Epidermodysplasia verruciformis human papillomaviruses in skin cancers and in the immunopathogenesis of psoriasis

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Abstract

Epidermodysplasia verruciformis (EV), a rare genetic disease associated with specific human papillomaviruses (HPVs) and skin cancers, regarded as a model of cutaneous viral cancerogenesis, has raised recently an enormous interest in general medicine since EV HPVs, non contagious for normal population due to genetic restriction, were found in cutaneous precancers and cancers in the immunosuppressed and immunocompetent individuals. EV HPVs are quite unusual human papillomaviruses causing a rare genetic disease EV only in susceptible individuals. The recent epidemiological, immunological and immunogenetic studies disclosed that specific HPVs of this rare genetic disease play a substantial role in malignant and benign epidermal proliferations also in non EV patients. Patients with EV are immunotolerant towards own EV HPVs throughout the whole life, whereas the oncogenic types of EV HPVs induce cancers. In this review we present virological, immunological and immunogenetic data on epidermodysplasia verruciformis, including the most recent detection of two novel specific genes whose mutations are responsible for the disease. We discuss the involvement of EV HPVs in premalignancies and non melanoma skin cancers in the general population. The most interesting new finding was disclosure of a very high prevalence of potentially oncogenic types EV HPV5 and 8 in psoriasis. In spite of association with the same potentially oncogenic EV HPVs in EV and psoriasis and in spite of close localization of the two susceptibility loci on chromosomes 17qter and 2 in both diseases, these two disorders differ entirely in their pathogenesis, clinical, pathological, immunological and immunogenetic characteristics. We found that EV HPVs present in psoriatic keratinocytes may contribute to the complex immunopathogenesis of the disease, to the sustained T cell activation and self-perpetuation of the immune process. Since the patients have only partially alleviated genetic restriction to high risk EV HPVs these viruses are able to replicate in proliferating and differentiating psoriatic keratinocytes. The novel selective immunosuppressive therapies for psoriasis interfere with and block various stages of interconnected activation and proliferation of keratinocytes and closely linked EV HPVs.

Key words: *genetic skin cancer, papillomaviruses in skin cancer, papillomaviruses in psoriasis*

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What is known about epidermodysplasia verruciformis

Epidermodysplasia verruciformis (EV) was described in 1922 as a genodermatosis [1] and later found to be associated with widespread cutaneous HPV infection. Since in over 50% cases develop skin cancers this life-long infection is in essence a genetic cancer reported as a first model of human viral oncogenesis [2].

Virological associations

A further progress was characterization of two types of EV specific HPVs - non oncogenic, associated with benign

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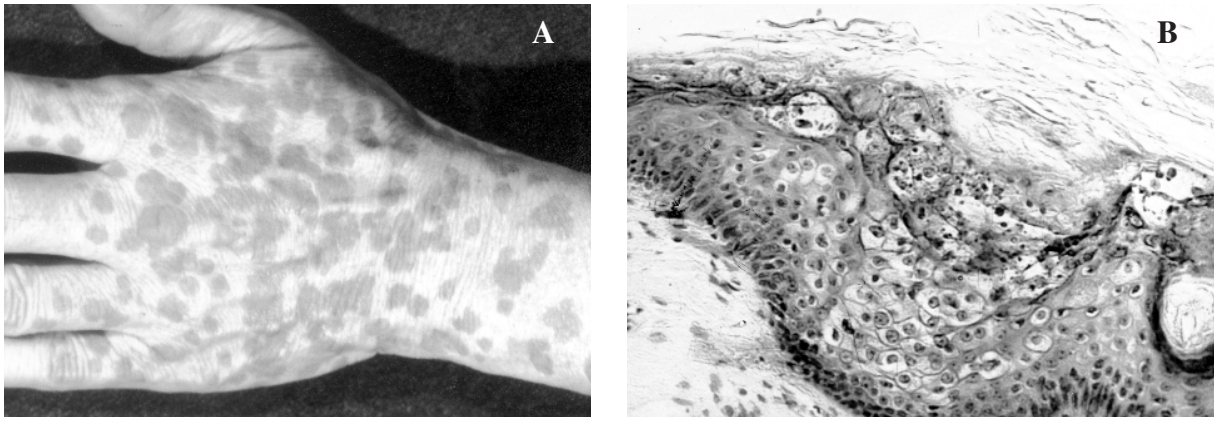

