Title
Cobalt and copper are candidates as co-carcinogens in the pathogenesis of cutaneous melanoma

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Authors
Meyskens, FL
Yang, S
Farmer, PJ
et al.

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The 3,3,4,4,5,5-hexahydroxystilbene impairs melanoma progression in a metastatic mouse model

Melanin is a complex biopolymer synthesized in organelles called melanosomes that are critically involved in the regulation of proliferation, apoptosis and tumor cell migration. In our recently established, spontaneously metastatic human melanoma SCID mouse model, we demonstrate that M8 significantly impairs tumor growth, inhibits cell proliferation and induces apoptosis in a dose dependent manner. Furthermore, mice treated with M8 showed less metastasis to distant lymph nodes compared to littermates receiving solvent. Podoplanin labeling reveals reduced perilymphatic vascular density in M8 treated mice. In conclusion, M8 exerts pronounced antiproliferative effects on melanoma cells through the induction of apoptosis and cell cycle arrest at the G2/M boundary. Furthermore, the M8 mediated inhibition of melanoma metastasis to distant lymph nodes appears to be achieved through diminution of tumor-associated lymphatic vessels. Our data indicate that M8 is a novel and potent approach for the treatment of melanoma.

Identification of novel small molecule inducers of melanin production

Activating mutations of the oncoproteins BRAF (V600E) or NRAS (Q61R) are commonly found in malignant melanomas. Intriguingly, the same genetic changes and often at higher rates are detected in benign nevi composed mostly of senescent melanocytes. We have previously shown that in normal melanocytes ectopic expression of BRAF600E and NRAS61R induces different types of stress responses ultimately leading to the activation of cellular senescence. How oncogene-mediated senescence is overcome during melanoma genesis, and whether aggressive melanoma cells retain the ability to undergo senescence is unclear. Here we report that shRNA-mediated inhibition of C-MYC in several BrafV600E- or Nras(Q61R)-expressing tumor-derived melanoma cell lines resulted in permanent growth inhibition accompanied by activation of senescence-associated β-galactosidase and formation of senescence-associated heterochromatin foci. Cell morphology of MYC-depleted BrafV600E- or Nras(Q61R)-expressing melanoma cells closely resembled that of normal melanocytes undergoing senescence induced by BRAFV600E or NRAS(Q61R), respectively. Additionally, senescing melanocytes overexpressing either of the above oncoproteins demonstrate gradual reduction in C-MYC mRNA and protein levels. Reciprocally, overexpression of C-MYC in normal melanocytes, as well as in the cell lines obtained from patients with melanoma, results in reduced expression of C-MYC. Cell cycle analysis of M8 treated cells showed a decrease in the percentage of cells in S phase and an increase in the percentage of cells in G1. Furthermore, western blotting of M8 treated cells revealed a decrease in the levels of cyclin D1 and cyclin E, whereas the levels of cyclin A and cyclin B were unchanged. In conclusion, these results suggest that C-MYC is an important regulator of senescence and that the inhibition of C-MYC may be a viable strategy for the treatment of melanoma.

C-MYC controls senescence in melanoma cells

BMP-4 regulation of MITF expression in cultured human melanocytes

The 3,3,4,4,5,5-hexahydroxystilbene impairs melanoma progression in a metastatic mouse model

BMP-4, a member of the TGF-β superfamily, is critical for melanocyte differentiation and melanogenesis. BMP-4 expression is upregulated in melanoma cells and is associated with an increased melanin production. In vitro, BMP-4 significantly increases melanin production, whereas in vivo, BMP-4 has been shown to reduce tumor growth. However, the underlying mechanisms by which BMP-4 regulates melanin production are not well understood. In this study, we investigated the effects of BMP-4 on melanin production and MITF expression in human melanocytes. Our results showed that BMP-4 significantly increased melanin production and MITF expression in human melanocytes. These findings suggest that BMP-4 may be a potential target for the treatment of melanoma.

Identification of novel small molecule inducers of melanin production

ABSTRACTS

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