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The Invisible Enemy – How Human Papillomaviruses Avoid Recognition and Clearance by the Host Immune System

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Abstract: Human papillomavirus (HPV) needs to persist in squamous epithelia for a certain amount of time to complete its reproductive cycle. Therefore, the virus has evolved multiple immune evasion strategies. The interplay of these immune evasion mechanisms with the host immune system decides whether a HPV infection is cleared or becomes persistent. Clearance of HPV-induced lesions is mediated by a cellular immune response, consisting of both cytotoxic T lymphocyte and T helper cell responses. Persistent HPV infection, on the other hand, is the single most important risk factor for the development of HPV-associated premalignant lesions and HPV-driven cancers. This article reviews the immune evasion mechanisms employed by high-risk HPVs to escape host immune recognition and attack.

Keywords: Cancer, human papillomavirus (HPV), immune response, immune evasion.

INTRODUCTION

Cervical carcinoma and several other malignancies arise as a consequence of persistent infection with high-risk types of human papillomavirus (HPV). Papillomaviruses are small nonenveloped double-stranded DNA viruses with strict tissue and species specificity. Over 190 distinct genotypes have been identified to date, 151 of them isolated from humans [1]. Papillomaviruses exclusively infect squamous epithelia, i.e. skin and mucosae. Skin types induce common warts, and may be implicated in non-melanoma skin cancer [2]. The mucosal types of HPV fall in two groups – so-called low-risk types (mainly HPV 6 and 11), which induce genital warts, and the high-risk types, which lead to cervical carcinoma and several other malignancies, such as anal cancer and oropharyngeal carcinomas [3, 4]. The most prevalent high-risk HPV types are HPV16 and HPV18, being responsible for 50% and 20%, respectively, of cervical cancer cases globally [5]. The extracervical HPV-mediated cancers are almost exclusively caused by HPV16. Taken together, HPV causes 530,000 new cancer cases and 275,000 deaths each year [6].

Natural history studies indicate that nearly every sexually active individual will acquire at least one high-risk HPV infection during their lifetime [7, 8]. Fortunately, the majority of HPV infections are eradicated by the host immune system within 1-2 years of acquisition (median 6 months) [9], and only <1% of infected people develop HPV-mediated cancers [10, 11]. Nevertheless, immune clearance of HPV is much slower than clearance of most other viruses, and the fact that some HPV-associated lesions can persist and progress into cancer emphasizes the capacity of HPV to escape host immune surveillance. Detailed understanding of these events on a cellular and molecular level may result in therapeutic strategies to overcome immune escape. This review will focus on the immune evasion strategies employed by HPV. In this context, it is necessary to give an overview of the HPV life cycle first.

The HPV Infectious Life Cycle

HPV exclusively infects the basal layer of epithelial cells, after the basement membrane of a squamous epithelium has been exposed by a microwound [12]. The HPV genome consists of approximately 8 kb circular, double-stranded DNA, which is organized into coding and non-coding regions. 6 early open reading frames (ORFs) encode early proteins: E1, E2, E4, E5, E6 and E7; and 2 late ORFs encode late proteins: L1 and L2. The non-coding regulatory region is critical for initiation of viral DNA replication and transcription of the viral genes [12-14]. The initial phase of HPV infection is characterized by presence of the virus as an episome in the basal layer of undifferentiated epithelial cells, which is maintained only at very low levels (50 to 100 copies per cell) [15]. Viral proteins are expressed at low levels as well and confined mainly to the nucleus of the basal cells [16]. Viral genome replication requires two viral initiation factors: E1, which contains helicase-ATPase activity, and E2 with multiple activities in replication, transactivation and repression. Because HPV does not encode DNA polymerase activity for viral genome replication, the host DNA replication machinery is required. However, in squamous epithelia, only the basal cells divide and DNA replication activity is normally suppressed in differentiating cells that exit from the basal layer. To hold the cellular replication machinery active, the viral proteins E6 and E7 are produced, which inactivate p53 and the retinoblastoma protein (pRb), respectively, to prevent cell growth arrest and delay differentiation. E7 binds the unphosphorylated form of pRb and forces infected keratinocytes to remain in a proliferative state. Moreover, it stimulates cyclin A and E, promoting G0/G1 progression.

