

Setting the Sun on Skin Cancer

Interferon- γ has been found to promote UV-induced melanoma in a mouse model.

A series of experiments designed to understand how solar ultraviolet (UV) radiation causes aggressive cutaneous melanoma has led to an unanticipated discovery that could upend assumptions about the relationship between interferon proteins and cancer. Interferon- γ (IFN- γ), which traditionally has been thought to contribute to an innate defense system against cancer, under some circumstances may promote melanoma and incite the development of tumors. This finding from Glenn Merlino, Ph.D., Co-Chief of CCR's Laboratory of Cancer Biology and Genetics, and Research Fellow M. Raza Zaidi, Ph.D., was published in the January 27, 2011, issue of *Nature*.

Over the past decade, these researchers used genetically engineered mice first to establish, and then to dissect, the connection between exposure to UV radiation and the initiation of melanoma. The current work—made possible through long-term collaborations with Edward De Fabo, Ph.D., and Frances Noonan, Ph.D., of George Washington

University Medical Center—was their latest attempt to define the molecular mechanisms of this cause-and-effect relationship. The results of this study offer the possibility that the inhibition of IFN- γ immediately after sunburn might block the carcinogenic activation of melanocytes, the skin's pigment-producing cells, by UV radiation.

Crucial to the experiments was the development of a unique genetically engineered mouse in which the melanocytes were labeled with a green fluorescent protein. This fluorescent tag allowed melanocytes to be visually tracked and isolated and enabled researchers to evaluate, for the first time, their response to UV radiation while in their natural environment in a living animal.

The researchers observed that UV radiation doses equivalent to those causing sunburn in human skin triggered aberrant growth and migration of melanocytes in mouse skin. UV radiation exposure also persistently activated genes known to respond to IFN- γ , including genes that may help tumor cells evade

detection and attack by the immune system. When the activity of IFN- γ was inhibited, the growth and migration of melanocytes remained normal after exposure to UV radiation.

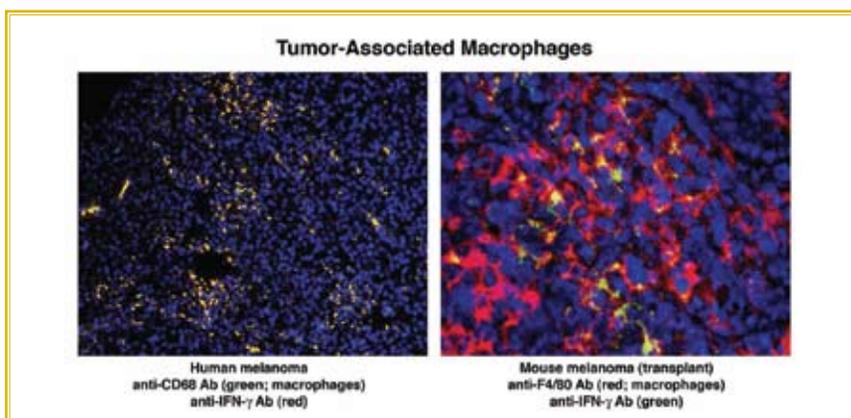
"Interferons have long been touted as anti-tumorigenic and cytostatic—that they have an inhibitory effect on cellular growth," said Dr. Zaidi. "The finding that IFN- γ can have a profoundly different effect—that it can exacerbate the growth of melanoma—is a paradigm-shifting discovery."

The team additionally showed that white blood cells known as macrophages were producing the IFN- γ . Macrophages significantly enhanced melanoma tumor growth when researchers injected them under the skin of healthy mice along with cultured mouse melanoma cells, and this effect was abolished by blocking IFN- γ activity. The researchers also identified IFN- γ -producing macrophages in 70 percent of 27 human melanomas they examined, supporting the possibility that IFN- γ plays a role in this type of cancer—not just in mice, but also in humans.

Moreover, Dr. Zaidi noted, inhibiting IFN- γ immediately after sunburn, an approach that he and his colleagues are pursuing, may prove to be an effective preventive strategy against UV radiation-induced melanoma. The discovery could one day lead to drug treatments that block this mechanism and thus the cancer's growth, potentially saving many from the lethal threat of skin cancer.

To learn more about Dr. Merlino's research, please visit his CCR Web site at <http://ccr.nci.nih.gov/staff/staff.asp?Name=merlino>.

(Image: R. Zaidi, CCR)



A human melanoma tumor, *left*, and a transplanted mouse melanoma tumor, *right*, show infiltration of macrophages. While a subset of mouse tumor macrophages display expression on interferon-gamma (IFN- γ), virtually all the macrophages in human melanoma express this protein (identified by the yellow colored overlap of the two antibodies).