



# Role of HPVs in oncogenesis

**Epidermodysplasia verruciformis  
as a model in studies on the role of  
papovaviruses in oncogenesis.**

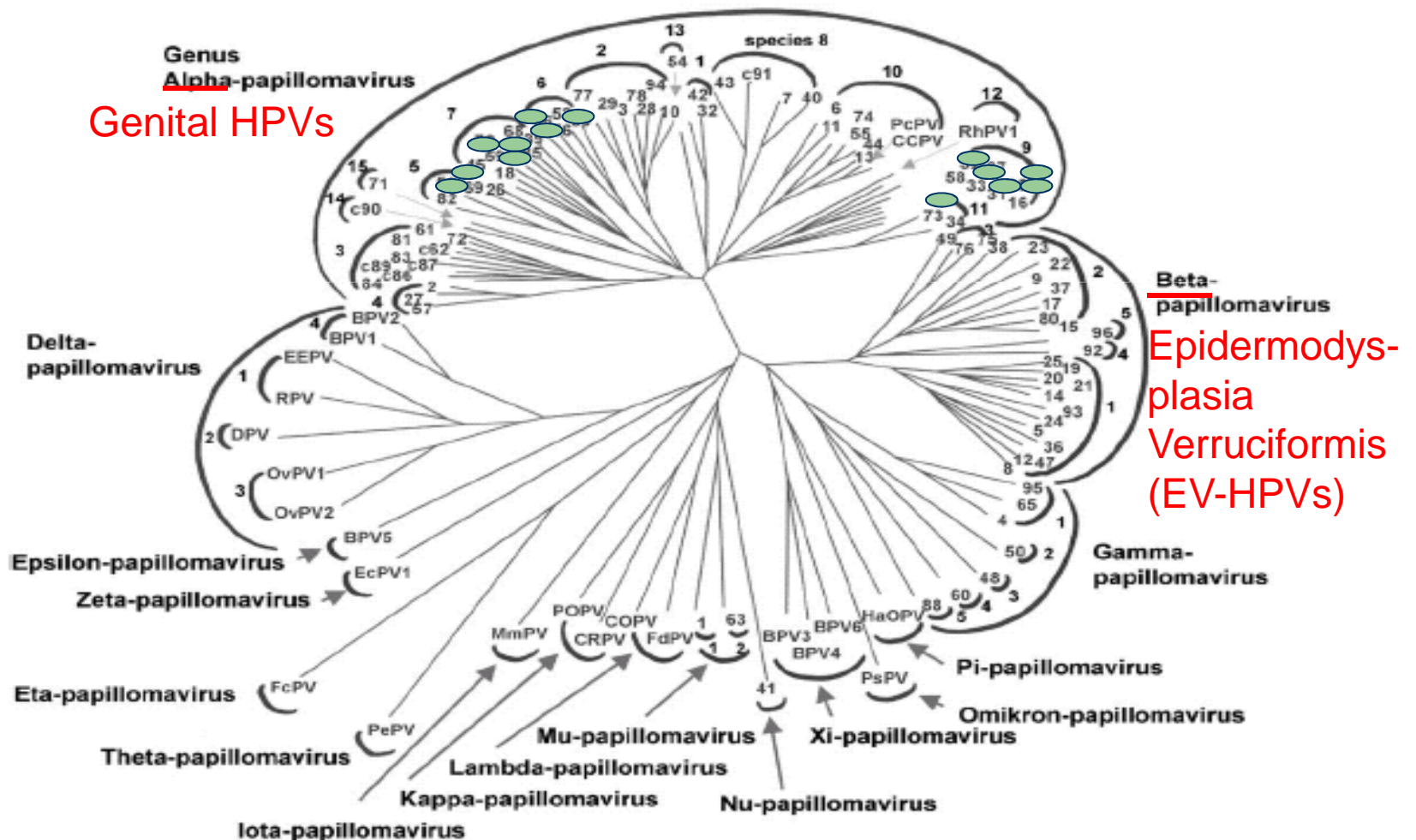
*S. Jablonska et al. Cancer Res* **1972**