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The E6 protein induces the rapid degradation of p53 through ubiquitin-dependent proteolysis to prevent apoptosis and allows cell survival [13, 17-19].

The expression of these early viral genes is tightly controlled under the differentiation program of keratinocytes and increased only when keratinocytes migrate through the upper layers of the epithelium. When the infected keratinocytes enter the differentiating compartment in the suprabasal layers of the epithelium, the expression of all viral genes is induced to accelerate viral genome replication, with amplification of viral copy number to thousands of copies per cell [12, 14]. The final stage of HPV infection leads to packing of amplified genomes into infectious particles formed by the L1 and L2 proteins, which spontaneously self-assemble into icosahedral capsids. New virus particles are produced within the uppermost layers of the epithelium, and released by the normal process of epithelial cell shedding at the end of their lifespan [12].

IMMUNE EVASION STRATEGIES EMPLOYED BY HPV

Protective immunity results from the interplay of non-specific innate immunity and antigen-specific adaptive immunity. The innate immune system senses "danger" *via* signals from molecules that would normally not be found in the human body, such as damaged tissue, repetitive surface structures of bacterial cell walls, or DNA sequences containing typical viral sequence motives. These structures are recognized by pattern recognition receptors, such as e.g. Toll-like receptors (TLRs) [20, 21]. Sentinel cells, such as dendritic cells (DCs) or Langerhans cells (LCs) in the skin and mucosa, continuously screen the environment and - if triggered - coordinate innate immune effectors and the initiation of an adaptive immune response [22]. HPV has evolved mechanisms both to avoid initial recognition and to interfere with adaptive immunity.

Establishment of Immunological Ignorance

The key viral strategy to avoid the host immune system is to maintain a low profile. The virus exclusively infects epithelial cells, and the whole replicative cycle happens outside the basement membrane, away from the dermal immune effector cells.

The virus encodes only non-secreted proteins, which are mostly localized in the nucleus of infected cells and expressed at a very low level. To keep expression of the viral genes low, HPV utilizes two mechanisms: the viral protein E2 acts as a repressor of other early gene expression in basal cells [12]. Moreover, HPV exploits the redundancy in the genetic code. The codon usage pattern in the HPV genome differs from the commonly used mammalian codons. The potency of this mechanism has been demonstrated by studies replacing viral codons with codons preferentially used in keratinocytes, which led to significant protein up-regulation [23, 24]. This strategy helps HPV to be invisible to the host immune system at the early stage of viral infection.

Increased viral protein expression only occurs in keratinocytes in the upper layers of the epithelium where the immune system has limited access. Furthermore, there is no viremia, no cell death, and no cell lysis upon viral shedding [16]. Additionally, HPV E6 and E7 have been implicated in direct inhibition of TLR9-mediated pathways by down-regulating the transcription of the TLR9 gene [25].

Thus, HPV infection does not elicit any danger signals, which would be crucial for activation and trafficking of antigen presenting cells (APCs), production of pro-inflammatory cytokines and initiation of adaptive immune responses [12, 14].

Modulation of Apoptosis

Apoptosis – programmed cell death – is regulated physiologically and genetically, and plays a central role in development, morphogenesis, normal cell turnover and immune system function [26, 27]. Two major apoptotic pathways have been identified, both activating effector caspases. The extrinsic death receptor pathway starts with ligation of a death ligand (CD95L) to its transmembrane death receptor (CD95), followed by activation of caspases in the death-inducing signaling complex. The intrinsic pathway involves mitochondria, which release caspase-activating proteins into the cytosol, thereby forming the apoptosome where caspases will bind and become activated [26, 27]. Apoptosis resistance is an important aspect in viral infection and progression to cancer, because it might contribute to immune escape. Virus-infected or tumor cells can acquire resistance to apoptosis by the expression of anti-apoptotic proteins or by the down-regulation or mutation of pro-apoptotic proteins. Indeed, HPVs have evolved mechanisms to modulate apoptosis to avoid immune attack and establish successful infection [28] (Fig. **1**). The E5 protein inhibits tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL)- and CD95L-mediated apoptosis at early stages of HPV infection when the viral genome is episomal [29, 30]. E5 promotes down-regulation of the CD95 receptor and CD95 surface location, and additionally modulates the formation of the death-inducing signaling complex (DISC) [29, 31]. The E6 protein impairs apoptosis through the ATP-dependent degradation of pro-apoptotic proteins such as p53, FADD, procaspase-8, or c-Myc, employing the ubiquitin-proteasome pathway [32-34].

