**[Frontiers in Bioscience 7, d2058-2071, October 1, 2002]**

# HPV INNATE IMMUNITY

**Craig D. Woodworth**

*Biology Department, Clarkson University, Potsdam, NY*

## TABLE OF CONTENTS



## 1. ABSTRACT

HPV infections of the epidermis and anogenital tract occur frequently in healthy individuals, and 'high risk' HPV types are a major risk factor for cervical cancer. The first line of defense against HPV is the innate immune system, which provides non specific protection against a variety of pathogens and also enhances the adaptive immune response. However, HPV-infected cells often evade innate immune recognition and elimination. HPV gene expression and release of virus occur in superficial squamous cells where virus antigens are not readily detected, and keratinocytes are not lysed during HPV infection so there is no inflammatory response. In addition, HPV early proteins inhibit specific components of the innate immune system. E6 and E7 inhibit signaling by type I interferons and decrease expression of multiple interferon-inducible genes. E5 and E7 inhibit expression of major histocompatibility complex class I proteins on the cell surface. HPV-infected cells are resistant to lysis by natural killer (NK) cells, but are sensitive to cytokine-activated NK cells. Activated macrophages also kill HPV-infected cells and control malignant development. Thus, innate immunity is important for prevention of HPV infections, but HPV often persists due to evasion or inactivation of innate defenses.

## 2. INTRODUCTION

Papillomaviruses are a family of DNA tumor viruses that infect keratinocytes and induce papillomas as part of their normal life cycle (1, 2). Papillomaviruses infect a wide variety of organisms in a species-specific manner, and over 100 types infect humans. HPVs specifically target keratinocytes of the skin or mucosal surfaces, including the oral cavity and anogenital tract. Cutaneous HPV infections such as plantar warts are common, and anogenital HPV infections are widespread in sexually active individuals (3). Although most HPVs cause benign papillomas, a subset of 'high risk' types contribute to the development of anogenital cancer (4). HPV infection is also associated with development of laryngeal carcinomas, a subset of head and neck cancers (5), and skin cancers in patients with epidermodysplasia verruciformis (6). Early detection of anogenital HPV infections by PAP screening is effective in prevention of cervical cancer. However, detection and treatment are not available in many developing countries where cervical carcinoma is a leading cause of cancer death. HPV-associated cancers occur frequently in patients who have a weakened immune system, such as allograft recipients and individuals with AIDS (7, 8).

Multiple components of the innate and adaptive immune systems are mobilized to recognize HPV infections and to eliminate virus-infected cells. The first line of defense consists of the innate immune response that occurs in the epidermal or mucosal epithelium (9, 10). Innate immunity is the non specific resistance to infection that occurs when pathogens are encountered for the first time. It differs from adaptive immunity in that it does not depend on previous exposure to a specific antigen for development of a strong response. Innate immunity to HPV is mediated by several mechanisms including induction of

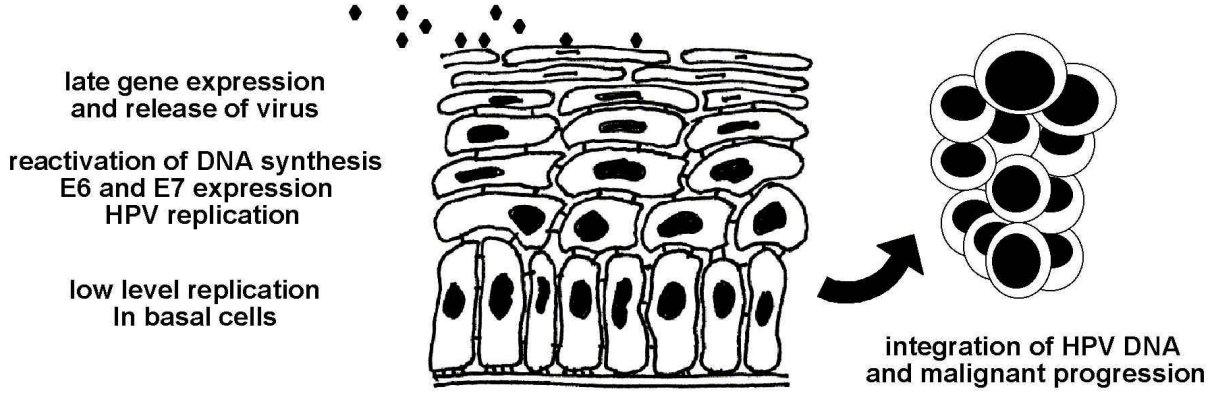


**Figure 1.** The HPV life cycle is closely dependent upon epithelial differentiation. HPV infects basal cells and undergoes low level episomal replication. As keratinocytes undergo squamous differentiation, E7 reactivates host cell DNA synthesis and HPV genomes are replicated at a high level. Late gene expression, virion production, and release of virus occurs in superficial squamous cells.

interferon and activation of macrophages and NK cells. The innate response also stimulates the adaptive immune system to eradicate virus-infected cells. However, many HPV infections are not quickly eliminated by mucosal immunity. Presumably, this is because production of virions does not cause cell lysis and an inflammatory response. Furthermore, HPV gene expression and virus production occur in differentiating squamous epithelial cells that do not interact with immunocompetent cells within the mucosa. It also appears that HPV proteins physically associate with and inhibit the function of specific components of innate immunity.

The innate immune response to HPV infection is incompletely understood. However, it is important for several reasons. HPV infections are a major public health problem. They are one of the most common sexually transmitted infections, and they often progress to cancer. The innate immune response is critical because it is the first line of protection against HPV. Furthermore, the innate response enhances the adaptive cell mediated immune response that induces papilloma regression (11). Prophylactic vaccines to prevent HPV infection are currently being evaluated in clinical trials, and therapeutic vaccines to treat cervical cancer are under development (12, 13). Understanding the innate response to the virus may suggest ways for improving topical treatment of HPV infections or HPV vaccines. The goal of this review is to discuss important mechanisms by which the innate immune system responds to HPV infection, and to describe strategies that the virus has evolved to evade or disable these responses.

## 3. PAPILLOMAVIRUS LIFE CYCLE

The HPV life cycle is dependent upon epithelial differentiation **(Figure 1)**. HPVs enter squamous epithelia through cuts or abrasions and they establish an infection in the basal layer. HPV genes are expressed at a low level and the virus replicates as an episome in basal cells. However, virus expression and production of virions are induced greatly during epithelial differentiation as infected cells are pushed into the superficial layers of epithelium (14). This is a great advantage for the virus because the viral proteins are isolated from the mucosal immune system. It also creates a problem. Since HPVs do not encode a DNA polymerase or genes necessary for virus DNA replication, they rely on host cell enzymes. Unfortunately, the host cell DNA replication machinery is switched off during the process of terminal differentiation. The HPV E6 and E7 proteins serve a critical function by uncoupling host cell DNA synthesis from terminal differentiation. This allows the virus to reactivate cellular DNA polymerases and related enzymes in superficial squamous cells that are undergoing differentiation.

HPVs are double stranded DNA viruses that have a circular genome of approximately 8 kB. The genome organization of different HPV types is similar and is typified by the most common high risk type, HPV-16 (Figure 2). There are 3 major regions. The long control region (LCR) contains the origin of replication and multiple binding sites for transcription factors that regulate virus gene expression. The early region of HPV-16 contains 6 genes (E1 to E7) that control virus gene expression and DNA replication. The late region encodes the major and minor viral capsid proteins (L1 and L2). The function of each gene is listed in Table 1. As mentioned above, the E7 protein is critical for reactivation of host cell DNA synthesis. E7 accomplishes this task by binding to the retinoblastoma protein (pRB). The normal function of pRB is to prevent cells from progressing through the restriction point of the cell cycle and entering S phase. The E7 protein binds to pRB, inactivates its function, and causes increased degradation (15). This allows differentiating cells that express E7 to enter S phase. The HPV E6 protein also serves a critical role. It binds to E6-associated protein and causes increased degradation of the p53 tumor suppressor protein (16). The normal function of p53 is to block aberrant entry into S phase by inducing cell cycle arrest or apoptosis. By inactivating p53 function, E6 assures that HPV-infected cells will actively synthesize virus DNA. The

**Table 1.** Functions of HPV genes in productive infection

| Gene | Function |
|---|---|
| E1 | encodes a helicase for episomal replication of virus DNA |
| E2 | regulates early gene expression, facilitates initiation of virus DNA replication |
| E4 | alters the cytoskeleton to facilitate virus release |
| E5 | alters endosomal pH and recycling of growth factor receptors to the cell surface |
| E6 | inactivates p53 function and inhibits apoptosis |
| E7 | binds to pRB and reactivates host DNA synthesis |
| L1 | major capsid protein |
| L2 | minor capsid protein |

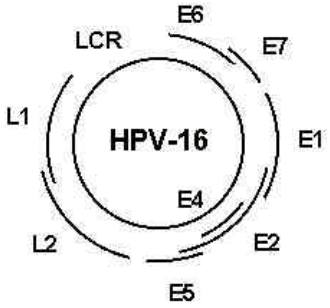


**Figure 2.** Genomic organization of HPV-16. HPV-16 consists of a circular double-stranded DNA of approximately 8 kB. The LCR regulates virus gene expression, the early genes (E1-E7) control the virus life cycle, and the late genes (L1 and L2) encode capsid proteins.

E1 and E2 proteins bind to the origin of replication and are important for replication of HPV as an episome in infected cells. E2 also interacts with the LCR and regulates transcription of HPV genes. The E5 gene encodes a short hydrophobic protein that inserts into biological membranes. This protein interacts with the vacuolar ATPase and prevents proper acidification of endosomes (17). One outcome is increased recycling of receptors, including the epidermal growth factor receptor (EGF-R), from the endosome to the cell surface, which promotes cell proliferation. Alterations in endosome acidification might also inhibit antigen processing and presentation of peptides at the cell surface for immune recognition. The E4 gene is expressed late in infection. It destabilizes the cytoskeleton and facilitates release of virus particles (18). The L1 and L2 genes encode the major and minor capsid antigens, respectively. They are expressed only in terminally differentiated cells, which is advantageous for the virus because these proteins are immunogenic. Clinical trials are underway to evaluate prophylactic vaccines based on virus-like particles composed of L1 (12).

