

The role of the cAMP signaling pathway activated by the melanocortin 1 receptor in the DNA damage response of human melanocytes to UV

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Background

Melanoma is one of the deadliest cancers accounting for an estimated 10,000 deaths each transformation of melanocytes. Exposure to UV leads to DNA damage, mainly in the form of the DNA photoproducts, cyclobutane pyrimidine dimers (CPDs). If UV-induced DNA damage in melanocytes is not repaired, mutations occur that can lead to melanoma. Human melanocytes express the melanocortin 1 receptor (MC1R), a membrane bound G_s protein-coupled receptor. Activation of the MC1R by its agonist α -melanocyte stimulating hormone (α -MSH) activates the cyclic-AMP (cAMP) pathway and stimulates DNA repair, hence preventing malignant transformation of melanocytes.

Hypothesis

In this study, we tested the hypothesis that MC1R and its signaling pathway enhances DNA repair by activation of the key DNA damage sensor ATM, which activates downstream stress-induced MAP kinases, JNK and p38, and eventually the tumor suppressor p53.

Methods

To test our hypothesis, human melanocytes cultured from neonatal foreskins were irradiated with UV, and then treated with 0 (Control), α -MSH alone, or α -MSH in combination with agouti signalling protein (ASIP), the physiological antagonist of MC1R, or with H89, an inhibitor of the cAMP-dependent protein kinase A (PKA). Proteins were extracted at three time points after UV exposure, and Western blot analysis was carried out to detect the phosphorylation (activation) of ATM, JNK, p38 and p53. We also tested the effect of inhibiting PKA on the α -MSH-induced enhancement of CPD repair in UV-irradiated melanocytes.

Results

Our findings show increased phosphorylation of ATM, JNK, p38 and p53 in response to UV exposure, and augmentation of this effect with α -MSH treatment. Potentiation of the effect of UV by α -MSH was inhibited by combined treatment with either ASIP or H89. Treatment with H89 also inhibited the enhancement of CPD repair by α -MSH.

Conclusion

These results demonstrate that activation of the MC1R by α -MSH modulates the DNA damage response of melanocytes to UV by enhancing the activation of ATM and its downstream targets p38 and JNK and p53. The inhibitory effects of ASIP and H89 on these effects of α -MSH, and inhibition of the effect of α -MSH on CPD repair provide evidence for the significance of activation of the MC1R by α -MSH and the cAMP pathway in promoting the DNA damage response of melanocytes to UV.

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