Interestingly, recent studies suggest that high-risk HPV proteins E6 and E7 are able to independently activate low levels of caspases upon epithelial differentiation to induce productive viral replication, representing a way by which HPV controls viral gene expression in differentiating cells [35]. HPV-mediated caspase activation is associated with increased levels of anti-apoptotic factors, which may be important in providing a balance between cell viability and cell death upon differentiation. E7-mediated activation of caspases is inhibited in E6-expressing cells and may occur only in the absence of E6 [35]. It is intriguing that HPV can inhibit apoptosis in undifferentiated cells, but influence apoptotic signaling pathways in differentiating cells. It is possible that during a productive viral life cycle both inhibition and induction of apoptosis are required, and that E6 controls apoptosis pathways in both directions, depending on the differentiation stage [31, 35]. Nevertheless, this phenomenon still needs to be investigated in more detail.

Dysregulation of Interferon Responses

Interferons (IFNs) are widely expressed cytokines that have potent anti-viral, immunostimulatory, and growth-inhibitory

effects. The two main classes of interferons comprise type I IFNs (IFN-α, IFN-β, IFN-κ) and type II IFN (IFN-γ). Type I IFNs are the first line of immune defense against viral infections, causing the so-called "antiviral state" in infected cells, and enhancing immune responses through the stimulation of dendritic cells. This indicates that IFN-α and IFN-β act as an important link between innate and adaptive immunity [36]. Upon viral infection, a signal transduction pathway involving the TYK2 and JAK1 kinases is activated, leading to a transcription factor complex composed of STAT1, STAT2, and interferon regulatory factor 9 (IRF-9), and the increased production of IFN-α and IFN-β *via* IRF-3 and IRF-7 [37]. Like most DNA viruses, HPV is able to directly modulate the interferon signaling cascade and IFN synthesis (Fig. **1**). During infection with high-risk HPV, the E6 protein can inhibit IRF3 transactivation, preventing IFN-β induction [38]. HPV E6 has also been postulated to interfere with the TYK2 kinase, which is required for the activation of IFN-stimulated gene (ISG) transcription. Dysfunction of TYK2 prevents its binding to the IFN receptor and blocks phosphorylation of TYK2, STAT1 and STAT2, thus dysregulating the JAK-STAT activation machinery [39]. The E7 protein is able to inhibit the IRF1 and IRF9 transcription factors, which contribute to ISG transcription. E7 binds to the p48/IRF9 complex and abrogates its translocation to the nucleus, thereby inhibiting the formation of the IFN-stimulated gene factor 3 (ISGF3) transcription complex that binds the IFN-specific response element (ISRE) in the nucleus [40]. Interaction of the E7 protein with IRF1 is characterized by recruiting histone deacetylases to the IFN-β promoter site, thus blocking transcription [41, 42]. *In vivo* HPV E7 inhibits the trans-activation function of IRF1, which leads to down-regulation of TAP1 (transporter associated with antigen processing 1), IFN-β, and MCP1 (monocyte chemo-attractant protein-1) [43].

More recently, it was found that high-risk HPV E6 plays a potential role in repression of the constitutive transcription of IFN-κ *via* reduction of ISG expression [44, 45]. IFN-κ not only regulates antiviral-ISG expression and components of the IFN pathway, but also maintains the expression of pathogen recognition receptors such as TLR3, which in turn control inducible IFN expression in normal human keratinocytes [45]. Taken together, the HPV E6 and E7 proteins directly influence expression and functions of IFNs to prevent host immune attack.

