Pigmentation plays a protective role against damage caused by ultraviolet (UV) irradiation. Humans with fair skin and light hair have a higher susceptibility to UV-induced DNA damage that can lead to the development of skin cancers. The melanocytes found in the skin and hair follicles depend on different signaling molecules for their proper development and pigment production. α-Melanocyte Stimulating Hormone (α-msh) binds to the Melanocortin 1 receptor (Mc1r) to regulate pigment production and the switch between eumelanin and pheomelanin. Lethal yellow mice (Ay) overexpress the agouti signaling protein, which inhibits the binding of α-msh, resulting in a yellow coat color phenotype. Endothelin 3 (Edn3) encodes for a ligand involved in melanocyte development by regulating the differentiation, proliferation and migration of melanocyte precursors. A tetracycline inducible transgenic mouse in which Edn3 was placed under the keratin 5 promoter (K5-tTA; TRE-Edn3-lacZ) displays a hyperpigmentation phenotype due to the accumulation of melanocytes in the skin and an increase in hair pigment. Comparative analysis of dorsal hairs from Ay and Ay; K5-tTA; TRE-Edn3-lacZ mice using high performance liquid chromatography showed that transgenic Edn3 expression significantly increased both eumelanin and pheomelanin. No significant difference in the number of follicular melanocytes between Edn3 transgenic and non-transgenic mice was evidenced by immunofluorescence using an antibody against Tyrosinase related protein 1. Gene expression analysis of hair follicles showed that Edn3 upregulates the expression of melanogenic genes. Deactivation of transgenic Edn3 is possible with doxycycline (dox) treatment. To test if transgenic Edn3 expression is required to rescue and maintain a dark pigmentation phenotype in Ay mice, dox was administered during embryonic and postnatal development to manipulate transgenic Edn3 expression. Results showed that transgenic Edn3 expression is required to maintain a dark pigmentation phenotype after birth but is independent of a developmental requirement. Transgenic Edn3 expression in Mc1r+/e mice also resulted in a darkened coat color. Our results indicate that the paracrine expression of Edn3 from keratinocytes is capable of generating and maintaining a dark coat color by the regulation of melanogenic genes independent of Mc1r signaling. The results of this study may open new approaches to the treatment of hypopigmentation disorders.

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