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EPIGENETIC ALTERATIONS INDUCED BY GYNECOLOGY ONCOVIRUSES FROM VIRAL PERSISTENCE TO CARCINOGENESIS

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Abstract

Gynecologic oncoviruses that are important in the genesis of malignancies of the female reproductive tract include Human Papillomavirus (HPV), Epstein - Barr virus (EBV), and Human Herpesviruses (HHV). These DNA viruses become persistent or latent infections by regulating host DNA epigenetics to avoid recognition by the immune system and induce oncogenesis. Oncoproteins of viruses (e.g., HPV E6/E7, EBV LMP1/EBNA1) bind DNA methyltransferases, histone modifiers, and non-coding RNAs which results in hypermethylated tumor-suppressor genes (p53, Rb, PTEN) and activation of oncogenic pathways (PI3K/AKT and MAPK). Gene silencing by DNA methylation of viral and cellular promoters keeps the virus in latency, whereas immune evasion (H3K9me3, H3K27me3) and antiforapoptotic (miR-BARTs, miR-203) viral microRNAs keep the viruses hidden. The accrued epigenetic reprogramming of host chromatin results in instability of the genome and generation of a pro-oncogenic microenvironment which propagates malignant transformation. These epigenetic changes caused by the virus are clinically promising diagnostic biomarkers (e.g., CADM1, MAL, miR-124) and potential therapeutic targets, with DNMT and HDAC inhibitors labeling to restore normal expression of these genes. HPV vaccination and antiviral therapy are further preventive measures that induce viral epigenetics to decrease the persistence of infections and cancer. This complex interaction of viral persistence by host epigenetic control offers novel information on precision-based gynecologic oncology, with a potential of using reversible epigenetic processes to prevent or treat cancerous lesions associated with the virus.

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1. INTRODUCTION

Human Papillomavirus (HPV), Epstein Barr virus (EBV) and Human Herpesviruses (HHV, especially HHV-8) are gynecologic oncoviruses that have a significant role in the etiology of multiple malignancies of the female reproductive system, including cervical, vulvar-vaginal, ovary, and endometrial cancer [1].

HPV is the most important as it causes more than 70% of cases of cervical cancer on Earth, more than 600 thousand new cases and 340 thousand deaths each year [2].

