

Opioid-mediated immunosuppression as a novel mechanism for the immunomodulatory effect of ultraviolet radiation

Sir,
The suppressive effect of ultraviolet (UV) radiation on

the immune system has been harnessed elegantly in the treatment of many dermatological disorders. Several pathways for UV-induced immune suppression are suggested.

UV light induces the release of immunosuppressive cytokines from keratinocytes and immunocytes.^[1] It inhibits antigen presentation of the antigen-presenting cells through suppression of the expression of major histocompatibility complex II and other costimulatory molecules.^[1] UV light causes apoptosis of leukocytes and induces regulatory T cells with suppressor activity.^[1] UV radiation converts trans-urocanic acid into cis-urocanic acid, which exerts immunosuppressive effects.^[1] UVB-induced DNA damage is another major molecular trigger of UV-mediated immunosuppression.^[1] Herein, we would like to shed further light on UV-induced immunosuppression by providing a novel mechanism.

When given a blinded choice between UV and non-UV-emitting tanning beds, frequent tanners overwhelmingly prefer UV beds.^[2] A non-UV-emitting tanning bed is similar to a UV-emitting bed except that it has a filter that is opaque to the UV light.^[2] A questionnaire testing shows that frequent tanning has features of an addictive behavior.^[3] Despite the presence of some controversies, research shows that UV radiation can induce endorphin production by keratinocytes, which may explain the addiction to tanning seen in frequent tanners.^[4] Moreover, in a recent study on a group of frequent tanners, naltrexone, an endorphin antagonist, induced the withdrawal symptoms in frequent tanners while such symptoms were not observed with placebo or with infrequent tanners receiving naltrexone.^[5]

Opioids exert several immunosuppressive effects. Injection of morphine to vertebrate animals resulted in deficient macrophage function.^[6] Morphine antagonizes interleukin-1 α (IL-1 α) and tumor necrosis factor- α (TNF- α) induced chemotaxis in human leukocytes.^[6] It upregulates neutral endopeptidase in granulocytes.^[6] Neutral endopeptidase is an important control factor for the inflammatory responses in skin disorders. Morphine treatment increases IL-4 and IL-5 levels and decreases the IL-2 and interferon- γ (IFN- γ) levels.^[7] Therefore, by promoting the production of pro-T-helper-2 (Th2) cytokines and inhibition of pro-Th1 cytokines, it causes committing Th0 cell to a Th2 phenotype, with the resultant impairment of cellular immunity.^[7]

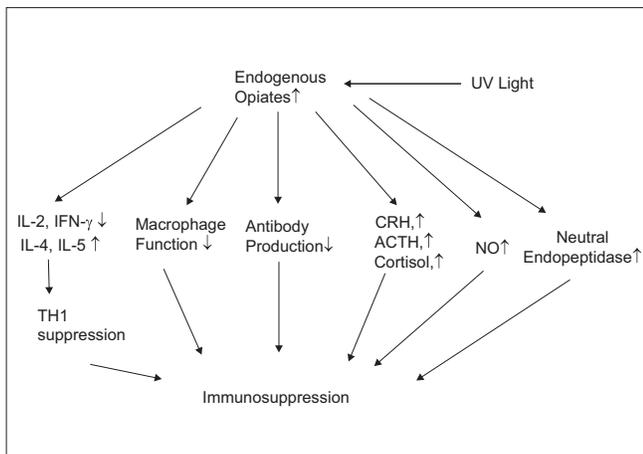


Figure 1: Mechanisms of immunosuppression induced by ultraviolet-released endogenous opioids

Morphine inhibits the expression of antigenic markers for T-helper cells and also the respiratory burst of these cells.^[6] This drug suppresses antibody production in response to the T cell-dependent antigens.^[6] It also leads to elevated plasma levels of corticotropin-releasing hormone (CRH), adrenocorticotrophic hormone (ACTH) and glucocorticoids.^[6] Therefore, through suppression of the immune system, morphine increases the susceptibility to various types of opportunistic infections.^[6]

A functional relationship between endogenous opiates and the immune system is based on the demonstration of special opiate receptors (μ_3) on immune cells, which enables these compounds to directly inhibit the immune activities.^[6] Under stressful conditions, endogenous morphine helps other immunosuppressive compounds such as ACTH and IL-10 to lower the hyperstimulation of stimulatory molecules such as IL-1 and TNF- α .^[6] Morphine stimulation by μ_3 leads to nitric oxide (NO) release.^[6] Basal unstimulated NO is released in the body to oppose the pro-inflammatory state and to downregulate immunocytes.^[6] Morphine may enhance this inhibitory state by enhancing the normal basal actions of NO.^[6]

In short, given the immunomodulatory effects of opioids, we suggest that a part of UV-induced immunosuppression occurs through the release of endogenous opiates [Figure 1]. Therefore, we conclude that topical opioid antagonists could serve as a novel class of protective agents against UV-induced skin cancers and their addition to the popular cancer preventive agents could provide a better protective effect.

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