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Dermatol Clin 24 (2006) 19 – 25

DERMATOLOGIC
CLINICS

Ultraviolet Immunosuppression: Mechanisms and Consequences

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Sun exposure and its effects on cutaneous immunity integrate a complex network of biologic processes. An immune response, such as contact hypersensitivity (CHS), requires a coordinated series of molecular and cellular events in multiple organs. Sun damage alters many of the key pathways involved in generating an appropriate immune response to an antigen. These modifications take place at various points from the absorption of ultraviolet (UV) radiation by specific chromophores in the skin to the generation and action of effector cells that lead to the observed clinical CHS response. Evaluation of skin immune responsiveness is therefore an excellent short-term surrogate for long-term consequences of sun exposure, such as immune suppression and skin cancer risk. Moreover, intervention strategies such as the use of sunscreens, aimed at preventing these adverse effects of solar radiation, may be tested via their effects on cutaneous immunity (Fig. 1).

Key elements of utraviolet immune suppression

Antigen-presenting cells

Epidermal Langerhans cells (LCs) are the principal antigen-presenting cells (APCs) in the skin. They have an extensive network of dendrites reaching up to the stratum corneum to detect and recognize foreign antigens that contact the epidermal surface. They comprise the major immune surveillance network of the skin. Often described as sentinels of the cutaneous immune system, these cells first encounter antigens, whether in the form of infectious agents, contact allergens, or tumor antigens. LCs take up and process the antigen, recoil their dendrites, and migrate through the skin and afferent lymphatics to the regional draining lymph node. Through antigen processing, LCs gain functional maturity marked by expression of class II major histocompatibility complex (MHC) and costimulatory molecules (B7-1 and -2) on their surface. In the lymph node, mature LCs efficiently present antigen on class II MHC to $CD4^+$ T lymphocytes. On re-exposure, the activated T cells are then capable of producing an antigen-specific immune response. Cutaneous immunity depends on proper functioning of LCs. Exposure to UVB radiation (280–320 nm) has been shown to alter LC number, morphology, and antigen-presenting function [1]. Within hours of UV exposure, LCs begin migrating from the irradiated epidermis, without the functional maturity to mount an immune response. In response to foreign antigen, UV-irradiated LCs fail to stimulate T-helper (Th)1 cells but preferentially activate Th2 cells, resulting in increased generation of suppressor T cells [2]. Thus migration of LCs coupled with differential activation of Th subsets after antigen exposure translates to a decreased or absent ability to mount an appropriate immune response. Consequently, microbial antigens may be tolerated, and tumor growth rather than re-

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0733-8635/06/$ – see front matter
doi:10.1016/j.det.2005.08.003

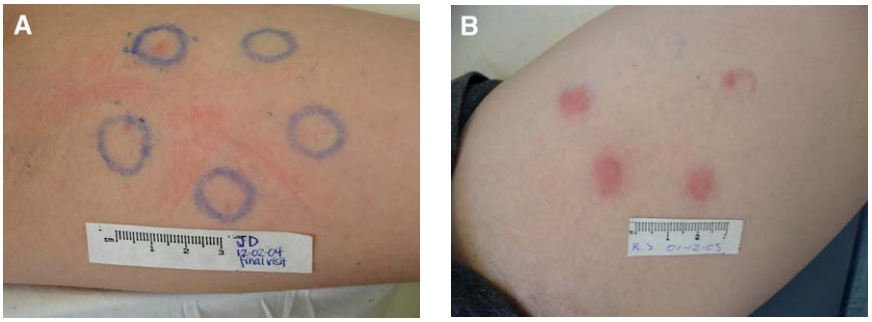

Fig. 1. (*A*) A negative contact sensitivity response was observed when the allergen dinitrochlorobenzene (DNCB) was applied over skin that has been previously irradiated with a suberythemogenic dose of ultraviolet (UV). Even at a suberythemogenic UV dose, immune suppression may be observed in vivo. (*B*) In contrast, a positive contact hypersensitivity response was demonstrated when DNCB was applied over skin that was UV-irradiated in the presence of a broad-spectrum SPF 15 sunscreen.

jection occurs. Similar to UVB, UVA radiation (320 to 400 nm) also causes a reduction in LC number and disruption of their functional capacity [3]. These effects of UVA may partially explain its suppressive effects on in vivo contact sensitivity that have been observed in both animal and human studies [4,5].

Cytokines

UV-induced immune suppression is modulated through the participation of a number of cytokines including but not limited to interleukin (IL)-1β, tumor necrosis factor (TNF)-α, IL-10, and IL-12 [1,6]. After UV exposure, immunosuppressive cytokines TNF-α and IL-10 are released from damaged keratinocytes. TNF-α is a proinflammatory cytokine that causes the upregulation of intercellular adhesion molecule (ICAM) and MHC class I and class II [7]. TNF-α and IL-1β have been implicated in directing LC migration after UV radiation [8,9]. In vivo studies have implicated TNF-α in UV-induced CHS suppression, but not delayed-type hypersensitivity (DTH) suppression or tolerance [10]. When irradiated mice were pretreated with anti–TNF-α antibodies, there was significant reduction of LC migration and CHS suppression [8]. This effect has been mediated via the TNF-α receptor 2 (p75) [10]. IL-10 was first proposed as an important mediator of UV immune suppression when in vitro studies demonstrated its production by keratinocytes in culture after UVB or UVAI irradiation [7,11]. When neutralizing antibodies (Abs) against IL-10 were added to the supernatant from UV-irradiated keratinocytes, the suppressive activity of UV was diminished. Additionally, the injection of anti–IL-10 antibodies to UV-treated mice blocked the in vivo induction of immune suppression [11,12]. Other studies have shown that IL-10 plays a role in the UV-induced suppression of DTH but not CHS. This implies that UV-induced suppression of DTH and CHS are mediated through different pathways. In addition to its role in DTH suppression, IL-10 plays a critical role in the induction and transfer of hapten-specific tolerance. After injection of T lymphocytes from UV-irradiated mice, the neutralization of IL-10 in vivo to recipient mice was associated with a loss of hapten-specific tolerance. The mechanism by which IL-10 suppresses the immune response also involves modulation of antigen presentation by LC. IL-10 inhibits costimulatory molecules such as class II MHC and B7 expression. IL-10 release by UV-irradiated keratinocytes preferentially activates Th2 cells. A study by Ullrich [13] demonstrated that spleen cells from UV-treated mice do not effectively present antigen to Th1 cell clones and that injection of anti–IL-10 antibody to the mice restored this ability. However, UV exposure enhanced presentation to Th2 cells, and this effect is inhibited by injection of anti–IL-10 antibody. The induction of T suppressor cells then leads to release of additional suppressive cytokines, such as IL-4 and IL-10. These studies indicate that the IL-10 released by UV-irradiated keratinocytes modulates antigen presentation by LCs such that there is preferential activation of Th2 cells that then secrete additional immune suppressive cytokines and suppress cell-mediated immune responses [12,13]. This supports existing data indicating that UV radiation results in sup-