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Survey

The role of interleukin 10 in human papilloma virus infection and progression to cervical carcinoma

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ABSTRACT

Although Human Papillomavirus (HPV) exerts a vital influence on cervical carcinogenesis, other factors influence the development of a squamous intraepithelial lesion (SIL) that may or not progress to cervical cancer. Among several cytokines, Interleukin 10 (IL-10) stands out as an important anti-inflammatory factor, leading to immune system evasion through an immunosuppressive state. In the cervical microenvironment, during different stages of HPV infection, IL-10 production can be induced and maintained by different cell sources, including infected keratinocytes, some subsets of dendritic cells (DC), tumor associated macrophages (TAM), T regulatory cells (Treg) and tumor cells. Further, a wide range of effects can be exerted by IL-10 on different cell populations, such as inhibiting proinflammatory cytokine production, DCs differentiation, antigen presenting function and T-helper 1 (Th1) polarization. IL-10 is one of several cytokines involved in cancer development and sustenance, although its role in cancer is still controversial and poorly understood. However, cervical IL-10 levels tend to increase in parallel to SIL development and are even higher within cervical tumors. Accumulating data have shown that after HPV infection, IL-10 levels are enhanced as a result of HPV E2, E6 and E7 proteins action over IL-10 gene transcription, while IL-10 stimulates HPV E6 and E7 expression. Therefore, this interplay between HPV and IL-10 creates a vicious cycle that could favor an immunosuppressive microenvironment in the cervix, facilitating the progression of a simple HPV infection to SIL or cervical cancer.

Contents

1. Introduction

Several viruses are capable of transforming infected cells into benign or malignant tumor cells, stimulating cell growth and survival by a wide range of mechanisms. Different oncogenic DNA viruses present this ability, including Human Papillomavirus (HPV), which is a well-established cause of squamous

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intraepithelial lesions (SIL) and cervical cancer [1,2]. Some HPV early oncoproteins are strictly correlated with cervical cancer initiation and progression, showing tumor-promoting activities [3]. In spite of its importance to cervical carcinogenesis, factors other than HPV influence SIL progression. In the cervical microenvironment, several immune components play important roles in establishing HPV infection as well as on SIL regression or progression to cervical cancer. One of these components is Interleukin 10 (IL-10), an immunoregulatory cytokine, produced by many cell types. After HPV infection, HPV proteins seem to influence IL-10 expression, while IL-10 induces some HPV proteins expression, leading to an amplified state of immunosuppression, allowing SIL development and, eventually, progression to cervical cancer [4].

2. HPV structure and regulatory proteins

The Papillomaviridae family comprises small circular double-stranded DNA viruses (i.e., approximately 50–52 nm in diameter) that replicate their genomes using the host enzymatic machinery, ensuring a high degree of proof reading with low mutation rates [5]. To date, more than 200 types of HPV have been identified and approximately 150 have been sequenced [6]. The viral genome contains approximately 8000 base pairs (bp) (6000–8000 bp), typically compounding a non-coding segment named upstream regulatory region (URR), involved in transcription and replication control, and eight open reading frames (ORF) divided in two regions, the early (E) and the late (L) regions. The E region encodes for six genes (E1, E2, E4, E5, E6, and E7) involved in multiple activities including viral replication and cell transformation, while the L region encodes for the L1 and L2 genes, producing the capsid proteins required for virion assembly (Fig. 1A and B) [7,8].

The URR has approximately 1000 bp, separating the early and late regions, and contains the origin of DNA replication as well as several sequences such as transcription factor-binding sites that are involved in protein expression regulation [1,9]. Viral genes expression including E6 and E7 oncogenes is mostly controlled by a promoter located at the URR and augments as differentiation of suprabasal layers occurs, thus playing an indirect role in both gene expression and viral protein production. In addition, URR is also used for HPV classification, having a relevant role in the phylogenetic analysis of HPV types [10,11].