**Condylomata acuminata and human genital  
cancer.**

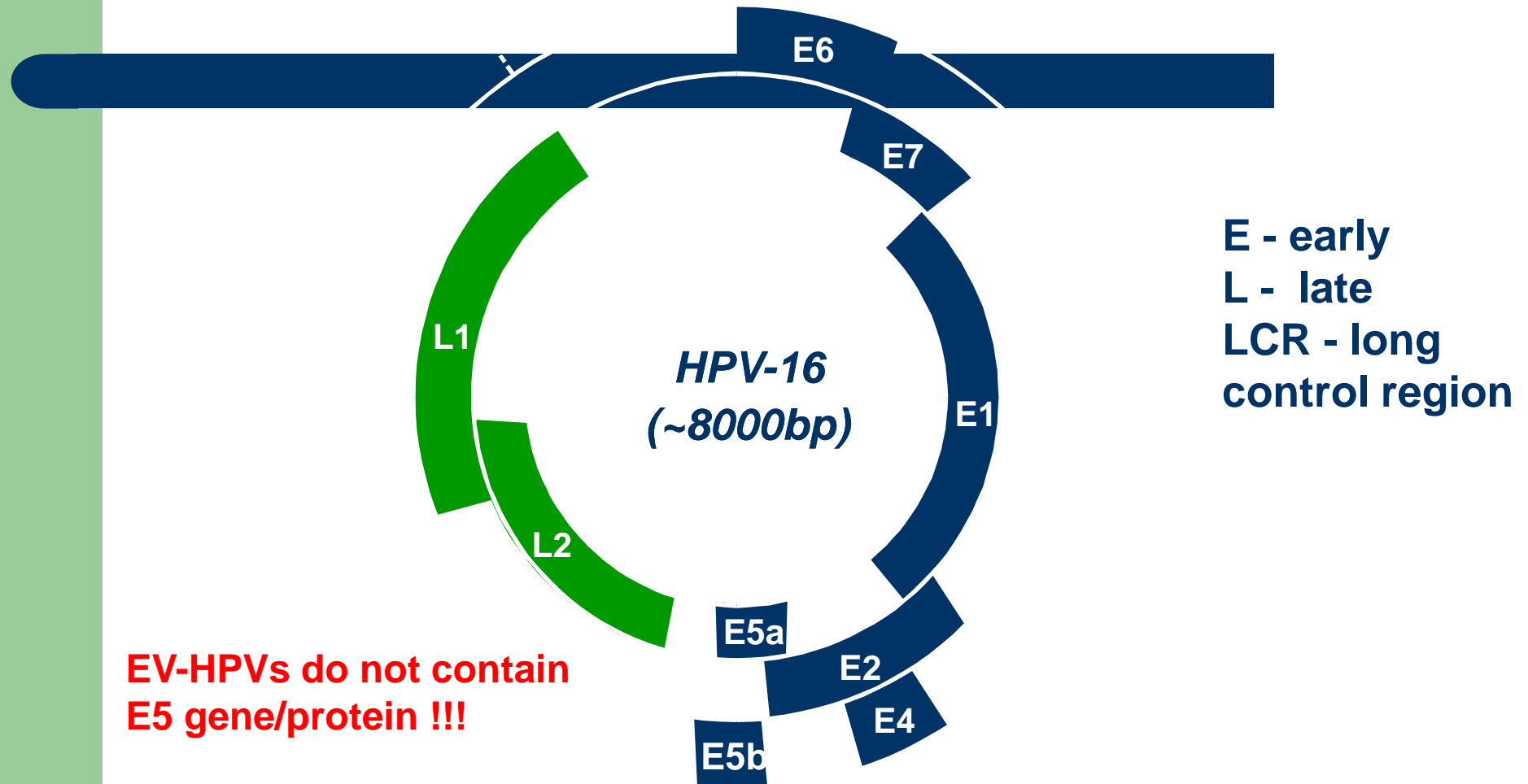
*H. zur Hausen et al. Cancer Res* **1975**



# Phylogenetic tree of HPVs



# HPV Genome





# Epidermodysplasia verruciformis (EV)

- Onset at early childhood (4-6 yrs)
- Plane warts, red plaques, PV-like lesions
- Onset of skin malignancies (4th decade of life)
- Massive infection with EV HPV (oncogenic HPV5 and HPV8)
- Specific defect of cell-mediated immunity against EV HPV

