Acute and chronic effects of ultraviolet irradiation on neonatal Tyr-Hras ink4a/Arf mice

William H. Tolleson, Paul C. Howard, Anna A. Shvedova, Elena R. Kisin, Ashley R. Murray, Jason C. Doss, Alan R. Warbritton, Letha H. Couch, William B. Melchior Jr and Lynda Chin
DOI: Published May 2005

Proc Amer Assoc Cancer Res, Volume 46, 2005

Abstract 4766

Chronic exposure to ultraviolet (UV) radiation is associated with increased risk for nonmelanoma skin cancers. The links between acute UV exposures, oxidative stress, and DNA damage have been studied extensively. However, the connection between UV exposure and increased risk for cutaneous melanoma is more complex. Some epidemiological results have identified a correlation between UV exposure and increased risk of cutaneous melanoma. Furthermore, weakly pigmented individuals exhibit higher risks for cutaneous melanoma. But "UV signature mutations," a hallmark of photo-induced nonmelanoma skin cancers, are not typically observed in cutaneous melanoma. Recently, emphasis has been placed on the possibility that intense, short-term photo-exposures prior to adulthood may increase the risk for cutaneous melanoma later in life. Inactivation of the overlapping p16ink4a and p19Arf tumor suppressor genes is frequently detected in human cutaneous melanomas. In the presence of homozygous ink4a/Arf deletions, 50% of transgenic mice expressing the H-ras oncogene controlled by the human tyrosinase promoter (Tyr-Hras) develop spontaneous cutaneous melanoma by 6 months, approximately 5-fold more frequently than in ink4a/Arf heterozygotes. We exposed the dorsal skin surfaces of Tyr-Hras ink4a/Arf+/– neonatal mice to daily treatments with UVA+UVB radiation (0.0, 1.0, 2.0, 3.0 J/cm^2) administered on postnatal days (PND) 3-7 using a fluorescent UV lamp assembly and passed through a layer of cellulose acetate film to remove UVC. UV dose-dependent increases were detected in edema, inflammation, apoptotic cells, epidermal necrosis, accumulation of pyrimidine dimers, and thiobarbituic acid reactive substances (TBARS). There were also dose-dependent decreases in antioxidant reserve, glutathione levels, and protein thiols. Additional mice exposed to 0.0, 1.0, or 2.0 J/cm^2 UVA+UVB daily on PND3 - PND7 were monitored for 12 months. A UV-dependent earlier onset of skin lesions was revealed by Kaplan-Meier analysis, supporting the hypothesis that moderate or severe childhood or adolescent sunburns increases the risk for cutaneous melanoma.

- American Association for Cancer Research