Cells that are infected with 'high risk' HPVs may undergo malignant transformation. Although HPV replicates normally as an episome in infected epithelial cells, the virus DNA can integrate into the host cell genome. This event terminates the virus life cycle. Integration targets fragile sites within the cell DNA (19), but it occurs randomly with respect to the virus sequence. However, integration events that disrupt the E1/E2 region are selected for because they provide a growth advantage to the cell. Loss of E2 results in stabilization of E6 and E7 RNAs (20), and increased production of E6 and E7 proteins drives cells continuously through the cell cycle. High-level expression of E6 and E7 induces genetic instability, and contributes to clonal evolution of the cancer. Most cervical cancers arise in the transformation zone, a narrow region between the ectocervix and endocervix (21). The first stage of malignant development is cervical intraepithelial neoplasia (CIN). These cells are aberrant, but they have not invaded the basement membrane, so they are premalignant. CIN can regress, persist, or progress to invasive cancer. It has been estimated that 1 to 3% of CINs eventually become malignant, therefore, additional genetic or environmental factors must contribute to cervical cancer.

## 4. INNATE IMMUNITY

The innate immune system is the first line of defense against infection. It provides non specific immunity without the requirement for repeated exposure to pathogens, and it protects against a broad range of infectious agents (reviewed in 9,10). Most infections that are detected by the innate immune system are controlled quickly. Innate immunity is also very important for establishing an effective adaptive immune response via alterations in expression of specific cytokines and adhesion molecules. The innate immune system has a relatively small number of receptors but these recognize a wide variety of pathogens. This is possible because these receptors recognize common pathogen-associated molecular patterns (PAMPs) that are not shared by host cells. Examples include the CpG dinucleotide that is methylated in mammalian DNA but not in viruses and bacteria, and double-stranded RNA, that is produced during viral infection. PAMPs are recognized by a limited number of pattern recognition receptors (PRRs). These receptors are expressed on epithelial cells and leukocytes that are the first to encounter infectious agents. One interesting PRR is the Toll-like receptor 4 that is the receptor for lipopolysaccharide (22). This receptor contains an intracellular domain analogous to the IL-1 receptor, and ligand binding activates the transcription factor NF-kB and production of proinflammatory cytokines. The receptor for the CpG dinucleotide is a powerful adjuvant for innate immune activation and has strong Th1-inducing ability. Thus, it may be useful as an immunomodulator or vaccine adjuvant (9).

The first line of innate defense consists of epithelial cells that cover the cutaneous and the mucosal surfaces of the body. These cells form stratified squamous epithelia that provide a physical barrier to infection. Squamous cells contain an internal rigid cytoskeleton of keratin filaments that is linked to the cytoskeleton of adjacent cells through desomosomes. In the skin, epithelial cells undergo keratinization and form thick cornified envelopes that resist penetration by bacteria and viruses. In mucosal epithelia, the cells do not form cross-linked

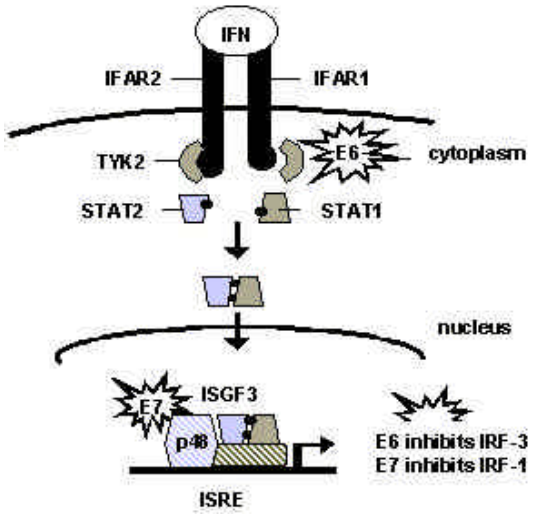


**Figure 3.** Signal pathway for type I IFNs. Binding of IFN to the IFN receptor induces tyrosine phosphorylation via TYK2 and activation of STAT1 and 2. These dimerize and bind along with p48 to the ISRE to induce expression of IFN-responsive genes. HPV E6 and E7 proteins interact with specific signal components and inhibit IFN-mediated gene expression.

envelopes, however, they release mucin, which inhibits viral attachment and penetration of the epithelial surface. Keratinocytes actively participate in innate immunity. They produce a variety of microbiocidal peptides, interferons, and proinflammatory or immunoregulatory cytokines (9, 23, 24). They also express cell surface proteins including major histocompatibility complex class (MHC) I antigens and adhesion molecules that direct interactions between keratinocytes and cells of the immune system. Release of proinflammatory cytokines, such as IL-1 alpha, is directly induced by damage to keratinocytes. IL-1 alpha induces expression of a wide variety of cytokines and chemokines that increase vascular permeability causing an influx of plasma proteins such as complement. Cytokines also recruit and activate a variety of leukocytes to the mucosal epithelium. Macrophages are phagocytic cells that express PRRs for recognition of microbes and infected cells. They kill virus-infected cells and release a variety of cytokines such as IL-1 and TNF-alpha that amplify the inflammatory response. Macrophages also release growth factors that stimulate fibrosis and wound healing. The mucosa contains different types of intraepithelial lymphocytes. NK cells circulate in the bloodstream and are recruited by the innate immune response. These cells express PRR and kill infected cells by releasing cytotoxic granules. NK cells can be activated by cytokines such as IFNs and IL-12 to kill more efficiently. The epithelium also contains lymphocytes that express gamma/delta T cell receptors (9, 25). These cells are capable of cytotoxic activity and they also produce epithelial growth factors. The function of gamma/delta T cells is incompletely understood.

## 5. INTERACTIONS BETWEEN HPV AND THE INNATE IMMUNE SYTSTEM

HPV infection does not readily stimulate an inflammatory response. In fact, chronic HPV expression at low levels may produce immune tolerance to infected epithelia (26). Recent reviews have described how HPV interacts with the immune system (11, 12, 27), and how the virus can evade or inactivate specific immune functions (28, 29). HPVs have evolved several mechanisms to bypass immune recognition or killing. The virus does not have a blood-born phase of infection; therefore, the mucosal immune system serves a major role in protection. HPV infection does not cause lysis of keratinocytes, so the inflammatory response is not activated during a productive infection. HPVs restrict production and release of virus to terminally differentiated squamous cells that are distant from cytokines and immunocompetent cells in the submucosa. In short, the virus uses normal epithelial differentiation to minimize recognition or interaction with the immune system. This discussion will focus on 2 questions. What components of the innate immune system are effective against HPV? How does the virus fight back to inhibit innate immune function?

### 5.1. Interferons

IFNs are a family of cytokines that have important functions in the immune response (reviewed in 30). Type I IFNs, including IFN-alpha and beta, are produced by epithelial cells and contribute to the first line of antiviral defense. They induce an antiviral state in infected cells and adjacent uninfected cells, they inhibit proliferation, and they induce apoptosis of virus-infected cells (31). In contrast, IFN-gamma is produced by cytokine-activated T cells and NK cells, and is an important modulator of immune function. The antiviral activity of IFN is mediated by several components. IFNs induce PKR, a double stranded RNA dependent protein kinase that inactivates protein synthesis. IFN activates 2-5 oligoadenylate synthetase, which stimulates RNAse L and degradation of viral RNA. IFN also induces the MX proteins which directly interfere with viral replication (30). Both type I and II IFNs inhibit expression of E6 and E7 RNAs in HPV-immortalized cells (32-37). IFN-alpha also inhibits immortalization of keratinocytes by HPV-16 (34). Although several types of IFN reduce HPV gene expression, IFN-gamma is most effective (32). Down regulation of HPV E6 and E7 RNAs is mediated at both the transcriptional and posttranscriptional level, and resistance to the inhibitory action of IFN develops in cervical carcinoma cells lines (32). IFNs have been used to treat HPV infections and HPV-associated disease in cutaneous, oral, and anogenital epithelia. However, the effectiveness of therapy has not been consistent. Some patients have significant improvement, whereas others have partial or poor responses. IFN-gamma is more effective than IFN-alpha or beta. Interestingly, patients who express lower levels of the HPV E7 protein are more likely to respond to IFN treatment (38).

Recent work has converged to show that the E6 and E7 proteins of high risk HPV-16 and –18 specifically inhibit IFN expression and signaling (reviewed in 39). Figure 3 illustrates the major components of the signaling pathway for IFN-alpha and beta and identifies points where HPV blocks signaling. IFNs bind to cell surface receptors and stimulate signaling by activating the JAK-STAT pathway (30). Receptor activation induces tyrosine

phosphorylation of JAK1 and TYK2, which in turn phosphorylates tyrosine residues on the cytoplasmic portion of the IFN receptor. This allows binding of STAT1 and STAT2 via SH2 domains. The bound STATs become phosphorylated, they dimerize, and are transported to the nucleus where they bind to the IFN-stimulated response element (ISRE) in the presence of a 48 kD protein known as ISGF3-gamma. This complex binds to the ISRE and activates transcription of IFN-responsive genes.

'High risk' HPV E6 oncoproteins inhibit the IFN signaling pathway by at least 2 distinct mechanisms. HPV-18 E6 protein physically associates with TYK2 in the region necessary for TYK2-IFN receptor association (40). Binding to E6 prevents TYK2 from associating with the receptor and phosphorylating JAK and STAT. In HT1080 cells that express HPV-18 E6, there is inhibition of JAK-STAT activation in response to IFN-alpha. This results in impaired binding and transactivation by ISGF3. IFN signaling is inhibited by both HPV-16 and –18 E6 whereas low risk HPV-11 E6 is less effective. Ronco et. al. have described a distinctly different mode of inhibition by E6 (41). HPV-16 E6 protein binds to IFN regulatory factor-3 (IRF-3) and inhibits activity. IRF-3 is activated in cells by exposure to double stranded RNA or by virus infection. It forms a stable complex with additional factors including p300/CBP and this activates transcription from the ISRE that regulates expression of IFN-beta (42). The ability of HPV-16 E6 to bind and inhibit IRF-3 activity is biologically important because primary human keratinocytes that express HPV-16 E6 have decreased production of IFN-beta after Sendai virus infection (41). The response is specific to HPV-16 E6 because low risk HPV-6 E6 and high risk HPV-18 E6 only bind weakly to IRF-3. Together, the results indicate that E6 proteins from high-risk HPV types allow the virus to escape the normal antiviral response mediated by IFN-alpha and beta.

