Specific Human Papillomaviruses Could Participate in Epidermal Hyperproliferation and Autoimmune Phenomena in Psoriasis

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Sir,

We have read with interest the paper by Kirby et al. (1) on a possible involvement of cytomegalovirus (CMV) and human herpes viruses (HHV) 6 and 7 in psoriasis. We agree with the authors' criteria for a candidate etiologic agent in psoriasis which should: (i) be common; (ii) have a predominantly asymptomatic primary infection; (iii) be able to remain latent and reactivate within the host; (iv) be capable of being detected in the skin; and (v) be able to induce a local inflammatory response.

The authors found no evidence to link CMV, HHV6 and HHV7 with the development of plaque psoriasis. The main feature in plaque psoriasis is clonal intra-epidermal expansion of CD8+ lymphocytes suggestive of a classical pathway of antigen activation. Such CD8+ cells could recognize a putative (auto)antigen (i.e. viral peptides) presented on the surface of psoriatic keratinocytes in the context of MHC class I molecules. Since the target structure for the psoriatic inflammatory reaction seems to be localized to the uppermost parts of the epidermis (accumulation of polymorphonuclears, so-called Munro abscess), the putative (auto)antigen should be expressed in this area.

Two of the criteria (iii and iv) proposed by Kirby et al. could be slightly modified for psoriasis to involve keratinocytes; an etiologic agent should: (iii) be able to remain latent and reactivate within the host keratinocytes; (iv) be capable of being detected in keratinocytes.

Neither the studied viruses (CMV, HHV6 and 7) nor HIV and HCV fulfil the revised criteria in contrast to the strictly epitheliotropic human papillomavirus genotypes associated with epidermodysplasia verruciformis (EV-HPVs). In our previous studies (2, 3) we found that DNA of EV-HPV (e.g. HPV5) is detected in over 80% of psoriatic skin specimens (2), that latent EV-HPV infection is activated in concert with keratinocyte proliferation (3), and that antibodies are elicited to viral capsid proteins (2, 3).

We agree that initiation of a psoriatic process is probably due to activation of CD4+ lymphocytes by superantigens (bacterial, viral or others). Th1 proinflammatory cytokines stimulate keratinocyte proliferation, and thus may lead to the activation of latent EV-HPV infection. Moreover, recently, it has been shown that proinflammatory cytokines, interferon γ and interleukin 17, present in large amounts in psoriatic lesions, could directly stimulate the promoter of EV-HPV type 20 (4).

EV-HPVs could contribute to the pathogenesis of psoriasis in several ways (5, 6). Early proteins E6 and E7 are known to stimulate keratinocyte proliferation. On the other hand, these proteins and capsid proteins L1 and L2 could serve as a target for humoral and cellular autoimmune reactions. Viral peptides could be recognized on the surface of keratinocytes by CD8+ lymphocytes in the context of class I MHC molecules. Capsid proteins expressed in terminally differentiating keratinocytes could be recognized by specific antibodies, leading to complement activation, attraction of polymorphonuclears, thus resulting in Munro abscess formation.

EV-HPVs are known pathogens showing exclusive tropism for keratinocytes, and fully dependent on keratinocyte proliferation and differentiation for their replication. This close relationship between EV-HPVs and keratinocytes strongly suggests that the viral proteins could be involved in epidermal hyperproliferation, such as psoriasis. Further evidence of a possible involvement of EV-HPVs in psoriasis is the co-localization of susceptibility loci for psoriasis and for epidermodysplasia verruciformis to the same chromosomal region 17 q25 (7).

We do not claim that EV-HPVs are etiologic agents in psoriasis, but there is sufficient evidence to suggest that these viruses may play a role in the development and maintenance of plaque psoriasis, both by stimulation of epidermal hyperproliferation and by self-perpetuation of autoimmune phenomena.

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Editor comment: Kirby et al. have been given the opportunity to respond to this letter but they have nothing further to comment.