Regulation of skin pigmentation by interrupting melanosome transport and finding a novel function of Prohibitin on it

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Melanocytes are unique cells that produce specific melanin-containing intracellular organelles called melanosomes. Melanosomes are lysosome-related organelles specialized in melanin synthesis. The movement of melanosome was mediated by the formation of a Rab27a-Melanophilin-MyosinVa protein complex. Melanosomes are transported from the perinuclear area of melanocytes toward the plasma membrane as they become more melanized and finally transferred to keratinocyte. We screened several compounds which can affect melanosome transport in melanocytes. Using a pharmacophore modeling, we found a compound which inhibits the binding of Rab27a and Melanophilin. We also found some compounds which affect the expression of Rab27a, Melanophilin and MyosinVa from a cell-based screening. We showed that the regulation of these proteins can affect skin pigmentation from reconstituted skin or animal study.
These results showed that regulation of melanosome transport can be a good target for searching depigmenting agent.

Prohibitin (PHB, also known as PHB1 or BAP32), is a highly conserved 31kDa protein that expressed in many cellular compartments, such as mitochondria, nucleus, cytosol, and plasma membrane, and plays roles in regulating the transcription of genes, apoptosis, and mitochondrial biogenesis. There is a report that Prohibitin expression is required for the stimulation of pigmentation by melanogenin. However, no studies have been published on the function of PHB in melanocytes, especially in melanosome transport. We found that PHB is located in the melanosome and perinuclear aggregation of melanosome is induced when expression of PHB is reduced with no influence on melanin contents. PHB binds directly to Rab27a and Mlph but not Myosin-Va. Rab27a and Mlph bind to specific domains of PHB. Reduced expression of PHB led to the impaired binding affinity between Rab27a and Mlph. From these results, we found that PHB regulates melanosome transport by linking to Rab27a and Mlph in melanocytes. Targeting and regulating PHB not only manages pigmentation in melanocytes, but also controls hyperpigmentation in melanoma