Although it is widely accepted that exposure to UV radiation contributes to the initiation of skin cancers, mechanisms of tumorigenesis and development are not fully understood. Inflammatory and immune responses have been implicated. Research has elucidated a complex and comprehensive local response to UV exposure that culminates in modulation of an immune response in the skin. Studies have shown that UV-irradiated keratinocytes secrete IL-1, IL-6, IL-10, IL-12, TNF-α, prostaglandin E2 and other immune mediators and have even found some of these mediators in the serum of mice exposed to UV radiation. This latter finding supports the existence of a systemic immune response to UV radiation. Recent research further supports an immunomodulatory effect of UV irradiation by showing that it can influence apoptosis of peripheral blood mononuclear cells.

**Backgrounder:**

**Apoptosis and Carcinogenesis**

Apoptosis has been implicated in tumor proliferation but has also been implicated in the body’s natural defenses against cancer. As described by Raj, et al., apoptosis can defend against cutaneous cancers by eliminating cells in the upper epidermis with pre-malignant genetic alterations. Alternatively, apoptosis can arise in direct response to exposure to carcinogenic stimuli. Zhivotovsky and Orrenius’ provide a comprehensive overview of the role of apoptosis in carcinogenesis, highlighting an important development that occurred more than three decades ago when researchers noted that apoptosis may be more important for tumor growth than is mitosis. Today, research into cancer therapies includes extensive study of apoptosis with emphasis on uncovering methods to harness the process to combat tumors.

Among stimuli shown to influence apoptosis is UV radiation. Previous research has investigated the pro- and anti-apoptotic response of keratinocytes to UV exposure; UVB (290-320nm) exposure is the most extensively studied apoptosis inducer in keratinocytes, according to Raj, et al. So-called sunburn cells (UVB-exposed dyskeratotic keratinocytes with condensed or absent nuclei and eosinophilic cytoplasm) are in the process of UVB-induced apoptosis. Data show that other UV wavelengths may also induce KC apoptosis: as energy increases or wavelength decreases, the rate of apoptosis climbs.

The evidence seems to clearly support a connection between UV irradiation and keratinocyte apoptosis, but the relationship between exposure to radiation, keratinocyte apoptosis, and skin cancer formation and proliferation is less obvious. Among theories to explain the inter-relationship is the suggestion that apoptosis of normal keratinocytes clears space for clonal expansion. UV-induced apoptosis may also encourage the proliferation of p53 mutant genes.

**“Distant” Apoptosis and UVB**

Local cutaneous effects of skin exposure to UVB have been implicated in genetic mutations and apoptosis, which may contribute to development of SCC and BCC. Researchers have now shown that UVB irradiation can modulate apoptosis of peripheral blood mononuclear cells, suggesting an additional mechanism for UV-induction of tumor formation and growth.

Earlier research had shown that UV-irradiation—particularly at erythemogenic doses—influences serum cytokines, and there is some evidence that sub-erythemogenic doses also modulate cytokines. Narbutt, et al. randomized a cohort of 105 healthy volunteers with Fitzpatrick skin types II or III to undergo exposure to UVB at different dosages and durations: A. Whole-body irradiation at 0.7UVB MED for 10 consecutive days; B. Same protocol for group A with the addition of a single UVB exposure at 3MED; C. Irradiation with solar-simulated radiation (SSR) at 1.2SED (Standard erythema dose) to the buttock for 10 consecutive days followed by a single UVB exposure at 3MED; D. Irradiation with a single dose of 3UVB MED to buttock. Serum levels of various cytokines were measured before and after irradiation.

There was a statistically significant increase in IL-8 serum level in groups A and B at day 10 with no influence from the additional dose in group B; there was a slight but statistically significant increase in TNF-α serum levels in groups A and B at day 10. There was a trend toward increased IL-10 levels in
apoptotic, whereas Bax is pro-apoptotic. Using a protocol similar to that of their earlier study, the team randomized 98 healthy volunteers into four groups: A. Whole-body irradiation at 0.7UVB MED for 10 consecutive days plus a single UVB exposure at 3MED; B. Whole body irradiation with solar-simulated radiation for 10 consecutive days plus a single UVB exposure at 3MED; C. Single dose of 3MED on a discreet body area; D. Single dose of 4MED on a discreet body area.

Results showed that 10 consecutive days of UVB or SSR irradiation increased the apoptosis of peripheral blood mononuclear cells, although no single dose (even that given following a 10-day exposure cycle) affected apoptosis. Researchers identified an increase in Bax and p73 protein expression and down regulation of Mcl-1 and Bcl-2, which correlated with apoptosis.

The Bcl family of proteins are anti-apoptotic, whereas Bax is pro-apoptotic. P73 is also apoptotic, particularly against tumors, and is actually a target of cancer therapy development.

Putting it Together
Researchers and clinicians alike still have much to learn about the enigma of apoptosis, which paradoxically may be both a cause of and a treatment for cancer. The effects of UV irradiation on the skin and its contribution to tumorigenesis also remains rife for further investigation. Of note, much of the research on apoptosis has been limited to murine models, as Raj, et al. note, but human keratinocytes have been shown to be more susceptible to UV- and drug-induced apoptosis.

Despite gaps in our knowledge regarding the particulars, the evidence from current and past research suggests that cumulative UV exposure, even at sub-MED doses, produces local effects on irradiated skin and also confers systemic effects. Among these inflammatory and immunomodulatory effects is apoptosis. The current Narbutt study7 confirms apoptosis of peripheral blood monoclonal cells but was not intended to explore the effects of cell death. Whether UV-induced systemic apoptosis contributes directly to tumorigenesis or if it indirectly supports tumorigenesis through down-regulation of immune response and/or increasing inflammation remains to be determined. Perhaps multiple actions are present.

The bottom line for patients and the dermatologists who treat them is to recognize that UV exposure unquestionably has local cutaneous as well as systemic effects that can be detrimental to the body. Avoidance of UV exposure, through practice of sun avoidance and use of appropriate sunscreens, is crucial. Clinicians should continue to keep abreast of developments in cancer therapeutics, particularly those related to the therapeutic targeting of apoptosis.

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