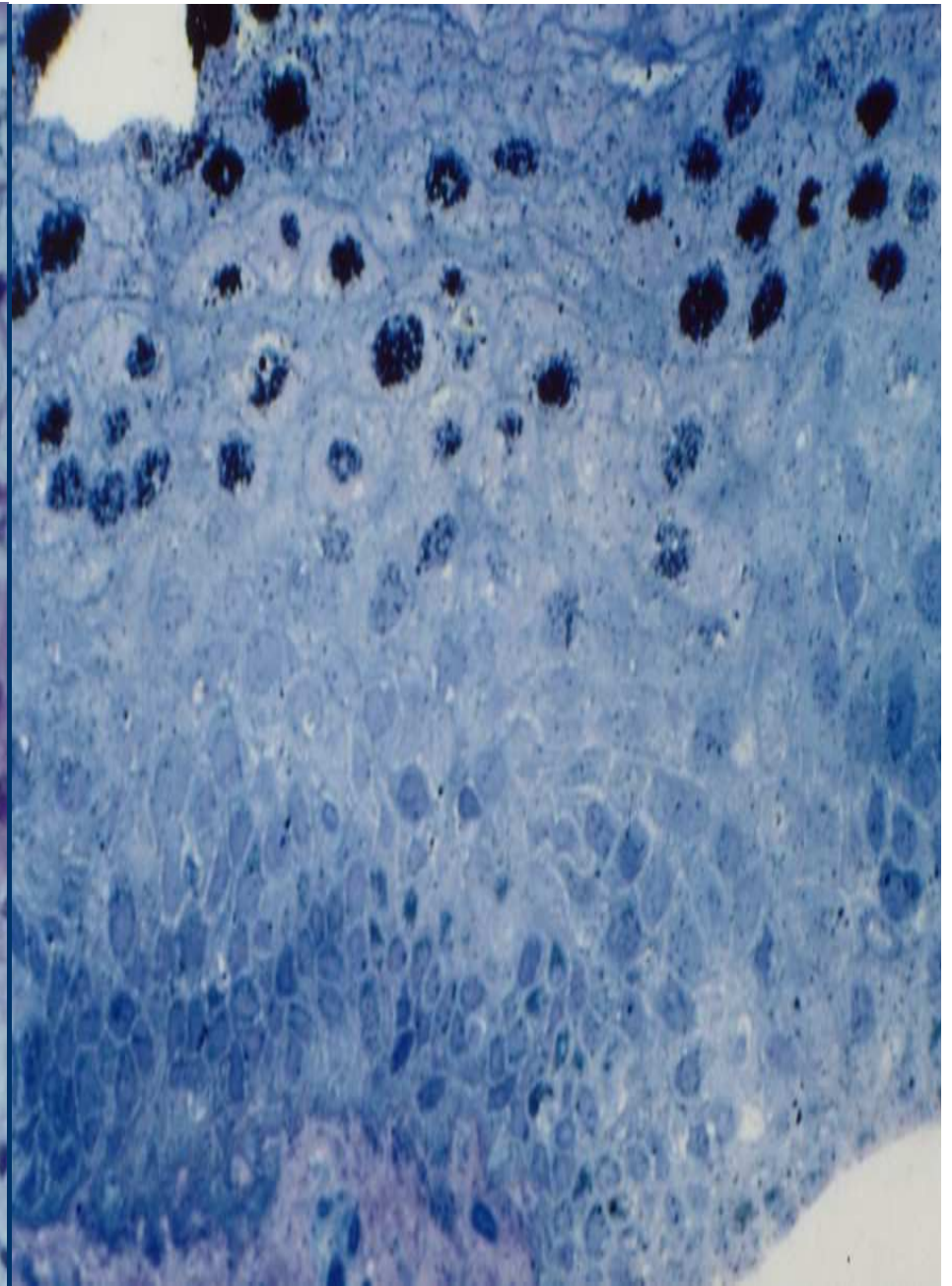
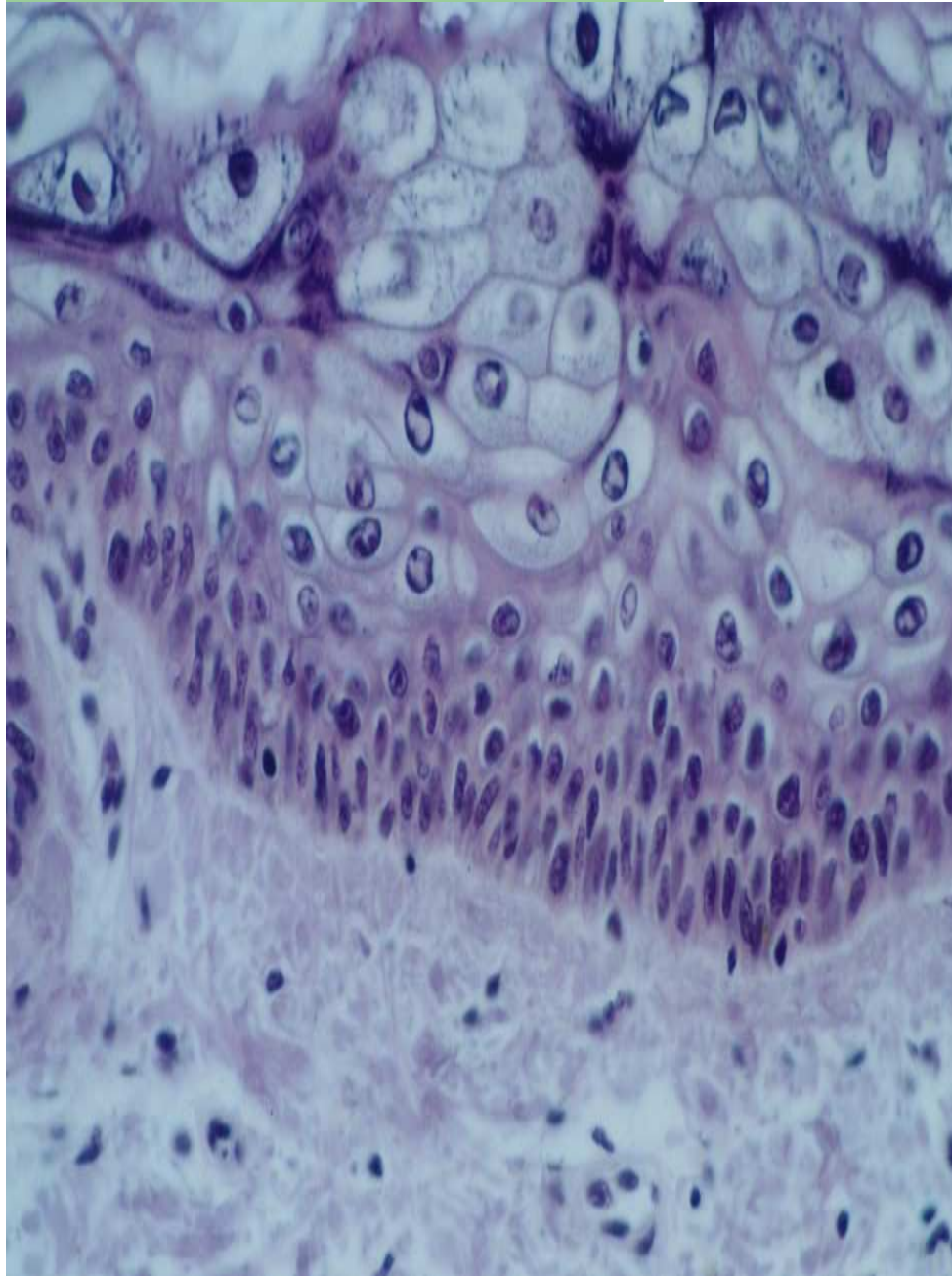




**Epidermodysplasia verruciformis (EV)**








# Mutations in two adjacent novel genes are associated with epidermodysplasia verruciformis

Published online 11 November 2002; doi:10.1038/ng1044

Epidermodysplasia verruciformis (OMIM 226400) is a rare autosomal recessive genodermatosis associated with a high risk of skin carcinoma that results from an abnormal susceptibility to infection by specific human papillomaviruses (HPVs). We recently mapped a susceptibility locus for epidermodysplasia verruciformis (*EV1*) to chromosome 17q25. Here we report the identification of nonsense mutations in two adjacent novel genes, *EVER1* and *EVER2*, that are associated with the disease. The gene products *EVER1* and *EVER2* have features of integral membrane proteins and are localized in the endoplasmic reticulum.

