Modulation of soluble Adenylyl Cyclase (sAC) as a Method of Altering Melanocyte Pigmentation

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Technology description

Pharmacologic soluble Adenylyl Cyclase (sAC) regulators have been identified as a new class in pigment modifying agents.

Technology Overview

Understanding how baseline pigmentation is controlled has numerous implications due to its significance from both a psychological and health-related stand point. To date knowledge regarding signaling pathways that control pigmentation have been limited to changes in gene expression . Melanin pigments are synthesized by melanocytes in specialized organelles called melanosomes. Melanin is classified into eumelanin and pheomelanin, which are made in eumelanosomes and pheomelanosomes, respectively.

While several key characteristics of the melanin pigment system such as identifying the enzymes needed for melanin synthesis have been well studied, several other questions remain unanswered, such as what controls the activity of these enzymes after melanosomes are formed?

Cyclic AMP (cAMP) is a key signaling molecule in the synthesis of melanin, and transmembrane adenylyl cyclases (tmACs) play a key role in melanogenesis. Melanosomal pH has been implicated in the formation and maturation of melanosomes and in maintaining the ratio of eumelanin to pheomelanin. However, the regulation of melanosomal pH by cAMP was unknown.

The inventor has found that sAC, a non-canonical source of cAMP, acts as a pH sensor. The loss of sAC activity or the use of sAC inhibitors, leads to elevated melanosomal pH levels, which in turn, leads to an increase in the synthesis of melanin. Thus, agents that can modulate the levels of sAC could be used to regulate melanin pigment levels.

Further exploration of sAC’ s role in melanogenesis may offer new mechanisms that control human skin pigmentation and skin cancer risk, and due to the similarity between melanosomes, lysosomes and other organelles, understanding how sAC regulates organelle pH has implications for other cells and tissues.

Topical treatment of mice with sAC inhibitors has been shown to increase pigmentation in the skin and hair. These results firmly establish a second cAMP-signaling pathway regulating pigmentation, in which the loss of sAC-specific cAMP increases melanin production.

Neuromelanin is a dark pigment found in the brain which is structurally related to melanin and is produced using similar mechanisms as the skin. Patients with Parkinson's disease have been shown to

have 50% the amount of neuromelanin in the substantia nigra part of the brain as compared to similar patients of their same age, but without Parkinson's. The death of neuromelanin-containing neurons in the brain have been linked to Parkinson's disease and also have been visualized in vivo with neuromelanin MRI. As it is believed that neuromlanin plays a vital role in preventing cell death in certain parts of the brain, the ability to increase levels of neuromelanin could be utilized for the treatment for Parkinson’ s disease.

Institution

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