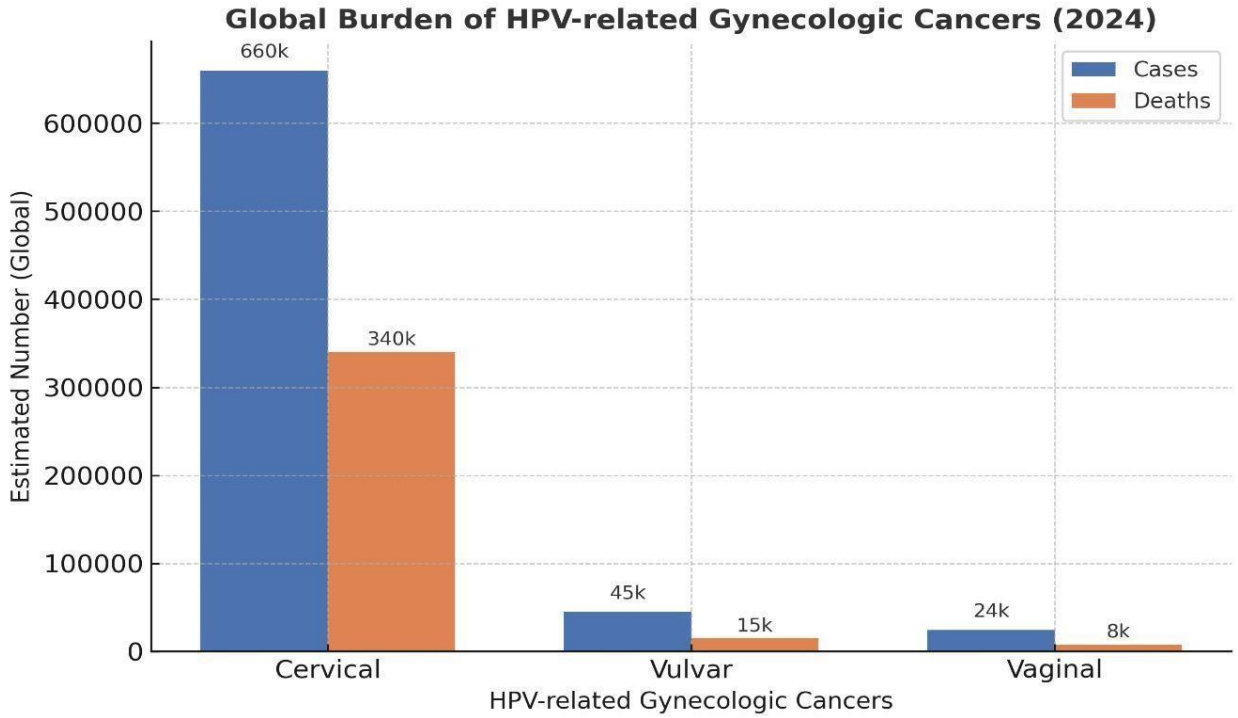

Figure 1: HPV virus gynecologic cancer burden all over the world (2024).

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The pathogenesis of endometrial and ovarian carcinogenesis that involves chronic inflammation and oncogenes has also been attributed to the EBV and HHV-8 [1]. The growing incidence of these virus-associated gynecologic cancers has necessitated the necessity to understand viral oncogenesis, enhance early detection and preventive measures like vaccination and molecular diagnostics to protect the health of women around the world [3]. Concept of Epigenetics are defined as heritable variations in gene expression which can take place without a change in the underlying sequence of DNA [4]. These changes control the process and timelessness of the activation or silencing of particular genes thus affecting cell differentiation, development, and reaction to external cues [5]. DNA methylation, a major epigenetic process that suppresses gene transcription by covalently attaching methyl groups to cytosine residues, histone modifications (acetylation and methylation), and non-coding RNAs (miRNAs and lncRNAs), which post-transcriptionally regulate gene expression, are the key epigenetic processes [6].These mechanisms ensure normal cellular homeostasis, and their malfunction can be the cause of aberrant gene silencing or activation, which is involved in the emergence of multiple diseases, such as cancer [7]. Gynecologic archeoviruses have developed complex systems to control the host epigenetic systems to facilitate viral survival, multiplication and oncogenesis [8]. These viruses modify the main regulatory mechanisms including the DNA methylation, the histone modification, and expression of non-coding RNAs, which result in silencing tumor-suppressor genes and oncogenic pathway activation [9].Oncolytic human papillomavirus (HPV) E6 and E7 induce hypermethylation of promoters, e.g. p53 and p16INK4a, which interferes with cell-cycle regulation and apoptosis [10].Epstein-Bar virus (EBV) latent membrane proteins (LMP1, LMP 2A) also utilize DNA methyltransferases (DNMTs) and histone Deacetylases (HDACs) to reprogram host chromatin in order to remain in a latent and immune-evasive state [11]. Human herpesvirus (HHV-6/7) also alters histone marks (H3K27me3, H3K9ac) in order to silence antiviral genes and create openings in the viral genome to allow its integration [12]. These changes make oncoviruses highly effective in order to redefine the host epigenetic environment, which guarantees its long-term survival, genomic instability, and increased vulnerability to malignant transformation [13]. Constant exposure of gynecologic oncoviruses initiates a process of persistent infection with gynecologic oncoviruses that results in a cycle of epigenetic reprogramming and genomic instability finally leading to the malignant change [14]. Constant presence in the viruses causes aberrant methylation of DNA, histone modification and non-coding RNA dysregulation, which causes silencing of tumor-suppressor genes and activation of oncogenic signaling pathways [13]. Indicatively, long-term articulation of HPV E6/E7 or EBV LMP1 encourages hypermethylation of p53 and RASSF1A that disable apoptosis and cell-cycle management. With time, these accrued changes enable the viral genomes to remain in the host cells, avoid the immune response, and convert normal epithelial cells to cancerous phenotypes [15]. This is an epigenetic-regulated switch between infection and transformation that is a main hallmark of virus-related cancers, which provides the high association between persistent infection and malignancy of the cervix, ovarian, and endometrial [16]. A number of oncoviruses have been implicated in the pathogenesis of gynecologic malignancies with Human Papillomavirus (HPV) being the best studied.HPV-16 and -18 are the most common high-risk genotypes, which explained its involvement in over 95% of cervical cancer, as well as vaginal and vulvar carcinoma due to the E6 and E7 activities of these virus types inactivating tumor suppressors p53 and Rb