Fig. 1. Epidermodysplasia verruciformis associated with EV HPVs
A. Verruca plana-like lesions on the hands
B. Histologic features of benign EV lesion. Cytopathic effect specific of EV HPV starting from the suprabasal layer and involving the whole epidermis. Clarification of cytoplasm, small, pyknotic nuclei

lesions, and potentially oncogenic – associated with skin cancers and precancerous changes [3, 4]. About 20 EV types of over 100 known HPV types were characterized in EV lesions, most of them associated with benign lesions, and only a few, mainly HPV5 and HPV8, were found to have a high oncogenic potential.

Clinical manifestations

The clinical manifestations [5-7] are limited to the skin. The changes are polymorphous: verruca-plana or pityriasis versicolor-like, red, brownish and achromic plaques, verruca seborhoica- and papilloma-like lesions. Mucous membranes are not involved and internal organs not affected. The course is diverse, the progress is rather slow. First lesions usually start to appear at the ages 5-8 years, and remain throughout the like as verruca plana-like with characteristic cytopathic effect (Fig. 1a, b). In the third-fourth decade of life develop, mostly in sun-exposed areas, multiple premalignant and malignant changes: actinic keratosis, Bowen's disease, carcinoma in situ, preinvasive and invasive cancers (Fig. 2a, b). Metastases are rare, seen almost exclusively in cases treated with X rays which act as a potent co-cancerogen.

Immunogenetics

The most characteristic feature of epidermodysplasia verruciformis is immunotolerance toward own EV HPVs. However this infectious disease is not contagious for non EV patients due to genetic restriction towards EV HPVs in the general population [8]. In the rabbit Shope papilloma-

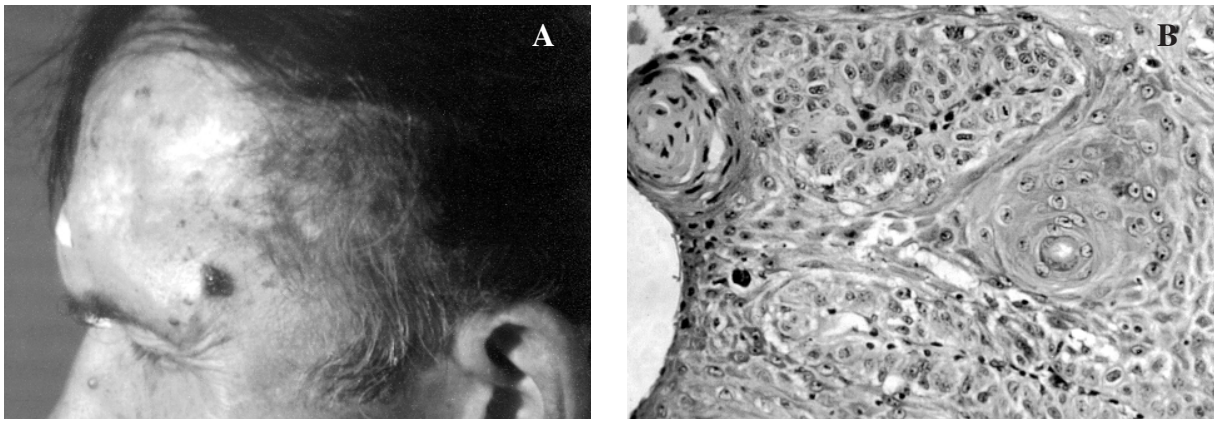

Fig. 2. Malignant progression in epidermodysplasia verruciformis
A. Multiple precancerous lesions on the forehead. Squamous cell carcinoma in the temporal area
B. Histological features of squamous cell carcinoma associated with EV HPV5, originating from hair follicles

carcinoma complex, which is considered as a model of EV [9], malignant progression and regression of rabbit papillomas were shown to be closely linked to MHC class II genes [10, 11]. However in a study on a large group of 57 EV patients we failed to reveal positive and negative associations with MHC class II DR-DQ haplotypes. Recently were characterized two adjacent genes on chromosome 17qter named EVER1 and EVER2 whose mutations are responsible for EV and susceptibility to EV HPVs [12]. It is still not known whether these genes control the interactions between EV HPVs and keratinocytes or are involved in the complex immune reactions against EV HPVs. Mutations of one of these genes were detected in all EV patients, in the Polish patients EVER2 was found mutated (to be published). Disclosure of EVER mutations could be helpful in recognizing the risk for the infection in the families of EV patients, as we could confirm in our familial cases.

