Protection of Human Melanocytes from UV-Induced Mutagenesis by Enodothelin-1 and Alpha Melanocortin Stimulating Hormone

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In the epidermis, melanin synthesis by melanocytes is a major protective mechanism against sun-induced damage. Epidermal melanocytes that are derived from embryonic neural crest are differentiated cells with a low proliferation capacity, and insuring their livelihood is vital for photoprotection. Ultraviolet radiation (UVR) causes DNA damage in melanocytes, which can lead to melanocyte cell death or to mutagenesis, leaving the skin more susceptible to photocarcinogenesis. Therefore, it is critical to reduce the damage placed on melanocytes by UVR. Skin cancer risk is in large part determined by the ability of epidermal cells to remove DNA damage, making it imperative to find ways to promote DNA repair in these cells. Numerous clinical and epidemiological studies have shown that the risk for skin cancer inversely correlates with skin pigmentation. The response of melanocytes to UVR is mediated by a variety of paracrine factors, two of which are α-melanocortin (α-MSH) and endothelin-1 (ET-1). Human melanocytes respond to these two factors with increased melanogenesis and survival. α-MSH and ET-1 play a critical role in the melanogenic (i.e. tanning) response to UVR, and inability to respond to α-MSH due to mutations in the melanocortin 1 receptor gene that codes for its receoptor is associated with inability to tan and increased risk for skin cancer. We hypothesized that ET-1 and a-MSH promote the survival of epidermal melanocytes by limiting UVR-induced DNA damage. To test our hypothesis, we utilized the southwestern DNA blot technique to determine the induction and repair of cyclopyrimidine dimers (CPD) and 6-4 photoproducts in multiple primary human melanocyte cultures derived from donors with different pigmentary phenotypes, in the absence or presence of a-MSH and ET-1. These experiments confirmed that UVR induces the formation of DNA photoproducts in a dose-dependent fashion, and showed that a-MSH enhances the repair of CPD, as evidenced by faster removal of these photoproducts within 24 h after irradiation with UVR. At the dose of 0.1 nM ET-1, we did not detect any effect on induction or repair of CPD. Further experiments are needed to elucidate the effects of higher concentrations of ET-1 on DNA repair in human melanocytes. Our results demonstrate the importance of a-MSH in maintenance of genomic stability of human melanocytes and reducing the chance for melanoma formation. Additionally, these results offer an explanation for the increased risk of skin cancer, mainly melanoma, in individuals that express loss of function mutations in the melanocortin 1 receptor.