The high risk E7 protein also inhibits the IFN signaling pathway (43). HPV-16 E7 protein binds to p48, a component of the ISGF3 transcription complex (Figure 3). The interaction occurs with a portion of E7 that is needed for binding to pRB. The functional outcome is that E7 is able to inhibit activation by ISGF3 and IFN function (44). Two other groups have described a distinctly different mechanism by which high risk HPV E7 proteins inhibit IFN signaling. Park et. al. (45) and Pera et. al. (46) have shown that the HPV-16 E7 protein interacts with and inactivates the transcription factor IRF-1. IRF-1 is an important intermediate in IFN signaling and may be responsible for the antiproliferative effects of IFNs (30). This effect is not specific for high risk E7 because HPV-11 is also effective (45). The association between E7 and IRF-1 is mediated via the pRB binding domain of E7 and the transactivation domain of IRF-1. The mechanism of inhibition by E7 may involve recruitment of the transcriptional inhibitor, histone deacetylase, to the IRF-1 promoter (45).

The molecular interactions between E6/E7 and IFN signaling components are biologically important in keratinocytes. Two independent studies using cDNA microarrays have shown that IFN-inducible genes are down regulated in keratinocytes that express HPV-16 E6/E7 or in cells immortalized by HPV31. Chang et. al. have performed microarray analysis of HPV-31-immortalized keratinocytes (47). They found that expression of multiple IFN-inducible genes was significantly decreased and that STAT1 was reduced. Nees et. al. examined keratinocytes that were infected with retroviruses that encoded HPV-16 E6, E7, or both E6 and E7 (48). E6 down regulated multiple IFN-responsive genes, whereas E7 alone was less effective. However, coexpression of E6 and E7 decreased IFN-responsive genes more efficiently than E6 alone. E6 also decreased expression of STAT1 in the nucleus and decreased binding of STAT1 to the ISRE. All of these *in vitro* experiments were performed using immortal cell lines or retrovirus-infected keratinocytes that expressed high levels of E6 or E7 proteins. What does this mean in the pathogenesis of HPV infections *in vivo*? The effectiveness of IFN regulation by HPV may depend on the relative levels of expression of E6 and E7 proteins versus levels of IFN signaling molecules. Papillomas or CINs that express high levels of E6 and E7 may be most resistant to IFN. Interestingly, this observation has been made previously in the clinic (38). Patients that expressed high levels of E7 in condyloma tissue were resistant to IFN treatment, whereas patients with low E7 were sensitive. HPV-16 E6 and E7 are up regulated during progression of CIN (14), and thus, these lesions may be more resistant to IFN. Decreased levels of IFN-beta and gamma have been observed in CIN and cancer relative to normal cervical epithelium (49-51). Cervical carcinoma cells have reduced IFN responsiveness (32, 52). Together, these results indicate that high-level expression of the HPV E6 and E7 proteins down regulates IFN expression and signaling.

**5.2. Inflammation**

The inflammatory response serves a central role in innate immunity. The 3 major functions of inflammation are to recruit inflammatory mediators to the infection, wall off and resolve the infection, and repair tissue damage. Inflammation is stimulated by proinflammatory cytokines such as IL-1 and TNF-alpha. The natural target of HPV infection, the keratinocyte, sequesters large amounts of IL-1 alpha that is released after injury to induce inflammation (53, 54). IL-1 alpha and TNF-alpha stimulate changes in adhesion molecules, capillary permeability, and release of secondary cytokines and chemokines. These alterations orchestrate the inflammatory response. The acute inflammatory response normally leads to elimination of infection and repair of tissue damage. On the other hand, chronic inflammation occurs when infection persists. Continued persistence of inflammation is an important risk factor for several human cancers (55), and inflammatory mediators contribute to HPV-associated cancer in a mouse model (56). Proinflammatory cytokines including IL-1 and TNF-alpha, down regulate expression of HPV E6 and E7 oncogenes in keratinocytes at the level of transcription (57). Similar effects have been observed for other immunoregulatory cytokines including IFNs (32, 34, 37), TGF-beta (58), and growth factors such as keratinocyte growth factor (KGF) (59) and EGF (60). Interestingly, the soluble IL-6 receptor,

which can be released by keratinocytes, activates HPV-18 expression via a STAT3 dependent mechanism (61). It seems that proinflammatory cytokines are generally negative regulators of HPV gene expression, although effects may vary depending upon the experimental conditions and the presence of other cytokines or growth factors.

A hallmark of HPV infection is the absence of an inflammatory response. Basal cells express low levels of HPV early proteins, they do not undergo lysis, and they are not rapidly recognized or destroyed by resident leukocytes such as NK cells and tissue macrophages. Furthermore, keratinocytes release virions only in the superficial layers, far removed from leukocytes and endothelial cells in the submucosa. HPV infections can persist or remain latent for long periods, and may induce tolerance to HPV antigens (26). Recent studies suggest that HPV early gene products directly block activity of inflammatory mediators. The HPV16 E6 protein inhibits expression of the proinflammatory cytokine IL-18 (62), a member of the IL-1 family (63). The mechanism of inhibition is unclear, but occurs at the post transcriptional level. Soluble E6 and E7 proteins bind to the IL-18 receptor and compete with IL-18 for binding (64). Soluble HPV-16 E6 protein also binds to the TNF type 1 receptor and protects cells from TNF-alpha mediated apoptosis (65). These results are interesting and await further exploration. Other studies have shown that the HPV-16 E7 protein sensitizes keratinocytes to TNF-alpha mediated apoptosis (66, 67), and that apoptotic keratinocytes release large amounts of IL-1 alpha (54). Surprisingly, high level expression of HPV-16 and BPV-1 E6 proteins also sensitizes cells to TNF-alpha-mediated apoptosis (68, 69). This is unexpected because an important function of E6 is to induce degradation of p53 to prevent apoptosis. In summary, *in vitro* studies have shown that HPV E6 and E7 proteins exhibit both anti-inflammatory and proinflammatory effects.

Although HPV infection does not readily induce an acute immune response, expression and release of specific proinflammatory cytokines does increase in high grade CIN and cervical cancer (70-75). Cytokines that are up regulated include IL-1, TNF-alpha, IL-12, IL-10, and TGF-beta. Interestingly, these findings are at odds with reports that describe decreased release of proinflammatory cytokines in cultures of HPV-immortalized cells and cervical carcinoma cell lines (52, 76). The difference between *in vitro* and *in vivo* results suggests that increased release of proinflammatory cytokines during progression is not an inherent property of carcinoma cells, but is due to the microenvironment within the developing tumor. What causes increased inflammation in CIN and cancer? Macrophages produce proinflammatory cytokines and macrophages are increased in CIN (77, 78) and cervical carcinomas (72). Expression of HPV E6 and E7 RNAs is strongly unregulated in high grade CIN and cervical cancer (14). This is important because E7 sensitizes cells to undergo apoptosis (54, 66) and IL-1 alpha release. However, increased proliferation and apoptosis are characteristics of many cancers, including those with no HPV. Thus, proinflammatory mediators might originate from infiltrating leukocytes or apoptotic epithelial cells.

Does chronic inflammation contribute to cervical cancer? Epidemiologic studies have shown a trend of increasing cervicitis associated with high grade CIN in HPV-infected women (79, 80). Cytokines such as TNF-alpha and IL-1 exert pleiotropic effects on keratinocytes. Most work has been performed *in vitro* and it is difficult to extrapolate results to a developing tumor. TNF-alpha inhibits proliferation of normal keratinocytes as well as HPV-immortalized and carcinoma cell lines (81-84), and TNF promotes apoptosis of keratinocytes (66, 67). On the other hand, both IL-1 and TNF-alpha help to orchestrate wound healing by stimulating fibroblasts to produce paracrine growth factors such as KGF (85). Proinflammatory cytokines are also able to stimulate growth of HPV-immortal cell lines and cervical carcinoma cells under suboptimal growth conditions by inducing an autocrine pathway involving the EGF-R (86-88). The latter may be biologically relevant because cervical cancer evolves in an environment where an adequate supply of blood and oxygen is limited by tumor expansion. Studies using a mouse model of multistage carcinogenesis elicited by HPV-16 indicate that inflammatory cells can be coconspirators in carcinogenesis (56). The proinflammatory cytokine IL-8 is increased in cervical cancer, and prognosis of patients with high IL-8 is extremely poor (89). However, there is also evidence that inflammatory mediators can inhibit HPV-associated carcinogenesis. Merrick et. al. have shown that over expression of IL-1 alpha in HPV-transformed keratinocytes inhibits the ability of these cells to form tumors in nude mice (76). Rosl and workers have shown that induction of the chemokine MCP-1 in HeLa carcinoma cells induces macrophage infiltration and retards tumor growth in nude mice (90). Thus, the role of chronic inflammation in cervical cancer requires further investigation.

**5.3. NF-kB**

NF-kB is a transcription factor that serves a central role in activating the cellular response to stress. NF-kB stimulates multiple genes that regulate the inflammatory and immune responses (91). These include proinflammatory cytokines, anti apoptotic genes, growth factors, and adhesion molecules. Many DNA tumor viruses activate NF-kB (reviewed in 92), and activation is important for their viral life cycle or for transformation. HPV-16 has a weak but functional binding site for NF-kB in the long control region, however, this site may act as a transcriptional inhibitor (93). This would be an interesting mechanism for reducing inflammatory signals in HPV-infected keratinocytes. Recent evidence clearly shows that activation of NF-kB contributes to tumor development in a variety of tissues (94). NF-kB is activated in HPV-immortalized keratinocytes during malignant conversion, and inhibition of NF-kB suppresses anchorage dependent growth (95). Studies using microarray analysis show that NF-kB and NF-kB-responsive genes are unregulated in HPV-immortalized cervical keratinocytes (48). Together, these results suggest that NF-kB activation contributes to HPV-associated carcinogenesis and that pharmacologic inhibition of NF-kB might be an effective treatment for cervical cancer.