Immune defect. Abnormal immune responses

A genetically transmitted specific defect of cutaneous cell-mediated immunity appears to be highly characteristic of the disease [13, 14]. Thus the skin responses to locally applied sensitizers, eg. DNCB, are absent in all patients [7]. In some cases with widespread skin changes, immunosuppression may be more pronounced, mainly due to a high viral load and extended co-infection with HPV3, virus that causes plane warts in the general population [15]. Although EV HPVs are not contagious for non-EV patients due to genetic restriction, in heavily immunosuppressed individuals, mainly in transplant recipients, in whom the warts and wart-like lesions are very numerous, EV HPV DNA could be sometimes transiently detected in warts induced by HPV3 not having clinical and histological features of EV [16]. In single cases of HIV infection and severe immunosuppression a symptomatic epidermodysplasia verruciformis was reported [17, 18].

Mechanism of transformation

Tumors developing in EV patients differ from cancers induced by genital high risk HPVs since EV HPV DNA is non integrated with the host DNA (except for extremely rare cases of metastases). Although mRNA EV HPVs and oncoproteins E6 and E7 are always present in tumor tissue, E6 does not degrade p53 [19] and E7 has a very low, if any, transforming activity [20, 21]. The mechanism of keratinocyte transformation by oncogenic EV HPVs is not entirely clear, but the dysfunction of p53 gene appears to play a part. Some p53 mutations were found specific of UVB sun mutations, as in C->T substitutions and CC->IT double base mutations in skin cancers in the general population. However some other mutations could result from high expression of the oncoproteins E6 and E7 of EV HPVs [22].

The role of sun

UVB may be one of the main factors in the development of immune suppression, specifically of impairment of contact sensitivity. Depending on the extent of this defect, some locally generated UVB-inducible cytokines could alter the function of antigen-presenting cells, although the number and distribution of Langerhans cells in EV was found unchanged [23]. Chronic UVB irradiation may induce cytokines with immunosuppressive properties. TNFα was found to prevent Langerhans cells from migrating to the regional lymph nodes [24] and mediate urocanic acid - induced immunosuppression after UVB exposure [25], and TGFβ is a cytokine with a variety of immunosuppressive effects. Both TNFα and TGFβ were found overexpressed in benign and malignant EV lesions [26]. Thus cytokines, especially TGFβ may be responsible for a relatively slow progression of EV tumors, as shown in some experimental models [27, 28]. In the in vitro study we also found increased production of immunosuppressive cytokine IL-10 after stimulation of PBMC from EV patients with virus-like particles (VLP) EV HPV 5 [29].

Why EV HPVs are ubiquitous HPVs but specific for EV?

EV HPVs are believed to be specific of EV because with previously used less sensitive, however specific molecular techniques Southern blot and molecular hybridization in situ EV HPVs were disclosed exclusively in patients with EV. The breakthrough in virological research was introduction of nested PCR [30] in several modifications and with the use of various, degenerate and specific primers, HPV DNA was disclosed in cancers and precancers in immunosuppressed [31-34] and immunocompetent population [35], but also in the normal skin [36] and the hair follicles [37, 38]. Thus it became evident that EV HPVs are ubiquitous HPVs present as a latent infection and in minute amounts especially in malignant tumors, but also in immunocompetent individuals. The question arises why these ubiquitous HPVs should be referred to as EV specific HPVs [39]. We believe that the term EV HPVs should be retained because these viruses produce the disease exclusively in specially susceptible EV patients [40] having specific genetic defect. Other persons are often infected, but the infection is symptomfree.Thus EV HPVs differ from all other HPVs, and their importance was established both for cutaneus oncogenesis and benign epidermal proliferation.