A recent genome-wide expression profiling study in HPV-infected basal keratinocytes [46] revealed that HPV not only influences the interferon pathway, but also dampens a whole network of genes downstream of the pattern recognition receptors (PRRs, such as TLRs and RIG-I-like receptors), including antimicrobial molecules, chemotactic and pro-inflammatory cytokines, the inflammasome, and components of the antigen processing machinery. IL-1β and IL-6 were found to be at the center of this network. The fact that HPV was only found to dampen, but not to completely block, PRR signaling corresponds to the clinical finding that HPV clearance is slow but eventually successful in the majority of infected individuals.

Perturbation of Antigen Processing and Presentation

T cells - both CD8+ cytotoxic T lymphocytes (CTLs) and CD4+ helper T cells (Th) - play a critical role in HPV control and clearance [47]. The major histocompatibility complex (MHC) - in humans known as human leukocyte antigen (HLA) - is a key player in the antigen-specific cell-mediated immune response. These cell surface molecules act as restricting elements in the recognition of antigens by T cells. MHC class I (MHC-I) presents antigen to CTLs. MHC class II (MHC-II) surface expression is restricted to professional antigen presenting cells (APCs), such as macrophages, B-cells and especially dendritic cells (DCs) that present antigen to T helper cells (Th) [48]. Many viruses down-regulate MHC molecules to evade recognition and elimination by the immune system and HPV is not an exception [49-52].

Antigen processing consists of cellular and viral antigens being degraded by the proteasome. Resulting peptides are transported into the endoplasmatic reticulum by TAP, where they are loaded on empty MHC molecules. Complete MHC-peptide-complexes are then transported to the cell surface *via* the Golgi apparatus, and the peptides presented by MHC to the immune system.

Disruption of antigen processing and presentation mediated by HPV includes decreased expression of the proteasome subunits LMP2 and LMP7 [53], decreased expression of transporter subunits (TAP1 and TAP2) [53], and decreased expression of MHC-I itself [53] (Fig. **1**). The E7 protein of high-risk HPV has been found to repress the MHC class I heavy chain gene promoter [54]. In addition, E7 also possesses the ability to repress the bi-directional promoter that regulates expression of both LMP2 and TAP1 [54]. The reduced expression of these antigen processing machinery components may cause impaired production of HPV epitopes, leading to a reduced HPV epitope repertoire [55]. HPV E5 has been reported to down-regulate HLA-A and -B cell surface expression, but no decrease was found in total HLA-C and -E class I expression [30, 56]. This reduction is likely due to impaired MHC class I trafficking, caused by direct interaction of the E5 protein with the MHC class I heavy chain *via* the leucine pairs present in the first transmembrane domain [57]. Another mechanism is the arrest of MHC class I molecules in the Golgi apparatus (GA), caused by E5-induced alkalization of the GA and endosomes *via* interaction with the 16 kDa pore subunit of vacuolar-ATPase (V-ATPase) [58, 59]. Consistent with its role in the alkalinization of endosomes, E5 can prevent the endosomal breakdown of the invariant chain, a chaperone important in the maturation of MHC class II, leading to inhibition of expression of surface MHC class II [60].

The functional effect of the down-regulation of MHC class I and class II molecules on the surface of HPV-positive cells is reduced recognition by T cells, leading to an escape from immunosurveillance. As HLA-C and -E are still expressed, HPV-infected cells do not become targets of natural killer (NK) cells, which recognize and kill cells with reduced MHC class I expression.

Modulation and Trafficking of Antigen Presenting Cells

Langerhans cells (LCs) are immature dendritic cells of myeloid origin resident in squamous epithelia. The normal function of LCs is to screen cell surfaces for pathogens, capture antigens by micropinocytosis or mannose receptor-mediated uptake, process captured proteins into

immunogenic peptides, migrate out of the epithelium to the lymph nodes and present peptides in the context of MHC molecules to T cells, thereby initiating antigen-specific immune responses. Because of their role in initiating antiviral immune responses, DCs and LCs represent ideal targets for immune evasion by viruses.