Do HPV proteins directly activate NF-kB? The BPV-1 E5 protein stimulates NF-kB activation via

induction of superoxide radicals (96). This is consistent with the observation that E5 stimulates activation of EGF-R signaling (17) and that ras, which signals downstream of the EGF-R, induces activation of NF-kB (97). The effects of the HPV-16 E6 and E7 proteins on activation of NF-kB appear to vary and may depend upon the cell type and experimental conditions. For example, the HPV-16 E6 protein stimulates expression of NF-kB responsive genes and increases binding to an NF-kB consensus sequence in differentiating cultures of normal cervical epithelial cells (48). Increased NF-kB activation has also been observed in human laryngeal tissue infected with HPV-6 or 11 (98). However, other studies report down regulation of NF-kB activation in response to HPV-16 E6 or E7. For example, Patel and coworkers have shown that HPV-16 E6 inhibited the intrinsic transcriptional activity of CBP/p300 and decreased the ability of p300 to activate p53- and NF-kB-responsive promoter elements (99). HPV-16 E6 has been reported to inhibit NF-kB activity in the A2780 ovarian carcinoma cell line (100), and NF-kB binding activity was inhibited by conditional expression of HPV-16 E7 in 14/2 BRK cells (46). The latter observations, showing downregulation of NF-kB by HPV E6 and E7, are consistent with the fact that HPV infection does not stimulate production of inflammatory mediators. Therefore, it will be important to understand the basis for these differing observations and to establish how NF-kB activity is regulated in cervical keratinocytes during infection and development of CIN. Up regulation of NF-kB by viral proteins might be important for stimulation of the inflammatory response to the virus. Furthermore, pharmacologic inhibition of NF-kB activation in cervical cancer cells might promote apoptosis and optimize chemotherapy (94).

### 5.4. Cytokines and adaptive immunity

Cytokines released during the innate immune response help to activate a strong adaptive response. Inflammatory mediators such as TNF-alpha and IL-1 stimulate several important processes including maturation of dendritic cells for antigen presentation (101) and increased expression of MHC class I and II proteins for immune recognition and antigen presentation to lymphocytes. Innate immune receptors, such as PRRs, are designed to detect fungi, bacteria, and viruses, and activation induces a Th1 type pattern of cytokine release (10). Regression of HPV infection is associated with a Th1 type cell mediated immune response (11, 102) that is characterized by a massive mononuclear cell infiltration, up regulation of adhesion molecules, and apoptosis of infected keratinocytes. In contrast, persisting HPV-infected lesions exhibit no inflammation and may develop immune tolerance (28). The development of CIN has been associated with a Th2 pattern of cytokine secretion in which the ratio of IL-12/IL-10 is reduced (49, 103), and immunosuppressive cytokines such as TGF-beta and IL-10 are increased (70, 77, 104). The innate immune system can be activated to enhance HPV regression. Topical immunomodulators such as imiquimod act by inducing cytokine secretion (TNF-alpha, IFN-alpha, and IL-12) from monocytes and macrophages. These cytokines enhance the Th1 type of cell mediated immune response and are used in the clinic to treat HPV infections (105).

### 5.5. Macrophages

An important component of the innate immune response consists of phagocytic cells. Recruitment of polymorhonuclear leukocytes (PMNs) and monocytes to the site of an infection is mediated by release of specific cytokines and chemokines from infected or injured tissue. PMNs are the first to arrive and they are short-lived. Monocytes are long lived and differentiate into macrophages that actively destroy infected cells. Zur Hausen has described a system for intracellular surveillance of persistent HPV infections (106). The hypothesis is that cervical cancer results from deficient cellular control of HPV gene expression, and that normal control is mediated by factors released from macrophages. Several studies have reported that macrophages are increased in HPV infections or CIN (77, 78) and cervical carcinoma (72) and that these cells are present in both the epithelium and the underlying stroma. Activated macrophages kill HPV-16 transformed cells (107, 108). Regressing papillomas have a significant infiltration of macrophages that stain positive for TNF-alpha, and this correlates with apoptosis of infected epithelial cells (102).

Monocyte chemotactic protein (MCP-1) is clearly involved in intracellular surveillance of HPV infection. MCP-1 is a chemokine of the CC family that stimulates chemotaxis of monocytes. Rosl and coworkers have shown that the MCP-1 gene is actively expressed in cultured HeLa cervical carcinoma cells but that it is rapidly inactivated when these cells are grafted to nude mice. Introduction of a constitutively expressed MCP-1 gene significantly retards growth of HeLa cells *in vivo* (90). Similar results have been obtained by another group using MCP-3 (109). Furthermore, expression of MCP-1 is decreased in high grade CIN relative to normal cervical epithelium (110) and epithelial cells that express HPV-16 E6/E7 RNA do not produce MCP-1 (111). This suggests that MCP-1, MCP-3, and macrophages serve an important role in controlling malignant development.

### 5.6. Natural killer cells

NK cells are a subpopulation of lymphocytes that recognize and destroy infected or damaged cells in a nonspecific manner. NK cells release cytotoxic granules onto the surface of target cells and kill by apoptosis. They also release TNF-alpha and IFN-gamma, which enhance the inflammatory and immune responses. NK cells express PRR that recognize antigens that are common on many infected cells. They also express inhibitory receptors that interact with MHC class I proteins on target cells. Pathogen-infected cells often express reduced levels of MHC class I peptides and are more sensitive to NK lysis. In fact, HPV-infected keratinocytes (112, 113) or malignantly transformed cells (114) have decreased expression of MHC class I antigens. NK cells are found reproducibly in the stroma of HPV-infected CIN (115), and they can be activated by treatment with cytokines to produce lymphokine activated killer cells (LAK cells). HPV-16-immortalized epithelial cells and cervical carcinoma cell lines are relatively resistant to NK killing, but sensitive to LAK cell lysis (116, 117). Some HPV-containing cells release IL-6 which enhances their susceptibility to lysis

(118). Lysis by NK cells is abrogated in patients who have precancerous or cancerous HPV-induced lesions (119). Abrogation is associated with a restricted ability of the NK cells to recognize specific target cells (120). Interestingly, cells transformed by the adenovirus 5 E1A gene are sensitive to NK lysis, whereas the same cells transformed by HPV-16 E7 are resistant (121), and this difference has been shown to correlate with malignant potential in mice (122). In this regard, soluble E6 and E7 oncoproteins of HPV-16 inhibit the ability of NK cells to produce IFN in an *in vitro* assay (64). There is also reduced expression of signal transducer zeta chain in NK cells in patients with CIN and cervical cancer (123). This might result in reduced cell function, such as production of TNF-alpha.

### 5.7. Histocompatibility antigens and adhesion molecules

Interactions between keratinocytes and leukocytes are regulated by cell surface proteins such as MHC class I and intracellular adhesion molecule-1 (ICAM-1). MHC class I proteins are normally expressed at the surface of epithelial cells and regulate presentation of intracellular antigens and immune recognition by T cells. Epithelial cells do not normally express MHC class II molecules, but they are up regulated by proinflammatory cytokines such as TNF-alpha and IFN-gamma. MHC class I expression is down regulated in premalignant keratinocytes from skin and larynx, and in a large percentage of cervical cancers (112, 124-128). Down regulation is a potential mechanism for HPV-infected keratinocytes to evade recognition and killing by cytotoxic T cells. However, down regulation of MHC expression also sensitizes cells to NK cell killing. A variety of mechanisms have been described for decreased MHC class I expression. These include altered transcription or translation of MHC class I genes, loss of heterozygosity, loss of up regulation by TNF-alpha, and inhibition by papillomavirus E5 or E7 proteins (113, 129-132). Stable expression of MHC class I on the cell surface requires loading with antigenic peptide in the endoplasmic reticulum by the peptide transporter, encoded by the transporter associated with antigen presentation (TAP-1). Expression or function of TAP-1 is altered in HPV infection and cervical cancer (112, 126, 133, 134). Recent studies suggest that altered function is directly induced by papillomavirus E7 or E5 proteins. The HPV-11 E7 protein can be coimmunoprecipitated with TAP-1 from laryngeal papilloma cells (131). Purified E7 protein inhibits ATP-dependent peptide transport *in vitro*, suggesting that the interaction between E7 and TAP-1 prevents efficient peptide transport and MHC class I expression *in vivo.* Conditional expression of the HPV-16 E7 protein from a tetracycline-regulated promoter induced decreased expression of RNA for TAP-1 (132). The HPV-18 E7 protein caused decreased expression for the MHC class I heavy chain promoter and repression of the TAP-1 promoter (113). Thus, E7 may inhibit TAP-1 function at both the transcriptional and post transcriptional level. Fibroblasts that express bovine papillomavirus-1 (BPV-1) E5 protein do not express MHC class I protein on the cell surface, but retain it intracellularly (130). This occurs in cells that express E5 either stably or transiently. In BPV-infected lesions, down regulation of TAP-1 and MHC class I function would interfere with antigen presentation and immune recognition of virus-infected cells.

ICAM-1 serves as a receptor for the beta2 integrins LPA-1 and MAC-1, which are expressed on leukocytes. The expression of ICAM-1 is significantly induced on keratinocytes in high grade CIN (72, 135), however, this increase does not appear to be directly related to expression of HPV genes. Expression of additional cell adhesion molecules including VCAM-1 and E-selectin was also increased on high grade CIN. Enhanced expression of adhesion molecules may be functionally important for local recruitment of immunocompetent cells. Huang et. al. (136) have shown that LAK cell killing was reduced by blocking ICAM-1 on keratinocytes.. Interestingly, recent work indicates that soluble HPV-16 E7 protein can cause increased expression of adhesion molecules including ICAM-1, VCAM-1, and E-selectin on cervical microvascular endothelial cells (137).

## 6. PERSPECTIVE

The innate immune response utilizes multiple methods to recognize and eliminate HPV-infected cells. However, HPVs have evolved several strategies for evading recognition by the innate immune system, and there is growing evidence that HPV early gene products inactivate specific components of innate immunity (Table 2). Some of these interactions are well documented, such as the ability of the E6 and E7 proteins to interfere with expression and signaling by type I IFNs. Others, such as inhibition of IL-18 signaling by HPV E6 and E7 proteins, are intriguing and should be explored further. HPV immunity in the reproductive tract is mainly mediated by the mucosal immune system. Despite its importance, the mucosal immune response is not clearly understood, and more information is needed regarding which components are critical for preventing HPV infections. For example, many cervical HPV infections and almost all cervical cancers originate in a narrow region called the transformation zone. Recent evidence has suggested that innate immune function might be altered within this region and that this might contribute to the susceptibility of this site for malignant conversion (138). The role of NF-kB in HPV infection needs clarification. There have been conflicting reports indicating that E6 and E7 proteins either activate or inhibit NF-kB. This is an important question because down regulation of NF-kB activity by HPV could represent a powerful way to evade innate immunity. CIN and cervical carcinoma are often accompanied by chronic cervicitis, and specific immunosuppressive and proinflammatory cytokines are increased in these lesions (70-75). Chronic inflammation is a risk factor for several human cancers, therefore, it will be important to understand whether it has a role in to cervical carcinogenesis.

