Exposure to solar ultraviolet (UV) light is a risk factor for the induction of melanoma, but the precise mechanism remains unclear. The increased incidence of the disease in xeroderma pigmentosum patients, whose cells cannot repair DNA damage caused by defects in nucleotide excision repair, demonstrates that UV-induced DNA damage and mutagenesis can play a role in melanoma. I propose, therefore, that solar exposure in the UVA and UVB range produces a mixture of DNA photoproducts, some being typical pyrimidine dimers and others the result of photosensitizing reactions with melanin precursors that produce DNA damage that requires the nucleotide excision repair or base excision repair pathways. Not all of these damages necessarily produce typical UV-specific mutations in target genes; the association of melanoma induction with acute burns suggests that high UV doses can overwhelm intracellular antioxidant defense mechanisms to produce DNA damage. The progression of melanomas is additionally enhanced by early deletions involving one or more of the nucleotide excision repair (NER) genes that leads to enhanced genomic instability.

Key Words: Ultraviolet (UV) light; DNA damage; DNA repair; nucleotide excision repair; transcription-coupled repair; base excision repair; excision; polymerase; low fidelity; mutation.
INTRODUCTION AND HYPOTHESIS

The incidence of melanoma has been increasing worldwide over many decades \(^1\). The reasons for the increased incidence of melanoma are varied, and include increased ultraviolet (UV) exposure, changing leisure activities, change in clothing, environmental factors, and changes in the histological criteria for diagnosing melanoma \(^2\). The role of sun exposure in melanoma induction remains difficult to explain in molecular detail. Melanoma develops from the malignant transformation of melanocytes located in the epidermis, dermis, or mucosa, often occurring in pigmented nevi rather than in isolated melanocytes. Several important genes that act at early stages of melanoma induction have been identified, including \(p16\) and \(B-RAF\). However, the precise molecular mechanisms that result in mutagenesis of these genes is still a mystery. Excessive sun exposure may predispose a susceptible individual to the development of melanoma, but the link between UV exposure and melanoma is not as strong as in squamous cell carcinomas, in which p53 mutations with a UV signature are seen \(^3\). Evidence is strong in studies with the marsupial, \(Monodelphis\), and the platyfish, \(Xiphophorus\), that typical UV photoproducts can initiate melanomas \(^4,5\). Recently developed mouse models also demonstrate that neonatal UV exposure can cause melanoma development \(^6–8\). Some of these studies also indicate that the wavelengths for melanoma induction can involve longer UVA wavelengths than for nonmelanoma skin cancers \(^9\). Intermittent exposure and exposure in an individual’s early years apparently play a greater role than chronic exposure or exposures in later life. For example, the greatest increases in incidence of melanomas are seen on the lower extremities in women and the trunk in men \(^2\). Severe sunburns in childhood or sun exposure in sunny locales during childhood also increase the risk of melanoma \(^10,11\). Melanomas are also more common in light-skinned individuals, particularly those with red or blond hair who freckle easily \(^12,13\). There is an association between the risk of developing melanoma and having specific mutations in the melanocortin-1 receptor \(^12\), which plays a key role in determining the type of melanin produced in melanocytes, eumelanin or pheomelanin. One of the stronger examples of a major role for UVB exposure in melanoma is the increased incidence of the disease in xeroderma pigmentosum (XP) patients who cannot repair UVB damage because of defects in nucleotide excision repair (NER) \(^14\). However, even here, the distribution of melanomas over the body resembles that in the normal population, and is not on the commonly exposed regions of the skin. Taken together, these data suggest that UV does indeed play a role in the development of melanoma, although its exact role is not completely understood. Therefore, I propose the following simple, testable hypothesis for the role of solar exposure in melanoma induction: solar exposure in the UVA and UVB range produces a mixture of DNA photoproducts, some being typical pyrimidine dimers and others the result of photosensitizing reactions with melanin precursors that produce DNA damage that requires the NER or base excision repair (BER) pathways. Not all of these damages necessarily produce typical UV-specific mutations in target genes; the association of melanoma induction with acute burns suggests that high UV doses are required to overwhelm intracellular antioxidant defense mechanisms. The progression of melanomas is additionally enhanced by early deletions involving one or more of the NER genes that leads to enhanced genomic instability.

This chapter will expand on this hypothesis and will discuss various mechanisms of DNA damage and repair and evidence from XP and other animal models for the induction of melanoma by solar exposure.