It has been reported that upon HPV infection the number of LCs is significantly reduced in the infected section of the epithelium. This was attributed to E6-mediated reduced expression of the epithelial adhesion molecule E-cadherin on HPV-infected keratinocytes [61, 62]. LCs normally adhere to keratinocytes *via* this molecule, and migrate out of areas with reduced E-cadherin expression. Furthermore, E6 and E7 down-regulate macrophage inflammatory protein (MIP)-3α expression [63], leading to reduced attraction of APCs to the infected regions (Fig. **2**).

The influence of HPV on the trafficking of immune cells has been investigated by employing HPV virus-like particle (VLP) technology. It has been found that the L1 major capsid protein, when self-assembled into VLPs, induces DC maturation through the overexpression of CXC receptor 4 (CXCR4), *via* the activation of the NF-κB and mitogen-activated protein kinase (MAPK) signaling pathways [64]. L1 VLPs also increased the production of pro-inflammatory cytokines and chemokines by DCs, the enhanced migration of DCs, and the induction of an HPV16-specific CD8+ T cell response. However, natural HPV capsids are composed of L1 and L2, and HPV L1L2 VLPs do not induce LC maturation. Instead, they suppress the generation of an effective HPV-specific immune response *via* the deregulation of the PI3K-Akt pathway in LCs, suggesting that the HPV minor capsid protein is also involved in immune evasion, by inhibiting the maturation of LCs [65, 66]. Taken together, these mechanisms result in suboptimal antigen capture and/or LC activation, which would be necessary for the initiation of anti-viral T cell responses.

Polarization of T Cell Phenotypes

The polarization of CD4+ T cells occurs upon interaction of naïve CD4+ T cells with their cognate antigen and depends on the cytokine environment. CD4+ T cells include T helper type 1 (Th1) cells, which stimulate cellular immune responses; Th2 cells, which promote humoral responses; Th17 cells, which contribute to the elimination of extracellular pathogens; and Foxp3+ regulatory T (Treg) cells, which prevent the development of autoimmunity. Th1 cells secrete high levels of IFN-γ and interleukin (IL)-2. The differentiation of Th1 is controlled by IL-12, in synergy with IL-18. IL-12 signals through JAK2 and TYK2, and activates mainly STAT4, a key transcription factor for Th1 consolidation [67]. Th2 cells secrete high amounts of IL-4, IL-5, IL-9 and IL-13. The acquisition of the Th2 phenotype is essentially driven by IL-4, which activates both JAK1 and JAK3 and the transcription factor STAT6 [68]. Several lines of evidence suggest that cell-mediated immune responses involving Th1 and CTL are essential for eradicating established HPV infections [69-71].

A further immune evasion mechanism employed by HPV is to inhibit the Th1-response by inducing a shift from Th1 to Th2 (Fig. **2**). HPV-related lesions have been found to be characterized by weak or absent IFN-γ-associated Th1 cell responses, but an up-regulation of Th2 cytokines (including IL-10) [72, 73]. IL-10 production at an early HPV-associated disease stage may decrease immune recognition of HPV by down-regulating expression of HLA class I [72] and up-regulation of non-classical HLA-G molecules [74]. It has been demonstrated that HLA-G can inhibit the activity of CTLs as well as natural killer (NK) cells [75, 76]. Moreover, HLA-G may modulate DC maturation, trafficking, antigen presentation and their cross-talk with T and NK cells [77].

Along the same lines, CD1d expression is changed in HPV-infected cells. CD1d is an important player in innate immune responses and can modulate adaptive immune cells by altering the Th1/Th2 polarization. The E5 protein interacts with the chaperone calnexin in the endoplasmic reticulum (ER) and likely impairs calnexin-mediated CD1d folding, thereby arresting CD1d molecules in the ER and interrupting appropriate trafficking of CD1d to the surface of HPV-infected cells. It has also been demonstrated that E5 inhibits CD1d-mediated IL-12 production [78].

Taken together, HPV-infection leads to a polarization of the composition of effector T cells in the lesion microenvironment that favors immune escape.

