



Papillomaviruses

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Abstract

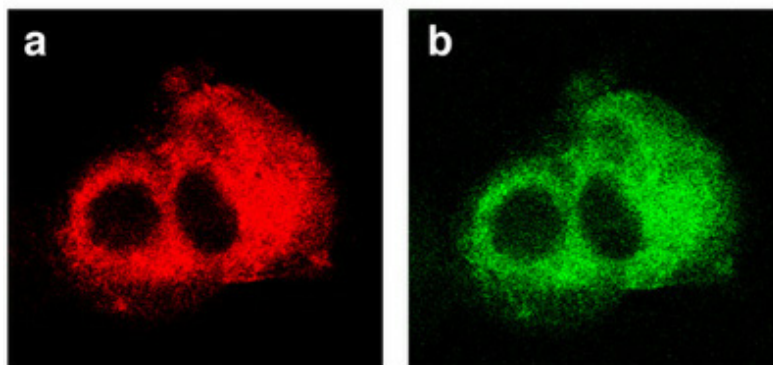
Certain human papillomavirus (HPV) genotypes display an oncogenic potential. These viruses most often cause inapparent infections of the skin and genital mucous membranes. They may induce intraepithelial lesions that most frequently regress but may occasionally progress into invasive cancer. Such a process accounts for the great majority of carcinomas of the uterine cervix. Model diseases allow us to analyze the factors underlying the interindividual variation in the susceptibility to oncogenic papillomaviruses and the mechanisms involved.

Annual Report

Susceptibility genes to infection with oncogenic HPVs: epidermodysplasia verruciformis Michel Favre

Epidermodysplasia verruciformis (EV), is a rare autosomal recessive genodermatosis, characterized by an abnormal susceptibility to HPV5 and related HPVs. HPV5 infection of EV patients is associated with a risk of developing skin carcinomas. EV HPVs are widespread but their pathogenicity in the general population remains unknown.

The genetic study of consanguineous families, in collaboration with L.-A. Rueda (Bogota) and B. Bouadjar (Algiers), allowed us to map a major susceptibility locus for EV (EV1) in the chromosomal region 17q25. We very recently identified nonsense mutations affecting two adjacent novel genes (*EVER1*, *EVER2*) localized in *EV1*. These mutations, when homozygous, segregate with the disease and inactivate one of the two genes. *EVER1* and *EVER2* proteins display no homology with known human proteins. They are located in the endoplasmic reticulum (Photo). This first identification of genes conditioning the susceptibility to oncogenic HPVs opens new avenues to understand the cellular or immunologic mechanisms involved in the control of latency and pathogenicity of these viruses. Current experiments are aimed at unraveling the function of *EVER* genes.



Do HPVs associated with epidermodysplasia verruciformis play a role in psoriasis? Michel Favre, Gérard Orth

Psoriasis is a hyperproliferative, inflammatory skin disease with a strong genetic background. The activation of T lymphocytes by as yet unidentified keratinocyte antigens plays a central role in the pathogenesis of the disease. In collaboration with S. Majewski and S. Jablonska (Warsaw), we showed that the prevalence of antibodies specific of the capsid proteins of HPV5, the genotype associated with EV carcinomas, is 10-20-fold higher in patients

with psoriasis as compared to the general population. We detected HPV5 and other EV HPVs in over 80% of psoriasis plaques by a PCR approach. The EV1 susceptibility locus for EV is mapped within a susceptibility locus for familial psoriasis in 17q25. Our aim is to determine whether the variability of *EVER1* and *EVER2* genes plays a part in the pathogenesis of psoriasis and whether the expression of EV HPV proteins contributes to the epidermal hyperproliferation and autoimmune phenomena that characterize the disease.

Genetic factors controlling the evolution of lesions induced by oncogenic PVs F. Breitburd

Our aim is to understand the factors controlling the regression or persistence and malignant progression of skin warts induced in domestic rabbits by the cottontail rabbit PV, for which we characterized two subtypes, CRPVa and CRPVb. We have found that wart evolution depends both on the virus subtype and on polymorphic MHC genes involved in the binding of antigenic peptides and their presentation to T lymphocytes. We have identified a haplotype of these genes that, when homozygous, is associated with a mode of wart evolution depending on the virus subtype: regression (CRPVb) or persistence (CRPVa). We have observed that regression involves an early massive infiltration of warts by CD4+ T cells followed by CD8+ T cells and macrophages. By swapping different regions between the two viral DNAs, we constructed infectious chimeric genomes and identified the subgenomic region encoding the viral protein(s) likely to be target(s) for regression. This region contains the gene encoding the E6 oncoproteins and that encoding the CRPV specific E8 protein, that we found to play a major role in wart formation and growth. The data demonstrate unambiguously the role of both the host immunogenetic factors and the virus genetic variation in the expression of the oncogenic potential of papillomaviruses.

HPV-associated cervical intraepithelial neoplasia in HIV-infected women Gérard Orth

HIV infection and the resulting immunodeficiency are associated with an increased prevalence and severity of cervical intraepithelial neoplasia (CIN) caused by genital HPV genotypes. These lesions are potential precursors of carcinoma of the uterine cervix. In collaboration with I. Heard (Hôpital G. Pompidou), we have analyzed the impact of highly active antiretroviral therapy (HAART) on the regression of low- or high-grade CIN towards normality or a lower grade in seropositive women. This study disclosed a two-fold higher risk of regression among patients receiving HAART as compared to patients without HAART. A greater increase of CD4 cell counts was observed among patients showing regression under HAART, which suggests some restoration of specific cell-mediated immune responses. Virologic follow-up of the patients, however, showed that cervical HPV infection persists in the majority of cases, in spite of regression. Thus, the impact of HAART does not warrant modifying the gynecologic follow-up of HIV-infected patients under HAART.

Photo: Cytoplasmic localization of the EVER1 protein: EVER1 protein (a) has the same localization as calnexin (b), a protein of the endoplasmic reticulum.

Keywords: Oncogenic papillomaviruses, susceptibility genes, epidermodysplasia verruciformis, psoriasis, carcinoma of the uterine cervix, HIV, virology, genetics

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