophilin, and the actin-based motor myosin Va. Rab27A then promotes melanosome anchoring to the plasma membrane through its interaction with another Rab27A effector, Slp2-a. The knockdown of Slac2-a and Slp2-a by specific siRNA causes the peri-nuclear aggregation of melanosomes and the peripheral dilution of melanosomes, respectively. Another small GTPase, Rab38, the deficiency of which causes pigment dilution in *chocolate* mice, is involved in the transport of the melanogenic enzyme Tyrp1 to melanosomes through an interaction with its effector Varp. The knockdown of Varp by specific siRNA causes Tyrp1 to disappear in melanosomes, and the amount of melanin pigment significantly decreases. These findings can be applied to drug screening to inhibit or stabilize the function of Slac2-a, Slp2-a, and/or Varp. Actually, coumaric acid, which promotes the degradation of Slp2-a in cultured melanocytes, has recently been shown to inhibit melanosome transport. Therefore, the regulation of melanosome transport is now thought to help keep the skin white.

Key words: Griscelli syndrome, melanogenic enzyme, melanosome, membrane traffic, Rab effector.