IMMUNOSUPPRESSIVE MECHANISMS IN HPV-DRIVEN TUMORS

All immune evasion mechanisms discussed so far were studied relating to productive viral infection. Here, immune evasion increases the duration and size of HPV infection, thus raising the probability that some infected cells will become transformed [30]. Of note, most studies were done *in vitro*, and utilized overexpressed HPV proteins or even HPV-transformed cell lines. Thus, these data only mimic HPV infection of normal human keratinocytes and still need to be confirmed *in vivo*.

Upon malignant transformation, the HPV genome is often integrated into the DNA of the host cell. This integration is a terminal event for the life cycle of the virus, as many genes are lost in this process. It is therefore important to differentiate between immune evasion mechanisms which are active in HPV infection, and immune evasion mechanisms employed by HPV-driven tumors.

Most of the discussed immune evasion mechanisms are active in both scenarios, but there are several differences. First, one immune evasion mechanism is lost in tumor cells. As explained above, during the productive phase of the HPV life cycle, episomal transcription is tightly regulated by the viral transcription factor E2, resulting in low-level expression of E6 and E7. E2 is lost upon integration, therefore E6 and E7 are no longer kept at low levels, but are highly expressed [3, 79, 80]. This not only results in more targets for immune attack, but unfortunately also increases the risk of accumulation of cellular genetic and epigenetic changes and thus malignant transformation [81].

Second, several immune evasion strategies exist exclusively in tumors, and not in normal HPV infection. These include the recruitment of immune cells with immunosuppressive properties (Fig. **2**). Increasing evidence indicates that tumor-associated macrophages (TAMs) and other myeloid-derived cells such as myeloid-derived suppressor cells (MDSCs) play an important role in HPV-