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[17]. Epstein-Bar Virus (EBV) has become more often implicated in ovarian and endometrial cancer, in which the latent proteins (e.g., LMP1, EBNA1) play a role in overgrowing abnormal cell proliferation, immune evasion, and epigenetic dysregulation [18]. Human Herpesviruses (HHV) like Cytomegalovirus (CMV) are also known to be co-factors that alter the tumor microenvironment facilitating angiogenesis, chronic inflammation and immune modulation [19].Despite the reported dominance of HPV as the etiological agent, there are recent indications that EBV and CMV can be synergists or supportive agents of gynecologic oncogenesis [20].Biological characteristics of gynecologic oncoviruses, which allow them to cause long-term infection and carcinogenesis, include HPV, EBV and HHV. All are DNA viruses, with the HPV having a circular DNA, which is two-stranded and of the DNA genome [21]. EBV and HHV contain linear two-stranded DNA [22]. The most significant characteristic of these viruses is their ability to be in a latent state, in which they can be inactive in the host epithelial or lymphoid cells over a long periodand activate occasionally due to immunosuppressive or hormonal factors [23]. They are to a large extent attracted to epithelial tissues of cervix, vulva, vagina and endometrium where viral replication and persistence are able to interfere with normal cell differentiation and immune surveillance [24]. This latent infection in combination with tissue-specific tropism is the basis of their long-term oncogenic potential in the female reproductive tract [17].

1.1 Cancer Association Classification:

The oncoviruses that affect the gynecologic system may be classified according to their oncogenic potential and the association with a particular type of cancer [25].

- **Human Papillomaviruses (HPVs)**

Human Papillomaviruses are classified into high- risk and low-risk groups: high-risk viruses (HPV 16 and 18) are closely linked to cervical, vaginal and vaginal carcinoma, and low-risk viruses (HPV 6 and 11) are to be considered to be associated with benign lesions like genital warts [26].

- **Epstein - Barr virus (EBV)**

Epstein-Barr Virus is known to have three patterns of latency (I, II and III) that are characterized by a particular pattern of viral gene expression; each of these latency phases has been associated with various malignancies, with Latency II being the most common in epithelial tumors, such as rare ovarian and endometrial cancer [27].

- **Human Herpesviruses (HHV)**

Cytomegalovirus (CMV) and HHV-6/7 are non-directly oncogenic but can be co-factors, facilitating inflammation, immune suppression and angiogenesis that increase tumor progression in cancer associated with viruses in the gynecologic system [28].

1.2 Mechanism

The induction of carcinogenesis by gonococcal oncoviruses occurs mostly when the host cells are reprogrammed by epigenetics [29]. Oncoproteins E6 and E7 of HPV can stimulate hypermethylation of the tumor suppressor gene DNA and histone acetylation, which induces uncontrolled cell growth [30]. EBV has a role through its latent proteins (LMP1, EBNA1) recruiting DNA methyltransferases and histone modifiers and silencing of pro-apoptotic and immunoregulatory genes [31]. In the same manner, HHV and CMV infections provoke the changes in global methylation and chromatin remodeling and create a pro-oncogenic microenvironment via inflammatory and immune-evasive mechanisms [32]. Taken together, these viruses mediate host epigenetic machineries in order to perpetuate the viruses, evade the immune and promote malignant transformation [33]. The viral oncoproteins rearrange the DNA methylation of the host to facilitate oncogenesis and survival. HPV E6 and E7, and EBV LMP1 proteins raise the activity of DNA methyltransferases (DNMT1, DNMT3A, and DNMT3B) causing hypermethylation of tumor suppressor genes including p16, Rb, and PTEN resulting in transcriptional silencing [31].

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Methylation-inhibited repression of the cell cycle and apoptosis in favor of the malignant transformation occur [34]. Hypermethylation of p16 promoter by HPV16 E7, and the EBV retaining their latency by hypermethylating their own Cp promoter regions and thus blocking the viral antigen [35]. Epigenetic regulation of immune-regulatory genes facilitated immunity to escape and viral persistence underlying a key association between epigenetic deregulation and carcinogenesis caused by viruses [33]. Oncoviruses use host histone modification machineries to change the expression of gene and oncogenesis [15]. Interaction of viral proteins with histone acetyltransferases (HATs) and histone deacetyl transferases (HDACs) causes chromatin to be rearranged resulting in either activation or repression of essential cellular processes [36].

Uncontrolled histone acetylation and methylation are involved in chromatin accessibility-greater acetylation leads to chromatin relaxation and tumor oncogenes activation whereas repressive methylation (e.g., H3K9me3, H3K27me3) and deacetylation leads to chromatin condensing and silencing of tumor suppressors [37].EBV latent membrane protein 1 (LMP1) provokes H3K27me3 enrichment of the promoters of apoptotic and immune regulatory genes, making it easier to avoid the immune system and survive. HPV E7 modulates the histone acetylation state by engaging HDAC, so that it interrupts the normal cell cycle regulation and induces neoplastic change [38]. Figure 1.2 depicts the communication between the viral proteins and the host histone modification machinery, which shows the epigenetic reorganization of viral latency and oncogenesis.

