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Dimensions of Cooperative Cervical Oncogenesis in Abortive Infection by Human Papillomavirus

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Abstract

Induced proliferation of Human Papillomavirus genome and proliferation of host basal and suprabasal epithelial cells in the transformation zone are inherently linked in vegetative production of progeny viral particles, as evidenced by the association of late L1 and L2 late elements that encode capsid proteins in the superficial squamous cells of the cervix. Abortive infection is a staged series of networks that utilize cytokine activities towards the utilization of susceptible breakage points within the host cell genome towards an integration series of mechanisms that promotes the immortalization of the epithelial cells principally by the E7 and the transformation by E6 action. Oncogenic transformation is further enhanced by cooperative activities of combined E6-E7 that possibly act as fusion oncoproteins. One intriguing question is the possible dysfunctionality of episomal partitioning of HPV DNA and persistence and integration of this in oncogenesis, emphasizing possible roles of E2 protein of HPV type-16 in transformation.

Keywords:

Human Papillomavirus; Cervical carcinoma; Persistence of infection; Episomal DNA

Introduction

Persistence of infection of differentiating epithelial squamous cells resulting from infection by Human Papillomavirus (HPV) of basal cells constitutes an essential substratum for progression of possible pro-carcinogenic effects. Coinfection with various commonly occurring pathogens such as *Chlamydia, Trichomonas vaginalis* and also smoking, nutritional deficiencies and multiparity, may play specific roles in HPV persistence in the genital tract [1]. It is significant in this regard to consider the essential dichotomy of episomal viral DNA and integrated viral DNA in the progression of such persistent HPV infection in the epithelial cells. It would appear that the roles played by primary infection and of involvement of the basal/stem cells is a central mechanism in determining such carcinogenic progression as induced by high-risk types of HPV such as HPV-16, HPV-31, HPV-33 and HPV-35. HPV-18 induces oncogenic effects that result directly in high-grade intra-epithelial lesions and invasive carcinoma.

Episomal viral DNA is extra-chromosomal element present in cervical epithelial cells and coexists with integrated DNA within the host cell. The transformation zone is situated between the os and the squamous-columnar epithelial junction of the cervix and is particularly targeted in HPV infection. Subtypes of HPV show differential propensity to induce cervical carcinoma. Potential transcription units (ORFs) are divided into "early" and "late" (capsid) ORFs with replication and transcription start sites.

Integration

Within such context, integration of the HPV DNA into the epithelial host cell genome is essential for pro-carcinogenesis, but is itself insufficient for progression to transformation of the immortalized epithelial cells. Persistent infection and viral oncoproteins couple with deregulated immune responses that lead to severe tissue and systemic injury and consequent carcinogenesis [2]. Such conditioning effects are enhanced by modulating E6-E7 combined effects that greatly enhance efficiency of the transforming capabilities of these two oncoproteins. E1, E2, E4, and E7 are implicated in viral replication. E1 and E2 form a protein complex that aids in the binding of E1 to AT-rich sequence at the origin of viral replication. E6 binds p53 that is cleared by ubiquitin-dependent mechanisms. E7 binds to retinoblastoma gene with dissociation of the normal E2F-Rb family complex, enhancing degradation of pocket proteins (Rb, p107 and p130). STING (Stimulator of Interferon Genes) constitutes a key mediator of innate immune signaling and plays a role in HPV-associated cervical cancer [3].

Differentiation and proliferation

The otherwise natural processes of cell division and particularly also of differentiation of the infected squamous cells assume an important cascade of events in inducing the emergence and evolution of lesions within the squamous epithelial cells. Horizontal DNA transfer is possible through uptake of apoptotic HPV –positive cancer cells by primary fibroblasts promoting transformation [4].

Such scenario evolves in its own right in a manner that permits the proliferation of such cells that lead constitutively to amplification of the viral DNA genome.

