EFFECTS OF MELANOCORTINS (MSH) AND AGOUTI PROTEIN ON MELANOGENESIS IN B16 MELANOMA CELLS

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ABSTRACT

Two fundamentally different kinds of receptor binding molecules attach to melanocortin receptors (MC1R) of pigment cells to regulate the synthesis of either black or yellow melanin (eumelanogenesis or phaeomelanogenesis, respectively). Melanocyte Stimulating Hormone (MSH) acts as an agonist to stimulate while Agouti Protein (AP) acts antagonistically to inhibit cell signaling through the MC1R of pigment cells. The balance of these two peptides dictates whether black or yellow melanin is synthesized. Monoacetyl-alpha-Melanocyte Stimulating Hormone (monoac-αMSH), the melanogenically active MSH, is an acetylated form of the nonacetylated POMC-derived immature molecule - desacetyl-alpha-MSH (desac-αMSH). The lethal yellow mouse (Ay/a) exhibits yellow pigment synthesis and yellow hair. Excess AP and/or abnormal levels of desac-αMSH may be causal in the synthesis of yellow pigment.

We tested the hypothesis that desac-αMSH would induce a weak melanogenic response in B16 melanoma cells when compared to monoac-αMSH; if so, such a weakened response could result in yellow pigment synthesis. We also tested the hypothesis that AP acts antagonistically to monoac-αMSH; if so we would expect to see a graded decline in melanogenesis as AP is increased. B16 melanoma cells were cultured, treated with the three signaling peptides (two species of MSH and AP), harvested, and scored for parameters of cell signaling (synthesis of cyclic AMP) and melanogenesis—Tyrosine Hydroxylase (tritiated tyr assay) and Dopa Oxidase (Winder MBTH assay) activities of tyrosinase and total melanin (colorimetric assay) synthesis. Since desac-αMSH was comparable to monoac-αMSH in its ability to stimulate signaling and melanogenesis in all four assays, these data do not support the notion that an imbalance in the relative concentrations of the two species of αMSH is causal in the production of yellow coats in Ay/a mice. Furthermore, studies on the melanogenic effects of increasing concentrations of AP showed a dose-response effect, i.e., as the concentration of AP increased, melanogenesis decreased in a stepwise fashion. Melanogenesis in B16 melanoma cells is up-regulated by the agonists desac- and monoac-αMSH and downregulated by AP. Somehow, AP signals B16 cells by: 1) modulation of MC1R, 2) interaction with another receptor like an AP receptor, 3) promoting another kind of signaling mechanism, or 4) various combinations of 1-3 resulting ultimately in the down-regulation of melanogenesis.

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