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initiation and/or obviating the later pathogenesis of melanoma will be presented.

ES10-1 Antioxidants and redox-active metals in the epigenetic pathogenesis of cutaneous melanoma: epidemiologic and experimental evidence

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Our studies of the role of ROS and transcriptional response to redox stress in melanoma leads us to reconsider the role of UV, metals and antioxidants in the pathogenic process. An exploration of the role of melanin using EPR and other techniques by our labs suggests that it is converted from anti-oxidant to pro-oxidant early in pathogenesis which leads to melanosomal damage that serves as ongoing nidus for ROS generation. The involvement of redox-active metals is critical and in combination with UV leads normal melanocytes in vitro to resemble dysplastic melanocytes. A rethinking of the biological basis of the observation that severe sunburns early in life are dose-response predictors of risk for melanoma later in life raises the possibility that release of photolabile iron from Hgb and its binding to melanin with the onset of low-grade redox cycling may be at the root of this epidemiologic(EPI) observation. A re-examination of the epigenetic risk factors for melanoma has identified a large EPI that implicates heavy metal exposure, including markedly increased risks for melanoma in printers/lithographers, electrical industry workers, and hip replacements patients. Clinical imaging studies and two large studies that document the adverse effect of metallothionein expression on the outcome of primary melanoma offers ancillary support. Several EPI studies suggest a protective role of diet antioxidants(RR, 0.70) and an adverse effect of alcohol (RR, 2.5). These considerations, the role of copper in melanin synthesis, and the binding characteristics of metals to melanin, we propose that Fe^{+3} , Fe^{+2} , Cu^{+2} , and Cr^{+6} either alone or with UVL contribute significantly to the pathogenesis of melanoma. The potential for metal chelators and antioxidants as interventions by blocking the etiologic