High-risk HPV types with reduced immortalization capacity in vitro require more genetic host cell aberrations to facilitate

immortalization [5]. Permissive factors therefore are important mechanistic pathways that would allow for variable and modulatory effects in promoting variable oncogenic outcome of the virally infected epithelial cells. Perturbed keratinocyte differentiation by E6/E7 oncoproteins of high-risk HPV may confer 'stem cell like' attributes [6].

Molecular events

Significant outcome in pro-carcinogenetic evolution is a state of integrated HPV DNA status that implicates the altered functionalities of E6 and E7 oncoproteins, especially in terms of fusion protein creation. It is increasingly recognized that microbes resident in the human body play major roles in modifying carcinogenesis [7,8]. The effects of inhibition and degradation via the ubiquitin pathway of p53 by E6 and the inhibition of the retinoblastoma gene and subsequent released actions of E2F transcription factors are centered on essential loss of control of check-points in epithelial cell proliferation. Indeed, persistent proliferation of the infected squamous cells and also of the initially infected basal epithelial cells cooperatively induces host cell DNA damage, particularly chromosomal aneuploidy and hence resultant genetic instability.

The most studied aspects of HPV expression are the late proteins (L1 and L2), with most attention directed to L1. Most prominent is expression in koilocytotic cells that show perinuclear halo formation, and also hyperchromasia and atypia of the nuclei.

The heterogeneity of HPV status in individual cells emphasizes the need for clarification of HPV infection at the single-cell level [9].

E6 is considered a primary agent in inhibiting apoptosis and is more closely related to transformation of epithelial squamous cells, whereas E7 is primarily an agent in immortalizing cells through the promotion of proliferation of the host cells. The cooperative series of effects of combined E6-E7 action is therefore a strongly inducing cascade of events that promotes transformation of immortalized epithelial cells. There might be a possible connection between Bax expression and the development of cervical cell dysplasia [10].

Evolution of infection

HPV is the commonest sexually-transmitted virus, with the possible availability of a number of potential biomarkers [11]. The full evolving spectrum of infection of basal and squamous epithelial cells is intrinsically a parameter function of the proliferative activities of cells localized predominantly within the transformation zone between the os and the squamo-columnar cell junction. High parity and hormonal contraceptives have also been related to cervical cancer [12].

The pivotal entry mechanisms of HPV into such cells depend largely on micro-environmental conditioning [13] that specifically implicate receptors such as heparin sulfate, proteoglycans and alpha6-integrin, and particularly adhesion molecules per se. Co-infection of Epstein-Barr virus and HPV is implicated in many virally associated cancers including cervical carcinoma [14]. Within such milieu, a highly variable spectrum of possible biologic outcomes can result subsequent to such HPV entry within epithelial cells. Abnormal expression and promoter methylation of microRNAs are common during cervical carcinogenesis, particularly miR-124, miR-218 and miR-193b [15]. Inclusive dimensions of modulated effect cooperate within the essential utilization schemes of adoption of the epithelial cell machinery directed towards the usurpation of polymerases, cyclins and cyclin-dependent kinases of the host cells.

Aneuploidy

In a general and also specific sense, the creation of diploidy, poly-diploidy, and aneuploidy is implicitly accompanied by multi-polarity and centrosome multiplification that all exert a milieu of genetic instability. Also, activation of telomerase is significant. In such manner, cooperative multiplicity of effect is coupled especially to the integration of HPV genome within the host cell genome. A significant enrichment of overlapping nucleotides common to the human genome and HPV genome at integration breakpoints may be observed [16].

The equilibrium between interactive effects of episomal viral DNA elements and such integrated viral DNA constitutes a series of promotional effects that may operate within hormonal influences of estrogen and progesterone on the one hand and the effects of cytokine network operabilities on the other.

Cytokines such as Transforming growth factor-beta, Interleukin-18, Interferon-alpha, tumor necrosis factor-alpha would appear to operate as system pathways that incorporate inherent susceptibilites of host DNA to promote genomic damage. MiR-34a as a oncogene is a key player in carcinogenesis caused by HPV infection due to altered expression of multiple genes [17]. The actual process of integration of viral DNA within the host genome may not be essentially random but specifically targets DNA breakage point foci such as fragile DNA sites.

