Chronic stress accelerates ultraviolet-induced cutaneous carcinogenesis

Jason Parker, MS,a Sabra L. Klein, PhD,b Martha K. McClintock, PhD,c Warwick L. Morison, MD,a Xaobu Ye, MD, PhD,c Claudio J. Conti, DVM, PhD,f Norman Peterson, PhD,d Carlos H. Nousari, MD,8 and Francisco A. Tausk, MDa

Baltimore, Maryland; Chicago, Illinois; Houston, Texas; and Weston, Florida

Background: Physical and emotional stressors have been found to mediate a wide variety of biological changes including the facilitation of tumor progression; however most of these paradigms utilized artificial sources of neoplasms and stress.

Methods: Skh mice were exposed to carcinogenic doses of ultraviolet light (UV). The stressed group was subjected to the close proximity of fox urine as a source of stress from the presence of the odor of their natural predator, while the control group remained stress free.

Results: A significant acceleration in the development of cutaneous neoplasms was observed in mice that had been exposed to the stressor. The first tumor appeared in the group after 8 weeks, whereas nonstressed mice began to develop these by week 21.

Conclusion: These results suggest that stress plays a role in potentiating cutaneous carcinogenesis. (J Am Acad Dermatol 2004;51:919-22.)

There is evidence in support of the notion that chronic stress and negative emotional states not only impair coping with cancer, but can also have a deleterious impact on the progression of this disease.1 Obvious ethical concerns do not permit prospective human studies in the laboratory; therefore, numerous researchers have examined the effects of psychological and physical stressors on the facilitation of the progression of cancer in animal models.2 The difficulty of translating these findings to the problem of cancer in humans lies in the use of artificial models of tumor production (such as the development of metastasis originating from the injection of cancer cells) and the use of artificial stress paradigms that are not present in the natural habitat of the animal.

We hypothesized that ultraviolet B (UVB) exposure (akin to that which mediates solar induced carcinomas in human skin) in mice exposed to a well established,3 naturalistic, predator stress paradigm (fox urine and restraint) could serve as an effective murine model of stress-potentiated carcinogenesis. We found that this naturalistic stressor paradigm significantly accelerated the development of UV light-induced neoplasms.

MATERIALS AND METHODS

Animals

Female hairless SKH:H-1-hrBr mice (Charles River, Wilmington, Mass) were obtained at 6 weeks of age and were allowed to acclimatize for 2 weeks. Upon arrival, the mice were housed in groups of 5 in climate-controlled quarters (22°C ± 1°C at 50% humidity), with a 12 hour light/dark cycle under fluorescent lights, and fed ad libitum with a commercial diet and water. All procedures were approved by...
Forty mice were restrained for 60 minutes in ventilated conical tubes with a separate compartment containing a gauze impregnated with 1 mL of fox urine (Chagnon’s Trapping Supply, Manistique, Mich) as a source of predator odor.4 There was no direct contact between the animals and the gauze. Mice were stressed for 14 days before starting the irradiation protocol, and subsequently 3 times a week for the duration of the experiment. Forty control mice were housed in a separate room.

**UVB irradiation**

Mice were UV irradiated with a bank of 6 Westinghouse FS40 sunlamps (Westinghouse Electric Corp, Bloomfield, NJ) with a Kodacel filter (Eastman Kodak, Rochester, NY). The fluence was measured with an IL-1400 A Radiometer/Photometer coupled to PT&C detector (International Light, Newburyport, Mass). Mice were irradiated 3 times a week at noon in cages placed 30 cm from the light source, separated into 5 individual compartments by Plexiglas, and rotated to ensure homogeneous exposure. Initial light exposure began with a dose of 32.4 mJ/cm² and increased 5% per session to a maximum exposure of 288 mJ/cm². All mice were examined weekly for the development of skin lesions, and tumors were counted when they became larger than 2 mm in diameter. Mice were weighed monthly, without any significant difference in weight between groups.

**Statistics**

The probability of tumor-free survival was estimated by the Kaplan-Meier method, and log-rank statistics was used to determine whether the difference in tumor-free survival was statistically significant.

**RESULTS**

We found a significant acceleration in the development of tumors among mice exposed to the stressor paradigm. Neoplasms began appearing earlier (ie, by week 8) in animals that had been exposed to the stressor paradigm, compared with controls, which began expressing skin tumors 21 weeks after starting the UVB exposure (Fig 1). By 21 weeks, a 5-fold difference was found; 35% of the stressed mice had at least one neoplasm, whereas only 7% of the nonstressed mice had tumors, which varied between 2 mm and 2 cm in diameter (animals that had tumors larger than 2 cm were sacrificed following IACUC guidelines), and most were microscopically consistent with squamous cell carcinomas with fewer lesions diagnosed as papillomas.

