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Possible mechanisms and rankings for agents screened in the Human Cell Melanoma Prevention Assay.

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Abstract

Alterations to the tissue microenvironment appear to play a critical role in the initial stages of melanocyte to melanoma transition, the development of invasive potential, and the resistance to therapy (Postovit et al., Cancer Res, 66:7833, 2006). Given the importance of the E-cadherin/N-cadherin homeostatic tissue control of melanocyte growth and differentiation and the E-cadherin to N-cadherin switch that is found in the conversion from normal to metastatic melanoma, the interplay of the two endpoints may be relevant for identifying possible melanoma prevention activity. We have developed a melanoma chemoprevention assay based on this cadherin switch using human radial growth melanoma cells. The four endpoints examined were: induction of annexin V (apoptosis), induction of HLA-ABC, cell surface expression of E-cadherin, and N-cadherin. Only limited responses were observed with the annexin V and HLA-ABC endpoints; however, the cadherin endpoints appear to be informative. We screened eleven potential melanoma preventive agents that represent a broad range of mechanistic classes using this assay. E-Cadherin expression was enhanced for nine of eleven agents. The induced E-cadherin expression levels exceeded those found in the no UV/no drug control cells for four of the nine positive agents. Atorvastatin showed the greatest efficacy for this endpoint. An inhibition of N-Cadherin was produced by four of eleven agents: atorvastatin, Lovastatin, rosiglitazone maleate, and Verapamil. With the exception of Verapamil, these agents inhibited cell surface N-cadherin expression at six or more concentrations. The potential melanoma prevention efficacies for the more potent agents were ranked as follows: rosiglitazone maleate > atorvastatin > Lovastatin > Rapamycin, gemfibrozil. Each of these agents was active at concentrations that are clinically achievable. Supported by NCI contract #N01-CN-43300.

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