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Control of immune escaped human papilloma virus is regained after therapeutic vaccination

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High-risk human papillomaviruses infect the basal cells of human epithelia. There it deploys several mechanisms to suppress pathogen receptor recognition signalling, impeding the immune system to control viral infection. Furthermore, infected cells become more resistant to type I and II interferon, tumour necrosis factor-α and CD40 activation, via interference with downstream programs halting viral replication or regulating the proliferation and cell death. Consequently, some infected individuals fail to raise early protein-specific T-cell responses that are strong enough to protect against virus-induced premalignant disease and ultimately cancer. Therapeutic vaccines triggering a strong T-cell response against the early proteins can successfully be used to treat patients at the premalignant stage but combinations of different treatment modalities are required for cancer therapy.

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Introduction

Progressive infections show split immunity to HPV late and early proteins

About 80% of sexually active individuals become infected with a high-risk HPV type (hrHPV). While most hrHPV infections (90%) are controlled within two years [1], viral persistence may lead to malignancies. The hrHPV are responsible for ~5% of all human cancers. Of the 14 different hrHPV types detected in cervical carcinoma, HPV16 and 18 are the most prevalent. HPV16 is the dominant type in all other HPV-induced cancers [2,3].

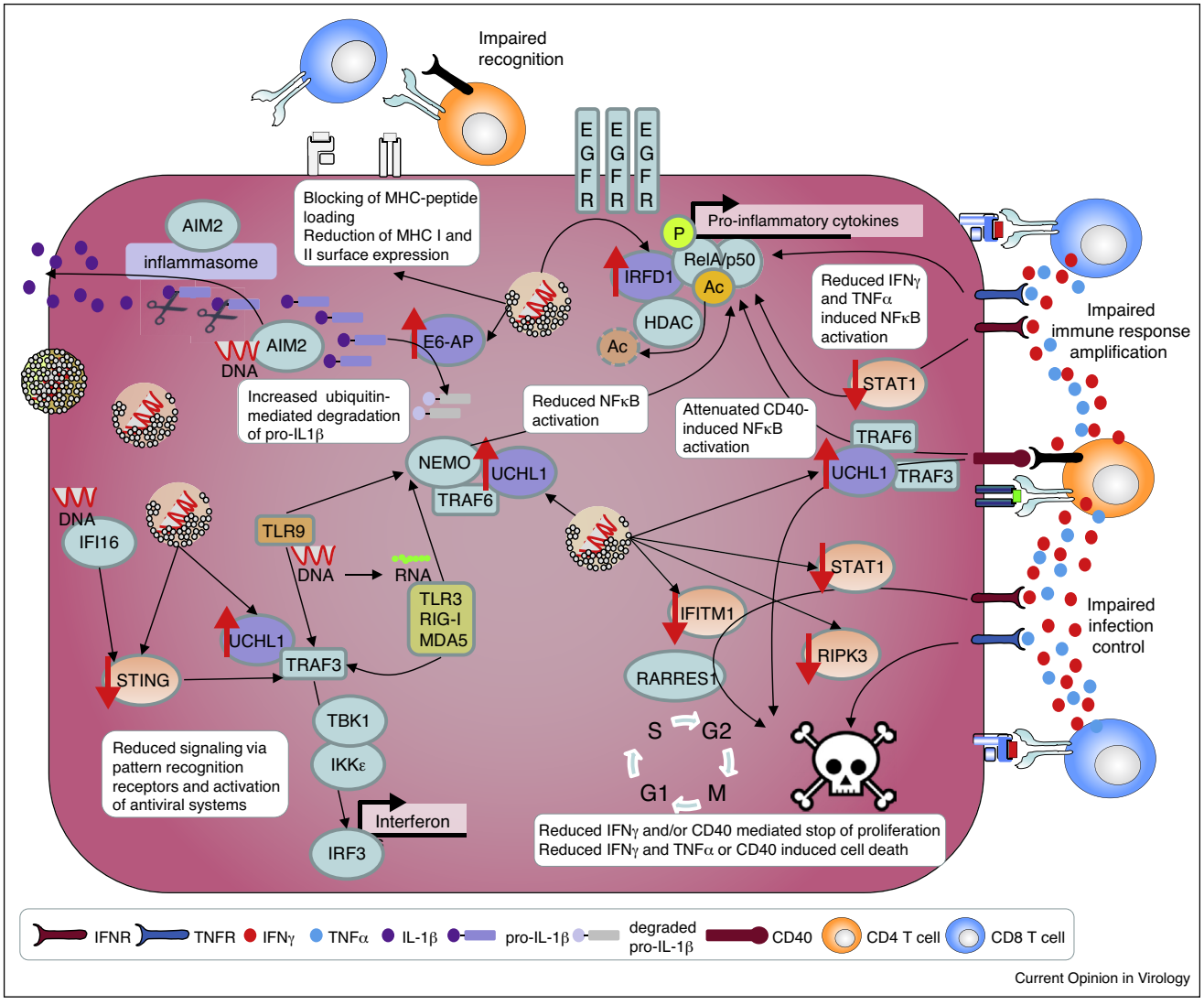
HPV exclusively infect keratinocytes (KCs) in the basal layer of the epidermis and mucosal epithelia, through micro-wounds and abrasions. In the large majority of exposed but healthy individuals strong type 1 (IFNγ, TNFα, IL-2 producing) T-cell responses to the structural protein L1 as well as the early proteins E2, E6 and E7 are detected [4–7]. Stimulation of the L1-specific immune response most likely occurs via the uptake of virions, produced during the productive phase of the infection, by the Langerhans cells that reside in the epidermis. T-cell responses to L1 are detected in healthy individuals and in patients with premalignant lesions or cancer [7]. While they reflect a productive infection, they do not contribute to the control of viral infection as L1 is not expressed in the first few layers of the proliferating infected basal cells. In these layers, however, the early proteins E2, E6 and E7 are produced and immunity may be induced if these proteins are taken up by professional antigen presenting cells. However, type 1 T-cell responses to the early proteins are weak at best in patients with persistent infections.