EV HPVs in malignant cutaneus tumors

Appearance of great numbers of warts and wart-like keratotic lesions in immunosuppressed population, often in close localization to or converting into skin cancers was suggestive of a relationship between warts and cancers. The

incidence of wart-like lesions and development of cancers was found to increase with duration and intensity of immunosuppression, the age of patients, environmental factors, especially sun exposure, etc. [41]. It was found that 9 years after transplantation the incidence of cancers was over 40% and of warts 89% [42]. However the prevalence of HPVs in cancers and precancers also depends on the method of detection. With the introduction of nested PCR technique EV HPV DNA was detected in transplant recipients in a much higher prevalence than found previously with the use of less sensitive methods [for review see: 30, 43-45]. With an improved technique the percentage of positive results for EV HPV DNA in SCC in immunosuppressed population was over 90% according to de Villiers [31], 84% for SCC and 75% for premalignant changes according to Harwood et al. [46] and 68% for cancer and premalignancies according to Berkhout et al. [34]. Further studies disclosed EV HPVs also in tumors of immunocompetent individuals, but the rate of detection was lower: 27-31% [35, 46], similar to that in basal cell carcinoma – about 36% [46, 47]. In should be stressed that only diverse EV HPVs and related sequences were present in cancers and precancers. However, no oncogenic EV HPV5 and HPV8 were disclosed, and no specific EV HPV type was associated with cutaneous malignancy. More importantly, no mRNA and no oncoproteins E6/E7 were detected in skin cancers, the viral load was very low, thus the role of EV HPVs in cutaneous oncogenesis is not entirely clear. However the association between the number of wart-like keratotic lesions and development of skin cancers in immunosuppressed population favored some involvement of EV HPVs in cutaneous oncogenesis. It appears that in the very early stages of oncogenesis EV HPVs mainly enhance the epidermal proliferation, as evidenced by a higher prevalence of EV HPV DNA in actinic keratoses than in squamous cell carcinomas. In our recent study on a large series of premalignancies and cancers we found in immunocompetent individuals EV HPV DNA in 57% of actinic keratoses vs. 45% of cutaneous cancers [48]. In later stages of cutaneous oncogenesis the sun-induced p53 mutations may facilitate the persistence of genotoxic effect and survival of UV-damaged cells leading to tumor development. Additional enhancing effect on cutaneous oncogenesis may have inhibition of sun-induced apoptosis by E6 protein of cutaneous HPVs, including oncogenic EV HPVs [49]. This effect appears to occur through stimulation of degradation of Bak, abrogating in this way its antiapoptotic activity. The lower detection rate in SCC may suggest that other cancerogenic and mutagenic factors are more important than EV HPVs in later stages of cancerogenesis [48]. Some involvement of EV HPVs in cutaneous malignancies is also confirmed by detection of antibodies to LI HPV8 capsid proteins [50] which is suggestive of activation of HPV life cycle and viral proliferation in differentiating keratinocytes.

EV HPVs in psoriasis

Since EV HPVs were found in such a high prevalence in tumors both in immunosuppressed and immunocompetent populations we were interested whether they are also present in benign epidermal proliferations. As a model of benign hyperproliferative disease we have chosen psoriasis. A quite unexpected finding was detection of EV HPV DNA in over 90% of plaques psoriatic, in about 80% high risk EV HPV5 or related HPVs [51]. These findings were confirmed by Pfister' group who disclosed high prevalence of potentially oncogenic HPV8 , HPV5 and closely related EV HPV36 [52]. In both studies high risk HPVs showed remarkable heterogeneity, as in patients with EV. Sequencing PCR products we have characterized 27 variants of EV HPV5 and 10 variants of EV HPV 36. The role EV HPVs in psoriasis remained unclear because of low amounts of EV HPV DNA and no mRNA and no E6/E7 oncoproteins in psoriatic epidermis. However with the use of specific ELISA and virus – like particles prepared in baculovirus system in about 25% of psoriatic patients were disclosed antibodies to HPV5 capsid LI protein [51]. Most importantly, recently we detected in over 50% of psoriatic patients antibodies to oncoproteins E6/E7 HPV5, i.e. in the prevalence similar as in patients with EV (53), and much superior to that found for HPV16 VLP) in genital HPV16 – associated cancers [54]. These findings strongly suggest that EV HPVs are expressed in psoriatic plaques and the viral cycle is activated in concert with proliferation and differentiation of keratinocytes since HPVs are unable to replicate outside the host cell.