Ramoz, Favre, Orth, et al. Nature Genetics, 2002



**EVER 1/EVER2 proteins are expressed in the cytoplasm and co-localized with calnexin, an integral membrane protein located in the endoplasmic reticulum of keratinocytes and lymphocytes**

**HPV - keratinocyte interactions ?**

**HPV - lymphocyte interactions ?**



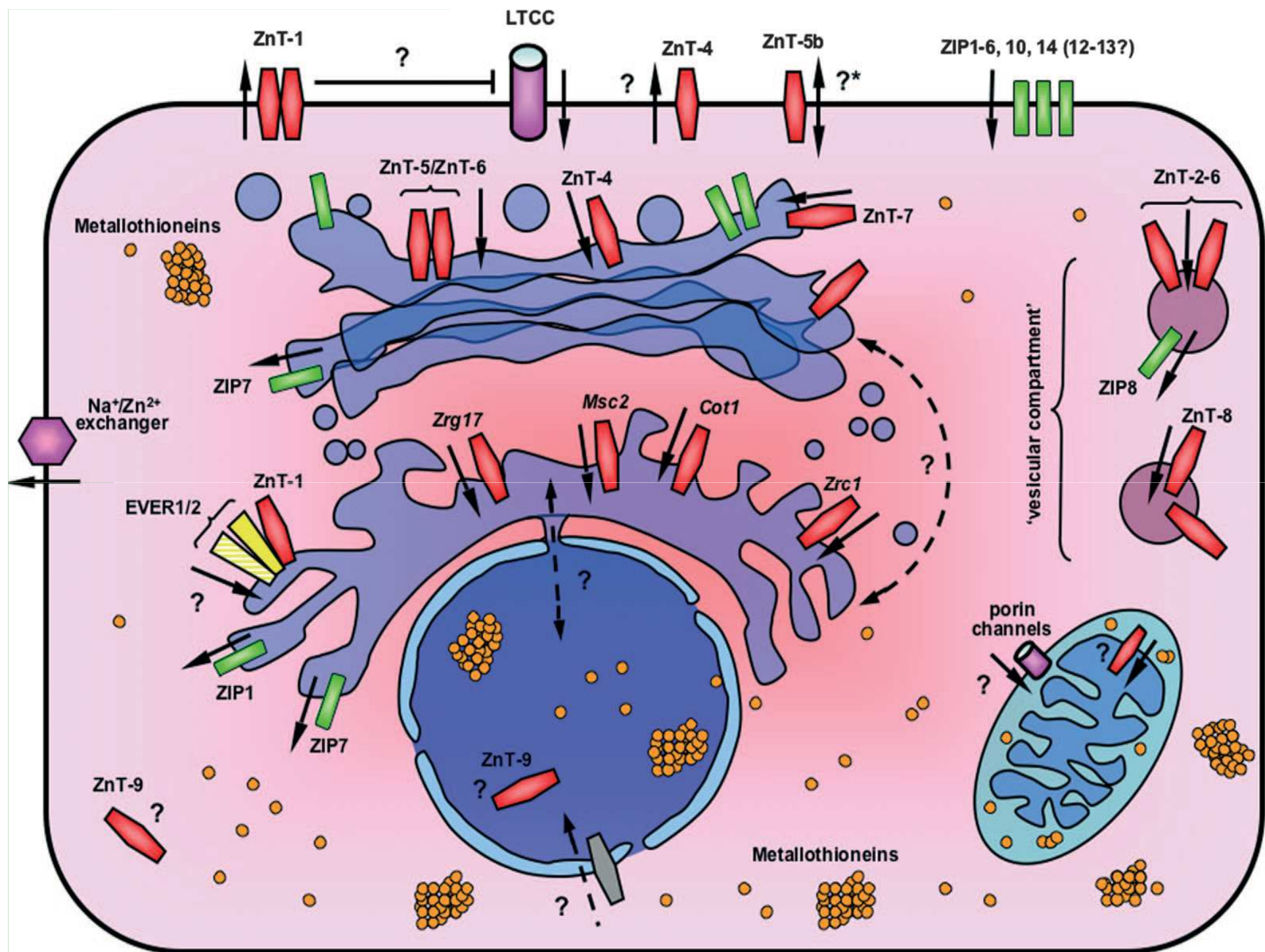


# Regulation of cellular zinc balance as a potential mechanism of EVER-mediated protection against pathogenesis by cutaneous oncogenic human papillomaviruses

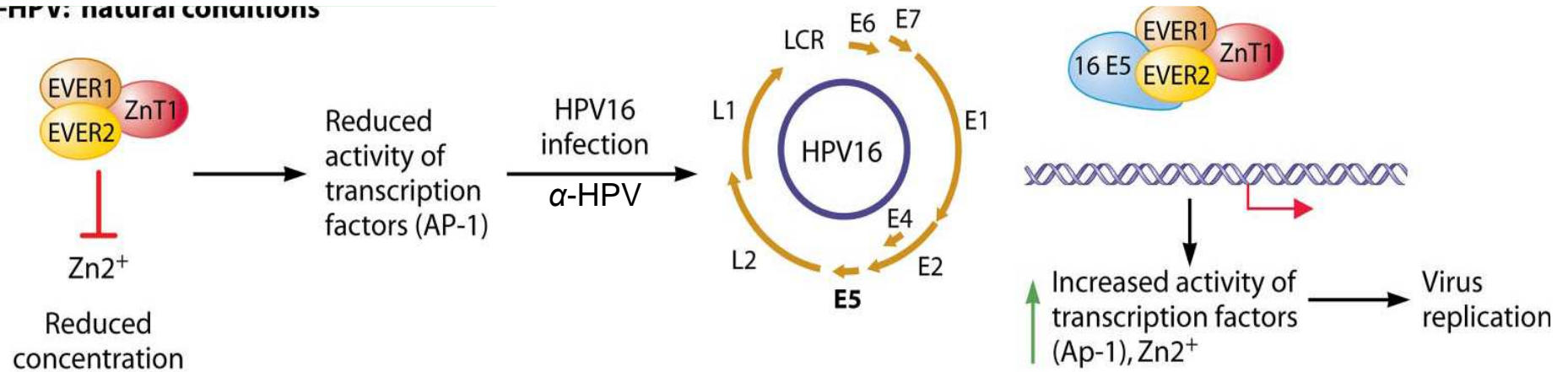
Maciej Lazarczyk, Christian Pons , José -Andres Mendoza, Patricia Cassonnet, Yves Jacob, and Michel Favre