The E region encodes the viral regulatory proteins, which are required for viral DNA replication. Together, E1, E2 and E4 proteins are responsible for viral amplification and release. E1 has a role in viral DNA replication, acting as an origin recognition site and presenting an ATP-dependent DNA helicase activity. E2 acts as a coactivator of viral DNA replication downregulating E6 and E7 expression when present in high levels, regulates cell cycle and apoptosis and activates late genes expression. In addition, E4 enhances viral genome amplification and binds to cytoskeletal proteins, disrupting cytoskeletal structure during the G2 phase in which the keratinocytes (KC) are tied in, supporting viral release [12–14]. E5, E6 e E7 proteins show tumor-promoting activities, with E6 and E7 corresponding to the primary transforming viral proteins. E5 appears to act by modulating the activity of different cellular proteins, enhancing the transforming activities of E6 and E7, promoting hyperproliferation of infected cells and contributing to tumor progression. In turn, E6 protein seems to affect several signaling pathways in the infected cell, promoting multiple effects including loss of DNA damage repair, cellular immortalization,

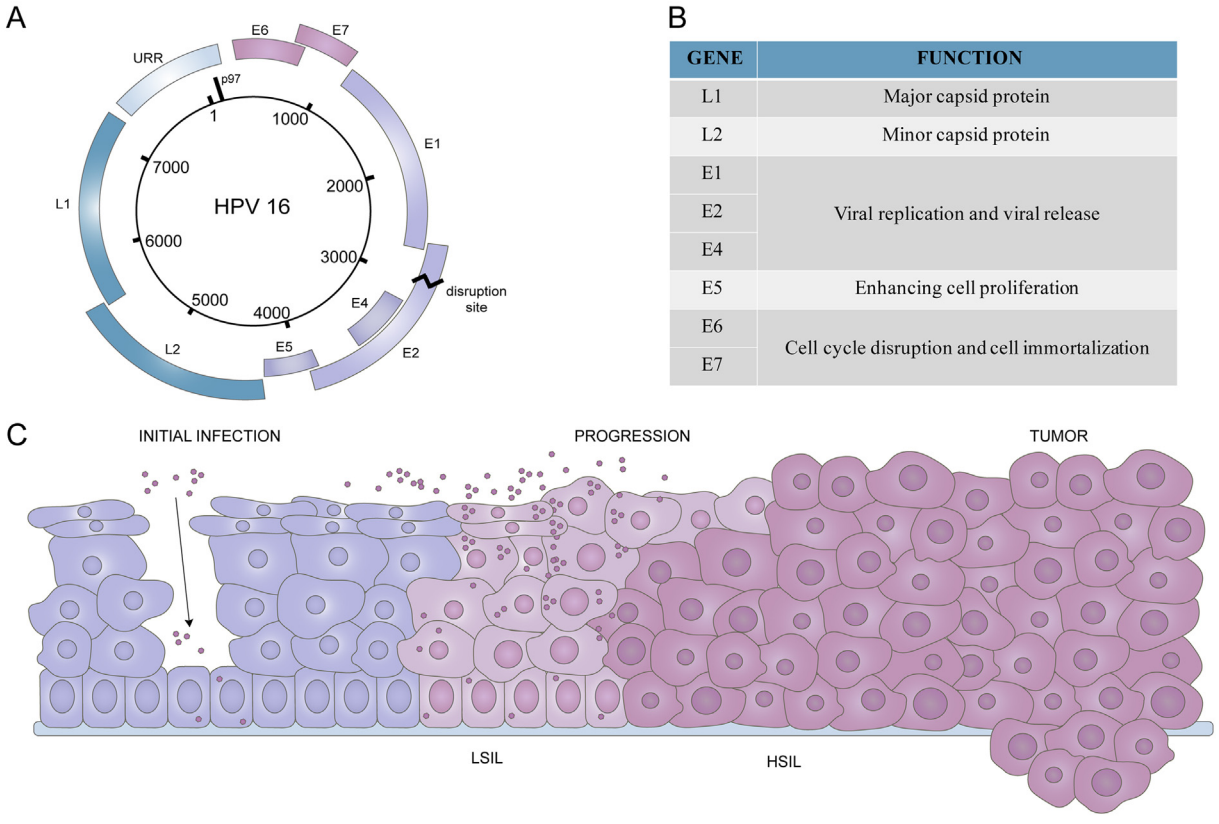

Fig. 1. HPV and SIL Progression. (A) HPV genome showing the URR and the E (E1, E2, E4, E5, E6, and E7) and L (L1 and L2) genes, as well as (B) the basic functions of those regulatory proteins. (C) Different stages of cervical carcinogenesis, passing through initial HPV infection (asymptomatic), which may progress to LSIL and latter to HSIL, culminating in cervical carcinoma.