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EDITORIAL

Sunlight and skin cancer

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It is well known that chronic exposure to ultraviolet (UV) radiation present in sunlight is responsible for the induction of most nonmelanoma skin cancer (NMSC) in humans. Wavelengths in the UV-B (290–320 nm) region of the solar spectrum are absorbed into the skin, producing erythema, burns, and eventually skin cancer. NMSC is the most common type of human cancer. Recent surveys indicate that around one million new cases of skin cancer are diagnosed each year in the United States, about 70% of which result from repeated exposure of the skin to sunlight. Laboratory studies have shown that UV-B region of the solar spectrum is responsible for this effect. The first step in UV skin carcinogenesis involves the induction of DNA damage. Occasional mistakes during the repair of this damage leads to the incorporation of wrong bases into the genetic material. The DNA damage that is left unrepaired may also disrupt cellular processes by obstructing the DNA and RNA synthesizing machineries and introduce wrong bases into the DNA. These types of mistakes often result in mutation leading to loss or inappropriate expression of affected genes. Recent studies indicate that genetic alterations in the *p53* tumor suppressor gene play an important role in the development of skin cancer. The p53 protein is also involved in programmed cell death (apoptosis), and it has been proposed that p53 serves as a "guardian of the genome" by aiding DNA repair or causing elimination of cells with excessive DNA damage. Unrepaired photoproducts in the *p53* gene are transformed into mutations thereby initiating the process of carcinogenesis. Following repeated exposures to UV, keratinocytes carrying *p53* mutations acquire a growth advantage by virtue of their increased resistance to apoptosis. Recent studies have shown that UV-B damaged keratinocytes (sunburn cells) are eliminated by Fas/Fas-ligand interaction and that this pathway is dysregulated during UV skin carcinogenesis resulting in accumulation of *p53* mutations in DNA damaged keratinocytes. These results demonstrate a link between *p53* pathway and Fas/Fas-ligand pathway and that dysregulation of both pathways can lead to the pathogenesis of UV-induced skin cancer.

Several studies have shown that UV induces unique types of *p53* mutations in skin cancers at a high frequency that are not commonly found in other types of human cancer. Analogous to human skin cancers, skin cancers induced in laboratory mice by UV radiation also display UV signature *p53* mutations at a high frequency. More interestingly, *p53* mutations are also present in sun-exposed skin and it can serve as an indicator of prior solar exposure in humans. It has been shown that *p53* mutations in mouse skin arise as early as one week of chronic UV-irradiation and the frequency of *p53* mutations reach a maximum at 4–8 week of UV exposure. These results suggest that *p53* mutations arise well before skin cancer development and that they can serve as a surrogate early biological endpoint in skin cancer prevention studies. In fact, it has been shown that application of SPF-15 sunscreens to mouse skin before each UV-irradiation protect mice against induction of *p53* mutations as well as skin cancer development.

In addition to the *p53* gene, another tumor suppressor gene known as *patched (ptc)* has been implicated in nevoid basal cell carcinoma syndrome (NBCCS). NBCCS, also called basal cell nevus syndrome or Gorlin's syndrome, is a rare autosomal dominant disorder characterized by multiple BCCs that appear at a young age on sun-exposed areas of the skin. Studies of NBCCS patients have shown that they have both germ-line and somatic mutations in the *ptc* gene. Somatic *ptc* mutations have been found in BCCs from otherwise normal individuals suggesting that genetic alterations in the *ptc* gene may also play a role in the development of BCC.

In summary, recent advances have aided in the understanding of the mechanisms by which UV radiation induces skin cancer. Continued efforts should result in a greater understanding of the genetic mechanisms involved in the function of tumor suppressor and oncogenes that are now known, as well as genes yet to be discovered. The efforts of research in skin cancer may help to increase overall awareness of the harmful effects of UV exposure and result in better methods of skin cancer prevention and treatment.

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