Based on the model of skin grafted onto SCID mouse of Nickoloff [55] two steps in autoimmune pathway of psoriasis could be recognized. The first step would be a polyclonal activation of CD4+ T cells by superantigens (eg. streptopcocci) and the second step – autoimmune reaction between the putative autoantigen and superantigen-preactivated autoreactive T lymphocytes. Superantigen (microbial) driven polyclonal expansion of T cells is characteristic of guttate psoriasis (Fig. 3a). In plaque psoriasis there is a specific immune response to the putative antigen present in the psoriatic epidermis (Fig. 3b).

The intraepidermal CD8 + T cells with oligoclonal Vβ expansion [56, 57] could recognize viral peptides of the putative autoantigen in the context of class I MHC molecules on keratinocytes which leads to the autoimmune reaction and release of cytokines, mainly IFNγ [58]. On the other side, LI and E6/E7 EV HPV proteins expressed on the keratinocytes of the upper epidermis in psoriatic plaque, could serve also as a target for the generated anti-HPV5 antibodies [59, 60]. This specific reaction results in activation of a chemoattractive complement components, attraction of polymorphonuclears and formation of Munro abscesses, a highly characteristic feature of psoriasis [61] (Fig. 3c). Selfperpetuation of this immunological events and

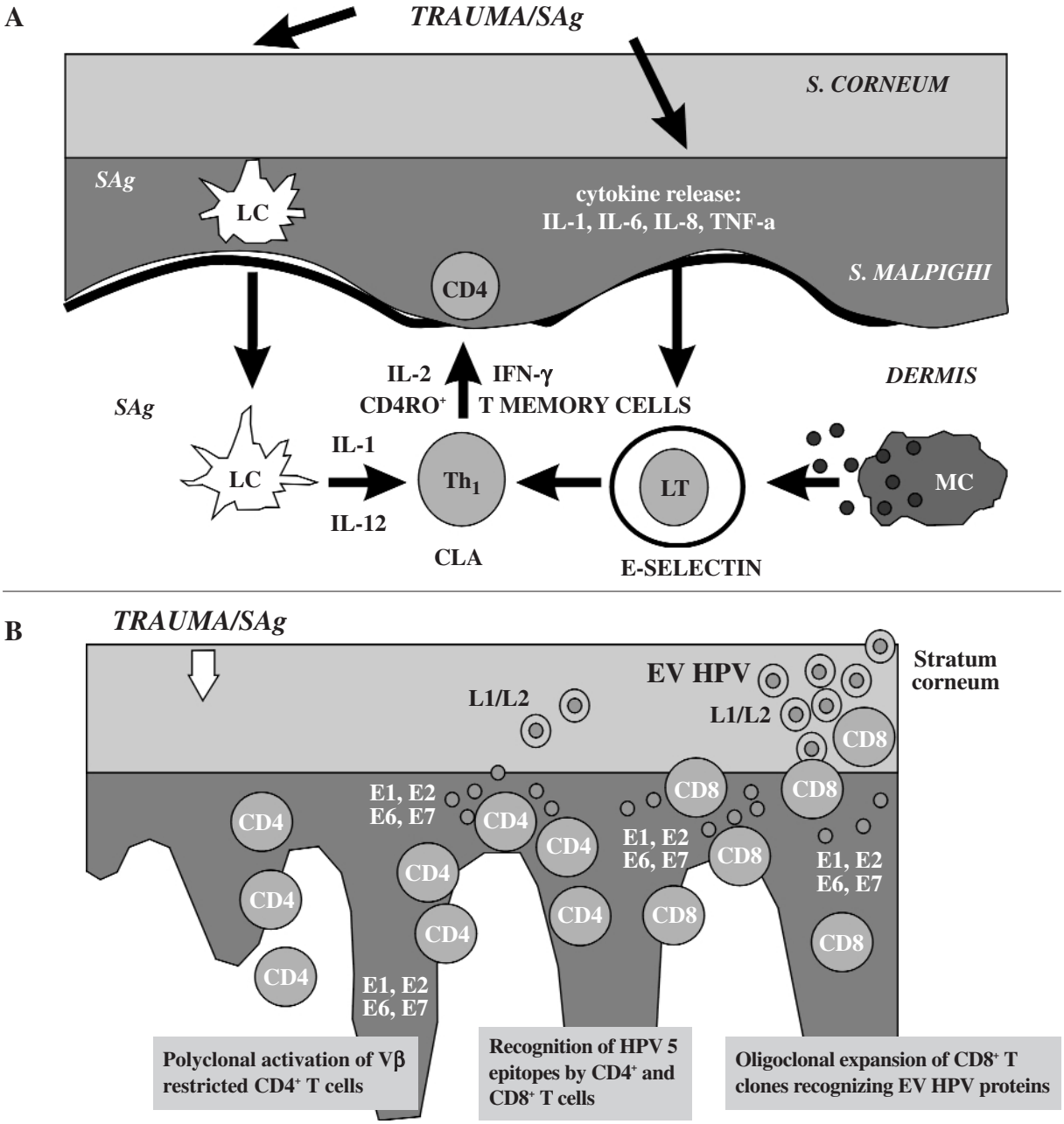

Fig. 3. Involvement of EV HPVs in the immunopathogenesis of psoriasis

