Parallel Symposium No. 12

Papillomaviruses and Human Cancer

Chair
Harald zur Hausen
Deutsches Krebsforshungszentrum, Heidelberg

Co-Chair
Manlio Ferrarini
Istituto Nazionale per la Ricerca sul Cancro, Genoa

PS 12.1

Stefania Jabłońska, Sławomir Majewski
Epidermodysplasia verruciformis /EV/: A model for a role of local immune response to potentially oncogenic human papillomaviruses /HPVs/
Dermatology Department, Warsaw School of Medicine

The tumors associated with potentially oncogenic EV-specific HPVs have extremely low metastatic potential found to be related with the markedly increased expression in the EV skin lesions of mRNA coding for TGF_β and TNF_α as compared to actinic keratosis and SCC in the general population. Increased TNF_α expression with induced expression of ICAM-1 and HLA-DR molecules could contribute to abnormal reactivity of EV patients to ultraviolet radiation, and to enhancement of presentation of EV-HPVs by HLA-DR+ keratinocytes in a tolerogenic manner. Our studies suggest that the abnormalities in the production of some immunomodulatory cytokines may play a crucial role in the derangements of immune control of HPV infections and of HPV associated cancerogenesis.
The increased expression of TGF_β appears to be responsible for local immunosuppression characteristic of EV.

PS 12.2

HUMAN PAPILLOMAVIRUSES AND SKIN CARCINOGENESIS

Gérard ORTH, Institut Pasteur, Paris, France

The first evidence for the oncogenic potential of HPVs was obtained in epidermodysplasia verruciformis (EV), a rare disease characterized by an abnormal genetic susceptibility to a group of specific HPVs and the development of skin carcinomas, usually on sun-exposed areas. At least 20 specific HPVs have been characterized so far in benign EV lesions. Only HPV5 and, less frequently, HPV5-related types (HPV8,14,17,20) are detected, as episomal DNA molecules, in EV malignant lesions and cancers. Transcription of HPV5 and 8 E6 and E7 genes is detected in EV cancers. Comparison of different isolates of HPV5 and 8 has disclosed an allelic polymorphism of the E6 gene. To what extent this modulates the oncogenic potential of these viruses remains to be studied. Most patients present some impairment of cell-mediated immunity. An EV-like syndrome associated with EV-specific HPVs has been described in iatrogenically or genetically immunosuppressed patients. However, data available do not point to a major role of known HPVs in skin carcinogenesis in this high-risk population, or in the general population.

PS 12.3

Strategies for intervention against HPV associated tumours.

L. Crawford, A. Storey and J. Zhou, I.C.R.F. Tumour Virus Group, Department of Pathology, Cambridge, England.

Two possible strategies will be discussed. The first involves the use of antisense oligonucleotides designed to interfere with production of the E6 and E7 transforming proteins of the malignant HPV types (HPV16 and HPV18). The second involves immunisation with viral proteins expressed by the appropriate vectors with the intention of generating prophylactic immunity against the initial HPV infection using virus particle component proteins, or therapeutic immunity against the pre-malignant cell, mediated by viral early proteins. Recombinant vaccinia virus expressing HPV16-L1 has been shown to generate cytotoxic T cells in mice and thus could be the first step towards generating a prophylactic vaccine.

PS 12.4

NEGATIVE REGULATION OF HPV18 TRANSCRIPTION IN SOMATIC CELL HYBRIDS

Frank Rösl and Harald zur Hausen, Institut für Angewandte Tumorvirologie, Deutsches Krebsforschungszentrum, Heidelberg, F.R.G.

To investigate the effect of non-malignant human keratinocytes on the transcriptional regulation of the upstream regulatory region (URR) of the human papilloma virus type 18 (HPV18), "universal fuser" clones of a heterologous HPV16 positive cervical carcinoma cell line (SiHa) were established. The SiHa cells, which are resistant to G418 and deficient for HPRT, also harbour a chloramphenicol-acetyl-transferase (-CAT) gene which is under the control of the HPV18 URR. While the marker gene is constitutively expressed in the malignant cervical carcinoma cells, the CAT activity is completely extinguished after fusion with non-tumorigenic human keratinocytes.

We describe the differentiation properties of these hybrids and provide evidence that the down-regulation of HPV18 URR transcription is mediated by trans-acting negative regulatory factors derived from the non-malignant fusion partner.