The difference in tumor-free survival between stressed and nonstressed groups was statistically significant ($P = .012$) (Fig 2). The median time of tumor-free and 95% CI were estimated as 24 (23, 26) weeks and 27 (24, 27) weeks for stressed mice and nonstressed mice, respectively.

**DISCUSSION**

We stressed mice by mimicking the presence of a natural predator, without means of escape, resulting in a significant acceleration in the rate of development of UVB-induced cutaneous neoplasms. Psychosocial stressors play a significant role in the function of the skin through effects on circulating and local inflammatory cells and antigen-presenting cells,7 transepidermal water loss,8 pigmentation,9 as well as by altering DNA repair,10,11 apoptosis,12 and natural killer cell cytotoxicity.13 Stress may increase carcinogenesis synergistically with UV through modulation of the DNA machinery,10,14 decreased cytolysis of transformed cells,15 or altered immunologic recognition of mutant cells.16 Studies in humans have found that chronic stressors correlate with altered immunity and increased susceptibility to infections,2 progression of HIV disease,17 and development of cancer.18 Conversely, psychosocial interventions have been reported to enhance the survival of patients with cancer,19 including melanoma.20
Although we cannot extrapolate that stress in mice and in humans is identical, the significant acceleration of tumor formation by stress exposure found in this study provides the background support to study the role of stressors in facilitating human cutaneous neoplasms. Further insight in the underlying mechanisms that mediate the accelerating effects of stress on UV mediated carcinogenesis may allow us to design translational psychosocial and pharmacological interventions that can be applied to protect against the development of skin cancers in humans.

We are very grateful to Megan Brown for her excellent assistance.

REFERENCES
VOLUNTEERS ABROAD

You will find, as you look back upon your life, that the moments that stand out are the moments when you have done things for others.
—Henry Drummond

The Task Force for Education and Volunteers Abroad of the American Academy of Dermatology (AAD) was established four years ago. Its purpose is to disseminate educational materials abroad and also provide volunteer opportunities for dermatologists to serve in developing countries.

The AAD recently formed an alliance with Health Volunteers Overseas (HVO), a nonprofit dedicated to improving global health through education. For the past 17 years, HVO has supported volunteers from many specialties in 25 countries. They have identified potential sites and designed educational programs that will be staffed by volunteers. The AAD is in the process of developing an official Dermatology Overseas program within the structure of HVO. Volunteer positions in Cambodia and Peru are currently available for dermatologists through the AAD and HVO. Uganda and Palau have recently been added to the overseas program. Many other sites are currently being assessed for future development.

In April 2004, Orthopedics Overseas conducted a 2-day workshop to prepare participants for overseas volunteer assignments and provide them with specific skills for teaching orthopedics in developing countries. The Task Force for Education and Volunteers Abroad hopes to develop a similar course specific to the needs of dermatology volunteers.

The AAD has recently launched a competitive grant program to support one or two AAD members to volunteer to teach in a developing country. The grant is for either $10,000 for one applicant or $5000 each for two applicants. Guidelines and the application for the grant can be obtained through the AAD.

In September 2003, AAD president Raymond L. Cornelison, Jr, MD, convened a special conference to address his presidential initiative on Skin Care in Developing Countries. A group of 35 international experts discussed how best to improve care of and prevention of skin diseases in developing countries. They specifically emphasized the importance of teaching simple preventative skin care measures for common diseases such as pyodermas, scabies, etc., to appropriate health care providers. A pilot program is being inaugurated in Haiti and another is being developed in Mexico. This project will continue under the aegis of the Task Force for Education and Volunteers Abroad.

Four years go, we had no mechanism to allow volunteers to serve abroad. Today many sites are available and more are under development. Volunteers generally stay between two and four weeks, though longer stays are possible depending on the location. The emphasis is on teaching and not just providing dermatologic care. By stressing the teaching role we will have a longer-lasting impact. The volunteer program is growing rapidly because of the enthusiasm and excitement of the volunteers. For more information about any of the task force’s activities, please contact the AAD or HVO at the addresses below.

Walter G. Larsen, MD  
Immediate Past Chairman of the  
Task Force for Education and Volunteers Abroad  
American Academy of Dermatology  
930 East Woodfield Road  
Schaumburg, IL 60173  
Phone: (847) 330-0230  
www.aad.org  
E-mail: volunteer@aad.org

James O. Ertle, MD  
Immediate Past Chairman of the  
Committee on International Affairs  
Health Volunteers Overseas  
1900 E St, NW  
Suite 310  
Washington, DC 20036  
www.hvousa.org  
E-mail: info@hvousa.org