A. Development of earliest psoriatic lesion (guttate psoriasis). Trauma or some bacterial and/or viral superantigens (SAg) from the circulation or skin surface, by release of cytokines (mainly proinflammatory IL-1, IL-6, IL-8, TNFα) start the inflammatory process. Due to the action of superantigens, Langerhans cells migrate into the corium, in which dendritic cells are accumulated. Through release of cytokines (mainly IL-1 and IL-12) they activate T cell proliferation (preferentially CD4) and production of IL-2 and IFNγ. Recruitment of T lymphocytes is facilitated by cytokine-induced adhesion molecules (eg. E-selectin) and by mast cell mediators, increasing vascular permeability. The ligand for E-selectin is cutaneous leukocyte antigen (CLA) present on activated T cells. These migrate into the epidermis starting inflammatory process

B. Development of plaque psoriasis. Proliferation of keratinocytes induced by activated CD4+ T lymphocytes promotes vegetative cycle of HPV5, and expression of early HPV genes (E1-E7) and viral DNA replication, whereas capsid protein synthesis occurs in the upper layers of the epidermis. HPV5 proteins could be recognized by superantigen preactivated T cells. CD4+ lymphocytes facilitate production of autoantibodies against viral peptides, mainly E6/E7 and capsid epitopes (L1/L2). CD8+ lymphocytes might recognize endogenously processed viral peptides presented by keratinocytes in the context of class I MHC