Abortive infections

Abortive infection by HPV is a staged series of induced proliferation and transformation of host epithelial cells that is linked to possible forms of latent infection. Many long non-coding RNAs may interact with proteins/mRNAs (especially HPV protein) and miRNAs, as well as RNA N-methyladenosine methylation of these long non-coding RNAs [18]. Vegetative forms of productive HPV infection lead to active proliferation of the viral genome on the one hand and contrast with the possible oncogenic effects of such abortive infection.

For unknown reasons, there is highly variable risk conferred by even closely related variant lineages of HPV even within each HPV type [19]. The persistence of the latent forms of integrated HPV DNA is linked to abortive infections of the epithelial cells, including probably the infection of the basal and stem cells that include in turn the production of progeny forms of the HPV virus and their transfer to one daughter cell. Bacterial vaginosis and inflammatory reactivity are independently associated with increased severity of cervical neoplasia in HPV-infected women [20]. In such manner, the subsequent maturation programs of the suprabasal epithelial cells constitute the spread of proliferative cycles of the host cells and of the incorporated viral genomes.

Regulatory elements

The upstream regulatory region is susceptible to the transregulatory actions of E1, and also the operative influences of E2 on partitioning of episomal DNA viral elements on cell division; such actions are deterministic setting for an evolution of viral effects that are inherently highly variable in outcome. A majority of HPV infected women do not exhibit clinical evidence of the genital infection, even in the initial established forms of diffuse involvement of the lower genital tract.

HPV can evade immune response and such immunotolerance of the host is a principal mechanism involved in cervical carcinogenesis [21].

Of the patients that are symptomatic, only a minority progress to a stage of intra-epithelial lesion creation. In addition, the emergence of high-grade intra-epithelial lesions is itself variable in end-point determination, and CIN3 may in many instances fail to progress to invasive carcinoma. MicroRNAs regulate gene expression; cyclin E1 positively regulates cell cycling and is frequently upregulated and so indicates poor outcome in squamous cell carcinoma; miR-16-1 post-transcriptionally downregulates its expression and may play a central role in modulating cell cycling in cervical cancer [22]. Advancing CIN disease severity, on the other hand, is related to increased diversity of vaginal microbiota and may promote HPV persistence and carcinogenesis [23]. Also, infiltrating lymphocytes infected with Epstein-Barr virus may play a role in cervical carcinogenesis related to episomal high-risk HPV [24].

Proliferative maturation of epithelial cells

The E4 protein, particularly when fused to E1 protein, is linked to regulatory functions that combine with effects of proliferative maturation of the squamous epithelial cells to induce viral replication. E2 protein could also play a role in HPV-induced cervical carcinogenesis [25].

The proliferative activities of the suprabasal epithelial cells and their concurrent programs of maturation progress towards the emergence of koilocytotic atypia; these also migrate towards the surface of the epithelial lining of the transformation zone. The active proliferation of these maturing squamous cells is inherent to vegetative production of HPV virions and is observed within condylomatous cells. It is significant to note also in some cases of combined condylomas and high-grade intra-epithelial lesions in the same affected patient promotes transformation of the condylomatous lesions towards oncogenesis.

Conclusion

Abortive infection constitutes a staged series of mechanistic pathways that may be inherently linked to a postulated latent form of persistent infection by HPV within the transformation zone of the cervix. It may be postulated that cooperative effects of combined vegetative and abortive forms of infection of the basal and suprabasal epithelial cells contribute to a long persistent form of induced involvement of the transformation zone that alternates to incorporate combined production of new virions. on the one hand, and persistent integration of the HPV within the host epithelial cell genome.

Integration of HPV is linked inherently to such phenomenon of vegetative proliferation and also transformation of immortalized cells. Oncogenesis results when integration of the HPV DNA evolves within the host cell genome. E1-E2 proteins tend to inhibit the oncogenic effects of E6 and E7. In this regard, it is significant to note the disruption of E1 and E2 production during the integration processes of HPV DNA.

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