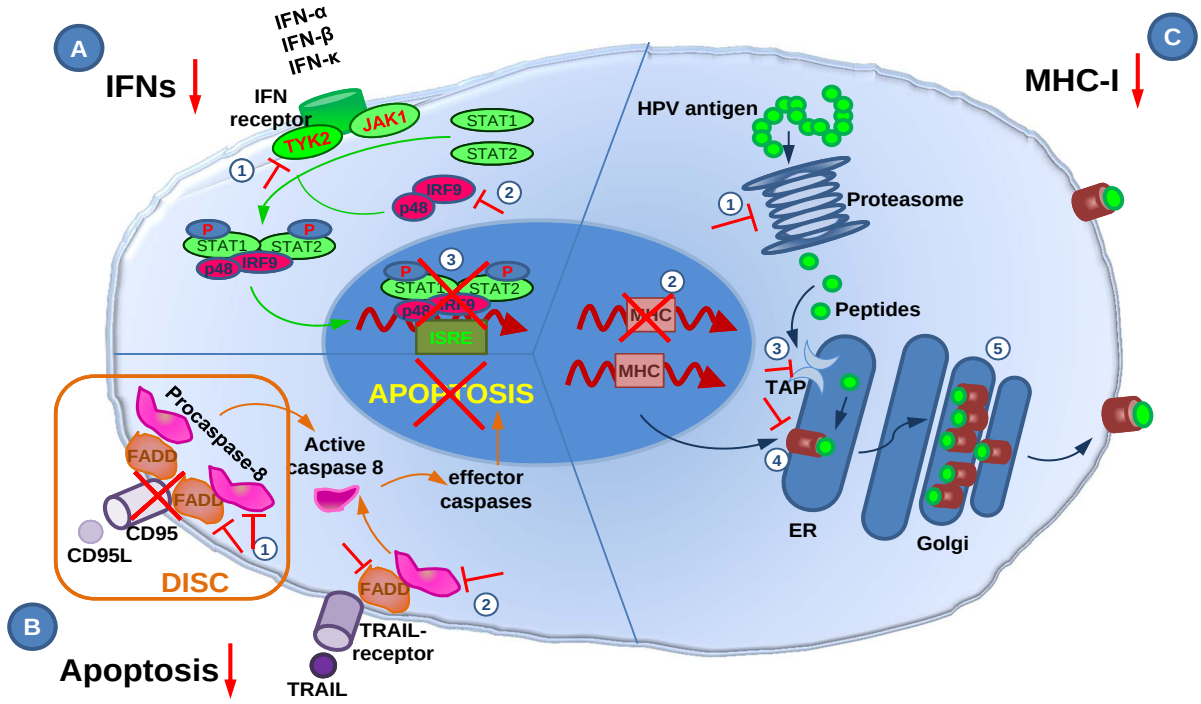

Fig. (1). Intracellular HPV immune evasion mechanisms. (**A**) HPV dysregulates the interferon response *via* interaction with the TYK2 kinase (**1**) and the p48/IRF9 complex (**2**), thus inhibiting the formation of the ISGF3 transcription complex that binds ISRE in the nucleus (**3**). (**B**) HPV promotes apoptosis resistance through down-regulation of the CD95 receptor on the cell surface and modulation of the DISC formation (**1**), and by degradation of the pro-apoptotic molecules FADD and procaspase-8 (**2**). (C) HPV causes reduction of antigen presentation by down-regulation of the antigen processing machinery *via* inhibition of expression of proteasome subunits (**1**), MHC class I (**2**), TAP (**3**), and reduction of MHC-I trafficking by direct interaction with the MHC-I heavy chain (**4**) and arresting of MHC-I molecules in the Golgi apparatus (**5**).

associated carcinogenesis. TAMs are macrophages differentiated predominantly into a M2 phenotype [82, 83] and are able to suppress antiviral T cell responses [84]. These myeloid cells secrete regulatory cytokines such as IL-10 and transforming-growth factor β (TGFβ) and induce T regulatory cells or lymphocyte cell death [82, 83]. Elevated levels of IL-10 as well as increased numbers of tumor infiltrating macrophages are correlated with progression of HPV-associated lesions [85, 86]. Moreover, MDSCs are also characterized by significant production of reactive oxygen species (ROS) triggered by ARG1 [87]. ROS may induce T cell dysfunction through the down-regulation of the CD3 ζ-chain of the T cell receptor complex [88], thus MDSCs are able to inhibit CTL activation [89]. However, the impact of MDSCs on HPV-associated lesions is not yet fully elucidated.

A large number of studies support a crucial role of CD4+ CD25+ regulatory T cells (Tregs) in immune homeostasis, tolerance, infection and tumor immunity [90, 91]. Tregs have been observed to infiltrate tumor masses, especially in the early stage of tumor progression [92]. Tregs are able to strongly inhibit cytokine production and proliferation of activated naive CD4+ T cells and natural killer cells (NK) as well as prevent activation of CTLs. Additionally, Tregs can activate immunosuppressive functions of immune cells by IL-10 as well as TGF β-dependent mechanisms [91, 92]. Increased frequencies and suppressive activity of Tregs have been observed in cervical cancer patients, both at the tumor site and in draining lymph nodes, and are likely to contribute to the impaired HPV-specific immune response observed in these patients [92, 93]. Increased Tregs numbers have been found to be strongly associated with an increased risk for progression of premalignant lesions to cancer [94, 95]. However, it is still unclear whether persistent HPV infection is responsible for increased numbers of Tregs, or whether increased Treg frequencies lead to persistence.

FINAL REMARKS

HPV has evolved to evade human immune detection in multiple ways to establish an infection and maintain a persistent life cycle that leads to viral reproduction. Exactly this persistence is the greatest risk factor for the development of HPV-mediated invasive malignancies.

The most important HPV immune evasion mechanism is to become invisible to the host immune system. This includes the absent triggering of any danger signals, as HPV infection causes no cytolysis, no cytopathic cell death, and no inflammation. Suppression of the interferon response, resistance to immune-mediated apoptosis, down-regulation of adhesion molecules for APCs, and active MHC class I down-regulation and impaired antigen presentation have also been shown to play a critical role in HPV immune evasion.