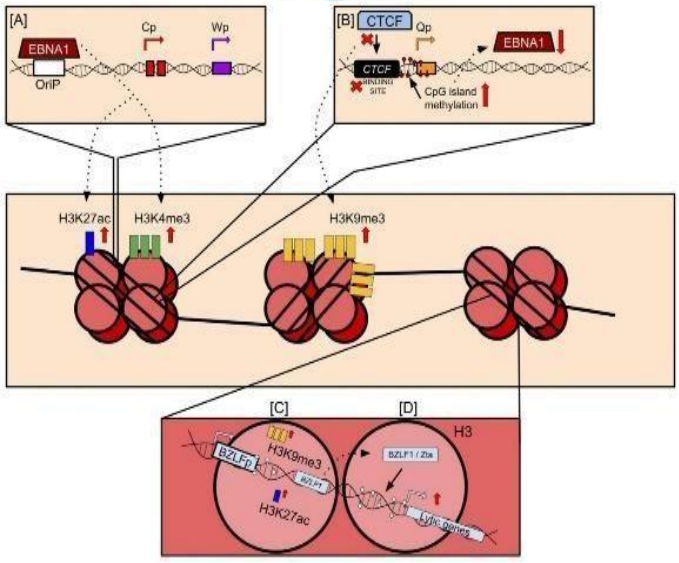

Figure 1.2 Diagrammatic display of the histone modifications in the instance of viral infection.

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Viral proteins like EBNA1 bind to host chromatin to cause modifications in histone marks (e.g. H3K27ac, H3K4me3, and H3K9me3) that control the expression of genes, viral latency and oncogenic transformation [33]. The classes of the non-coding RNAs (ncRNA) that are important epigenetic regulators used by oncoviruses to regulate host gene expression and control persistent infection include microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) [39]. Virus-encoded miRNAs and lncRNAs can change the key cellular pathways through promoting cell growth, suppressing apoptosis, and affecting the immune response [40]. EBV-encoded miR-BARTs that inhibit pro-apoptotic genes like PUMA and BIM and therefore induce cell survival and viral latency [41]. MiR-203 under the control of HPV affects keratinocyte differentiation and leads to the differentiation of epithelial cells. These are ncRNA-based interactions between virus and host, and an extensive way through which gynecologic oncoviruses maintain oncogenic capability and avoid immune surveillance [42]. Viral infection and the integration of the genome cause significant alterations in the host chromatin structure, which cause transcriptional dysregulation and oncogenic metamorphosis [15]. The loss of the natural positioning of nucleosomes and the change of local chromatin accessibility by the introduction of viral DNA, e.g., HPV into host chromosomes, promotes aberrant oncogenes expression and silences tumor suppressor genes [43]. The viral proteins are also known to communicate with host chromatin remodelers and histone-modifying enzymes leading to a continuously modified epigenetic environment that promotes viral pathogenicity, immune evasion and cancerogenic signaling [44]. These epigenetic changes of chromatin are a pivotal point between viral latency and malignant transformation of cancers of the female reproductive system [14]. Multilayered epigenetic reprogramming typically occurs as a result of viral infection in gynecologic cancers where DNA methylation, histone modifications and non-coding RNAs work together to alter gene expression [33]. The crosstalk gives a synergistic capability of viral oncoproteins actuating both DNMTs and histone-modifying enzymes and also moderating both host and viral miRNAs to silence tumor suppressor genes and activate oncogenic pathways [9]. The combination of these mechanisms creates an epigenetic memory, which is stable, allowing the virus to be in latency, cell proliferation that is uncontrolled, and malignant transformation [11].

1.3 Viral persistence and latency epigenetic regulation:

Viral persistence or latency is the capacity of oncoviruses to persist in the host cells in an inactive or slow growing state without being totally eradicated by the immune system [45]. This chronic infection is one of the major stages in the gynecologic oncogenesis, as it allows the persistent expression of viral oncoproteins that interfere with cellular homeostasis [17]. The epigenetic changes (DNA methylation, histone remodeling and non-coding RNA regulation) are central in the maintenance of latency through silencing viral lytic genes and modifying host immune-related pathways [46]. As shown in Figure 1.3 Viral promoter DNA Methylation and histone alterations (H3K9me3, H3K27me3) repress viral lytic gene expression and viral miRNAs preserve immune evasion and host cell survival to promote persistent infection and eventual oncogenic transformation.