A major goal of HPV research is to develop effective vaccines to prevent HPV infection or to treat cervical cancer. The effectiveness of prophylactic vaccination has been established in animal models, and human trials using virus-like particles are underway (12). A important problem in development of therapeutic vaccines

**Table 2.** Effects of papillomavirus early genes on specific components of the innate immune system

| Gene | Interaction with innate immune system | References |
|---|---|---|
| HPV-16 E7 | Interacts with p48 to inhibit IFN-responsive genes | 43 |
| HPV-16 E7 | Binds To IRF-1 and inhibits IFN-beta production | 45,46 |
| HPV-18 E6 | Interacts with TYK2 and inhibits the ISRE | 40 |
| HPV-16 E6 | Binds To IRF-3 and inhibits expression of IFN-beta | 41 |
| HPV-16 E6/E7 | Inhibits expression of IFN-inducible genes in keratinocytes | 48 |
| HPV-16 E6/E7 | Binds to the IL-18 receptor and inhibits ability of NK cells to produce IFN | 64 |
| HPV-16 E6 | Binds to the TNF R1 and inhibits function | 65 |
| HPV-16 E7 | Stimulates apoptosis of keratinocytes and release of IL-1alpha | 54 |
| HPV-16 E7 | Sensitizes keratinocytes to TNF-mediated apoptosis | 66,67 |
| HPV-16E6 | Increases expression of NF-kB responsive genes | 48 |
| HPV-16 E6 | Decreases activation of NF-kB | 99,100 |
| BPV-1 E5 | Stimulates activation of NF-kB | 96 |
| HPV-16 E6/E7 | Expression reduces sensitivity to NK lysis | 116,117,121 |
| HPV-11 E7 | Binds to TAP-1 and inhibits ATP-dependent peptide transport | 131 |
| HPV-16/18 E7 | Decreases transcription from MHC heavy chain and/or TAP-1 promoters | 113,132 |
| HPV-16 E7 | Increases expression of ICAM-1, VCAM, and E-selectin on endothelial cells | 137 |
| BPV-1 E5 | Induces intracellular retention of MHC class I peptides | 130 |

for cervical cancer is that immune deficiency often accompanies the disease. Innate immune mediators including cytokines and adhesion molecules augment the effectiveness of the adaptive immune response. Recent work has shown the importance of PRRs such as the toll-like receptor 4 in stimulation of NF-kB and directing the immune response toward a Th1 phenotype (9). It will be important to understand how activation of specific components of innate immune response can be used to enhance adaptive immunity and maximize effectiveness of vaccines.

## 7. REFERENCES


1. McMurray, H. R., D. Nguyen, T. F. Westbrook, & D. J. McAnce: Biology of human papillomaviruses. *Int J Exp Pathol* 82, 15-33 (2001)
2. Stubenrauch, F. & L. A. Laimins: Human papillomavirus life cycle: active and latent phases. *Semin Cancer Biol* 9, 379-386 (1999)
3. Aral, S. O.: Sexually transmitted diseases: magnitude, determinants and consequences. *Int J STD AIDS* 12, 211-215 (2001)
4. Schiffman, M. H. & L. A. Brinton: The epidemiology of cervical carcinogenesis. *Cancer* 76, 1888-1901 (1995)
5. Munger, K.: The role of human papillomaviruses in human cancers. *Front Biosci* 7, d641-649 (2002)
6. Majewski, S., S. Jablonska, & G. Orth: Epidermodysplasia verruciformis. Immunological and nonimmunological surveillance mechanisms: role in tumor progression. *Clin Dermatol* 15, 321-334 (1997)
7. Gillison, M. L., W. M. Koch, R. B. Capone, M. Spafford, W. H. Westra, L. Wu, M. L. Zahurak, R. W. Daniel, M. Viglione, D. E. Symer, K. V. Shah, & D. Sidransky: Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. *J Natl Cancer Inst* 92, 709-720 (2000)
8. Frisch, M., R. J. Biggar, & J. J. Goedert: Human papillomavirus-associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome. *J Natl Cancer Inst* 92, 1500-1510 (2000)
9. Uthaisangsook, S., N. K. Day, S. L. Bahna, R. A. Good, & S. Haraguchi: Innate immunity and its role against infections. *Ann Allergy Asthma Immunol* 88, 253-264; quiz 265-256, 318 (2002)
10. Janeway, C. A., Jr. & R. Medzhitov: Innate immune recognition. *Annu Rev Immunol* 20, 197-216 (2002)
11. Stanley, M. A.: Immunobiology of papillomavirus infections. *J Reprod Immunol* 52, 45-59 (2001)
12. Stern, P. L., M. Brown, S. N. Stacey, H. C. Kitchener, I. Hampson, E. S. Abdel-Hady, & J. V. Moore: Natural HPV immunity and vaccination strategies. *J Clin Virol* 19, 57-66 (2000)
13. Da Silva, D. M., G. L. Eiben, S. C. Fausch, M. T. Wakabayashi, M. P. Rudolf, M. P. Velders, & W. M. Kast: Cervical cancer vaccines: emerging concepts and developments. *J Cell Physiol* 186, 169-182 (2001)
14. Stoler, M. H., C. R. Rhodes, A. Whitbeck, S. M. Wolinsky, L. T. Chow, & T. R. Broker: Human papillomavirus type 16 and 18 gene expression in cervical neoplasias. *Hum Pathol* 23, 117-128 (1992)
15. Boyer, S. N., D. E. Wazer, & V. Band: E7 protein of human papilloma virus-16 induces degradation of retinoblastoma protein through the ubiquitin-proteasome pathway. *Cancer Res* 56, 4620-4624 (1996)
16. Scheffner, M., B. A. Werness, J. M. Huibregtse, A. J. Levine, & P. M. Howley: The E6 oncoprotein encoded by human papillomavirus types 16 and 18 promotes the degradation of p53. *Cell* 63, 1129-1136 (1990)
17. Straight, S. W., B. Herman, & D. J. McCance: The E5 oncoprotein of human papillomavirus type 16 inhibits the acidification of endosomes in human keratinocytes. *J Virol* 69, 3185-3192 (1995)
18. Doorbar, J., S. Ely, J. Sterling, C. McLean, & L. Crawford: Specific interaction between HPV-16 E1-E4 and cytokeratins results in collapse of the epithelial cell intermediate filament network. *Nature* 352, 824-827 (1991)

