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LETTER TO THE EDITOR

Ultraviolet Light (UV)-Induced Immunosuppression: Is Vitamin D the Missing Link?

To the Editor: As shown by the work of Adorini et al. [2003], Griffin and Kumar [2003], and Van Etten et al. [2003], that has been recently published in this journal, the field of immunomodulatory properties of vitamin-D-analogs is growing rapidly. We would now like to discuss in this context a new concept concerning vitamin-D and UV-induced immunosuppression (UVS). UVS, including UV-mediated suppression of contact hypersensitivity (CHS) and tolerance, has been extensively studied during the past decades (For review see Schwarz [2002]). However, the pathogenetic mechanisms that underlie UVS are up to now only poorly understood. Interestingly, recent investigations analyzing the vitamin D system in the skin and the effects of vitamin D analogs on the immune system now indicate that at least some of the major UV-induced immunosuppressive effects are mediated via induction of vitamin D synthesis in the skin. Recently, it has been shown that contrary to earlier assumptions, the skin does not exclusively produce vitamin D but also possesses the enzymatic machinery to convert vitamin D to 1,25-dihydroxyvitamin D_3, the biologically active vitamin D metabolite [Lehmann et al., 2000; Lehmann et al., 2001]. In conclusion, UV-irradiation of the skin not exclusively induces the production of vitamin D but additionally the local synthesis of the biologically active vitamin D metabolite, 1,25-dihydroxyvitamin D_3 in the skin. Locally produced 1,25-dihydroxyvitamin D_3 is now recognized as a major regulator of cell growth in a broad variety of tissues, including the skin [Reichrath et al., 1999]. However, recent investigations strongly support the concept, that 1,25-dihydroxyvitamin D_3 additionally represents a potent immunoregulatory agent, and that at least part of the immunosuppressive effects of UV-light, that include suppression of CHS, are mediated via local synthesis of 1,25-dihydroxyvitamin D_3 in the skin. In vitro studies have shown that UV-induced inhibition of CHS is mediated via alterations of Langerhans cells, which are the crucial cells in the epidermis for sensitization (Reviewed in Schwarz [2002]). These alterations of Langerhans cells are associated with a loss of their antigen presenting function (Reviewed in Singh et al. [1999]; Griffin et al. [2000]; Schwarz [2002]). It has now been demonstrated that 1,25-dihydroxyvitamin D_3 and its analogs modulate function of dendritic cells via a vitamin D receptor-dependent pathway that inhibits differentiation and promotes a persistent state of dendritic cell immaturity in vitro and in vivo [Griffin et al., 2001]. In summary, these investigations show that 1,25-dihydroxyvitamin D_3 exerts effects on Langerhans cells, that are characteristic of UV-induced suppression of CHS. Additionally, it has been shown that other immunomodulatory effects that are characteristic for UVS, including induction of $CD4^+CD25^+$ T regulatory cells [Kao et al., 2001; Gregori et al., 2002] and T regulatory 1 cells [Barrat et al., 2002; Schwarz, 2002], effects on T-cell infiltration in various models of Th 1 mediated autoimmune diseases, and on cytokine profiles in skin cells, are mediated by 1,25-dihydroxyvitamin D_3 [Adorini, 2000, 2002; Gregori et al., 2001a,b, 2002; Penna and Adorini, 2001; Mathieu and Adorini, 2002; Schwarz, 2002]. Furthermore, it has been demonstrated that 1,25-dihydroxyvitamin D_3 has the capacity to inhibit costimulatory pathways for T-cell activation [Penna and Adorini, 2001]. The mechanisms by which 1,25-dihydroxyvitamin D_3 acts as an immunosuppressive agent were shown to include reduced expression of the NF-kappaB proteins c-Rel and Rel B but not Rel A

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[Xing et al., 2002]. Taken together, these investigations now strongly support the concept that UVS is at least in part mediated via local production of 1,25-dihydroxyvitamin D_3 in the skin. For UVB-irradiation has been shown to increase serum levels of 1,25-dihydroxyvitamin D_3, this concept also explains the observation, that higher UVB doses in the range of $2kJ/m^2$ can also affect immune reactions initiated at distant, non-UV-exposed sites, a phenomenon called systemic immunosuppression [Schwarz, 2002]. In conclusion, a strong body of evidence supports the concept that 1,25-dihydroxyvitamin D_3 can now be recognized as the missing link that explains at least in part the mechanisms that underlie the pleiotropic immunosuppressive effects of UV-light.

Future experiments will have to be performed to confirm this hypothesis and to determine to what extent UVS is mediated via 1,25-dihydroxyvitamin D_3. These experiments should include studies to analyze immunosuppressive effects of UV-light in patients or animals (i.e., 25-hydroxyvitamin D-1α-hydroxylase knock out mice) with vitamin D-dependent rickets type I that are characterized by a genetic defect in the 25-hydroxyvitamin D-1α-hydroxylase gene leading to inability of kidney, skin, and other tissues to convert 25-hydroxyvitamin D_3 to 1,25-dihydroxyvitamin D_3. The lack in 1α-hydroxylase-activity that abolishes the ability to produce 1,25-dihydroxyvitamin D_3 after UVB irradiation should result in significant reduction of UVS. Additionally, it should be demonstrated that systemic application of 1,25-dihydroxyvitamin D_3 at comparable doses induces immune reactions that correspond to the phenomenon called systemic immunosuppression [Schwarz, 2002] that has been described after irradiation with higher UVB doses at distant, non-UV-exposed sites. Using in vivo models of hyper contactsensitivity, double-blind studies should be performed to compare effects of UVB-irradiation and topical treatment with vitamin D analogs. It can be speculated that these studies will soon show the final proof of concept that vitamin D is the missing link mediating ultraviolet (UV)-induced immunosuppression.

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