*J Exp Med. Vol. 205, No. 1, January 21, 2008 35-42*

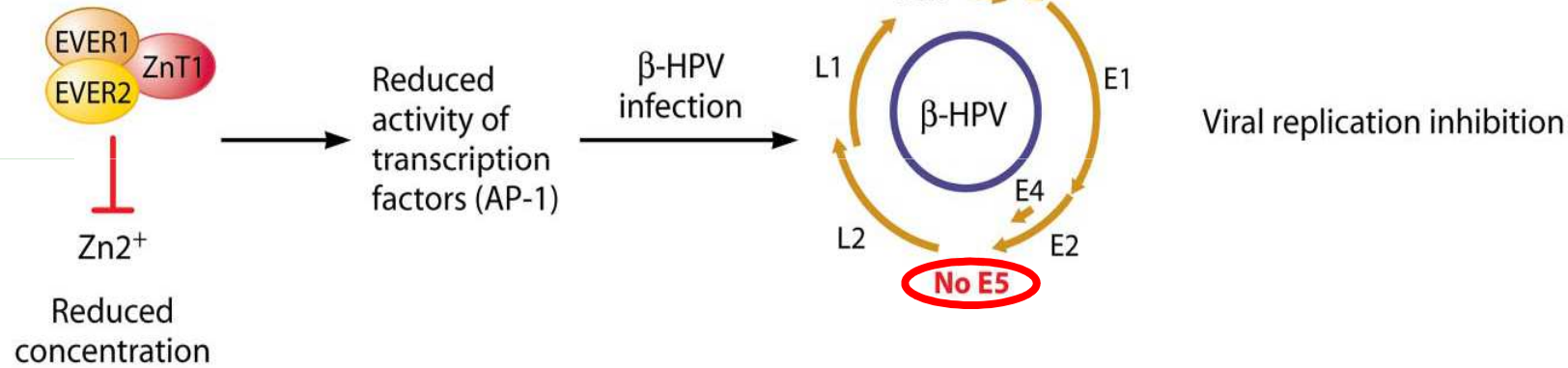




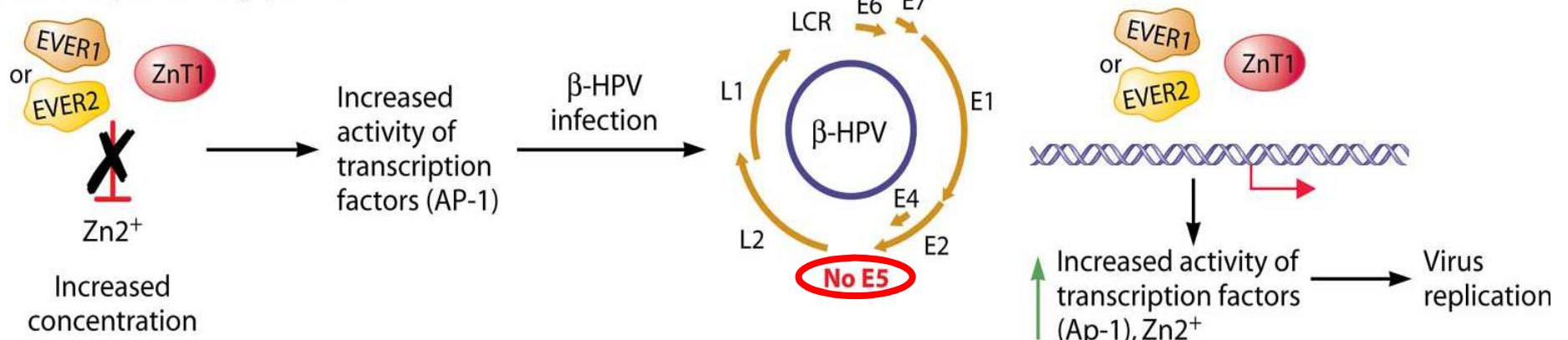
### A $\alpha$ -HPV: natural conditions



### B $\beta$ -HPV: natural conditions



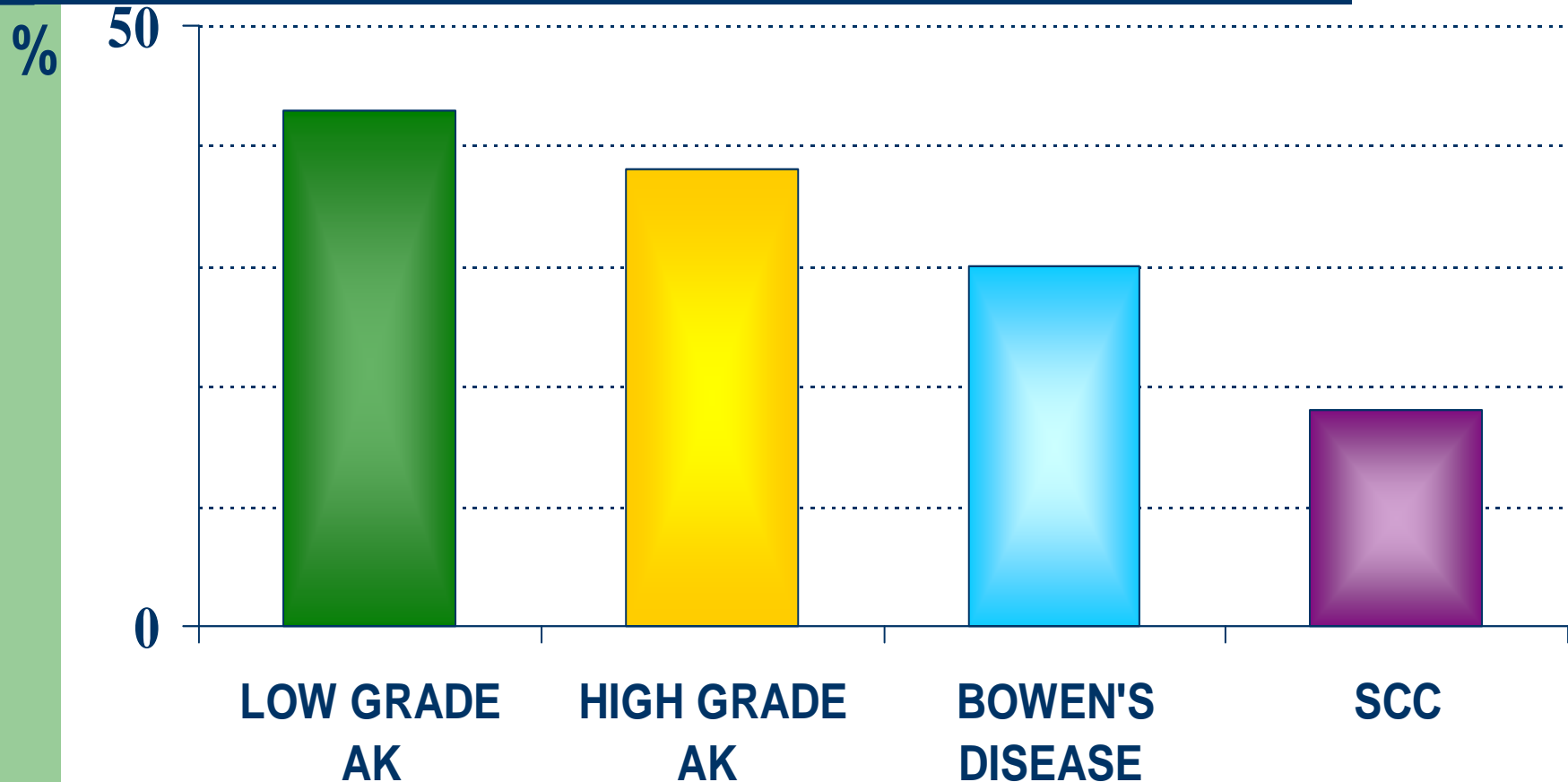