19. Popescu, N. C. & J. A. DiPaolo: Integration of human papillomavirus 16 DNA and genomic rearrangements in immortalized human keratinocyte lines. *Cancer Res* 50, 1316-1323 (1990)
20. Jeon, S. & P. F. Lambert: Integration of human papillomavirus type 16 DNA into the human genome leads to increased stability of E6 and E7 mRNAs: implications for cervical carcinogenesis. *Proc Natl Acad Sci U S A* 92, 1654-1658 (1995)
21. Burghardt, E. & A. G. Ostor: Site and origin of squamous cervical cancer: a histomorphologic study. *Obstet Gynecol* 62, 117-127 (1983)
22. Poltorak, A., X. He, I. Smirnova, M. Y. Liu, C. V. Huffel, X. Du, D. Birdwell, E. Alejos, M. Silva, C. Galanos, M. Freudenberg, P. Ricciardi-Castagnoli, B. Layton, & B. Beutler: Defective LPS signaling in C3H/HeJ and C57BL/10ScCr mice: mutations in Tlr4 gene. *Science* 282, 2085-2088 (1998)
23. Yang, D., O. Chertov, & J. J. Oppenheim: The role of mammalian antimicrobial peptides and proteins in awakening of innate host defenses and adaptive immunity. *Cell Mol Life Sci* 58, 978-989 (2001)
24. Nickoloff, B. J. & L. A. Turka: Immunological functions of non-professional antigen-presenting cells: new insights from studies of T-cell interactions with keratinocytes. *Immunol Today* 15, 464-469 (1994)
25. Ferrick, D. A., D. P. King, K. A. Jackson, R. K. Braun, S. Tam, D. M. Hyde, & B. L. Beaman: Intraepithelial gamma delta T lymphocytes: sentinel cells at mucosal barriers. *Springer Semin Immunopathol* 22, 283-296 (2000)
26. Doan, T., K. Herd, M. Street, G. Bryson, G. Fernando, P. Lambert, & R. Tindle: Human papillomavirus type 16 E7 oncoprotein expressed in peripheral epithelium tolerizes E7-directed cytotoxic T-lymphocyte precursors restricted through human (and mouse) major histocompatibility complex class I alleles. *J Virol* 73, 6166-6170 (1999)
27. Konya, J. & J. Dillner: Immunity to oncogenic human papillomaviruses. *Adv Cancer Res* 82, 205-238 (2001)
28. Tindle, R. W.: Immune evasion in human papillomavirus-associated cervical cancer. *Nature Rev Cancer* 2, 59-65 (2002)
29. Frazer, I. H., R. Thomas, J. Zhou, G. R. Leggatt, L. Dunn, N. McMillan, R. W. Tindle, L. Filgueira, P. Manders, P. Barnard, & M. Sharkey: Potential strategies utilised by papillomavirus to evade host immunity. *Immunol Rev* 168, 131-142 (1999)
30. Stark, G. R., I. M. Kerr, B. R. Williams, R. H. Silverman, & R. D. Schreiber: How cells respond to interferons. *Annu Rev Biochem* 67, 227-264 (1998)
31. De Marco, F., V. Manni, N. Guaricci, A. Muller, & M. L. Marcante: Induction of apoptotic cell death by IFNbeta on HPV-16 transformed human keratinocytes. *Antiviral Res* 42, 109-120 (1999)
32. Woodworth, C. D., U. Lichti, S. Simpson, C. H. Evans, & J. A. DiPaolo: Leukoregulin and gamma-interferon inhibit human papillomavirus type 16 gene transcription in human papillomavirus-immortalized human cervical cells. *Cancer Res* 52, 456-463 (1992)
33. Johnson, J. A., H. K. Hochkeppel, & J. D. Gangemi: IFN-tau exhibits potent suppression of human papillomavirus E6/E7 oncoprotein expression. *J Interferon Cytokine Res* 19, 1107-1116 (1999)
34. Khan, M. A., W. H. Tolleson, J. D. Gangemi, & L. Pirisi: Inhibition of growth, transformation, and expression of human papillomavirus type 16 E7 in human keratinocytes by alpha interferons. *J Virol* 67, 3396-3403 (1993)
35. Perea, S. E., O. Lopez-Ocejo, R. Garcia-Milian, & M. J. Arana: Interferon-alpha elicits downregulation of human papillomavirus 18 mRNA in HeLa cells by selective repression of endogenous viral transcription. *J Interferon Cytokine Res* 15, 495-501 (1995)
36. Fontaine, V., E. van der Meijden, & J. ter Schegget: Inhibition of human papillomavirus-16 long control region activity by interferon-gamma overcome by p300 overexpression. *Mol Carcinog* 31, 27-36 (2001)
37. Nawa, A., Y. Nishiyama, N. Yamamoto, K. Maeno, S. Goto, & Y. Tomoda: Selective suppression of human papilloma virus type 18 mRNA level in HeLa cells by interferon. *Biochem Biophys Res Commun* 170, 793-799 (1990)
38. Arany, I., A. Goel, & S. K. Tyring: Interferon response depends on viral transcription in human papillomavirus-containing lesions. *Anticancer Res* 15, 2865-2869 (1995)
39. Koromilas, A. E., S. Li, & G. Matlashewski: Control of interferon signaling in human papillomavirus infection. *Cytokine Growth Factor Rev* 12, 157-170 (2001)
40. Li, S., S. Labrecque, M. C. Gauzzi, A. R. Cuddihy, A. H. Wong, S. Pellegrini, G. J. Matlashewski, & A. E. Koromilas: The human papilloma virus (HPV)-18 E6 oncoprotein physically associates with Tyk2 and impairs Jak-STAT activation by interferon-alpha. *Oncogene* 18, 5727-5737 (1999)
41. Ronco, L. V., A. Y. Karpova, M. Vidal, & P. M. Howley: Human papillomavirus 16 E6 oncoprotein binds to interferon regulatory factor-3 and inhibits its transcriptional activity. *Genes Dev* 12, 2061-2072 (1998)
42. Hiscott, J., P. Pitha, P. Genin, H. Nguyen, C. Heylbroeck, Y. Mamane, M. Algarte, & R. Lin: Triggering the interferon response: the role of IRF-3 transcription factor. *J Interferon Cytokine Res* 19, 1-13 (1999)
43. Barnard, P. & N. A. McMillan: The human papillomavirus E7 oncoprotein abrogates signaling mediated by interferon-alpha. *Virology* 259, 305-313 (1999)
44. Barnard, P., E. Payne, & N. A. McMillan: The human papillomavirus E7 protein is able to inhibit the antiviral and anti-growth functions of interferon-alpha. *Virology* 277, 411-419 (2000)
45. Park, J. S., E. J. Kim, H. J. Kwon, E. S. Hwang, S. E. Namkoong, & S. J. Um: Inactivation of interferon regulatory factor-1 tumor suppressor protein by HPV E7 oncoprotein. Implication for the E7-mediated immune evasion mechanism in cervical carcinogenesis. *J Biol Chem* 275, 6764-6769 (2000)
46. Perea, S. E., P. Massimi, & L. Banks: Human papillomavirus type 16 E7 impairs the activation of the interferon regulatory factor-1. *Int J Mol Med* 5, 661-666 (2000)
47. Chang, Y. E. & L. A. Laimins: Microarray analysis identifies interferon-inducible genes and Stat-1 as major transcriptional targets of human papillomavirus type 31. *J Virol* 74, 4174-4182 (2000)
48. Nees, M., J. M. Geoghegan, T. Hyman, S. Frank, L. Miller, & C. D. Woodworth: Papillomavirus type 16

oncogenes downregulate expression of interferon-responsive genes and upregulate proliferation-associated and NF-kappaB-responsive genes in cervical keratinocytes. *J Virol* 75, 4283-4296 (2001)
49. El-Sherif, A. M., R. Seth, P. J. Tighe, & D. Jenkins: Quantitative analysis of IL-10 and IFN-gamma mRNA levels in normal cervix and human papillomavirus type 16 associated cervical precancer. *J Pathol* 195, 179-185 (2001)
50. Cintorino, M., S. A. Tripodi, R. Romagnoli, F. Ietta, M. G. Ricci, & L. Paulesu: Interferons and their receptors in human papillomavirus lesions of the uterine cervix. *Eur J Gynaecol Oncol* 23, 145-150 (2002)
51. Pao, C. C., C. Y. Lin, D. S. Yao, & C. J. Tseng: Differential expression of cytokine genes in cervical cancer tissues. *Biochem Biophys Res Commun* 214, 1146-1151 (1995)
52. Woodworth, C. D. & S. Simpson: Comparative lymphokine secretion by cultured normal human cervical keratinocytes, papillomavirus-immortalized, and carcinoma cell lines. *Am J Pathol* 142, 1544-1555 (1993)
53. Ansel, J. C., T. A. Luger, D. Lowry, P. Perry, D. R. Roop, & J. D. Mountz: The expression and modulation of IL-1 alpha in murine keratinocytes. *J Immunol* 140, 2274-2278 (1988)
54. Iglesias, M., K. Yen, D. Gaiotti, A. Hildesheim, M. H. Stoler, & C. D. Woodworth: Human papillomavirus type 16 E7 protein sensitizes cervical keratinocytes to apoptosis and release of interleukin-1alpha. *Oncogene* 17, 1195-1205 (1998)
55. Dalgleish, A. G. & K. J. O'Byrne: Chronic immune activation and inflammation in the pathogenesis of AIDS and cancer. *Adv Cancer Res* 84, 231-276 (2002)
56. Coussens, L. M., C. L. Tinkle, D. Hanahan, & Z. Werb: MMP-9 supplied by bone marrow-derived cells contributes to skin carcinogenesis. *Cell* 103, 481-490 (2000)
57. Kyo, S., M. Inoue, N. Hayasaka, T. Inoue, M. Yutsudo, O. Tanizawa, & A. Hakura: Regulation of early gene expression of human papillomavirus type 16 by inflammatory cytokines. *Virology* 200, 130-139 (1994)
58. Woodworth, C. D., V. Notario, & J. A. DiPaolo: Transforming growth factors beta 1 and 2 transcriptionally regulate human papillomavirus (HPV) type 16 early gene expression in HPV-immortalized human genital epithelial cells. *J Virol* 64, 4767-4775 (1990)
59. Zheng, J., O. Saksela, S. Matikainen, & A. Vaheri: Keratinocyte growth factor is a bifunctional regulator of HPV16 DNA-immortalized cervical epithelial cells. *J Cell Biol* 129, 843-851 (1995)
60. Yasumoto, S., A. Taniguchi, & K. Sohma: Epidermal growth factor (EGF) elicits down-regulation of human papillomavirus type 16 (HPV-16) E6/E7 mRNA at the transcriptional level in an EGF-stimulated human keratinocyte cell line: functional role of EGF-responsive silencer in the HPV-16 long control region. *J Virol* 65, 2000-2009 (1991)
61. Smola-Hess, S., U. S. de Silva, D. Hadaschik, & H. J. Pfister: Soluble interleukin-6 receptor activates the human papillomavirus type 18 long control region in SW756 cervical carcinoma cells in a STAT3-dependent manner. *J Gen Virol* 82, 2335-2339 (2001)
62. Cho, Y. S., J. W. Kang, M. Cho, C. W. Cho, S. Lee, Y. K. Choe, Y. Kim, I. Choi, S. N. Park, S. Kim, C. A. Dinarello, & D. Y. Yoon: Down modulation of IL-18 expression by human papillomavirus type 16 E6 oncogene via binding to IL-18. *FEBS Lett* 501, 139-145 (2001)
63. Dinarello, C. A.: Interleukin-18. *Methods* 19, 121-132 (1999)
64. Lee, S. J., Y. S. Cho, M. C. Cho, J. H. Shim, K. A. Lee, K. K. Ko, Y. K. Choe, S. N. Park, T. Hoshino, S. Kim, C. A. Dinarello, & D. Y. Yoon: Both E6 and E7 oncoproteins of human papillomavirus 16 inhibit IL-18-induced IFN-gamma production in human peripheral blood mononuclear and NK cells. *J Immunol* 167, 497-504 (2001)
65. Filippova, M., H. Song, J. L. Connolly, T. S. Dermody, & P. J. Duerksen-Hughes: The Human Papillomavirus 16 E6 Protein Binds to Tumor Necrosis Factor (TNF) R1 and Protects Cells from TNF-induced Apoptosis. *J Biol Chem* 277, 21730-21739 (2002)
66. Stoppler, H., M. C. Stoppler, E. Johnson, C. M. Simbulan-Rosenthal, M. E. Smulson, S. Iyer, D. S. Rosenthal, & R. Schlegel: The E7 protein of human papillomavirus type 16 sensitizes primary human keratinocytes to apoptosis. *Oncogene* 17, 1207-1214 (1998)
67. Basile, J. R., V. Zacny, & K. Munger: The cytokines tumor necrosis factor-alpha (TNF-alpha ) and TNF-related apoptosis-inducing ligand differentially modulate proliferation and apoptotic pathways in human keratinocytes expressing the human papillomavirus-16 E7 oncoprotein. *J Biol Chem* 276, 22522-22528 (2001)
68. Rapp, L., Y. Liu, Y. Hong, E. J. Androphy, & J. J. Chen: The bovine papillomavirus type 1 E6 oncoprotein sensitizes cells to tumor necrosis factor alpha-induced apoptosis. *Oncogene* 18, 607-615 (1999)
69. Liu, Y., V. Tergaonkar, S. Krishna, & E. J. Androphy: Human papillomavirus type 16 E6-enhanced susceptibility of L929 cells to tumor necrosis factor alpha correlates with increased accumulation of reactive oxygen species. *J Biol Chem* 274, 24819-24827 (1999)
70. Tjiong, M. Y., N. van der Vange, J. S. ter Schegget, M. P. Burger, F. W. ten Kate, & T. A. Out: Cytokines in cervicovaginal washing fluid from patients with cervical neoplasia. *Cytokine* 14, 357-360 (2001)
71. Tartour, E., A. Gey, X. Sastre-Garau, C. Pannetier, V. Mosseri, P. Kourilsky, & W. H. Fridman: Analysis of interleukin 6 gene expression in cervical neoplasia using a quantitative polymerase chain reaction assay: evidence for enhanced interleukin 6 gene expression in invasive carcinoma. *Cancer Res* 54, 6243-6248 (1994)
72. Davidson, B., I. Goldberg, & J. Kopolovic: Inflammatory response in cervical intraepithelial neoplasia and squamous cell carcinoma of the uterine cervix. *Pathol Res Pract* 193, 491-495 (1997)
73. McGlennen, R. C., R. S. Ostrow, L. F. Carson, M. S. Stanley, & A. J. Faras: Expression of cytokine receptors and markers of differentiation in human papillomavirus-infected cervical tissues. *Am J Obstet Gynecol* 165, 696-705 (1991)
74. Wei, L. H., M. L. Kuo, C. A. Chen, W. F. Cheng, S. P. Cheng, F. J. Hsieh, & C. Y. Hsieh: Interleukin-6 in cervical cancer: the relationship with vascular endothelial growth factor. *Gynecol Oncol* 82, 49-56 (2001)
75. Tjiong, M. Y., N. van der Vange, F. J. ten Kate, A. H. S. P. Tjong, J. ter Schegget, M. P. Burger, & T. A. Out:

Increased IL-6 and IL-8 levels in cervicovaginal secretions of patients with cervical cancer. *Gynecol Oncol* 73, 285-291 (1999)
76. Merrick, D. T., G. Winberg, & J. K. McDougall: Re-expression of interleukin 1 in human papillomavirus 18 immortalized keratinocytes inhibits their tumorigenicity in nude mice. *Cell Growth Differ* 7, 1661-1669 (1996)
77. al-Saleh, W., S. L. Giannini, N. Jacobs, M. Moutschen, J. Doyen, J. Boniver, & P. Delvenne: Correlation of T-helper secretory differentiation and types of antigen-presenting cells in squamous intraepithelial lesions of the uterine cervix. *J Pathol* 184, 283-290 (1998)
78. Tay, S. K., D. Jenkins, P. Maddox, N. Hogg, & A. Singer: Tissue macrophage response in human papillomavirus infection and cervical intraepithelial neoplasia. *Br J Obstet Gynaecol* 94, 1094-1097 (1987)
79. Castle, P. E., S. L. Hillier, L. K. Rabe, A. Hildesheim, R. Herrero, M. C. Bratti, M. E. Sherman, R. D. Burk, A. C. Rodriguez, M. Alfaro, M. L. Hutchinson, J. Morales, & M. Schiffman: An association of cervical inflammation with high-grade cervical neoplasia in women infected with oncogenic human papillomavirus (HPV). *Cancer Epidemiol Biomarkers Prev* 10, 1021-1027 (2001)
80. Parashari, A., V. Singh, M. M. Gupta, L. Satyanarayana, D. Chattopadhya, P. Sodhani, & A. Sehgal: Significance of inflammatory cervical smears. *Apmis* 103, 273-278 (1995)
81. Malejczyk, J., M. Malejczyk, F. Breitburd, S. Majewski, A. Schwarz, N. Expert-Besancon, S. Jablonska, G. Orth, & T. A. Luger: Progressive growth of human papillomavirus type 16-transformed keratinocytes is associated with an increased release of soluble tumour necrosis factor (TNF) receptor. *Br J Cancer* 74, 234-239 (1996)
82. Malejczyk, M., J. Jozwiak, A. Osiecka, P. I. Roszkowski, W. Mazurkiewicz-Smoktunowicz, T. T. Rogozinski, L. Walczak, S. Jablonska, S. Majewski, & J. Malejczyk: Serum levels of soluble tumor-necrosis-factor receptors in patients with benign and malignant HPV-associated anogenital lesions. *Int J Cancer* 73, 16-19 (1997)
83. Vieira, K. B., D. J. Goldstein, & L. L. Villa: Tumor necrosis factor alpha interferes with the cell cycle of normal and papillomavirus-immortalized human keratinocytes. *Cancer Res* 56, 2452-2457 (1996)
84. Rosl, F., M. Lengert, J. Albrecht, K. Kleine, R. Zawatzky, B. Schraven, & H. zur Hausen: Differential regulation of the JE gene encoding the monocyte chemoattractant protein (MCP-1) in cervical carcinoma cells and derived hybrids. *J Virol* 68, 2142-2150 (1994)
85. Rubin, J. S., H. Osada, P. W. Finch, W. G. Taylor, S. Rudikoff, & S. A. Aaronson: Purification and characterization of a newly identified growth factor specific for epithelial cells. *Proc Natl Acad Sci U S A* 86, 802-806 (1989)
86. Woodworth, C. D., E. McMullin, M. Iglesias, & G. D. Plowman: Interleukin 1 alpha and tumor necrosis factor alpha stimulate autocrine amphiregulin expression and proliferation of human papillomavirus-immortalized and carcinoma-derived cervical epithelial cells. *Proc Natl Acad Sci U S A* 92, 2840-2844 (1995)
87. Wu, S., C. M. Boyer, R. S. Whitaker, A. Berchuck, J. R. Wiener, J. B. Weinberg, & R. C. Bast, Jr.: Tumor necrosis factor alpha as an autocrine and paracrine growth factor for ovarian cancer: monokine induction of tumor cell proliferation and tumor necrosis factor alpha expression. *Cancer Res* 53, 1939-1944 (1993)
88. Iglesias, M., G. D. Plowman, & C. D. Woodworth: Interleukin-6 and interleukin-6 soluble receptor regulate proliferation of normal, human papillomavirus-immortalized, and carcinoma-derived cervical cells in vitro. *Am J Pathol* 146, 944-952 (1995)
89. Fujimoto, J., I. Aoki, S. Khatun, H. Toyoki, & T. Tamaya: Clinical implications of expression of interleukin-8 related to myometrial invasion with angiogenesis in uterine endometrial cancers. *Ann Oncol* 13, 430-434 (2002)
90. Kleine, K., G. Konig, J. Kreuzer, D. Komitowski, H. Zur Hausen, & F. Rosl: The effect of the JE (MCP-1) gene, which encodes monocyte chemoattractant protein-1, on the growth of HeLa cells and derived somatic-cell hybrids in nude mice. *Mol Carcinog* 14, 179-189 (1995)
91. Pahl, H. L.: Activators and target genes of Rel/NF-kappaB transcription factors. *Oncogene* 18, 6853-6866 (1999)
92. Hiscott, J., H. Kwon, & P. Genin: Hostile takeovers: viral appropriation of the NF-kappaB pathway. *J Clin Invest* 107, 143-151 (2001)
93. Fontaine, V., E. van der Meijden, J. de Graaf, J. ter Schegget, & L. Struyk: A functional NF-kappaB binding site in the human papillomavirus type 16 long control region. *Virology* 272, 40-49 (2000)
94. Baldwin, A. S.: Control of oncogenesis and cancer therapy resistance by the transcription factor NF-kappaB. *J Clin Invest* 107, 241-246 (2001)
95. Li, J. J., J. S. Rhim, R. Schlegel, K. H. Vousden, & N. H. Colburn: Expression of dominant negative Jun inhibits elevated AP-1 and NF-kappaB transactivation and suppresses anchorage independent growth of HPV immortalized human keratinocytes. *Oncogene* 16, 2711-2721 (1998)
96. Kilk, A., T. Talpsepp, U. Vali, & M. Ustav: Bovine papillomavirus oncoprotein E5 induces the NF kappa B activation through superoxide radicals. *Biochem Mol Biol Int* 40, 689-697 (1996)
97. Finco, T. S., J. K. Westwick, J. L. Norris, A. A. Beg, C. J. Der, & A. S. Baldwin, Jr.: Oncogenic Ha-Ras-induced signaling activates NF-kappaB transcriptional activity, which is required for cellular transformation. *J Biol Chem* 272, 24113-24116 (1997)
98. Vancurova, I., R. Wu, V. Miskolci, & S. Sun: Increased p50/p50 NF-kappaB activation in human papillomavirus type 6- or type 11-induced laryngeal papilloma tissue. *J Virol* 76, 1533-1536 (2002)
99. Patel, D., S. M. Huang, L. A. Baglia, & D. J. McCance: The E6 protein of human papillomavirus type 16 binds to and inhibits co-activation by CBP and p300. *Embo J* 18, 5061-5072 (1999)
100. Vikhanskaya, F., C. Falugi, P. Valente, & P. Russo: Human papillomavirus type 16 E6-enhanced susceptibility to apoptosis induced by TNF in A2780 human ovarian cancer cell line. *Int J Cancer* 97, 732-739 (2002)
101. Kimber, I., M. Cumberbatch, R. J. Dearman, M. Bhushan, & C. E. Griffiths: Cytokines and chemokines in the initiation and regulation of epidermal Langerhans cell mobilization. *Br J Dermatol* 142, 401-412 (2000)