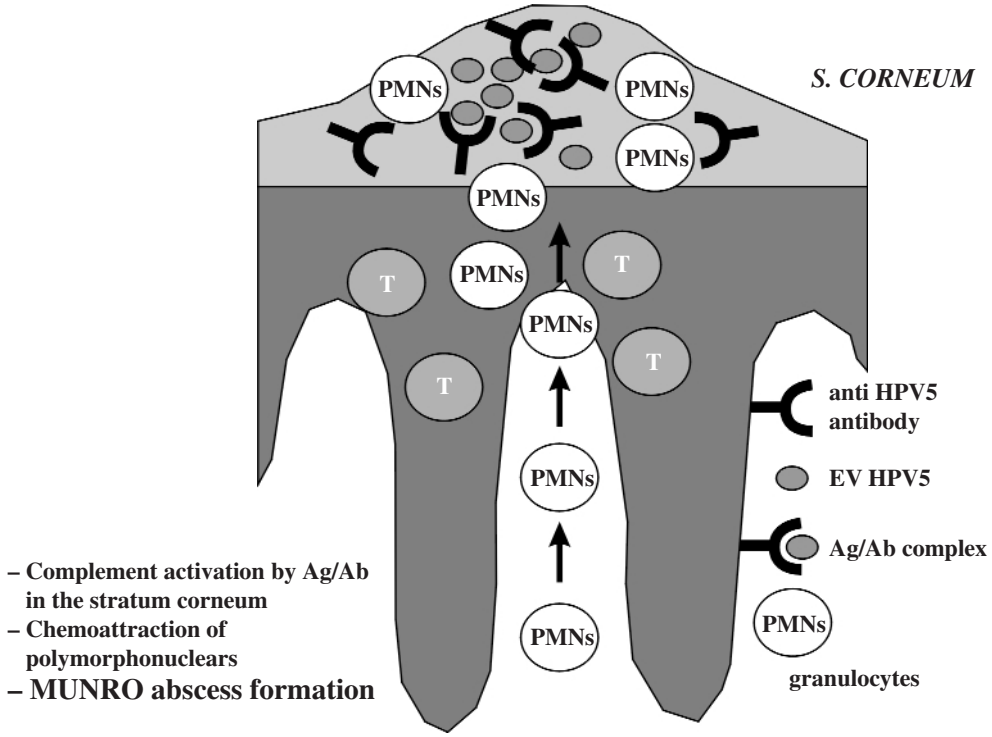

Fig. 3. Involvement of EV HPVs in the immunopathogenesis of psoriasis
C. Munro abscess formation. Reaction between viral proteins in the upper epidermis recognized by specific anti-HPV5 antibodies, leads to activation of chemotactic complement components, attraction of polymorphonuclears (PMNs) and formation of Munro abscesses. The accumulation of PMNs in the stratum corneum is a most characteristic feature of psoriasis, and the site of effector immune reaction strongly indicates that putative antigen is present in the stratum corneum

the sustained hyperproliferation in genetically predisposed individuals is due to induction of autoreactive T cells by EV HPV antigens, and production of proinflammatory cytokines, mainly IFNγ and IFNγ – inducing cytokines.

High risk EV HPVs are not a cause of psoriasis but are involved in its pathogenesis

EV HPV5 and 8 are not a cause of this genetic disease since they become activated also in other benign epidermal proliferations, eg. in healing processes in burns or in autoimmune bullous diseases [62]. We found that in the epidermal repair are generated antibodies to HPV5 L1 protein which are present until the healing is complete, and then disappear spontaneously. The influx of inflammatory cells releasing proinflammatory cytokines and growth factors leads to epidermal hyperproliferation allowing reepitelization of the wound [63] through activation of the transient amplifying cells adjacent to the tips of dermal papillae and having high proliferative potential [64, 65]. Early oncoproteins of EV HPVs, present in normal conditions in the hair follicles and interfollicular epidermis, could enhance epidermal proliferation, thus playing role in wound healing. However, in contrast to psoriasis, the process of repair is transient, whereas in psoriasis it is sustained by the inflammatory immune responses, induced by autoreactive T and B lymphocytes. We have recently shown that HPV5 VLPs stimulate IFNγ production by T cells from patients with psoriasis, but not from patients with healing wounds [66].

Why skin cancer is infrequent in psoriasis that is associated with potentially oncogenic EV HPVs

The question arises why skin cancers are relatively rare in psoriasis in spite of association with high risk EV HPVs, and in spite of applied therapies with immunosuppressive and cancerogenic drugs and UV irradiation. The reason for this appears to be the inflammatory process with enhanced activity of NK-T cells [67], proteases released from accumulations of polymorphonuclears, the accelerated keratinocyte turnover and constant desquamation of the upper parts of the epidermis, which prevents persistence in the skin of transformed cells. Thus, in contrast to epidermodysplasia

verruciformis, potentially oncogenic EV HPVs in psoriasis appear only to enhance proliferation of keratinocytes and stimulate immune reactions, not promoting cancerogenesis. However excessive doses of PUVA (over 2500J/cm^2) and intensive sun exposure might be cancerogenic [68, 69]. Rare cancers developing in these cases were found to harbor some EV HPV5 DNA which was not disclosed in cancers not associated with psoriasis [45, 70, 71].

The novel therapies in psoriasis targeting selectively components of immune system

The immunotherapies with the use of monoclonal antibodies interfering with T cell activation and inflammatory cytokines inducing keratinocyte proliferation partially block different components of the immunopathogenic pathway of psoriasis, and therefore are beneficial for the patient. Being more selective than drugs producing global immunosuppression they interfere with various stages in autoimmune pathway of psoriasis with antiproliferative effect [72-74]. Inhibition of keratinocyte proliferation might be achieved also by UV irradiation and PUVA, which have a direct effect on keratinocytes and also decrease the immune responses. Thus in psoriasis, in contrast to epidermodysplasia verruciformis, associated with the same potentially oncogenic EV HPVs, immunosuppression is highly beneficial whereas in patients with EV immunosuppressive drugs could lead to increased activation of EV HPVs and tumor progression. The UV radiations, effective in psoriasis, are highly dangerous in patients with EV enhancing cancer development, invasive growth and metastasis formation.

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