### C $\beta$ -HPV: epidermodysplasia verruciformis



# EV-HPV DNA PREVALENCE IN SKIN TUMORS

HPV DNA

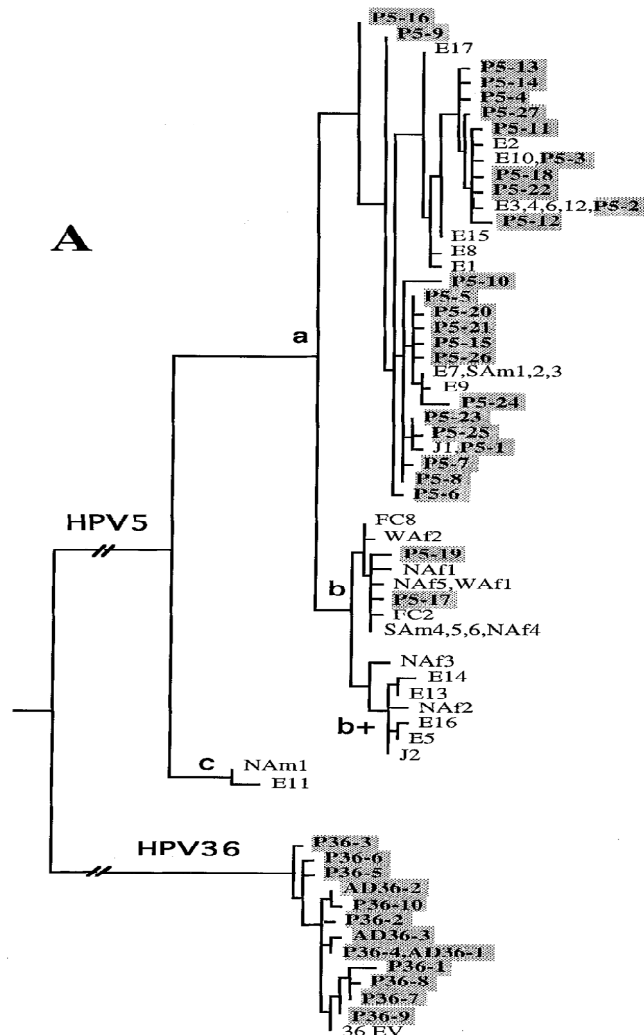
*(EV subgenus-specific PCR)*





# Psoriasis: A Possible Reservoir for Human Papillomavirus Type 5, the Virus Associated with Epidermodysplasia Verruciformis