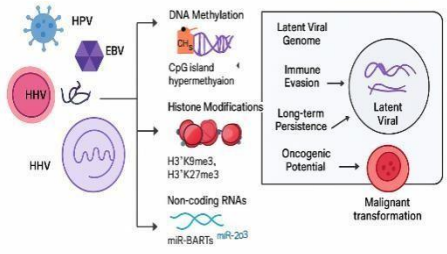

Figure 1.3: ***Diagrammatic representation of epigenetic control of viral latency.***

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These are permanent epigenetic changes that enable viruses to avoid immune response, extend their existence in epithelial cells and produce a cellular environment that facilitates malignant transformation [47]. Epigenetic alterations are critical towards sustaining the viral latency through the control of viral and host gene expression [48]. Viral promoter genes are silenced by DNA methylation to avoid active replication and allow long term persistence within host cells [49]. Heterochromatin formation over viral genomes is encouraged by histone modifications like H3K9me3 and H3K27me3 and ensures transcriptional repression [50]. EBV silences lytic cycle genes by means of methylation of its Cp/Wp promoters and HPV silences viral replication genes by means of methylation and histone deacetylation [51]. These persistent changes in epigenetics enable the viruses to escape the immune system, which predetermines the latent, persistent condition predisposing the oncogenic transformation [11]. Chronic viral infection creates a chronic cellular milieu which is conducive to oncogenesis [52]. The sustained presence of the virus with epigenetic changes of the DNA through hypermethylation of DNA and modification of histones and non-coding RNA dysregulation of normal gene expression and cellular homeostasis [9]. These modifications silence the tumor suppressor genes, activate the oncogenic pathways and suppress immune surveillance [53]. Persistent HPV infection which sustains E6/E7 transcription resulting in p53/Rb inactivation, and EBV latency which facilitates DNA methylation patterns which favor unregulated proliferation. Therefore, viral persistence serves as an initiator of progressive genomic and transcriptional disturbance and eventually leads to malignant change in gynecological tissues [54]. Epigenetic deregulation is an essential intermediate between the malignancy transformation and viral survival in the body [11]. The hypermethylation of tumor suppressor genes (e.g. p53, Rb, and PTEN) induced by viral oncoproteins cause cell cycle abnormalities and genomic abnormalities [55]. Simultaneously, histone modifications and viral/non-coding RNAs engage oncogenic transduction such as PI3K /AKT and MAPK, which facilitates unregulated cell growth and survival [56]. Antigen presentation is inhibited through the methylation of immune-regulatory genes, which allows immunity to evade viral infection and prolongs the viral life cycle. These interconnected epigenetic responses restructure the host genome and induce the shift in viral latency to oncogenesis in gynecological malignancies [9].

2. CLINICAL IMPLICATIONS

Knowledge of the epigenetic changes on oncoviruses in gynecology are very diagnostic and therapeutic. The use of DNA methylation biomarkers (CADM1, MAL, miR-124, etc.) has been suggested as a promising method of HPV-related lesion detection at an early stage, which is more accurate than the conventional cytology [57]. Epigenetic drugs, such as the DNMT, HDAC inhibitors, among others, are also under investigation on the treatment side of the story to reverse deviant methylation and histone modifications and, as such, to restore normal gene expression in HPV-positive and other virus-driven tumors. Other preventive measures, including HPV vaccine and antiviral therapy, also have an indirect impact on viral-driven epigenetic pathways and, as a consequence, decrease the persistence of infection and the development of cancer [58]. By a combination of these insights, the personalized, epigenetically informed approach to gynecologic oncology is on the way.

3. FUTURE DIRECTIONS

Further studies are required in the future to explain the exact molecular interaction between viral oncoproteins and host epigenetic regulators to find new or alternative treatment targets. The multi-omics solution, combining methylation,

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histone, and non-coding RNA data, would help to improve the timely diagnosis and individual therapy of the gynecologic cancer caused by the virus. The new approaches to prevent malignant transformation might be the development of epigenetic-based antivirals and vaccines against viral latency strategies. Further, reversible epigenetic changes may offer a route to accuracy epigenetic therapy in HPV, EBV, and HHV-associated gynecologic malignant cells.

4. CONCLUSION

Viral persistence and cancer development in gynecologic oncoviruses are directed by epigenetic changes. Better understanding of these processes can enhance the early diagnosis and specific treatment. Reversible epigenetic modifications are now promising new prospects of preventing malignancies caused by the virus.

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