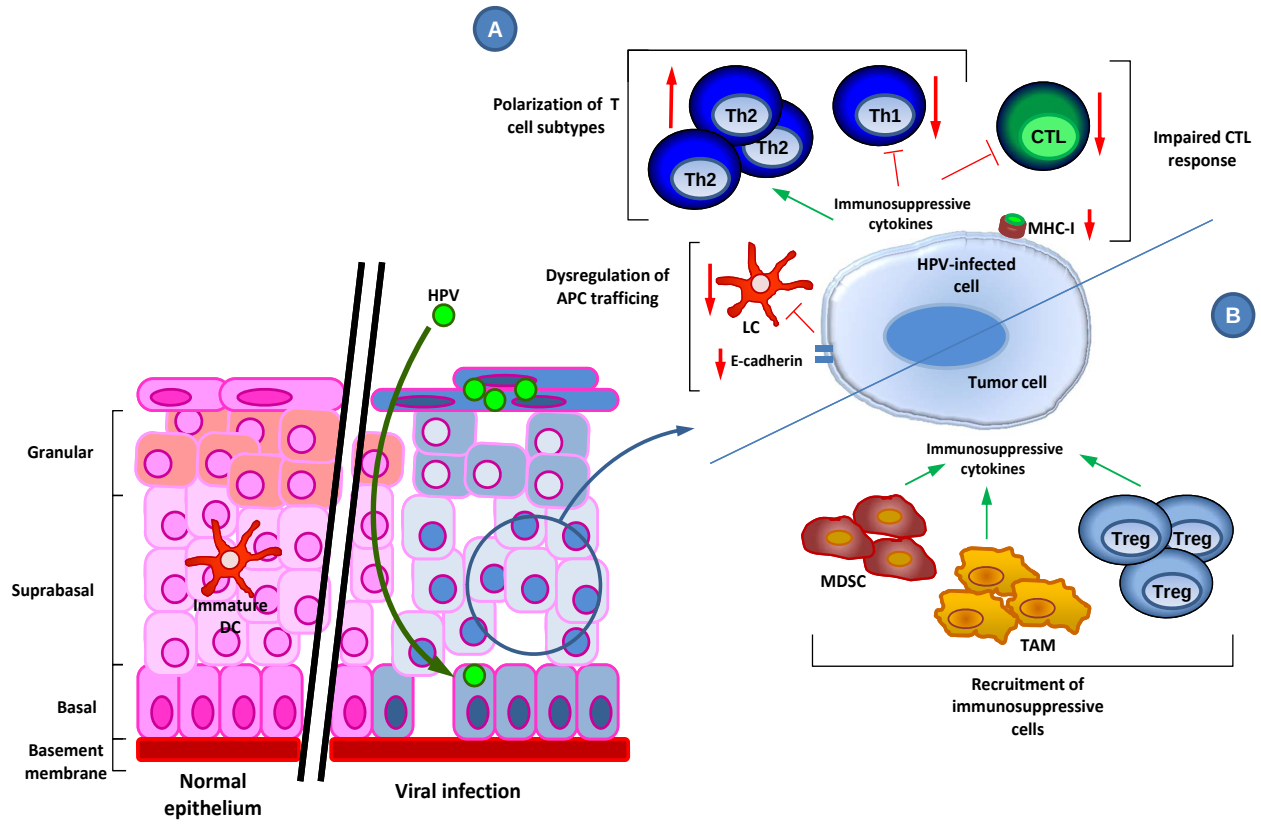

Fig. (2). HPV-mediated effects on the host immune response. (**A**) Immune evasion mechanisms employed by a HPV-infected cell are polarization of T cell subtypes, inhibition of the CTL response and modulation of APC trafficking. (**B**) Immune evasion mechanisms of HPV-driven malignantly transformed cells include recruitment of immunosuppressive cells, leading to immunosuppressive cytokine production.

Nevertheless, most HPV-associated lesions are eventually eradicated by the host immune system, and only a small percentage progresses to invasive malignancies. Virus-specific CD4+ and CD8+ T cell responses are essential for the immune control of HPV infection. Therefore, therapeutic vaccines eliciting the desired immune responses are considered to be attractive treatment options, and are actively investigated. Unfortunately, most HPV immunotherapies studies to date have yielded disappointing clinical results. A detailed understanding of the molecular mechanisms underlying HPV immune escape is therefore necessary to further improve therapeutic vaccine strategies.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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