Ultraviolet damage, DNA repair and vitamin D in nonmelanoma skin cancer and in malignant melanoma: an update.

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Abstract

Skin exposure with UV radiation (UV) is the main cause of skin cancer development. Epidemiological data indicate that excessive or cumulative UV exposure takes place years and decades before the resulting malignancies arise. The most important defense mechanisms that protect human skin against UV radiation involve melanin synthesis and active repair mechanisms. DNA is the major target of direct or indirect UV-induced cellular damage. Low pigmentation capacity in white Caucasians and rare congenital defects in DNA repair are mainly responsible for protection failures. The important function of nucleotide excision DNA repair (NER) to protect against skin cancer becomes obvious by the rare genetic disease xeroderma pigmentosum, in which diverse NER genes are mutated. In animal models, it has been demonstrated that UVB is more effective to induce skin cancer than UVA. UV-induced DNA photoproducts are able to cause specific mutations (UV-signature) in susceptible genes for squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). In SCC development, UV-signature mutations in the p53 tumor suppressor gene are the most common event, as precancerous lesions reveal ~80% and SCCs > 90% UV-specific p53 mutations. Mutations in Hedgehog pathway related genes, especially PTCH1, are well known to represent the most significant pathogenic event in BCC. However, specific UV-induced mutations can be found only in ~50% of sporadic BCCs. Thus, cumulative UVB radiation cannot be considered to represent the only etiologic risk factor for BCC development. During the last decades, experimental animal models, including genetically engineered mice, the Xiphophorus hybrid fish, the South American oppossum and human skin xenografts, have further elucidated the important role of the DNA repair system in the multi-step process of UV-induced melanomagenesis. An increasing body of evidence now indicates that nucleotide excision repair is not the only DNA repair pathway that is involved in UV-induced tumorigenesis of melanoma and nonmelanoma skin cancer. An interesting new perspective in DNA damage and repair research lies in the participation of mammalian mismatch repair (MMR) in UV damage correction. As MMR enzyme hMSH2 displays a p53 target gene, is induced by UVB radiation and is involved in NER pathways, studies have now been initiated to elucidate the physiological and pathophysiological role of MMR in malignant melanoma and nonmelanoma skin cancer development. Interestingly, increasing evidence now demonstrates an important function of the vitamin D endocrine system (VDES) for prevention of BCC, SCC and melanoma, identifying the vitamin D receptor as a tumor suppressor in the skin.
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