HPV targets the squamous epithelium found beneath the foreskin of the penis and also the cervix. Infection of basal epithelial cells is necessary for HPV replication and it is thought that virus particles gain access to these cells through microabrasion or microwounding that exposes the basement membrane. The L1 capsid protein on the surface of the HPV virion interacts with α6β4 integrins that are upregulated on basal epithelial cells during wound repair. Interaction with α6β4 integrin promotes internalisation of virus. Circumcision may reduce the risk of HPV infection via the removal of target cells present in the squamous epithelium beneath the foreskin. Antibodies to the capsid proteins L1 and L2 of HPV may be important in blocking attachment of virus to receptors on basal epithelial cells during microwound healing.
HPV takes advantage of the differentiation pathway of keratinocytes that are destined to die naturally (anoikis). Since HPV is not cytolytic and does not cause viraemia, there is no inflammation and subsequent activation of the immune system. Infection of basal epithelial cells establishes a latent infection with low level replication of the viral episome and minimal viral protein expression. Following differentiation of the keratinocyte, early HPV genes are expressed and the viral episome is further amplified to higher copy numbers. Viral late protein expression and virus assembly occurs during terminal differentiation of the keratinocyte and viruses are shed from the outermost layer of epithelial cells.
HPV is not cytolytic and does not cause viraemia, hence, there is no inflammation and immune activation. HPV E6 and E7 oncoproteins interfere with type 1 interferon responses that initiate intracellular antiviral cascades. A lack of release of pro-inflammatory cytokines limits the activation of resident skin Langerhan’s cells required for induction of adaptive immunity. HPV escapes CD8+ cytotoxic T cell detection by downregulating cell surface HLA class I receptors. This is mediated by HPV E5 proteins that promote entrapment of peptide-loaded HLA class I receptors in the Golgi body. Although the loss of HLA class I receptors on the cell surface activates natural killer cells, few natural killer cells are present in this cell layer. The site of HPV infection is a major contributor to survival due to reduced immune surveillance.
The development of cancer associated with high risk HPV types, such as HPV-16 and -18, is dependent on viral inactivation of cellular tumour suppressor proteins p53 and retinoblastoma protein (pRb) followed by the accumulation of DNA damages. Inactivation of p53 and pRb is mediated by viral oncoproteins E6 and E7. Increased synthesis of E6 and E7 occurs following chromosomal integration of HPV genomes carrying a disrupted E2 gene that is required for regulation of E6 and E7 transcription. In the absence of cellular p53, DNA damages can accumulate without repair and the removal of pRb allows cells with DNA damages to undergo cell division. Together these factors can promote the generation of a cell with a malignant phenotype although the process can take several years to develop.
HPV genetic material is replicated in the nucleus of infected cells in the form of a closed circular episome that is amplified to high copy numbers following differentiation of basal epithelial cells into keratinocytes. Importantly, the HPV E2 gene encodes a transcription factor E2 that suppresses transcription of HPV E6 and E7 oncoproteins. E6 and E7 proteins mediate the destruction of cellular tumour suppressor proteins p53 and retinoblastoma protein (pRb) which may lead to the development of carcinoma. E6 and E7 gene transcription is only increased when the E2 gene is disrupted.
The role of p53 protein is to respond to DNA damages and functions as a nuclear transcription factor that activates transcription of genes involved in arrest of the cell cycle and induction of DNA repair systems or the induction of apoptosis. Retinoblastoma protein (pRb) functions to inactivate the transcription factor E2F-DP that is required to initiate transcription of genes involved in DNA replication. These two proteins are essential to prevent cells with damaged DNA from dividing and are known as tumour suppressor proteins. In the absence of HPV E6 and E7, p53 and pRb function normally and reduce the risk of malignant cell transformation.
In certain instances during the replication cycle of HPV, the episomal DNA can be linearised and integrated into chromosomal DNA. A breakpoint that disrupts the HPV E2 gene will prevent the synthesis of E2 proteins that normally regulate the transcription of E6 and E7 oncoproteins. An increase in the production of E6 and E7 is associated with the risk of development of carcinoma due to the inactivation of cellular tumour suppressor proteins p53 and Retinoblastoma protein (pRb) that normally function to prevent cells with DNA damages from proliferating.
Integration of the HPV genome with a disrupted E2 gene into host chromosomal DNA is a necessary event that can lead to the development of carcinoma. The E2 gene encodes a transcription factor that regulates the transcription of HPV E6 and E7 oncoproteins. In the absence of E2, increased synthesis of E6 and E7 protein occurs. E6 binds to p53 in the cytosol and also recruits the E6AP ubiquitin ligase that ubiquitinates p53 and targets it for proteosomal degradation. Similarly, HPV E7 binds to pRb in the cytosol and recruits the cullin 2 ubiquitin ligase that ubiquitinates pRb and promotes proteosomal degradation. Loss of cellular p53 and pRb tumour suppressor proteins allows a cell with DNA damages to divide and thereby increases the risk of cancer development.
High risk HPV types, such as HPV-16 and -18, have a tropism for squamous epithelium found at mucosal sites such as the cervix and beneath the foreskin. In most healthy individuals HPV is detected and cleared by the immune system, however in some cases the virus persists for extended periods of time which can ultimately lead to the development of carcinoma. In immunocompromised individuals, particularly HIV-infected people, persistence of HPV infection is more common due to diminished immune responses and hence risk of cancer development is increased.