102. Hagari, Y., L. R. Budgeon, M. D. Pickel, & J. W. Kreider: Association of tumor necrosis factor-alpha gene expression and apoptotic cell death with regression of Shope papillomas. *J Invest Dermatol* 104, 526-529 (1995)
103. Clerici, M., M. Merola, E. Ferrario, D. Trabattoni, M. L. Villa, B. Stefanon, D. J. Venzon, G. M. Shearer, G. De Palo, & E. Clerici: Cytokine production patterns in cervical intraepithelial neoplasia: association with human papillomavirus infection. *J Natl Cancer Inst* 89, 245-250 (1997)
104. Mota, F., N. Rayment, S. Chong, A. Singer, & B. Chain: The antigen-presenting environment in normal and human papillomavirus (HPV)-related premalignant cervical epithelium. *Clin Exp Immunol* 116, 33-40 (1999)
105. Hengge, U. R., B. Benninghoff, T. Ruzicka, & M. Goos: Topical immunomodulators--progress towards treating inflammation, infection, and cancer. *Lancet Infect Dis* 1, 189-198 (2001)
106. zur Hausen, H.: Intracellular surveillance of persisting viral infections. Human genital cancer results from deficient cellular control of papillomavirus gene expression. *Lancet* 2, 489-491 (1986)
107. Denis, M., K. Chadee, & G. J. Matlashewski: Macrophage killing of human papillomavirus type 16-transformed cells. *Virology* 170, 342-345 (1989)
108. Banks, L., F. Moreau, K. Vousden, D. Pim, & G. Matlashewski: Expression of the human papillomavirus E7 oncogene during cell transformation is sufficient to induce susceptibility to lysis by activated macrophages. *J Immunol* 146, 2037-2042 (1991)
109. Wetzel, K., P. Menten, G. Opdenakker, J. Van Damme, H. J. Grone, N. Giese, A. Vecchi, S. Sozzani, J. J. Cornelis, J. Rommelaere, & C. Dinsart: Transduction of human MCP-3 by a parvoviral vector induces leukocyte infiltration and reduces growth of human cervical carcinoma cell xenografts. *J Gene Med* 3, 326-337 (2001)
110. Kleine-Lowinski, K., R. Gillitzer, R. Kuhne-Heid, & F. Rosl: Monocyte-chemo-attractant-protein-1 (MCP-1)-gene expression in cervical intra-epithelial neoplasias and cervical carcinomas. *Int J Cancer* 82, 6-11 (1999)
111. Riethdorf, L., S. Riethdorf, K. Gutzlaff, F. Prall, & T. Loning: Differential expression of the monocyte chemoattractant protein-1 gene in human papillomavirus-16-infected squamous intraepithelial lesions and squamous cell carcinomas of the cervix uteri. *Am J Pathol* 149, 1469-1476 (1996)
112. Vambutas, A., V. R. Bonagura, & B. M. Steinberg: Altered expression of TAP-1 and major histocompatibility complex class I in laryngeal papillomatosis: correlation of TAP-1 with disease. *Clin Diagn Lab Immunol* 7, 79-85 (2000)
113. Georgopoulos, N. T., J. L. Proffitt, & G. E. Blair: Transcriptional regulation of the major histocompatibility complex (MHC) class I heavy chain, TAP1 and LMP2 genes by the human papillomavirus (HPV) type 6b, 16 and 18 E7 oncoproteins. *Oncogene* 19, 4930-4935 (2000)
114. Glew, S. S., M. E. Connor, P. J. Snijders, C. M. Stanbridge, C. H. Buckley, J. M. Walboomers, C. J. Meijer, & P. L. Stern: HLA expression in pre-invasive cervical neoplasia in relation to human papilloma virus infection. *Eur J Cancer* 29A, 1963-1970 (1993)
115. Tay, S. K., D. Jenkins, & A. Singer: Natural killer cells in cervical intraepithelial neoplasia and human papillomavirus infection. *Br J Obstet Gynaecol* 94, 901-906 (1987)
116. Furbert-Harris, P. M., C. H. Evans, C. D. Woodworth, & J. A. DiPaolo: Loss of leukoregulin up-regulation of natural killer but not lymphokine-activated killer lymphocytotoxicity in human papillomavirus 16 DNA-immortalized cervical epithelial cells. *J Natl Cancer Inst* 81, 1080-1085 (1989)
117. Wu, R., N. Coleman, & M. Stanley: Different susceptibility of cervical keratinocytes containing human papillomavirus to cell-mediated cytotoxicity. *Chin Med J (Engl)* 109, 854-858 (1996)
118. Malejczyk, J., M. Malejczyk, A. Urbanski, A. Kock, S. Jablonska, G. Orth, & T. A. Luger: Constitutive release of IL6 by human papillomavirus type 16 (HPV16)-harboring keratinocytes: a mechanism augmenting the NK-cell-mediated lysis of HPV-bearing neoplastic cells. *Cell Immunol* 136, 155-164 (1991)
119. Malejczyk, J., S. Majewski, S. Jablonska, T. T. Rogozinski, & G. Orth: Abrogated NK-cell lysis of human papillomavirus (HPV)-16-bearing keratinocytes in patients with pre-cancerous and cancerous HPV-induced anogenital lesions. *Int J Cancer* 43, 209-214 (1989)
120. Malejczyk, J., M. Malejczyk, S. Majewski, G. Orth, & S. Jablonska: NK-cell activity in patients with HPV16-associated anogenital tumors: defective recognition of HPV16-harboring keratinocytes and restricted unresponsiveness to immunostimulatory cytokines. *Int J Cancer* 54, 917-921 (1993)
121. Routes, J. M. & S. Ryan: Oncogenicity of human papillomavirus- or adenovirus-transformed cells correlates with resistance to lysis by natural killer cells. *J Virol* 69, 7639-7647 (1995)
122. Routes, J. M., S. Ryan, H. Li, J. Steinke, & J. L. Cook: Dissimilar immunogenicities of human papillomavirus E7 and adenovirus E1A proteins influence primary tumor development. *Virology* 277, 48-57 (2000)
123. Kono, K., M. E. Ressing, R. M. Brandt, C. J. Melief, R. K. Potkul, B. Andersson, M. Petersson, W. M. Kast, & R. Kiessling: Decreased expression of signal-transducing zeta chain in peripheral T cells and natural killer cells in patients with cervical cancer. *Clin Cancer Res* 2, 1825-1828 (1996)
124. Viac, J., C. Soler, Y. Chardonnet, S. Euvrard, & D. Schmitt: Expression of immune associated surface antigens of keratinocytes in human papillomavirus-derived lesions. *Immunobiology* 188, 392-402 (1993)
125. Connor, M. E. & P. L. Stern: Loss of MHC class-I expression in cervical carcinomas. *Int J Cancer* 46, 1029-1034 (1990)
126. Keating, P. J., F. V. Cromme, M. Duggan-Keen, P. J. Snijders, J. M. Walboomers, R. D. Hunter, P. A. Dyer, & P. L. Stern: Frequency of down-regulation of individual HLA-A and -B alleles in cervical carcinomas in relation to TAP-1 expression. *Br J Cancer* 72, 405-411 (1995)
127. Hilders, C. G., J. G. Houbiers, E. J. Krul, & G. J. Fleuren: The expression of histocompatibility-related leukocyte antigens in the pathway to cervical carcinoma. *Am J Clin Pathol* 101, 5-12 (1994)

128. Cromme, F. V., P. J. Snijders, A. J. van den Brule, P. Kenemans, C. J. Meijer, & J. M. Walboomers: MHC class I expression in HPV 16 positive cervical carcinomas is post-transcriptionally controlled and independent from c-myc overexpression. *Oncogene* 8, 2969-2975 (1993)
129. Brady, C. S., J. S. Bartholomew, D. J. Burt, M. F. Duggan-Keen, S. Glenville, N. Telford, A. M. Little, J. A. Davidson, P. Jimenez, F. Ruiz-Cabello, F. Garrido, & P. L. Stern: Multiple mechanisms underlie HLA dysregulation in cervical cancer. *Tissue Antigens* 55, 401-411 (2000)
130. Ashrafi, G. H., E. Tsirimonaki, B. Marchetti, P. M. O'Brien, G. J. Sibbet, L. Andrew, & M. S. Campo: Down-regulation of MHC class I by bovine papillomavirus E5 oncoproteins. *Oncogene* 21, 248-259 (2002)
131. Vambutas, A., J. DeVoti, W. Pinn, B. M. Steinberg, & V. R. Bonagura: Interaction of human papillomavirus type 11 E7 protein with TAP-1 results in the reduction of ATP-dependent peptide transport. *Clin Immunol* 101, 94-99 (2001)
132. Um, S. J., J. W. Rhyu, E. J. Kim, K. C. Jeon, E. S. Hwang, & J. S. Park: Abrogation of IRF-1 response by high-risk HPV E7 protein in vivo. *Cancer Lett* 179, 205-212 (2002)
133. Cromme, F. V., J. Airey, M. T. Heemels, H. L. Ploegh, P. J. Keating, P. L. Stern, C. J. Meijer, & J. M. Walboomers: Loss of transporter protein, encoded by the TAP-1 gene, is highly correlated with loss of HLA expression in cervical carcinomas. *J Exp Med* 179, 335-340 (1994)
134. Ritz, U., F. Momburg, H. Pilch, C. Huber, M. J. Maeurer, & B. Seliger: Deficient expression of components of the MHC class I antigen processing machinery in human cervical carcinoma. *Int J Oncol* 19, 1211-1220 (2001)
135. Coleman, N., I. M. Greenfield, J. Hare, H. Kruger-Gray, B. M. Chain, & M. A. Stanley: Characterization and functional analysis of the expression of intercellular adhesion molecule-1 in human papillomavirus-related disease of cervical keratinocytes. *Am J Pathol* 143, 355-367 (1993)
136. Huang, G. T., X. Zhang, & N. H. Park: Increased ICAM-1 expression in transformed human oral epithelial cells: molecular mechanism and functional role in peripheral blood mononuclear cell adhesion and lymphokine-activated-killer cell cytotoxicity. *Int J Oncol* 17, 479-486 (2000)
137. D'Anna, R., H. Le Buanec, G. Alessandri, A. Caruso, A. Burny, R. Gallo, J. F. Zagury, D. Zagury, & P. D'Alessio: Selective activation of cervical microvascular endothelial cells by human papillomavirus 16-e7 oncoprotein. *J Natl Cancer Inst* 93, 1843-1851 (2001)
138. Giannini, S. L., P. Hubert, J. Doyen, J. Boniver, & P. Delvenne: Influence of the mucosal epithelium microenvironment on Langerhans cells: implications for the development of squamous intraepithelial lesions of the cervix. *Int J Cancer* 97, 654-659 (2002)

**Key Words:** HPV, Papillomavirus, Innate Immunity, Inflammation, Cytokines, Cervical Cancer, Interferon, Macrophage, Review

**Send correspondence to:** Craig D. Woodworth, Department of Biology, Science Center, Clarkson University, Potsdam, NY 13699, Tel: 315-268-2391, Fax: 315-268-7118, E-mail: woodworth@clarkson.edu