Favre, Orth, Majewski, Pura, Jablonska. *J Invest Dermatol*; 110:311–317, 1998

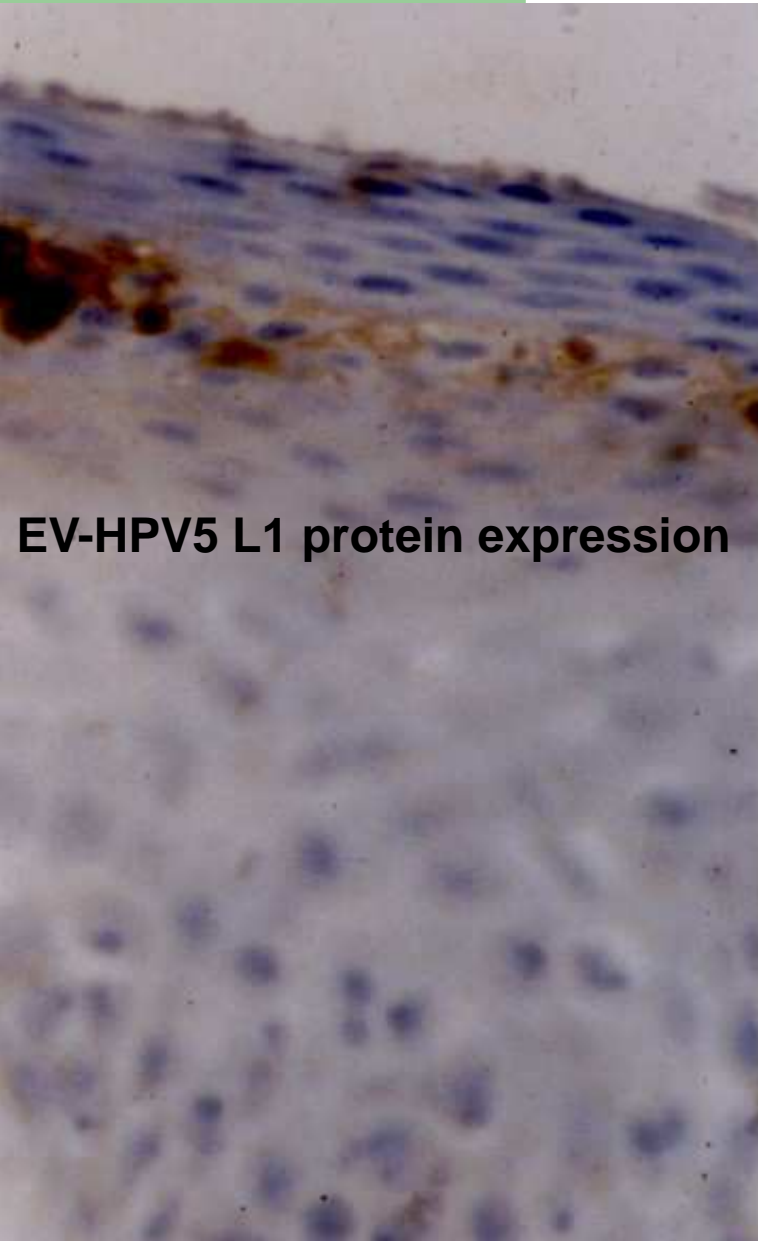




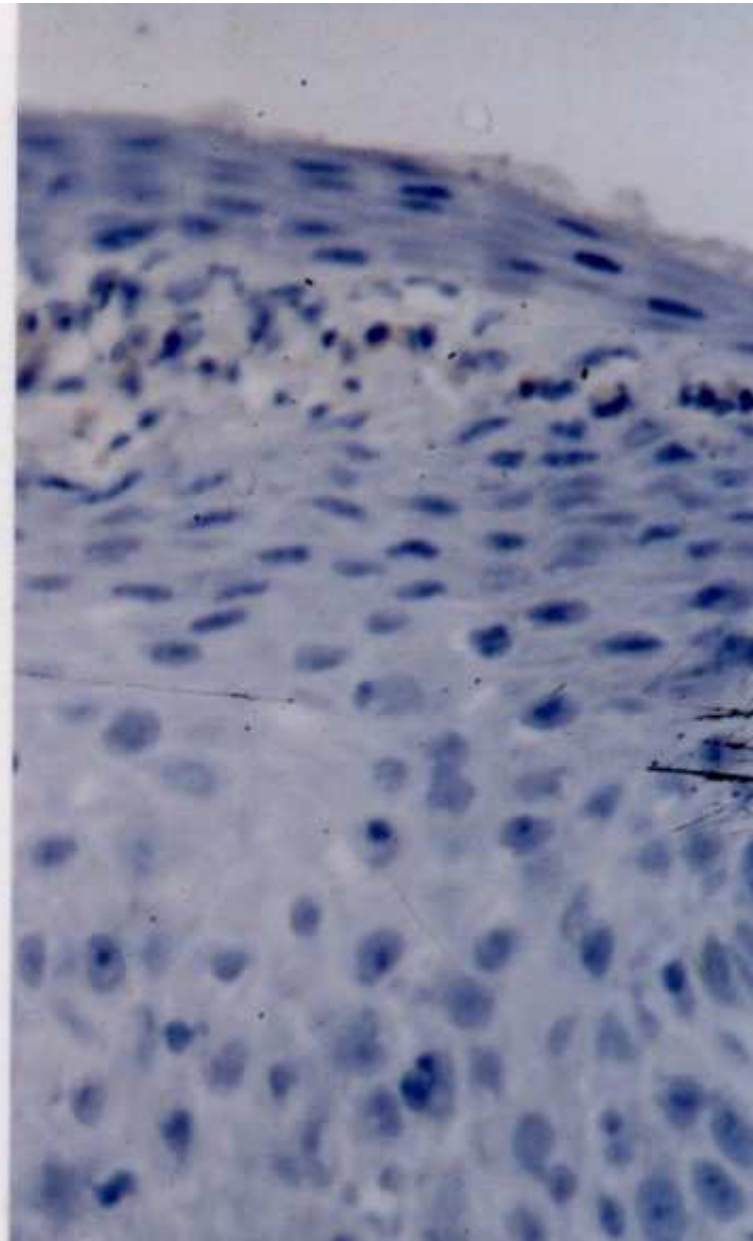
## Possible involvement of EV-HPVs in psoriasis, i.e. a model of benign keratinocyte hyperproliferation

