International Agency for Research on Cancer

World Health Organization

Some cutaneous HPV types may be involved in Non-Melanoma Skin Cancer development

Lyon, France and Heidelberg, Germany, 18 July 2011-

In a joint paper published on July 14, 2011 in PloS Pathogens[1], the German Cancer Research Center (*Deutsches Krebsforschungszentrum*, DKFZ) and the WHO's International Agency for Research on Cancer (WHO/IARC) conclude that a viral infection with a certain type of human papillomavirus may cooperate with UV light exposure in the development of non-melanoma skin cancer(NMSC).

Skin cancer on the rise

Non-melanoma skin cancer is the most common form of malignancy in adult Caucasian populations, with more than a million cases recorded each year in the USA alone[2].

Lifestyle risk factors… but

The incidence of these cancers is continuously rising due mainly to the aging structure of Western populations, and as a result of growing prosperity, permitting more visits to countries with high sun exposure, which is a key risk factor for NMSC, as well as lifestyle habits associated with prolonged voluntary sun exposure for tanning purposes[3].

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[1] Daniele Viarisio, Karin Mueller-Decker, Ulrich Kloz, Birgit Aengeneyndt, Annette Kopp-Schneider, Hermann-Josef Gröne, Tarik Gheit, Christa Flechtenmacher, Lutz Gissmann and Massimo Tommasino: E6 and E7 from beta HPV38 cooperate with ultraviolet light in the development of actinic keratosis-like lesions and squamous cell carcinoma in mice. PLoS Pathogen 2011 http://www.plospathogens.org/article/info:doi/10.1371/journal.ppat.1002125

[2] Hatfield LA, Hoffbeck RW, Alexander BH, Carlin BP.Comput Stat Data Anal. 2009 Jun 15;53(8):3001-3015 report the incidence in USA of over 1 million of NMSC per year, including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).

[3] See IARC Monograph Volume 100D, in press, summarized in A review of human carcinogens—Part D: radiation, The Lancet Oncology, Volume 10, Issue 8, pages 751 - 752, August 2009. doi:10.1016/S1470-2045(09)70213-X. See also Ananthaswamy HN, Loughlin SM, Cox P, Evans RL, Ullrich SE, Kripke ML (1997) Sunlight and skin cancer: inhibition of p53 mutations in UV-irradiated mouse skin by sunscreens. Nat Med 3: 510-514, Armstrong BK, Kricker A (2001) The epidemiology of UV induced skin cancer. J Photochem Photobiol B 63: 8-18 and Preston DS, Stern RS (1992) Nonmelanoma cancers of the skin. N Engl J Med 327: 1649-1662.

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… Immune system disorders also etiological factor for NMSC

Impairment of the immune system also appears to play an important role in NMSC. Indeed, immunosuppressed organ transplant recipients (OTRs) have a 50–100-fold increased risk of developing NMSC compared to the general population. NMSCs occur 10–20 years earlier in immunosuppressed than in immunocompetent individuals, and the cumulative incidence of skin cancer in patients under immunosuppressive treatment for 10–25 years is approximately 30–40%. Thus, NMSCs cause a severe discomfort in OTR individuals, who often, due to the high number of skin lesions, cannot be treated with conventional surgery.

Strong suspicion of etiological role for infectious agent

The link with immune status strongly supports the role of an infectious agent in NMSC. Biological and epidemiological studies indicate that a sub-group of cutaneous human papillomaviruses (HPVs), refered to as *beta HPV types*, are associated with skin carcinogenesis. However, their direct role in cancer development and in particular whether they synergize with other risk factors, like UV irradiation, remain to be proven.

DKFZ-IARC collaboration

In a collaborative DKFZ-IARC program, we have developed a novel experimental animal model to further evaluate the role of beta HPVs in skin carcinogenesis. We have generated transgenic (Tg) mice expressing the viral oncoproteins E6 and E7 from cutaneous beta HPV38 in the basal layer of the epidermis. We found that chronic skin UV irradiation of these transgenic animals promoted the formation of skin lesions that resembled the squamous cell carcinoma (SCC)-precursor lesions in humans, actinic keratosis and subsequently SCC, closely mimicking the scenario observed in humans. In contrast, wild-type mice developed neither actinic keratosis nor SCC when exposed to the same dose of UV. Dr Christopher Wild, Director, IARC, indicated that "[Our] study shows the existence of a synergy between

UV and cutaneous beta HPV in the induction of pre-malignant and malignant skin lesions in this animal model, supporting the further investigation of the role of these viruses in the development of skin cancer in people."

The way forward: possibilities for action

"The establishment of the involvement of beta cutaneous HPV types in NMSC development is of paramount importance", continued Dr Lutz Gissmann, Head of the Division of Genome Modifications and Carcinogenesis at DKFZ, "since it may offer the possibility, if causality is established, of novel prophylactic strategies for this disease based on the generation of specific vaccines, as shown for the HPV types associated with cervical cancer". This strategy may be highly beneficial for OTRs, who could be vaccinated before the initiation of the immune suppressive therapy. "However, further research, particularly in humans, is needed in the next decades to understand whether beta HPV prophylactic strategies may possibly have a positive impact on the prevention of NMSC", he concluded.

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