Role of the Melanocortin 1 Receptor in the Response of Normal Human Melanocytes to Ultraviolet Rays.

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Background:
Normal human melanocytes respond to alpha-melanocyte stimulating hormone (alpha-MSH) with increased cAMP formation, proliferation, and stimulation of the activity of tyrosinase, the rate-limiting enzyme in the melanin synthetic pathway. alpha-MSH induces eumelanin synthesis, which is thought to confer photoprotection to the skin. alpha-MSH elicits its biological effects by binding to the melanocortin 1 receptor (MC1 R). Human melanocytes respond to irradiation with ultraviolet rays (UVR) with a dose-dependent increase in cell death and growth arrest. An increase in tyrosinase activity is only detectable when irradiated melanocytes are concomitantly treated with ?-MSH or any other cAMP inducer. Stimulation of cAMP formation by alpha-MSH also enables melanocytes to partially recover from the UVR-induced growth arrest.

Hypothesis:
We have investigated the hypothesis that activation of the MC1 R plays an important role in the response of human melanocytes to UVR.

Methods:
The dose-dependent responses of various melanocyte cultures to alpha-MSH or UVR were determined by measuring cAMP level, proliferation rate, and tyrosinase activity.

Results:
We compared the responses of 4 primary human melanocyte cultures, (NHM 1 - 4). We found that NHM1 and 2 responded to alpha-MSH with a dose-dependent increase in cAMP formation, tyrosinase activity and cell proliferation, beginning at a dose of 0.1 nM. NHM3 and 4 had a shift to the right in the dose-response curves in all three assays. When these four cultures were irradiated a single time with increasing doses of UVR (7, 14, or 21 mJ/cm2), no growth arrest was observed in response to the lowest dose of UVR and profound stimulation of proliferation, comparable to that observed in non-irradiated melanocytes, was observed following alpha-MSH treatment. Significant growth arrest was observed when cells were irradiated with 14 mJ/cm 2, and concomitant treatment with alpha-MSH increased the proliferation of NHM I and 2, but not NHM3 or 4. Irradiation with 21 mJ/cM2 resulted in extensive cell death, an effect that was most pronounced in NHM-3 and 4. In NHM-3, no stimulation of tyrosinase activity was observed following ?-MSH treatment of control or UV-irradiated melanocytes. Preliminary results of genetic analysis of the MC1R gene revealed point mutations in the coding region of the gene in NHM-3 and 4. The influence of these mutations on the extent of UV-induced DNA photoproducts in these cultures will be evaluated.