*Majewski et al. Immunol Today 1998*

- 17 qter region (**PSORS-2 locus**)
  - *EVER1 / EVER2* (?), other genes (?)
- High prevalence (95%) of EV HPV DNA
- Presence of antibodies to:
  - HPV5 L1 protein (25-30%)
  - HPV5 E6/E7 oncoproteins (60%)
- CMI to EV HPV antigens

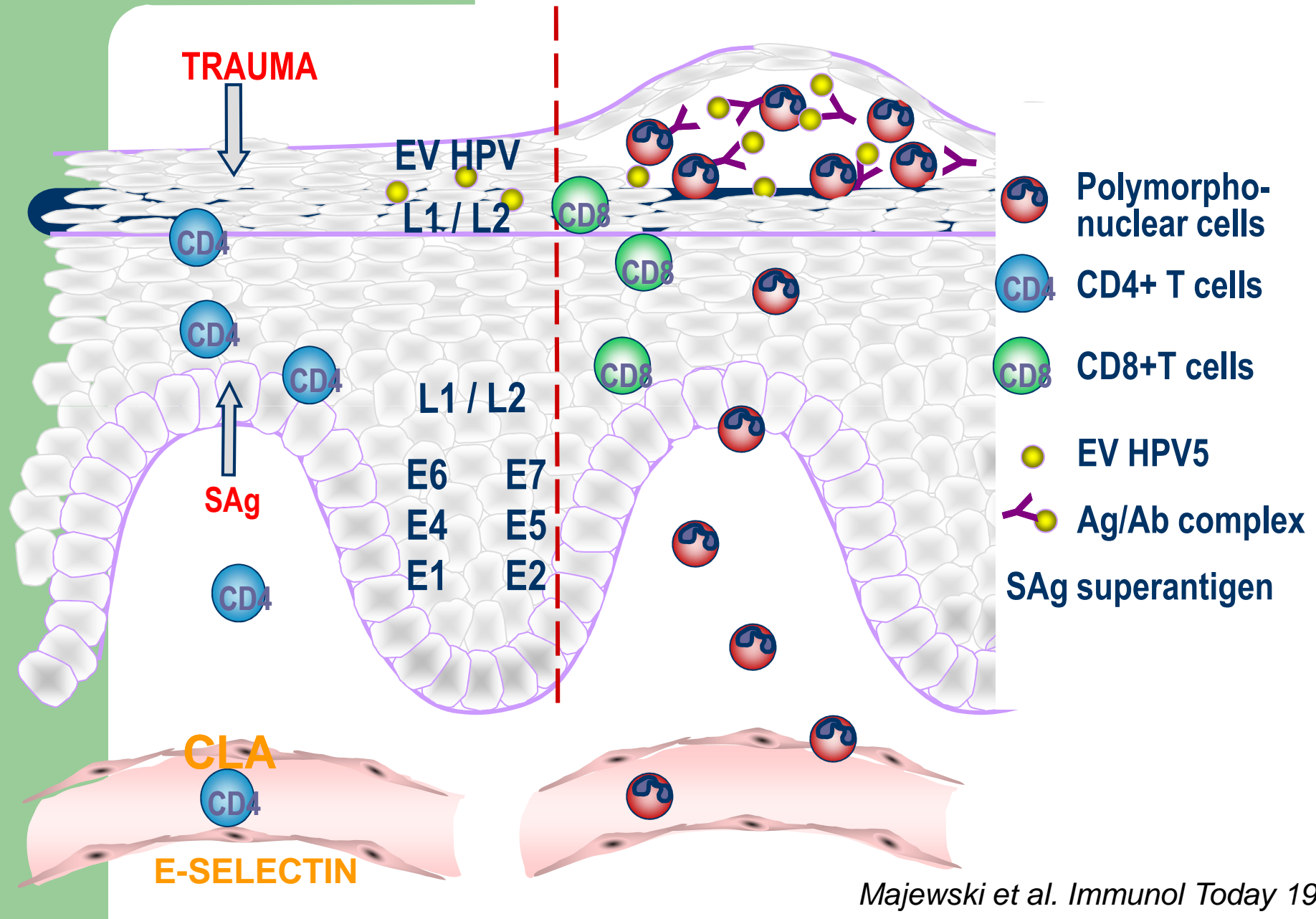


**EV-HPV5 L1 protein expression**



## Guttate psoriasis

## Plaque psoriasis





## Future studies

- Polymorphism *EVER1/2* genes (rs 7208422, and others) in actinic keratosis, cutaneous and mucosal SCC.
- Correlation of *EVER1/2* genes' polymorphism with humoral and cell-mediated immunity against EV-HPVs
- Other biological significance of *EVER1/2* genes' polymorphism (cutaneous and mucosal cancers, psoriasis)



# Future studies

- Role of EV-HPV E6/E7 oncoproteins in regulation of Langerhans' cells functions
- Role of EV-HPV E6/E7 oncoproteins in regulation of chemokines' and defensins' expression in premalignant and malignant skin tumors