The HPV infected skin expresses the cytosolic DNA sensors STING, AIM2 and IFI16. HPV DNA can trigger the latter two resulting in the secretion of IL-1β and IL-18 [8]. These cytokines mediate local and systemic immune responses to infection [9] and might be critical for early immune control of virus replication [10–12]. Hence, there is a period in which an HPV infection may trigger a protective T-cell response, dominated by CD4+ T-cells [5,6,12,13,14•], but if this response is too weak or too late HPV may deploy several mechanisms to suppress the pathogen recognition receptor pathways [15–19,20••,21–23]. Importantly, as HPV infection does not cause viremia or cell lysis, either intact immune signalling or minor trauma to the lesion [24] is crucial to induce protective immunity.

Mechanisms used by HPV to prevent immune control

Basal KCs express several pattern-recognition receptors (PRR) that can recognize viral DNA or RNA (Figure 1). PRR ligation results in the production of type I interferon and pro-inflammatory cytokine production through signaling via interferon regulatory factor (IRF) and nuclear factor of kappa-light-chain-enhancer of activated B cells (NFκB) activating pathways. Several genome-wide transcription studies reported that hrHPV types have found means to suppress PRR- and type I IFN-induced signaling pathways [22]. Recently it was found that the cells in hrHPV-positive low-grade lesions display higher levels of

Figure 1



High-risk human papillomavirus deploys countermeasures to prevent immune control.
High-risk HPV can infect basal keratinocytes. The virus can be recognized by the pattern recognition receptors for viral DNA: IFI16, AIM2, TLR9 and for viral RNA: TLR-3, RIG-I, MDA-5. Most of these will activate interferon production via TRAF3-TBK1-IKKε-IRF3 interactions but this is prevented by downregulation of STING and the upregulation of UCHL1, which inactivates TRAF3 via deubiquitination. UCHL1 also suppresses TLR9 and TLR3/RIG-I/MDA5-mediated activation of NFκB via interaction with TRAF6 and degradation of NEMO. While viral DNA may activate the formation of the AIM2 inflammasome, required to cleave pro-IL1β into the potent immune activating cytokine IL-1β, the upregulation of E6-AP results in the ubiquitination of pro-IL1β targeting it for proteasomal degradation. Activated CD4+ type 1 T cells express CD40L and produce IFNγ and TNFα. Activation of CD40 and the IFNγ receptor (IFNR) result in proliferative arrest of cells, but this is impaired by the downregulation of STAT1 and IFITM1 (downstream of IFNR) and deactivation of TRAF3 (downstream of CD40) by UCHL1, with as result less upregulation of the antiproliferative gene RARRES1. RIPK3 is one of the key components in necroptosis, which is down-regulated by hrHPV, resulting in reduced IFNγ and TNFα induced necroptosis. High-risk HPV induces the overexpression of epidermal growth factor receptors (EGFR) and this increases the expression of IFRD1. IFRD1 mediates RelA K310 deacetylation thereby attenuating the transcriptional activity of NFκB. The resistance will be similar to CD8+ T-cell produced IFNγ and TNFα. Black arrows indicate the normal reactivity in the cell after stimulation. The purple proteins are upregulated and orange proteins are downregulated as a result of hrHPV infection.

E2 than normal hrHPV-infected cells, and this coincided with downregulation of STING [20••]. Furthermore, hrHPV upregulated UCHL1, a deubiquitinase which was shown to inactivate TRAF3 and mediates the degradation of NEMO [15] and it may inhibit TLR9 expression [25]. Notably, prednisolone- and hydroxychloroquine-mediated downregulation of TLR7 and TLR9, respectively, is associated with HPV infections [26]. As a consequence, persistently hrHPV-infected cells will be less equipped to attract and activate the