Available online at www.sciencedirect.com
SCIENCE DIRECT
Cancer Letters 224 (2005) 213–219
CANCER Letters
www.elsevier.com/locate/canlet

Human herpesvirus type 6 and type 1 infection increases susceptibility to nonmelanoma skin tumors

Janaína Luisa Leite[a], Hamilton Ometto Stolf[b], Nilton Ávila Reis[a], Laura S. Ward[a,*]

[a]*Laboratory of Cancer Molecular Genetics, Department of Medicine, School of Medicine, State University of Campinas (Unicamp), 45 Olympio Pattaro, Campinas, São Paulo 13085-045, Brazil*
[b]*Dermatology, Department of Medicine, School of Medicine, State University of São Paulo (Unesp), Botucatu, São Paulo, Brazil*

Received 6 July 2004; received in revised form 1 November 2004; accepted 4 November 2004

Abstract

In order to investigate herpesvirus (HHV) role in the susceptibility to skin cancer, we compared HHV6 and HHV1 incidence in DNA samples extracted from 120 lesions and 41 normal skin tissues. HHV6 (31.7%) and HHV1 (23.8%) were detected more frequently in skin cancer than in control individuals (14.6 and 5%, respectively) ($P=0.0391$ and $P=0.00094$, respectively). The risk of presenting basal cell carcinomas (BCC) was more than 3 times higher for HHV-6 infected patients (OR = 3.182; 95% CI: 1.125–8.997). The risk for HHV-1 infected individuals of presenting BCC and squamous cell carcinomas was increased 8 and 6 times, respectively (OR = 8.125; 95% CI: 1.735–38.043 and OR = 6.290; 95% CI: 1.283–30.856, respectively).

Keywords: Herpesvirus; Cutaneous; Cancer; Infection; Virus; Susceptibility

1. Introduction

Virus infections have emerged, in the past few years, as major causal cancer factors. Some of these cancers are very common, leading to the assumption that up to 20% of all cancers worldwide may have a viral etiology, including hepatitis B virus-related hepatocarcinomas, Epstein-Barr virus, human papillomavirus, human T-cell leukemia virus type 1 and hepatitis C virus, plus several candidate human cancer viruses [1,2]. Tumor viruses establish long-term persistent infections in humans, and cancer is usually an accidental side effect of viral replication strategies. Viruses are usually incomplete carcinogens, and the known human cancer viruses display different roles in cell transformation [3]. There is strong evidence that viral infections may affect the cellular DNA repair system, supposedly allowing the accumulation of mutations in growth regulatory genes. Also, processes and reactants associated with a virus-induced inflammatory response may predispose to cancer. It is possible that other normal mechanisms of host homeostasis and response to infection, under the pressure of chronic viral replication, may go awry and promote tumor outgrowth. Finally, the hit-and-run

* Corresponding author. Tel./fax: 55 19 3788 8020.
E-mail address: ward@unicamp.br (L.S. Ward).

0304-3835/$ - see front matter © 2004 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.canlet.2004.11.010

mechanism of viral involvement in carcinogenesis cannot be ruled out, although the concept that a virus can initiate the transformation process through a mutagenic mechanism and then disappear without leaving viral traces has fallen out of favor [3].

Both human herpes virus type 6 (HHV6) and type 1 (HHV1), also denominated human herpes simplex virus, are epitheliotropic by nature and their life cycle is closely linked to the terminal differentiation of the squamous cells. They are found worldwide and are among the most frequent causes of viral infections in immunocompetent as well as in immunocompromised patients but, unlike Epstein Barr and Kaposi Sarcoma virus, HHV1 and HHV6 are not definitively associated with cancer [4–7]. On the other hand, HHV6 has been detected in oral squamous carcinomas, cervical carcinomas, Hodgkin's and non-Hodgkin's lymphomas among other malignancies [8,9]. Also, neoplastic transformation of nontumorigenic human epidermal keratinocytes and murine fibroblasts was demonstrated with HHV6 DNA [10]. These facts suggest that HHV6 may have some role in the development of human malignancies of the skin. The mechanism involved in HHV6 associated malignancy may be related to the fact that, in both immunocompetent and immunosuppressed hosts, HHV6 produces an oncogenic protein called ORF-1 (open reading frame 1) that binds to wild-type p53 and inhibits regulation of the cell cycle [11,12]. HHV1 can infect both skin and nerves and develop latent infection within the dorsal root and trigeminal ganglia [13]. HHV1 was also associated with many types of cancer, including squamous cell carcinomas, and there is evidence that the virus may determine genetic cellular modification in vitro and in experimental in vivo models [11,14,15].

This study was designed to investigate the role of HHV6 and HHV1 in the susceptibility to sporadic skin cancers.

2. Materials and methods

2.1. Subjects

The study was approved by the Ethics Committees of the School of Medicine, State University of São Paulo-Botucatu (UNESP), and informed written consent was obtained from all individuals.

One hundred-twenty adult individuals (56 females and 64 males, 11–92 years old, 63.8 ± 15.7 years old) consecutively referred to the outpatient Surgical Dermatology Clinic of UNESP because of skin conditions were enrolled in the study after agreeing to participate. There were 51 basal cell carcinomas (BCC), 41 squamous cell carcinomas (SCC) and 9 malignant melanomas (MM). Nineteen lesions were classified as benign: 5 keratoacanthomas, 12 actinic keratoses and 2 melanocytic nevi. Surgical excision margins were drawn by the surgeon (HOS) according to current guidelines [16–18]. We were able to obtain lesion samples from each patient and also a normal portion of adjacent skin. Type of tumors and grade of differentiation, with particular attention to the cases classified as benign, were obtained from surgical and pathological records. Diagnoses were all reviewed and confirmed by experienced pathologists of UNESP.

A subgroup of 25 skin lesion patients was considered immunocompromised because of organ transplantation ($n = 11$ cases), use of immunosuppressive therapy ($n = 9$ cases) or other advanced

Table 1
Clinical features including age (X ± SD and range in years), gender (F, female; M, male) and color (W, white; NW, non-white) among individuals from the control group, patients with benign skin lesions, basal cell carcinomas (BCC), squamous cell carcinomas (SCC) and malignant melanomas (MM)

	Age (X ± SD)	Age range	Sex		Color	
			M	F	W	NW
Controls	46.7 ± 5.3	21–52	19	22	39	2
Benign	61.38 ± 16.06	21–86	11	8	19	0
BCC	65.88 ± 11.62	45–90	26	25	49	2
SCC	59.82 ± 19.45	11–92	24	17	41	0
MM	74.33 ± 11.30	51–88	3	6	8	1