Cis-urocanic acid, a sunlight-induced immunosuppressive factor, activates immune suppression via the 5-HT_{2A} receptor

Jeffrey P. Walterscheid[*,†], Dat X. Nghiem[*,†], Nasser Kazimi[*], Leta K. Nutt[†,‡], David J. McConkey[†,‡], Mary Norval[§], and Stephen E. Ullrich[*,†,¶]

*Department of Immunology and Center for Cancer Immunology Research and ‡ Department of Cancer Biology, University of Texas M. D. Anderson Cancer Center, Houston, TX 77030; †Graduate School of Biomedical Sciences, University of Texas, Houston, TX 77030; and §Medical Microbiology, University of Edinburgh Medical School, Edinburgh EH8 9AG, Scotland

Edited by Richard B. Setlow, Brookhaven National Laboratory, Upton, NY, and approved September 18, 2006

Received for publication April 17, 2006.

Abstract: Exposure to UV radiation induces skin cancer and suppresses the immune response. To induce immune suppression, the electromagnetic energy of UV radiation must be absorbed by an epidermal photoreceptor and converted into a biologically recognizable signal. Two photoreceptors have been recognized: DNA and *trans*-urocanic acid (UCA). *Trans*-UCA is normally found in the outermost layer of skin and isomerizes to the cis isomer upon exposure to UV radiation. Although UCA was identified as a UV photoreceptor years ago, and many have documented its ability to induce immune suppression, its exact mode of action remains elusive. Particularly vexing has been the identity of the molecular pathway by which *cis*-UCA mediates immune suppression. Here we provide evidence that *cis*-UCA binds to the serotonin [5-hydroxytryptamine (5-HT)] receptor with relatively high affinity (K_d = 4.6 nM). Anti-*cis*-UCA antibody precipitates radiolabeled 5-HT, and the binding is inhibited by excess 5-HT and/or excess *cis*-UCA. Similarly, anti-5-HT antibody precipitates radiolabeled *cis*-UCA, and the binding is inhibited by excess 5-HT or excess *cis*-UCA. Calcium mobilization was activated when a mouse fibroblast line, stably transfected with the human 5-HT_{2A} receptor, was treated with *cis*-UCA. *Cis*-UCA-induced calcium mobilization was blocked with a selective 5-HT_{2A} receptor antagonist. UV- and *cis*-UCA-induced immune suppression was blocked by antiserotonin antibodies or by treating the mice with 5-HT_{2A} receptor antagonists. Our findings identify *cis*-UCA as a serotonin receptor ligand and indicate that the immunosuppressive effects of *cis*-UCA and UV radiation are mediated by activation of the 5-HT_{2A} receptor.

Key Words: immune regulation • inflammation • serotonin • UV radiation